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New methodologies in transition metal catalysis. Organofluorine chemistry as the benchmark application.

Tesis Doctoral

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CERTIFICAN:

Que la presente Tesis Doctoral, titulada "**New methodologies in transition metal catalysis. Organofluorine chemistry as the benchmark application**", ha sido realizada bajo su dirección en el Departamento de Química Orgánica de la Universidad de Valencia, por el licenciado en Química **D. Javier Miró Arenas**, y autorizan su presentación para que sea calificada como Tesis Doctoral.

Valencia, Febrero 2017

Fdo. Santos Fustero Lardiés

Fdo. Carlos del Pozo Losada

A mi familia

List of abbreviations

[M]	metal complex
[N-F]	electrophilic *N*-fluorine source
[O]	oxidant
Å	armstrongs
Ac	acetyl
aq	aqueous
Ar	aryl
atm	atmospheres
$B_2(pin)_2$	bis(pinacolato)diboron
BEMP	2-*tert*-butylimino-2-diethyl-amino-1,3-dimethylperhydro-1,3,2-diazaphos-phorine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
br	broad
Bu	butyl
Bz	benzoyl
CAN	cerium ammonium nitrate
CAPT	chiral anion phase-transfer
cat	catalytic amount
Cbz	carboxybenzyl
CEYM	cross enyne metathesis
CM	cross metathesis
Cy	cyclohexyl
d	doublet
dan	1,8-diaminenaphtalene
DAR	Diels Alder reaction
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density-functional theory
DIBAL-H	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethyl formamide
DOS	diversity-oriented synthesis
dr	diastereomeric ratio
dtbbpy	di-*tert*-butylbipyridine
E	electrophile
e.g.	for example
ECP	effective core potential
ee	enantiomeric excess
EI	electronic impact
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
EYM	enyne metathesis
FDA	food and drug administration
FG	functional group
g	grams
GC-MS	gass chromatography-mass spectrometry
gem	geminal
Glc	glucosyl
h	hours
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular or-bital
HPLC	high-performance liquid chro-matography
HRMS	high-resolution mass spectro-metry
Hz	Hertzs
i.e.	that is
IMDAR	intramolecular Diels Alder re-action
^{i}Pr	isopropyl
LG	leaving group
Ln	ligand
Ln*	chiral ligand

LRMS	low-resolution mass spectrometry
m	meta
M	molar
m	multiplet
MALDI	matrix-assisted laser desorption
Me	methyl
min	minutes
mp	melting point
Ms	mesyl, methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
N	normal
NCE	new chemical entity
nd	not determined
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
no	not observed
Ns	nosyl, nitrobenzenesulfonyl
Nu	nucleophile
o	ortho
ºC	degrees Celsius
ORTEP	oak ridge thermal ellipsoid plot
p	para
PA	phosphoric acid
PET	positron emission tomography
Piv	pivaloyl, trimethylacetyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PTC	phase-transfer catalyst
Py	pyridine
PyrOX	pyridine-oxazoline
q	quartet
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis
R_F	fluorine-containing substituent
rt	room temperature
s	singlet
sat	saturated
SM	starting material
t	triplet
TBS	*tert*-butyl dimethyl silyl
^{t}Bu	*tert*-butyl
TCB	1,2,4,5-tetracyanobenzene
Tf	triflyl, trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TLC	thin-layer chromatography
T_{major}	retention time of major enantiomer
T_{minor}	retention time of minor enantiomer
TMS	trimethyl silyl
TOF	time of flight
Tol	tolyl
Ts	tosyl, toluenefulfonyl
TS	transition state
UV	ultraviolet
w/o	without
δ	chemical shift
μW	microwave irradiation

Abstract

Organofluorine compounds have found increasing applications in medicinal, agrochemical and materials sciences. Due to its singularity, fluorine is able to induce significant alterations on key physicochemical properties, such as lipophilicity, electron-density distribution, acid-base properties, hydrogen-bonding capability, and even on conformational equilibria. Nevertheless, fluorine is scarcely found in naturally occurring organic molecules, and the vast majority of fluorine-containing molecules are synthetic. Therefore, the development of new practical methodologies for the generation of fluorine-containing organic frameworks, either by site selective fluorination reactions or yielding them from simple fluorinated building blocks, is of great interest to the synthetic community. On this basis, the present thesis discloses a novel series of synthetic methodologies based on transition metal catalysis, ultimately establishing organofluorine chemistry as their top benchmark application. Herein, we disclose the discovery of the beneficial effect of 1,7-octadiene on assisting enyne metathesis reactions, the generation of a new family of fluorinated α-amino acid derivatives by means of gold-catalysis and the development of two new methodologies for the enantioselective palladium-catalyzed 1,1-difunctionalization of terminal alkenes, including a selective electrophilic fluorination reaction.

Resumen

A lo largo de las últimas décadas, los compuestos organofluorados han encontrado numerosas aplicaciones dentro del campo de las industrias farmacéutica y agroquímica, así como en ciencias de los materiales. Dadas las singulares propiedades del átomo de flúor, éste es capaz de inducir alteraciones significativas en propiedades físico-químicas de las moléculas como lipofilia, distribución de cargas, acidez-basicidad, capacidad de formar enlaces de hidrógeno e incluso, equilibrios conformacionales. Sin embargo, la presencia de flúor en productos naturales es escasa. De hecho, la gran mayoría de las moléculas orgánicas que contienen flúor son sintéticas. De ahí el gran interés por parte de la comunidad sintética en el desarrollo de nuevas metodologías para la introducción de flúor en moléculas orgánicas, bien sea mediante reacciones de fluoración selectivas sobre posiciones específicas de la molécula, o bien mediante el empleo de *building blocks* fluorados, y así construir la nueva molécula alrededor de estos sillares. En este contexto, en la presente tesis doctoral se describe el desarrollo de nuevas metodologías sintéticas catalizadas por complejos de metales de transición, estableciendo la química de flúor como el principal marco de aplicación de dichas metodologías. El descubrimiento del efecto beneficioso del empleo de 1,7-octadieno en reacciones de metátesis de eninos, la generación de una nueva familia de derivados fluorados de α-aminoácidos mediante catálisis con complejos de oro, así como el desarrollo de dos nuevas metodologías sintéticas para la 1,1-difuncionalización enantioselectiva de alquenos terminales, incluyendo una nueva reacción de fluoración electrofílica selectiva, serán objeto de discusión en la presente memoria.

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General introduction, overview and objectives

The generation of new chemical entities, NCEs, (i.e. original structural skeletons capable of interacting with a therapeutic target) is currently one of the most important bottlenecks along the **drug discovery** process. Indeed, within the field of the pharmaceutical industry, the development of new drugs has been steadily declining over the last 15-20 years mainly due to the lack of NCEs. Consequently, the design and development of **new synthetic methodologies** leading to diverse molecular structures represents a significant goal within the area of Organic Chemistry.

In this context, it is well known that 20% of the marketed drugs contain fluorine atoms in their structures and around 50% possess at least one stereocenter.

The paramount role displayed by **fluorine** in the growth and development of medicinal chemistry is firmly established (*Figure 0.1*),[1] providing remarkable breakthroughs in this arena. Lot of commonly used drugs contain fluorine atoms in their skeleton. For instance, 2nd Fluticasone (Seretide) by GSK, 4th Rosuvastatin (Crestor) by AstraZeneca, 17th Sitagliptin (Januvia) by MSD, 20th Tenofovir (Atripla) by Gilead, 25th Celecoxib (Celebrex) by Pfizer or 28th Ezetimibe (Zetia) by MSD, were placed up in the worldwide ranking of top-selling drugs in 2013.

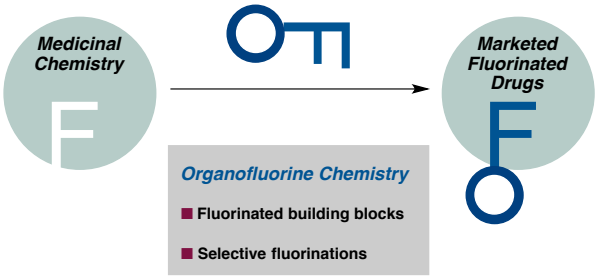


Figure 0.1. Organofluorine chemistry in medicinal chemistry.

[1] (a) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358. (b) Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

The combination of a high electronegative character, along with a moderate size, ascribed a highly polarized character to the C–F bond. As a result, acid-base properties, electron-density distribution, or hydrogen-bonding capability, among other physicochemical properties, might be modulated, resulting in improved pharmacological profiles, such as increased lipophilicity, bioavailability or metabolic stability.[2] Arguably, these particular effects imparted by fluorine explain why it becomes so attractive in drug design, achieving a significant impact in a wide range of medical applications, including anaesthetics, anti-inflammatory drugs, anti-tumour, anti-viral and anti-bacterial agents, or cholesterol inhibitors. But popularity of fluorine is not just tied to medicinal chemistry, as it has reached as well other industrial areas such as agrochemicals,[3] material science[4] or tracers for positron emission tomography (PET).[5]

Nevertheless, despite its widespread distribution in nature (fluorine is the 13th most abundant element in the Earth's crust), the presence of fluorine in natural organic molecules is scarce,[6] and most of the fluorine-containing organic molecules are man-made. Therefore, the development of new methodologies that gain access into new fluorinated derivatives are always in great demand.

In this respect, two main strategies have been followed in order to access to fluorinated organic molecules. One is the use of either nucleophilic or electrophilic fluorinating reagents.[7] Even though research for the development of new selective fluorinating reagents able to form C–F bonds from either C–H bonds or functional groups are currently ongoing, selective fluorination on specific positions of an organic framework is often challenging. Hence, a more flexible synthetic strategy

[2] (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (c) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041.

[3] (a) Fujiwara, T.; O'Hagan, D. *J. Fluorine Chem.* **2014**, *167*, 16. (b) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2013**, *152*, 2. (c) Jeschke, P. *Pest Manag. Sci.* **2010**, *66*, 10. (d) Jeschke, P. *ChemBioChem* **2004**, *5*, 570. (e) Banks, R. E.; Smart, B. E.; Tatlow, J. C. Organofluorine Chemistry: Principles and Commercial Applications; Plenum Press: New York, 1994.

[4] Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

[5] (a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.* **2016**, *116*, 719. (b) Chansaenpak, K.; Vabre, B.; Gabbai, F. P. *Chem. Soc. Rev.* **2016**, *45*, 954. (c) Buckingham, F.; Gouverneur, V. *Chem. Sci.* **2016**, *7*, 1645.

[6] (a) Chan, K. K. J.; O'Hagan, D. *Methods Enzymol.* **2012**, *516*, 219. (b) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127. (c) Paul, E. A.; Huang, P. M. Chemical aspects of soil. In *Handbook of Environmental Chemistry*; Hutzinger, O., Ed.; Springer-Verlag: Berlin, 1980; pp 69−86. Selected examples: (d) Jaivel, N.; Uvarani, C.; Rajesh, R.; Velmurugan, D.; Marimuthu, P. *J. Nat. Prod.* **2014**, *77*, 2. (e) Xu, X.-H.; Yao, G.-M.; Li, Y.-M.; Lu, J.-H.; Lin, C.-J.; Wang, X.; Kong, C.-H. *J. Nat. Prod.* **2003**, *66*, 285.

[7] (a) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612. (d) Ma, J.-A.; Li, S. *Org. Chem. Front.* **2014**, *1*, 712. (e) Bizet, V.; Besset, T.; Ma, J.-A.; Cahard, D. *Curr. Top. Med. Chem.* **2014**, *14*, 901. (f) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289. (g) Liann, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (h) Zhao, Y.; Pan, Y.; Sim, S.-B. D.; Tan, C. H. *Org. Biomol. Chem.* **2012**, *10*, 479. (i) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929. (j) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (k) Valero, G.; Companyó, X.; Rios, R. *Chem. Eur. J.* **2011**, *17*, 2018. (l) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (m) Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal.* **2010**, *352*, 2708. (n) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (o) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065. (p) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (q) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. (r) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561.

based on the use of simple and readily available fluorine-containing compounds as building blocks,[8] building the new molecule around these scaffolds, plays an important role as a powerful supplement to direct fluorination methods.

On the other hand, the significance of enantiomerically pure compounds in the pharmaceutical industry has motivated vast scientific efforts towards the development of stereoselective methodologies for their preparation, especially after the FDA's policy statement for the development of new stereoisomeric drugs in 1992.[9] This paradigmatic shift from racemates to single-enantiomer drugs (*Figure 0.2*)[10] brought **asymmetric synthesis** into the mainstream in the drug discovery process. In general, the additional cost of producing one enantiomer of a chiral molecule makes up for the development work needed to elucidate the toxicological and pharmacokinetic profile of the undesired enantiomer (distomer).

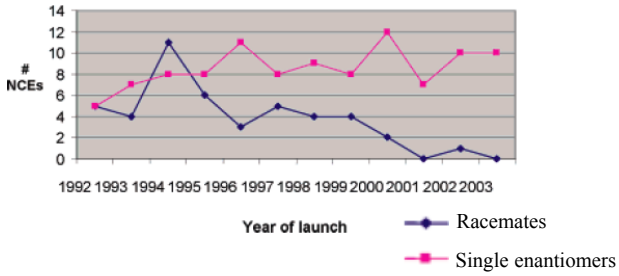


Figure 0.2. Evolution of single enantiomers vs racemates as NCEs.

The synthetic efforts towards the development of new asymmetric synthetic methodologies was recognized in 2001 with the Chemistry Nobel Prize awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless, for the design and development of catalytic methods for the construction of chiral molecules based on the utilization of *transition metal catalysis*.[11] Alternatively, enzymes have been successfully employed as catalysts of certain reactions in a highly specific and efficient manner (*biocatalysis* or *enzymatic catalysis*).[12] In the past decade, *organocatalysis*, i.e. use of small organic

[8] (a) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 3328. (b) Dmowski, W. *J. Fluorine Chem.* **2012**, *142*, 6. (c) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904. (d) Dmowski, W. *J. Fluorine Chem.* **2011**, *132*, 504. (e) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (f) Fustero, S.; Sanz-Cervera, J.-F.; Aceña, J. L.; Sánchez-Roselló, M. *Synlett* **2009**, 525. (g) Wu, J.; Cao, S. *Curr. Org. Chem.* **2009**, *13*, 1791. (h) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943. (i) Fustero, S.; Sanz-Cervera, J.-F.; Piera, J.; Sánchez-Roselló, M.; Chiva, G.; Simón-Fuentes, A. *J. Fluorine Chem.* **2004**, *125*, 621. (j) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131.

[9] Tomaszewski, J.; Rumore, M. M. *Drug Dev. Ind. Pharm.* **1994**, *20*, 119.

[10] Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734.

[11] (a) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

[12] (a) Kielbasinski, P.; Ostaszewski, R.; Szymanski, W. In *In Enzymatic Catalysis Today and Tomorrow*; Wiley-Blackwell: 2010; pp 95-120. (b) Lozano, P.; de Teresa, D.; Iborra, J. L. In *In Enzymatic Catalysis*; Wiley-VCH Verlag GmbH & Co.

molecules to catalyze organic transformations, emerged as a versatile and useful tool for addressing contemporary challenges in asymmetric synthesis.[13]

Beyond its application in asymmetric catalysis, the use of transition metals in organic synthesis has been immense over the past decades, being under continuous innovation and finding increasing applications. Likewise, transition metals have been successfully incorporated into the ever-growing field of organofluorine chemistry with remarkable and often unexpected results.[14]

On the other hand, one of the main interests of academia and industry is the enhancement of synthetic efficiency. In this sense, *tandem catalysis*, which can be defined as a set of reactions catalyzed independently by one or more catalysts in a consecutive manner, is becoming increasingly important in several areas of organic chemistry, including natural products' synthesis, drug discovery, and process chemistry.[15] Likewise, it is one of the strategies used by nature in the preparation of biomolecules.[16] In this manner, using single starting materials, molecular complexity can be increased in a single operation, thus allowing the synthesis of complex molecules and avoiding the loss of time and product associated with the isolation and purification of intermediates in multistep sequences. This approach provides environmental and economic benefits, besides fulfilling the principles of green chemistry. However, the difficulty in the optimization of the separated processes independently has made these methods very challenging.

Given this perspective, the overarching goal of this research thesis was to implement, but also design new transition metal-catalyzed methods that complement the modern organic chemistry toolbox, establishing organofluorine chemistry as the top benchmark application. The employed feed back research strategy, from transition metal catalysis to organofluorine chemistry, and *vice versa*, proved as a highly fruitful approach (*Figure 0.3*), allowing us to reach the below described achievements.

KGaA: 2010; Vol. 4, pp 281-302. (c) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*, 2nd ed., Wiley-VCH: Weinheim 2002.

[13] For selected reviews on asymmetric organocatalysis, see: (a) Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346. (b) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774. (c) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406. (d) Jacobsen, E. N.; MacMillan, D. W. C. *Proceed. Nat. Acad. Sci.* **2010**, *107*, 20618. (e) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (g) List, B. *Chem. Rev.* **2007**, *107*, 5413.

[14] Catalán, S.; Muñoz, S. B.; Fustero, S. *Chimia*, **2014**, *68*, 382.

[15] Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem. Eur. J.* **2009**, *15*, 12168.

[16] (a) Hornsby, C. E.; Paton, R. S. *Nat. Chem.* **2014**, *6*, 88. (b) Davis, B. G. *Nat. Chem.* **2010**, *2*, 85.

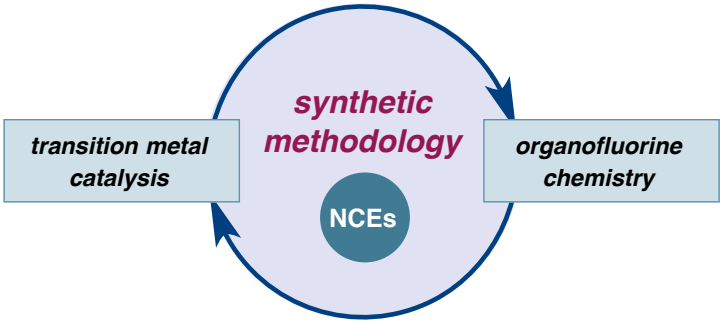
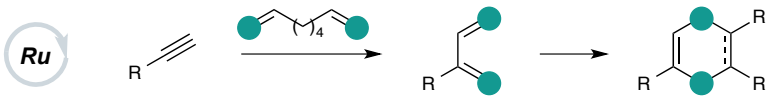
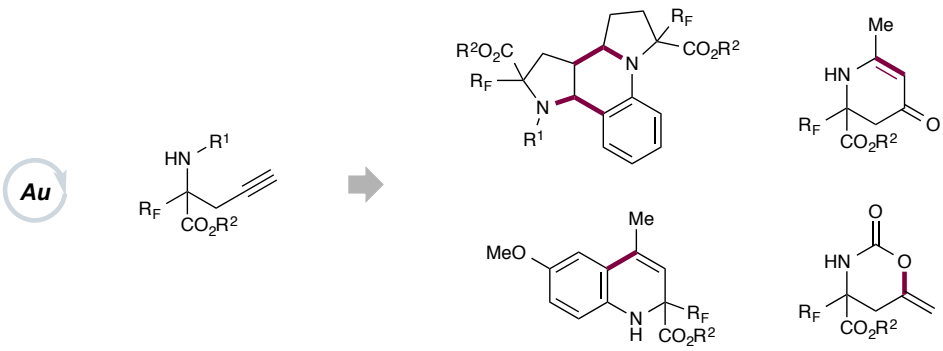


Figure 0.3. Research approach.

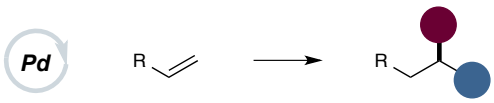
Chapter 1 discloses the discovery of the beneficial effect of 1,7-octadiene as an *in situ* source of ethylene gas in cross enyne metathesis processes. This finding was illustrated in a novel tandem cross enyne metathesis-Diels Alder reaction, which was further extended to difluoropropargyl amides, allowing us to validate this method *versus* previously reported Mori's conditions.



In *Chapter 2*, diversity oriented synthesis (DOS) principle was applied in order to access to new families of fluorine-containing heterocyclic scaffolds by means of gold-catalyzed tandem sequences and starting from a common skeleton, fluorinated homopropargyl α-amino esters. Remarkably, all the accessed new entities contained a quaternary α-amino acid unit, and most of the developed strategies could be further extended to their non-fluorinated counterparts.



Last two chapters disclose two new methodologies for the enantioselective palladium-catalyzed 1,1-difunctionalization of terminal alkenes.



Chapter 3 was developed along an internship at the University of California, Berkeley, under the supervision of Prof. F. Dean Toste and in collaboration with Dr. Hosea M. Nelson and Dr. Brett. D. Williams. This chapter describes a modular and step-economical palladium-catalyzed method for the direct preparation of chiral benzyl boronates from terminal alkenes via a three-component Heck-Matsuda arylation-Miyaura borylation cascade reaction. The process was rendered enantioselective through the use of chiral anion phase-transfer (CAPT) technology, establishing the first illustration of cooperative CAPT and transition metal catalysis.

Finally, inspired by the 1,1-difunctionalization reaction manifold applied in *Chapter 3*, we developed the palladium-catalyzed β,β-fluoroarylation of α,β-unsaturated carbonyl-derived systems *via* a single-step three-component Heck arylation-oxidative fluorination cascade reaction (*Chapter 4*). This chapter was developed in collaboration with Prof. F. Dean Toste.

Chapter 1

1,7-Octadiene-assisted tandem multicomponent cross enyne metathesis-Diels Alder reaction. A useful alternative to Mori's conditions

1.1. Introduction and current state-of-the-art.

The metathesis reaction has become one of the most powerful synthetic tools for the creation of C–C bonds.[17] Even though the first metathesis reaction was described in 1955, it was not until the 90s, with the advent of stable metal-carbene catalysts developed by Schrock, Grubbs and Hoveyda, mostly based on molybdenum or ruthenium (*Figure 1.1*),[18] that metathesis processes became a useful method in synthetic organic chemistry.[19] In general, these catalysts showed wide functional group tolerance and stability to air and moisture, whilst enabling metathesis under mild reaction conditions.

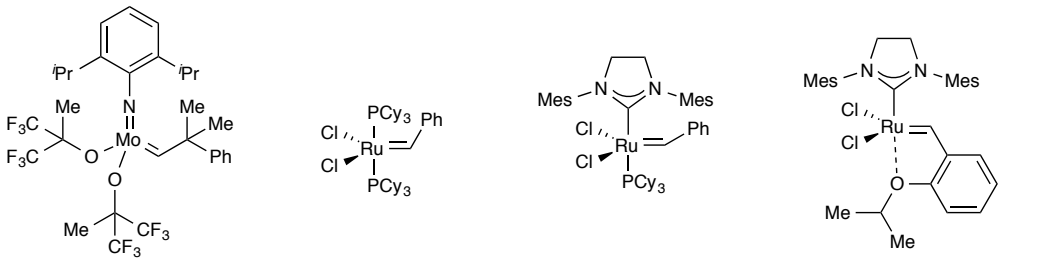


Figure 1.1. Selected carbene-type catalysts employed in metathesis.

[17] (a) Fürstner, A. *Science*, **2013**, *341*, 1357. (b) Kotha, S.; Dipak, M. K. *Tetrahedron*, **2012**, *68*, 397. (c) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389. (d) Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305. (e) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (f) Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 34.

[18] (a) Poulsen, S. C.; Madsen, R. *Synthesis*, **2003**, 1. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039. (c) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. G. Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (d) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

[19] The relevance of this transformation was recognized in 2005 with the Nobel Prize for three of its main contributors, Yves Chauvin, Robbert H. Grubbs and Richard R. Schrock: (a) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760. (b) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748.

The term "metathesis", taken from Greek and meaning "change of position", describes the exchange of carbon atoms between a pair of π-C–C bonds. Among the different variants of metathesis reactions (*Figure 1.2*), enyne metathesis[20] has emerged as a singular process since a new functionality in the product, different from those of the starting materials, is generated in the product. Moreover, in comparison with olefin metathesis or alkyne metathesis (formal substitution reactions), enyne metathesis is an atom economical process, since no byproducts are formed (it resembles an addition event).

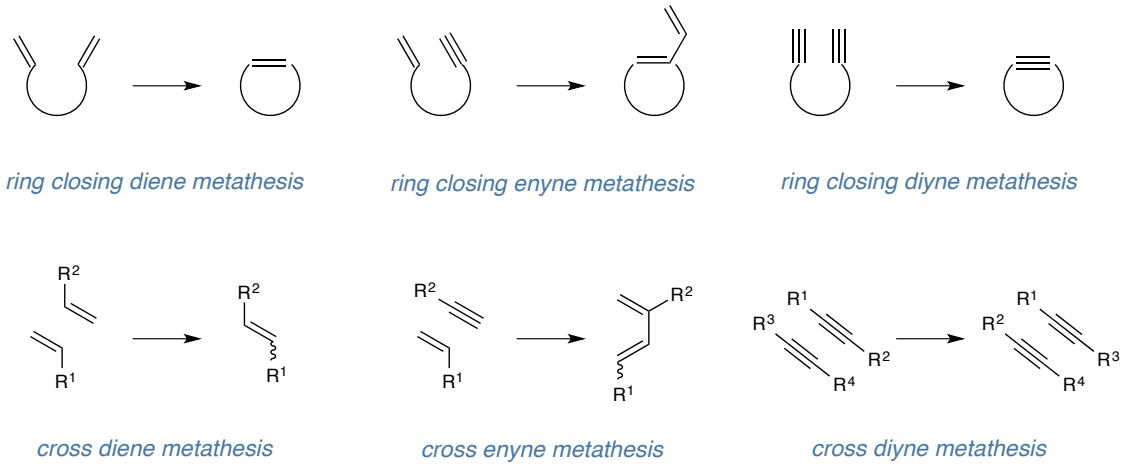
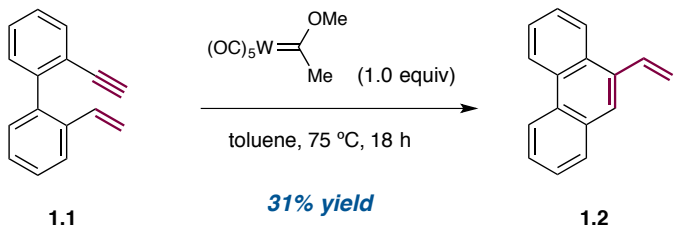


Figure 1.2. Metathesis reactions.

This reorganization of an alkene and an alkyne to produce a 1,3-diene was first reported by Katz in 1985, using stoichiometric amounts of a tungsten Fischer-type carbene (*Scheme 1.1*).[21]

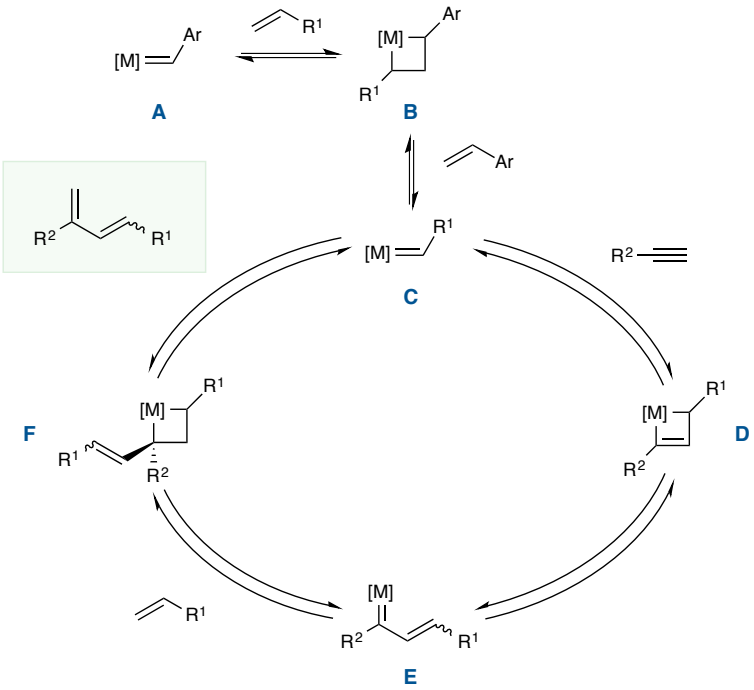


Scheme 1.1. Katz's seminal report (1985).

Though the mechanism by which enyne metathesis occurs is not yet clear, the formation of the diene can be explained as follows (*Scheme 1.2*). The reaction would be initiated by a [2+2]

[20] (a) Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509. (b) Diver, S. T.; Geissert, A. J. *Chem. Rev.* **2004**, *104*, 1317.
[21] (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737. (b) Katz, T. J.; Sivavec, T. M. *Tetrahedron Lett.* **1985**, *26*, 2159.

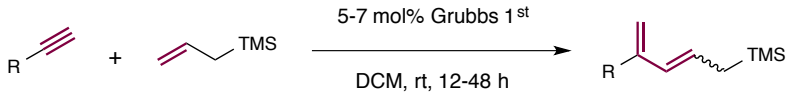
cycloaddition of the benzylidene metal carbene **A** to the alkene counterpart, rendering metallacyclobutane **B**. Then, cycloelimination would release a styrene derivative, which generally does not interfere in cross metathesis reactions. Resulting vinyl carbene **C**, the active catalytic species, would then react with the alkyne moiety, yielding metallacyclobutene **D**. A new [2+2] retro-cycloaddition step would give rise to dienic metal carbene **E**, which would react with another alkene molecule, thus releasing final diene and the catalytically active species **C**, completing the catalytic cycle.



Scheme 1.2. EYM mechanism.

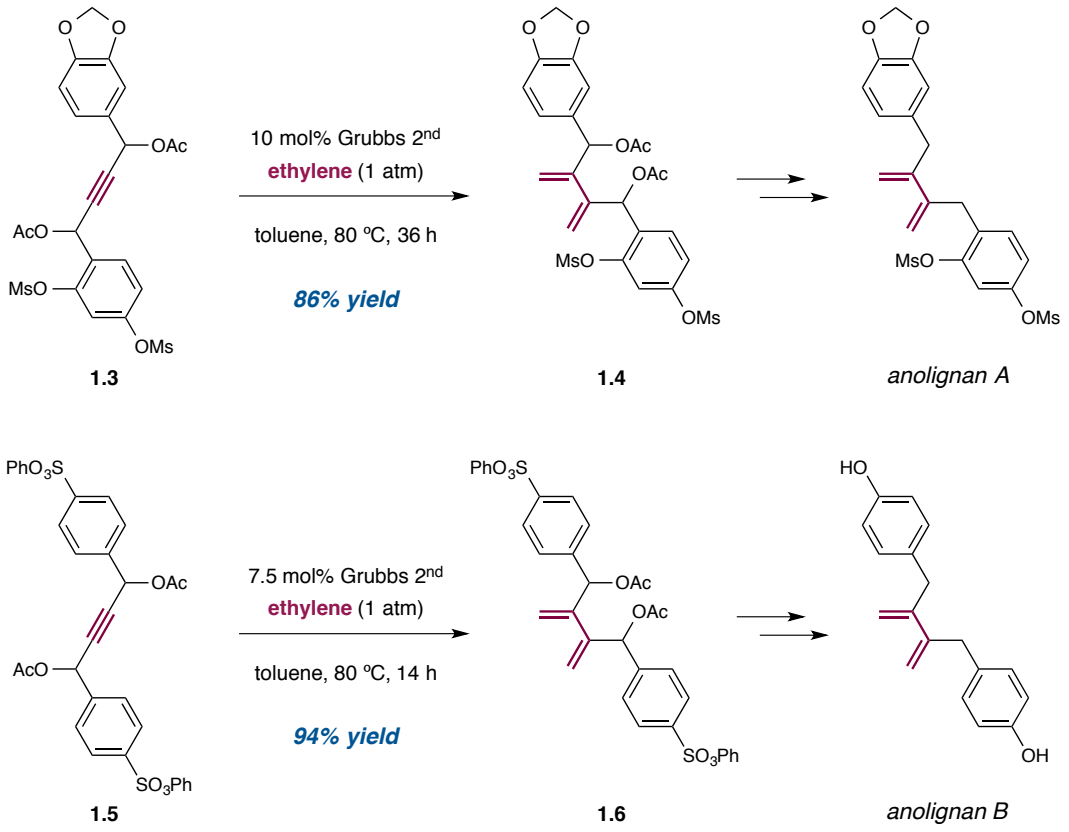
Enyne metathesis has found both intra- (ring-closing enyne metathesis, RCEYM) and intermolecular (cross enyne metathesis, CEYM) applications. While examples of RCEYM are well documented in the literature, the intermolecular CEYM reaction has found fewer applications, mainly due to the difficulties associated in controlling the stereoselectivity of the newly formed double bond, leading to mixtures of *E*/*Z*-isomers. Indeed, these problems arose in the first reported example of CEYM (*Scheme 1.3*).[22]

[22] Stagies, R.; Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2518.



Scheme 1.3. First intermolecular EYM (Blechert, 1997).

Typically, this problem has been circumvented by bubbling ethylene gas into the reaction mixture as the olefinic coupling partner, since ethylene's symmetry avoids these selectivity issues.[23] For instance, CEYM was a key step in the Mori's synthesis of reverse transcriptase inhibitors of HIV-1 *anolignan A* and *anolignan B* (*Scheme 1.4*).[24]

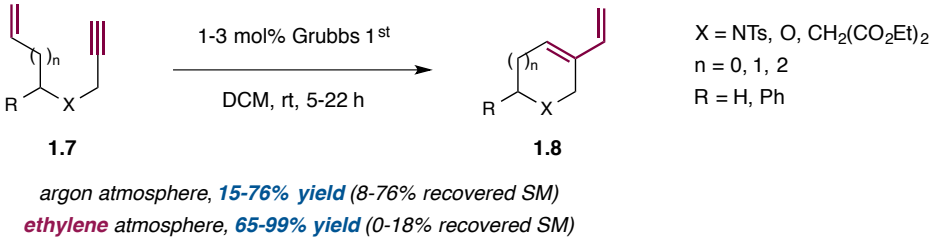


Scheme 1.4. Previous work by Mori (2002).

Likewise, the development of enyne metathesis has lagged behind its diene counterpart, probably due to its less predictable nature as regards to regioselectivity. Cross diene metathesis and cross diyne metathesis arise as potential competitive processes when dealing with an alkene and an alkyne at the same time.

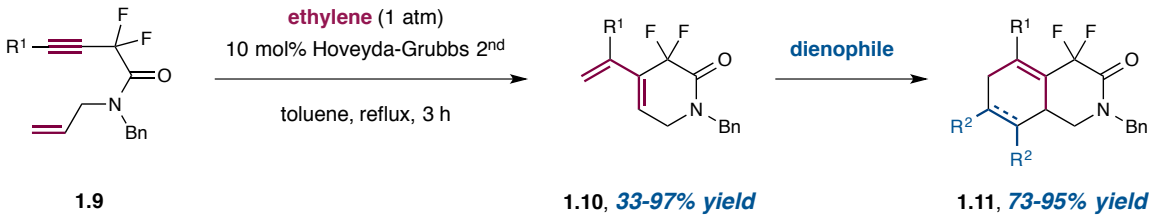
[23] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.
[24] Mori, M.; Tonogaki, K.; Nishiguchi, N. *J. Org. Chem.* **2002**, *67*, 224.

The discovery of the beneficial effect of ethylene by Mori *et al.* changed this tendency.[25] They observed a significant improvement in the efficiency of the RCEYM reaction leading to dienes **1.8** when the reaction was carried out under an atmosphere of ethylene, i.e. the so-coined Mori's conditions (*Scheme 1.5*).



Scheme 1.5. Mori's conditions (Mori, 1998).

In our own lab, in collaboration with the Hammond group, we confirmed the beneficial effect of an ethylene atmosphere in the RCEYM of 1,7-enynes **1.9**.[26] Yields of fluorolactams **1.10** increased from ~20% up to ~70% under Mori's conditions (*Scheme 1.6*).

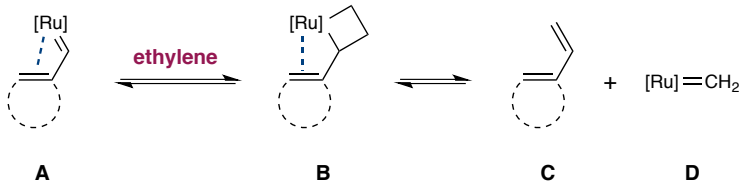


Scheme 1.6. Previous work by Fustero and Hammond (2008).

In these cases, ethylene does not act as a coupling partner, i.e. it is not integrated into the product, but instead acts as a promoting agent, triggering the metathesis reaction. Though it is not clear how it interferes to increase the efficiency of the whole process, some authors have stated the intermediacy of species **A**, with an additional coordinative interaction between the ruthenium metal center and the vinyl moiety (*Scheme 1.7*).[27] On the basis of the stability imparted by this chelate effect, such type of ruthenium-carbene species **A** would hinder the regeneration of catalytically active ruthenium species **D**. Nevertheless, under an ethylene atmosphere, the high concentration of this olefin presumably favours the transference of the methylene group *via* intermediate **B**, rendering the

[25] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.
[26] Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656.
[27] Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics*, **2001**, *20*, 3845.

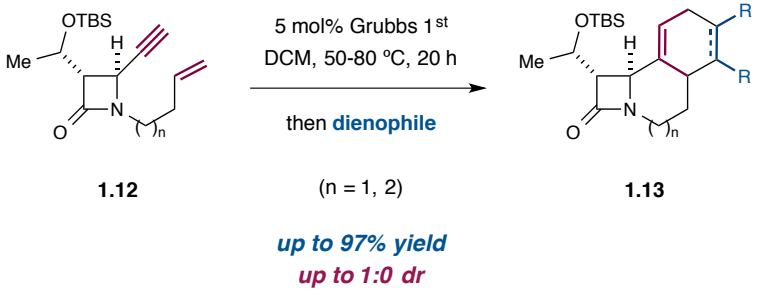
corresponding 1,3-diene **C**, and regenerating the catalytically active species **D**. Thus, ethylene improves the turnover of the ruthenium alkylidene **A**.[28]



Scheme 1.7. Key intermediate species in CEYM.

As mentioned above, enyne metathesis processes have an added value in comparison to other metathesis variants, since the generated 1,3-dienes are highly valuable synthetic intermediates suitable to participate in further metathetic and non-metathetic transformations,[29] such as cycloaddition, cyclopropanation, or hydrovinylation reactions, either in a stepwise or a tandem manner. Arguably, this metathesis cascade chemistry has emerged as a powerful tool for the synthesis of skeletally diverse small molecules, converting the resulting diene intermediate into other useful functionalities.

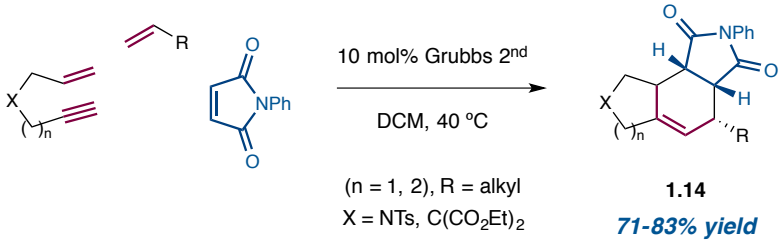
The inherent tandem nature of enyne metathesis is particularly appealing in its combination with the Diels Alder reaction, enabling the easy generation of diverse poly(hetero)cyclic and benzannulated products, thus increasing molecular complexity in a quite simple manner.[30] This strategy has allowed the synthesis of a wide variety of natural and non-natural products. For instance, Savignac and Genêt developed the one-pot synthesis of polycyclic β-lactams **1.13** based on a tandem RCEYM-Diels Alder reaction (*Scheme 1.8*).[31]



Scheme 1.8. Previous work by Savignac and Genêt (2004).

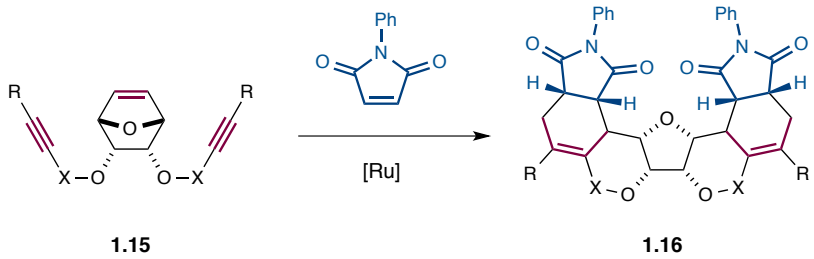
[28] For another example on the beneficial effect of ethylene, see: Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.
[29] Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269.
[30] Kotha, S.; Chavan, A. S.; Goyal, D. *ACS Comb. Sci.* **2015**, *17*, 253.
[31] Desroy, N.; Robert-Peillard, F.; Toueg, J.; Hénaut, C.; Duboc, R.; Rager, M.-N.; Savignac, M.; Genêt, J.-P. *Synthesis*, **2004**, 2665.

On the other hand, Lee and coworkers employed 1,6- and 1,7-enynes in a triple tandem RCEYM-cross metathesis-Diels Alder cascade reaction, yielding final cycloadducts **1.14** in good yields (*Scheme 1.9*).[32]



Scheme 1.9. Previous work by Lee (2003).

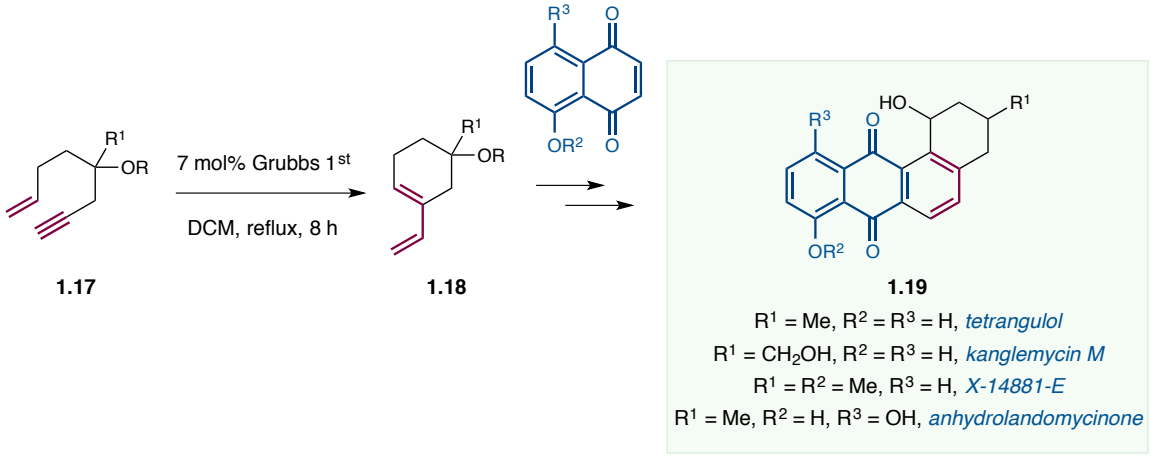
Similarly, Plumet and coworkers reported another triple tandem ring opening metathesis-RCEYM-Diels Alder reaction for the preparation of heteropolycycles **1.16**, starting from norbornene derivatives **1.15** (*Scheme 1.10*).[33]



Scheme 1.10. Previous work by Plumet (2009).

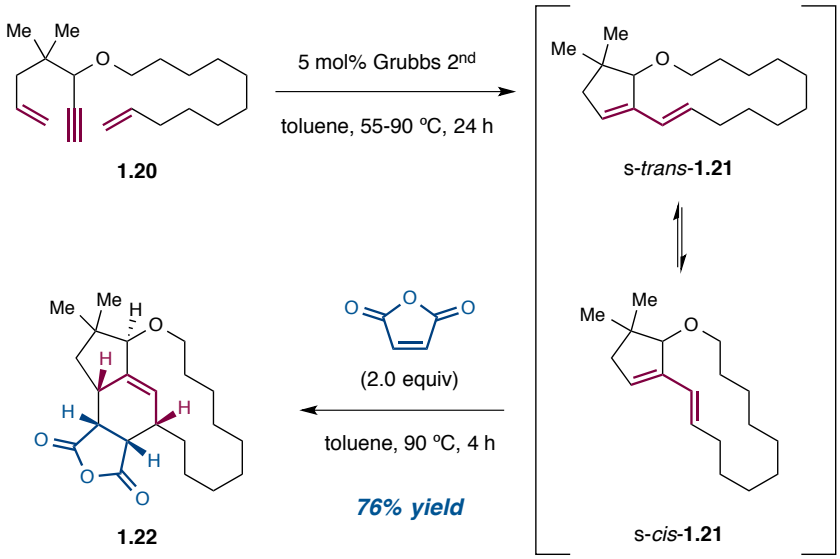
The carbotetracyclic skeleton **1.19**, featured in several antibiotics, can be afforded by means of a stepwise RCEYM-Diels Alder sequence (*Scheme 1.11*).[34]

[32] Lee, H. Y.; Kim, H.-Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.
[33] (a) Ljarilla, A.; Murcia, A.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2009**, 822. For previous similar reaction sequences, see: (b) Banti, D.; North, M. *Adv. Synth. Catal.* **2002**, *344*, 694. (c) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561.
[34] Vanga, D. G.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2012**, 2250.



Scheme 1.11. Previous work by Kaliappan (2012).

In 2010, Choi and coworkers reported a tandem RCEYM-RCM reaction over dieneyne **1.20**, which rendered macrocyclic diene **1.21**. This was prone to participate in a [4+2] cycloaddition with maleic anhydride, although only when adopting an s-*cis* conformation (*Scheme 1.12*).[35]

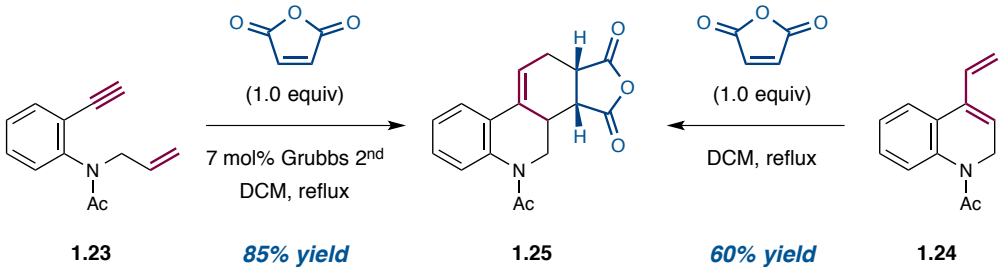


Scheme 1.12. Previous work by Choi (2010).

Sometimes, the ruthenium species employed to catalyze the metathesis transformation can impart a beneficial effect in the subsequent cycloaddition. This effect was reported by Pérez-Castells and coworkers in the preparation of steroid-like compounds **1.25** (*Scheme 1.13*).[36] While yields

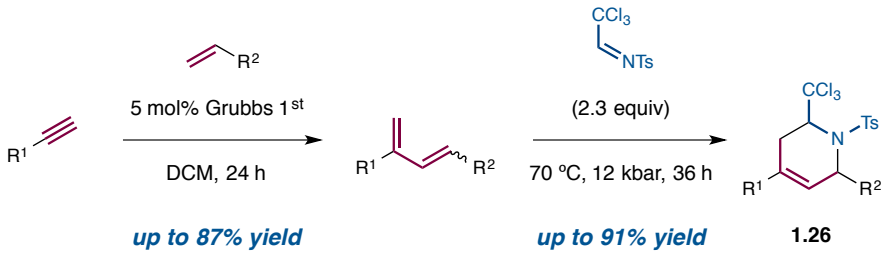
[35] Park, H.; Hong, Y.-L.; Kim, Y.-B.; Choi, T.-L. *Org. Lett.* **2010**, *12*, 3442.
[36] Rosillo, M.; Domínguez, G.; Casarrubios, L.; Amador, U.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084.

reached up to 85% when carrying out the process in a tandem fashion, the Diels Alder cycloaddition from isolated 1,3-diene **1.24**, in the absence of the [Ru] catalyst, occurred in lower 60% yield.



Scheme 1.13. Previous work by Pérez-Castells (2004).

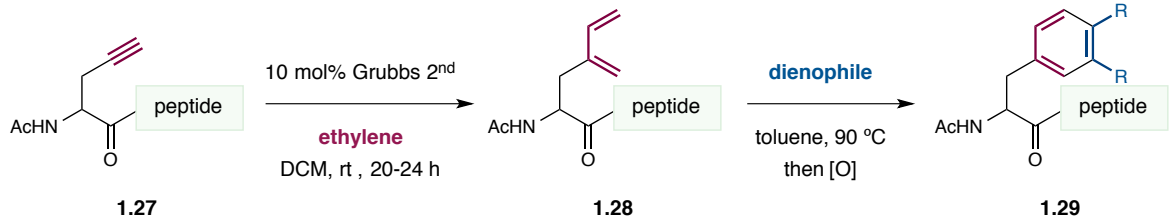
Although they are more challenging, intermolecular enyne metathesis reactions have also been successfully applied in tandem sequences with [4+2] cycloadditions. For instance, Schürer and Blechert reported the preparation of highly substituted tetrahydropyridines **1.26** by means of a one-pot CEYM-hetero-Diels Alder sequence (*Scheme 1.14*).[37] The same sequence was further applied to prepare pseudo-oligosaccharides.[38]



Scheme 1.14. Previous work by Schürer and Blechert (1999).

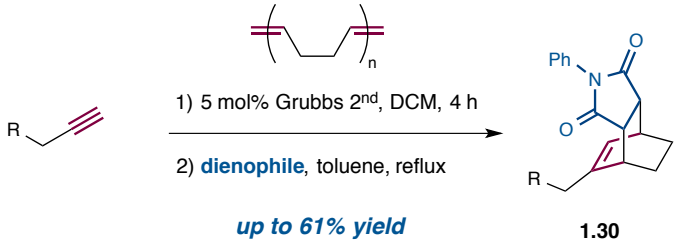
More recently, a CEYM-Diels Alder sequence was utilized in the synthesis of phenylalanine-based di- and tri-peptides **1.29**, but in a stepwise fashion (*Scheme 1.15*).[39]

[37] Schürer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877.
[38] Schürer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203.
[39] Kotha, S.; Goyal, D.; Thota, N.; Srinivas, V. *Eur. J. Org. Chem.* **2012**, 1843.



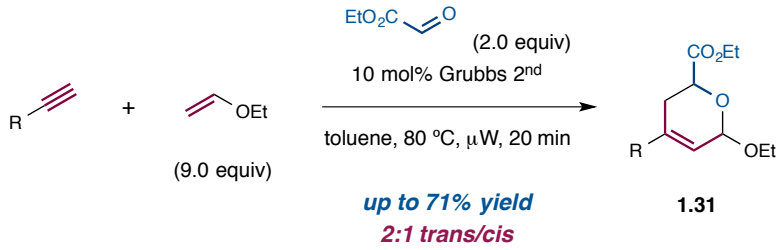
Scheme 1.15. Previous work by Kotha (2012).

Previously, the Diver group disclosed a CEYM reaction between terminal alkynes and polybutadiene, giving rise to cyclic 1,3-hexadienes, suitable to be trapped later by dienophiles such as *N*-phenylmaleimide, in a one-pot procedure (*Scheme 1.16*).[40]



Scheme 1.16. Previous work by Diver (2004).

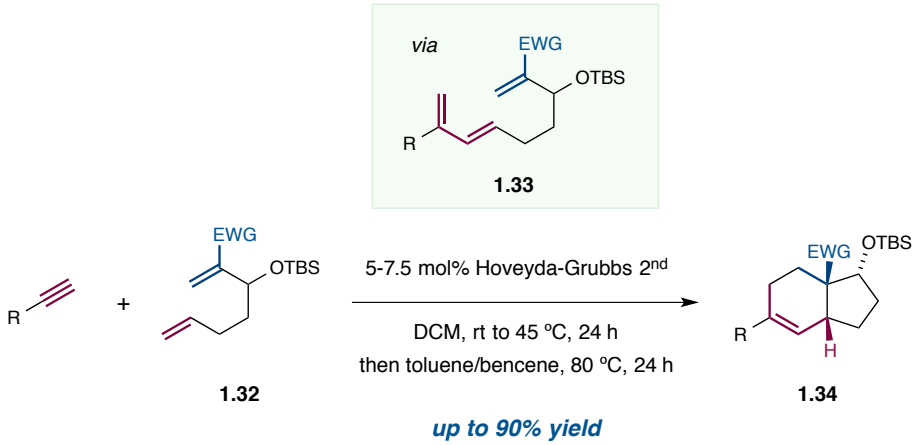
Additionally, a multicomponent CEYM-intermolecular hetero-Diels Alder reaction involving alkynes, ethyl glyoxalate and ethyl vinyl ether was reported for the preparation of 2,3-dihydropyrans **1.31** (*Scheme 1.17*).[41]



Scheme 1.17. Previous work by Botta (2009).

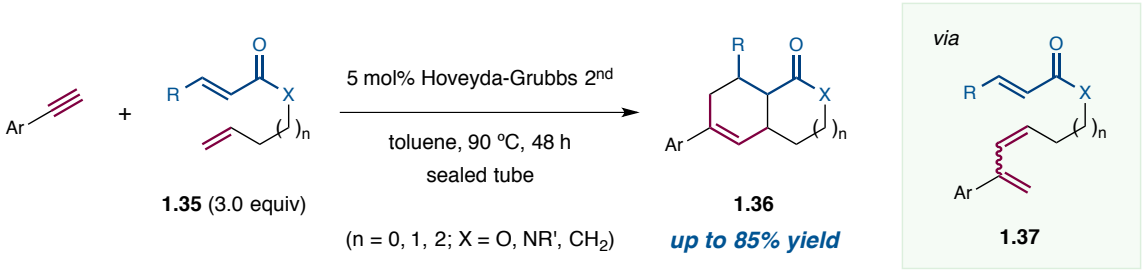
[40] Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110.
[41] (a) Castagnolo, D.; Botta, L.; Botta, M. *Carbohydr. Res.* **2009**, *344*, 1285. (b) Castagnolo, D.; Botta, L.; Botta, M. *Tetrahedron Lett.* **2009**, *50*, 1526.

In 2005, the Blechert group published a CEYM-intramolecular Diels Alder reaction by combining Baylis-Hillman adducts **1.32** with terminal alkynes in the presence of second generation Hoveyda-Grubbs catalyst (*Scheme 1.18*).[42] After the initial formation of the triene **1.33**, avoiding RCM of diene **1.32**, a spontaneous intramolecular Diels Alder reaction rendered highly functionalized bicyclic derivatives **1.34** in a very efficient manner.



Scheme 1.18. Previous work by Blechert (2005).

Similarly, we have recently published a tandem CEYM-intramolecular Diels Alder reaction involving aromatic terminal alkynes and conjugated carbonyl-derived systems **1.35** with a remote double bond (*Scheme 1.19*).[43] The overall process enables the preparation of different-sized linear bicyclic scaffolds **1.36** in a very simple manner.

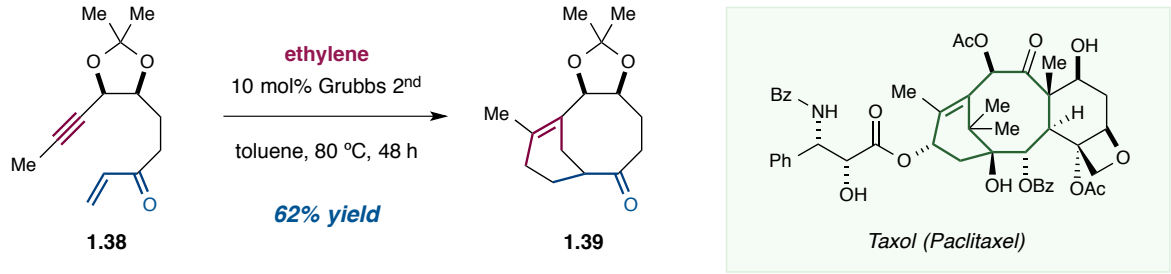


Scheme 1.19. Further work by Fustero (2015).

Furthermore, several authors have applied the enyne metathesis-Diels Alder sequence to the synthesis of common skeletons featuring in various natural products. For instance, the bridged bicycle

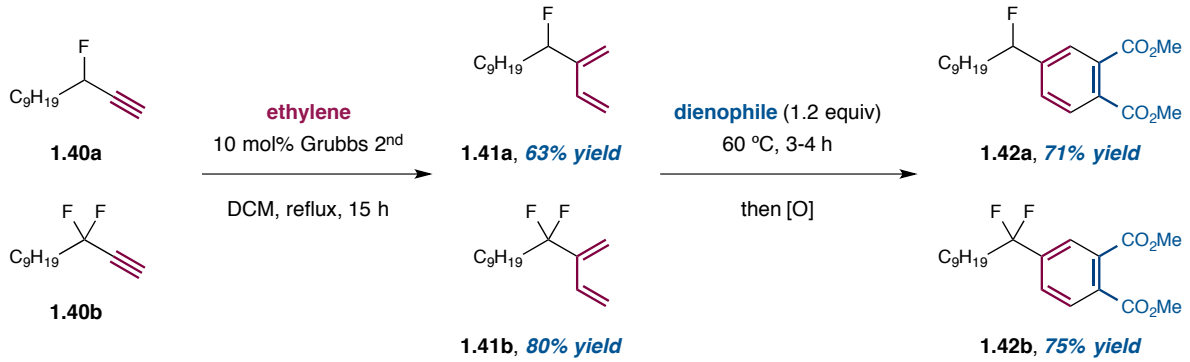
[42] Mix, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 2015.
[43] Miró, J.; Sánchez-Roselló, M.; Sanz, A.; Rabasa, F.; del Pozo, C.; Fustero, S. *Beilstein J. Org. Chem.* **2015**, *11*, 1486.

skeleton embedded in natural alkaloids like *taxol*, could be prepared by means of a tandem CEYM-intramolecular Diels Alder reaction (*Scheme 1.20*).[44]



Scheme 1.20. Previous work by Kaliappan (2006).

On the other hand, despite the increasing interest in organofluorine chemistry, the use of fluorinated building blocks in such enyne metathesis-Diels Alder sequences has scarcely been explored.[45] To the best of our knowledge, just one example from Grée's and Kaliappan's laboratories was reported (*Scheme 1.21*). They designed a CEYM-Diels Alder sequence from propargyl fluorides **1.40**, followed by a final oxidation step, as a novel strategy for the preparation of benzyl fluorides **1.42**.[46]

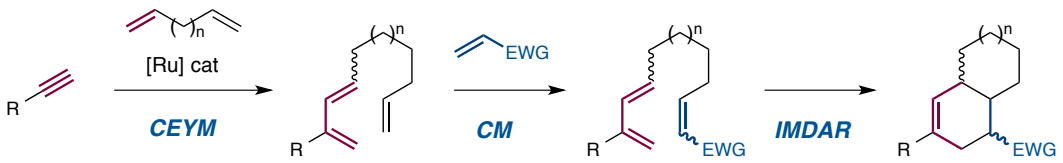


Scheme 1.21. Previous work by Grée and Kaliappan (2008).

[44] Kaliappan, K.; Ravikumar, V.; Pujari, S. A. *Tetrahedron Lett.* **2006**, *47*, 981.
[45] For a recent revision on metathesis reactions with fluorinated substrates, see: Fustero, S.; Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.* **2015**, *115*, 871.
[46] Pujari, S. A.; Kaliappan, K. P.; Valleix, A.; Grée, D.; Grée, R. *Synlett*, **2008**, 2503.

1.2. 1,7-Octadiene-assisted tandem multicomponent cross enyne metathesis-Diels Alder reaction.

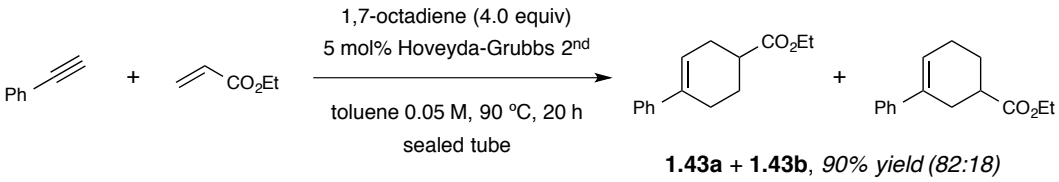
Given this perspective, during the course of an on-going project in our laboratory aimed at the development of new tandem protocols, we envisioned a procedure to carry out a CEYM-CM-Diels Alder reaction: a triple tandem protocol (*Scheme 1.22*). In this context, the CEYM of an alkyne and an 1,n-diene would render a new 1,3-diene functionality bearing a pendant double bond suitable for a subsequent CM reaction that would convert this olefin into a good dienophile for an intramolecular Diels Alder reaction (IMDAR).



Scheme 1.22. Our original idea.

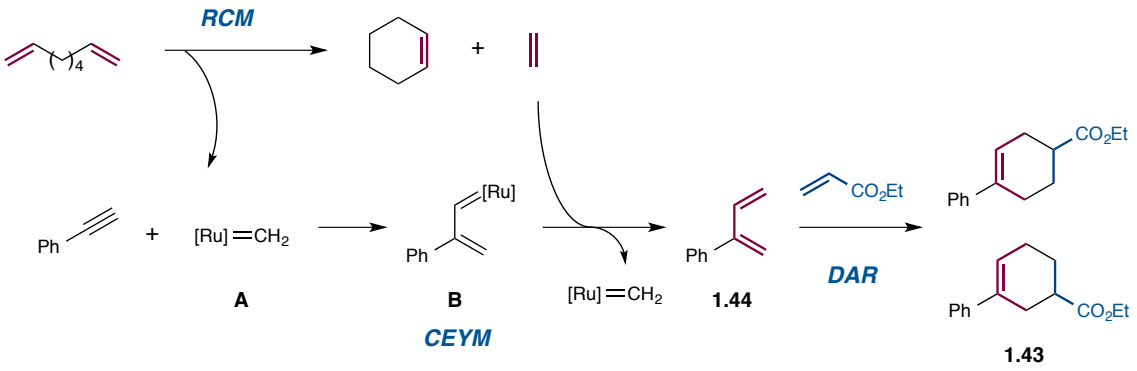
1.3. Results and discussion.

Within this pursuit, phenyl acetylene was subjected to the tandem protocol by treatment with 5 mol% second generation Hoveyda-Grubbs catalyst in the presence of 1,7-octadiene (4.0 equiv) and ethyl acrylate (3.0 equiv). However, when this mixture was heated in toluene at 90 ºC for 6 hours, instead of the expected bicyclic derivative, a mixture of regioisomers **1.43a** and **1.43b** was isolated in an excellent 90% yield and 82:18 ratio (*Scheme 1.23*).[47]



Scheme 1.23. Preliminary result.

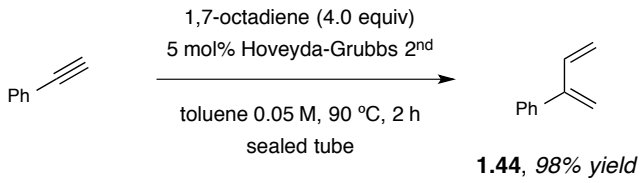
This result indicated that ring-closing metathesis (RCM) reaction of 1,7-octadiene is more favourable than the attempted cross-metathesis protocol (*Scheme 1.24*). As a result, cyclohexadiene and ethylene are released. The ruthenium carbene is then prone to carry out CEYM reaction between phenyl acetylene and *in situ* generated ethylene to afford intermediate diene **1.44**. Under the reaction conditions, in the presence of ethyl acrylate, diene **1.44** is trapped in a Diels Alder fashion affording regioisomers **1.43a** and **1.43b**. The overall process constitutes a novel tandem multicomponent CEYM-Diels Alder reaction.



Scheme 1.24. Proposed mechanism.

[47] Conditions were taken from a previously evaluated CEYM-Diels Alder protocol under Mori's conditions: Fustero, S.; Bello, P.; Miró, J.; Sánchez-Roselló, M.; Haufe, G.; del Pozo, C. *Beilstein J. Org. Chem.* **2013**, *9*, 2688. Reducing the equivalents of either dienophile or 1,7-octadiene resulted in lower yields.

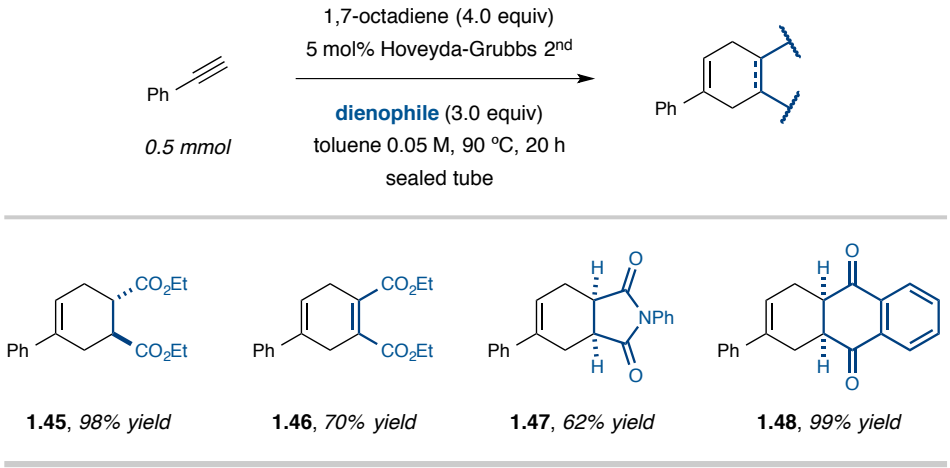
With these data in hand, we firstly evaluated the formation of proposed 1,3-diene in the presence of 1,7-octadiene (*Scheme 1.25*). Thus, when phenylacetylene was heated with 1,7-octadiene as the internal source of ethylene in the presence of 5 mol% second generation Hoveyda-Grubbs catalyst in toluene at 90 ºC, complete formation of the diene **1.44** was observed after two hours. Under these conditions, diene **1.44** was isolated in 98% yield after flash chromatography, confirming the above proposed mechanistic outcome (*Scheme 1.24*).



Scheme 1.25. Formation of diene **1.44**.

These conditions were further extended to different starting alkynes and dienophiles. Several dienophiles were tested, as depicted in *Table 1.1*.

Table 1.1. Dienophile scope.[a]

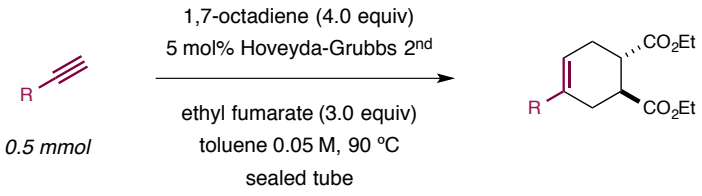


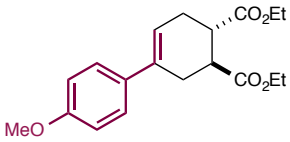
[a] Isolated yields.

Other than ethyl acrylate, ethyl fumarate and 1,4-benzoquinone gave the desired products **1.45** and **1.48**, respectively, in quantitative yield. Diethyl acetylene dicarboxylate gave rise to final product **1.46** in a 70% yield and no aromatization was observed after purification. *N*-phenyl maleimide was also a good partner for the tandem protocol, affording cycloadduct **1.47** in 62% yield.

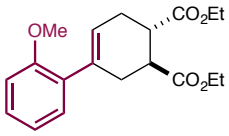
Thereafter, we explored the efficiency of the process with different terminal alkynes (*Table 1.2*), using ethyl fumarate as the dienophile to avoid regioselectivity issues.

Table 1.2. Alkyne scope.[a]

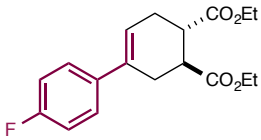




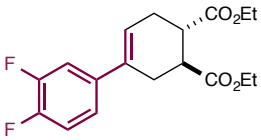
1.49, *99% yield* (20 h)



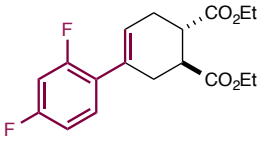
1.50, *99% yield* (20 h)



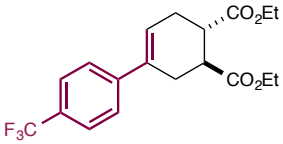
1.51, *99% yield* (20 h)



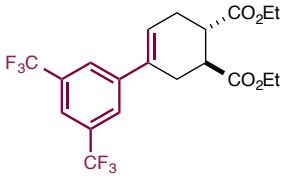
1.52, *99% yield* (20 h)



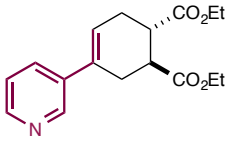
1.53, *86% yield* (20 h)



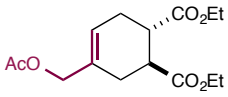
1.54, *99% yield* (20 h)



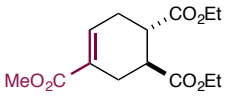
1.55, *95% yield* (30 h)



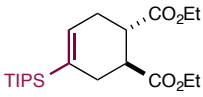
1.56, *50% yield* (22 h)



1.57, *42% yield* (28 h)



1.58, *46% yield* (20 h)

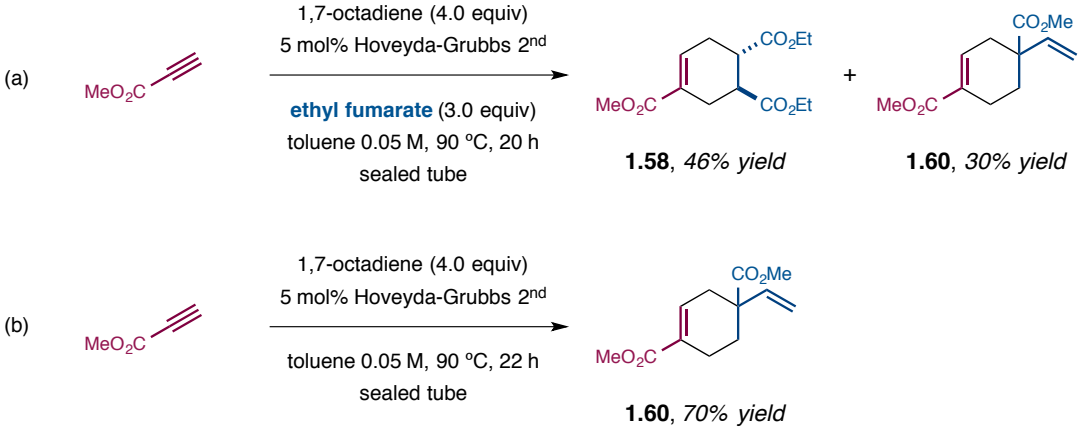


1.59, *31% yield* (72 h)

[a] Isolated yields.

Regarding the alkyne scope, the tandem protocol proceeded with excellent efficiency with aromatic terminal alkynes, affording the final adducts in excellent yields (**1.49-1.55**). Aromatic alkynes with either electron-donating (**1.49-1.50**) or electron-withdrawing (**1.54-1.55**) substituents reacted with ethyl fumarate in almost quantitative yield in most cases. Likewise, steric effects on the aryl ring did not have a detrimental effect on the efficiency of the process (**1.50**, **1.52-1.53**). However, with heteroaromatic alkynes (**1.56**), aliphatic alkynes (**1.57**), or deactivated alkynes (**1.58**), the overall process was less effective, yielding the final products in moderate yields. The reaction also took place with the very sterically demanding triisopropyl silyl acetylene, albeit in a modest 31% yield after 72 hours (**1.59**).

When methyl propiolate was used as the starting alkyne, besides the desired product **1.58** (46% yield), compound **1.60** was isolated in 30% yield (*Scheme 1.26a*). This product arises from the highly regioselective Diels Alder reaction between two molecules of the intermediate diene, one of them acting as the diene counterpart and the other one as the dienophile through the most electron deficient double bond.[48] In the presence of ethyl fumarate, this dimerization event competes with the Diels Alder reaction with ethyl fumarate. In fact, when we carried out the process in the absence of ethyl fumarate, compound **1.60** was isolated in 70% yield in a regioselective fashion after 22 hours (*Scheme 1.26b*).

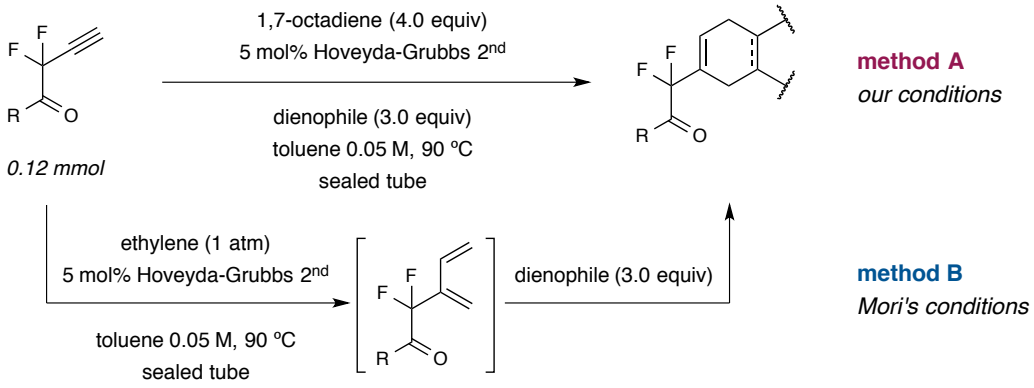


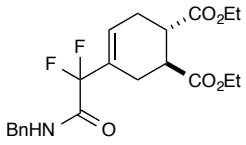
Scheme 1.26. Multicomponent reaction with methyl propiolate.

Finally, we decided to validate our strategy *versus* Mori's conditions. To this end, several difluoropropargyl carbonyl derivatives were subjected to the developed reaction conditions, in the presence of 1,7-octadiene as an *in situ* ethylene source (*Table 1.3*). The obtained carbo- and hetero-cycles were previously prepared in our laboratory in a one-pot procedure under Mori's conditions, i.e. under ethylene's atmosphere.[47]

[48] For a related RCEYM-Diels Alder dimerization process, see: Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277.

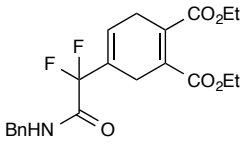
Table 1.3. Validation *versus* Mori's conditions.[a]





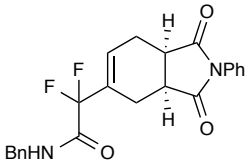
1.61

(A) *70% yield* (20 h)
(B) *55% yield* (8 h)



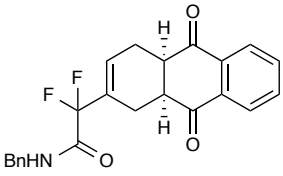
1.62

(A) *55% yield* (6 h)
(B) *51% yield* (6 h)



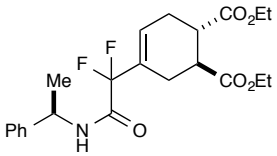
1.63

(A) *63% yield* (24 h)
(B) *50% yield* (4 h)



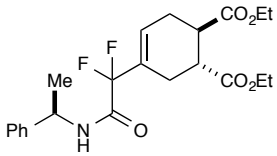
1.64

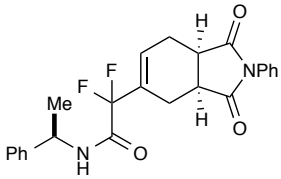
(A) *50% yield* (24 h)
(B) *47% yield* (24 h)

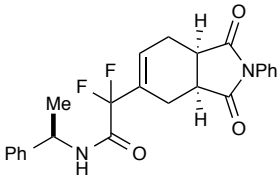


1.65

(A) *73% yield, 1:1 dr* (24 h)
(B) *87% yield, 1:1 dr* (4 h)

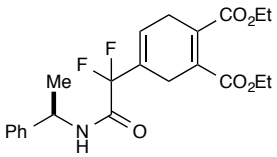






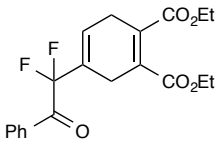
1.66

(A) *70% yield, 1:1 dr* (10 h)
(B) *74% yield, 1:1 dr* (20 h)



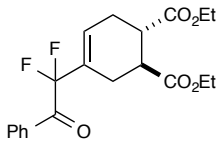
1.67

(A) *60% yield* (24 h)
(B) *63% yield* (10 h)



1.68

(A) *55% yield* (15 h)
(B) *48% yield* (4 h)



1.69

(A) *70% yield* (17 h)
(B) *58% yield* (12 h)

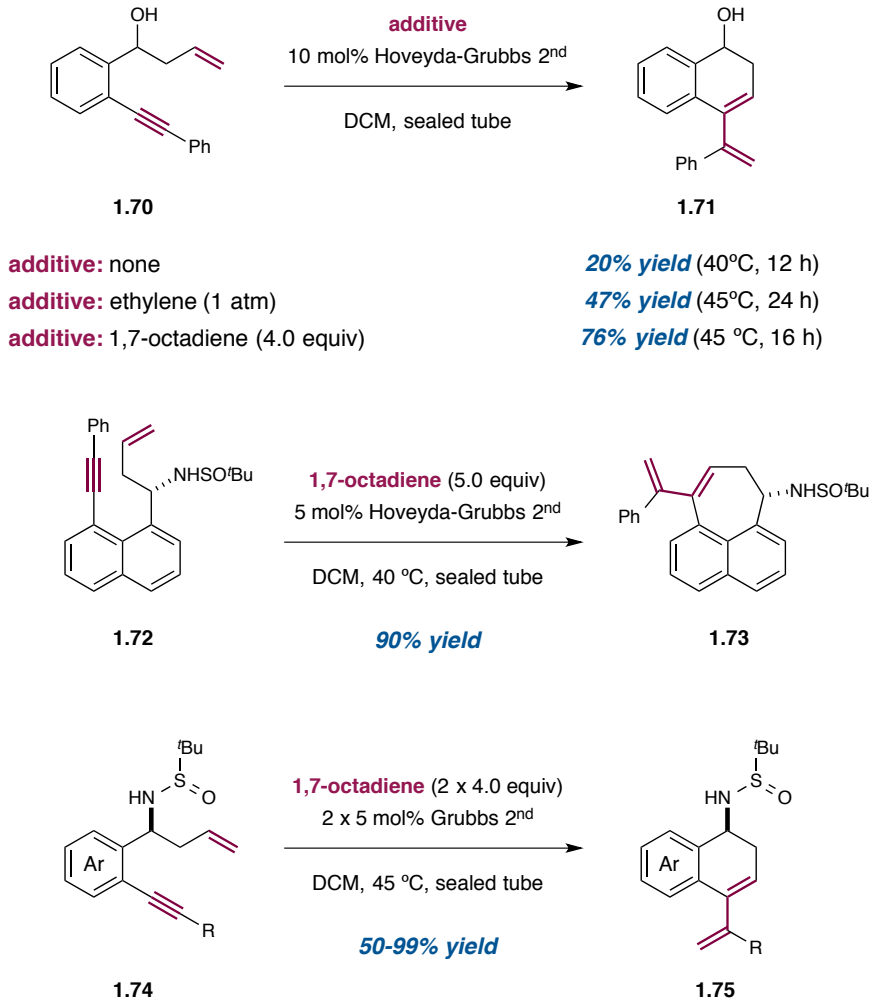
[a] Isolated yields.

Benzyl difluoropropargyl amide reacted with ethyl fumarate to give adduct **1.61** in improved 70% yield when comparing to Mori's conditions (55% yield). Diethyl acetylene dicarboxylate afforded diene **1.62** in comparable 55% yield (*versus* 51% yield). *N*-phenyl maleimide and *para*-benzoquinone were also good partners for the tandem process, affording cycloadducts **1.63** and **1.64** in slightly better 63% and 50% yields, compared to previous results (50% and 47% yield, respectively).

With chiral starting materials, an inseparable 1:1 mixture of diastereoisomers was obtained (**1.65-1.66**), which indicates that the chiral information is too far from the reacting center. On the other hand, fluorinated ketones were also adequate substrates, providing better yields than the one-pot procedure (**1.68-1.69**).

These results indicate that afforded yields under the newly developed conditions (method A) were comparable to those previously obtained under Mori's conditions (method B).

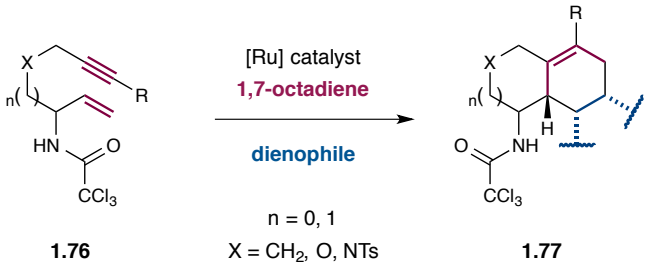
The developed methodology has been further successfully employed in our research group in different projects within diversity-oriented synthesis,[49] providing better results in comparison to Mori's conditions (*Scheme 1.27*).



Scheme 1.27. Further work by Fustero (2016).

[49] (a) Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506. (b) Herrera, L.; Barrio, P.; Ibáñez, I.; Román, R.; Mateu, N.; Fustero, S. *Org. Lett.* **2016**, *18*, 4722. (c) Lázaro, R.; Barrio, P.; Finamore, C.; Román, R.; Fustero, S. *Struct. Chem.* **2016**, DOI: 10.1007/s11224-016-0849-z.

Likewise, Sutherland and coworkers have reported the synthesis of amino-substituted indanes and tetralins based on a one-pot RCEYM-Diels Alder cascade reaction under our developed conditions.[50] The use of 1,7-octadiene as an *in situ* source of ethylene allowed complete conversion of enynes **1.76** to the corresponding *exo*-dienes **1.77**, greatly increasing the efficiency of the overall sequence in most cases (*Scheme 1.28*).



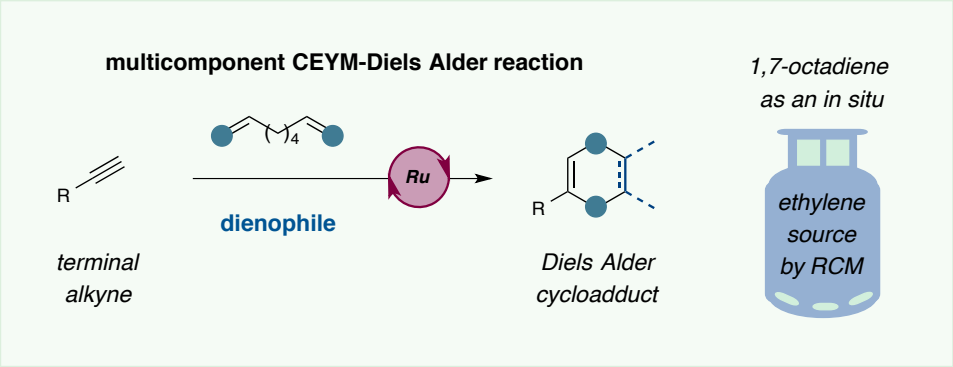
1.76 **1.77**

Scheme 1.28. Further work by Sutherland (2013-2016).

[50] (a) Grafton, M. W.; Farrugia, L. J.; Sutherland, A. *J. Org. Chem.* **2013**, *78*, 7199. (b) Grafton, M. W.; Johnson, S. A.; Farrugia, L. J.; Sutherland, A. *Tetrahedron*, **2014**, *70*, 7133. (c) Calder, E. D. D.; Grafton, M. W.; Sutherland, A. *Synlett*, **2014**, *25*, 1068. (d) Mostafa, M. A. B.; Grafton, M. W.; Wilson, C.; Sutherland, A. *Org. Biomol. Chem.* **2016**, *14*, 3284.

1.4. Conclusions.

We found that liquid 1,7-octadiene can act as a useful ethylene surrogate by RCM, establishing a complementary method to Mori's conditions in EYM-type processes, thus avoiding the use of flammable ethylene gas. The utility of this finding was illustrated in a novel multicomponent tandem CEYM-Diels Alder reaction (*Scheme 1.29*).[51] Aliphatic, aromatic and fluorinated alkynes, along with several dienophiles, were compatible substrates under the developed conditions, being particularly efficient with aromatic alkynes.



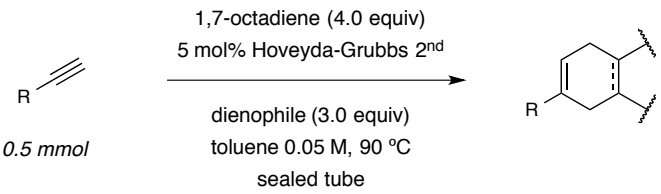
Scheme 1.29. Multicomponent CEYM-Diels Alder reaction.

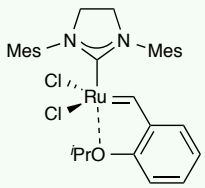
[51] Fustero, S.; Bello, P.; Miró, J.; Simón, A.; del Pozo, C. *Chem. Eur. J.* **2012**, *18*, 10991.

1.5. Experimental section.

General remarks: Unless otherwise noted, reactions were carried out under argon atmosphere and all reagents were purchased from commercial suppliers and used without further purification. The solvents were purified prior to use: THF, diethyl ether and toluene were distilled from sodium/benzophenone, dichloromethane and acetonitrile were distilled from calcium hydride. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). Melting points were measured on Büchi B-540 apparatus. ^{1}H, ^{13}C and ^{19}F spectra were recorded on 300 MHz and 500 MHz Bruker spectrometers. Chemical shifts (δ) are given in ppm relative to the residual solvent signals (chloroform, 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Coupling constants (*J*) are given in Hertz (Hz). Letters m, s, d, t and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. Letters br indicate that the signal is broad. High-resolution mass spectra were carried out on an AB SCIEX TripleTOF™ 5600 LC/MS/MS system in ESI mode [*Conditions: Ion source gas 1 (GC1): 35 psi; Ion source gas 2 (GC2): 35 psi; Curtain gas 1: 25 psi; Temperature: 450 ºC; Ion Spray Voltage (ISVF): 5500; Infusion positive mode*] by the University of Valencia Mass Spectrometry Service.

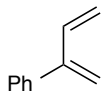
1.5.1. General procedure for the multicomponent tandem protocol.



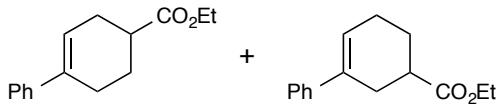


Hoveyda-Grubbs catalyst 2nd generation

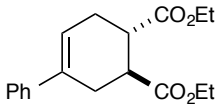
A solution of Hoveyda-Grubbs catalyst second generation (5 mol%), 1,7-octadiene (4.0 equiv), alkyne (1.0 equiv, 0.5 mmol), and the corresponding dienophile (3.0 equiv) in dry toluene (0.05 M, 10.0 mL) was heated at 90 ºC in a sealed tube. The reaction mixture was stirred at this temperature until TLC showed total consumption of the starting material. Then, solvents were removed under reduced pressure and the crude mixture was purified by flash column chromatography.



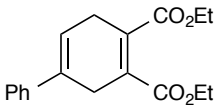
2-Phenyl-1,3-butadiene. Following the general procedure described above and before adding the dienophile, the crude mixture was subjected to flash chromatography affording 65 mg of **1.44** (98% yield) as a colourless oil starting from 51 mg of phenyl acetylene. Spectra matches previously reported data.[52]



Ethyl 3-phenyl-3-cyclohexene carboxylate + ethyl 4-phenyl-3-cyclohexene carboxylate. Following the general procedure described above, 115 mg of an inseparable mixture of regioisomers **1.43a** + **1.43b** (82:18, 99% yield) were obtained as a yellowish oil starting from 51 mg of phenyl acetylene. Spectra matches previously reported data.[53]

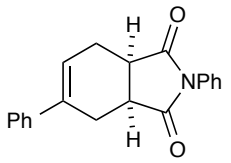


***Trans*-diethyl 4-phenyl-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 148 mg of **1.45** (98% yield) were obtained as a yellowish oil starting from 51 mg of phenyl acetylene. Spectra matches previously reported data.[53]

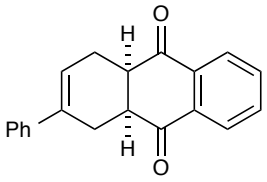


Diethyl 4-phenyl-1,4-cyclohexadiene dicarboxylate. Following the general procedure described above, 105 mg of **1.46** (70% yield) were obtained as a yellowish oil starting from 51 mg of phenyl acetylene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, J = 6 Hz, 3H), 1.25 (t, J = 6 Hz, 3H), 3.11-3.19 (m, 2H), 3.29-3.35 (m, 2H), 4.19 (q, J = 6 Hz, 2H), 4.20 (q, J = 6 Hz, 2H), 6.00-6.03 (m, 1H), 7.16-7.34 (m, 5H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.0, 29.1, 29.7, 61.1, 61.2, 119.2, 125.0, 127.5, 128.4, 131.8, 132.5, 132.6, 139.9, 167.8, 167.9. HRMS (ES) calc. for (M^+-2) $C_{18}H_{19}O_4$: 209.1278, found: 209.1287.

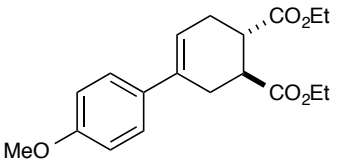
[52] Lindh, J.; Sävmarker, J.; Nilsson, P.; Sjöber, P. J. R.; Larhed, M. *Chem. Eur. J.* **2009**, *15*, 4630.
[53] Pidaparthi, R. R.; Junker, C. S.; Welker, M. E.; Day, C. S.; Wright, M. W. *J. Org. Chem.* **2009**, *74*, 8290.



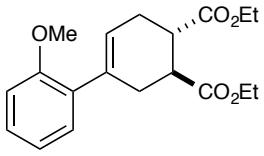
2,5-Diphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione. Following the general procedure described above, 94 mg of **1.47** (62% yield) were obtained as a yellowish oil starting from 51 mg of phenyl acetylene. Spectra matches previously reported data.[53]



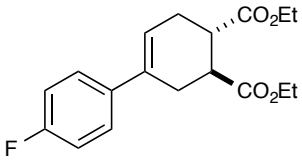
2-Phenyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione. Following the general procedure described above, 143 mg of **1.48** (99% yield) were obtained as a yellowish oil starting from 51 mg of phenyl acetylene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.36 (d, J = 18 Hz, 1H), 2.53 (d, J = 17 Hz, 1H), 2.64 (d, J = 18 Hz, 1H), 2.85 (d, J = 17 Hz, 1H), 3.35 (dd, J_1 = 11 Hz; J_2 = 6 Hz, 1H), 3.46 (dd, J_1 = 11 Hz; J_2 = 6 Hz, 1H), 5.98 (s, 1H), 7.11-7.28 (m, 4H), 7.65 (dd, J_1 = 5 Hz; J_2 = 3 Hz, 2H), 7.96 (d, J = 3 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 25.3, 26.7, 46.1, 47.0, 121.5, 125.2, 126.8, 126.9, 127.1, 128.2, 133.9, 134.3, 134.7, 141.0, 197.7, 198.0. HRMS (ES) calc. for (M^++1) $C_{20}H_{17}O_2$: 289.1223, found: 289.1232.



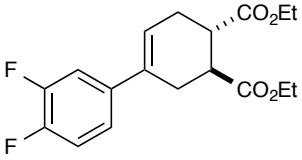
***Trans*-diethyl 4-(4-methoxyphenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 164 mg of **1.49** (99% yield) were obtained as a yellowish oil starting from 66 mg of 1-ethynyl-4-methoxybenzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.29-2.41 (m, 1H), 2.47-2.66 (m, 2H), 2.76-2.84 (m, 1H), 2.85-3.04 (m, 2H), 3.79 (s, 3H), 4.16 (q, J = 7.1 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 5.97 (t, J = 2.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 28.6, 30.2, 41.1, 42.0, 55.2, 60.6, 60.6, 113.7, 120.3, 126.2, 133.5, 134.5, 158.9, 174.6, 174.7. HRMS (ES) calc. for (M^++1) $C_{19}H_{24}O_5$: 333.1697; found: 333.1700.



***Trans*-diethyl 4-(2-methoxyphenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 165 mg of **1.50** (99% yield) were obtained as a yellowish oil starting from 66 mg of 1-ethynyl-2-methoxybenzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.29-2.39 (m, 1H), 2.53-2.75 (m, 3H), 2.90-3.03 (m, 2H), 3.78 (s, 3H), 4.09-4.21 (m, 4H), 5.72-5.74 (m, 1H), 6.83-6.91 (m, 2H), 7.09 (dd, J_1 = 7.4 Hz, J_2 = 1.9 Hz, 1H), 7.19-7.25 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.0, 28.5, 31.4, 41.0, 41.9, 55.2, 60.3, 60.4, 110.5, 120.4, 123.4, 128.3, 129.4, 131.6, 135.7, 156.5, 174.7, 174.8. HRMS (ES) calc. for (M^++1) $C_{19}H_{24}O_5$: 333.1697, found: 333.1703.

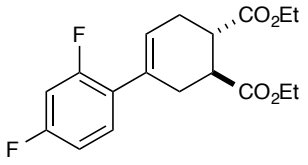


***Trans*-diethyl 4-(4-fluorophenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 159 mg of **1.51** (99% yield) were obtained as a yellowish oil starting from 60 mg of 1-ethynyl-4-fluorobenzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.32-2.42 (m, 1H), 2.49-2.67 (m, 2H), 2.73-2.81 (m, 1H), 2.86-3.05 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 6.00 (t, J = 2.4 Hz, 1H), 6.99 (dd, J_1 = J_2 = 8.7 Hz, 2H), 7.31 (dd, J_1 = 8.7 Hz, J_2 = 5.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.0, 28.4, 30.1, 40.9, 41.8, 60.8, 60.6, 115.0 (d, $^{2}J_{CF}$ = 21.3 Hz), 121.8, 126.6 (d, $^{3}J_{CF}$ = 7.9 Hz), 134.1, 136.8, 162.0 (d, $^{1}J_{CF}$ = 246.3 Hz), 174.3, 174.4. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -115.9 (s, 1F). HRMS (ES) calc. for (M^++1) $C_{18}H_{21}FO_4$: 321.1497, found: 321.1491.

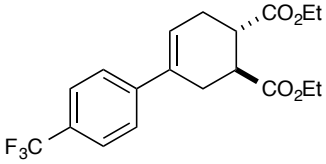


***Trans*-diethyl 4-(3,4-difluorophenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 167 mg of **1.52** (99% yield) were obtained as a yellowish oil starting from 69 mg of 1-ethynyl-2,4-difluorobenzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, J = Hz, 3H), 1.24 (t, J = Hz, 3H), 2.28-2.74 (m, 3H), 2.82-3.01 (m, 2H), 4.10-4.18 (m, 4H), 5.99-6.00 (m, 1H), 7.01-7.14 (m, 3H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.0, 28.3, 29.7, 40.7, 41.6, 60.6, 60.7, 113.9 (d, $^{2}J_{CF}$ = 17.4

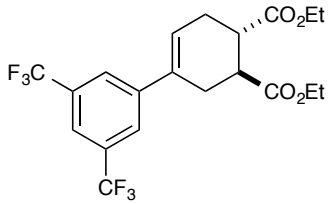
Hz), 116.8 (d, $^{2}J_{CF}$ = 17.4 Hz), 120.9 (dd, $^{3}J_{CF}$ = 6.0 Hz, $^{4}J_{CF}$ = 3.5 Hz), 122.94 (d, $^{5}J_{CF}$ = 1.3 Hz), 133.2, 137.8 (dd, $^{3}J_{CF}$ = 5.6 Hz, $^{4}J_{CF}$ = 3.9 Hz), 148.1 (dd, $^{1}J_{CF}$ = 49.0 Hz, $^{2}J_{CF}$ = 13.3 Hz), 151.3 ($^{1}J_{CF}$ = 49.0 Hz, $^{2}J_{CF}$ = 13.3 Hz), 174.2, 174.3. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -138.4 (d, $^{3}J_{FF}$ = 21.5 Hz, 1F), -140.4 (d, $^{3}J_{FF}$ = 21.5 Hz, 1F). HRMS (ES) calc. for (M^{+}+1) $C_{18}H_{20}F_2O_4$: 339.1402, found: 339.1400.



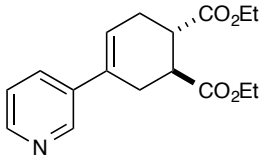
***Trans*-diethyl 4-(2,4-difluorophenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 145 mg of **1.53** (86% yield) were obtained as a yellowish oil starting from 69 mg of 1-ethynyl-3,4-difluorobenzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, *J* = 7.0 Hz, 3H), 1.24 (m, *J* = 7.2 Hz, 3H), 2.29-2.40 (m, 1H), 2.49-2.70 (m, 3H), 2.87-3.02 (m, 2H), 4.10-4.19 (m, 4H), 5.84-5.85 (m, 1H), 6.71-6.82 (m, 2H), 7.11-7.19 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 28.3, 31.0 (d, $^{5}J_{CF}$ = 3.0 Hz), 40.7, 41.65, 60.6, 60.7, 104.0 (t, $^{2}J_{CF}$ = 27.2 Hz), 111.0 (dd, $^{2}J_{CF}$ = 21.1 Hz, $^{4}J_{CF}$ = 3.8 Hz), 125.6 (d, $^{4}J_{CF}$ = 2.3 Hz), 125.9 (d, $^{2}J_{CF}$ = 3.8 Hz), 129.9 (dd, $^{3}J_{CF}$ = 9.1 Hz, $^{3}J_{CF}$ = 6.0 Hz), 131.0 (d, $^{3}J_{CF}$ = 1.5 Hz), 159.2 (dd, $^{1}J_{CF}$ = 160.1 Hz, $^{3}J_{CF}$ = 12.1 Hz), 162.5 (dd, $^{1}J_{CF}$ = 158.5 Hz, $^{3}J_{CF}$ = 12.1 Hz), 174.3, 174.5. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -111.5 (d, $^{4}J_{FF}$ = 7.3 Hz, 1F), -112.4 (d, $^{4}J_{FF}$ = 7.3 Hz, 1F). HRMS (ES) calc. for (M^{+}+1) $C_{18}H_{20}F_2O_4$: 339.1402, found: 339.1410.



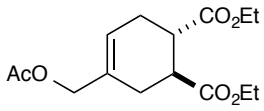
***Trans*-diethyl 4-(4-trifluoromethylphenyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 183 mg of **1.54** (99% yield) were obtained as a yellowish oil starting from 85 mg of 1-ethynyl-4-(trifluoromethyl)benzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 2.32-2.44 (m, 1H), 2.51-2.69 (m, 2H), 2.73-2.81 (m, 1H), 2.86-3.04 (m, 2H), 4.11-4.20 (m, 4H), 6.12-6.13 (m, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.0, 28.4, 29.7, 40.7, 41.6, 60.6, 60.7, 124.1(q, $^{1}J_{CF}$ = 271.5 Hz), 124.1, 125.1 (q, $^{3}J_{CF}$ = 3.7 Hz), 125.2, 128.9 (q, $^{2}J_{CF}$ = 32.6 Hz), 134.0, 144.1, 174.2, 174.3. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -62.9 (s, 3F). HRMS (ES) calc. for (M^{+}+1) $C_{19}H_{21}F_3O_4$: 371.1465; found: 371.1462.



***Trans*-diethyl 4-[3,5-bis(trifluoromethyl)phenyl]-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 207 mg of **1.55** (95% yield) were obtained as a yellowish oil starting from 119 mg of 1-ethynyl-3,5-bis(trifluoromethyl)benzene. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.39-2.51 (m, 1H), 2.58-2.83 (m, 3H), 2.92-3.10 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.21-6.23 (m, 1H), 7.74 (s, 1H), 7.76 (s, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 28.2, 29.5, 40.6, 41.5, 60.9, 61.0, 120.7 (sept, $^{3}J_{CF}$ = 3.8 Hz), 123.3 (q, $^{1}J_{CF}$ = 272.5 Hz), 125.2, 125.8, 131.7 (q, $^{2}J_{CF}$ = 33.2 Hz), 133.1, 142.9, 174.0, 174.1. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -63.4 (s, 6F). HRMS (ES) calc. for (M^++1) $C_{20}H_{20}F_6O_4$: 439.1339, found: 439.1341.

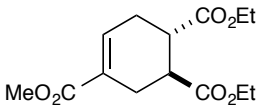


***Trans*-diethyl 4-(3-pyridyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 76 mg of **1.56** (50% yield) were obtained as a yellowish oil starting from 52 mg of 3-ethynylpyridine. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.35-2.46 (m, 1H), 2.52-2.71 (m, 2H), 2.75-2.83 (m, 1H), 2.89-3.07 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.09-6.13 (m, 1H), 7.23 (ddd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, J_3 = 0.6 Hz, 1H), 7.62 (ddd, J_1 = 8.0 Hz, J_2 = 2.2 Hz, J_3 = 1.7 Hz, 1H), 8.47 (dd, J_1 = 4.7 Hz, J_2 = 1.1 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 28.4, 29.6, 40.8, 41.6, 60.8, 60.8, 123.1, 123.9, 132.3, 132.5, 136.2, 146.7, 148.4, 174.3, 174.4. HRMS (ES) calc. for (M^++1) $C_{17}H_{21}NO_4$: 304.1543, found: 304.1538.

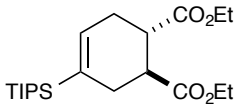


***Trans*-diethyl 4-acetoxymethyl-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 64 mg of **1.57** (42% yield) were obtained as a yellowish oil starting from 49 mg of prop-2-yn-1-yl acetate. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 2.18-2.28 (m, 2H), 2.36-2.53 (m, 2H), 2.78-2.93 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H),

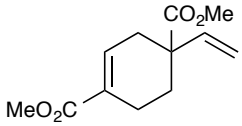
4.16 (q, *J* = 7.1 Hz, 2H), 4.46 (s, 2H), 5.74-5.75 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 20.9, 27.8, 28.6, 41.0, 41.3, 60.7, 60.7, 67.6, 124.0, 131.3, 170.8, 174.4, 174.5. HRMS (ES) calc. for (M^++1) $C_{15}H_{22}O_6$: 299.1489, found: 299.1492.



***Trans*-diethyl 4-methoxycarbonyl-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 65 mg of **1.58** (46% yield) were obtained as a yellowish oil starting from 42 mg of methyl propiolate. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.30-2.42 (m, 2H), 2.57-2.68 (m, 1H), 2.74-2.89 (m, 3H), 3.73 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 6.93-6.95 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 13.9, 26.5, 28.0, 40.2, 40.9, 51.6, 60.6, 128.3, 136.7, 166.4, 173.8, 173.9. HRMS (ES) calc. for (M^++1) $C_{14}H_{20}O_6$: 285.1333, found: 285.1327.



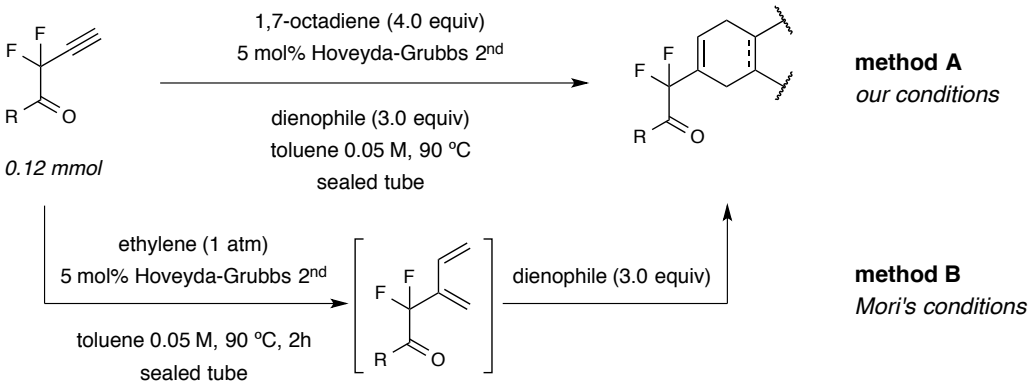
***Trans*-diethyl 4-(triisopropylsilyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above, 44 mg of **1.59** (31% yield) were obtained as a yellowish oil starting from 112 mg of ethynyltriisopropylsilane. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.03-1.05 (m, 21H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.14-2.32 (m, 2H), 2.41-2.57 (m, 2H), 2.73-2.90 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.94-5.97 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.2, 17.7, 18.7, 29.7, 31.5, 41.3, 41.9, 60.5, 132.3, 135.5, 175.0, 175.2. HRMS (ES) calc. for (M^++1) $C_{21}H_{38}O_4Si$: 383.2612, found: 283.2623.



Dimethyl 1-vinyl-3-cyclohexene-1,4-dicarboxylate. Following the general procedure described above, 75 mg of **1.60** (70% yield) were obtained as a yellowish oil starting from 42 mg of methyl propiolate. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.75-1.84 (m, 1H), 2.03-2.12 (m, 1H), 2.26-2.39 (m, 3H), 2.74-2.83 (m, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 5.08 (d, *J* = 17.5 Hz, 1H), 5.14 (d, *J* = 10.7 Hz, 1H), 5.85 (dd, J_1 = 17.4 Hz, J_2 = 10.7 Hz, 1H), 6.92-6.96 (m, 1H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 21.7, 29.4,

32.1, 47.2, 51.5, 52.2, 115.2, 129.3, 137.0, 139.3, 167.3, 174.8. HRMS (ES) calc. for (M^++1) $C_{12}H_{16}O_4$: 225.1121, found: 225.1110.

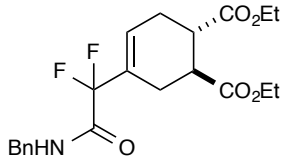
1.5.2. Validation of 1,7-octadiene-assisted tandem protocol *versus* Mori's conditions.[54]



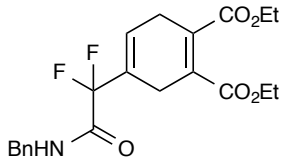
Method A. A solution of Hoveyda-Grubbs catalyst second generation (5 mol%), 1,7-octadiene (4.0 equiv), alkyne (1.0 equiv, 0.12 mmol), and the corresponding dienophile (3.0 equiv) in dry toluene (0.05 M, 2.4 mL) was heated at 90 ºC in a sealed tube. The reaction mixture was stirred at this temperature until TLC showed total consumption of the starting material. Then, solvents were removed under reduced pressure and the crude mixture was purified by flash column chromatography.

Method B. Ethylene gas was bubbled through a solution of Hoveyda-Grubbs catalyst second generation (5 mol%) in dry toluene (0.05 M, 2.4 mL) for 3 minutes at room temperature in a sealed tube. Difluoroalkyne (1.0 equiv, 0.12 mmol) was added next and it was heated at 90 ºC for 2 hours. Once the intermediate diene was formed (by TLC), it was cooled to room temperature and the corresponding dienophile (3.0 equiv) was added. After the indicated time, solvent was removed and the reaction mixture was purified by flash column chromatography.

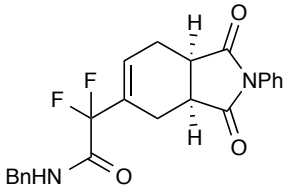
[54] Starting fluorinated amides and ketone were previously reported: (a) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251. (b) Fustero, S.; Bello, P.; Fernández, B.; del Pozo, C.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 7690. (c) Ref. 26.



***Trans*-diethyl 4-(2-(benzylamino)-1,1-difluoro-2-oxoethyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above (method A), 34 mg of **1.61** (70% yield) were obtained as a white solid starting from 25 mg of *N*-benzyl-2,2-difluorobut-3-ynamide. m.p. 61-63 ºC. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, *J*= 7.2 Hz, 3H), 1.25 (t, *J*= 7.2 Hz, 3H), 2.23-2.38 (m, 2H), 2.51-2.61 (m, 2H), 2.81-2.95 (m, 2H), 4.14 (q, *J*= 7.11 Hz, 4H), 4.50 (d, *J*= 5.8 Hz, 2H), 6.22 (br s, 1H), 6.70 (br s, 1H), 7.27-7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ. 14.1, 25.0, 27.3, 40.3, 40.6, 43.6, 60.9, 60.9, 114.7 (t, $^{1}J_{CF}$= 251.4 Hz), 127.5, 127.84, 128.0, 128.9, 128.9 (t, $^{2}J_{CF}$= 24.2 Hz), 136.72, 163.2 (t, $^{2}J_{CF}$= 30.9 Hz), 173.7, 173.9. ^{19}F-NMR ($CDCl_3$, 282 MHz): -136.4 (d, J_{FF}= 258.2 Hz, 1F), -137.5 (d, J_{FF}= 258.2 Hz, 1F). HRMS (ES) calc. for (M^++1) $C_{21}H_{26}F_2NO_5$: 410.1774, found: 410.1776.

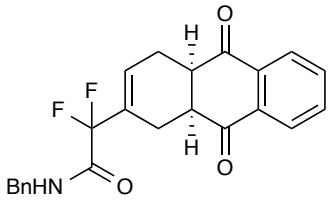


Diethyl 4-(2-(benzylamino)-1,1-difluoro-2-oxoethyl)-1,4-cyclohexadiene-1,2-dicarboxylate. Following the general procedure described above (method A), 27 mg (55% yield) of **1.62** were obtained as a dark brown oil starting from 25 mg of *N*-benzyl-2,2-difluorobut-3-ynamide. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, *J*= 7.2 Hz, 3H), 1.30 (t, *J*= 7.2 Hz, 3H), 3.10 (s, 4H), 4.23 (q, *J*= 7.2 Hz, 4H), 4.50 (d, *J*= 6Hz, 2H), 6.22 (br s, 1H), 6.70 (br s, 1H), 7.26-7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 13.9, 14.0, 25.3 (t, $^{3}J_{CF}$= 3.0 Hz), 28.1, 43.6, 61.3, 61.4, 114.5 (t, $^{1}J_{CF}$= 251.8 Hz), 125.1 (t, $^{3}J_{CF}$= 8.7 Hz), 126.9 (t, $^{2}J_{CF}$= 24.0 Hz), 127.8, 128.0, 128.9, 131.1, 131.3, 136.6, 162.6 (t, $^{2}J_{CF}$= 30.4 Hz), 167.0, 167.3. ^{19}F-NMR ($CDCl_3$, 282 MHz): -108.6 (s, 2F). HRMS (EI) calc. for (M^+) $C_{21}H_{23}F_2NO_5$: 407.1544, found: 407.1546.

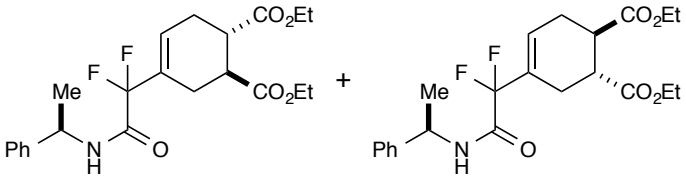


***N*-benzyl-2-(1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-5-yl)-2,2-difluoroacetamide.** Following the general procedure described above (method A), 31 mg of **1.63** (63% yield) were obtained as a dark brown oil starting from 25 mg of *N*-benzyl-2,2-difluorobut-3-ynamide. ^{1}H-NMR

($CDCl_3$, 300 MHz): δ 2.32-2.47 (m, 2H), 2.82-2.93 (m, 2H), 3.27-3.38 (m, 2H), 4.46 (d, *J*= 5.7 Hz, 2H), 6.49-6.55 (m, 1H), 6.68 (br s, 1H), 7.27-7.47 (m, 10H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 22.8, 23.9, 38.7, 39.1, 43.7, 114.2 (t, $^1J_{CF}$= 251.0 Hz), 126.5, 127.9, 128.0, 128.7, 128.9, 129.1, 129.9 (t, $^3J_{CF}$= 8.9 Hz), 131.8, 131.9 (t, $^2J_{CF}$= 24.4 Hz), 136.6, 162.8 (t, $^2J_{CF}$= 30.1 Hz), 177.7, 178.1. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -106.5 (d, J_{FF}= 258.1 Hz, 1F), -108.7 (d, J_{FF}= 258.4 Hz, 1F). HRMS (EI) calc. for (M^+) $C_{23}H_{20}F_2N_2O_3$: 410.1442, found: 410.1445.

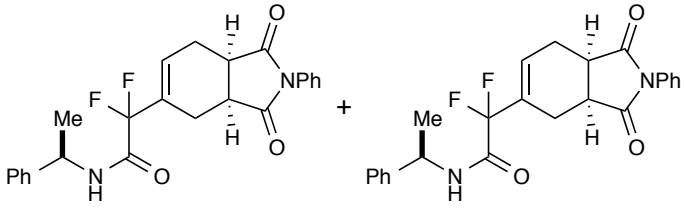


***N*-benzyl-2-(9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracen-2-yl)-2,2-difluoroacetamide.** Following the general procedure described above (method A), 24 mg (50% yield) or **1.64** were obtained as a dark brown oil starting from 25 mg of *N*-benzyl-2,2-difluorobut-3-ynamide. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.35-2.45 (m, 2H), 2.57-2.70 (m, 2H), 3.37-3.43 (m, 1H), 3.45-3.50 (m, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 6.23-6.28 (m, 1H), 6.8 (br s, 1H), 7.27-7.38 (m, 5H), 7.73-7.79 (m, 2H), 7.99-8.07 (m, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ. 22.0, 24.3, 43.6, 45.6, 45.8, 114.6 (t, $^1J_{CF}$= 250.9 Hz), 126.9, 127.0, 127.4 (t, $^3J_{CF}$= 8.6 Hz),127.8, 127.9, 128.6 (t, $^2J_{CF}$= 29.2 Hz), 128.8, 133.6, 133.7, 134.6, 136.1, 163.1 (t, $^2J_{CF}$= 30.6 Hz), 197.0, 197.1. ^{19}F-NMR ($CDCl_3$, 282 MHz): -107.5 (s, 2F). HRMS (ES) calc. for (M^++1) $C_{23}H_{20}F_2NO_3$: 396.1406, found: 396.1404.

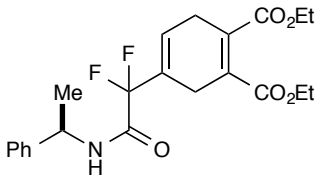


***Trans*-diethyl 4-(1,1-difluoro-2-oxo-2-((*S*)-1-phenylethylamino)ethyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above (method A), 37 mg (73% yield) of **1.65** were obtained as a dark brown oil starting from 27 mg of (*R*)-2,2-difluoro-*N*-(1-phenylethyl)but-3-ynamide. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, *J*= 7.2 Hz, 6H), 1.54 (d, *J*= 6.9 Hz, 3H), 2.20-2.31 (m, 2H), 2.52- 2.58 (m, 2H), 2.79-2.92 (m, 2H), 4.13 (c, *J*= 7.2 Hz, 4H), 5.08-5.18 (m, 1H), 6.17 (br s, 1H), 6.64 (d, *J*= 6.64 Hz, 1H), 7.27-7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 21.3, 24.9, 27.2, 40.3, 40.6, 49.2, 60.8, 60.9, 114.6 (t, $^1J_{CF}$= 251.7 Hz), 126.1, 127.8, 127.8 (t, $^3J_{CF}$= 8.7 Hz), 128.8, 128.9 (t, $^2J_{CF}$= 24.0 Hz), 141.7, 162.3 (t, $^2J_{CF}$= 30.5 Hz), 173.7, 173.8. ^{19}F-NMR ($CDCl_3$, 282 MHz): -

106.7 (d, J_{FF}= 258.7 Hz, 1F), -106.8 (d, J_{FF}= 258.1 Hz, 1F), -107.9 (d, J_{FF} = 258.9 Hz, 1F), -107.9 (d, J_{FF}= 258.7 Hz, 1F). HRMS (ES) calc. for (M^++1) $C_{22}H_{28}F_2NO_5$: 424.1936, found: 424.1940.

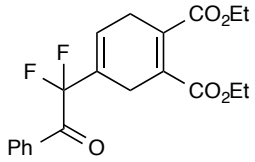


2-(1,3-Dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-5-yl)-2,2-difluoro-N-((*S*)-1-phenylethyl) acetamide. Following the general procedure described above (method A), 36 mg (70% yield) of **1.66** were obtained as a dark brown solid starting from 27 mg of (*R*)-2,2-difluoro-*N*-(1-phenylethyl)but-3-ynamide. m.p. 113-115 ºC. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.53 (d, *J*= 6.9 Hz, 3H), 2.31-2.46 (m, 2H), 2.76-2.91 (m, 2H), 3.25-3.36 (m, 2H), 5.04-5.16 (m, 1H), 6.45-6.51 (m, 1H), 6.65 (br s, 1H), 7.22-7.48 (m, 10H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 21.1, 21.3, 22.7, 23.8, 38.7, 39.0, 49.2, 49.3, 114.0 (t, $^1J_{CF}$= 251.6 Hz), 114.1, (t, $^1J_{CF}$= 252 Hz), 126.1, 126.2, 126.4, 126.5, 127.7, 127.8, 128.6, 128.7, 128.8, 129.1, 129.8 (t, $^3J_{CF}$= 8.7 Hz), 129.8 (t, $^3J_{CF}$= 8.8 Hz), 131.7, 131.8, 131.8 (t, $^2J_{CF}$= 24.6 Hz), 131.9 (t, $^2J_{CF}$= 24.6 Hz), 161.9 (t, $^2J_{CF}$= 30 Hz), 177.7, 177.8, 178.1, 178.2. ^{19}F-NMR ($CDCl_3$, 282 MHz): -105.9 (d, J_{FF}=259.7 Hz, 1F), -106.4 (d, J_{FF}=257.6 Hz, 1F), -108.6 (d, J_{FF}=259.7 Hz, 1F), -108.8 (d, J_{FF}=257.6 Hz, 1F). HRMS (EI) calc. for (M^+) $C_{24}H_{22}F_2N_2O_3$: 424.1598, found: 424.1599.

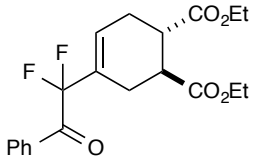


(*R*)-Diethyl 4-(1,1-difluoro-2-oxo-2-(1-phenylethylamino)ethyl)cyclohexa-1,4-diene-1,2-dicarboxylate. Following the general procedure described above (method A), 30 mg (60% yield) of **1.67** were obtained as a dark brown oil starting from 27 mg of (*R*)-2,2-difluoro-*N*-(1-phenylethyl)but-3-ynamide. $[\alpha]^{25}_D$ = -88.9 (c = 1.0 in $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, *J* = 7.2 Hz, 6H), 1.56 (d, *J* = 6.9 Hz, 3H), 3.12 (s, 4H), 4.23 (q, *J* = 7.2 Hz, 4H), 5.14 (quint, *J* = 7.2 Hz, 1H), 6.17-6.19 (m, 1H), 6.58 (br s, 1H), 7.29-7.39 (m, 5H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.4, 14.4, 21.8, 25.7 (t, $^4J_{CF}$ = 2.6 Hz), 28.5, 49.7, 61.8, 62.4, 114.9 (t, $^1J_{CF}$ = 251.6 Hz), 125.6 (t, $^3J_{CF}$ = 8.7 Hz), 126.6, 127.3 (t, $^3J_{CF}$ = 24.2 Hz), 128.3, 129.3, 131.6, 131.8, 142.1, 162.6 (t, $^3J_{CF}$ = 30.4 Hz), 167.5, 167.8. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -106.8 (d, J_{FF} = 258.7 Hz, 1F), -106.9 (d, J_{FF} = 258.6 Hz, 1F), -107.9 (d, J_{FF} = 258.6 Hz,

1F), -108.0 (d, J_{FF} = 258.7 Hz, 1F). HRMS (EI) calc. for (M^++1) $C_{22}H_6F_2NO_5$: 422.1774, found: 422.1753.



Diethyl 4-(1,1-difluoro-2-oxo-2-phenylethyl)-1,4-cyclohexadiene-1,2-dicarboxylate. Following the general procedure described above (method A), 25 mg (55% yield) of **1.68** were obtained as a dark brown oil starting from 22 mg of 2,2-difluoro-1-phenylbut-3-yn-1-one. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, J = 7.2Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 3.16 (s, 4H), 4.17 (q, J = 7.2 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 6.19-6.20 (br m, 1H), 7.47 (dd, J_1 = J_2 = 6 Hz, 2H), 7.63 (tt, J_1 = 7.2 Hz, J_2 = 1.5 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 13.9, 14.0, 25.3 (t, $^4J_{CF}$ = 2.8 Hz), 28.1, 61.4, 61.5, 116.3 (t, $^1J_{CF}$ = 251.9 Hz), 125.7 (t, $^3J_{CF}$ = 8.6 Hz), 128.0 (t, $^2J_{CF}$ = 23.8 Hz), 128.7, 130.2 (t, $^4J_{CF}$ = 2.9 Hz), 131.2, 131.3, 132.0, 134.5, 167.0, 167.3, 188.5 (t, $^2J_{CF}$ = 30.6 Hz). ^{19}F-NMR ($CDCl_3$, 282 MHz): -103.2 (s, 2F). HRMS (EI) calc. for (M^+) $C_{20}H_{20}F_2O_5$: 378.1269, found: 378.1279.



***Trans*-diethyl 4-(1,1-difluoro-2-oxo-2-(phenylamino)ethyl)-4-cyclohexene-1,2-dicarboxylate.** Following the general procedure described above (method A), 32 mg (70% yield) of **1.69** were obtained as a yellow oil starting from 22 mg of 2,2-difluoro-1-phenylbut-3-yn-1-one. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.23-2.41 (m, 2H), 2.51-2.64 (m, 2H), 2.84-2.98 (m, 2H), 4.14 (q, J= 7.2 Hz, 4H), 6.17-6.22 (m, 1H), 7.48 (dd, J_1 = J_2 = 7.8 Hz, 2H), 7.63 (tt, J_1 = 7.2 Hz, J_2 = 1.5 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 14.1, 25.0, 27.3, 40.4, 40.6, 60.9, 61.0, 116.4 (t, $^1J_{CF}$ = 251.42 Hz), 128.3 (t, $^3J_{CF}$ = 8.3 Hz), 128.7, 130.1 (t, $^2J_{CF}$ = 24.2 Hz), 130.1 (t, $^4J_{CF}$ = 2.27 Hz), 132.2, 134.4, 173.7, 173.9, 188.8 (t, $^2J_{CF}$ = 30.96 Hz). ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -111.7 (d, J_{FF} = 272.2 Hz, 1F), -112.8 (d, J_{FF} = 272.2 Hz, 1F). HRMS (EI) calc. for (M^++1) $C_{20}H_{23}F_2O_5$: 381.1508, found: 381.1514.

Chapter 2

Differential reactivity of fluorinated homopropargyl-α-amino esters *versus* Au(I) complexes. The role of nitrogen protecting group

2.1. Introduction and current state-of-the-art.

2.1.1. A brief on gold catalysis.

Despite the ubiquitous presence of gold along the history (jewelry, currency or medicine), not up to the end of the last century gold became a precious metal for chemists. By this short period of time, gold catalysis has become a fundamental and innovative synthetic tool for the generation of C–C and C-heteroatom bonds. This golden age is most likely due to the unique ability exhibited by Au(I) species to act as a π-soft Lewis acids towards non-activated multiple C–C bonds (alkynes, allenes, alkenes, 1,3-dienes or enynes),[55] promoting the addition of a wide variety of nucleophiles, both inter- and intra-molecularly, under mild reaction conditions while showing high functional group tolerance.[56]

Under this scenario, gold complexes emerged as well-suited catalysts for the combination of several transformations in a tandem fashion, opening new avenues to build up molecular complexity.[57] These tandem methodologies are becoming increasingly important among different areas of organic chemistry, as one of the main interests for both academia and industry is the enhancement of synthetic efficiency.

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[55] (a) Hashmi, A. S. K. *Acc. Chem. Res*. **2014**, *47*, 864. (b) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877. (c) Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889. (d) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (e) Zhang, D.-H.; Tang, X.-Y.; Shi, M. *Acc. Chem. Res.* **2014**, *47*, 913. (f) Fürstner, A. *Acc. Chem. Res.* **2014**, *47*, 925. (g) Alcaide, B.; Almendros, P. *Acc. Chem. Res.* **2014**, *47*, 939. (h) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953. (i) Yeom, H.-S.; Shin, S. *Acc. Chem. Res.* **2014**, *47*, 966. (j) Obradors, C.; Echavarren, A. M. *Chem. Commun*. **2014**, *50*, 16. (k) Muratore, M. E.; Homs, A.; Obradors, C.; Echavarren, A. M. *Chem. Asian J.* **2014**, *9*, 3066.

[56] Cycloisomerization and cycloaddition reactions of polyunsaturated compounds should be noted as well.

[57] (a) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331. (b) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028.

Even though less Lewis acidic Ag(I) or Pt(II) complexes, among others, can occasionally accomplish gold-catalyzed transformations,[58] no other late transition metal shows the breadth of applications displayed by homogeneous Au(I) complexes. This singular behavior has been attributed to relativistic effects.[59]

As soft centers, gold species show low oxophilicity.[60] Thus, gold-catalyzed reactions do not require rigorous inert conditions. Nevertheless, in the presence of water or alcohols, gold species may interact with them enhancing their Brönsted acidity, rendering actually Lewis acid assisted-Brönsted acid catalyzed processes.[61]

Among the different species susceptible to be activated by gold complexes, alkyne activation has been the most commonly exploited. Frenking and coworkers studied Au^{+}-acetylene and Au^{+}-ethylene interactions, showing that the latter is 10 $kcal \cdot mol^{-1}$ more stable.[62] That means that the alkynophilicity exhibited by gold complexes responds to a kinetic origin. Compared to alkynes, higher π^* energy levels for alkenes result in larger gaps with nucleophile's HOMO.

It is commonly accepted that these types of gold-catalyzed nucleophilic additions over C–C multiple bonds involves two steps (*Scheme 2.1*). Nucleophilic *anti*-addition over a π-C–C bond activated by the gold complex,[63] gives rise to a *trans*-alk(en)yl-gold intermediate[64] that is now prone to be trapped by any electrophile present in the reaction media, commonly a proton through a protodeauration step, rendering the product and restoring the catalytically active species. Alternatively, these vinyl gold intermediates may evolve through the coined carbene pathway, displaying versatile reactivities.[65]

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[58] (a) Muñoz, M. P. *Chem. Soc. Rev.* **2014**, *43*, 3164. (b) Fürstner, A. *Chem. Soc. Rev*. **2009**, *38*, 3208.

[59] (a) Leyva-Pérez, A.; Corma, A. *Angew. Chem. Int. Ed*. **2012**, *51*, 614. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

[60] (a) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed*. **2007**, *46*, 3410. (b) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

[61] (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924. (b) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem. Int. Ed*. **2011**, *50*, 9919. (c) Chen, C. H.; Wang, C. D.; Hsieh, Y. F.; Liu, R. S. *Org. Biomol. Chem*. **2014**, *12*, 9831.

[62] Nechaev, M. S.; Rayón, V. M.; Frenking, G. *J. Phys. Chem. A* **2004**, *108*, 3134.

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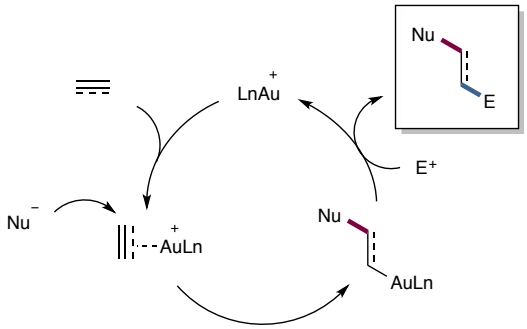

Scheme 2.1. Catalytic cycle for gold-catalyzed nucleophilic additions.

In order to implement catalysis, ancillary ligands play a pivotal role tuning reactivity of gold catalysts.[66] So a careful choice of an appropriate ligand (with accurate steric and electronic properties) comes essential to endorse the desired reactivity. For instance, deauration is usually a fast step, being the electronic activation the rate-limiting step, especially when dealing with soft nucleophiles or less reactive substrates such as alkenes or allenes. Under this scenario, gold complexes derived from electron-withdrawing ligands would favour nucleophilic addition, increasing the overall efficiency of the process. Nevertheless, deauration might be the rate-limiting step as well. In the presence of basic nucleophiles like amines, any acid present in the media will see diminished its acidity. Under these conditions, the use of electron-rich ligands would favour the electrophilic attack over the vinyl-gold intermediate.

But beyond this simplistic picture of gold-catalysis, ligand effects may influence catalysis from different angles, tuning reactivity and selectivity. Additionally, despite significant efforts were directed towards gold asymmetric catalysis[67] based on the application of chiral ligands, the linear geometry of Au(I) complexes[68] converted this strategy in a challenging task, which prompted alternative strategies, namely the use of chiral counterions.[69] Counterion effects may have deep outcomes in gold-catalyzed transformations.[70] Linear gold chloride complexes bearing phosphines or *N*-heterocyclic carbenes as ligands are quite common precatalysts that need to be activated by chloride abstraction with a silver salt. In this manner, chloride is replaced by a weakly coordinating ligand, generating more active gold species and in turn enabling its replacement by the reactive substrate *via* π-coordination. Nevertheless, this ligand exchange occurs *via* an associative mechanism,[71] a triggering

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[67] Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567.
[68] Highly enantioselective Au(III)-catalyzed transformations remain unreported.
[69] Pioneering work by Toste *et al.*, see: Hamilton, G. L.; Kang, E. J.; Miriam, M.; Toste, F. D. *Science*, **2007**, *317*, 496.
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[71] (a) Xi, Y.; Wang, Q.; Su, Y.; Li, M.; Shi, X. *Chem. Commun*. **2014**, *50*, 2158. (b) Brooner, R. E. M.; Robertson, B. D.; Widenhoefer, R. A. *Organometallics*, **2014**, *33*, 6466. (c) Zhdanko, A.; Maier, M. E. *Organometallics* **2013**, *32*, 2000.

aspect in gold catalysts preparation that should not be overlooked, since the invoked and so-called "silver effects" have demonstrated not play an innocent role in gold catalysis.[72]

On the other hand, while most of gold-catalyzed reactions are based on its ability to act as soft Lewis acids, activating C–C multiple bonds, its competency towards the formation of σ-complexes with heteroatoms has been proved as well. This bifunctional character exhibited by gold salts as σ- and π-Lewis acids was highlighted in the regiodivergent cyclization of halogenated allenones reported by Gevorgyan in 2005.[73] Regardless the use of Au(III) species as precatalysts for the activation of unsaturated C–C bonds, it has been also proved their competency towards the formation of σ-complexes with heteroatoms. At higher oxidation states, gold species act as hard Lewis acids. It is at lower oxidation states when relativistic effects raise their greatest sway, i.e. when gold catalysis' genuineness arises. Nevertheless, the use of Au(III) precatalysts is still surrounded by many uncertainties regarding the actual oxidation state and structure of the catalytic species.[74]

Furthermore, despite their soft Lewis acidity, Au(I) species can form as well σ-acetylide complexes with terminal alkynes. Since Toste group highlighted a dual σ,π-activation mode in the Au(I)-catalyzed cycloisomerization of 1,5-allenynes,[75] σ,π-digold complexes have been recognized as relevant complexes in homogeneous Au(I) catalysis, mainly in reactions of diynes.[76]

Beyond their use as π-carbophilic Lewis acids, gold-complexes have been also successfully applied in cross-coupling reactions. The high redox potential of Au(I)/Au(III) redox couple (+1.41V)[77] was the reason because the use of gold variants on cross coupling reactions, following an analogous catalytic mode to other transition metal like Pd(0)/Pd(II) redox couple (+0.92V), were a significant challenge. The use of external oxidants such as Selectfluor has changed this tendency allowing catalytic turnover of Au(I) to Au(III) and finally the generation of C–C and C-heteroatom bonds *via* reductive elimination from Au(III) species (*Scheme 2.2*).[78] These transformations constitute a new paradigm in gold chemistry, expanding the utility of gold catalysis.

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[72] (a) Homs, A.; Escofet, I.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 5782. (b) Zhu, Y.; Day, C. S.; Zhang, L.; Hauser, K. J.; Jones, A. C. *Chem. Eur. J.* **2013**, *19*, 12264. (c) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

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[75] Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc*. **2008**, *130*, 4517.

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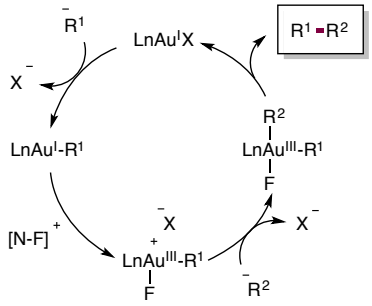

Scheme 2.2. Catalytic cycle for Au(I)/Au(III) coupling reactions.

Considering the unique modes of activation of unsaturated bonds exhibited by gold salts, its combination with either fluorinated building blocks or fluorinated reagents will open new avenues for the development of new methodologies in fluoroorganic chemistry. Indeed, gold and fluorine faithfully form a fruitful partnership,[79] and different types of reactivity arise from their combination.

2.1.2. Fluorinated building blocks in gold-catalyzed processes.

The use of fluorinated building blocks is one of the main approaches to access fluorinated scaffolds. Its combination with gold salts, proficient to promote new activation modes triggering unconventional reactivity patterns, opens new avenues in organofluorine chemistry. This partnership allows the preparation of great-demanded fluorinated skeletons, otherwise difficult to access. Nevertheless, only a few reports concerning the use of fluorinated starting materials have been devised to date.

The first contribution in this area was due to Hayashi and coworkers. An in-depth study was carried out in their laboratory, evaluating the aldol condensation of isocyanoacetic acid derivatives **2.1** with fluorinated prochiral aldehydes,[80] ketones[81] and imines.[82] Hydrolysis of the corresponding oxazolines **2.2**, **2.3** or imidazolines **2.4** resulted in a new family of fluorinated α-amino acid derivatives (*Scheme 2.3*).

Gouverneur, V. *Chem. Eur. J.* **2011**, *17*, 8248. (e) Garcia, P.; Malacria, M.; Aubert, C.; Gandon, V.; Fensterbank, L. *ChemCatChem* **2010**, *2*, 493.

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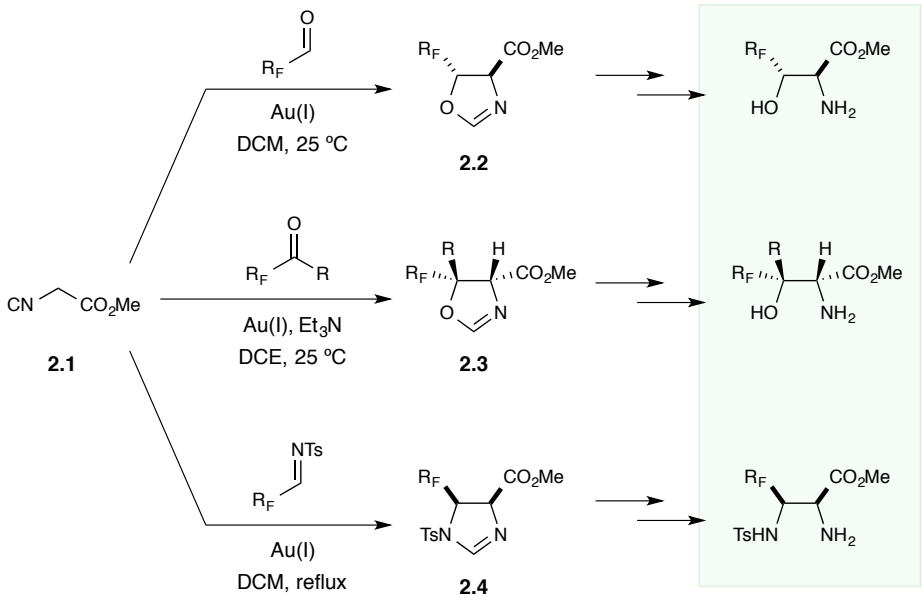
[80] (a) Soloshonok, V. A.; Kacharov, A. D.; Hayashi, T. *Tetrahedron*, **1996**, *52*, 245. (b) Soloshonok, V. A.; Hayashi, T. *Tetrahedron: Asymmetry*, **1994**, *5*, 1091. (c) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713.

[81] (a) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, M.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470. (b) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Hayashi T. *Tetrahedron Lett.* **1996**, *37*, 7845.

[82] Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969.



Scheme 2.3. Previous work by Hayashi (90s).

Among other transition metal species, gold was able to coordinate the isonitrile moiety, lowering the pk_a of hydrogens at the α-position of the isocyanoacetate derivative **2.1** and, in turn, promoting an aldol-type condensation with a carbonyl derivative in the presence of a properly base. The participation of gold became essential enabling milder reaction conditions, since stronger bases employed in conventional aldol-type reactions would adversely affect functional group tolerance.

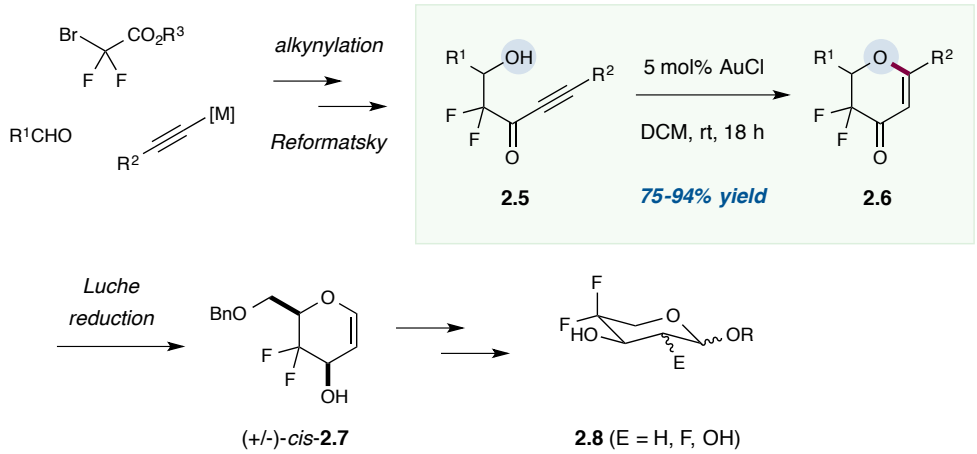
Nevertheless, this former contribution lacks from the singularity commonly ascribed to gold, and other transition metal complexes, such as Cu(I), Pd(II), Ag(I) or Rh(I), enabled this transformation as well. This feature might be significant regarding the role displayed by gold in this transformation, performing a σ-activation rather than a π-activation, being this latter closely related with its recent breakthrough in organometallic catalysis as a soft Lewis acid.

Taking this into account, Gouverneur's contribution in 2008[83] may be considered at the starting line of this on-going race. The relatively lateness-stage of this work compared to the gold rush emergence in the early 2000[84] is meaningful. Furthermore, the relevance of this pioneering work goes beyond being one of the first examples combining fluorinated building-blocks and gold catalysis, placing the first stone on the probably most fruitful outcomes resulting from the gold-fluorine partnership, as it constitutes one of the first examples of gold-mediated C–F bond formation.

Gouverneur's work described the Au(I)-catalyzed 6-*endo*-dig heterocyclization of β-hydroxy-α,α-difluoroynones **2.5**, leading access to a new family of fluorinated dihydropyranones **2.6**. This cyclization is efficiently promoted by AuCl in DCM, independently of the alkyne substitution or the

[83] Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2008**, *47*, 7927.
[84] Hashmi, A. S. K. *Gold Bull.* **2004**, 51.

ancillary group attached to the β-hydroxy group (*Scheme 2.4*). Despite this transformation is extensive to their non-fluorinated counterparts, remarkably, *gem*-difluoro substitution does not come innocent. Fluorine does reduce nucleophilicity of the proximal hydroxyl group preventing cyclization under basic or acidic conditions or by alternative catalytic systems. Just gold proves capable to catalyze this transformation in an efficient manner. This methodology was further applied for the synthesis of fluorinated carbohydrate analogues.[85]

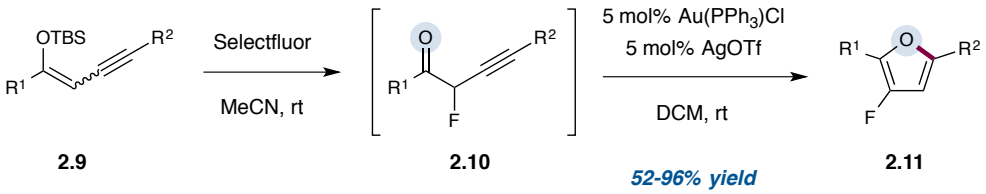


Scheme 2.4. Previous work by Gouverneur (2008).

This type of gold-catalyzed alkoxycyclizations were further exploited in the synthesis of diversely substituted β-fluorofurans, great demanded submotifs in the pharmaceutical industry. According to the significance of furan ring featuring among lead compounds and biologically active natural products,[86] fluorinated derivatives may provide implemented pharmacological profiles. Previously reported methodologies were scarce and operate in low yields or with poor selectivity, normally entailing aggressive conditions.[87]

In 2010, Dembinski and coworkers reported the gold-catalyzed preparation of fluorofurans **2.11** starting from monofluoroynones **2.10**.[88] These ketones are readily accessed by electrophilic monofluorination with Selectfluor of silyl enol ethers **2.9** derived from their corresponding non-fluorinated ynones. Whereas $AuCl_3$ gave rise to complex reaction mixtures, combination of $Au(PPh_3)Cl$ and AgOTf in DCM at room temperature provided unsymmetrically 2,5-substituted-3-fluorofurans **2.11** in good yields (*Scheme 2.5*).

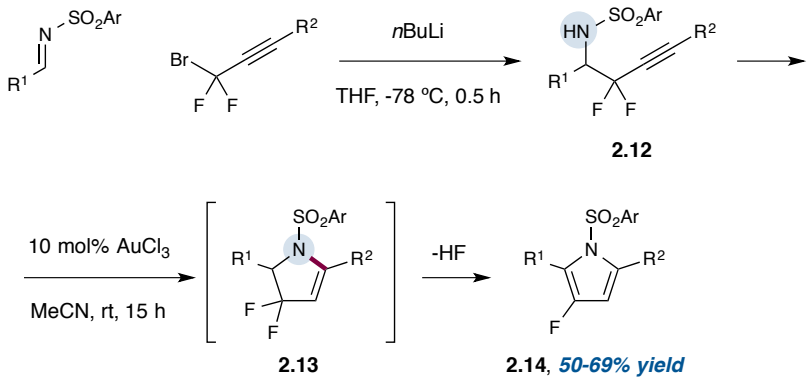
[85] Giuffredi, G. T.; Bernet, B.; Gouverneur, V. *Eur. J. Org. Chem.* **2011**, 3825.
[86] (a) Wu, Y.-J. *Progress in Heterocyclic Chem.* **2012**, *24*, 1-53. (b) Yeung, K.-S.; Peng, X.-S.; Wu, J.; Hou, X.-L. *Progress in Heterocyclic Chem.* **2012**, *24*, 205-241.
[87] Serdyuk, O.; Butin, A.; Abaev, V. *J. Fluorine Chem.* **2010**, *131*, 296.
[88] Li, Y.; Wheeler, K. A.; Dembinski, R. *Adv. Synth. Catal.* **2010**, *352*, 2761.



Scheme 2.5. Previous work by Dembinski (2010).

Besides oxygen-containing heterocycles, gold catalysis has opened new and efficient synthetic pathways for the preparation of fluorinated nitrogen-containing heterocycles by means of the intramolecular hydroamination reaction. Fluorine-containing pyrroles, pyrazoles, imidazoles, isoindolines, or isoquinolines, among others, constitute a class of important structural units for both pharmaceutical and agrochemical industries. Hence, the development of new methods to access these privileged structures are of high value.[89]

In 2009, De Kimpe and coworkers reported the preparation of 3-fluoropyrroles **2.14**, readily accessible by means of a gold-catalyzed 5-*endo*-dig cyclization and spontaneous dehydrofluorination of electron-deficient *gem*-difluorohomopropargyl-*N*-tosyl amines **2.12** (*Scheme 2.6*).[90] Starting amines were prepared by addition of the *gem*-difluoropropargyl bromides developed by Hammond and coworkers,[91] to the corresponding *N*-tosyl imines, previous lithium-bromine exchange.

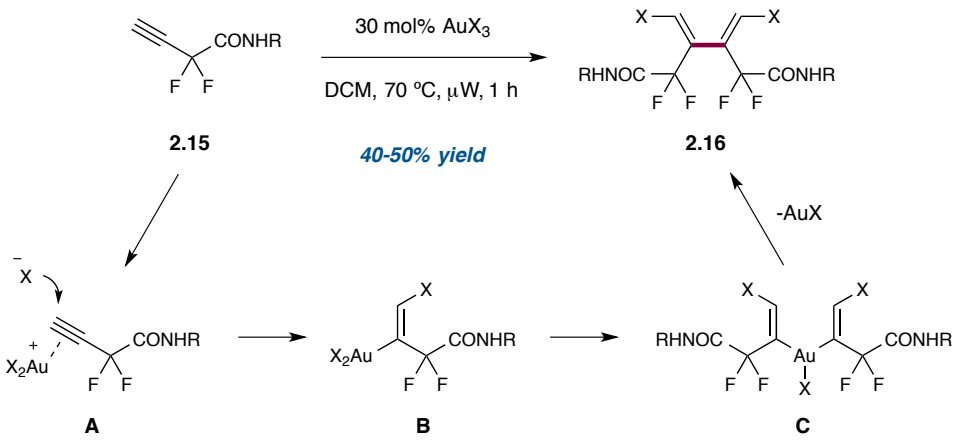


Scheme 2.6. Previous work by De Kimpe (2009).

These fluorinated building blocks were used as well in the preparation of *gem*-difluoropropargyl amides **2.15**. Intramolecular 4-*exo*-dig and 5-*endo*-dig hydroamination reactions of **2.15** were reported by our research group under palladium catalysis and basic conditions respectively,

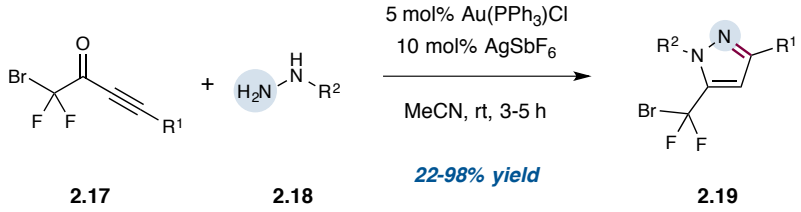
[89] Petrov, C. A. Ed. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Applications*; John Wiley & Sons: Hoboken, NJ, USA, 2009.
[90] Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett*. **2009**, *11*, 2920.
[91] Xu, B.; Mae, M.; Hong, J. A.; Li, Y.; Hammond, G. B. *Synthesis* **2006**, 803.

rendering fluorinated β- and γ-lactams regioselectively.[54a] However, hydroamination was not accomplished under gold catalysis. Instead, in the presence of Au(III) salts an unprecedented head-to-head dimerization of the starting amides **2.15** was observed.[54b] This novel reactivity pattern seems to be induced by the *gem*-difluoro moiety, which displays a critical role. According to the electron-withdrawing effect imparted by fluorine, fluorine substitution decreases nucleophilicity of the nitrogen atom to such an extent to prevent hydroamination but, at the same time, assists the gold catalyst activating the triple bond towards the intermolecular nucleophilic addition of a halogen atom from the gold salt. Afforded vinyl Au(III) intermediate **B** then undergoes an additional halogen addition to generate divinyl intermediate **C**, which finally renders diene **2.16** by means of reductive elimination (*Scheme 2.7*). Attempts to perform the process catalytically by adding external oxidants and halogen sources failed, so the process results stoichiometric in gold.



Scheme 2.7. Previous work by Fustero (2009).

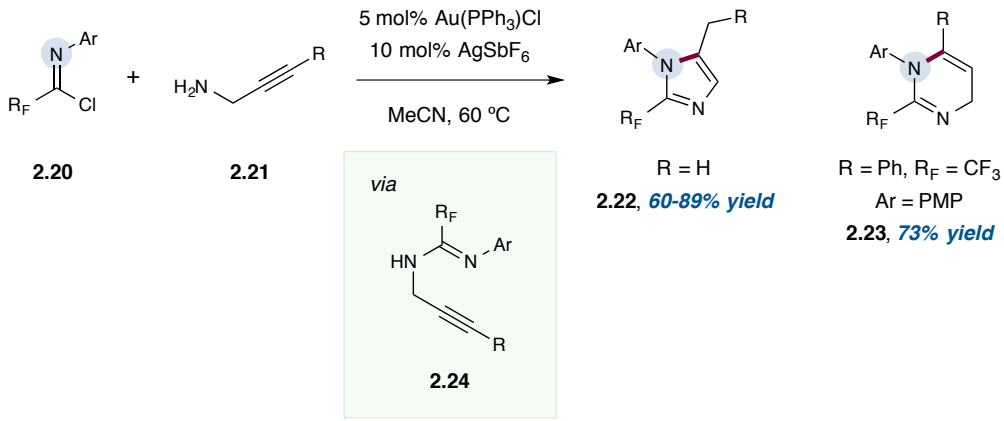
Gold complexes work efficiently as well catalyzing the formation of 5-difluoropyrazoles **2.19** with high selectivity from fluorinated alkynyl ketones **2.17** and hydrazines **2.18** (*Scheme 2.8*).[92] Authors sustain that the observed regioselectivity results from a kinetic control, since nucleophilic attack by the primary amine is less sterically hindered.



Scheme 2.8. Previous work by Wu (2011).

[92] Li, S.; Li, Z.; Peng, D.; Li, Y.; Zhu, J.; Xie, H.; Yuan, Y.; Chen, Z.; Wu, Y. *Chin. J. Chem*. **2011**, *29*, 2695.

On the other hand, fluorinated propargyl amidines **2.24** undergo, in the presence of Au(I) complexes, a 5-*exo*-dig cyclization to afford 2-fluorinated 5-methylimidazoles **2.22**.[93] Under optimized conditions, their preparation could be set in a one-pot procedure from the corresponding fluorinated imidoyl chlorides **2.20** and propargyl amines **2.21**. While the overall process showed good compatibility to several functional groups, its efficiency was affected by electronics on the arylamine, being slightly lowered with electron-deficient ones. Even though protodeauration step used to be the rate-limiting step when dealing with basic amines, reported results point to the electronic activation as the higher barrier to overcome. Presumably, electron-withdrawing groups reduce amine's nucleophilicity, affecting the efficiency of the overall process. In contrast to terminal alkynes, the use of internal propargyl amines completely changed regioselectivity, rendering 1,4-dihydropyrimidines **2.23** in high yield resulting from a 6-*endo*-dig cyclization (*Scheme 2.9*).

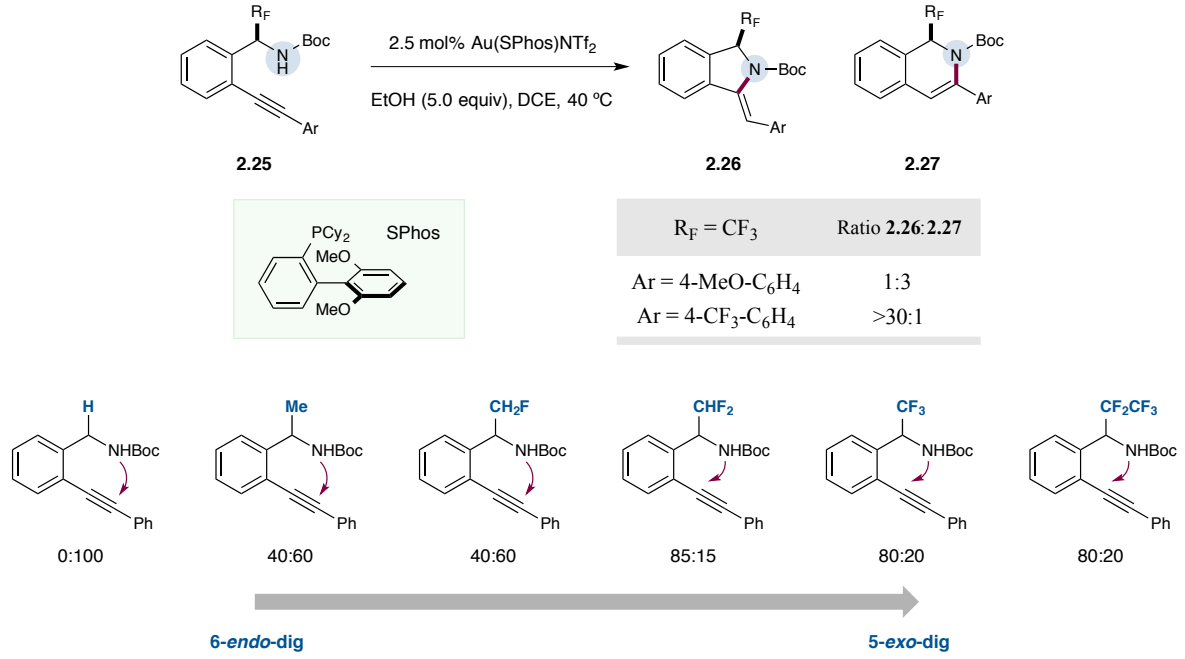


Scheme 2.9. Previous work by Wu (2012).

A good example to illustrate the implications that fluorine substitution may have in gold-catalyzed reactions was reported by our group in 2013.[94] It was proved that fluorine substitution plays a critical role in the regiochemical outcome of the intramolecular hydroamination of *ortho*-alkynyl benzyl carbamates **2.25** (*Scheme 2.10*). Typically, regioselectivity in such type of processes is highly dependent on the electronics of the aryl substituent at the alkyne. While electron-donating substituents tends to favor 6-*endo*-dig cyclization (being the major products isoquinolines **2.27**), electron-withdrawing substituents favor 5-*exo*-dig pathway, with the preferred formation of isoindolines **2.26**. In this case, likely a steric than an electronic effect was imparted by fluorine substitution, since gradual introduction of fluorine atoms at the α-position of the benzyl carbamate promoted 5-*exo*-dig

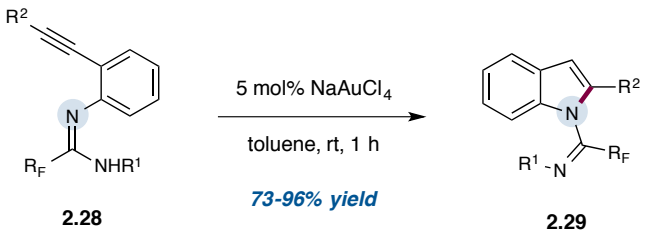
[93] Li, S.; Li, Z.; Yuan, Y.; Peng, D.; Li, Y.; Zhang, L; Wu, Y. *Org. Lett.* **2012**, *14*, 1130.
[94] Fustero, S.; Ibáñez, I.; Barrio, P.; Maestro, M. A.; Catalán, S. *Org. Lett.* **2013**, *15*, 832.

cyclization over 6-*endo*-dig pathway, leading to isoindoline derivatives **2.26** as the major products, in striking contrast to their previously reported non-fluorinated counterparts.[95]



Scheme 2.10. Previous work by Fustero (2013).

Regiochemistry was also critical in the intramolecular hydroamination of *N*-(*ortho*-alkynyl)aryl-*N'*-substituted trifluoro- and bromodifluoro-acetamidines **2.28**,[96] since up to three types of cyclization pathways may operate: 7-*endo*-dig, 6-*exo*-dig or 5-*endo*-dig. While copper and silver salts provided low conversions and poor selectivities respectively, 5-*endo*-dig cyclization took place efficiently in the presence of 5 mol% $NaAuCl_4 \cdot 2H_2O$ in toluene at room temperature to render indoles **2.29** in good yields (*Scheme 2.11*). The process was highly selective independently of the electronics on the substituents at the alkyne moiety, unless terminal alkynes were employed.



Scheme 2.11. Previous work by Wu (2012).

[95] (a) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V.; Raju, P. V. K.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, 1999. (b) Enomoto, T.; Girard, A.-L.; Obika, S.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 9158. (c) Enomoto, T.; Obika, S.; Yasui, Y.; Takemoto, Y. *Synlett*, **2008**, *11*, 1647. (d) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem*. **2007**, *72*, 4462.

[96] Zhu, J.; Xie, H.; Chen, Z.; Li, S.; Wu, Y. *Org. Biomol. Chem.* **2012**, *10*, 516.

2.2. Gold-promoted differential reactivity of fluorinated homopropargyl-α-amino esters.

Homopropargyl amines are ubiquitous substrates in gold catalysis.[97] These compounds have been used as suitable starting materials in several processes that involve an initial intramolecular hydroamination of the triple bond. The subsequent combination of this C–N bond formation with further transformations in a tandem or a one-pot manner was traduced in the development of new methodologies for the preparation of a wide variety of nitrogen-containing heterocycles, including piperidines, pyrrolidines or tetrahydroquinolines, among others. However, very few reports concerning the use of fluorinated starting materials have been devised to date. This is probably due to the absence of efficient methods to access fluorinated homopropargyl amines.

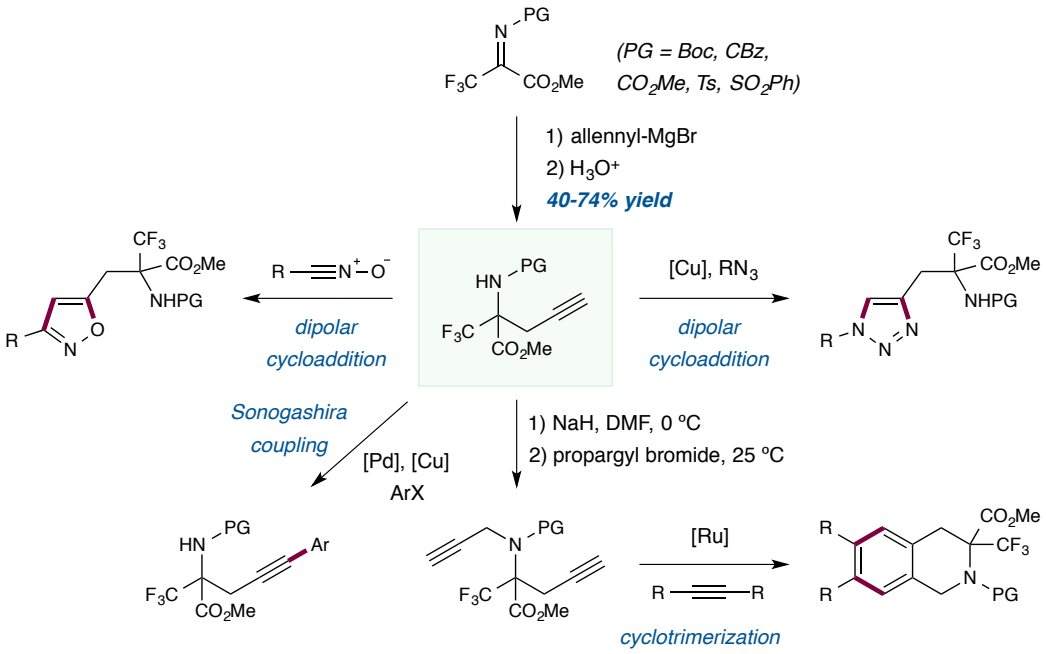
In this sense, fluorinated homopropargyl amino esters were synthesized to date by addition of allenyl magnesium bromide to the corresponding α-imino esters. However, only highly electrophilic imino esters (bearing carbamates or sulphonamides at the nitrogen end) were compatible with this methodology. Resulting amino esters were used as starting materials in dipolar type cycloadditions with azides and nitrile oxides.[98] The functionalization of the terminal alkyne position was possible by means of a Sonogashira type coupling.[99] Alternatively, the propargylation of the nitrogen afforded the corresponding alkylated product, which in its reaction with another alkyne in the presence of a ruthenium catalyst afforded the cyclotrimerization product (*Scheme 2.12*).[100]

[97] Selected examples: (a) Shu, C.; Li, L.; Yu, Y.-F.; Jiang, S.; Ye, L.-W. *Chem. Commun*. **2014**, *50*, 2522. (b) Zheng, Z.; Tu, H.; Zhang, L. *Chem. Eur. J.* **2014**, *20*, 2445. (c) Yu, Y.-F.; Shu, C.; Shen, C.-H.; Li, T.-Y.; Ye, L.-W. *Chem. Asian J.* **2013**, *8*, 2920. (d) Shu, C.; Liu, M.-Q.; Wnag, S.-S.; Li, L.; Ye, L.-W. *J. Org. Chem.* **2013**, *78*, 3292. (e) Liu, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 7301. (f) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011. (g) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun*. **2011**, *47*, 218. (h) Yeom, H.-S.; So, E.; Shin, S. *Chem. Eur. J.* **2011**, *17*, 1764. (i) Cui, L.; Li, C.; Zhang, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9178. (j) Kim, C.; Bae, H. J.; Lee, J. H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660. (k) Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

[98] (a) Vorobyeba, D. V.; Sokolova, N. V.; Nenajdenko, V. G.; Peregudov, A. S.; Osipov, S. N. *Tetrahedron*, **2012**, *68*, 872. (b) Vorobyeba, D. V.; Karimova, N. M.; Odinets, I. L.; Röschenthaler, G.-V.; Osipov, S. N. *Org. Biomol. Chem.* **2011**, *9*, 7335. (c) Shchetnikov, G. T.; Peregudov, A. S.; Osipov, S. N. *Synlett*, **2007**, 136.

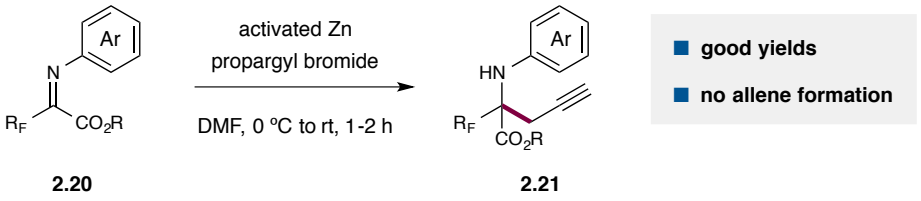
[99] Shchetnikov, G. T.; Zotova, M. A.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Eur. J. Org. Chem.* **2010**, 1587.

[100] Shchetnikov, G. T.; Osipov, S. N.; Bruneau, C.; Dixneuf, P. H. *Synlett*, **2008**, 578.



Scheme 2.12. Reactivity of fluorinated homopropargyl amines (Osipov).

Pleasantly, we found suitable conditions to access to these templates (**2.21**) in an efficient manner. This methodology was based on the addition of propargyl zinc to the corresponding fluorinated α-imino esters **2.20**, employing DMF such as solvent, under *Barbier*-type conditions (*Scheme 2.13*).[101]

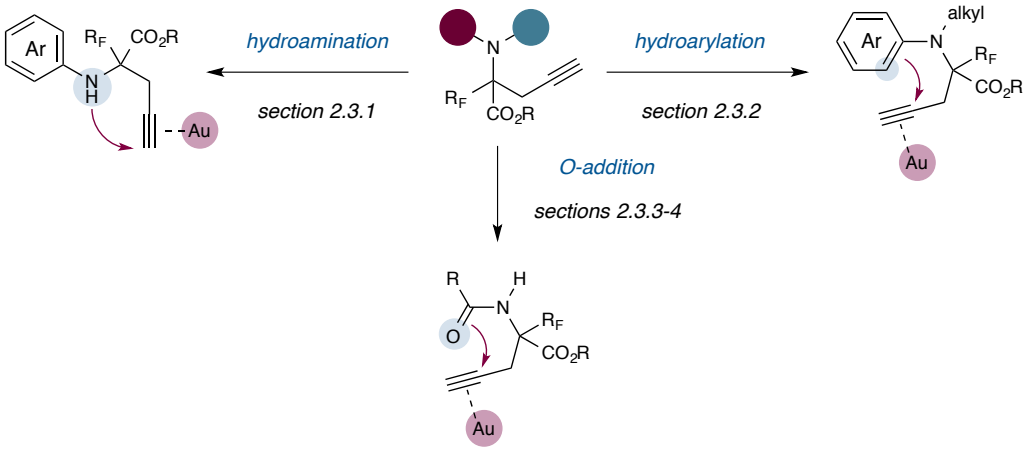


Scheme 2.13. Propargylation of fluorinated α-imino esters.

Given the new activation modes of alkynes promoted by gold, besides its peculiar reactivity, we envisioned the possibility of performing a differential reactivity of those amino esters in the presence of gold salts, just by changing the substitution pattern on the nitrogen atom;[102] thus, leading access to new families of fluorinated *N*-heterocycles (*Scheme 2.14*).

[101] Following conditions developed by Bonnet-Delpon *et al.*: Magueur, G.; Legros, J.; Meyer, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **2005**, 1258.

[102] For a previous example of switching the pathway when placing a substituent on the amine group, see: Hashmi, A. S. K.; Molinari, L.; Rominger, F.; Oeser, T. *Eur. J. Org. Chem.* **2011**, 2256.



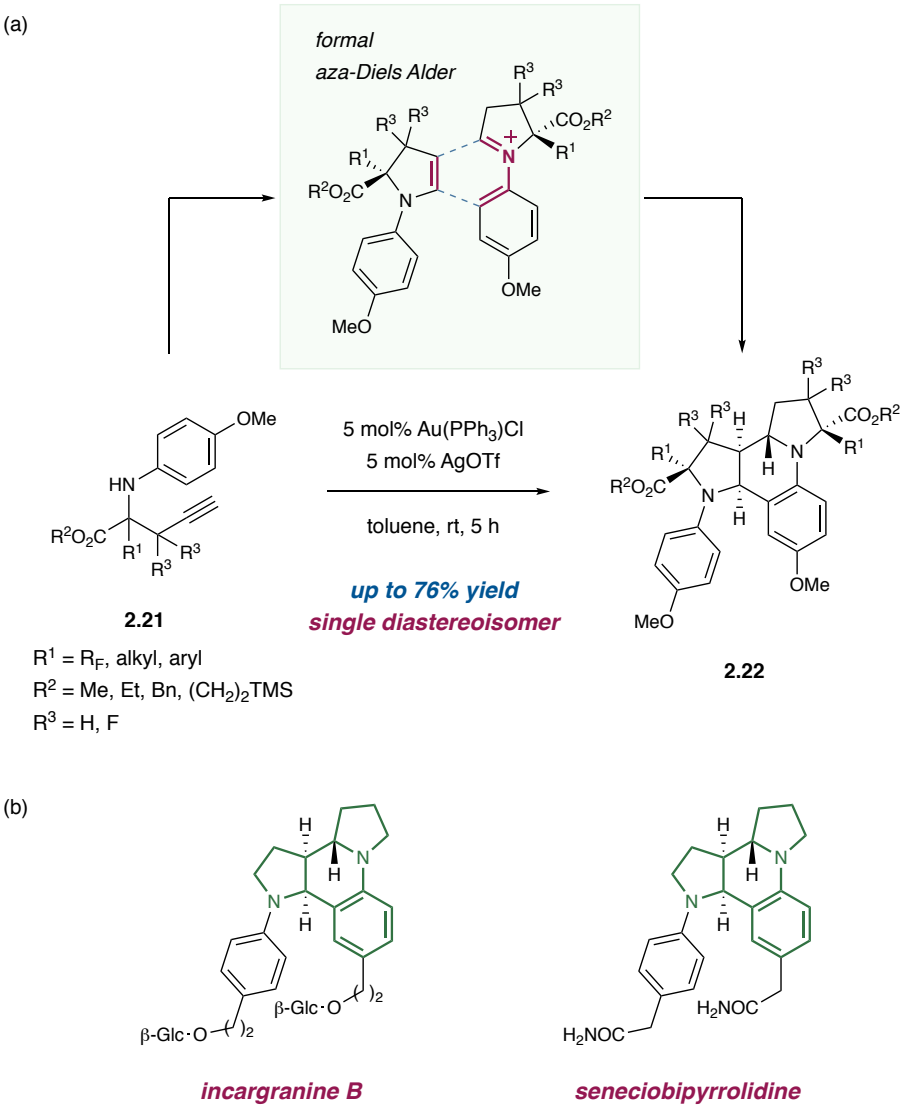
Scheme 2.14. Outline: differential reactivity.

Hence, we could expect that with substrates containing an aromatic substituent, a hydroamination-type process would occur. However, the blockage of the amine group by alkylation would avoid the hydroamination step, and a hydroarylation-type process could be expected instead. Finally, if the nitrogen substituent is protected as a carbamate or an amide, in the presence of an appropriate gold catalyst, we hypothesize that the reaction would start by attack of the carbonyl oxygen atom onto the activated triple bond.

2.3. Results and discussion.

2.3.1. Gold-catalyzed tandem hydroamination-formal aza-Diels Alder reaction.

Given this perspective, we firstly envisioned the access to a new family of fluorinated proline derivatives by means of an intramolecular hydroamination reaction. Along this search, we found that substrates containing aromatic groups evolved in a tandem hydroamination-formal aza-Diels Alder cascade reaction (*Scheme 2.15a*), generating tetracyclic frameworks **2.22** in a single step.[103]



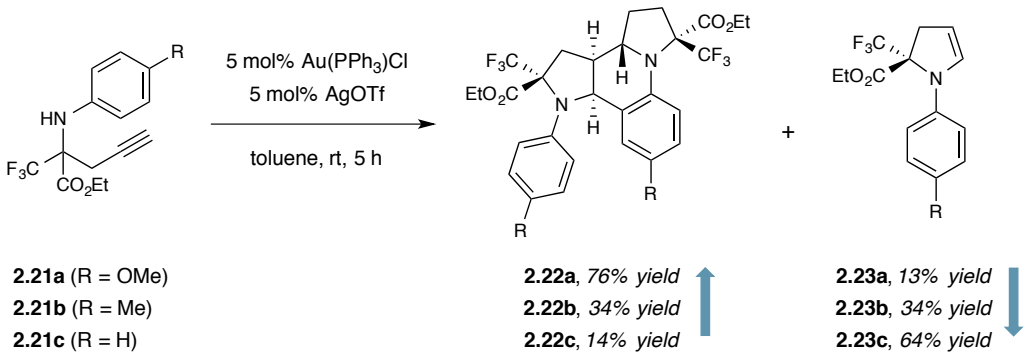
Scheme 2.15. (a) Our previous work: tandem hydroamination-formal aza-Diels Alder reaction. (b) Natural octahydro-dipyrroloquinoline alkaloids.

[103] This work was developed along with Dr. Paula Bello: (a) Fustero, S.; Bello, P.; Miró, J.; Sánchez-Roselló, M.; Maestro, M. A.; González, J.; del Pozo, C. *Chem. Commun.* **2013**, *49*, 1336. This one and the herein presented work inspired Liu and coworkers to further extend this protocol and develop an enantioselective version: (b) Yu, X.-L.; Kuang, L.; Chen, S.; Zhu, X.-L.; Li, Z.-L.; Tan, B.; Liu, X.-Y. *ACS Catal.* **2016**, *6*, 6182. (c) Ma, C.-L.; Li, X.-H; Yu, X.-L; Zhu, X.-L.; Hu, Y.-Z.; Dong, X.-W.; Tan, B.; Liu, X.-Y. *Org. Chem. Front.* **2016**, *3*, 324.

In the overall process, the simultaneous generation of four new bonds and three stereocenters occurred, giving rise to the final products as single diastereoisomers. Notably, the accessed octahydro-dipyrroloquinoline framework is found in a wide range of biologically active alkaloid natural products such as *incargranine B* and *seneciobipyrrolidine* (*Scheme 2.15b*).

The initial results of the tandem process showed that several fluorinated and non-fluorinated starting amino esters **2.21** were compatible with the tandem protocol. Besides, this reaction was very efficient when the aryl substituent on the nitrogen atom is a PMP (*para*-methoxyphenyl) group; however, attempts to extend the tandem protocol to starting substrates containing other aromatic groups with different electronic properties were ineffective, leading to a dramatic decrease in the product yields.

When fluorinated propargyl amino ester **2.21a** was treated with $Au(PPh_3)Cl$ and AgOTf in toluene at room temperature, tetracyclic compound **2.22a** was obtained in 76% yield, together with a small amount (13% yield) of the hydroamination product **2.23a** (*Scheme 2.16*). With substrate **2.21b**, bearing a *para*-tolyl group, an equimolecular amount of **2.22b** and the hydroamination product **2.23b** were obtained; whereas with substrate **2.21c**, which contained an unsubstituted phenyl group at the *N*-terminus, the hydroamination product **2.23c** was the major product (64% yield).



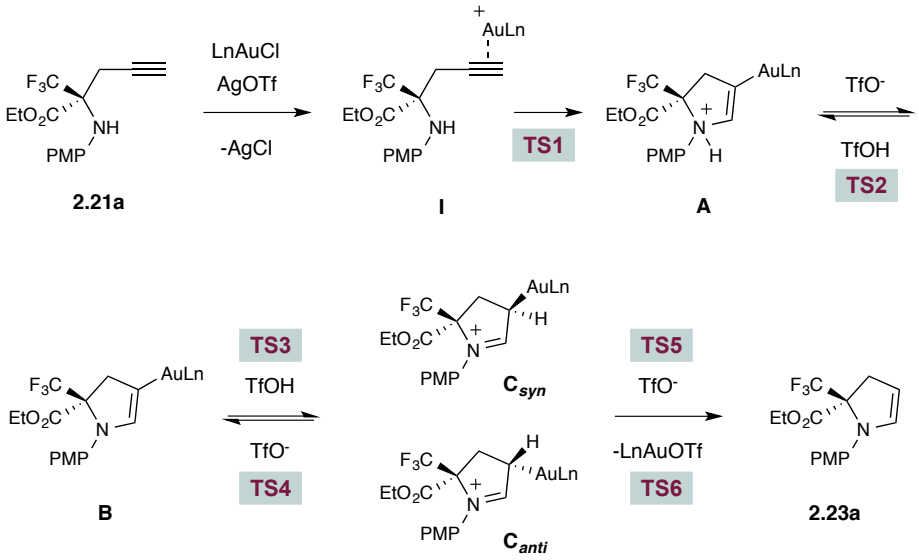
Scheme 2.16. Au(I)-mediated tandem protocol with amines **2.21a-c**.

In order to gain some insights into the mechanistic details of this transformation,[104] a theoretical study using the Density-Functional Theory (DFT) was carried out.[105] In the aforementioned Au(I)-mediated cascade reaction, $Au(PPh_3)OTf$ was assumed to be the catalytically active species and the complex $[Me_3PAu]^+$ was used as a model in the theoretical study.[106] Full methodological details of this theoretical study are shown in the *Experimental Section 2.5.1.5*.

[104] Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.
[105] Theorethical calculations were carried out by Dr. J. González from Universidad de Oviedo.
[106] For a theoretical study on the nature of the catalytically active species in Au(I)-mediated reactions, see: Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.

Based on the results of these calculations, we propose a plausible mechanistic explanation for the formation of the tetracyclic structures **2.22**, involving an initial hydroamination reaction followed by an asymmetric dimerization pathway. The full process, which can be viewed as a Povarov-type reaction, is depicted in *Scheme 2.17* and *Scheme 2.18*.[107]

The initial step is the activation of the alkyne moiety of substrate **2.21a** through the coordination of the gold catalyst, which acts as a π-Lewis acid, with the triple bond. This step has a negligible energy barrier and proceeds to give complex **I**, which is 16.6 kcal·mol^{-1} more stable than the reactants. Cyclic intermediate **A** is then formed by the attack of the amine nitrogen atom on the triple bond in a favored 5-*endo*-dig cyclization.[108] Then, intermediate **A** releases a proton, which leads to the formation of triflic acid and intermediate **B**, which in turn reacts with this released triflic acid molecule to give two diastereomeric iminium salts, $\mathbf{C}_{syn}$ and $\mathbf{C}_{anti}$. Intermediates **C** undergo now deauration to lead enamine derivative **2.23a**, whereas the catalyst Au(Ln)OTf is regenerated.



Scheme 2.17. Mechanistic proposal (first stage).

[107] Only the intermediates with relative configuration that lead to the experimentally observed product are represented. For a related gold-catalyzed Povarov-type reaction further developed in our lab involving fluorinated α-imino esters and furans, see: Sanz-Vidal, A.; Miró, J.; Sánchez-Roselló, M.; del Pozo, C.; Fustero, C. *J. Org. Chem.* **2016**, *81*, 6515.

[108] For a review on Baldwin's rules in alkynes' cyclization reactions, see: Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.

The most relevant geometrical and energetic features of the stationary points that were found for the transformation of compound **2.21a** into intermediates **C** and **2.23a** are depicted in *Figure 2.1*.[109]

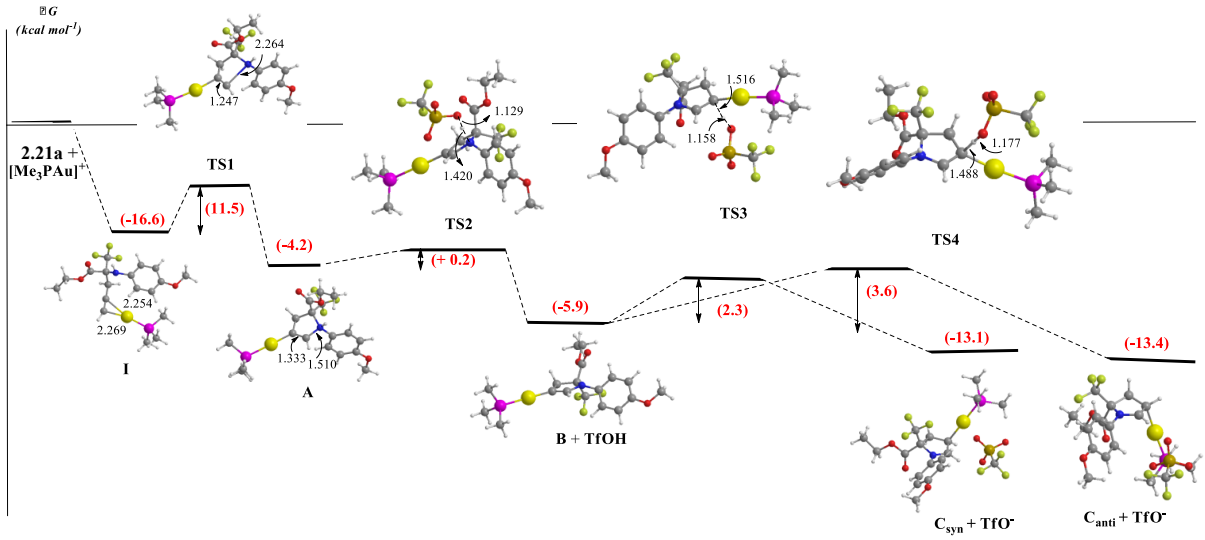


Figure 2.1. Stationary points located for the cyclization reaction of **2.21a**, leading to intermediates $\mathbf{C}_{syn}$ and $\mathbf{C}_{anti}$.

Complex **I**, corresponding to alkyne's activation by gold, shows an asymmetric coordination of the $[AuPMe_3]^+$ complex to the triple blond, and the C–C bond length is slightly increased (1.230 Å vs 1.208 Å in **2.21a**). Transition state **TS1** shows one imaginary vibrational frequency with a normal mode that corresponds to the formation of the N–C bond in a hydroamination process. The distance between the two carbon atoms, which initially corresponds to a triple bond, increases from 1.208 Å in **2.21a** up to 2.264 Å in **TS1**. Transition state **TS2**, involved in the deprotonation of intermediate **A**, shows an imaginary normal mode that corresponds to the proton transfer from the nitrogen atom of **A** to the oxygen atom of the triflate anion, then leading to the formation of intermediate **B**. As can be seen from the values of the N–H (1.420 Å) and O–H (1.129 Å) bond lengths in **TS2**, the proton has already been transferred from the nitrogen atom of **A** to the oxygen atom of the triflate. The activation Gibbs free energy for each of these reactions was calculated to be 11.5 and 0.2 kcal·mol^{-1}, respectively.

The reaction at the β-position of the enamine intermediate **B** with triflic acid, which gives rise to the diastereoisomeric iminium intermediates $\mathbf{C}_{syn}$ and $\mathbf{C}_{anti}$, takes place through two possible transition states, **TS3** or **TS4**, depending on the stereochemistry of the proton addition. The imaginary normal mode in these transition states involves both the proton transfer and the shortening of the N–C bond. **TS3**, which gives rise to intermediate $\mathbf{C}_{syn}$, presents an activation barrier of 2.3 kcal·mol^{-1};

[109] Lengths are in Å and Gibbs free energies in kcal·mol^{-1}.

whereas **TS4**, which renders intermediate $\mathbf{C}_{anti}$, is predicted to be 1.3 kcal·mol^{-1} less stable than **TS3**. On the other hand, levels of stability for both intermediates, $\mathbf{C}_{syn}$ and $\mathbf{C}_{anti}$, are similar, being this later slightly favored (0.3 kcal·mol^{-1}).

The stationary points for the deauration reaction of these intermediates are shown in *Figure 2.2*.[109] In this step, the hydroamination product **2.23a** is formed and the catalytically active species Au(Ln)OTf is regenerated. Product **2.23a** can be formed from either $\mathbf{C}_{syn}$ or $\mathbf{C}_{anti}$ *via* **TS5** and **TS6**, respectively. The imaginary normal mode in these transition states corresponds to the Au–O bond formation and the C–Au bond cleavage, as might be expected from nucleophilic attack of the triflate anion onto the AuL moiety. Deauration step from both $\mathbf{C}_{syn}$ and $\mathbf{C}_{anti}$ intermediates is slightly endothermic (-15.4 and -17.0 kcal·mol^{-1}), with activation barriers of 14.5 and 13.2 kcal·mol^{-1}.

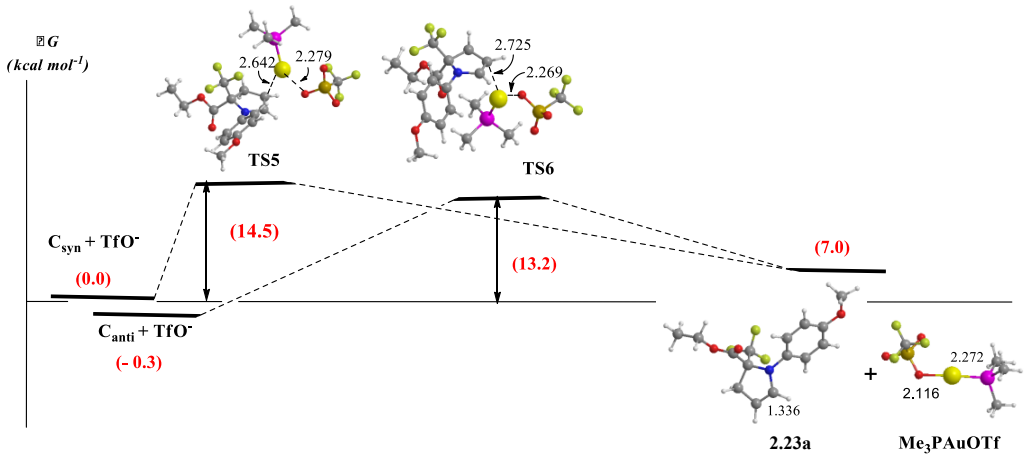
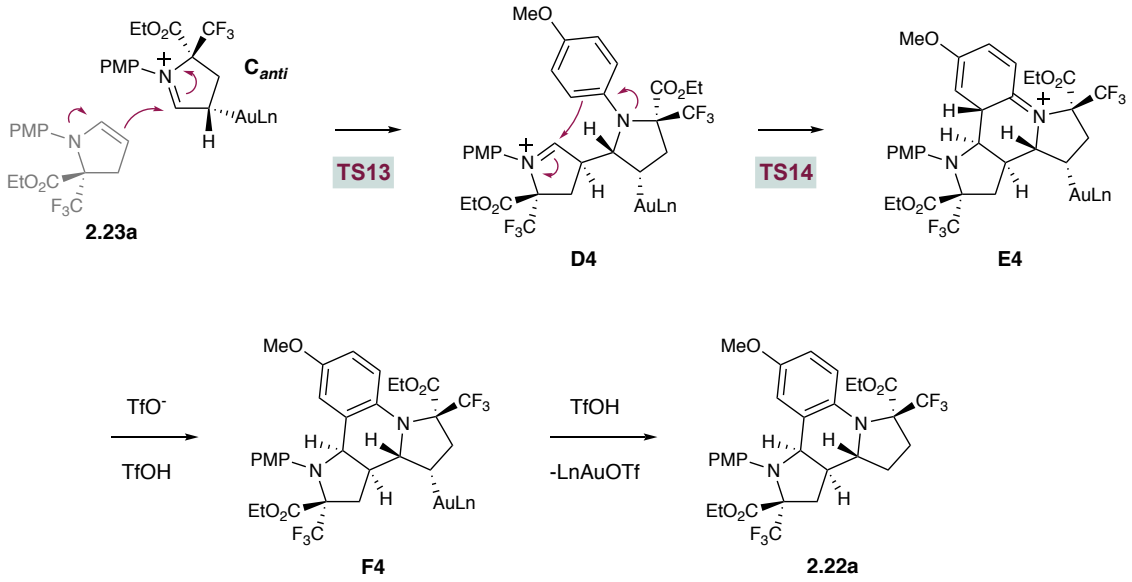


Figure 2.2. Stationary points for the deauration reaction that leads to intermediate **2.23a**, and Au(PPh_3)OTf.

After the hydroamination step, an asymmetric dimerization pathway involving hydroamination product **2.23a** and either of the iminium intermediates **C**, accounts for the formation of the tetracyclic skeleton (*Scheme 2.18*). Since both the nucleophilic carbon atom of **2.23a** and the electrophilic iminium carbon atom of **C** are prochiral, addition could lead to the formation of up to eight diastereoisomers of intermediate **D** (4 from $\mathbf{C}_{syn}$ and 4 from $\mathbf{C}_{anti}$). Then, a new enamine attack, but in an intramolecular fashion through the *ortho* position of the PMP ring, builds the tetracyclic skeleton (intermediate **E**). Overall, these last two steps may be considered together as a formal, step-wise aza-Diels Alder reaction. The triflate-promoted re-aromatization of **E** gives rise to intermediate **F** and triflic acid, which in turn will participate in the protodeauration of **F** to form the final product **2.22a**.



Scheme 2.18. Mechanistic proposal (second stage).

According to the experimental evidence, the tetracyclic structures **2.22a** were obtained in most cases as single diastereoisomers, attesting for a high level of facial stereoselectivity in the addition of **2.23a** onto iminium intermediate **C**. In *Figure 2.3*[109] are depicted the four reaction pathways with lowest Gibbs free energies for the transformation of **2.23a** into tetracyclic intermediate **E**.

For the reaction of **2.23a** with $\mathbf{C}_{anti}$ or $\mathbf{C}_{syn}$, the lowest Gibbs free energies for the first enamine attack are 27.6 (**TS17**), 28.2 (**TS7**), 29.6 (**TS9**), and 31.9 kcal·mol^{-1} (**TS13**). For **TS17** and **TS9**, intermediates **D6** and **D2** are not very stable (26.3 and 29.2 kcal·mol^{-1}), so they can easily revert back towards the reactants. On the other hand, intermediate **D1** is 3.2 kcal·mol^{-1} more stable than **TS7**. However, the Gibbs free energy for the cyclization step *via* **TS8** is very high (37.5 kcal·mol^{-1}). The reaction of **2.23a** with $\mathbf{C}_{anti}$ with a relative *Si*/*Si* approach appears as the more energetically favorable pathway, yielding intermediate **E4** preferentially.

Examination of the geometry of the transition state structures (**TS7**, **TS9**, **TS13**, **TS17**) and the corresponding intermediates (**D1**, **D2**, **D4**, **D6**) helps to shed some light on the origin of the observed stereochemical outcome. In **D1** and **D4**, the more stable intermediates, the trifluoromethyl groups appear in an *anti* relative disposition, which minimizes the steric interactions. Besides, the steric effect of the trifluoromethyl group appears to strongly destabilize the transition state structure **TS8** relative to **TS14**. The combination of these two steric effects explains the selective formation of intermediate **E4** and the observed diastereisomer of final product **2.22a**.

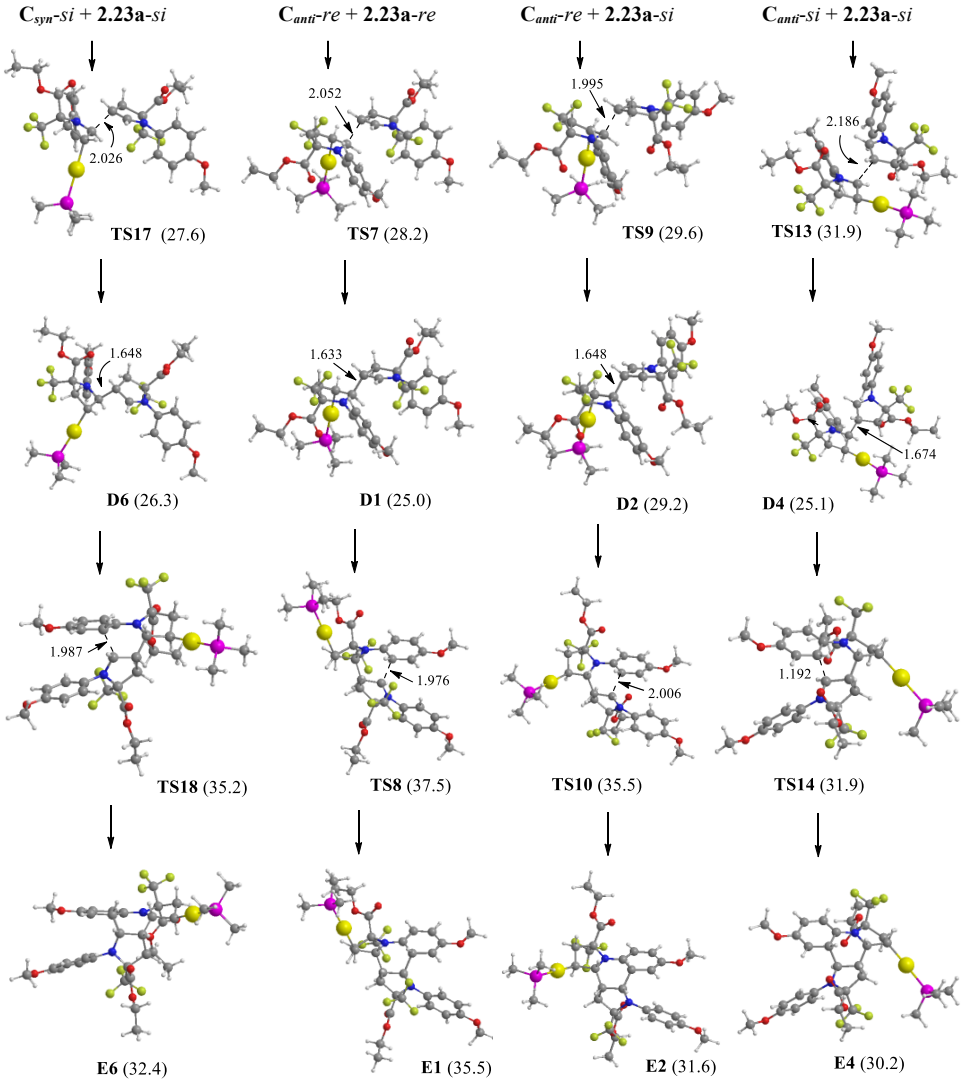
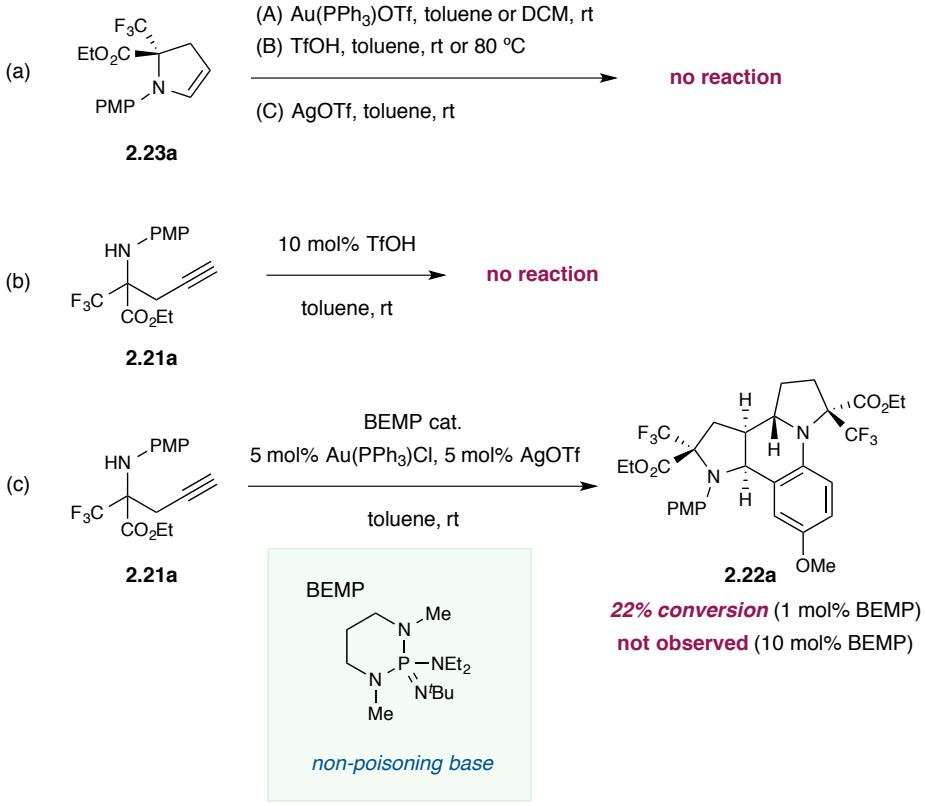


Figure 2.3. Stationary points located for the addition reaction of **2.23a** to intermediates **C**, with the specification of the reaction stereochemistry.

Considering this computational mechanistic study, the key step for the success of the tandem process is enamine attack of pyrroline **2.23** to the iminium functionality of **C**$_{anti}$. As the hydroamination product **2.23a** arises from the deauration of **C**$_{anti}$, a low rate of reaction is required in this step to increase the effective concentration of intermediate **C**$_{anti}$, enabling its reaction with **2.23a**.

Additional experiments were performed to provide further evidence for the mechanistic pathway proposed above. For instance, the formal aza-Diels Alder reaction might be further promoted by the triflic acid instead of gold. Several authors have suggested that hydroamination products analogous to **2.23a** could be protonated by triflic acid, which would give rise to iminium intermediates

of type **C**, thus initiating a dimerization protocol.[110] Likewise, it is well known that gold itself can activate enamines and enol ethers for the nucleophilic attack.[111] To prove our mechanistic proposal, substrate **2.23a** was independently treated with $Au(PPh_3)OTf$ (*Scheme 2.19a*, *conditions A*), triflic acid (*Scheme 2.19a*, *conditions B*), and silver triflate (*Scheme 2.19a*, *conditions C*). In all cases, the starting material remained unaltered, even when the reaction was heated up to 80 ºC for several hours.



Scheme 2.19. Mechanistic insights.

Alternatively, hydroamination reactions can also be promoted by Brönsted acids;[112] therefore, triflic acid could be the catalyst of the tandem protocol. However, no reaction was observed when compound **2.21a** was treated with triflic acid in toluene after 24 h at room temperature (*Scheme 2.19b*); therefore, TfOH is not the catalyst of the process. These observations are in agreement with

[110] Similar mechanistic outcomes were simultaneously reported: (a) Galván, A.; Calleja, J.; Fañanás, F. J.; Rodríguez, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 6038. (b) Ref. 97c: Yu, Y.-F.; Shu, C.; Shen, C.-H.; Li, T.-Y.; Ye, L.-W. *Chem. Asian J.* **2013**, *8*, 2920.

[111] For some representative examples, see: (a) Goutham, K.; Rao Mangina, N. S. V. M.; Suresh, S.; Raghavaiah, P.; Karunakar, G. V. *Org. Biomol. Chem.* **2014**, *12*, 2869. (b) Chiarucci, M.; di Lillo, M.; Romaniello, A.; Cozzi, P. G. Cera, G.; Bandini, M. *Chem. Sci.* **2012**, *3*, 2859. (c) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585. (d) Saito, A.; Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923.

[112] (a) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (b) Li, Z.; Zhang, J.; Brouver, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (d) Miura, K.; Hosomi, A. *Synlett*, **2003**, 143.

the relevance of intermediate **C** in the tandem process and corroborate that the hydroamination product, by itself, does not undergo the tandem protocol.

In addition, compound **2.21a** was subjected to the reaction conditions in the presence of BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), a non-poisoning base. In the presence of 10 mol% BEMP and 5 mol% $Au(PPh_3)OTf$, the reaction did not proceed and the starting material was recovered unaltered (*Scheme 2.19c*). With 1 mol% BEMP and 5 mol% $Au(PPh_3)OTf$, the rate of the reaction was slowed, and after 20 h at room temperature only 22% conversion was reached (*Scheme 2.19c*). The former experiment, with 10 mol% BEMP, indicates that all the triflic acid necessary to close the catalytic cycle is captured by this strong phosphazene base, which inhibits the tandem sequence. However, with 1 mol% BEMP, the tandem process is diminished but not eliminated at all. As the catalytic activity of gold is diminished but not eliminated, an alternative mechanism where gold species act as a Brönsted acid instead of a Lewis acid to catalyze the formal aza-Diels Alder reaction cannot be overruled.[113] Arguably, neither a Lewis acid-assisted Brönsted acid catalysis may be discarded.[61a]

With these considerations and on the basis of the above-introduced categorization of gold-catalyzed reactions reported by Bo Xu and Hammond (see *Section 2.1.1*),[66a] in the present case, deauration would be the rate-limiting step. The triflic acid present in the media, released during the generation of the catalytic gold species, will be partially neutralized by the amine; thus, decreasing the rate of the deauration step and favoring the tandem sequence.

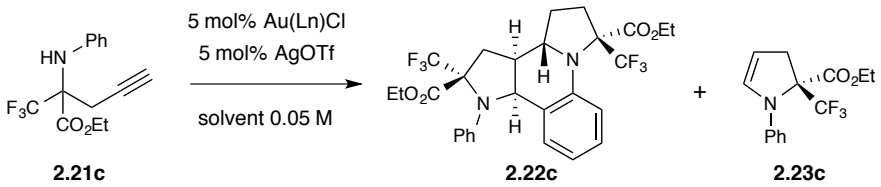
Additionally, in most of the isolated tetracycles **2.22**, the aromatic amine functionality is flanked with two electron-withdrawing groups, which compromise the basicity of the amine. However, when the aromatic substituent at the nitrogen atom is the PMP group (**2.21a**), the electon-donating properties of the methoxy group help to preserve the basicity on the nitrogen atom, which lowers the protodeauration rate, and this is subsequently translated into an improved ability for the tandem reaction to proceed. On the other hand, with less activated *para*-tolyl and phenyl groups (**2.21b**, **2.21c**), the basicity of the amine decreases, which increases the rate of deauration and, in turn, diminishes the formation of the tandem products, i.e. intermolecular enamine attack is not fast enough to compete with deauration.

According to the aforementioned studies of ligand effects on the kinetics of the deauration step, an electron-rich ligand should accelerate the deauration step. Conversely, electron-withdrawing ligands would decelerate it and, based on the previous mechanistic discussion, they would favour the tandem transformation.

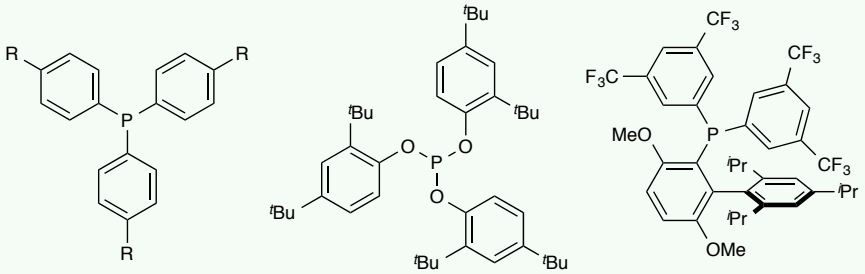
[113] The behavior of gold salts as Brönsted acids was previously invoked in gold-catalyzed processes: Yang, T.; Campbell, L; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070.

To test this hypothesis, substrate **2.21c** was subjected to the tandem reaction conditions in the presence of gold complexes bearing electronically deficient ligands relative to triphenylphosphine (*Table 2.1*, *entry 1*).

Table 2.1. Exploration of ligand effects.



entry	ligand	solvent, T	time	yield **2.22c**[a]	yield **2.23c**
1	PPh_3	toluene, 25 ºC	5 h	14%	64%
2	**L1**	toluene, 25 ºC	24 h	47%[b]	-
3	**L1**	DCM, 0 ºC	1 h	72%	<5%
4	**L2**	toluene, 25 ºC	12 h	51%	<5%
5	**L2**	DCM, 0 ºC	2 h	55%	<5%
6	**L3**	toluene, 25 ºC	1 h	48%	<5%
7	**L3**	DCM, 0 ºC	2 h	51%	<5%
8	**L3**	toluene, 0 ºC	2 h	58%	<5%
9	**L4**	toluene, 25 ºC	24 h	55%	<5%
10	**L4**	DCM, 0 ºC	15 h	53%	<5%



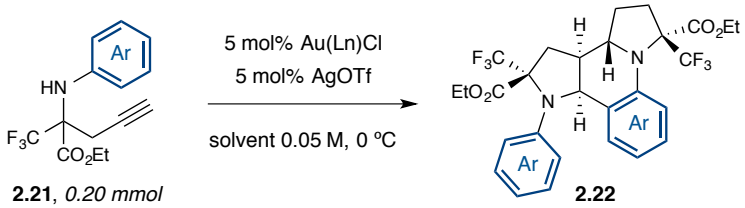
[a] Isolated yield of the major diastereoisomer. [b] 60% conversion.

In the first attempt with ligand **L1**, we observed that, after 24 h, only 60% conversion was achieved. Nevertheless, the exclusive formation of tetracycles was detected, albeit as a mixture of diastereoisomers, in which the major compound was **2.22c**, which was isolated in 47% yield (*entry 2*). The use of DCM as the solvent led to an unexpected increase in the reaction rate, with the reaction being completed in 1 h even at 0 ºC. In this case, the major isomer **2.22c** was isolated in 72% yield together with <5% yield of the hydroamination product **2.23c** (*entry 3*). Therefore, according to our

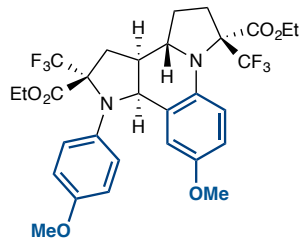
hypothesis, ligand **L1** decreases the protodeauration rate, which favours the tandem process, albeit with some erosion of the selectivity, and minimizes the formation of the hydroamination product. Following the same reaction trend, the use of ligand **L2**, provided tetracycle **2.22c** in 51% yield after 12 h in toluene, with complete conversion being achieve in this case (*entry 4*). When DCM was used as the solvent and the reaction was performed at 0 ºC, **2.22c** was isolated in 55% yield (*entry 5*). When ligand **L3**, which contains the phosphite unit with the most electron-deficient substituents, was used in the tandem reaction, either in toluene or in DCM, the reaction was completed in 2 h; however, these conditions did not improve the reaction yield (*entries 6-8*). Finally, the use of JackiePhos **L4**, afforded comparable results to **L2** in terms of reaction time and yield, in either toluene or DCM (*entries 9-10*).

We concluded that the optimum conditions to carry out the tandem process involved the use of ligand **L1** in DCM at 0 ºC, when the amino ester substrates contain non-activated or deactivated aromatic substituents attached to the nitrogen. These conditions were applied to other homopropargyl amines **2.21** and the obtained results are summarized in *Table 2.2*.

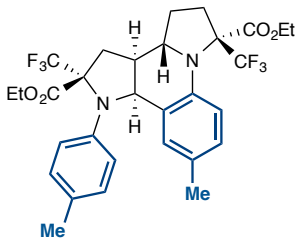
Table 2.2. Broadening the scope of the tandem protocol.[a]



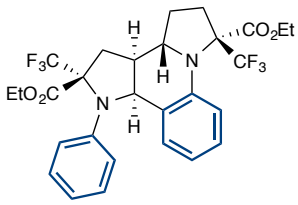
2.21, *0.20 mmol* — **2.22**



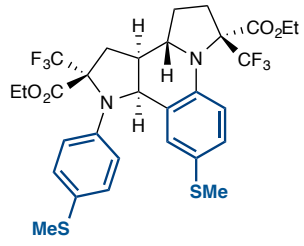
2.22a, *76% yield* (PPh_3, toluene)



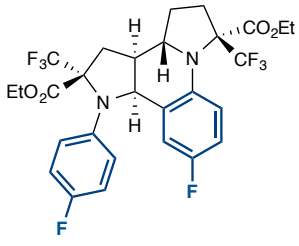
2.22b, *68% yield* (**L1**, DCM)



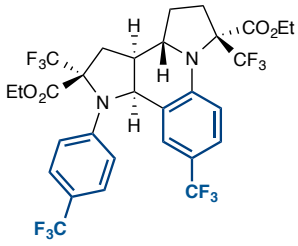
2.22c, *72% yield* (**L1**, DCM)



2.22d, *65% yield* (**L1**, DCM)



2.22e, *56% yield* (**L1**, DCM)



2.22f, *57% yield* (**L1**, DCM)

[a] Isolated yields.

Substrates **2.21b-f**, bearing a variety of electron-donating and electron-withdrawing substitutents on the aromatic ring other than PMP, underwent the tandem protocol very efficiently to afford tetracycles **2.22b-f** in good yields.

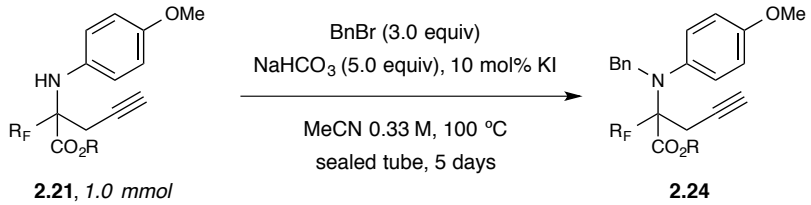
In summary, the results from the experimental ligand study and the theoretical calculations, led us to identify suitable conditions to broaden the scope of our tandem protocol, just by changing the ligand on Au(I) and the solvent.[114]

[114] Miró, J.; Sánchez-Roselló, M.; González, J.; del Pozo, C.; Fustero, S. *Chem. Eur. J.* **2015**, *21*, 5459.

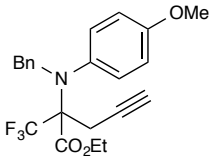
2.3.2. Gold-catalyzed synthesis of fluorinated 1,2-dihydroquinoline derivatives.

As it was mentioned above (*Scheme 2.14*), the blockage of the N–H bond of those aryl amines **2.21** by alkylation would inhibit the aforementioned tandem sequence. Instead, a hydroarylation-type reaction would be expected.[115] Nevertheless, the introduction of alkyl groups in compounds **2.21** proved to be troublesome. This is probably due to the low nucleophilicity of the nitrogen atom, since the α-carbon contains two electron-withdrawing groups. After several attempts, only substrates containing a *para*-methoxyphenyl group were alkylated in synthetically useful yields (*Table 2.3*).

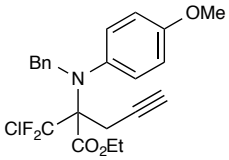
Table 2.3. Preparation of benzylated homopropargyl amino esters.[a]



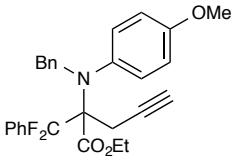
2.21, *1.0 mmol* — **2.24**



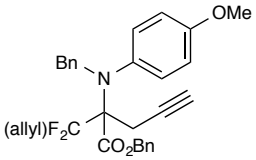
2.24a, *92% yield (58% conv)*



2.24b, *48% yield (39% conv)*



2.24c, *72% yield (64% conv)*



2.24d, *37% yield (53% conv)*

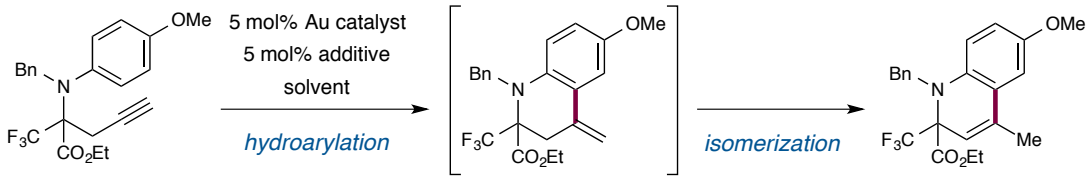
[a] Isolated yields.

Presumably, once again PMP group re-establishes the basicity of the nitrogen atom. Selected conditions involved the treatment of substrates **2.21** with benzyl bromide, using $NaHCO_3$ as base with a catalytic amount of KI in acetonitrile, heating the reaction mixture in a sealed tube at 100 ºC for 5 days. In this manner, benzylated propargyl amines **2.24** were isolated in moderate yields (*Table 2.3*).

[115] For the first example of gold-catalyzed hydroarylation, see: Hashmi, A. S. K.; Schwarz, L.; Choi, J.-Y.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285.

With these substrates in hand, compound **2.24a** was used as a model substrate to evaluate its reactivity versus gold salts (*Table 2.4*).

Table 2.4. Optimization of the tandem hydroarylation-isomerization reaction.

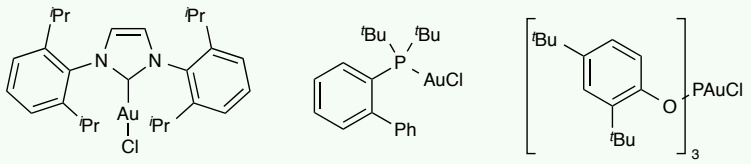


2.24a **2.25a** **2.26a**

entry	Au catalyst	additive	solvent, T	time	yield[a]	ratio **2.25a**:**2.26a**
1	AuCl	-	DCM, rt	24 h	-	-
2	$AuCl_3$	-	DCM, rt	24 h	-	-
3	**I**	AgOTf	DCM, rt	4 h	69%	1:1
4	**I**	AgOTf	MeCN, 85 ºC	12 h	48%	1:1
5	**I**	AgOTf	MeOH, 65 ºC	10 h	28%	1:4
6	**I**	AgOTf	toluene, rt	9 h	38%	1:2
7	**I**	$AgNTf_2$	DCM, rt	24 h	45%	1:1
8	**I**	$AgSbF_6$	DCM, rt	6 h	47%	0:1
9	**I**	$AgBF_4$	DCM, rt	4 h	30%	0:1
10	**II**	AgOTf	DCM, rt	1 h	57%	0:1
11	**III**	AgOTf	DCM, rt	1 h	40%	0:1
12	**IV**	AgOTf	DCM, rt	3 h	41%	0:1
13	**V**	AgOTf	DCM, rt	0.5 h	90%	0:1
14	-	AgOTf	DCM, rt	24 h	-	-
15	-	TfOH	DCM, rt	24 h	-	-

I, $Au(PPh_3)Cl$

II, $Au[P(4\text{-}CF_3\text{-}C_6H_4)_3]Cl$



III, Au(IPr)Cl **IV** **V**

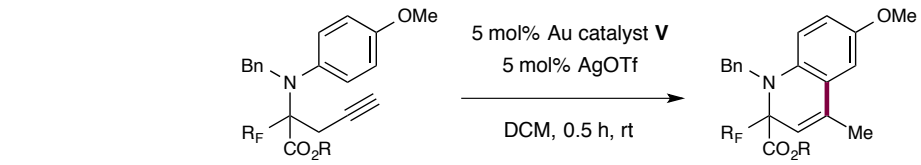
[a] Isolated yield.

With AuCl and $AuCl_3$ as the gold source, substrate **2.24a** was inert (*entries 1-2*). The change to $Au(PPh_3)Cl$ was critical, and an equimolecular mixture of **2.25a** and **2.26a** was detected in 69% yield (*entry 3*), this later arising from the isomerization of the former hydroarylation product **2.25a**. The use of other solvents and temperatures was traduced in an improvement of the **2.25a**:**2.26a** ratio, but in detriment of the final yield (*entries 4-6*). Other silver salts again yielded a better **2.25a**:**2.26a** ratio, but in moderate yields (*entries 7-9*). Finally, the influence of the gold species was evaluated

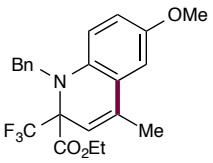
(*entries 10-13*). Among them, gold complex **V**, with a phosphite ligand, gave the best result in terms of yield and **2.25a**:**2.26a** ratio (*entry 13*). Worthy to note, neither the silver salt itself, nor triflic acid, catalyze the process (*entries 14-15*).

Optimized conditions were further extended to the rest of substrates **2.24**, giving rise to a new family of fluorinated dihydroquinoline derivatives **2.26** (*Table 2.5*).

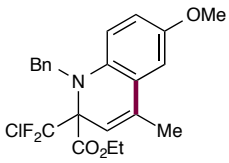
Table 2.5. Gold-catalyzed tandem hydroarylation-isomerization scope.[a]



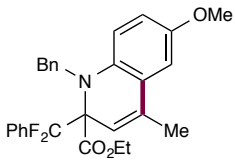
2.24, *0.12 mmol* — **2.26**



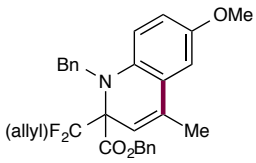
2.26a, *90% yield*



2.26b, *91% yield*



2.26c, *53% yield*



2.26d, *75% yield*

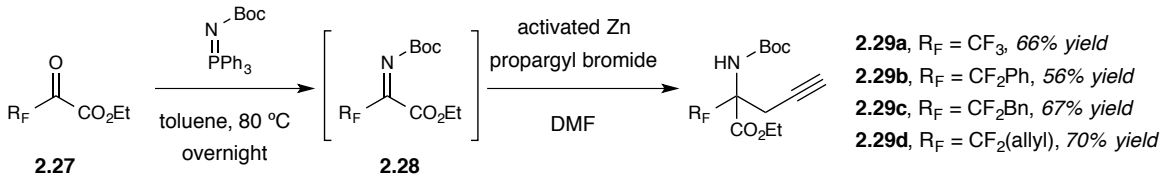
[a] Isolated yields.

To summarize, when starting amino esters bearing an aromatic substituent were benzylated at the nitrogen atom, the reaction with Au(I) species led to the formation of a new family of fluorinated dihydroquinolines **2.26** in a tandem hydroarylation-isomerization sequence.[116]

[116] (a) Sánchez-Roselló, M.; Miró, J.; del Pozo, C.; Fustero, S. *J. Fluorine Chem.* **2015**, *171*, 60. A similar hydroarylation process with fluorinated propargyl amines was previously reported: (b) Zhu, M.; Fu, W.; Zou, G.; Xun, C.; Deng, D.; Ji, B. *J. Fluorine Chem.* **2012**, *135*, 195.

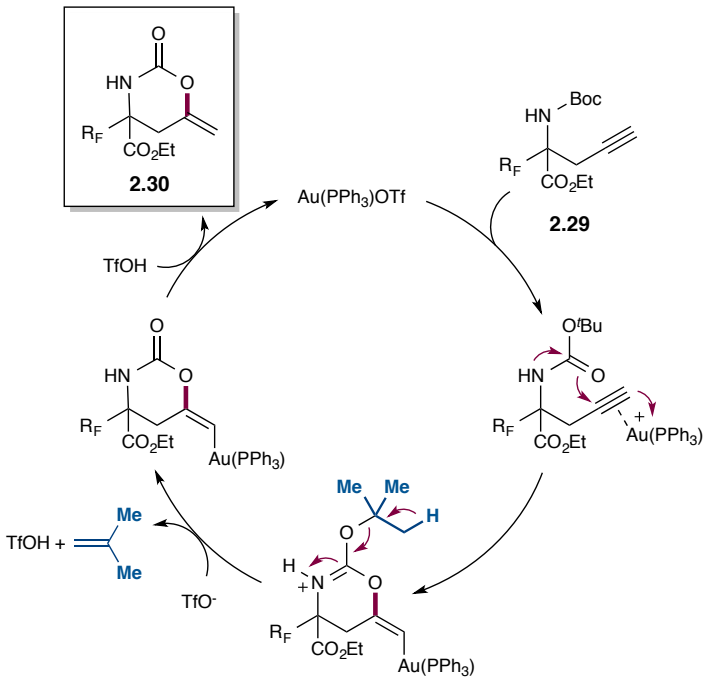
2.3.3. Gold-catalyzed *O*-addition with concomitant loss of isobutene.

We then synthesized the corresponding starting materials bearing a carbamate as the nitrogen protecting group (*Scheme 2.20*). Ketoesters **2.27** were treated with Boc-phosphazene **2.28** to render the corresponding *N*-Boc-imino esters **2.29** that were propargylated *in situ*, without further purification, to avoid decomposition.



Scheme 2.20. Preparation of starting *N*-Boc-propargyl amino esters.

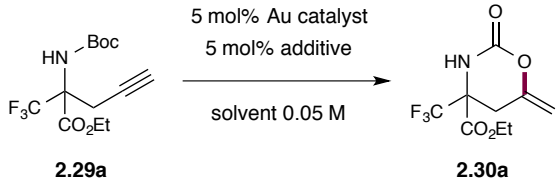
Using compound **2.29a** as model substrate, we tested its reactivity versus gold species (*Table 2.6*). First attempts with AuCl and $AuCl_3$, provided moderate yields of a six membered-ring carbamate **2.30a** with an exocyclic double bond (*entries 1-2*), derived from the carbonyl addition over the activated triple bond with concomitant loss of the *tert*-butyl moiety as isobutene (*Scheme 2.21*), i.e. the same reactivity pattern shown by its non-fluorinated counterparts.[97k]



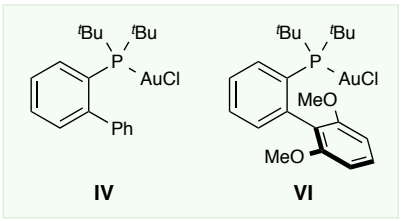
Scheme 2.21. Proposed mechanism.

A significant improvement was observed with $Au(PPh_3)Cl$, giving rise to **2.30a** in 71% yield in only 30 min (*entry 3*). The yield increased up to 91% when the reaction was performed in toluene (*entry 5*). The use of other gold species (*entries 6-7*) or other silver salts (*entries 8-10*) did not improve the efficiency of the reaction.

Table 2.6. Optimization of the gold-mediated carbonyl addition.



2.29a **2.30a**



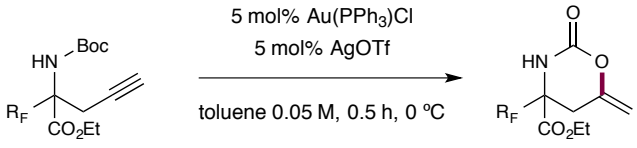
IV **VI**

entry	Au catalyst	additive	solvent, T	time	yield[a]
1	AuCl	-	DCM, rt	20 h	58%
2	$AuCl_3$	-	DCM, rt	20 h	35%
3	$Au(PPh_3)Cl$	AgOTf	DCM, 0 ºC	0.5 h	71%
4	$Au(PPh_3)Cl$	AgOTf	MeCN, rt	20 h	56%
5	$Au(PPh_3)Cl$	AgOTf	toluene, 0 ºC	0.5 h	91%
6	**IV**	AgOTf	toluene, 0 ºC	20 h	63%
7	**VI**	AgOTf	toluene, 0 ºC	0.5 h	73%
8	$Au(PPh_3)Cl$	$AgNTf_2$	toluene, 0 ºC	1 h	71%
9	$Au(PPh_3)Cl$	$AgSbF_6$	toluene, 0 ºC	1 h	80%
10	$Au(PPh_3)Cl$	$AgBF_4$	toluene, rt	20 h	37%

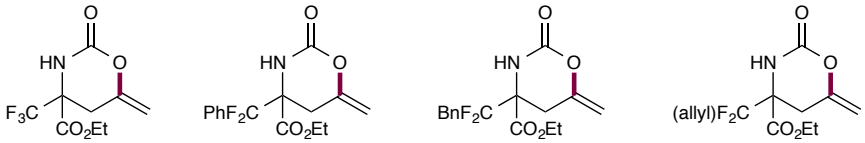
[a] Isolated yield.

Optimized condition were further extended to the rest of substrates **2.29**, giving rise to a small family of fluorinated oxazinanone derivatives **2.30** (*Table 2.7*).[116a]

Table 2.7. Scope of the gold-catalyzed cyclization.[a]



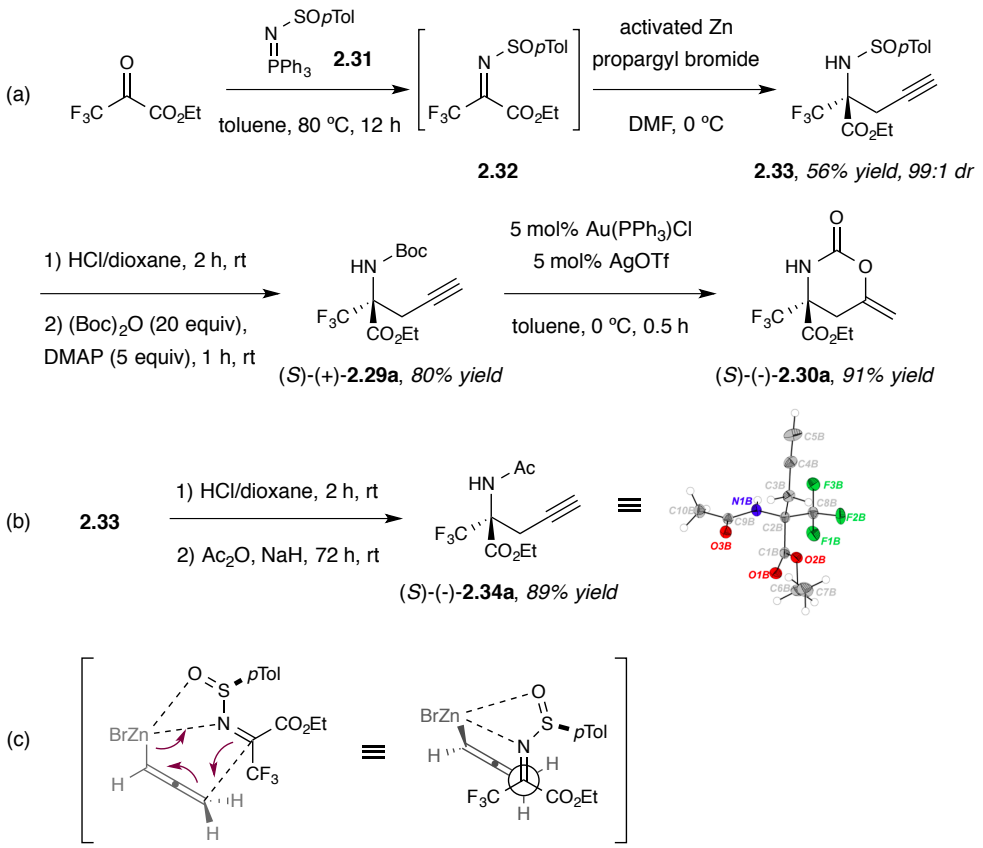
2.29, *0.20 mmol* **2.30**



2.30a, *91% yield* **2.30b**, *88% yield* **2.30c**, *71% yield* **2.30d**, *77% yield*

[a] Isolated yields.

The next step of our study was an asymmetric version of this sequence (*Scheme 2.22*). To this end, *para*-toluenesulfinyl amide was used as chiral auxiliary. Thus, ethyl trifluoropyruvate was subjected to an aza-Wittig reaction with chiral phosphazene **2.31**. The corresponding imino ester **2.32** was treated *in situ* with propargyl bromide and activated zinc in DMF under *Barbier*-type conditions. The addition of propargyl zinc was completely selective, affording homopropargyl sulfinyl amine **2.33** as a single diastereoisomer. Chiral auxiliary was removed and nitrogen reprotected with Boc to obtain the enantiomerically pure substrate (*S*)-(+)-**2.29a**. When **2.29a** was subjected to the optimized reaction conditions, the corresponding carbamate (*S*)-(-)-**2.30a** was obtained in excellent yield (*Scheme 2.22a*). Absolute configuration of the newly created stereocenter could be determined by X-ray analysis of the corresponding acetyl derivative **2.34a**, in turn obtained from sulfinyl amine **2.33** (*Scheme 2.22b*). The observed selectivity can be rationalized assuming the transition state depicted in *Scheme 2.22c*, in analogy with either proposed by Yus and Foubelo,[117] where zinc is doubly chelated.



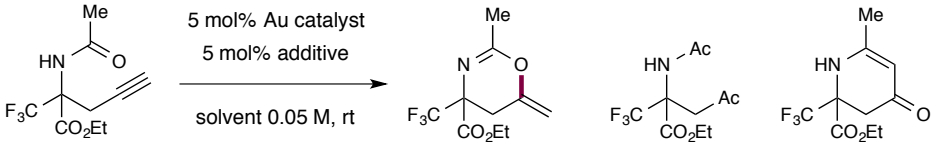
Scheme 2.22. (a) Asymmetric preparation of oxazine (*S*)-(-)-**2.30a**. (b) Absolute configuration. (c) Proposed transition state.

[117] García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2013**, 1287.

2.3.4. Tandem gold self-relay catalysis for the synthesis of dihydropyridinones. Combining σ and π Lewis acid properties of gold species.

Tert-butyl carbamate derivatives **2.29** can be easily converted into the corresponding homopropargyl amides **2.34**, giving access to a new candidate ready to extend our differential reactivity study. Compound **2.34a** was used as a model substrate to evaluate the reactivity towards gold species (*Table 2.8*).

Table 2.8. Reactivity of homopropargyl acetamide **2.34a** *vs* Au species.[a]



2.34a **2.35a** **2.36a** **2.37a**

entry	Au catalyst	additive	solvent	time	**2.35a** yield	**2.36a** yield	**2.37a** yield
1	$AuCl_3$	-	DCM	24 h	40%	40%	-
2	AuCl	-	DCM	24 h	37%	35%	-
3	$Au(PPh_3)Cl$	AgOTf	DCM	3 h	57%	30%	-
4	$Au(PPh_3)Cl$	$AgNTf_2$	DCM	6 h	50%	30%	-
5	$Au(PPh_3)Cl$	AgOTf + 3 A MS	DCM	3 h	73(83)%[b]	-	-
6	-	AgOTf	DCM	24 h	-	-	-
7	-	TfOH	DCM	24 h	-	-	-
8	$Au(PPh_3)Cl$	AgOTf	toluene	24 h	25%[c]	35%	-
9	$Au(PPh_3)Cl$	AgOTf	MeCN	22 h	35%[c]	34%	-
10	$Au(PPh_3)Cl$	AgOTf	MeOH	3 h	-	-	93%
11	$Au(PPh_3)Cl$	$AgNTf_2$	MeOH	5 h	-	-	87%
12	AuCl	-	MeOH	24 h	-	33%	47%

[a] Isolated yields. [b] Yield determined by GC-MS in brackets. [c] Incomplete conversion.

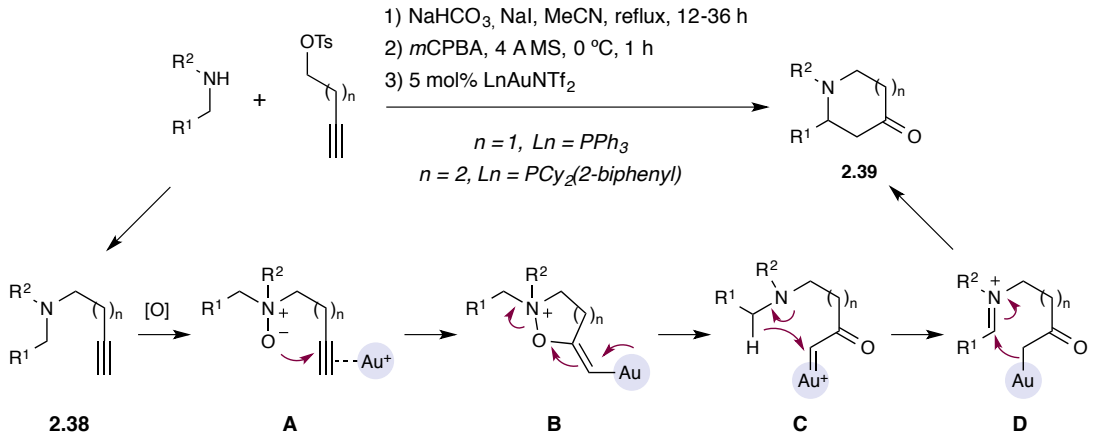
Initially, we treated substrate **2.34a** with $AuCl_3$ in DCM at room temperature. Oxazine **2.35a**, which arises from the addition of the carbonyl group to the triple bond according to the "classical" reactivity imparted by gold salts as soft π-carbophilic Lewis acids,[118] was obtained after 24 hours in 40% yield, besides 40% of **2.36a**, which comes from the hydration of the alkyne (*entry 1*). Similar results were obtained with AuCl (*entry 2*). However, the use of $Au(PPh_3)Cl$ in combination with AgOTf, led to a drastic decrease in reaction time. Total consumption of the starting material was observed after 3 hours, and oxazine **2.35a** was isolated in 57% yield, again with the acetyl derivative

[118] For a preceding example of gold-catalyzed oxazine synthesis, see: Hashmi, A. S. K.; Schuster, A. M.; Litters, S.; Rominger, F.; Pernpointner, M. *Chem. Eur. J.* **2011**, *17*, 5661.

2.36a (*entry 3*). The use of different silver salts led to comparable results (*entry 4*). At this point, it is important to mention that TLC (thin-layer chromatography) analysis revealed that product **2.36a** was derived from oxazine **2.35a** and it can be assumed to be formed from traces of water present in the reaction medium. The addition of molecular sieves 3 Å was enough to avoid hydrolysis, leading to a significant improvement in final yield (*entry 5*). Although the yield determined by GC-MS was 83%, the yield of the isolated oxazine **2.35a** was 72%, thus indicating that this compound is labile and decomposes during purification. Substrate **2.34a** was inert either in the presence of the silver salt or triflic acid, thus indicating the role of gold in catalyzing the reaction (*entries 6-7*). We then evaluated the effect of solvent. The use of toluene or acetonitrile diminished efficiency of the process (*entries 8-9*). However, the use of methanol gave a surprising result, in which the exclusive formation of dihydropyridinone **2.37a** was observed in excellent yield after 3 hours (*entry 10*). The use of silver triflimide gave comparable results, although with longer reaction times (*entry 11*). On the other hand, it took 24 h to complete the process when AuCl was used in methanol (*entry 12*). Moreover, in this case, dihydropyridinone **2.37a** was obtained besides **2.36a**.

Notably, accessed dihydropyridinone **2.37a** appears as a novel fluorinated analogous of the non-proteinogenic pipecolic acid. Furthermore, piperidine scaffold is a structural motif present in a large variety of biologically active natural alkaloids and drugs.[119] Several methodologies have been published giving access to this skeleton. In fact, later reported strategies are based on gold-catalyzed transformations.

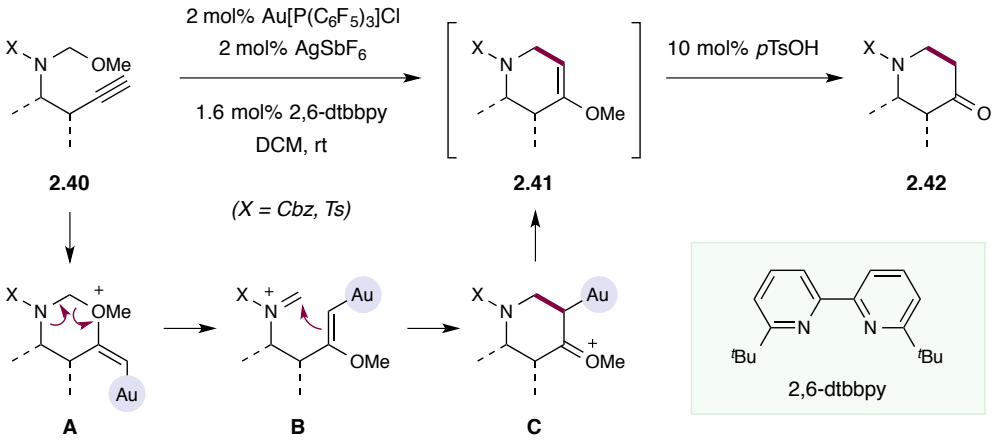
For instance, the Zhang group developed a one-pot synthesis of 4-piperidinones *via* a formal [4+2] cycloaddition (*Scheme 2.23*).[120] Once nitrone **A** is generated, gold catalyst promotes *O*-transference over the triple bond, rendering 4-piperidinone **2.39** after cycloisomerization.



Scheme 2.23. Previous work by Zhang (2009).

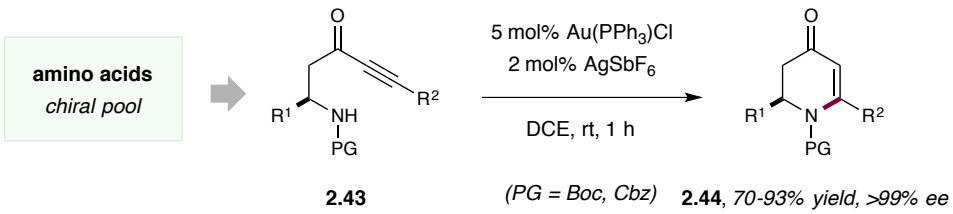
[119] (a) Comins, D. L.; O'Connor, S.; Al-awar, R. S. In *Comprehensive Heterocyclic Chemistry III*, (Eds: R. K. Alan, A. R. Christopher, F. V. S. Eric, J. K. T. Richard), ELSEVIER: Oxford, **2008**; p 41. (b) Buffat, M. G. P. *Tetrahedron*, **2004**, *60*, 1701. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron*, **2003**, *59*, 2953.
[120] Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394.

Alongside, Rhee demonstrated these heterocycles (**2.42**) were also readily accessible by means of a gold-catalyzed formal aza-Prins cyclization over mixed acetals **2.40** derived from homopropargyl amines (*Scheme 2.24*).[97j]



Scheme 2.24. Previous work by Rhee (2009).

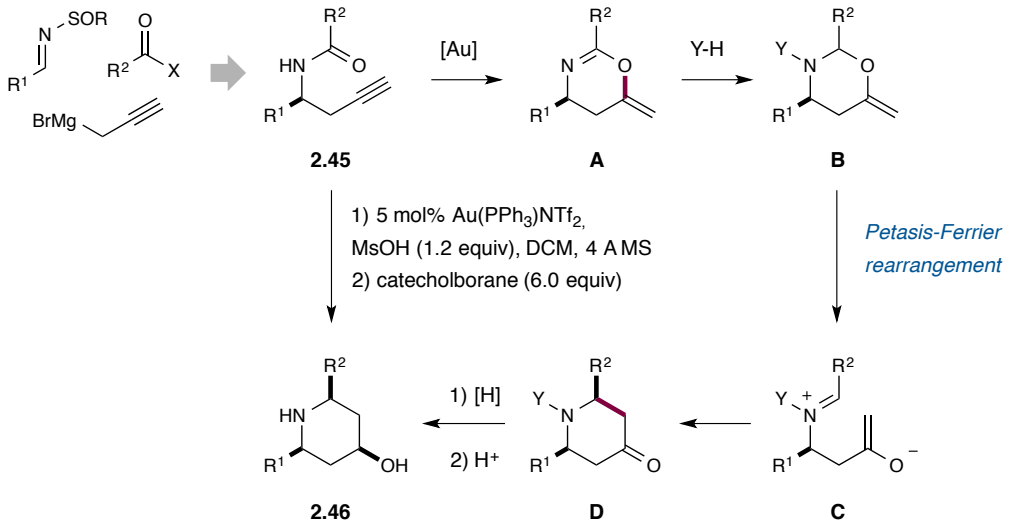
In 2011, Gouault *et al.* described the preparation of enantioenriched dihydropyridinones **2.44** by means of an intramolecular hydroamination reaction starting from chiral β-amino ynones **2.43** (*Scheme 2.25*).[121]



Scheme 2.25. Previous work by Gouault (2011).

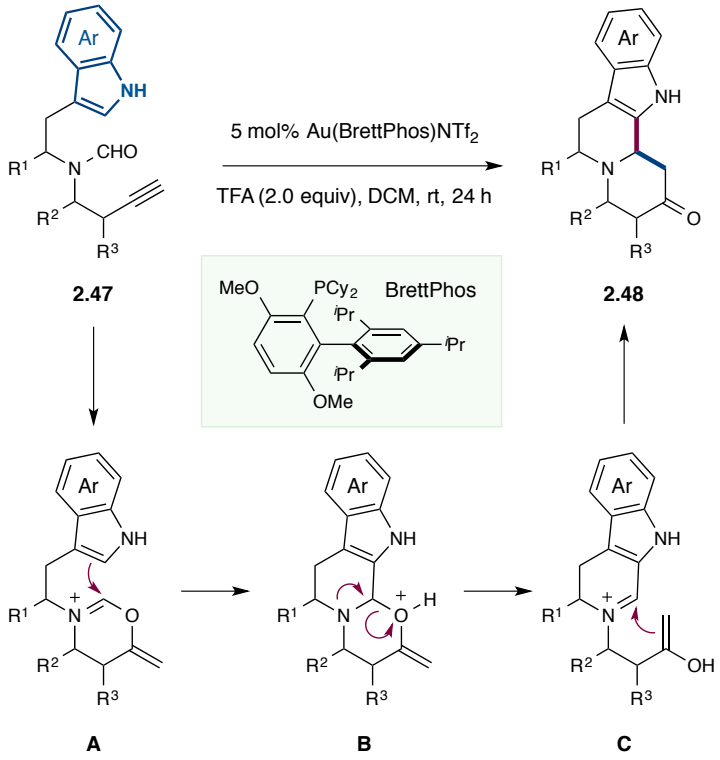
On the other hand, Zhang and coworkers reported that the alkyne moiety of *N*-homopropargyl amides **2.45** can be activated by gold, thus promoting addition of a carbonyl group to furnish the oxazine skeleton **A**. Furthermore, due to their high lability, these compounds were reduced *in situ* with catecholborane to the hemiaminal **B**, which in turn underwent a spontaneous aza-Petasis-Ferrier rearrangement, rendering piperidinones **D** and final reduction to the corresponding 4-piperidinols **2.46** (*Scheme 2.26*).[97i]

[121] Gouault, N.; Le Roch, M.; Cheignon, A.; Uriac, P.; David, M. *Org. Lett.* **2011**, *13*, 4371.



Scheme 2.26. Previous work by Zhang (2010).

They further extended this methodology to alternative nucleophiles instead of hydride. Moreover, the installation of the nucleophile over the amide group, enabled the preparation of bicyclic piperidinones **2.48**.[97e] Better results were obtained using indoles such as nucleophiles and formyl amides in order to minimize steric effects towards nucleophilic attack (*Scheme 2.27*).

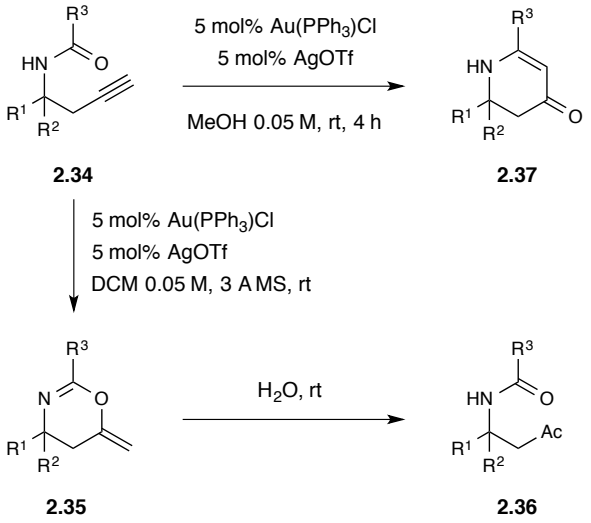


Scheme 2.27. Previous work by Zhang (2012).

Among reported gold-catalyzed reactions to access to this piperidine scaffold, our autocatalysis proposal fulfils the principle of synthetic efficiency.

With these results, we then decided to survey the scope of the process (*Table 2.9*).

Table 2.9. Preparation of oxazines **2.35**, acetyl derivatives **2.36**, and dihydropyridinones **2.37**.[a,b]



entry	R^1	R^2	R^3	**2.35** yield	**2.36** yield	**2.37** yield
1	CF_3	CO_2Et	Me	**2.35a**, 72(83)%	**2.36a**, 99%	**2.37a**, 93%
2	CF_2Ph	CO_2Et	Me	**2.35b**, 70(86)%	**2.36b**, 99%	**2.37b**, 93%
3	CF_2Bn	CO_2Et	Me	**2.35c**, 80(94)%	**2.36c**, 99%	**2.37c**, 80%
4	CF_2(allyl)	CO_2Et	Me	**2.35d**, 88(98)%	**2.36d**, 99%	**2.37d**, 94%
5	CF_3	CO_2Et	Et	**2.35e**, 61(95)%	**2.36e**, 99%	**2.37e**, 70%[c]
6	Ph	CO_2Et	Me	**2.35f**, 76%	**2.36f**, 84%	**2.37f**, 75%
7	CF_3	Ph	Me	**2.35g**, 74%	**2.36g**, 99%[d]	**2.37g**, 76%[d]
8	Ph	H	Me	-[e]	-	-

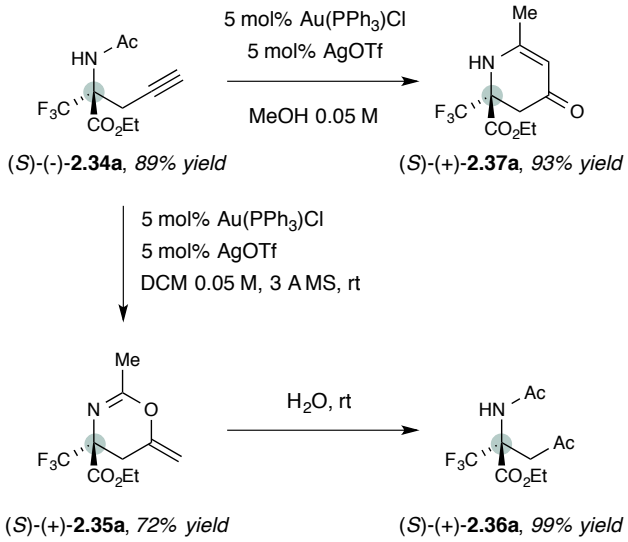
[a] Isolated yields. [b] Yield determined by GC-MS is given in brackets. [c] The formation of 28% of **2.36e** was also observed. [d] Hydrolysis required the addition of 5 mol% of $Au(PPh_3)$-Cl to activate oxazine **2.35g**. [e] The substrate remained unaltered in MeOH.

Thus, when homopropargyl amides **2.34** were treated with $Au(PPh_3)Cl$ in combination with AgOTf in DCM in the presence of molecular sieves, a clean formation of oxazines **2.35** was observed. Given their readily hydrolysis, these compounds partially decompose during purification, but was possible to obtain good yields of the isolated products. Hydrolysis of oxazines **2.35** took place in almost quantitative yields in all cases to render the formal alkyne's hydration products **2.36**. We might say that triple bond's hydration is assisted by the carbonyl moiety, throughout oxazine's formation and subsequent hydrolysis. As mentioned above, the solvent played a crucial role in the process, and the exclusive formation of dihydropyridinones **2.37** in MeOH was observed in good to excellent yields.

Thus, this protocol was extensive to both fluorinated (*entries 1-5*) and non-fluorinated (*entry 6*) ketoesters, other alkyl amides (*entry 5*), and even to ketimines (*entry 7*), obtaining the *O*-addition products **2.35**, alkyne's hydration diacetyls **2.36** and final dihydropyridinones **2.37** in general good yields.

In all cases, a quaternary center is present in the starting amides **2.34**. The reactivity of substrates arising from non-fluorinated aldimines was previously described.[97i] However, this type of substrates was inert under our conditions (*entry 8*), even in the presence of acidic additives to prevent the complexation of gold by the basic nitrogen atom. As in the tandem hydroamination-formal aza-Diels Alder reaction, the presence of the quaternary center plays a significant role, but we do not have an explanation so far for this different behaviour.

As for the carbamate derivatives, the employment of sulfinyl imines led us to access those entities in an enantiomerically pure form (*Scheme 2.28*). After completely selective addition of propargyl zinc to sulfinyl imine **2.32**, protecting group removal and acetylation led to the starting amide **2.34a** in enantiomerically pure form. Reaction of **2.34a** with $Au(PPh_3)OTf$ gave oxazine **2.35a** in DCM, acetyl derivative **2.36a** upon hydrolysis, and dihydropyridinone **2.37a** in MeOH.



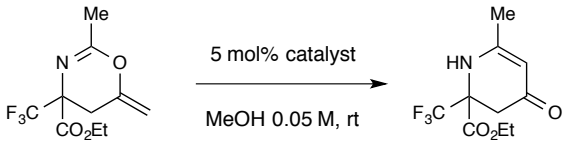
Scheme 2.28. Asymmetric version.

At this point, we decided to carry out some essays that shed some light onto the formation of the dihydropiridinone core **2.37**. Firstly, we discarded the low probable hypothesis that the hydration product was involved in its formation. Under initial conditions, diacetylated product **2.36a** remains unaltered after 24 hours.

On the other hand, TLC analysis confirmed the intermediacy of oxazine **2.35** when the reaction was performed in methanol, since we detected its formation and subsequent disappearance.

Thereby, it was clear that the first part of this transformation proceeded according to the "classical" reactivity exhibited by gold species as soft carbophilic π-Lewis acids; but, we were intrigued if gold, silver or even triflic acid might be involved in the evolution from the oxazine intermediate **2.35a** to the final dihydropyridinone **2.37a** (*Table 2.10*).

Table 2.10. Transformation of oxazine **2.35a** into dihydropyridinone **2.37a**.



2.35a **2.37a**

entry	catalyst	time	yield[a]
1	-	24 h	-
2	TfOH	6 h	61%
3	AgOTf	24 h	-
4	$Au(PPh_3)Cl/AgOTf$	0.5 h	71%
5	$BF_3{\cdot}OEt_2$	4 h	84%

[a] Isolated yield after column chromatography.

When oxazine **2.35a** was dissolved in dry methanol, it remained unaltered after 24 h at room temperature (*entry 1*). When a catalytic amount of triflic acid was added to the reaction mixture, total consumption of the starting material was observed after 6 hours, giving rise to **2.37a** in 61% yield (*entry 2*). On the other hand, the reaction in the presence of silver triflate did not proceed (*entry 3*). A completely different situation emerged with the addition of $Au(PPh_3)Cl$ in combination with AgOTf. The reaction was completed after 30 minutes, affording **2.37a** in 71% yield (*entry 4*). Finally, the use of a Lewis acid such as $BF_3{\cdot}OEt_2$ gave rise to the final product **2.37a** in 4 h and 84% yield (*entry 5*). These results hint the likely role displayed by gold species at the second stage of the process.

As it was discussed above (see *Section 2.1.1*), while great part of gold-catalyzed reactions stand on its ability to act as soft Lewis acids activating C–C multiple bonds, its competency towards the formation of σ-complexes with heteroatoms was also proved.

The dual role imparted by gold is supported by the use of AuCl as a suitable catalyst for the tandem sequence (*Table 2.8*, *entry 12*). Nevertheless, with this neutral species, softer than cationic $Au(PPh_3)OTf$, σ-activation is less efficient, which is traduced in longer reaction times and the appearance of some hydration product. The same effect was observed using silver triflimide that renders less cationic (softer) gold complexes (*Table 2.8*, *entry 11*). Furthermore, a Lewis acid such as

boron trifluoride was able to promote oxazine conversion into final dihydropyridinone (*Table 2.10*, *entry 5*), depicting the likely role played by gold.

Thereafter, we decided to firmly establish the ability of gold complex $Au(PPh_3)OTf$ to perform a σ-activation. For this purpose, we planned the isolation of an hypothetical intermediate complex of $Au(PPh_3)OTf$ with oxazine **2.35**, thus proving the identity of the involved species. To this end, oxazine **2.35a** was treated with 1.0 equivalents of the gold complex, previous filtration of the AgCl salt, in $CDCl_3$. After 10 minutes, clean formation of a new gold-oxazine species in 1:1 stoichiometry was observed by NMR. ^{1}H NMR signals of oxazine **2.35a**·$Au(PPh_3)OTf$ appeared shifted downfield when comparing with free oxazine **2.35a** (*Figure 2.4*), in agreement with a σ-coordination with the cationic gold species.

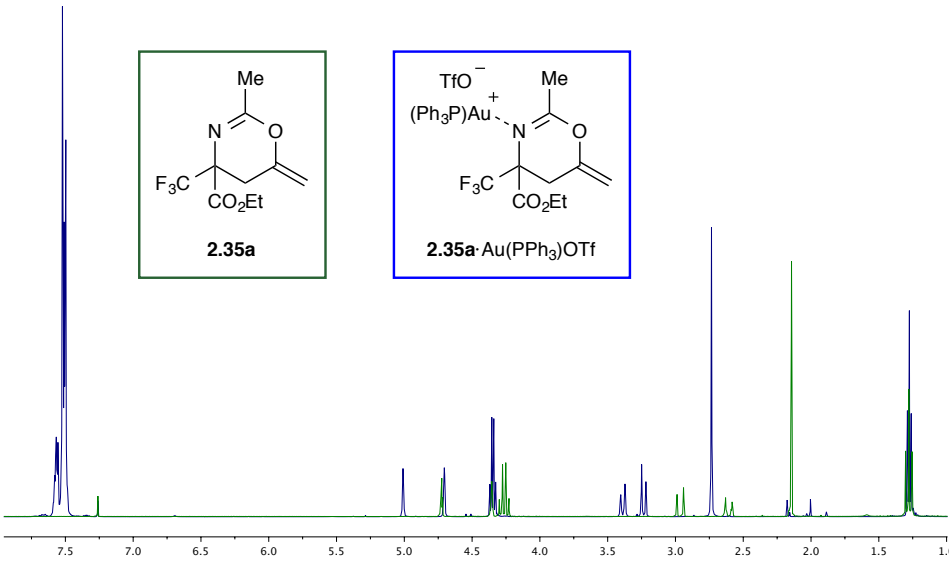


Figure 2.4. ^{1}H NMR of oxazine **2.35a** and gold-oxazine complex **2.35a**· $Au(PPh_3)OTf$.

Even more illustrative were the shifts registered in ^{13}C NMR, depicted in the below presented residual plot (*Figure 2.5*). In agreement with higher deviations registered for **a** and **b** carbon atoms, we hypothesized gold species was likely forming a σ-complex with oxazine **2.35a** through its imidate group. On the other hand, deviations registered for **c** and **d** carbon centers might be explained regarding to π-conjugation, once gold is coordinated to imidate group.

It is worth noting that although this σ-coordination is represented as a complexation through the nitrogen atom, gold coordination through the oxygen atom of the imidate group cannot be ruled out.

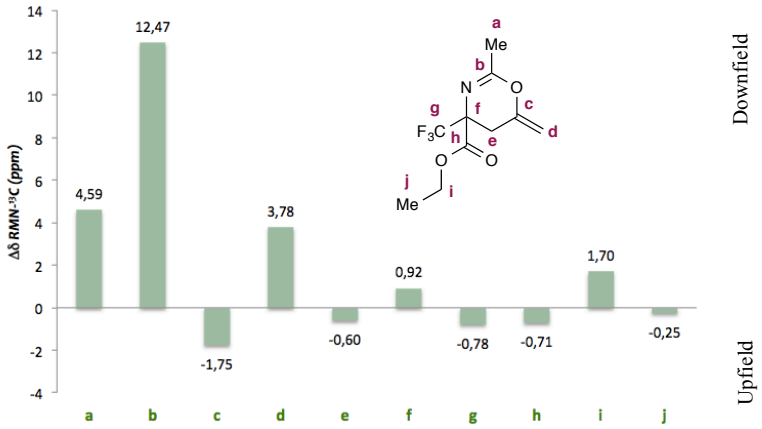
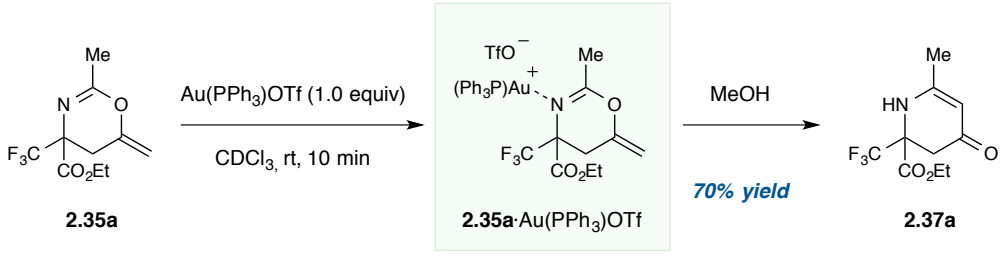


Figure 2.5. Residual plot for ^{13}C NMR shift differences between **2.35a** and **2.35a**·Au(PPh$_3$)OTf.

In addition, ^{31}P NMR spectroscopic analysis showed a singlet at δ 29.6 ppm, shifted lowfield in comparison with the signal for free Au(PPh$_3$)OTf, which appears at δ 27.5 ppm, according to its less cationic character after forming the σ-complex with oxazine **2.35a**. ^{19}F NMR analysis revealed two signals corresponding to the trifluoromethyl groups from the oxazine moiety and the triflate counterion. Low resolution mass spectrometric analysis (MALDI-TOF, matrix-assisted laser desorption ionization-time of flight) spectra indicated the existence of complex **2.35a**·Au(PPh$_3$)OTf, m/z 710.27. As expected, complex **2.35a**·Au(PPh$_3$)OTf turned into dihydropyridinone **2.37a** after removal of the solvent and the addition of methanol (*Scheme 2.29*).[122]

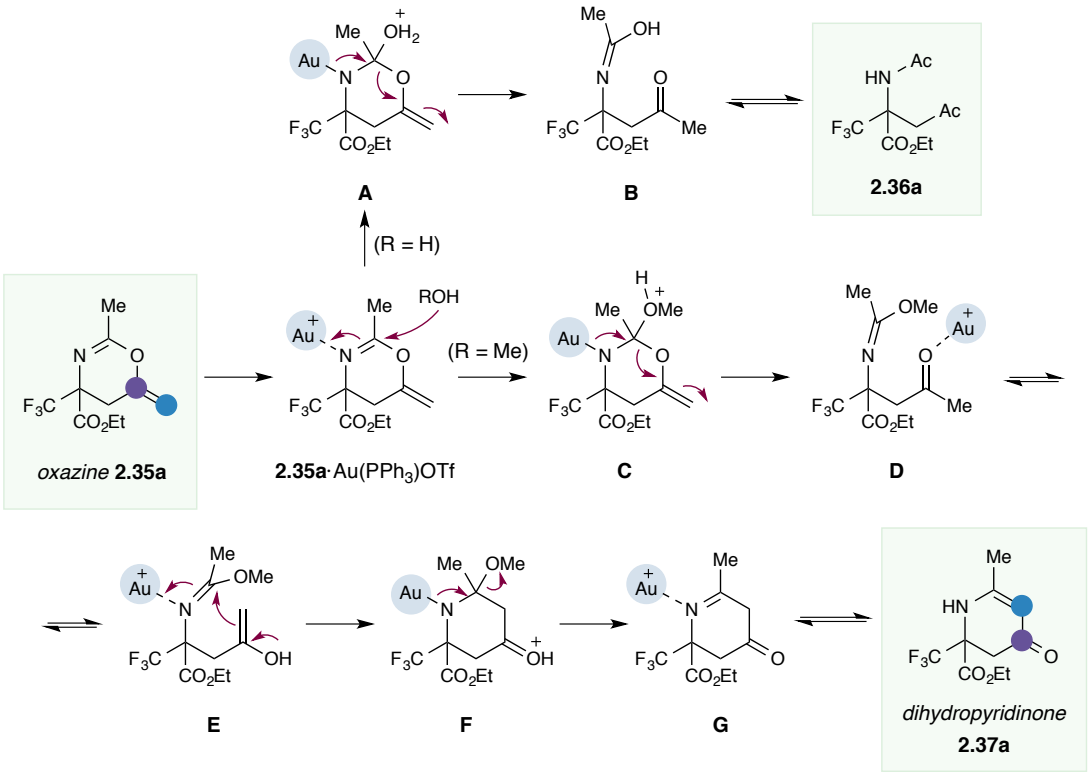


^{31}P NMR 29.6 (s) ppm
^{19}F NMR -73.6 (br s), -78.5 (s) ppm
LRMS (MALDI-TOF) 710.27

Scheme 2.29. Preparation of σ gold complex **2.35a**·Au(PPh$_3$)OTf.

[122] Although several gold intermediates were previously isolated, most of them are related to the π-Lewis acidity of gold species. (a) Liu, L.-P.; Hammond, G. B. *Chem. Soc. Rev.* **2012**, *41*, 3129. (b) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.

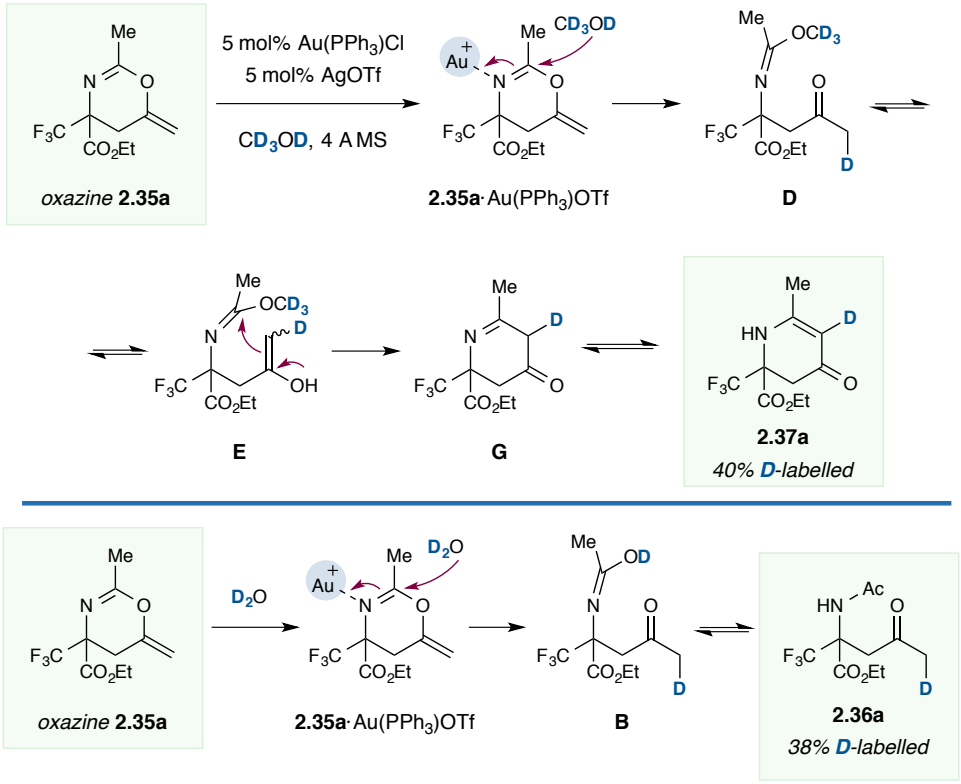
A plausible explanation of the reaction outcome is depicted in *Scheme 2.30*. After intramolecular carbonyl addition (first stage), σ-complexation of gold complex with intermediate oxazine **2.35a** promotes nucleophilic addition of an external nucleophile. When the nucleophile was water (R = H), the addition to complex **2.35a**·Au(PPh$_3$)OTf gave rise to hemiacetal **A**, in equilibrium with the opened intermediate **B**, thus rendering hydration product **2.36a** after tautomerization. A completely different situation appeared when the nucleophile was methanol (R = Me). Namely, the mixed acetal **C** formed, is susceptible to undergo a gold-catalyzed Petasis-Ferrier-type rearrangement.[123] Thus, the acetal moiety undergoes ring opening to form the imidate **D**, which cyclized again into piperidine **F**. Methanol elimination and further isomerization renders final dihyropyridinone **2.37a**.



Scheme 2.30. Mechanistic proposal (second stage).

Isotopic labeling experiments starting from the oxazine intermediate **2.35a** and using deuterated solvents, showed labels in the final dihydropiridinone **2.37a** and the hydration product **2.36a** that were in agreement with our mechanistic proposal (*Scheme 2.31*).

[123] (a) Minbiole, E. C.; Minbiole, K. P. C. *J. Antibiotics*. **2016**, *69*, 213-219. (b) Simth III, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. (c) Adriaenssens, L. V.; Hartley, R. C. *J. Org. Chem.* **2007**, *72*, 10287.



Scheme 2.31. Isotopic labelling experiments.

According to Patil and coworkers' categorization,[124] this process constitutes a new example on the challenging self-relay catalysis (also named autocatalysis),[125] as up to three distinct reactions, carbonyl addition-nucleophilic addition-Petasis-Ferrier rearrangement, are likely promoted by the same gold catalyst, standing on the dual ability of gold salts to act as σ and π Lewis acids (*Figure 2.6*).

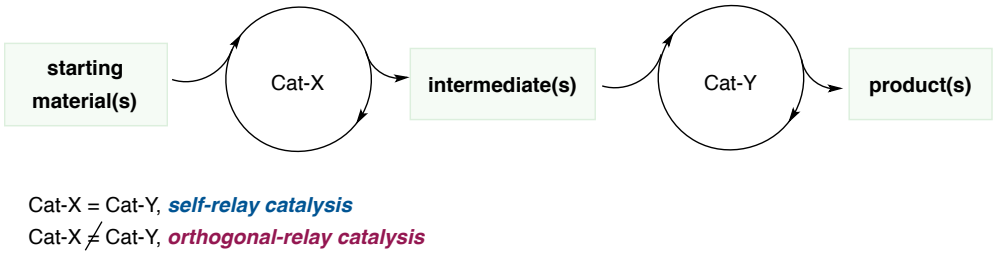


Figure 2.6. Relay catalysis.

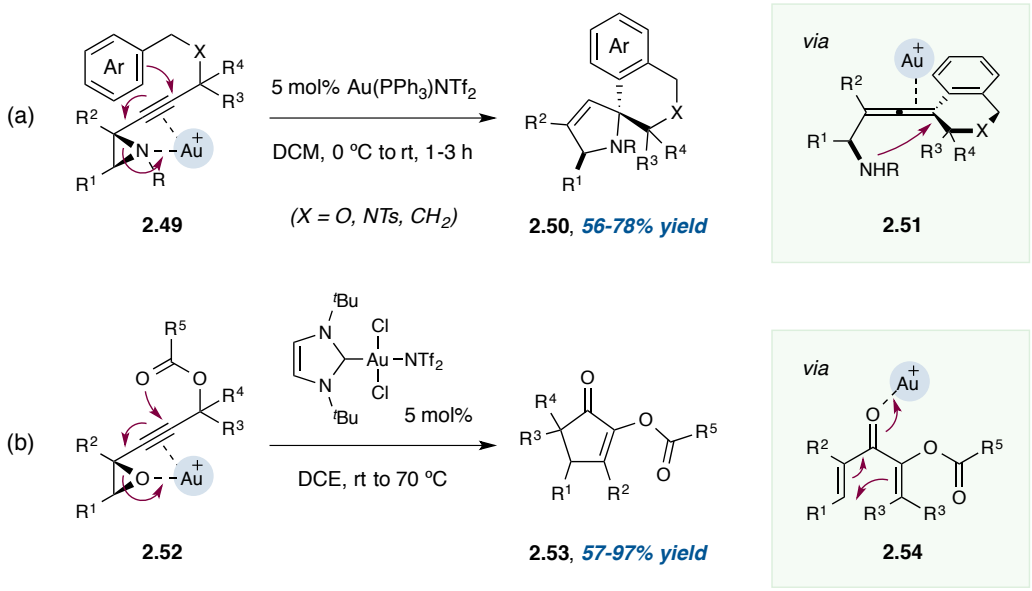
To the best of our knowledge, just a few examples have been described to date where gold imparts simultaneously both acidities, not only in self-relay processes, but also in an orthogonal-relay

[124] Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem.* **2012**, *10*, 211.
[125] Camp, J. E. *Eur. J. Org. Chem.* **2016**, DOI: 10.1002/ejoc.201600803.

catalysis, combining two gold salts with different hard-soft character (the so-called dual hard-soft gold catalysis).

For instance, the Pale group demonstrated that alkynyl aziridines **2.49**, can evolve, in the presence of Au(I) complexes, rendering the spyrocycles **2.50** through an intramolecular Friedel-Crafts reaction followed by the cyclization of the intermediate aminoallene **2.51**, based on a double gold σ and π activation (*Scheme 2.32a*).[126]

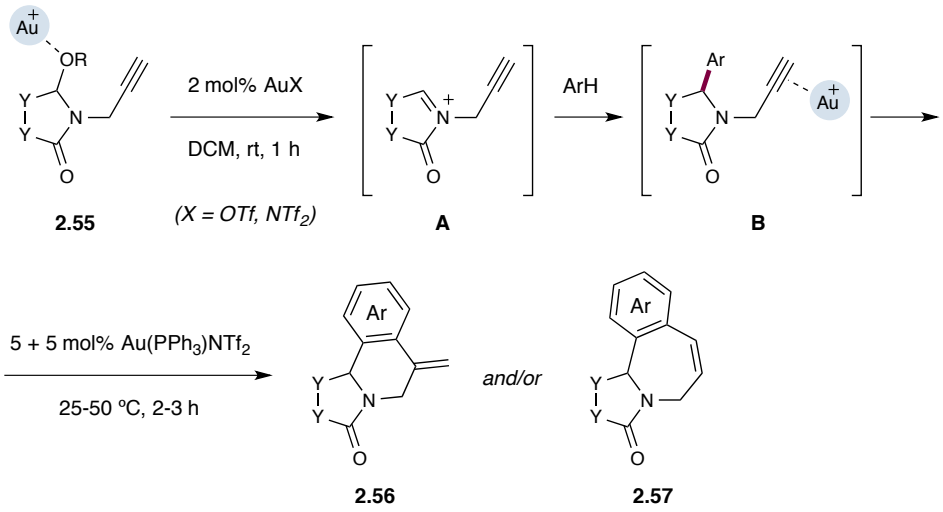
Following this principle, they were also able to access to divinyl ketones **2.52**, suitable to be activated by gold and render cyclopentenones **2.53** in a Nazarov-type reaction (*Scheme 2.32b*).[127]



Scheme 2.32. Previous work by Pale.

Latest contribution from the Dalla group disclosed their preliminary results in a new one-pot cascade α-amidoalkylation-hydroarylation procedure.[128] The novelty introduced by this work stands on the orthogonal-relay catalysis as a new manner to take advantage from the bifunctional character exhibited by gold salts (*Scheme 2.33*). It involved the sequential and combined use of two gold salts: one harder (AuOTf, $AuNTf_2$) promoting the *N*-acyl iminium formation (**A**), and either one softer (PPh_3AuNTf_2), able to activate the triple bond (**B**) towards the final hydroarylation step.

[126] Kern, N.; Blanc, A.; Weibel, J.-M.; Pale, P. *Chem. Commun.* **2011**, *47*, 6665.
[127] (a) Hoffmann, M.; Weibel, J.-M.; De Frémont, P.; Pale, P.; Blanc, A. *Org. Lett.* **2014**, *16*, 908. (b) Cordonnier, M.-C.; Blanc, A.; Pale, P. *Org. Lett.* **2008**, *10*, 1569.
[128] Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem. Eur. J.* **2012**, *18*, 14192.



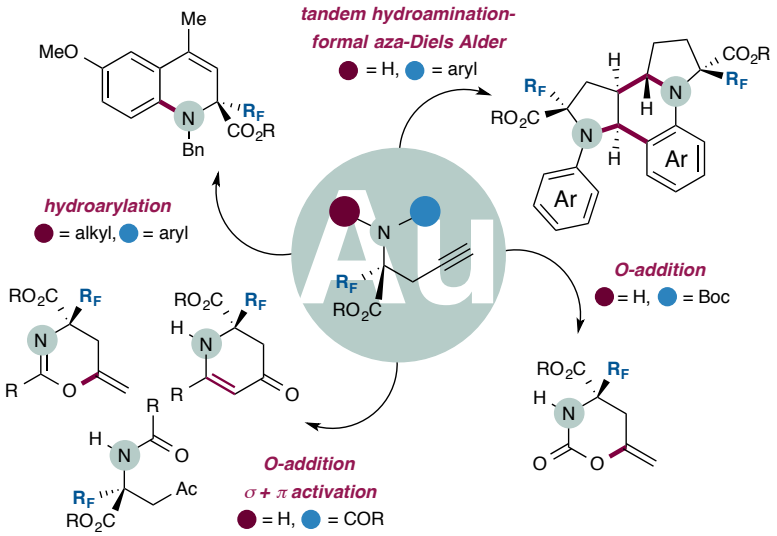
Scheme 2.33. Previous work by Dalla (2012).

To conclude, a new self-relay gold-catalyzed cascade reaction was developed.[129] This triple tandem process emerges as one of the few described examples that takes advantage and unify both the σ- and π-Lewis acid properties of gold salts, giving rise to a new family of dihydropyridinones, important structural pattern for the synthesis of biologically-relevant products.

[129] Fustero, S.; Miró, J.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2014**, *20*, 14126.

2.4. Conclusions.

In conclusion, the differential reactivity of homopropargyl α-amino esters was studied. Gold catalysis led us to access up to five different families of fluorinated nitrogen-containing heterocycles just by modifying the substitution pattern on the nitrogen atom (*Scheme 2.34*). It is important to point out that all new compounds contain, at least, one quaternary α-amino acid unit.



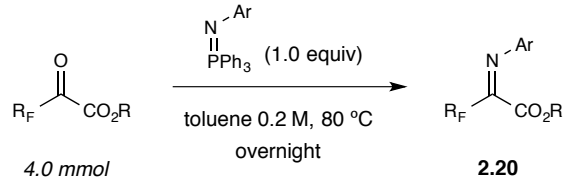
Scheme 2.34. Summary.

2.5. Experimental section.

General remarks: Unless otherwise noted, reactions were carried out under argon atmosphere and all reagents were purchased from commercial suppliers and used without further purification. The solvents were purified prior to use: THF, diethyl ether and toluene were distilled from sodium/benzophenone, dichloromethane and acetonitrile were distilled from calcium hydride. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). Melting points were measured on Büchi B-540 apparatus. ^{1}H, ^{13}C and ^{19}F spectra were recorded on 300 MHz and 500 MHz Bruker spectrometers. Chemical shifts (δ) are given in ppm relative to the residual solvent signals (chloroform, 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Coupling constants (*J*) are given in Hertz (Hz). Letters m, s, d, t and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. Letters br indicate that the signal is broad. High-resolution mass spectra were carried out on an AB SCIEX TripleTOF™ 5600 LC/MS/MS system in ESI mode [*Conditions: Ion source gas 1 (GC1): 35 psi; Ion source gas 2 (GC2): 35 psi; Curtain gas 1: 25 psi; Temperature: 450 ºC; Ion Spray Voltage (ISVF): 5500; Infusion positive mode*] by the University of Valencia Mass Spectrometry Service. Enantiomeric ratios were determined with the aid of HPLC analysis with ChiralPak OD-H, ChiralPak IC, or ChiralPak AD columns (25 cm x 0.46 cm).

2.5.1. Gold-catalyzed tandem hydroamination-formal aza-Diels Alder reaction.

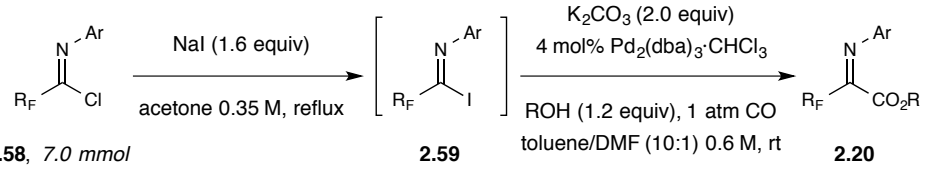
2.5.1.1. Preparation of *N*-aryl-α-imino esters.



Method A: Aza-Wittig reaction. To a solution of the corresponding *N*-aryl-iminophosphorane[130] (1.0 equiv, 4.0 mmol) in dry toluene (0.2 M, 20 mL) was added dropwise the corresponding ketoester (1.0 equiv, 4.0 mmol, neat) and the resulting solution was refluxed overnight. Then, the mixture was

[130] For the preparation of iminophosphoranes, see: (a) Alajarin, M.; López-Leonardo, C.; Berna, J. *Science of Synthesis* **2007**, *31b*, 1539. (b) Stauffer, S. R.; Sun, Y.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2000**, *8*, 1293. (c) Horner, L.; Oediger, H. *Justus Liebig Ann. Chem.* **1959**, *627*, 142.

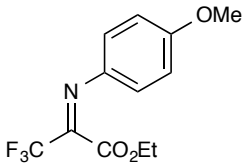
cooled to room temperature, and solvents evaporated under vacuum. Diethyl ether was then added (20 mL) and a white precipitated of triphenylphosphine oxide was formed. The solid was filtrated and washed with diethyl ether (3 x 10 mL) and after removal of solvents, the crude was subjected to flash column chromatography.



2.58, *7.0 mmol* **2.59** **2.20**

Method B: Alcoxycarbonylation reaction.[131] NaI (1.6 equiv, 11.5 mmol) was added to a solution of the corresponding imidoyl chloride **2.58**[132] (1.0 equiv, 7.0 mmol) in dry acetone (0.35 M, 20 mL) and the mixture was stirred at room temperature protected from light until total disappearance of the starting imidoyl chloride (as confirmed by GC-MS). The reaction mixture was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (3 x 15 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of solvents quantitatively gave the corresponding crude imidoyl iodide **2.59**, which was subsequently used in the next step of the synthesis without further purification.

A solution of imidoyl iodide **2.59** in a 10:1 toluene/DMF mixture (0.6M) and the corresponding alcohol (1.2 equiv, 8.5 mmol) were both added to a two-necked flask containing K_2CO_3 (2.0 equiv, 14.2 mmol) and 4 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.28 mmol). The reaction mixture was stirred at room temperature under CO atmosphere (1 atm) until the starting material was consumed, as confirmed by TLC. The crude reaction mixture was then filtered through a silica pad and washed with DCM. The solvents were removed under reduced pressure and the mixture was purified by flash column chromatography.

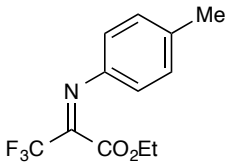


Ethyl (*E*)-3,3,3-trifluoro-2-((4-methoxyphenyl)imino)propanoate. Following the general procedure described above (method A), 946 mg of **2.20a** (yellow oil) were obtained from 680 mg of ethyl

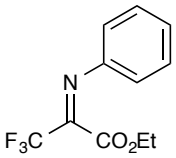
[131] (a) Fustero, S.; Navarro, A.; Pina, B.; García Soler, J.; Bartolomé, A.; Asensio, A.; Simón, A.; Bravo, P.; Fronza, G.; Volonterio, A.; Zanda, M. *Org. Lett.* **2001**, *3*, 2621. (b) Amii, H.; Kishikawa, Y.; Kageyama, K.; Uneyama, K. *J. Org. Chem.* **2000**, *65*, 3404.

[132] For the preparation of imidoyl chlorides, see: (a) Uneyama, K. *J. Fluorine Chem*. **1999**, *97*, 11. (b) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem*. **1993**, *58*, 32.

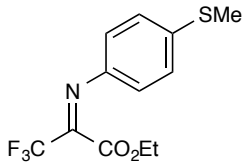
trifluoropyruvate and 1.53 g of 4-methoxy-*N*-(triphenylphosphoranilidene)aniline in 86% yield. The spectroscopic data were in agreement with previously reported data.[103a]



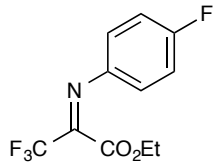
Ethyl (*E*)-3,3,3-trifluoro-2-(*p*-tolylimino)propanoate. Following the general procedure described above (method A), 912 mg of **2.20b** (yellow oil) were obtained from 680 mg of ethyl trifluoropyruvate and 1.47 g of 4-methyl-*N*-(triphenylphosphoranilidene)aniline in 88% yield. The spectroscopic data were in agreement with previously reported data.[103a]



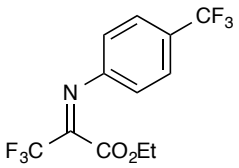
Ethyl (*E*)-3,3,3-trifluoro-2-(phenylimino)propanoate. Following the general procedure described above (method A), 735 mg of **2.20c** (yellow solid) were obtained from 680 mg of ethyl trifluoropyruvate and 1.41 g of *N*-(triphenylphosphoranilidene)aniline in 75% yield. The spectroscopic data were in agreement with previously reported data.[103a]



Ethyl (*E*)-3,3,3-trifluoro-2-((4-(methylthio)phenyl)imino)propanoate. Following the general procedure described above (method A), 759 mg of **2.20d** (yellow oil) were obtained from 0.68 g ethyl trifluoropyruvate and 1.60 g of 4-methylthio-*N*-(triphenylphosphoranilidene)aniline in 65% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.13 (t, J = 7.2 Hz, 3H), 2.47 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 6.93 (d, J_o = 8.4 Hz, 2H), 7.23 (d, J_o = 8.7 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.6, 15.6, 62.8, 118.2 (q, $^{1}J_{CF}$ = 278.6 Hz), 120.5, 126.7, 138.4, 143.1, 148.1 (q, $^{2}J_{CF}$ = 36.7 Hz), 159.6; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -70.1 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{12}H_{13}F_3NO_2S$: 292.0614; found: 292.0611.

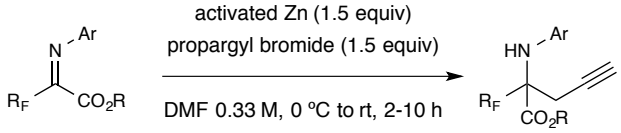


Ethyl (*E*)-3,3,3-trifluoro-2-((4-fluorophenyl)imino)propanoate. Following the general procedure described above (method B), 630 mg of **2.20e** (yellow oil) were obtained from 1.00 g of the corresponding imidoyl chloride in 54% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.13 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.1 Hz, 2H), 6.92-6.99 (m, 2H), 7.05-7.10 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.6, 62.9, 116.0 (d, $^{2}J_{CF}$ = 22.7 Hz), 118.1 (q, $^{1}J_{CF}$ = 278.6 Hz), 121.4 (d, $^{3}J_{CF}$ = 8.3 Hz), 142.4 (d, $^{4}J_{CF}$ = 3.0 Hz), 149.1 (q, $^{2}J_{CF}$ = 37.8 Hz), 160.0, 161.3 (d, $^{1}J_{CF}$ = 295.2 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -70.3 (s, 3F), -115.2 (dddd, $^{3}J_{FH} = J_1 = J_2$ = 8.2 Hz, $^{4}J_{FH} = J_3 = J_4$ = 4.8 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{11}H_{10}F_4NO_2$: 264.0642; found: 264.0634.



Ethyl (*E*)-3,3,3-trifluoro-2-((4-(trifluoromethyl)phenyl)imino)propanoate. Following the general procedure described above (method A), 1.22 g of **2.20f** (yellow liquid) were obtained from 807 mg ethyl trifluoropyruvate and 2.00 g of 4-trifluoromethyl-*N*-(triphenylphosphoranilidene)aniline in 82% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.06 (t, J = 7.2 Hz, 3H), 4.18 (q, J = 7.1 Hz, 2H), 7.01 (d, J_o = 8.1 Hz, 2H), 7.64 (d, J_o = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.5, 63.1, 117.9 (q, $^{1}J_{CF}$ = 278.6 Hz), 118.8, 123.8 (q, $^{1}J_{CF}$ = 271.8 Hz), 126.3 (q, $^{3}J_{CF}$ = 3.8 Hz), 128.8 (q, $^{2}J_{CF}$ = 33.0 Hz), 149.5, 150.3 (q, $^{2}J_{CF}$ = 37.0 Hz), 158.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -62.9 (s, 3F), -70.5 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{12}H_{10}F_6NO_2$: 314.0610; found: 314.0612.

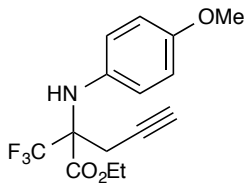
2.5.1.2. General procedure for the preparation of *N*-aryl propargyl-α-amino esters.



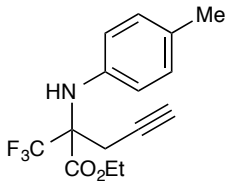
2.20 **2.21**

N-aryl imino ester **2.20** (1.0 equiv, 1.0 mmol) and propargyl bromide (1.5 equiv, 222 mg, 1.5 mmol) were dissolved in DMF (0.33 M, 3 mL). The solution was cooled to 0 °C, then activated zinc powder (1.5 equiv, 98 mg, 1.5 mmol) was added. The reaction mixture was then slowly warmed to room

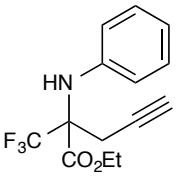
temperature. After 2-10 h (the reaction was monitored by TLC), the medium was cooled to 0°C and hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL), then extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous $MgSO_4$, filtered, and then solvents were evaporated. The residue was purified by flash column chromatography.



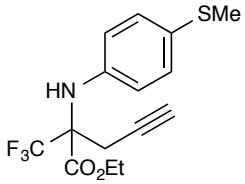
Ethyl 2-((4-methoxyphenyl)amino)-2-(trifluoromethyl)-4-pentynoate. Following the general procedure described above, 281 mg of **2.21a** (89% yield) were obtained as a light yellow oil starting from 275 mg of **2.20a**. Both enantiomers could be separated by HPLC semipreparative IC column chromatography in *n*-hexane:^{i}PrOH (95:5, isocratic method, 4 mL/min flux). (+)-(*S*)-**2.21a**: t_R = 10.693 min. $[\alpha]^{25}_D$ = +56.9 (*c* = 1.0 in $CHCl_3$). (-)-(*R*)-**2.21a**: t_R = 9.280 min. $[\alpha]^{25}_D$ = -56.9 (*c* = 1.0 in $CHCl_3$). Spectroscopic data were agreed with previously reported data.[103a] Absolute configuration could be established by its derivatization to compound **2.34a**, reported in *section 2.5.4.1*, following the general procedure (method B) described in that section. Following this methodology, 260 mg of (*S*)-**2.34a** (white solid) were obtained from 400 mg of (*S*)-**2.21a** in 80% yield. $[\alpha]^{25}_D$ = -6.4 (*c* = 1.0 in $CHCl_3$).



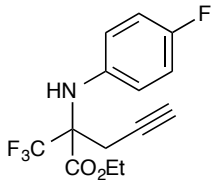
Ethyl 2-(*p*-tolylamino)-2-(trifluoromethyl)pent-4-ynoate. Following the general procedure described above, 249 mg of **2.21b** (96% yield) were obtained as a light yellow oil starting from 259 mg of **2.20b**. The spectroscopic data were in agreement with previously reported data.[103a]



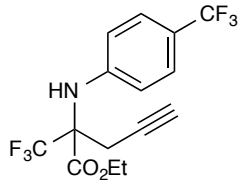
Ethyl 2-(phenylamino)-2-(trifluoromethyl)pent-4-ynoate. Following the general procedure described above, 277 mg of **2.21c** (97% yield) were obtained as a light yellow oil starting from 245 mg of **2.20c**. The spectroscopic data were in agreement with previously reported data.[103a]



Ethyl 2-((4-(methylthio)phenyl)amino)-2-(trifluoromethyl)pent-4-ynoate. Following the method described above, 255 mg of **2.21d** (77% yield) were obtained as yellowish oil starting from 291 mg of **2.20d**. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J = 7.2 Hz, 3H), 2.01 (t, J = 2.6 Hz, 1H), 2.44 (s, 3H), 3.11 (d, J = 2.7 Hz, 2H), 4.34-4.41 (m, 2H), 4.77 (br s, 1H), 6.87 (d, J_o = 8.7 Hz, 2H), 7.18 (d, J_o = 8.7 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 13.7, 17.0, 21.2 (q, $^{3}J_{CF}$ = 2.3 Hz), 63.5, 67.1 (q, $^{2}J_{CF}$ = 27.2 Hz), 72.6, 76.2, 120.8 (q, $^{5}J_{CF}$ = 2.0 Hz), 123.9 (q, $^{1}J_{CF}$ = 289.2 Hz), 128.7, 130.3, 140.5, 166.9 (q, $^{3}J_{CF}$ = 1.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -73.4 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{15}H_{17}F_3NO_2S$: 332.0927; found: 332.0937.



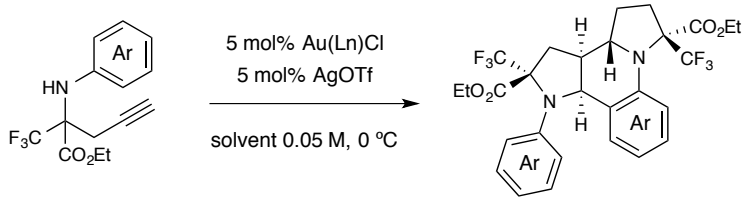
Ethyl 2-((4-fluorophenyl)amino)-2-(trifluoromethyl)pent-4-ynoate. Following method described above, 237 mg of **2.21e** (78% yield) were obtained as a brown oil starting from 263 mg of **2.20e**. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J = 7.1 Hz, 3H), 2.01 (t, J = 2.6 Hz, 1H), 3.00 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 3.09 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 4.32-4.42 (m, 2H), 4.71 (br s, 1H), 6.89-6.99 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 13.8, 21.1 (q, $^{3}J_{CF}$ = 2.3 Hz), 63.6, 67.6 (q, $^{2}J_{CF}$ = 26.8 Hz), 72.6, 76.5, 115.6 (d, $^{2}J_{CF}$ = 21.9 Hz), 123.4 (d, $^{3}J_{CF}$ = 1.5 Hz), 123.5 (d, $^{3}J_{CF}$ = 1.5 Hz), 123.9 (q, $^{1}J_{CF}$ = 289.2 Hz), 138.3 (d, $^{4}J_{CF}$ = 2.3 Hz), 158.8 (d, $^{1}J_{CF}$ = 240.8 Hz), 167.0 (q, $^{3}J_{CF}$ = 1.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -73.7 (s, 3F), -121.6 (dddd, $^{3}J_{FH} = J_1 = J_2$ = 7.9 Hz, $^{4}J_{FH} = J_3 = J_4$ = 5.1 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{14}H_{14}F_4NO_2$: 304.0955; found: 304.0950.



Ethyl 2-(trifluoromethyl)-2-((4-(trifluoromethyl)phenyl)amino)pent-4-ynoate. Following method described above, 300 mg of **2.21f** (85% yield) were obtained as a yellowish solid starting from 313 mg of **2.20f**. m.p. 50-52 ºC. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, J = 7.2 Hz, 3H), 2.00 (t, J = 2.7 Hz, 1H), 3.17 (dd, J_1 = 17.4 Hz, J_2 = 2.7 Hz, 1H), 3.28 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 5.19 (br s, 1H), 6.88 (d, J_o = 8.4 Hz, 2H), 7.45 (d, J_o = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5

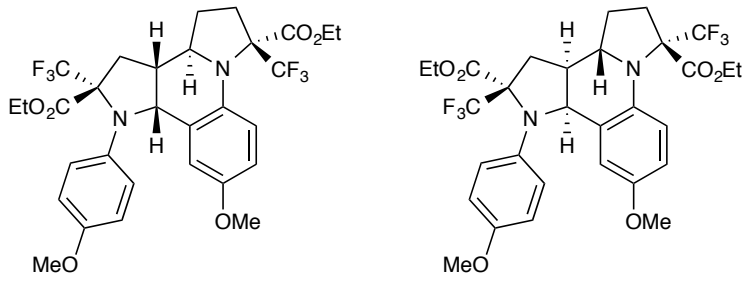
MHz) δ 13.8, 21.4 (q, $^{3}J_{CF}$ = 1.5 Hz), 64.0, 66.6 (q, $^{2}J_{CF}$ = 27.9 Hz), 73.2, 75.4, 117.3 (q, $^{4}J_{CF}$ = 2.3 Hz), 122.5 (q, $^{2}J_{CF}$ = 32.5 Hz), 124.0 (q, $^{1}J_{CF}$ = 288.4 Hz), 124.5 (q, $^{1}J_{CF}$ = 271.5 Hz), 126.4 (q, $^{3}J_{CF}$ = 3.8 Hz), 146.0, 166.7 (q, $^{3}J_{CF}$ = 0.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -62.2 (s, 3F), -73.0 (s, 3F); HRMS (ES) calc. for (M^{+}+1) $C_{15}H_{14}F_6NO_2$: 354.0923; found: 354.0919.

2.5.1.3. General procedure for the gold-catalyzed tandem hydroamination-formal aza-Diels Alder reaction.

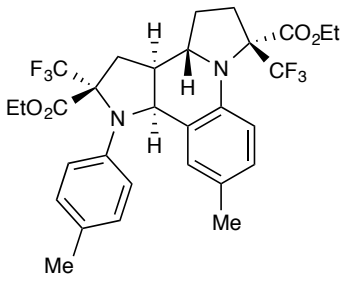


2.21, *0.20 mmol* **2.22**

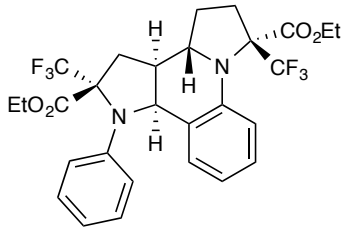
Active catalyst was form by stirring at 0 ºC a suspension of Au(Ln)Cl (5 mol%, Ln = PPh_3 or P(4-CF_3-C_6H_4)$_3$) and AgOTf (5 mol%) in dry toluene (Ln = PPh_3) or DCM (Ln = P(4-CF_3-C_6H_4)$_3$) (0.05 M, 4.0 mL) for 5 minutes. The corresponding propargyl-α-amino ester (1.0 equiv, 0.2 mmol) was added next. The reaction mixture was stirred at this temperature until TLC showed total consumption of starting material. Then, solvents were removed under reduced pressure and crude mixture was purified by flash column chromatography.



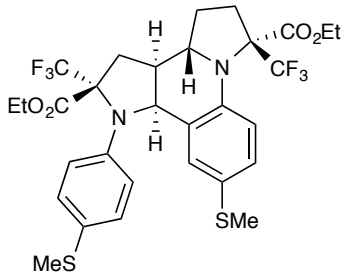
(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 10-methoxy-1-(4-methoxyphenyl)-2,6-bis(trifluorome-thyl)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-a:3',2'-c] quinoline-2,6-dicarboxylate.** Following the procedure described above (Ln = PPh_3), 48 mg of (+)-**2.22a** (76% yield) were obtained as a white solid starting from 63 mg of (+)-(*S*)-**2.21a**. $[\alpha]^{25}_{D}$ = +91.5 (*c* = 1.0 in $CHCl_3$). On the other hand, the opposite enantiomer (-)-**2.22a** was obtained in comparable yield starting from (-)-(*R*)-**2.21a**. $[\alpha]^{25}_{D}$ = -91.5 (*c* = 1.0 in $CHCl_3$). Spectroscopic data were agreed with previously reported data.[103a]



(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 10-methyl-1-*p*-tolyl-2,6-bis(trifluoromethyl)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-a:3',2'-c]quinoline-2,6-dicarboxylate.** Following the procedure described above, 20 mg of **2.22b** (34% yield) were obtained as a yellow oil starting from 60 mg of **2.21b** when Ln = PPh_3. This yield could be increased up to 68% (41 mg) employing the gold complex derived from Ln = $P(4\text{-}CF_3\text{-}C_6H_4)_3$. Spectroscopic data were agreed with previously reported data.[103a]

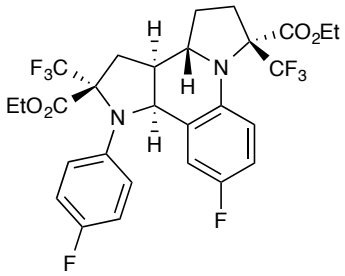


(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 1-phenyl-2,6-bis(trifluoromethyl)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-a:3',2'-c]quinoline-2,6-dicarboxylate.** Following the procedure described above, 8 mg of **2.22c** (14% yield) were obtained as a yellow oil starting from 57 mg of **2.21c** when Ln = PPh_3. The use of the gold species derived from Ln = $P(4\text{-}CF_3\text{-}C_6H_4)_3$ led us to increased the yield up to 72% (41 mg). Spectroscopic data were agreed with previously reported data.[103a]

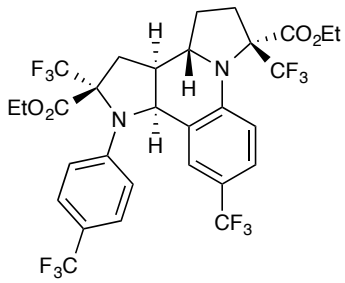


(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 10-(methylthio)-1-[4-(methylthio)phenyl]-2,6-bis(tri-fluoro-methyl)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-*a*:3',2'-*c*]quinoline-2,6-di-carboxylate.** Following the procedure described above (Ln = $P(4\text{-}CF_3\text{-}C_6H_4)_3$), 43 mg of **2.22d** (65% yield) were obtained as a colourless oil starting from 66 mg of **2.21d**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.89-1.95 (m, 1H), 1.98 (s, 3H), 2.16-2.23 (m, 1H), 2.42 (s, 3H), 2.44-2.56 (m, 4H), 2.80 (dd, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1H), 3.98-4.11 (m, 3H), 4.13-4.25 (m, 2H), 4.75 (d, J = 4.8 Hz, 1H), 6.60 (d, J_m = 2.4 Hz, 1H), 6.67 (d, J_o = 8.4 Hz, 1H), 6.96 (dd, J_o = 8.7 Hz, J_m = 2.4 Hz, 1H), 7.07-7.24 (m, 4H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.7, 13.8, 15.9, 18.4, 27.8, 33.6,

35.9, 37.5, 59.0, 62.2, 62.2, 62.3, 72.4 (q, $^{2}J_{CF}$ = 25.9 Hz), 74.0 (q, $^{2}J_{CF}$ = 27.6 Hz), 115.3 (q, $^{5}J_{CF}$ = 5.4 Hz), 122.2, 125.5 (q, $^{1}J_{CF}$ = 286.9 Hz), 125.8, 126.1 (q, $^{1}J_{CF}$ = 290.7 Hz), 126.4, 129.9, 131.5, 131.5, 133.9, 136.8, 139.1, 140.2, 168.2, 169.0; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -69.0 (s, 3F), -70.9 (s, 3F); HRMS (ES) calc. for (M^++H) $C_{30}H_{33}F_6N_2O_4S_2$: 663.1780; found: 663.1786.

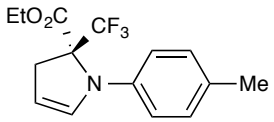


(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 10-fluoro-1-(4-fluorophenyl)-2,6-bis(trifluoromethyl)-2,3,3a, 3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-*a*:3',2'-*c*]quinoline-2,6-dicarboxylate.** Following the procedure described above (Ln = P(4-CF_3-C_6H_4)$_3$), 40 mg of **2.22e** (66% yield) were obtained as a colourless oil starting from 61 mg of **2.21e**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.89-1.98 (m, 1H), 2.16-2.24 (m, 1H), 2.34-2.61 (m, 4H), 2.80 (dd, J_1 = 14.4 Hz, J_2 = 7.5 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 4.02-4.08 (m, 1H), 4.14-4.26 (m, 2H), 4.73 (d, *J* = 4.5 Hz, 1H), 6.29 (dd, J_o = 9.6 Hz, J_m = 2.7 Hz, 1H), 6.65-6.79 (m, 2H), 6.90-7.00 (m, 2H), 7.21 (dd, J_o = 8.7 Hz, J_m = 5.1 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 150.9 MHz): δ 13.6, 13.8, 27.7, 33.5, 35.9, 36.9, 59.2, 62.1, 62.3, 72.5 (q, $^{2}J_{CF}$ = 26.2 Hz), 74.6 (q, $^{2}J_{CF}$ = 27.7 Hz), 115.0 (d, $^{2}J_{CF}$ = 22.6 Hz), 115.2 (d, $^{2}J_{CF}$ = 22.6 Hz), 116.7 (m), 118.4 (d, $^{2}J_{CF}$ = 22.6 Hz), 123.2 (d, $^{3}J_{CF}$ = 6.0 Hz), 125.5 (q, $^{1}J_{CF}$ = 288.2 Hz), 126.1 (q, $^{1}J_{CF}$ = 291.2 Hz), 132.3 (d, $^{3}J_{CF}$ = 9.1 Hz), 137.6 (d, $^{4}J_{CF}$ = 3.0 Hz), 138.0 (d, $^{4}J_{CF}$ = 3.0 Hz), 155.5 (d, $^{1}J_{CF}$ = 238.4 Hz), 161.2 (d, $^{1}J_{CF}$ = 246.0 Hz), 168.1, 168.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -68.7 (s, 1F), -69.1 (s, 3F), -69.4 (s, 1F), -71.3 (s, 3F); HRMS (ES) calc. for (M^++H) $C_{28}H_{27}F_8N_2O_4$: 607.1838; found: 607.1849.

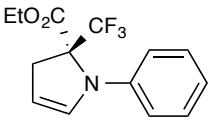


(2*R,3a*S**,3b*S**,6*R**,11b*S**)-Diethyl 2,6,10-tris(trifluoromethyl)-1-[4-(trifluoromethyl)phenyl]-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-*a*:3',2'-*c*]quinoline-2,6-dicarboxylate.** Following the procedure described above (Ln = P(4-CF_3-C_6H_4)$_3$), 40 mg of **2.22f** (57% yield) were obtained as a yellowish oil starting from 70 mg of **2.21f**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.06 (t, *J* = 7.2 Hz, 3H),

1.23 (t, J = 7.2 Hz, 3H), 1.90-1.99 (m, 1H), 2.27-2.35 (m, 1H), 2.44-2.65 (m, 4H), 2.87 (dd, J_1 = 14.4 Hz, J_2 = 6.9 Hz, 1H), 4.03-4.16 (m, 3H), 4.19-4.26 (m, 2H), 4.88 (d, J = 5.1 Hz, 1H), 6.75 (d, J_o = 8.7 Hz, 1H), 6.86 (d, J_m = 1.8 Hz, 1H), 7.20 (dd, J_o = 10.9 Hz, J_m = 1.8 Hz, 1H), 7.30 (d, J_o = 8.4 Hz, 2H), 7.50 (d, J_o = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.7, 13.8, 28.4, 33.8, 36.4, 38.3, 59.1, 62.0, 62.5, 62.6, 72.6 (q, $^2J_{CF}$ = 26.3 Hz), 73.4 (q, $^2J_{CF}$ = 28.0 Hz), 114.3 (q, $^4J_{CF}$ = 5.4 Hz), 119.8 (q, $^2J_{CF}$ = 33.0 Hz), 120.4, 124.0 (q, $^1J_{CF}$ = 270.6 Hz), 124.1 (q, $^1J_{CF}$ = 269.4 Hz), 125.3 (q, $^3J_{CF}$ = 3.8 Hz), 125.5 (q, $^1J_{CF}$ = 286.9 Hz), 125.6 (q, $^3J_{CF}$ = 3.8 Hz), 125.8 (q, $^1J_{CF}$ = 290.7 Hz), 128.2 (q, $^2J_{CF}$ = 32.6 Hz), 129.3 (q, $^3J_{CF}$ = 3.8 Hz), 129.5 (q, $^4J_{CF}$ = 1.3 Hz), 144.2, 145.3 (q, $^4J_{CF}$ = 1.3 Hz), 167.8, 168.6; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -62.6 (s, 3F), -63.1 (s, 3F), -68.8 (s, 3F), -70.4 (s, 3F); HRMS (ES) calc. for (M^++H) $C_{30}H_{27}F_{12}N_2O_4$: 707.1774; found: 707.1774.

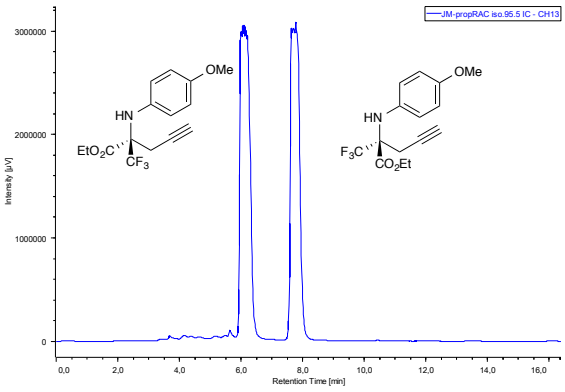


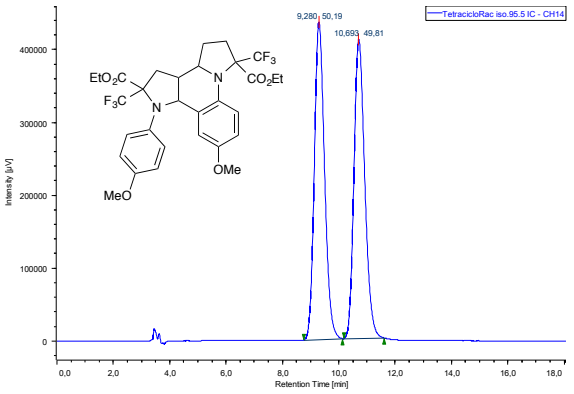
Ethyl 1-*p*-tolyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate. Following the procedure described above (Ln = PPh_3), 21 mg of **2.23b** (34% yield) were obtained as a colourless oil starting from 63 mg of **2.21b**. The use of the gold species derived from Ln = P(4-CF_3-C_6H_4)$_3$ reduced the formation of the hydroamination product down to 2% yield. Spectroscopic data were agreed with previously reported data.[103a]

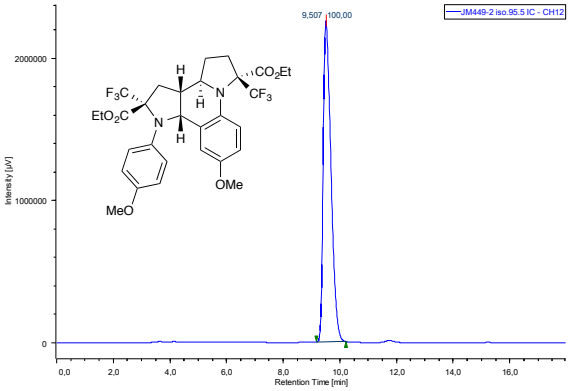


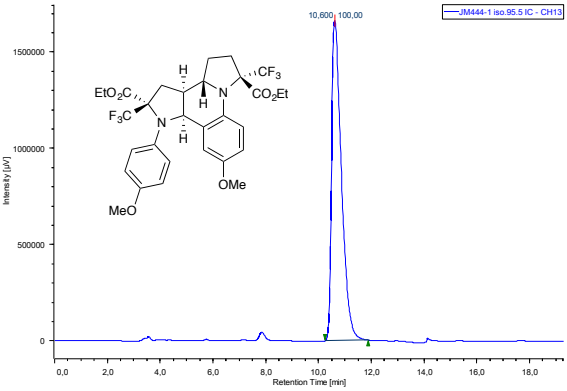
Ethyl 1-phenyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylate. Following the procedure described above (Ln = PPh_3), 36 mg of **2.23c** (64% yield) were obtained as a colourless oil starting from 57 mg of **2.21c**. The use of the gold species derived from Ln = P(4-CF_3-C_6H_4)$_3$ reduced the formation of the hydroamination product down to 3% yield. Spectroscopic data were agreed with previously reported data.[103a]

2.5.1.4. HPLC data.









2.5.1.5. Computational study.[133]

Theoretical methodology. The quantum chemical calculations described in this work were carried out with Gaussian09 package,[134] using density functional theory. A good theoretical treatment of gold is a challenge, mainly due to the importance of the relativistic effects.[135] However, a good balance between accuracy and computational cost can be achieved with the use of the hybrid functional B3LYP, using the 6-31G(d) basis set for the non-metalic atoms (C, H, N, P, F, O, S) and the Hay and Wadt pseudopotentials, in which the core orbitals are replaced by an effective core potential (ECP) and the valence orbitals are described by *ab initio* methods.[136] In this study, the pseudopotential LANL2DZ was employed. This level of theory has been shown to be adequate for the description of several catalytic systems.[137]

The potential energy surface for the reaction of amine **2.21a** and the model catalyst $[Au(PMe_3)]^+$, was extensively explored and the geometry of all the stationary points located was fully optimized. Each stationary point was characterized to be a minimum or a first-order saddle point (transition structure) by computing the harmonic vibrational frequencies. The connection of either, the reactants or products, with the corresponding transition structure was established by computation of the intrinsic reaction coordinate (IRC).[138]

Stationary points located for the reaction of 2.23a with intermediates C_{syn} and C_{anti}. According with the stereochemistry of reactants **2.23a**, C_{syn}, and C_{anti}, the potential energy surface for these reactions will have 16 possible transition structures and 16 possible minima. All these stationary points were located and characterized and are collected in tables *2.11-2.14*.[139]

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[133] For the cartesian coordinates, imaginary frequency (for the first-order saddle points), total electronic energy E (in hartrees), Gibbs free energy G (in hartrees), charge and multiplicity of the stationary points located, see ref. 114: Miró, J.; Sánchez-Roselló, M.; González, J.; del Pozo, C.; Fustero, S. *Chem. Eur. J.* **2015**, *21*, 5459.

[134] *Gaussian 09*, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. J.; Burant, C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. J.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2010**.

[135] For a review of the theoretical treatment of gold, see: Pykko, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412.

[136] Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

[137] See, for example: (a) Faza, O. N.; Rodríguez, R. A.; López, C. S. *Theor. Chem. Acc.* **2011**, *128*, 647. (b) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1078. (c) Comas-Vives, A.; González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F.; Ujaque, G. *J. Am. Chem. Soc.* **2006**, *128*, 4756. (d) Straub, B. F. *Chem. Commun.* **2004**, 1726. (e) Soriano, E.; Marco-Contelles, J. *Organometallics*, **2006**, *25*, 4542. (f) Nevado, C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155.

[138] For a detailed presentation of the theoretical methods, see: Jensen, F. *Introduction to Computational Chemistry*, 2nd edition, Wiley **2007**.

[139] ΔG in kcal·mol^{-1} and leghts in Å.

Table 2.11. Stationary points located for the reaction of intermediate $\mathbf{C}_{anti}$ (addition to the *Re*-face) with **2.23a** (**TS7** for the *Re*-face, **TS9** for the *Si*-face).

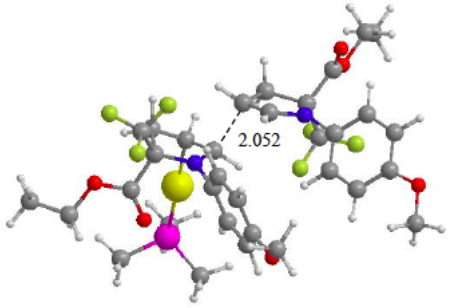
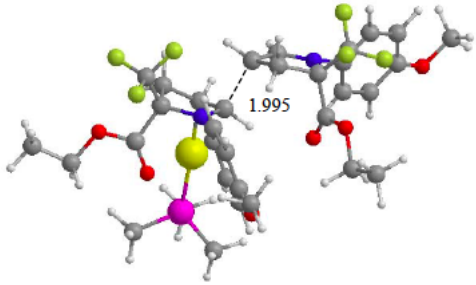
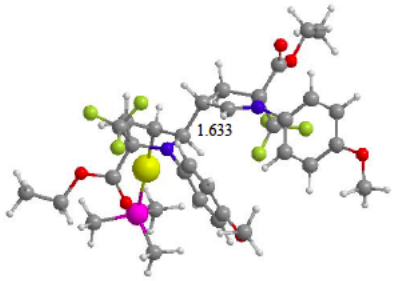
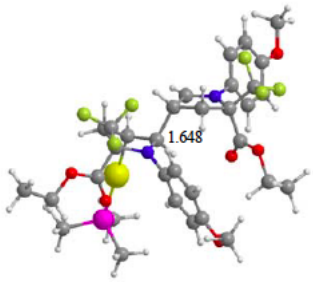
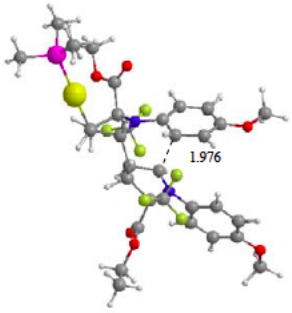
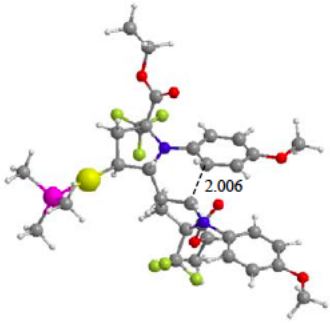
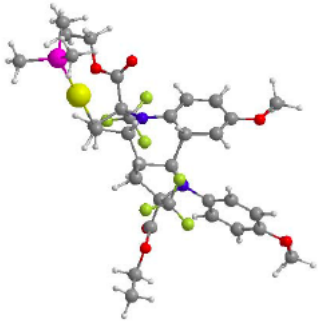
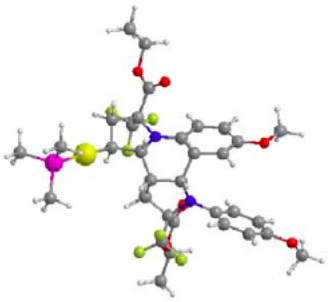
TS7 ΔG = 28.2 	**TS9** ΔG = 29.6 
D1 ΔG = 25.0 	**D2** ΔG = 29.2 
TS8 ΔG = 37.5 	**TS10** ΔG = 35.5 
E1 ΔG = 35.5 	**E2** ΔG = 31.6 

Table 2.12. Stationary points located for the reaction of intermediate $\mathbf{C}_{anti}$ (addition to the *Si*-face) with **2.23a** (**TS11** for the *Re*-face, **TS13** for the *Si*-face).

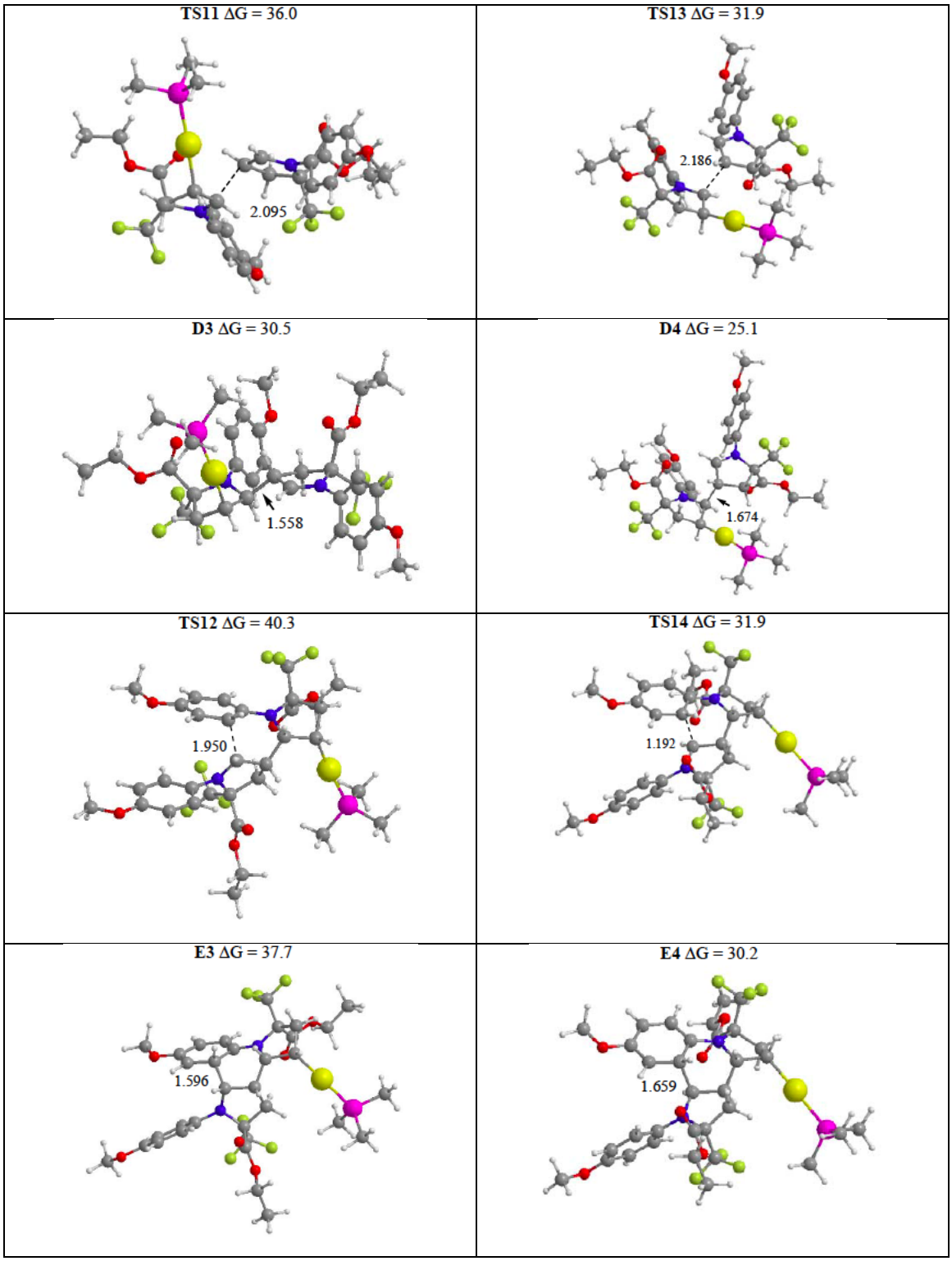


Table 2.13. Stationary points located for the reaction of intermediate $\mathbf{C}_{syn}$ (addition to the *Si*-face) with **2.23a** (**TS15** for the *Re*-face, **TS17** for the *Si*-face).

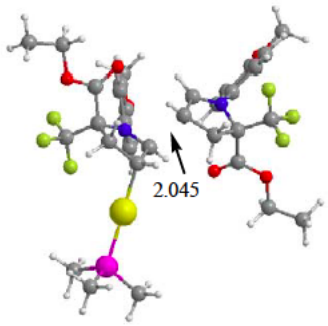
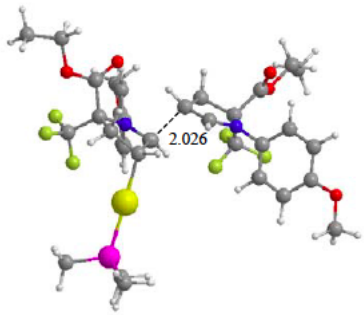
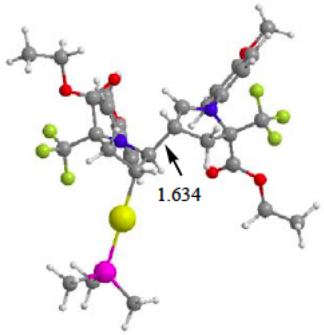
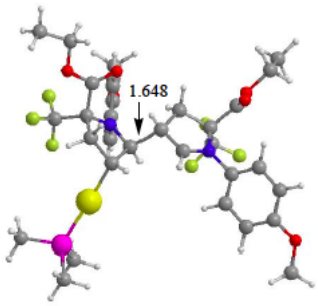
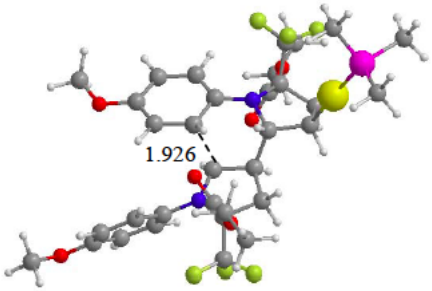
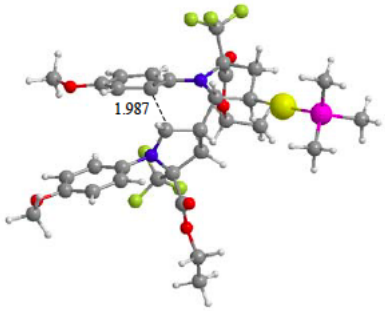
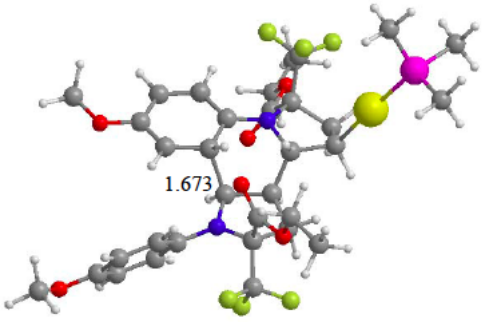
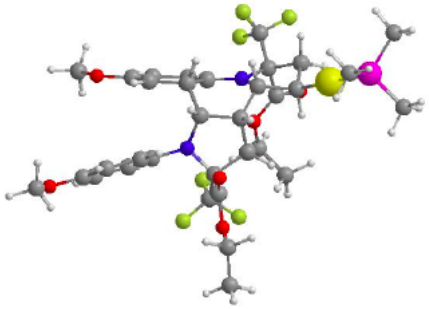
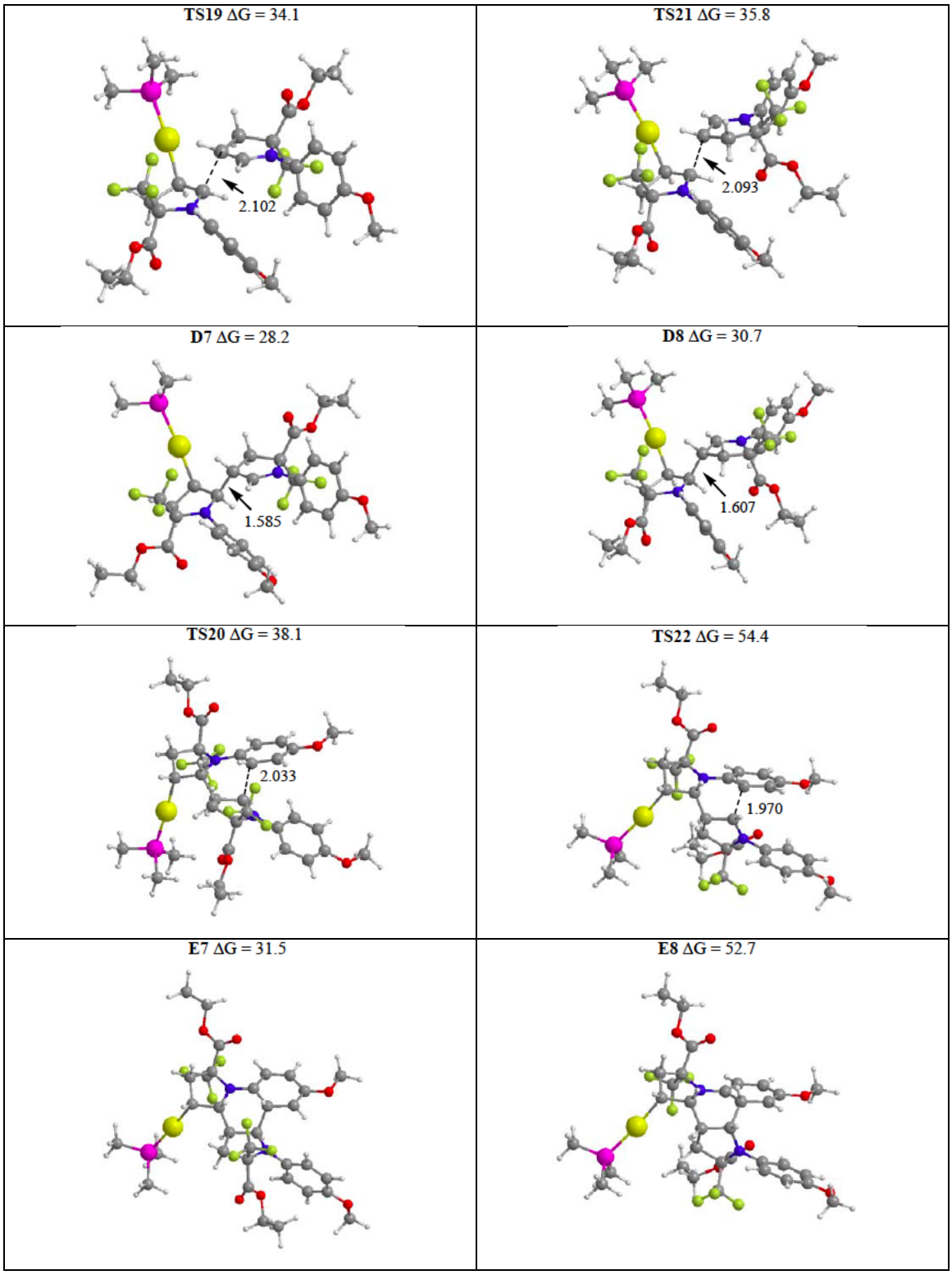
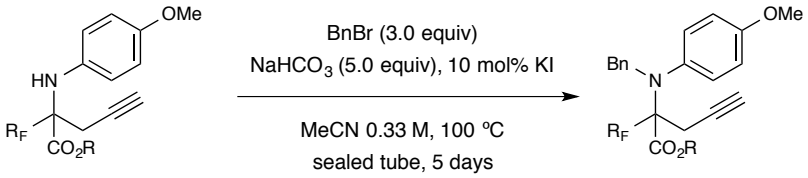
TS15 ΔG = 35.9 	**TS17** ΔG = 27.6 
D5 ΔG = 23.0 	**D6** ΔG = 26.3 
TS16 ΔG = 33.5 	**TS18** ΔG = 35.2 
E5 ΔG = 32.2 	**E6** ΔG = 32.4 

Table 2.14. Stationary points located for the reaction of intermediate $\mathbf{C}_{syn}$ (addition to the *Re*-face) with **2.23a** (**TS19** for the *Re*-face, **TS21** for the *Si*-face).



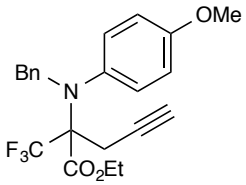
2.5.2. Gold-catalyzed synthesis of fluorinated 1,2-dihydroquinoline derivatives.

2.5.2.1. General procedure for the alkylation of propargyl-α-amino esters.



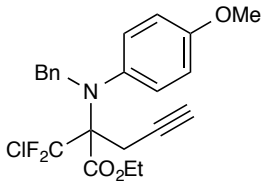
2.21, *1.0 mmol* **2.24**

Benzyl bromide (3.0 equiv, 3.0 mmol), $NaHCO_3$ (5.0 equiv, 5.0 mmol) and KI (10 mol%, 0.1 mmol) were added to a solution of the corresponding propargyl-α-amino ester **2.21**[140] (1.0 equiv, 1.0 mmol) in MeCN (0.33 M, 3 mL). The reaction mixture was heated in a sealed tube for five days at 90-100 ºC. The mixture was then cooled to room temperature, brine was added (10 mL) and the mixture extracted with Et_2O (3 x 10 mL). Combined organic phases were dried with anhydrous Na_2SO_4 and the solvents were evaporated. The crude product was purified over silica gel at least twice using mixtures of *n*-hexane:EtOAc and toluene:DCM.

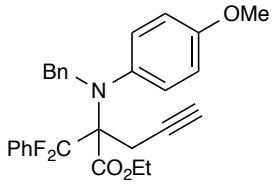


Ethyl 2-(benzyl(4-methoxyphenyl)amino)-2-(trifluoromethyl)pent-4-ynoate. Following the general procedure described above, starting from 315 mg of substrate **2.21a**, 216 mg of compound **2.24a** (yellow oil) were obtained in 92% yield and 58% conversion. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, J = 7.1 Hz, 3H), 1.97 (t, J = 2.7 Hz, 1H), 2.43 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 2.58 (dd, J_1 = 16.8 Hz, J_2 = 2.1 Hz, 1H), 3.60 (s, 3H), 4.22-4.36 (m, 4H), 6.59 (d, J_o = 9.0 Hz, 2H), 6.98-7.16 (m, 7H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.2, 24.6 (q, $^3J_{CF}$ = 1.5 Hz), 55.1, 57.1, 62.2, 72.0, 72.1 (q, $^2J_{CF}$ = 24.9 Hz), 77.1, 113.6, 125.3 (q, $^1J_{CF}$ = 289.2 Hz), 126.8, 127.9, 128.4, 131.4, 136.5, 138.4, 157.7, 167.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -71.1 (s, 3F); HRMS (ES) calc. para (M^++1) $C_{22}H_{23}F_3NO_3$: 405.1625; found: 405.1622.

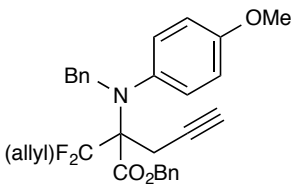
[140] Prepared according to general procedure indicated in *section 2.5.1.2* from the corresponding α-imino ester, in turn prepared by method A described in *section 2.5.1.1*.



Ethyl 2-(benzyl(4-methoxyphenyl)amino)-2-(chlorodifluoromethyl)pent-4-ynoate. Following the general procedure described above, starting from 332 mg of substrate **2.21g**, 79 mg of compound **2.24b** (yellowish oil) were obtained in 48% yield and 39% conversion. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.45 (t, J = 7.1 Hz, 3H), 2.13 (t, J = 2.4 Hz, 1H), 2.68 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 2.77 (dt, J_1 = 16.8 Hz, J_2 = 2.4 Hz, 1H), 3.74 (s, 3H), 4.38-4.56 (m, 4H), 6.74 (d, J_o = 8.7 Hz, 2H), 7.13-7.33 (m, 5H), 7.31 (d, J_o = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 26.0, 55.1, 57.6, 62.2, 72.2, 75.6 (t, $^{2}J_{CF}$ = 20.0 Hz), 77.4, 113.6, 126.7, 127.8, 128.6, 131.3, 131.7 (t, $^{1}J_{CF}$ = 307.2 Hz), 137.0, 138.3, 157.8, 167.1; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -52.8 (d, J_{FF} = 166.4 Hz, 1F), -56.13 (d, J_{FF} = 166.4 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{22}H_{23}ClF_2NO_3$: 422.1329; found: 422.1331.



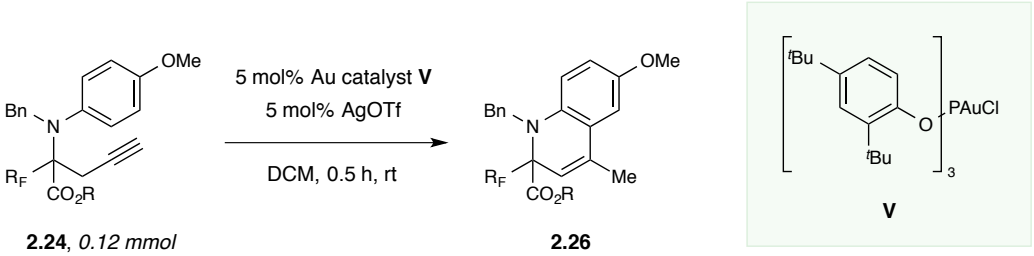
Ethyl 2-(benzyl(4-methoxyphenyl)amino)-2-(difluoro(phenyl)methyl)pent-4-ynoate. Following the general procedure described above, starting from 373 mg of substrate **2.21h**, 213 mg of compound **2.24c** (yellowish oil) were obtained in 72% yield and 64% conversion. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.53 (t, J = 7.2 Hz, 3H), 2.16 (t, J = 2.4 Hz, 1H), 2.23 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 2.59 (dt, J_1 = 16.5 Hz, J_2 = 2.9 Hz, 1H), 3.77 (s, 3H), 4.48-4.59 (m, 3H), 4.69 (d, J = 13.8 Hz, 1H), 6.70 (d, J_o = 9.0 Hz, 2H), 6.94 (d, J_o = 9.0 Hz, 2H), 7.23-7.28 (m, 5H), 7.46-7.57 (m, 3H), 7.86 (d, J_o = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.2, 25.9, 55.1, 57.3, 61.5, 71.9, 73.6 (t, $^{2}J_{CF}$ = 24.5 Hz), 78.6, 113.4, 122.8 (t, $^{1}J_{CF}$ = 258.2 Hz), 126.6, 127.5, 127.7, 127.9 (t, $^{3}J_{CF}$ = 6.8 Hz), 129.0, 130.0, 130.8, 134.9 (t, $^{2}J_{CF}$ = 26.8 Hz), 138.1, 138.7, 157.3, 168.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -94.6 (d, J_{FF} = 253.8 Hz, 1F), -98.4 (d, J_{FF} = 253.8 Hz, 1F); HRMS (ES) calc. for (M^+-C_7H_6) $C_{21}H_{22}F_2NO_3$: 374.1562; found: 374.1562.



Benzyl 2-(benzyl(4-methoxyphenyl)amino)-3,3-difluoro-2-(prop-2-yn-1-yl)hex-5-enoate. Following the general procedure described above, starting from 400 mg of substrate **2.21i**, 96 mg of

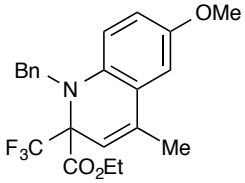
compound **2.24d** (colourless oil) were obtained in 37% yield and 53% conversion. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.03 (t, J = 2.6 Hz, 1H), 2.60 (dd, J_1 = 16.8 Hz, J_2 = 2.4 Hz, 1H), 2.75 (dt, J_1 = 16.8 Hz, J_2 = 2.4 Hz, 1H), 3.18-3.33 (m, 2H), 3.70 (s, 3H), 4.36 (d, J = 14.4 Hz, 1H), 4.42 (d, J = 14.4 Hz, 1H), 5.20-5.36 (m, 4H), 6.01 (dddd, J_1 = 14.1 Hz, J_2 = 10.5 Hz, J_3 = J_4 = 7.2 Hz, 1H), 6.64 (d, J_o = 9.0 Hz, 2H), 7.05-7.16 (m, 7H), 7.36-7.47 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 24.2 (t, $^{3}J_{CF}$ = 3.8 Hz), 39.0 (t, $^{2}J_{CF}$ = 23.8 Hz), 55.2, 57.1, 67.6, 72.1, 74.0 (t, $^{2}J_{CF}$ = 23.0 Hz), 79.4, 113.5, 120.1, 124.2 (t, $^{1}J_{CF}$ = 252.2 Hz), 126.6, 127.8, 128.4, 128.6, 128.8, 129.3 (t, $^{3}J_{CF}$ = 4.9 Hz), 131.1, 135.1, 138.0, 138.9, 157.3, 168.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -100.5 (ddd, J_{FF} = 254.1 Hz, $(J_{FH})_1$ = 27.1 Hz, $(J_{FH})_2$ = 13.3 Hz, 1F), -102.5 (ddd, J_{FF} = 254.6 Hz, $(J_{FH})_1$ = 27.1 Hz, $(J_{FH})_2$ = 13.0 Hz, 1F); HRMS (ES) calc. for (M^{+}+1) $C_{30}H_{30}F_2NO_3$: 490.2188; found: 490.2190.

2.5.2.2. General procedure for the tandem hydroarylation-isomerization reaction.



2.24, *0.12 mmol* **2.26**

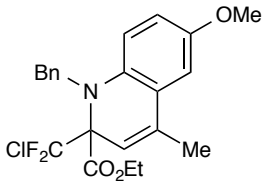
Over a solution of AuP[O(2,4-^{t}Bu-C_6H_3)]$_3$Cl **V** (5 mol%)[141] and the corresponding *N*-benzyl propargyl-α-amino ester **2.24** (1.0 equiv, 0.12 mmol) in dry DCM (0.05 M, 2.5 mL), AgOTf (5 mol%) was added. After 20 minutes at room temperature, total consumption of the starting material was observed by TLC, and the reaction crude was purified after removal of the solvents by column chromatography.



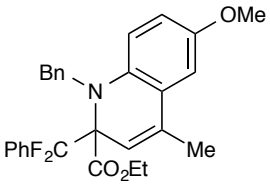
Ethyl 1-benzyl-6-methoxy-4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline-2-carboxylate. Starting from 50 mg of **2.24a**, according to general procedure described above, 45 mg of compound **2.26a** (yellow oil) were obtained in 90% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, J = 7.1 Hz, 3H), 2.15 (d, J = 1.5 Hz, 3H), 3.70 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.48 (d, J = 17.4 Hz, 1H), 4.57 (d,

[141] This gold species were prepared from $Au(SMe_2)Cl$. Over a solution of the phosphine P[O(2,4-^{t}Bu-C_6H_3)]$_3$ in dry DCM cooled at 0 ºC, 1 equiv of $Au(SMe_2)Cl$ was added. The mixture was stirred at room temperature until the reaction was completed (TLC or ^{31}P NMR). Removal of the solvent led to the gold complex.

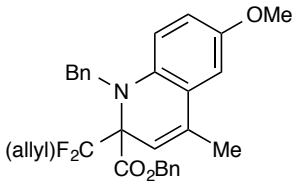
J = 17.4 Hz, 1H), 5.51 (s, 1H), 6.28 (d, J_o = 9.0 Hz, 1H), 6.54 (dd, J_o = 8.7 Hz, J_m = 3.0 Hz, 1H), 6.80 (d, J_m = 3.0 Hz, 1H), 7.17-7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 19.0, 52.7, 55.5, 62.7, 72.0 (q, $^2J_{CF}$ = 26.4 Hz), 111.1, 113.8, 113.9, 114.2, 122.3, 124.7 (q, $^1J_{CF}$ = 295.2 Hz), 126.4, 126.7, 128.3, 135.7, 136.0, 137.3, 152.0, 167.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -74.1 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{22}H_{23}F_3NO_3$: 406.1625; found: 406.1620.



Ethyl 1-benzyl-2-(chlorodifluoromethyl)-6-methoxy-4-methyl-1,2-dihydroquinoline-2-carboxylate. Following the general procedure described above, 46 mg of **2.26b** (colourless oil) were obtained in 91% yield, starting from 50 mg of **2.24b**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.12 (t, J = 7.1 Hz, 3H), 2.18 (d, J = 1.5 Hz, 3H), 3.70 (s, 3H), 4.14-4.24 (m, 2H), 4.59 (d, J = 17.7 Hz, 1H), 4.67 (d, J = 17.4 Hz, 1H), 5.62 (s, 1H), 6.30 (d, J_o = 8.7 Hz, 1H), 6.55 (dd, J_o = 9.0 Hz, J_m = 3.0 Hz, 1H), 6.81 (d, J_m = 3.0 Hz, 1H), 7.16-7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 19.0, 52.5, 55.5, 62.7, 75.5 (t, $^2J_{CF}$ = 21.9 Hz), 110.9, 113.9, 114.1, 115.4, 122.6, 126.5, 126.7, 128.3, 130.3 (t, $^1J_{CF}$ = 310.2 Hz), 135.6, 135.6, 137.3, 151.9, 167.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -59.3 (d, J_{FF} = 160.7 Hz), -60.5 (d, J_{FF} = 160.7 Hz); HRMS (ES) calc. for (M^++1) $C_{22}H_{23}ClF_2NO_3$: 422.1329; found: 422.1335.



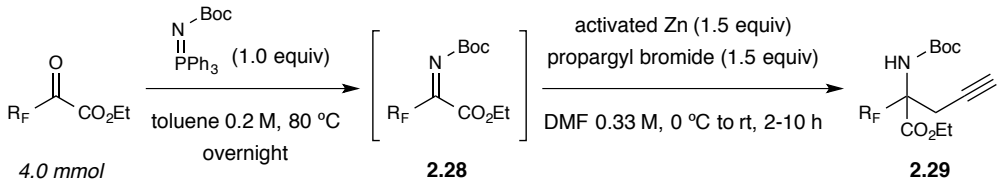
Ethyl 1-benzyl-2-(difluoro(phenyl)methyl)-6-methoxy-4-methyl-1,2-dihydroquinoline-2-carboxylate. Following the general procedure described above, 27 mg of **2.26c** (yellow oil) were obtained in 53% yield, starting from 50 mg of **2.24c**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.07 (t, J = 7.2 Hz, 3H), 2.09 (d, J = 1.5 Hz, 3H), 3.66 (s, 3H), 4.07-4.18 (m, 2H), 4.68 (d, J = 17.7 Hz, 1H), 4.78 (d, J = 17.7 Hz, 1H), 5.41 (s, 1H), 6.14 (d, J_o = 9.0 Hz, 1H), 6.43 (dd, J_o = 9.0 Hz, J_m = 3.0 Hz, 1H), 6.61 (d, J_m = 3.0 Hz, 1H), 7.13-7.32 (m, 8 H), 7.45-7.48 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 18.8, 52.6, 55.6, 62.1, 74.3 (t, $^2J_{CF}$ = 26.8 Hz), 110.6, 113.4, 113.6, 117.6 (t, $^4J_{CF}$ = 3.0 Hz), 122.5, 123.0 (t, $^1J_{CF}$ = 261.2 Hz), 126.4, 126.6, 127.0, 127.5 (t, $^3J_{CF}$ = 6.8 Hz), 128.1, 129.7, 134.2 (t, $^2J_{CF}$ = 25.3 Hz), 134.4, 136.5, 138.0, 151.3, 168.6; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -100.4 (d, J = 14.1 Hz); HRMS (ES) calc. for (M^++1) $C_{28}H_{28}F_2NO_3$: 464.2032; found: 464.2028.



Benzyl 1-benzyl-2-(1,1-difluorobut-3-en-1-yl)-6-methoxy-4-methyl-1,2-dihydroquinoline-2-carboxylate. Following the general procedure described above, 38 mg of **2.26d** (yellowish oil) were obtained in 75% yield, starting from 50 mg of **2.24d**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.03 (d, J = 1.2 Hz, 3H), 2.51-2.91 (m, 2H), 3.61 (s, 3H), 4.43 (d, J = 17.7 Hz, 1H), 4.55 (d, J = 17.7 Hz, 1H), 4.96 (dd, J_{trans} = 17.1 Hz, J_{gem} = 1.5 Hz, 1H), 5.01 (d, J = 12.9 Hz, 1H), 5.06 (dd, J_{cis} = 10.2 Hz, J_{gem} = 1.5 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.48 (s, 1H), 5.71 (dddd, J_1 = 13.5 Hz, J_2 = 9.9 Hz, J_3 = J_4 = 6.9 Hz, 1H), 6.17 (d, J_o = 8.7 Hz, 1H), 6.44 (dd, J_o = 9.0 Hz, J_m = 3.0 Hz, 1H), 6.67 (d, J_m = 2.7 Hz, 1H), 7.05-7.22 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 18.9, 37.9 (t, $^{2}J_{CF}$ = 23.8 Hz), 52.8, 55.5, 67.7, 73.7 (t, $^{2}J_{CF}$ = 23.8 Hz), 110.9, 113.8, 113.9, 117.4, 120.1, 122.5, 126.4, 126.6, 128.2, 128.3, 128.4, 128.6, 129.0, 129.7, 134.5, 135.0, 136.9, 137.9, 151.7, 168.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -102.9 (ddd, J_{FF} = 250.1 Hz, $(J_{FH})_1$ = 30.5 Hz, $(J_{FH})_2$ = 8.7 Hz, 1F), -104.6 (ddd, J_{FF} = 250.1 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 7.9 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{30}H_{30}F_2NO_3$: 490.2188; found: 490.2191.

2.5.3. Gold-catalyzed *O*-addition with concomitant loss of isobutene.

2.5.3.1. General procedure for the preparation of *N*-Boc-propargyl-α-amino esters.

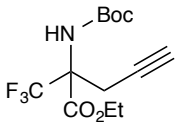


To a solution of *N*-Boc-iminophosphorane[142] (1.0 equiv, 4.0 mmol) in dry toluene (0.2 M, 20 mL), was added dropwise the corresponding ketoester[143] (1.0 equiv, 4.0 mmol) and the resulting solution was refluxed overnight. Once the mixture was cooled to room temperature, toluene was removed under reduced pressure. Diethyl ether was then added (20 mL) and a white precipitated of triphenylphosphine oxide was formed. The mixture was decanted and the solution was transferred to another flask under inert conditions; the residual solid was washed with diethyl ether (10 mL),

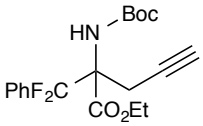
[142] *N*-Boc-iminophosphorane was prepared according to the procedure described in the literature: Vidal, J.; Guy, L.; Stérin, S.; Colle, A. *J. Org. Chem.*, **1993**, *58*, 4791.

[143] Ketoesters were obtained according to previously reported procedures: (a) Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron*, **2004**, *60*, 7731. (b) Parisi, M. F.; Gattuso, G.; Notti, A.; Raymo, F. M. *J. Org. Chem.* **1995**, *60*, 5174. (c) Shi, G.; Cai, W. *J. Org. Chem.* **1995**, *60*, 6289.

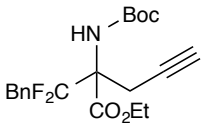
decanted and transferred again. The process was repeated 2 more times. After removal of the combined solvents, the crude was directly used in the next step without further purification due to the instability shown by the imino esters **2.28** towards hydrolysis. The crude was dissolved in DMF (0.33 M, 12 mL) and then propargyl bromide was added (1.5 equiv, 888 mg, 6.0 mmol). The solution was cooled to 0 °C, then activated zinc powder (1.5 equiv, 392 mg, 6.0 mmol) was added. The reaction mixture was then slowly warmed to room temperature. After 2-10 h (the reaction was monitored by TLC) the medium was cooled to 0°C and hydrolyzed with a saturated aqueous solution of NH_4Cl (50 mL), then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried with $MgSO_4$, filtered, and the solvents were evaporated. The residue was purified by flash chromatography over silica gel (hexanes/EtOAc 20:1) to afford *N*-Boc-homopropargyl amines **2.29**.



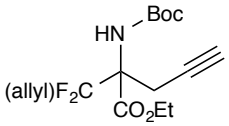
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)-4-pentynoate. Following the general procedure described above, 0.82 g of **2.29a** (colourless oil) were obtained from 0.68 g of ethyl trifluoropyruvate and 1.51 g of *N*-Boc-iminophosphorane in 66% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.34 (t, J = 7.2 Hz, 3H), 1.46 (s, 9H), 2.05 (t, J = 2.7 Hz, 1H), 3.10 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 3.74 (d, J = 17.1 Hz, 1H), 4.28-4.43 (m, 2H), 5.72 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 20.7, 28.1, 63.7, 64.5 (q, $^2J_{CF}$ = 28.7 Hz), 72.0, 76.3, 80.8, 123.4 (q, $^1J_{CF}$ = 287.9 Hz), 153.2, 165.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -74.7 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{13}H_{19}F_3NO_4$: 348.0820; found: 348.0819.



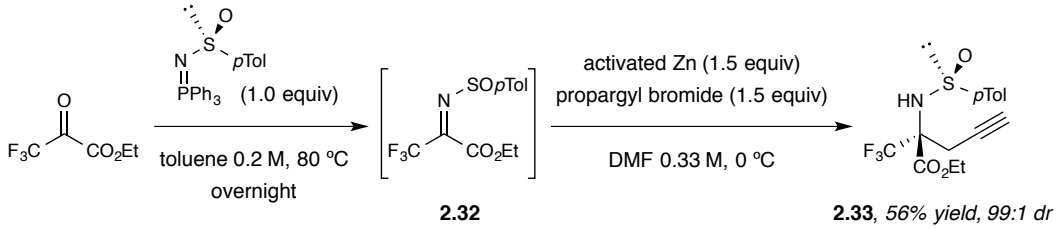
Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(difluoro(phenyl)methyl)-4-pentynoate. Following the general procedure described above, 0.54 g of **2.29b** (yellowish oil) were obtained from 0.60 g of ketoester **2.27b** and 1.00 g of *N*-Boc-iminophosphorane in 56% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, J = 7.2 Hz, 3H), 1.38 (s, 9H), 1.95 (t, J = 2.6 Hz, 1H), 3.22 (dd, J_1 = 16.5 Hz, J_2 = 2.1 Hz, 1H), 3.69 (d, J = 15.3 Hz, 1H), 4.19-4.36 (m, 2H), 5.73 (br s, 1H), 7.37-7.48 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 20.4, 28.1, 63.1, 67.6 (t, $^2J_{CF}$ = 28.2 Hz), 70.9, 78.1, 79.9, 120.2 (t, $^1J_{CF}$ = 257.5 Hz), 126.3 (t, $^3J_{CF}$ = 6.3 Hz), 128.1, 130.5 (t, $^4J_{CF}$ = 1.3 Hz), 132.9 (t, $^2J_{CF}$ = 25.7 Hz), 153.2, 167.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -101.4 (d, J_{FF} = 245.3 Hz, 1F), -102.8 (d, J_{FF} = 245.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{19}H_{24}F_2NO_4$: 368.1668; found: 368.1666.



Ethyl 2-((*tert*-butoxycarbonyl)amino)-2-(1,1-difluoro-2-phenylethyl)-4-pentynoate. Following the general procedure described above, 0.42 g of **2.29c** (colourless oil) were obtained from 0.40 g of ketoester **2.27c** and 0.62 g of *N*-Boc-iminophosphorane in 67% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.2 Hz, 3H), 1.40 (s, 9H), 1.94 (t, J = 2.7 Hz, 1H), 3.08-3.34 (m, 3H), 3.60 (d, J = 17.4 Hz, 1H), 4.17-4.28 (m, 2H), 5.72 (br s, 1H), 7.17-7.25 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.9, 20.7, 28.2, 38.9 (t, $^{2}J_{CF}$ = 23.8 Hz), 63.1, 66.6 (t, $^{2}J_{CF}$ = 26.0 Hz), 71.3, 78.1, 80.5, 121.5 (t, $^{1}J_{CF}$ = 255.2 Hz), 127.4, 128.2, 130.8, 131.6, 154.0, 168.1 (t, $^{3}J_{CF}$ = 2.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -104.0 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F), -105.5 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++Na) $C_{20}H_{25}F_2NO_4Na$: 404.1644; found: 404.1631.

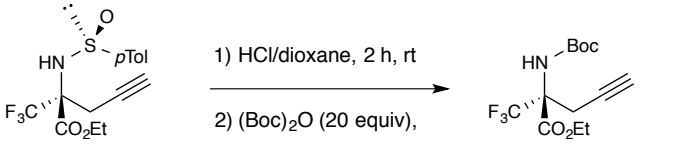


Ethyl 2-((*tert*-butoxycarbonyl)amino)-3,3-difluoro-2-(prop-2-yn-1-yl)-5-hexenoate. Following the general procedure described above, 0.75 g of **2.29d** (colourless oil) were obtained from 0.80 g of ketoester **2.27d** and 1.22 g of *N*-Boc-iminophosphorane in 70% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.98 (t, J = 2.6 Hz, 1H), 2.63-2.92 (m, 2H), 3.14 (dd, J_1 = 16.8 Hz, J_2 = 2.4 Hz, 1H), 3.59 (d, J = 16.8 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 5.20 (dd, J_1 = 9.9 Hz, J_2 = 1.5 Hz, 1H), 5.25 (d, J = 1.2 Hz, 1H), 5.73 (br s, 1H), 5.73-5.89 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 20.6, 28.2, 37.5 (t, $^{2}J_{CF}$ = 24.2 Hz), 63.1, 66.4 (t, $^{2}J_{CF}$ = 26.0 Hz), 71.2, 78.1, 80.4, 120.9, 121.8 (t, $^{1}J_{CF}$ = 254.8 Hz), 127.9 (t, $^{3}J_{CF}$ = 4.9 Hz), 153.9, 168.1 (t, $^{3}J_{CF}$ = 2.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -104.6 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 14.1 Hz, 1F), -105.8 (ddd, J_{FF} = 248.2 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{16}H_{24}F_2NO_4$: 332.1668; found: 332.1681.



2.32 **2.33**, *56% yield, 99:1 dr*

Synthesis of ethyl (*S*,*S*)-2-(4-methylphenylsulfinamido)-2-(trifluoromethyl)-4-pentynoate. Preparation of the propargyl-α-amino ester **2.33** was carried out according to the general procedure *2.5.3.1*, starting in this case from the (*S*)-*N*-(*p*-tolylsulfinylimino)triphenylphosphorane.[144] As occurred with *N*-Boc-imino esters, sulfinimine **2.32** was used *in situ* in the propargylation step, without further purification (attempts to purify it by flash chromatography on silica gel gave rise to extended hydrolysis). Following that procedure, 1.17 g of **2.33** (yellow dense oil) were obtained from 1.0 mL of ethyl trifluoropyruvate and 2.50 g of the iminophosphorane in 56% yield and 99:1 dr. Major diastereoisomer: $[\alpha]^{25}_{D}$ = -12.5 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.12 (t, *J* = 2.7 Hz, 1H), 2.33 (s, 3H), 3.22 (d, *J* = 2.7 Hz, 2H), 4.21-4.37 (m, 2H), 5.24 (br s, 1H), 7.23 (d, J_o = 7.8 Hz, 2H), 7.65 (d, J_o = 8.1 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 21.0 (q, $^3J_{CF}$ = 2.3 Hz), 21.2, 63.9, 66.9 (q, $^2J_{CF}$ = 28.9 Hz), 72.9, 76.3, 122.9 (q, $^1J_{CF}$ = 288.4 Hz), 125.7, 129.5, 141.7, 142.4, 165.0 (q, $^3J_{CF}$ = 1.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -75.7 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{15}H_{17}F_3NO_3S$: 348.0876; found: 348.0866.



2.33 (*S*)-(+)-**2.29a**, *80% yield*

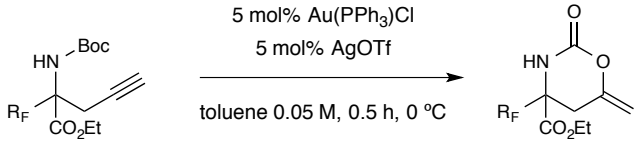
Ethyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(trifluoromethyl)pent-4-ynoate. The enantiomerically pure *N*-Boc-homopropargyl amine (*S*)-**2.29a** was obtained as a colourless oil following general procedure described bellow in 80% yield (71 mg) starting from 100 mg of sulfinylamine (*S*,*S*)-**2.33**. $[\alpha]^{25}_{D}$ = +2.8 (*c* = 1.0 in $CHCl_3$). Spectroscopic data were agreed with those indicated above.

Starting *p*-tolilsulfinamide (*S*,*S*)-**2.33** (1.0 equiv, 0.29 mmol) was treated with 20 equivalents of HCl in dioxane 4.0 M (1.5 mL, 5.76 mmol). After total consumption of the starting material (TLC), solvents were removed at reduced pressure. The crude was treated with *tert*-butyl carbamate anhydride (20.0 equiv, 1.26 g, 5.76 mmol) and DMAP (5.0 equiv, 141 mg, 1.15 mmol). After stirring the reaction mixture for half an hour at room temperature, the reaction mixture was hydrolyzed with an aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 x 10 mL). Combined organic layers were dried

[144] Preparation of (*S*)-*N*-(*p*-tolylsulfinylimino)triphenylphosphorane was afforded following the methodology previously described by our research group: Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, J. G.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449.

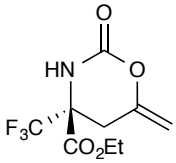
over anhydrous Na_2SO_4 and solvents were removed at reduced pressure. The crude was purified by column flash chromatography.

2.5.3.2. General procedure for the synthesis of the fluorinated alkylidene oxazinones.

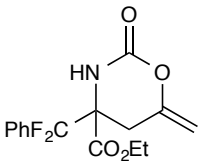


2.29, *0.20 mmol* **2.30**

Over a solution of $Au(PPh_3)Cl$ (5 mol%)[145] and the corresponding *N*-Boc-propargyl-α-amino ester **2.29** (1.0 equiv, 0.20 mmol) in dry toluene (0.05 M, 4.0 mL) at room temperature, AgOTf (5 mol%) was added. Once total consumption of the starting material was observed by TLC, the reaction crude was purified after removal of the solvents by column chromatography.



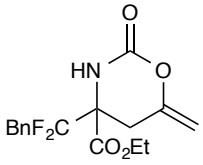
Ethyl (*S*)-6-methylene-2-oxo-4-(trifluoromethyl)-1,3-oxazinane-4-carboxylate. Following the general procedure described above, 46 mg of **2.30a** were obtained in 91% yield as a white solid, starting from 62 mg of **2.29a**. m.p. 121-123 ºC; $[\alpha]^{25}_D$ = -0.6 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, *J* = 7.2 Hz, 3H), 2.87 (dd, J_1 = 15.3 Hz, J_2 = 0.9 Hz, 1H), 3.09 (d, *J* = 15.3 Hz, 1H), 4.31-4.41 (m, 2H), 4.51 (t, *J* = 1.8 Hz, 1H), 4.87 (dd, J_1 = 2.1 Hz, J_2 = 1.5 Hz, 1H), 6.60 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 27.9, 61.8 (q, $^2J_{CF}$ = 29.4 Hz), 64.2, 97.3, 122.7 (q, $^1J_{CF}$ = 287.2 Hz), 147.3, 148.7, 164.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -76.5 (s, 3F); HRMS (ES) calc. for (M^++1) $C_9H_{11}F_3NO_4$: 254.0635; found: 254.0631.



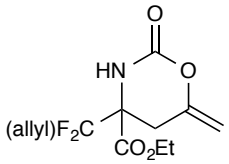
Ethyl 4-(difluoro(phenyl)methyl)-6-methylene-2-oxo-1,3-oxazinane-4-carboxylate. Following the general procedure described above, 55 mg of **2.30b** were obtained in 88% yield as a white solid,

[145] Non-commercially available gold species were prepared from $Au(SMe_2)Cl$. Over a solution of the corresponding phosphine (**Ln**) in dry DCM cooled at 0 ºC, 1 equiv of $Au(SMe_2)Cl$ was added. The mixture was stirred at room temperature until the reaction was completed (TLC or ^{31}P-NMR). Removal of the solvent led to the corresponding Au(**Ln**)Cl complex.

starting from 73 mg of **2.29b**. m.p. 149-151 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.22 (t, J = 7.1 Hz, 3H), 2.86 (d, J = 15.3 Hz, 1H), 3.08 (d, J = 15.0 Hz, 1H), 4.11-4.27 (m, 2H), 4.38 (s, 1H), 4.74 (dd, J_1 = 2.1 Hz, J_2 = 1.5 Hz, 1H), 6.12 (br s, 1H), 7.38-7.53 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 28.1 (t, $^{3}J_{CF}$ = 2.6 Hz), 63.3, 64.5 (t, $^{2}J_{CF}$ = 29.4 Hz), 96.2, 119.5 (t, $^{1}J_{CF}$ = 256.7 Hz), 126.1 (t, $^{3}J_{CF}$ = 6.4 Hz), 128.5, 131.2, 131.5 (t, $^{2}J_{CF}$ = 25.7 Hz), 148.6, 149.2, 166.6; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -104.5 (d, J_{FF} = 248.2 Hz, 1F), -106.0 (d, J_{FF} = 248.2 Hz, 1F); HRMS (ES) calc. for (M^{+}+1) $C_{15}H_{16}F_2NO_4$: 312.1042; found: 312.1048.



Ethyl 4-(1,1-difluoro-2-phenylethyl)-6-methylene-2-oxo-1,3-oxazinane-4-carboxylate. Following the general procedure described above, 46 mg of **2.30c** were obtained in 71% yield as a white solid, starting from 76 mg of **2.29c**. m.p. 113-115 ºC; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.34 (t, J = 7.5 Hz, 3H), 2.85 (d, J = 15.0 Hz, 1H), 3.02 (d, J = 15.0 Hz, 1H), 3.12-3.23 (m, 1H), 3.30-3.40 (m, 1H), 4.29-4.33 (m, 2H), 4.42 (d, J = 1.5 Hz, 1H), 4.81 (dd, J_1 = 2.0 Hz, J_2 = 1.0 Hz, 1H), 6.23 (br s, 1H), 7.24-7.25 (m, 2H), 7.31-7.35 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.0, 28.7 (t, $^{3}J_{CF}$ = 3.4 Hz), 38.6 (t, $^{2}J_{CF}$ = 24.2 Hz), 63.6, 64.1 (t, $^{2}J_{CF}$ = 26.4 Hz), 96.5, 120.5 (t, $^{1}J_{CF}$ = 254.4 Hz), 127.9, 128.5, 130.6, 130.7, 148.5, 149.3, 167.3 (t, $^{3}J_{CF}$ = 2.3 Hz); ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -105.7 (ddd, J_{FF} = 253.2 Hz, $(J_{FH})_1$ = 28.1 Hz, $(J_{FH})_2$ = 9.4 Hz, 1F), -106.8 (ddd, J_{FF} = 253.2 Hz, $(J_{FH})_1$ = 28.1 Hz, $(J_{FH})_2$ = 9.4 Hz, 1F); HRMS (ES) calc. for (M^{+}+1) $C_{16}H_{18}F_2NO_4$: 326.1198; found: 326.1192.

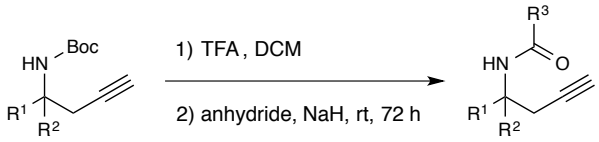


Ethyl 4-(1,1-difluorobut-3-en-1-yl)-6-methylene-2-oxo-1,3-oxazinane-4-carboxylate. Following the general procedure described above, 42 mg of **2.30d** were obtained in 77% yield as a colourless oil, starting from 66 mg of **2.29d**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, J = 7.1 Hz, 3H), 2.57-2.91 (m, 2H), 2.85 (d, J = 15.0 Hz, 1H), 3.00 (d, J = 15.0 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.44 (s, 1H), 4.80 (d, J = 1.5 Hz, 1H), 5.21-5.29 (m, 2H), 5.79 (dddd, J_1 = 17.2 Hz, J_2 = 10.3 Hz, J_3 = 6.9 Hz, J_4 = 6.9 Hz, 1H), 6.49 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 28.5 (t, $^{3}J_{CF}$ = 3.0 Hz), 37.1 (t, $^{2}J_{CF}$ = 24.2 Hz), 63.5, 63.9 (t, $^{2}J_{CF}$ = 26.4 Hz), 96.3, 120.6 (t, $^{1}J_{CF}$ = 254.4 Hz), 121.6, 127.0 (t, $^{3}J_{CF}$ = 4.9 Hz), 148.6, 149.4, 167.2 (t, $^{3}J_{CF}$ = 2.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -106.3 (ddd, J_{FF} = 251.0 Hz,

(J_{FH})$_1$ = 25.4 Hz, (J_{FH})$_2$ = 14.1 Hz, 1F), -107.6 (ddd, J_{FF} = 251.0 Hz, (J_{FH})$_1$ = 25.4 Hz, (J_{FH})$_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{12}H_{16}F_2NO_4$: 276.1042; found: 276.1044.

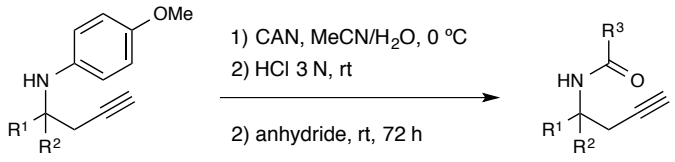
2.5.4. Tandem gold self-relay catalysis for the synthesis of dihydropyridinones.

2.5.4.1. General procedure for the preparation of homopropargyl amides.



2.29 **2.34**

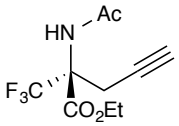
Method A. Over a solution of the corresponding *N*-Boc-propargyl-α-amino ester **2.29** (1.0 equiv, 1.3 mmol) in DCM (0.1 M, 13 mL) cooled at 0 ºC, trifluoroacetic acid (8.0 equiv, 0.8 mL, 10.4 mmol) was slowly added. The reaction mixture was stirred at room temperature until consumption of the starting material (detection by TLC). After removal of solvents at reduced pressure, the crude was dissolved in acetic/propionic anhydride (13 mL) and the mixture was cooled to 0 ºC. Then, sodium hydride (6.0 equiv, 187 mg, 7.8 mmol) was added in small amounts under vigorous stirring and the mixture was stirred at room temperature. Once the reaction was completed, anhydride was removed under vacuum and water was added to the crude mixture in order to exclude any trace of the anhydride. The mixture was extracted with EtOAc (3 x 50 mL). Combined organic layers were dried with anhydrous $MgSO_4$, filtered, and solvents were evaporated. The residue was purified by flash chromatography over silica gel.



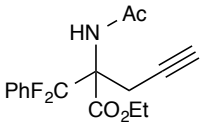
2.20 **2.34**

Method B. Over a solution of the corresponding homopropargyl aryl amine **2.20** (1.0 equiv, 0.1 mmol) in MeCN (0.05 M, 2 mL) cooled to 0 ºC, a solution of ceric ammonium nitrate, CAN (3.0 equiv, 0.3 mmol), in water (1 mL) was dropwise added. After one hour at this temperature, the starting material was consumed (TLC). Then, an aqueous solution of HCl 3N (5 mL) was added to the mixture, which was stirred for an additional hour at room temperature in order to hydrolyze the iminium intermediate. The mixture was neutralized with a saturated aqueous solution of $NaHCO_3$ and then extracted with EtOAc (4 x 10 mL). Combined organic layers were washed with Na_2SO_3 20%

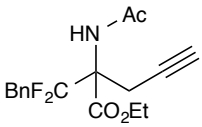
solution (10 mL) and dried over anhydrous Na_2SO_4. After removal of solvents under reduced pressure, the acetylation reaction was carried out as in method A without the need to add NaH.



Ethyl (*S*)-2-acetamido-2-(trifluoromethyl)-4-pentynoate. Following the general procedure described above (method A), 260 mg of **2.34a** (white solid) were obtained from 400 mg of **2.29a** in 80% yield. The enantiomerically pure acetamide (*S*)-**2.34a** was obtained following general procedure described above (method A)[146] in 89% yield (186 mg) starting from 300 mg of sulfinylamine (*S*,*S*)-**2.33**. m.p. 68-70 ºC; $[\alpha]^{25}_{D}$ = -6.4 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.02 (t, *J* = 2.7 Hz, 1H), 2.08 (s, 3H), 3.14 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 3.78 (dd, J_1 = 17.1 Hz, J_2 = 2.7 Hz, 1H), 4.29-4.39 (m, 2H), 6.60 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 20.5, 23.7, 63.8, 64.7 (q, $^2J_{CF}$ = 28.9 Hz), 71.9, 76.5, 123.2 (q, $^1J_{CF}$ = 287.7 Hz), 165.6, 169.5; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -74.0 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{10}H_{13}F_3NO_3$: 252.0842; found: 252.0842.



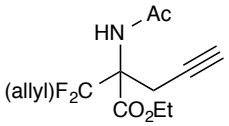
Ethyl 2-acetamido-2-(difluoro(phenyl)methyl)-4-pentynoate. Following the method described above (method A), 215 mg of **2.34b** (85% yield) were obtained as a white solid starting from 300 mg of **2.29b**. m.p. 87-89 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.96 (t, *J* = 2.8 Hz, 1H), 2.04 (s, 3H), 3.28 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 3.68 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 4.13-4.33 (m, 2H), 6.46 (br s, 1H), 7.37-7.50 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 20.3 (t, $^3J_{CF}$ = 2.5 Hz), 24.0, 63.1, 68.1 (t, $^2J_{CF}$ = 27.6 Hz), 70.9, 78.3, 120.2 (t, $^1J_{CF}$ = 257.5 Hz), 126.1 (t, $^3J_{CF}$ = 6.9 Hz), 128.1, 130.7 (t, $^4J_{CF}$ = 1.3 Hz), 132.6 (t, $^2J_{CF}$ = 25.7 Hz), 167.5 (t, $^3J_{CF}$ = 3.1 Hz), 169.4; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -101.4 (s, 2F); HRMS (ES) calc. for (M^++1) $C_{16}H_{18}F_2NO_3$: 310.1249; found: 310.1237.



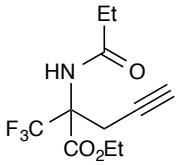
Ethyl 2-acetamido-2-(1,1-difluoro-2-phenylethyl)-4-pentynoate. Following the general procedure described above (method A), 154 mg of **2.34c** (yellow sticky oil) were obtained from 200 mg of **2.29c**

[146] In this case, deprotection of the corresponding sulfinyl amine was achieved by treatment with HCl in dioxane.

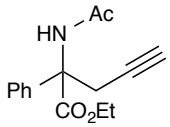
in 91% yield. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.24 (t, J = 7.0 Hz, 3H), 1.92 (t, J = 2.8 Hz, 1H), 1.99 (s, 3H), 3.14-3.29 (m, 3H), 3.69 (dd, J_1 = 17.0 Hz, J_2 = 2.5 Hz, 1H), 4.19-4.27 (m, 2H), 6.50 (br s, 1H), 7.17-7.25 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 20.5 (t, $^{3}J_{CF}$ = 3.8 Hz), 23.9, 39.2 (t, $^{2}J_{CF}$ = 23.2 Hz), 63.2, 67.1 (t, $^{2}J_{CF}$ = 25.7 Hz), 71.2, 78.1, 121.4 (t, $^{1}J_{CF}$ = 253.7 Hz), 127.4, 128.2, 130.8, 131.5 (t, $^{3}J_{CF}$ = 1.9 Hz), 167.9 (t, $^{3}J_{CF}$ = 2.5 Hz), 169.9; ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -103.1 (ddd, J_{FF} = 248.5 Hz, $(J_{FH})_1$ = 28.1 Hz, $(J_{FH})_2$ = 9.4 Hz, 1F), -104.3 (ddd, J_{FF} = 248.5 Hz, $(J_{FH})_1$ = 28.1 Hz, $(J_{FH})_2$ = 9.4 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{17}H_{20}F_2NO_3$: 324.1406; found: 324.1393.



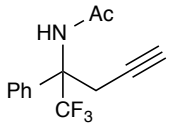
Ethyl 2-acetamido-3,3-difluoro-2-(prop-2-yn-1-yl)-5-hexenoate. Starting from 500 mg of **2.34d**, according to general procedure described above (method A), 408 mg of a white solid corresponding to **2.29d** were isolated in 99% yield. m.p. 48-50 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, J = 7.2 Hz, 3H), 1.93 (t, J = 2.6 Hz, 1H), 2.00 (s, 3H), 2.64-2.80 (m, 2H), 3.12 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 3.52 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 4.17-4.27 (m, 2H), 5.13 (ddd, J_1 = 8.4 Hz, J_2 = 2.7 Hz, J_3 = 1.2 Hz, 1H), 5.17 (dd, J_1 = 2.1 Hz, J_2 = 0.9 Hz, 1H), 5.67-5.80 (m, 1H), 6.73 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.6, 20.3 (t, $^{3}J_{CF}$ = 3.8 Hz), 23.5, 37.5 (t, $^{2}J_{CF}$ = 23.2 Hz), 62.9, 66.6 (t, $^{2}J_{CF}$ = 25.7 Hz), 71.0, 78.0, 120.7, 121.6 (t, $^{1}J_{CF}$ = 253.7 Hz), 127.6 (t, $^{3}J_{CF}$ = 5.0 Hz), 167.6 (t, $^{3}J_{CF}$ = 2.5 Hz), 169.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -103.9 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 22.6 Hz, $(J_{FH})_2$ = 14.1 Hz, 1F), -104.9 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 22.6 Hz, $(J_{FH})_2$ = 14.1 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{13}H_{18}F_2NO_3$: 274.1249; found: 274.1242.



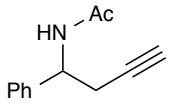
Ethyl 2-propionamido-2-(trifluoromethyl)-4-pentynoate. Following the general procedure described above (method A), using propionic anhydride instead of acetic anhydride, 216 mg of **2.34e** (white solid) were obtained from 400 mg of **2.29a** in 63% yield. m.p. 52-54 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, J = 7.7 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 2.01 (t, J = 2.6 Hz, 1H), 2.30 (d, J = 7.5 Hz, 1H), 2.35 (dd, J_1 = 7.8 Hz, J_2 = 0.3 Hz, 1H), 3.14 (dd, J_1 = 17.1 Hz, J_2 = 2.4 Hz, 1H), 3.84 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 4.35 (dq, J_1 = 7.1 Hz, J_2 = 1.2 Hz, 2H), 6.46 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 9.5, 13.8, 20.5 (q, $^{3}J_{CF}$ = 1.5 Hz), 30.2, 63.9, 64.7 (q, $^{2}J_{CF}$ = 28.9 Hz), 71.9, 76.6, 123.3 (q, $^{1}J_{CF}$ = 287.7 Hz), 165.7, 173.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -74.1 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{11}H_{15}F_3NO_3$: 266.0999; found: 266.0990.



Ethyl 2-acetamido-2-phenyl-4-pentynoate. Following the general procedure described above (method B), 69 mg of **2.34f** (brown solid) were obtained from 200 mg of **2.20g** in 43% yield. m.p. 98-100 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, J = 7.1 Hz, 3H), 2.00 (t, J = 2.7 Hz, 1H), 2.04 (s, 3H), 3.50 (dd, J_1 = 16.5 Hz, J_2 = 2.4 Hz, 1H), 3.76 (dd, J_1 = 16.8 Hz, J_2 = 2.7 Hz, 1H), 4.08-4.31 (m, 2H), 7.11 (br s, 1H), 7.30-7.41 (m, 3H), 7.45-7.49 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 23.3, 24.0, 62.3, 64.3, 71.0, 79.5, 125.7, 128.0, 128.4, 137.7, 169.1, 171.1; HRMS (ES) calc. for (M^++1) $C_{15}H_{18}NO_3$: 260.1208; found: 260.1195.

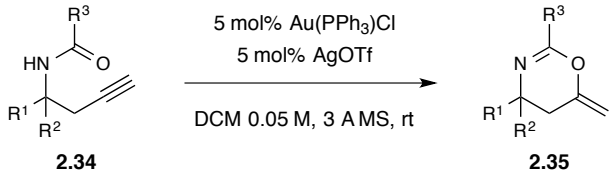


***N*-(1,1,1-trifluoro-2-phenylpent-4-yn-2-yl)acetamide.** Starting from 200 mg of **2.20h**, according to general procedure described above (method B), 123 mg of a brown solid corresponding to **2.34g** were isolated in 77% yield. m.p. 114-116 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.10 (t, J = 2.6 Hz, 1H), 2.12 (s, 3H), 3.51 (dd, J_1 = 17.1 Hz, J_2 = 2.4 Hz, 1H), 3.60 (dd, J_1 = 17.1 Hz, J_2 = 2.1 Hz, 1H), 6.16 (br s, 1H), 7.35-7.45 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 23.8, 23.9 (q, $^{3}J_{CF}$ = 1.5 Hz), 63.7 (q, $^{2}J_{CF}$ = 26.7 Hz), 71.9, 78.0, 125.0 (q, $^{1}J_{CF}$ = 286.1 Hz), 126.5 (q, $^{4}J_{CF}$ = 1.5 Hz), 128.5, 128.8, 135.1, 169.6; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -75.5 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{13}H_{13}F_3NO$: 256.0871; found: 256.0870.

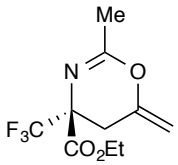


***N*-(1-phenylbut-3-yn-1-yl)acetamide.** Acetamide **2.34h** was prepared according to the procedure reported in the literature. Spectral data were in agreement with previously reported data.[97i]

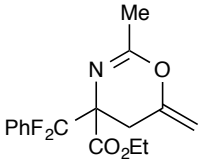
2.5.4.2. General procedure for the isolation of oxazines.



Over a solution of the corresponding homopropargyl amide **2.34** (1.0 equiv, 0.1 mmol) in dried DCM (0.05 M, 2 mL) prepared in a sealed tube charged with 3 Å molecular *sieves*, $Au(PPh_3)Cl$ (5 mol%) and AgOTf (5 mol%) were successively added. Once the reaction was completed, and after removal of solvents, the crude was purified by flash chromatography over silica gel.[147]



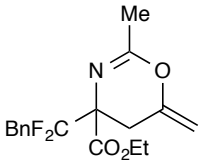
Ethyl (*S*)-2-methyl-6-methylene-4-(trifluoromethyl)-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Following the general procedure described above, 36 mg of (*S*)-**2.35a** (colourless oil) were obtained from 50 mg of (*S*)-**2.34a** in 72% (83%) yield. $[\alpha]^{25}_{D}$ = +73.4 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.14 (s, 3H), 2.61 (dt, J_1 = 14.4 Hz, J_2 = 1.8 Hz, 1H), 2.96 (d, *J* = 14.7 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.36 (t, *J* = 2.0 Hz, 1H), 4.72 (t, *J* = 1.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 21.1, 27.9 (q, $^3J_{CF}$ = 2.3 Hz), 62.9, 65.1 (q, $^2J_{CF}$ = 28.2 Hz), 95.0, 123.5 (q, $^1J_{CF}$ = 283.1 Hz), 147.9, 159.4, 166.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -77.5 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{10}H_{13}F_3NO_3$: 252.0842; found: 252.0839.



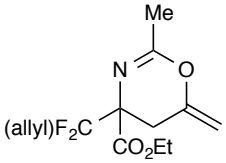
Ethyl 4-(difluoro(phenyl)methyl)-2-methyl-6-methylene-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Starting from 50 mg of **2.34b**, according to general procedure described above, 35 mg of a colourless oil corresponding to **2.35b** were isolated in 70% (86%) yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.17 (t, *J* = 7.1 Hz, 3H), 2.08 (s, 3H), 2.52 (dt, J_1 = 14.4 Hz, J_2 = 1.8 Hz, 1H), 3.08 (d, *J* = 14.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.29 (t, *J* = 1.8 Hz, 1H), 4.62 (t, *J* = 1.7 Hz, 1H), 7.35-7.46 (m, 3H), 7.59-7.62 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 14.0, 21.1, 28.7 (t, $^3J_{CF}$ = 3.8 Hz), 62.2, 67.6 (t, $^2J_{CF}$ = 28.2 Hz), 94.0, 119.9 (t, $^1J_{CF}$ = 252.5 Hz), 127.2 (t, $^3J_{CF}$ = 6.9 Hz), 127.7, 130.2, 133.5 (t, $^2J_{CF}$ =

[147] Yields in brackets were determined by GC/MS before purification by column chromatography.

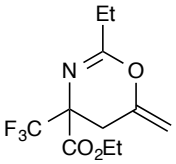
25.7 Hz), 149.3, 157.6, 168.3 (d, $^{3}J_{CF}$ = 1.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -104.5 (s, 2F); HRMS (ES) calc. for (M^++1) $C_{16}H_{18}F_2NO_3$: 310.1249; found: 310.1246.



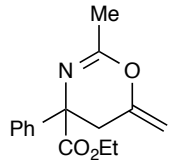
Ethyl 4-(1,1-difluoro-2-phenylethyl)-2-methyl-6-methylene-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Following the method described above, 40 mg of **2.35c** were obtained as a colourless oil in 80% (94%) yield starting from 50 mg of **2.34c**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.15 (s, 3H), 2.60 (dt, J_1 = 14.7 Hz, J_2 = 1.8 Hz, 1H), 2.96 (d, *J* = 14.4 Hz, 1H), 3.18-3.35 (m, 1H), 3.45-3.63 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.28 (t, *J* = 1.7 Hz, 1H), 4.65 (t, *J* = 1.7 Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 14.0, 21.1, 27.7 (t, $^{3}J_{CF}$ = 4.4 Hz), 38.2 (t, $^{2}J_{CF}$ = 23.8 Hz), 62.2, 66.7 (dd, $(^{2}J_{CF})_1$ = 27.6 Hz, $(^{2}J_{CF})_2$ = 25.1 Hz), 93.9, 121.4 (t, $^{1}J_{CF}$ = 250.6 Hz), 127.2, 128.1, 130.9, 132.3 (t, $^{3}J_{CF}$ = 1.9 Hz), 149.4, 157.9, 168.5 (d, $^{3}J_{CF}$ = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -107.8 (ddd, J_{FF} = 245.3 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F), -109.2 (ddd, J_{FF} = 245.3 Hz, $(J_{FH})_1$ = 28.2 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{17}H_{20}F_2NO_3$: 324.1406; found: 324.1406.



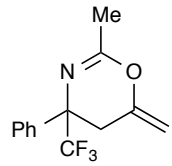
Ethyl 4-(1,1-difluorobut-3-en-1-yl)-2-methyl-6-methylene-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Starting from 50 mg of **2.34d**, according to general procedure described above, 44 mg of a colourless oil corresponding to **2.35d** were isolated in 88% (98%) yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.10 (s, 3H), 2.60 (dt, J_1 = 14.4 Hz, J_2 = 1.8 Hz, 1H), 2.64-2.82 (m, 1H), 2.94 (d, *J* = 14.7 Hz, 1H), 2.90-3.10 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.28 (t, *J* = 1.7 Hz, 1H), 4.63 (t, *J* = 1.7 Hz, 1H), 5.17-5.20 (m, 1H), 5.24 (dd, J_1 = 2.7 Hz, J_2 = 1.4 Hz, 1H), 5.79-5.93 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 14.0, 21.0, 27.7, 36.8 (t, $^{2}J_{CF}$ = 23.8 Hz), 62.2, 66.5 (dd, $(^{2}J_{CF})_1$ = 26.3 Hz, $(^{2}J_{CF})_2$ = 25.1 Hz), 93.9, 120.4, 121.6 (t, $^{1}J_{CF}$ = 250.0 Hz), 128.5 (t, $^{3}J_{CF}$ = 4.4 Hz), 149.4, 157.8, 168.5 (d, $^{3}J_{CF}$ = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -108.6 (ddd, J_{FF} = 248.2 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F), -109.8 (ddd, J_{FF} = 248.2 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{13}H_{18}F_2NO_3$: 274.1249; found: 274.1248.



Ethyl 2-ethyl-6-methylene-4-(trifluoromethyl)-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Following the general procedure described above, 31 mg of **2.35e** as a colourless oil in 61% (95%) yield, starting from 50 mg of **2.34e**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.40 (q, J = 7.6 Hz, 2H), 2.60 (dt, J_1 = 14.7 Hz, J_2 = 1.8 Hz, 1H), 2.96 (d, J = 14.4 Hz, 1H), 4.20-4.31 (m, 2H), 4.34 (t, J = 1.8 Hz, 1H), 4.72 (t, J = 1.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 10.4, 13.9, 28.1, 28.1 (q, $^{3}J_{CF}$ = 2.5 Hz), 62.8, 65.0 (q, $^{2}J_{CF}$ = 28.0 Hz), 94.8, 123.5 (q, $^{1}J_{CF}$ = 281.9 Hz), 148.0, 162.9, 166.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -77.6 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{11}H_{15}F_3NO_3$: 266.0999; found: 266.0987.

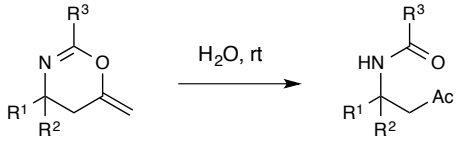


Ethyl 2-methyl-6-methylene-4-phenyl-5,6-dihydro-4*H*-1,3-oxazine-4-carboxylate. Following the general procedure described above, 38 mg of **2.35f** as a colourless oil in 76% yield, starting from 50 mg of **2.34f**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.09 (t, J = 7.1 Hz, 3H), 2.11 (s, 3H), 2.62 (d, J = 14.4 Hz, 1H), 3.07 (d, J = 14.1 Hz, 1H), 4.00-4.19 (m, 2H), 4.10-4.11 (m, 1H), 4.47 (dt, J_1 = 1.5 Hz, J_2 = 0.9 Hz, 1H), 7.16-7.29 (m, 3H), 7.36-7.40 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.0, 21.2, 35.0, 61.8, 64.3, 93.2, 125.6, 127.6, 128.5, 140.9, 150.5, 156.3, 172.1; HRMS (ES) calc. for (M^++1) $C_{15}H_{18}NO_3$: 260.1208; found: 260.1218.



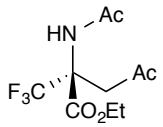
2-Methyl-6-methylene-4-phenyl-4-(trifluoromethyl)-5,6-dihydro-4*H*-1,3-oxazine. Following the method described above, 37 mg of **2.35g** were obtained as a colourless oil in 74% yield starting from 50 mg of **2.34g**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 3H), 2.86 (dt, J_1 = 14.4 Hz, J_2 = 1.8 Hz, 1H), 3.06 (d, J = 14.4 Hz, 1H), 4.18 (t, J = 1.8 Hz, 1H), 4.53 (t, J = 1.8 Hz, 1H), 7.31-7.40 (m, 3H), 7.48-7.51 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.1, 30.3, 62.3 (q, $^{2}J_{CF}$ = 27.4 Hz), 94.1, 125.3 (q, $^{1}J_{CF}$ = 283.1 Hz), 127.3, 128.4, 128.5, 136.7, 148.9, 157.4; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -79.0 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{13}H_{12}F_3NO$: 256.0871; found: 256.0860.

2.5.4.3. General procedure for the hydrolysis of oxazines.

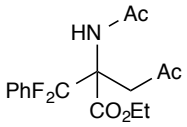


2.35 **2.36**

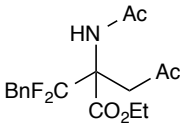
A suspension of the corresponding oxazine **2.35** in water was stirred at room temperature until TLC showed total consumption of the starting material. The mixture was extracted with EtOAc. Combined organic layers were dried over anhydrous Na_2SO_4. Then, solvents were removed under reduced pressure and crude mixture was purified by flash chromatography, isolating the final products in quantitative yields.



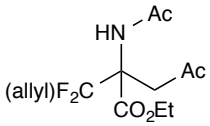
Ethyl (*S*)-2-acetamido-4-oxo-2-(trifluoromethyl)pentanoate. Following the general procedure described above, starting from 30 mg of (*S*)-**2.35a**, 32 mg of (*S*)-**2.36a** were isolated as a yellow oil in 99% yield. $[\alpha]^{25}_D$ = +9.1 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.01 (s, 3H), 2.19 (s, 3H), 3.27 (d, J = 18.0 Hz, 1H), 4.28-4.38 (m, 2H), 4.57 (d, *J* = 17.7 Hz, 1H), 6.67 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 24.5, 29.4, 41.1, 62.3 (q, $^2J_{CF}$ = 28.9 Hz), 63.9, 123.4 (q, $^1J_{CF}$ = 286.9 Hz), 166.3, 170.0, 203.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -75.9 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{10}H_{15}F_3NO_4$: 270.0948; found: 270.0945.



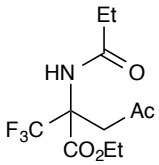
Ethyl 2-acetamido-2-(difluoro(phenyl)methyl)-4-oxopentanoate. Starting from 30 mg of **2.35b**, according to general procedure described above, 31 mg of a colourless oil corresponding to **2.36b** were isolated in 99% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.93 (s, 3H), 2.16 (s, 3H), 3.36 (d, *J* = 18.0 Hz, 1H), 4.18-4.28 (m, 2H), 4.53 (d, *J* = 18.0 Hz, 1H), 6.46 (br s, 1H), 7.34-7.50 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 24.6, 29.5, 41.8, 63.1, 66.2 (t, $^2J_{CF}$ = 29.4 Hz), 120.3 (t, $^1J_{CF}$ = 256.9 Hz), 126.3 (t, $^3J_{CF}$ = 6.3 Hz), 128.1, 130.6, 132.7 (t, $^2J_{CF}$ = 26.3 Hz), 168.2 (dd, $(^3J_{CF})_1$ = 3.4 Hz, $(^3J_{CF})_2$ = 1.3 Hz), 169.5, 204.1; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -102.4 (d, J_{FF} = 245.3 Hz, 1F), -103.9 (d, J_{FF} = 242.5 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{16}H_{20}F_2NO_4$: 328.1355; found: 328.1347.



Ethyl 2-acetamido-2-(1,1-difluoro-2-phenylethyl)-4-oxopentanoate. According to the general procedure described above, 21 mg of **2.36c** were isolated in 99% yield as a colourless oil starting from 20 mg of **2.35c**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, J = 7.2 Hz, 3H), 1.98 (s, 3H), 2.19 (s, 3H), 3.16-3.28 (m, 2H), 3.29 (d, J = 17.7 Hz, 1H), 4.24-4.35 (m, 2H), 4.47 (d, J = 17.7 Hz, 1H), 6.80 (br s, 1H), 7.24-7.34 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 24.5, 29.6, 39.0 (t, $^{2}J_{CF}$ = 23.8 Hz), 41.5 (t, $^{3}J_{CF}$ = 2.5 Hz), 63.2, 65.4 (t, $^{2}J_{CF}$ = 26.3 Hz), 121.6 (t, $^{1}J_{CF}$ = 254.3 Hz), 127.4, 128.3, 130.7, 131.7 (t, $^{3}J_{CF}$ = 2.5 Hz), 168.6 (t, $^{3}J_{CF}$ = 2.5 Hz), 170.2, 204.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -105.2 (dt, $(J_{FH})_1$ = 22.6 Hz, $(J_{FH})_2$ = 14.1 Hz, 2F); HRMS (ES) calc. for (M^++1) $C_{17}H_{21}F_2NO_4$: 342.1511; found: 342.1519.

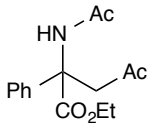


Ethyl 2-acetamido-3,3-difluoro-2-(2-oxopropyl)-5-hexenoate. Following the general procedure described above, starting from 20 mg of **2.35d**, 21 mg of **2.36d** were isolated as a colourless oil in 99% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.2 Hz, 3H), 1.98 (s, 3H), 2.15 (s, 3H), 2.54-2.86 (m, 2H), 3.22 (d, J = 17.7 Hz, 1H), 4.23-4.33 (m, 2H), 4.39 (d, J = 17.7 Hz, 1H), 5.19 (ddd, J_1 = 10.5 Hz, J_2 = 3.0 Hz, J_3 = 1.2 Hz, 1H), 5.22-5.25 (m, 1H), 5.79 (dddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.9 Hz, J_4 = 6.9 Hz, 1H), 6.75 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 24.5, 29.5, 37.4 (t, $^{2}J_{CF}$ = 23.8 Hz), 41.5 (t, $^{3}J_{CF}$ = 1.9 Hz), 63.2, 65.1 (t, $^{2}J_{CF}$ = 26.3 Hz), 120.7, 121.9 (t, $^{1}J_{CF}$ = 253.7 Hz), 127.9 (t, $^{3}J_{CF}$ = 4.4 Hz), 168.4 (t, $^{3}J_{CF}$ = 2.5 Hz), 170.1, 204.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -106.0 (ddd, $(J_{FH})_1$ = 21.9 Hz, $(J_{FH})_2$ = 18.6 Hz, $(J_{FH})_3$ = 15.0 Hz, 2F); HRMS (ES) calc. for (M^++1) $C_{13}H_{20}F_2NO_4$: 292.1355; found: 292.1351.

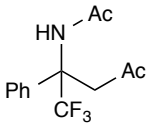


Ethyl 4-oxo-2-propionamido-2-(trifluoromethyl)pentanoate. Following the method described above, 32 mg of **2.36e** (99% yield) were obtained as a colourless oil starting from 30 mg of **2.35e**. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.11 (t, J = 7.7 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 2.25 (q, J = 7.6 Hz, 2H), 3.26 (dd, J_1 = 18.0 Hz, J_2 = 0.9 Hz, 1H), 4.28-4.38 (m, 2H), 4.58 (d, J = 17.7 Hz, 1H), 6.66 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 9.4, 13.7, 29.5, 30.6, 41.2, 62.9 (q, $^{2}J_{CF}$ = 28.8 Hz),

63.9, 123.5 (q, $^{1}J_{CF}$ = 286.9 Hz), 166.4, 173.7, 203.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -76.0 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{11}H_{17}F_3NO_4$: 284.1104; found: 284.1113.

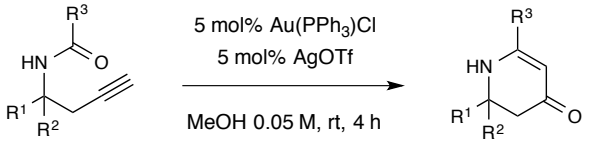


Ethyl 2-acetamido-4-oxo-2-phenylpentanoate. Following the general procedure described above, starting from 20 mg of **2.35f**, 18 mg of **2.36f** were isolated as a colourless oil in 84% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.15 (t, *J* = 7.1 Hz, 3H), 2.00 (s, 3H), 2.19 (s, 3H), 3.67 (d, *J* = 18.0 Hz, 1H), 4.05-4.25 (m, 2H), 4.40 (d, *J* = 18.0 Hz, 1H), 7.21 (br s, 1H), 7.25-7.37 (m, 3H), 7.40-7.44 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.7, 24.0, 30.2, 46.6, 62.3, 62.4, 125.5, 128.0, 128.6, 138.4, 168.9, 171.8, 205.8; HRMS (ES) calc. for (M^++1) $C_{15}H_{20}NO_4$: 278.1314; found: 278.1322.



***N*-(1,1,1-trifluoro-4-oxo-2-phenylpentan-2-yl)acetamide.** According to the general procedure described above,[148] 21 mg of **2.36g** were isolated in 99% yield as a white solid starting from 20 mg of **2.35g**. m.p. 144-146 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, 3H), 2.17 (s, 3H), 3.40 (d, *J* = 16.8 Hz, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 6.47 (br s, 1H), 7.33-7.46 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 24.2, 31.5, 43.4 (q, $^{3}J_{CF}$ = 0.8 Hz), 63.3 (q, $^{2}J_{CF}$ = 27.9 Hz), 125.2 (q, $^{1}J_{CF}$ = 286.1 Hz), 126.0 (q, $^{4}J_{CF}$ = 1.5 Hz), 128.6, 128.7, 135.8 (q, $^{3}J_{CF}$ = 0.8 Hz), 170.1, 203.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -74.6 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{13}H_{15}F_3NO_2$: 274.0977; found: 274.9994.

2.5.4.4. General procedure for the preparation of dihydropyridinones.

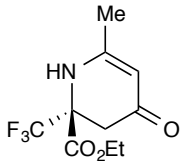


2.34 **2.37**

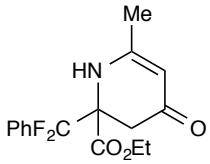
Over a suspension of the corresponding homopropargyl amide **2.34** or oxazines **2.35** (1.0 equiv, 0.12 mmol) and $Au(PPh_3)Cl$ (5 mol%) in dried MeOH (0.05 M, 2.5 mL), AgOTf (5 mol%) was added. The reaction mixture was stirred at room temperature until TLC showed total consumption of starting

[148] In this case, a catalytic amount of a Lewis acid such as $Au(PPh_3)Cl$ (5 mol%) was necessary to achieve the hydrolysis.

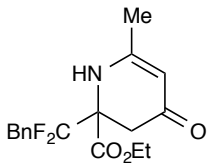
material. Then, solvents were removed under reduced pressure and crude mixture was purified by flash chromatography.



Ethyl (*S*)-6-methyl-4-oxo-2-(trifluoromethyl)-1,2,3,4-tetrahydropyridin-2-carboxylate. Following the general procedure described above, 47 mg of (*S*)-**2.37a** (colourless oil) were obtained from 50 mg of (*S*)-**2.34a** in 93% yield. $[\alpha]^{25}_{D}$ = +64.4 (*c* = 1.0 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, *J* = 7.1 Hz, 3H), 2.06 (s, 3H), 2.87 (d, *J* = 16.8 Hz, 1H), 3.00 (d, *J* = 16.8 Hz, 1H), 4.26-4.36 (m, 2H), 5.05 (s, 1H), 5.33 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 21.3, 36.6, 63.9, 65.6 (q, $^{2}J_{CF}$ = 28.9 Hz), 101.2, 123.5 (q, $^{1}J_{CF}$ = 286.9 Hz), 159.7, 166.7, 187.4; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -77.5 (s, 3F); HRMS (ES) calc. for (M^{+}+1) $C_{10}H_{13}F_3NO_3$: 252.0842; found: 252.0835.

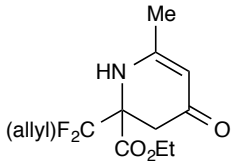


Ethyl 2-(difluoro(phenyl)methyl)-6-methyl-4-oxo-1,2,3,4-tetrahydropyridin-2-carboxylate. Following the method described above, 47 mg of **2.37b** (93% yield) were obtained as a white solid starting from 50 mg of **2.34b**. m.p. 147-149 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, *J* = 7.2 Hz, 3H), 1.99 (s, 3H), 2.82 (d, *J* = 16.5 Hz, 1H), 2.90 (d, *J* = 16.8 Hz, 1H), 4.12-4.23 (m, 2H), 4.86 (s, 1H), 5.36 (br s, 1H), 7.32-7.50 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.8, 21.4, 37.6 (t, $^{3}J_{CF}$ = 2.3 Hz), 63.0, 68.5 (t, $^{2}J_{CF}$ = 28.3 Hz), 100.8, 120.2 (t, $^{1}J_{CF}$ = 256.3 Hz), 126.2 (t, $^{3}J_{CF}$ = 6.4 Hz), 128.3, 130.9, 132.0 (t, $^{2}J_{CF}$ = 26.0 Hz), 160.1, 168.8 (d, $^{3}J_{CF}$ = 2.3 Hz), 188.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -104.2 (d, J_{FF} = 248.2 Hz, 1F), -107.0 (d, J_{FF} = 248.2 Hz, 1F); HRMS (ES) calc. for (M^{+}+1) $C_{16}H_{18}F_2NO_3$: 310.1249; found: 310.1260.

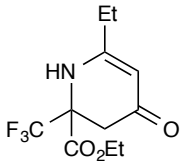


Ethyl 2-(1,1-difluoro-2-phenylethyl)-6-methyl-4-oxo-1,2,3,4-tetrahydropyridin-2-carboxylate. Following the general procedure described above, 40 mg of **2.37c** (white solid) were obtained from 50 mg of **2.34c** in 80% yield. m.p. 104-106 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.11 (s, 3H), 2.95 (d, *J* = 16.5 Hz, 1H), 3.13 (d, *J* = 16.2 Hz, 1H), 3.38-3.45 (m, 2H), 4.36-4.43 (m,

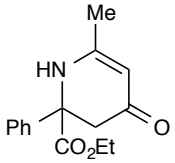
2H), 5.14 (s, 1H), 5.39 (br s, 1H), 7.36-7.49 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.0, 21.4, 37.9 (t, $^3J_{CF}$ = 2.3 Hz), 38.7 (t, $^2J_{CF}$ = 24.2 Hz), 63.2, 68.3 (t, $^2J_{CF}$ = 25.3 Hz), 100.9, 121.1 (t, $^1J_{CF}$ = 252.9 Hz), 127.7, 128.4, 130.7, 130.9 (t, $^3J_{CF}$ = 2.3 Hz), 160.6, 169.1 (d, $^3J_{CF}$ = 3.0 Hz), 188.5; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -106.1 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F), -108.4 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 11.3 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{17}H_{20}F_2NO_3$: 324.14.06; found: 324.1408.



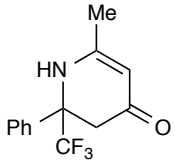
Ethyl 2-(1,1-difluorobut-3-en-1-yl)-6-methyl-4-oxo-1,2,3,4-tetrahydropyridin-2-carboxylate. Starting from 50 mg of **2.34d**, according to general procedure described above, 36 mg of a colourless oil corresponding to **2.37d** were isolated in 72% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, J = 7.2 Hz, 3H), 2.03 (s, 3H), 2.62-2.79 (m, 2H), 2.75 (d, J = 16.2 Hz, 1H), 2.95 (d, J = 16.5 Hz, 1H), 4.20-4.30 (m, 2H), 5.00 (s, 1H), 5.22 (ddd, J_1 = 12.6 Hz, J_2 = 2.7 Hz, J_3 = 1.2 Hz, 1H), 5.28 (ddd, J_1 = 6.0 Hz, J_2 = 2.4 Hz, J_3 = 1.2 Hz, 1H), 5.42 (br s, 1H), 5.80 (dddd, J_1 = 17.1 Hz, J_2 = 10.5 Hz, J_3 = J_4 = 6.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 21.4, 37.1 (t, $^2J_{CF}$ = 24.2 Hz), 37.9 (t, $^3J_{CF}$ = 2.3 Hz), 63.1, 68.1 (t, $^2J_{CF}$ = 24.9 Hz), 100.8, 121.3 (t, $^1J_{CF}$ = 253.3 Hz), 121.3, 127.2 (t, $^3J_{CF}$ = 4.9 Hz), 160.7, 169.0 (d, $^3J_{CF}$ = 3.0 Hz), 188.5; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -107.1 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 14.1 Hz, 1F), -109.0 (ddd, J_{FF} = 251.0 Hz, $(J_{FH})_1$ = 25.4 Hz, $(J_{FH})_2$ = 14.1 Hz, 1F); HRMS (ES) calc. for (M^++1) $C_{13}H_{18}F_2NO_3$: 274.1249; found: 274.1254.



Ethyl 6-ethyl-4-oxo-2-(trifluoromethyl)-1,2,3,4-tetrahydropyridin-2-carboxylate. Following the general procedure described above, starting from 50 mg of **2.34e**, 35 mg of **2.37e** were isolated as a yellow oil in 70% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.20 (t, J = 7.5 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 2.31 (q, J = 7.6 Hz, 2H), 2.89 (d, J = 17.1 Hz, 1H), 3.02 (d, J = 16.8 Hz, 1H), 4.27-4.37 (m, 2H), 5.09 (s, 1H), 5.20 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 11.3, 13.8, 28.2, 36.8, 63.9, 65.5 (q, $^2J_{CF}$ = 28.9 Hz), 99.6, 123.5 (q, $^1J_{CF}$ = 287.2 Hz), 164.8, 166.7, 187.7; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -77.5 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{11}H_{15}F_3NO_3$: 266.0999; found: 266.0991.

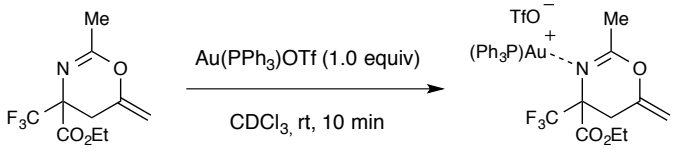


Ethyl 6-methyl-4-oxo-2-phenyl-1,2,3,4-tetrahydropyridine-2-carboxylate. Starting from 50 mg of **2.34f**, according to general procedure described above, 38 mg of a yellowish oil corresponding to **2.37f** were isolated in 75% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.07 (t, J = 7.2 Hz, 3H), 1.92 (s, 3H), 2.90 (d, J = 2.4 Hz, 2H), 4.00-4.14 (m, 2H), 4.83 (d, J = 0.9 Hz, 1H), 5.79 (br s, 1H), 7.17-7.29 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 21.2, 43.9, 62.4, 65.7, 100.7, 125.2, 128.5, 128.8, 138.2, 160.2, 171.9, 190.0; HRMS (ES) calc. for (M^++1) $C_{15}H_{18}NO_3$: 260.1208; found: 260.1218.



6-Methyl-2-phenyl-2-(trifluoromethyl)-2,3-dihydropyridin-4(1*H*)-one. Following the general procedure described above, 38 mg of **2.37g** (white solid) were obtained from 50 mg of **2.34g** in 76% yield. m.p. 130-132 ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H), 3.11 (s, 2H), 4.99 (s, 1H), 5.63 (br s, 1H), 7.37-7.45 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.4, 40.1, 64.6 (q, $^{2}J_{CF}$ = 27.9 Hz), 101.2, 125.0 (q, $^{1}J_{CF}$ = 284.6 Hz), 126.5, 128.9, 129.4, 134.3, 158.7, 188.5; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -78.2 (s, 3F); HRMS (ES) calc. for (M^++1) $C_{13}H_{13}F_3NO$: 256.0871; found: 256.0859.

2.5.4.5. Isolation and characterization of intermediate complex 2.35a·Au(PPh$_3$)OTf.



2.35a **2.35a**·Au(PPh$_3$)OTf

In a flask under inert atmosphere, a suspension of Au(PPh$_3$)Cl (1.0 equiv, 20 mg, 0.04 mmol) and AgOTf (1.0 equiv, 10 mg, 0.04 mmol) in $CDCl_3$, previously distilled over P_2O_5, was prepared. The mixture was stirred for 10 minutes at room temperature and then filtered over Celite in order to remove the precipitated silver salt. The filtrate was transferred to another flask containing oxazine **2.35a** (1.0 equiv, 10 mg, 0.04 mmol), previously prepared according to the procedure described in *section 2.5.4.2*. The mixture was stirred for ca. 10 minutes and immediately characterized by NMR spectroscopy. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.28 (t, J = 7.1 Hz, 3H), 2.73 (s, 3H), 3.23 (d, J = 15.6

Hz, 1H), 3.39 (d, J = 15.6 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.71 (t, J = 2.1 Hz, 1H), 5.01(t, J = 2.0 Hz, 1H), 7.49-7.59 (m, 15H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.7, 25.7, 27.3, 64.6, 66.0 (q, $^2J_{CF}$ = 28.0 Hz), 98.8, 120.8 (q, $^1J_{CF}$ = 319.5 Hz), 122.7 (q, $^1J_{CF}$ = 285.3 Hz), 127.4 (d, $^1J_{CP}$ = 65.2 Hz), 129.5 (d, $^3J_{CP}$ = 11.3 Hz), 132.5 (d, $^4J_{CP}$ = 2.5 Hz), 134.0 (d, $^2J_{CP}$ = 13.8 Hz), 146.1, 165.5, 171.8; ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -73.6 (s, 3F), -78.5 (s, 3F); ^{31}P-NMR ($CDCl_3$, 201.8 MHz): δ 29.6 (s, 1P); LRMS (MALDI-TOF) calc. for (M^+-OTf) $C_{28}H_{27}AuF_3NO_3P$: 710.13; found: 710.27.

2.5.4.6. X-Ray ORTEP of compound (-)-(*S*)-2.34a.[149]

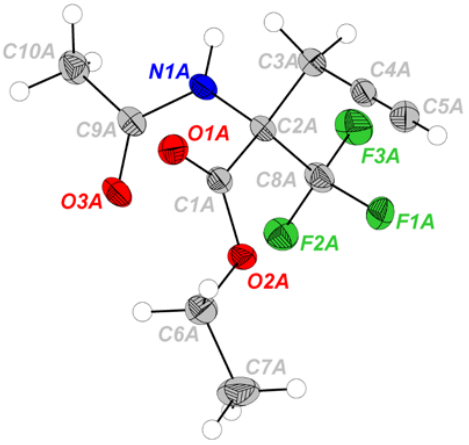


Figure 2.7. ORTEP of compound (*S*)-**2.34a**.

[149] CCDC 984448 contains the supplementary crystallographic data of compound (*S*)-**2.34a**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

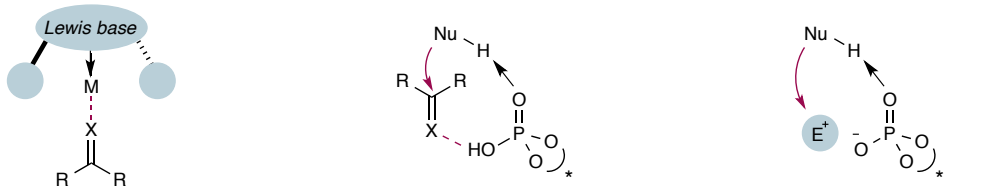
Chapter 3

Enantioselective 1,1-arylborylation of terminal alkenes. Merging chiral anion phase-transfer (CAPT) and transition metal catalysis

3.1. Introduction and current state-of-the-art.

Probably, one of the most important and challenging issues for reaching new achievements in asymmetric catalysis stands on the identification of novel and generic activation modes, induction and reactivity. Once an activation mode is established, it is relatively straightforward to use it as a platform for designing new asymmetric transformations, as well as new families of catalysts.

A generic activation mode in asymmetric catalysis describes a reactive species that can participate in many reaction types with consistently high levels of enantioselectivity. Such reactive species arises from the interaction of a chiral catalyst with a key functional group on the substrate in a highly organized and predictable manner. Based on the nature of this interaction, a well-defined number of key activation modes have been established (*Figure 3.1*).



(a) Lewis acid catalysis — *coordinative interactions*

(b) Brönsted acid catalysis — *hydrogen-bonding interactions*

(c) Ion-pairing catalysis — *electrostatic interactions*

Figure 3.1. Activation modes in asymmetric catalysis.

Among them, *Lewis acid catalysis* is possibly the most venerable mode (*Figure 3.1a*).[150] Most commonly, this activation mode involves a Lewis basic ligand, holding chirality, ancillary attached to

[150] Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

a Lewis acidic metal, which ultimately transfers chiral information to the substrate through the establishment of coordinative interactions.

A conceptually analogous activation mode, wherein the metal is replaced by a proton, is referred to as *Brönsted acid catalysis* (*Figure 3.1b*).[151] In this respect, chiral phosphoric acids, introduced by Akiyama and Terada,[152] have been extensively used. Their high acidity permits the activation of a broad range of substrates. Nevertheless, it also leads to an element of mechanistic uncertainty, as to whether the electrophile is essentially completely protonated and, thus, enantioinduction stands on an electrostatic ion-pairing interaction with the catalyst, or whether hydrogen-bonding interactions are responsible.

Taking this idea further, a mode of catalysis based on an ion-pair linked by electrostatic interactions can be considered apart, which is referred to as *ion-pairing catalysis* (*Figure 3.1c*).[153] Charged reagents and intermediates are ubiquitous species in organic chemistry. The interaction of these ionic species with chiral opposite-charged molecules has emerged as a powerful strategy in asymmetric catalysis.

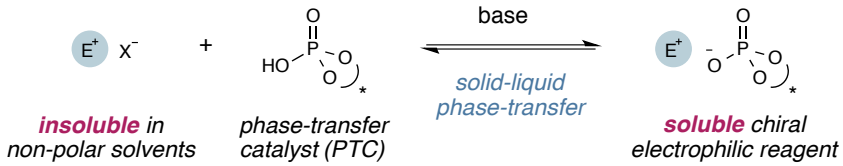
Ion-pairing catalysis is ruled by Coulomb's law, $E=(q_1 \cdot q_2)/(4\pi \cdot \varepsilon \cdot \varepsilon_0 \cdot r)$, which describes the attractive potential energy (E) between two opposite charged species (q_1, q_2). The magnitude of the electrostatic interaction is inversely related to the dielectric constant of the medium (ε). Thus, contact ion pairs would be energetically favourable in nonpolar solvents of low dielectric constant, whereas in solvents with higher dielectric constant, those pairs tend to be disrupted.

According to Anslyn and Dougherty,[154] an ion pair exists "*when a cation and an anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them. This means that the ions stay associated longer than the time required for Brownian motion to separate non-interacting species*". Arguably, inherent less directionality ascribed to coulombic interactions underlies the main challenge in designing stereoselective catalysts that operate under ion-pair principle.

The implementation of this ion-pairing activation mode by its merge with phase-transfer principle, established an innovative and general approach in asymmetric synthesis coined as **chiral anion phase-transfer (CAPT) catalysis** by the Toste group in 2011.[155] Attending to this principle, a lipophilic chiral phosphate salt (organocatalyst) activates, through ion-exchange, a cationic reagent or intermediate, otherwise insoluble and unreactive in a nonpolar media, bringing it into solution, while providing a chiral environment (*Scheme 3.1*). As a result, unselective background reactivity is

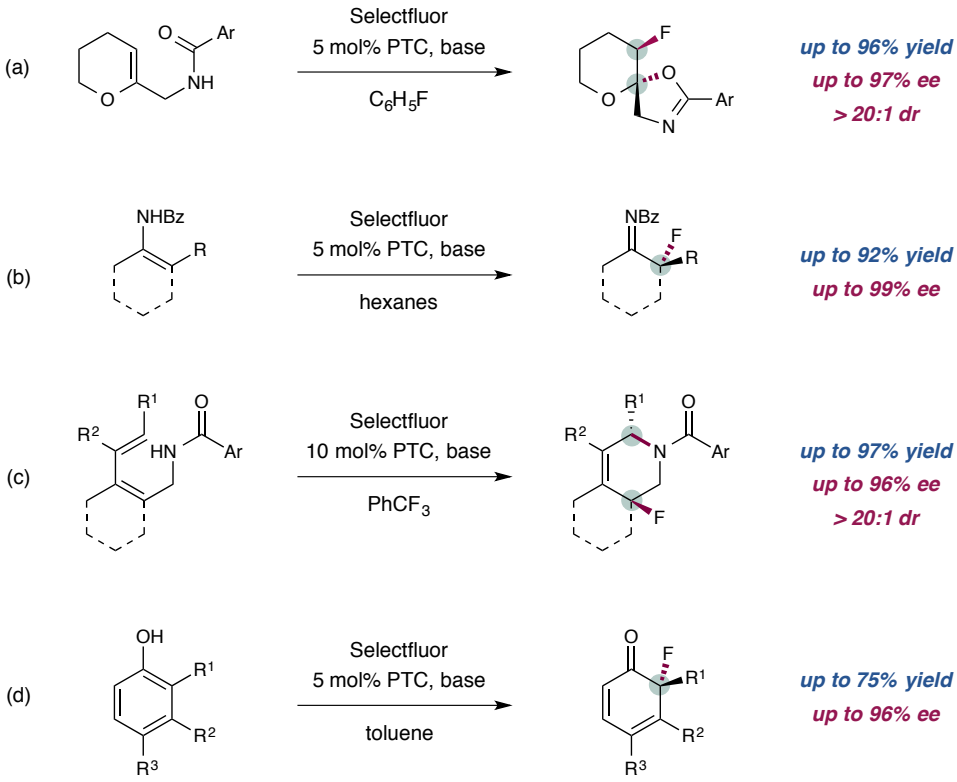
[151] (a) Terada, M. *Synthesis*, **2010**, 1929. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
[152] (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[153] (a) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534. (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chem.* **2012**, *4*, 603. (c) Mahlau, M.; List, B. *Isr. J. Chem.* **2012**, *52*, 630. (d) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.
[154] Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, 2006.
[155] Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science*, **2011**, *334*, 1681.

minimal, despite the use of a large excess of reagent relative to the catalyst or its high intrinsic reactivity.



Scheme 3.1. Chiral anion phase-transfer (CAPT) catalysis (Toste, 2011).

The potential of chiral anion phase-transfer technology was recently established throughout the enantioselective fluorination of olefins (*Scheme 3.2*). Excellent yields and enantioselectivities were achieved using Selectfluor as the electrophilic fluorinating reagent operating under CAPT principle.



Scheme 3.2. Asymmetric electrophilic fluorination via CAPT catalysis (selected examples).

Since their seminal contribution in 2011, the Toste group has vastly explored this state-of-the-art principle, applying CAPT strategy to carry out the enantioselective halofunctionalization of

different olefinic systems (*Scheme 3.2*), including enamides,[156] 1,3-dienes,[157] phenols,[158] or allylic alcohols,[159] besides showcasing the versatility of this protocol by its successful combination with classical chemical approaches like enamine catalysis[160] or the use of directing groups.[161]

The excellent results obtained in terms of yield and enantioinduction led to the exploration of alternative amenable electrophilic reagents (*Figure 3.2*), pushing the boundaries of CAPT catalysis.

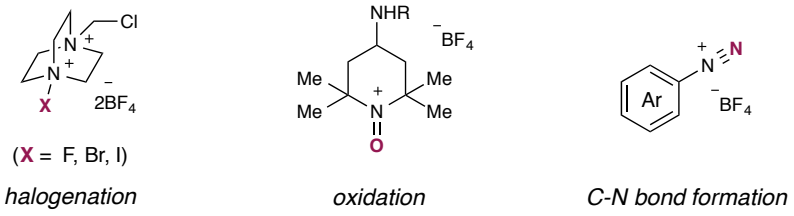
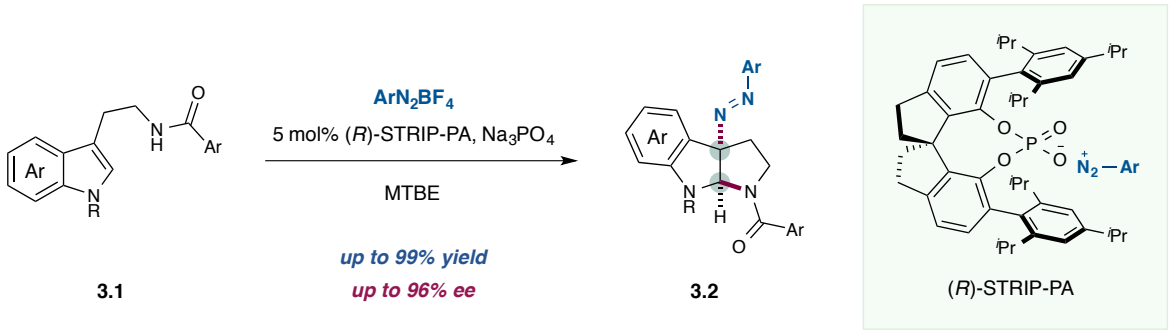


Figure 3.2. Cationic electrophiles amenable in CAPT catalysis.

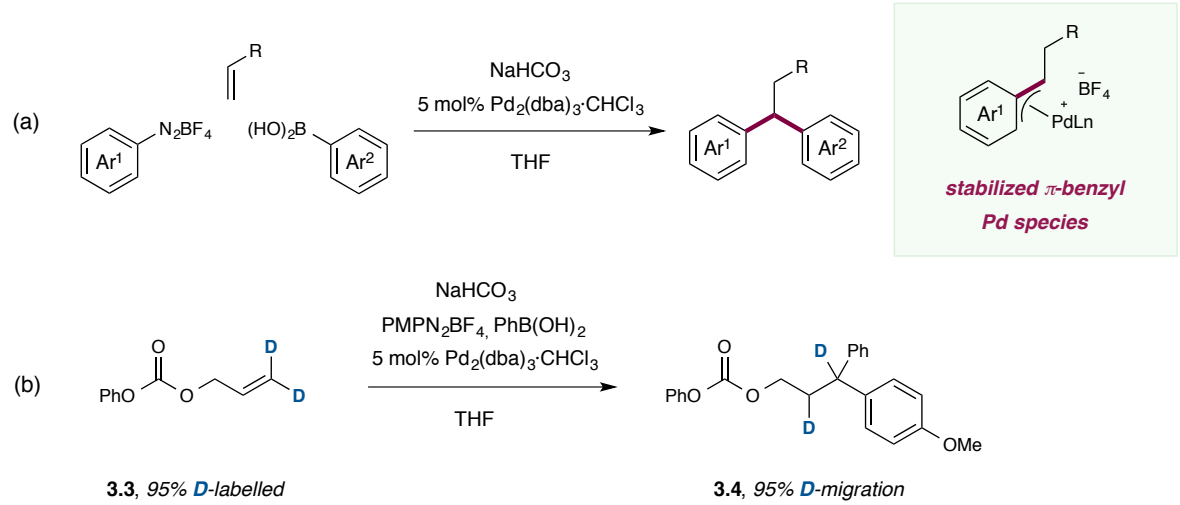
Besides halogen-based electrophiles,[162] CAPT strategy was amenable applicable in oxidative reactions.[163] Ongoing work in the Toste lab showed aryl diazonium salts' competency as nitrogen-centered electrophiles, since electron-rich olefins **3.1** were efficiently diazenated in high yields and enantioselectivities (*Scheme 3.3*).[164] Aryl diazonium salts have properties akin to other reagents successfully employed in CAPT, as they are highly reactive electrophiles that are sparsely soluble in a range of nonpolar solvents.



Scheme 3.3. Aryl diazonium salts as nitrogen-centered electrophiles (Toste, 2014).

[156] (a) Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376. (b) Honjo, T.; Phipps, R. J.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 9684.
[157] Shunatona, H. P.; Früh, N.; Wang, Y.-M.; Rauniyar, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 7724.
[158] Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268.
[159] Zi, W.; Wang, Y.-M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 12864.
[160] Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225.
[161] Wu, J.; Wang, Y.-M.; Drljevic, A.; Rauniyar, V.; Phipps, R. J.; Toste, F. D. *Proc. Nat. Acad. Sci. U.S.A.* **2013**, *110*, 13729.
[162] Wang, Y.-M.; Wu, J.; Hoong, C.; Rauniyar, V.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 12928.
[163] (a) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044; (b) Lackner, A. D.; Samant, A. V.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14090.
[164] (a) Nelson, H. M.; Patel, J. S.; Shunatona, H. P.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 170. (b) Nelson, H. M.; Reisberg, S. H.; Shunatona, H. P.; Patel, J. S.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5600.

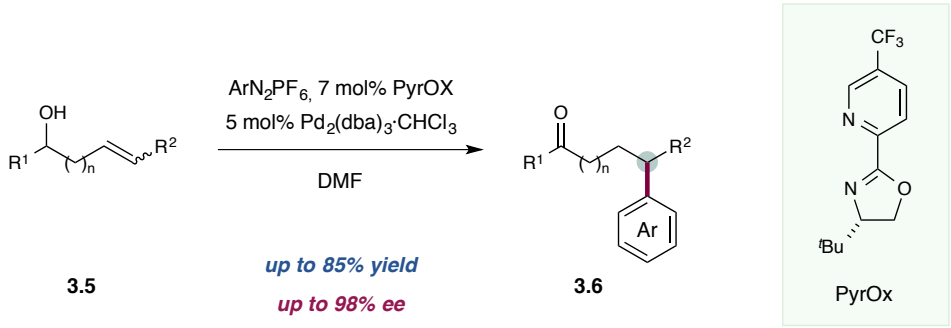
Actually, aryl diazonium species are also proven electrophiles utilized for the construction of C–C bonds. So we wondered if aryl diazonium salts may act as a viable source of electrophilic carbon in CAPT catalysis. In this respect, the Heck-Matsuda reaction is a variant of the Heck reaction that employs aryl diazonium salts as the electrophilic coupling partner instead of aryl halides or aryl triflates. In a recent related example, Sigman and coworkers reported the 1,1-diarylation of ethylene and allylic carbonates (*Scheme 3.4a*).[165] Outstandingly, the unusual 1,1-regioselectivity observed stands on the reversibility of the migratory insertion step and the intermediacy of stabilized π-benzyl-palladium species. The observed 1,1-regioselectivity was supported by isotopic labelling experiments (*Scheme 3.4b*), with 95% D-migration to β-carbon when deuterium-labelled substrate **3.3** was treated under reaction conditions.



Scheme 3.4. (a) Previous work by Sigman (2013). (b) Deuterium labelling experiments.

Nevertheless, enantioinduction in the Heck-Matsuda reaction has been always challenging, based on the reported incompatibility between the aryl diazonium salts and phosphine-type ligands routinely employed to transfer chiral information. Thus, despite the Heck-Matsuda reaction's ease of operation, the transformation has resisted numerous attempts to render it enantioselective, until Sigman reported in 2012 the use of chiral bidentate diimine ligands, which allowed raising good levels of enantioinduction (*Scheme 3.5*).[166]

[165] Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008.
[166] Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science*, **2012**, *338*, 1455.



Scheme 3.5. Enantioselective Heck arylation of acyclic alkenyl alcohols (Sigman, 2012).

Under this scenario, we posited the union of CAPT with transition metal catalysis to utilize aryl diazonium salts as a source of electrophilic carbon. We envisaged that the combination of aryl diazonium salts with unprecedented cooperative transition metal-CAPT catalysis[167] would provide an orthogonal approach to enantioselective arylation reactions.

In this sense, we were specially intrigued by the aforementioned 1,1-difunctionalization reaction manifold. However, instead of an aryl boronic acid, we opted for the use of a boron nucleophilic source such as *bis*(pinacolato)diboron ester, $B_2(pin)_2$, which would ultimately provide chiral benzyl boronic esters.

Enantioenriched organoboranes are ubiquitous substrates in modern organic chemistry. These are extremely valuable intermediates/reagents in chemical synthesis, since they can undergo a broad array of stereospecific and well-established transformations for the construction of either C–O, C–N, or C–C bonds (*Figure 3.3*).[168] These transformations include synthetically useful oxidation, amination, protodeborylation, arylation, and importantly series of C-based homologations. Outstandingly, such further functionalization usually occurs preserving the stereogenic integrity of the C–B linkage.

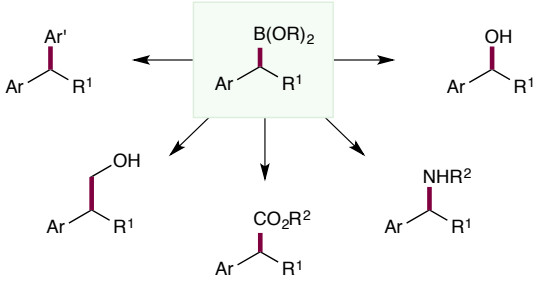


Figure 3.3. Boronic ester transformations.

[167] Inamdar, S. M.; Shinde, V. S.; Patil, N. T. *Org. Biomol. Chem.* **2015**, *13*, 8116.
[168] Hall, D. G. *Boronic Acids*, 2nd ed.; Wiley-VCH: Weinheim, 2011.

The shown versatility attests for their privileged role in diversity-oriented synthesis (DOS),[169] providing remarkable breakthroughs in this arena.

In particular, substituted scaffolds derived from benzyl boronic esters are common motifs featuring among current pharmaceuticals and natural products (*Figure 3.4*), becoming compelling chemical scaffolds/building blocks in drug discovery as well.

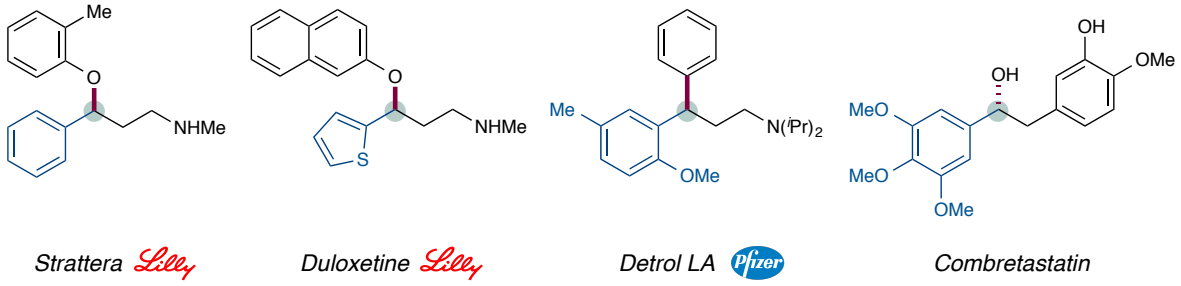
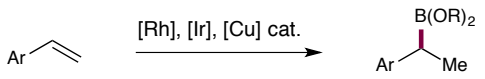


Figure 3.4. Selected pharmaceuticals.

Given the well-established and valuable role ascribed to organoboranes, borylation reactions constructing C–B bonds in a reliable, efficient and stereoselective manner are highly desirable. Devoted efforts from the chemical community have resulted in several catalytic enantioselective approaches, including:

-*Hydroborylation of alkenes*.[170] Since the pioneered work by Brown in the 1950s,[171] hydroborylation reaction, i.e. the *syn*-addition of a B–H bond across a C–C multiple bond, have been widely implemented, resulting in multiple metal-catalytic reactive systems, enabling boryl addition even onto C–heteroatom multiple bonds such as imines or aldehydes.

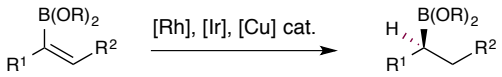


[169] Schreiber, S. L. *Nature* **2009**, *457*, 153.

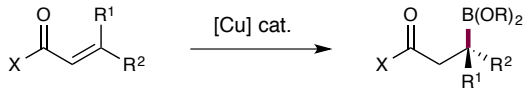
[170] Carroll, A. M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609. For recent selected examples, see: (a) Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6969. (b) Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H. *J. Am. Chem. Soc.* **2016**, *138*, 4338. (c) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 1465. (d) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2015**, *137*, 420.

[171] Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 2582.

-*Reduction of vinyl boronates*.[172] A few examples lying on the metal-catalyzed asymmetric hydrogenation of different families of alkenyl boronates, obtained by hydro- or diborylation reaction of alkynes, constitute another route of access.



-*Conjugate borylation*.[173] The metal-catalyzed β-borylation of α,β-unsaturated systems is probably the most extensively investigated strategy for the last years. Most of the reported transformations entail *in situ* generation of metal-boron species displaying as formal boron nucleophiles. In this sense, Cu(I) salts, in combination with different chiral ligands, have resulted quite effective.[174] Besides these, other metal-catalyzed (e.g. Rh)[175] and metal-free[176] selective boron additions onto α,β-unsaturated carbonyl-derived systems, including imines,[177] nitriles,[178] sulfones[179] and phosphine oxides,[180] have been reported. Likewise, the stereocontrolled addition of organometallic reagents onto preformed β-borylated conjugated systems is known.[181]



-*Allylic borylation*. Seminal report by Masuda and co-workers on the borylation of alkenyl triflates,[182] inspired the Hall group in the development of a new catalytic method for the

[172] (a) Smilovic, I. G.; Casas-Arcé, E.; Roseblade, S. J.; Nettekoven, U.; Zanotti-Gerosa, A.; Kovacevic, M.; Casar, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 1014. (b) Ding, J.; Lee, J. C. H.; Hall, D. G. *Org. Lett.* **2012**, *14*, 4462. (c) Jung, H.-Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron*, **2012**, *68*, 3444. (d) Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338.

[173] Calow, A. D.; Whiting, A. *Org. Biomol. Chem.* **2012**, *10*, 5485.

[174] For recent selected examples, see: (a) Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8809. (b) Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2015**, *51*, 11685. (c) Niu, Z.; Chen, J.; Chen, Z.; Ma, M.; Song, C.; Ma, Y. *J. Org. Chem.* **2015**, *80*, 602. (d) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 4186.

[175] Toribatake, K.; Zhou, L.; Tsuruta, A.; Nishiyama, H. *Tetrahedron*, **2013**, *69*, 3551.

[176] (a) Wu, H.; Garcia, J. M.; Haeffner, F.; Radomkit, S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 10585. (b) La Cascia, E.; Sanz, X.; Bo, C.; Whiting, A.; Fernández, E. *Org. Biomol. Chem.* **2015**, *13*, 1328. (c) Wu, H. Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277. (d) Ibrahem, I.; Breistein, P.; Córdova, A. *Chem. Eur. J.* **2012**, *18*, 5175. (e) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130.

[177] Solé, C.; Whiting, A.; Gulyás, H.; Fernández, E. *Adv. Synth. Catal.* **2011**, *353*, 376.

[178] Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2010**, *46*, 7525.

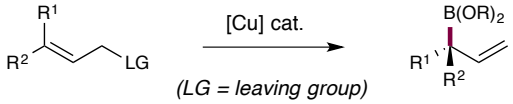
[179] Moure, A. L.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6701.

[180] Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867.

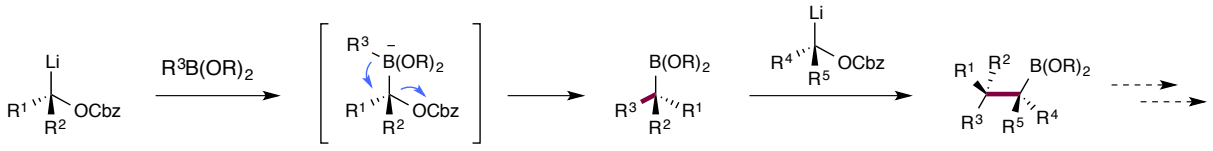
[181] Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544.

[182] Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis*, **2000**, 778.

stereoselective preparation of allylboronates.[183] Since that time, a few more contributions from Hall himself,[184] Hoveyda[185] and Ito,[186] have appeared leading to the preparation of optically active linear and carbocyclic (γ-alkoxyallyl)boronates, all of them based on the metal-catalyzed enantioselective boryl substitution of either allyl triflates, carbonates, or acetals, respectively.

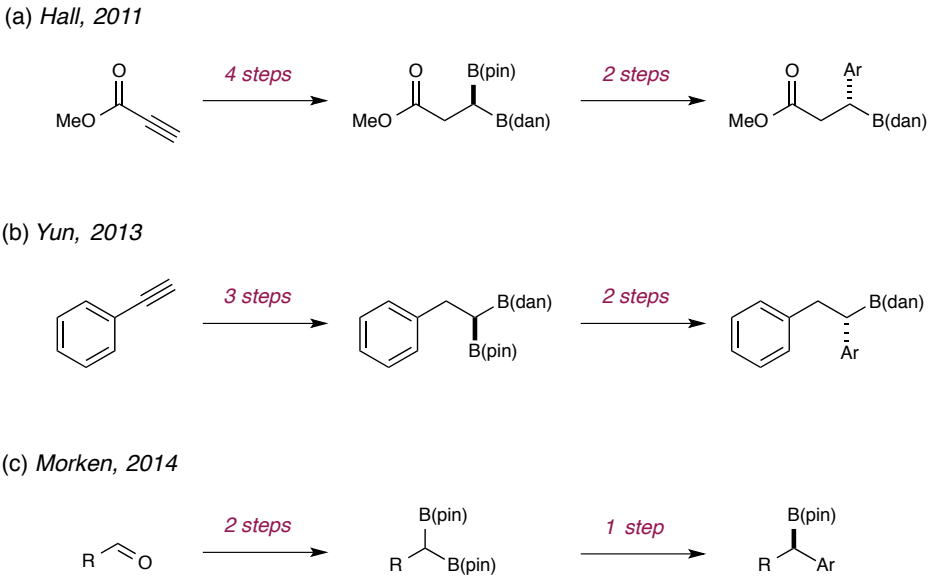


-1,2-Metalate rearrangements. Organoboronate (negatively charged boron) species, resulting from the addition of an organometallic reagent to the electrophilic boron atom of an organoboron species, are known to participate in a wide range of reactions that occur by stereospecific 1,2-metallate rearrangements.[187] These rearrangements usually occur *via* 1,2-carbon shift from boron to an adjacent sp^3-hybridized electrophilic center, with concomitant released of an appropriate attached leaving group. Based on the aforementioned stereospecific 1,2-metalate rearrangement, the Aggarwal group showed that chiral boronic esters can be generated in high enantiomeric ratios from the reaction of boronic esters with lithiated non-racemic carbamates derived from the corresponding alcohols.[188] The feasibility of Aggarwal's approach is implemented by the very well established methodology for the preparation of chiral benzylic alcohols. Potential and versatility of this lithiation-borylation methodology has been firmly established through the highly stereocontrolled total synthesis of diverse natural products and pharmaceuticals, and constitutes the mainstream in a one-pot assembly line protocol for the iterative extension of a starting boronic ester, through what they coined as a reagent-controlled homologation.[189] Though in Aggarwal's approach stereoselectivity of the metallate shift is driven by substrate control, a recent example from Morken's laboratory showcased that it can be dictated as well by a chiral catalyst.[190]



[183] Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612.
[184] Ding, Y.; Hall, D. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8069.
[185] Guzman-Martínez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.
[186] (a) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515. (b) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 560.
[187] (a) Negishi, E.-I. *Org. React.* **1985**, *33*, 1-246. (b) Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215.
[188] Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124.
[189] Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174.
[190] Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*, **2016**, *351*, 70.

Beyond "classical" approaches, several methods have been recently reported for the preparation of enantioenriched benzyl boronates relying on further transformations over pre-formed *gem*-bis-boronic alkanes, but in multistep synthetic sequences (*Scheme 3.6*).



Scheme 3.6. Recent examples of enantioselective 1,1-arylborylation.

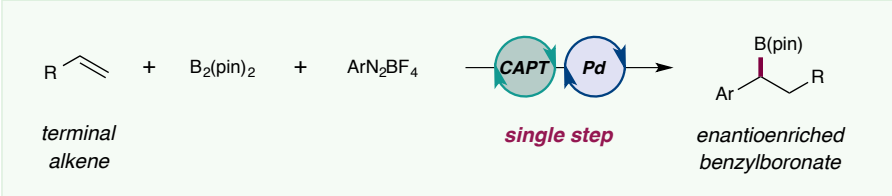
For instance, Hall and Yun reported the use of chiral non-racemic *gem*-diboronates in chemo- but non-stereoselective coupling reactions (*Scheme 3.6a-b*).[191] Enantioenriched *gem*-diboronyl derivatives were accessed through the asymmetric borylation of β-boronyl acrylic derivatives and styrenes, respectively, prepared in turn by hydroborylation of corresponding propiolates, in which can be considered as a sophisticated evolution of the above-discussed classical approaches.

More recently, in 2014, Morken *et al.* demonstrated the feasibility of an alternative related strategy entailing the palladium-catalyzed enantioselective Suzuki-Miyaura mono-cross-coupling of aryl and vinyl halides over readily accessed symmetric prochiral *gem*-diboronates (*Scheme 3.6c*).[192] Seminal Morken's contribution served to inspire new useful routes for the desymmetrization of prochiral *gem*-diboronates, such as the copper-catalyzed addition of *gem*-diboron reagents to aryl and vinyl aldehydes.[193]

[191] (a) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (b) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 3989.
[192] Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.
[193] (a) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176. (b) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918.

3.2. Enantioselective Pd-catalyzed 1,1-arylborylation reaction.

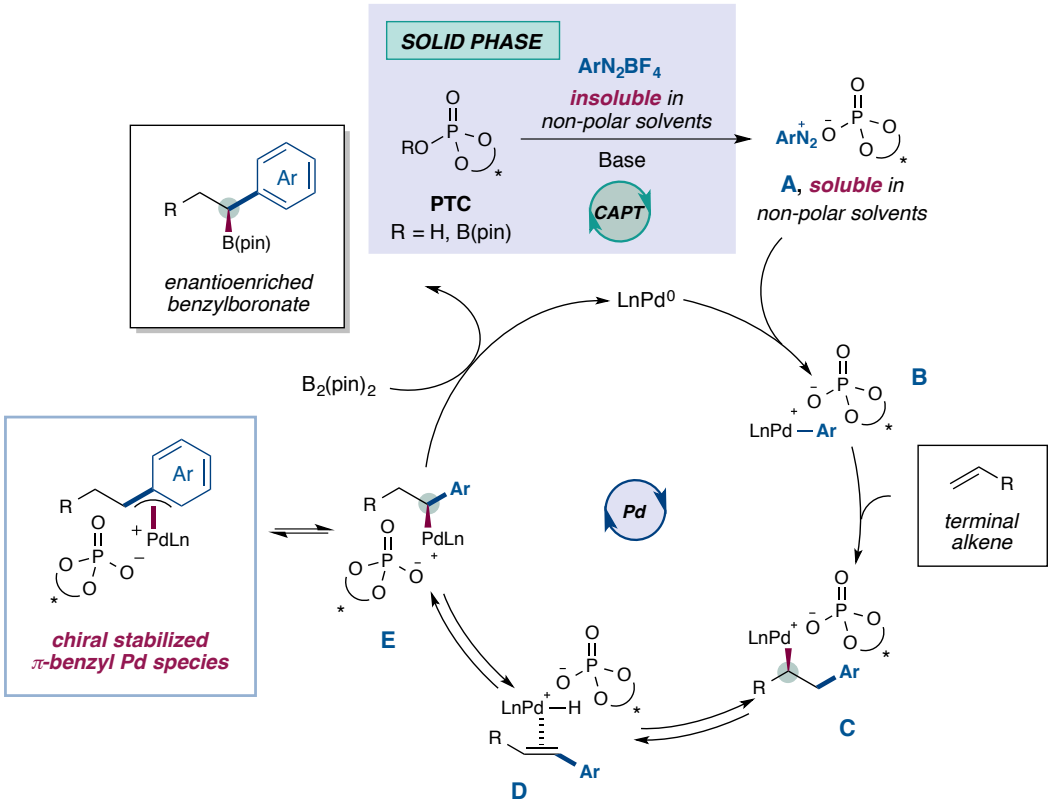
Given this perspective, the single-step installation of both the boronate and the aryl functional groups would be an ideal transformation from the perspective of both step-economy and synthetic divergence. Inspired by Sigman's reported examples on 1,1-difunctionalization of alkenes,[194] we consequently sought to expand CAPT strategy towards the direct 1,1-arylborylation of alkenes via a three-component Heck-Matsuda arylation-Miyaura borylation cascade reaction (*Scheme 3.7*).



Scheme 3.7. Enantioselective Pd-catalyzed 1,1-arylborylation reaction via CAPT catalysis.

We hypothesized that a CAPT strategy could enable association of a chiral anion (**PTC**) with the key cationic Pd(II) intermediates involved in the enantiodetermining step (*Scheme 3.8*). Under basic conditions, metathesis between the insoluble aryl diazonium salt and a chiral lipophilic phosphate anion (**PTC**), would provide a soluble, chiral ion pair **A**. Oxidative addition of a Pd(0) complex, followed by migratory insertion of the alkenyl coupling partner would render the enantioenriched cationic Pd(II) complex **C**. Then, reversibility of migratory insertion would result in the formation of a stabilized π-benzyl palladium species **E** through sequential β-hydride elimination and reinsertion steps. Transmetalation with a nucleophilic boron source and final reductive elimination would yield the enantioenriched borylated product, while regenerate both catalysts, the Pd(0) species and the phase-transfer catalyst.

[194] (a) Ref. 165.: Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008. (b) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372. (c) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (d) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848.

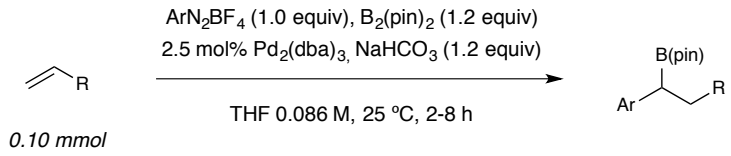


Scheme 3.8. Proposed dual catalytic cycle for cooperative Pd-CAPT 1,1-arylborylation.

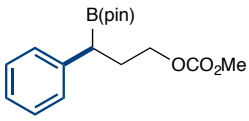
3.3. Results and discussion.

Given the lack of precedents for the devised transformation, we sought to provide proof-of-principle with the development of a non-stereoselective version under homogeneous conditions. This would serve as a testing ground of the potential applicability of the designed protocol as a general synthetic methodology.

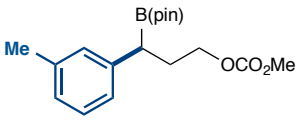
Table 3.1. Non-enantioselective scope.[a]



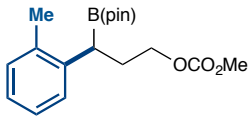
ArN_2BF_4 scope



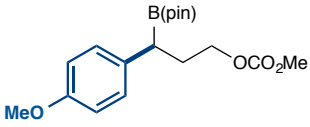
3.7, *72% yield*[b]



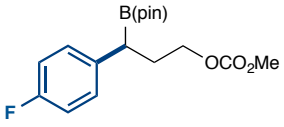
3.8, *90% yield*[b]



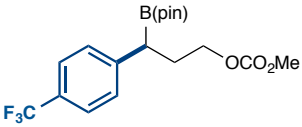
3.9, *89% yield*[b]



3.10, *90% yield*

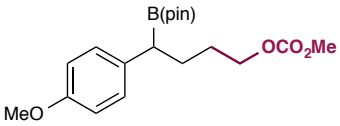


3.11, *94% yield*[b]

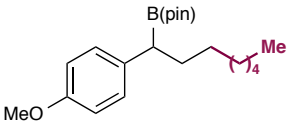


3.12, *71% yield*

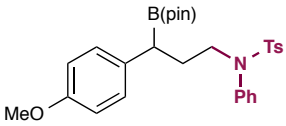
Olefin scope



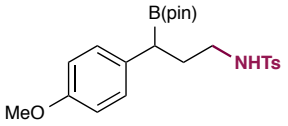
3.13, *74% yield*



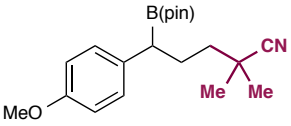
3.14, *90% yield*[b]



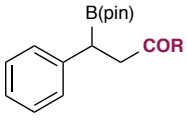
3.15, *85% yield*



3.16, *91% yield*



3.17, *99% yield*



3.18, *46% yield (R = OEt)*
3.19, *45% yield (R = Me)*
3.20, *57% yield*[b] *(R = H)*

[a] Isolated yields. [b] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard.

As starting point, we subjected allyl methyl carbonate under similar conditions to those previously reported by Sigman.[165] Pleasantly, after brief exploration on reaction conditions, we found that a THF suspension of catalytic $Pd_2(dba)_3$, $NaHCO_3$, phenyl diazonium tetrafluoroborate, allyl methyl carbonate, and $B_2(pin)_2$, smoothly provided racemic benzylboronate **3.7** in 72% yield at room temperature (*Table 3.1*). Both electron-rich and electron-poor aryl diazonium salts proved competent in this transformation, providing boronic esters **3.10** and **3.12** in 90% and 71% yield, respectively. Notably, the use of *meta*- and *ortho*-substituted aryl diazonium cations also provided the products in good yields (**3.8**-**3.9**). The utilization of homoallylic carbonates, as well as protected allylic amines, furnished the borylated products in good to excellent yields (**3.13**, **3.15**-**3.16**). Notably, the presence of chelating groups did not prevent catalysis (**3.17**). Furthermore, the cascade was even extensive to non-activated (**3.14**) and deactivated terminal alkenes (**3.18**-**3.20**), albeit in diminished yields.

Once provided proof-of-principle for the 1,1-arylborylation reaction, we focus our efforts towards rendering this process enantioselective *via* CAPT technology. Essentially, that would involve switching to a non-polar media while adding a phase-transfer catalyst. Nevertheless, it is expected that reactions that generate such complexity in one step, require fine-tuning in order to achieve the optimum results. Identification of an appropriate phase-transfer catalyst, base, solvent, etc, were instrumental for the successful phase-transfer event and are discussed *vide infra*.

-*Phase-Transfer Catalyst (PTC)*. One catalyst must both effectively phase-transfer and, subsequently, provide an adequate chiral environment around the cationic electrophile source to achieve high levels of stereoinduction. Successful enantioinduction heavily relies on the judiciously selection of the appropriate PTC, which is the workhorse of the reaction. Fortuitously, the Toste group had a large library of chiral phosphoric acids, which greatly expedited the screening of these catalysts (*Figure 3.5*). Effects on varying the R and R' groups of the catalyst were examined as well as catalysts's lipophilicity through partial saturation of the naphthyl moiety or the installation of extended alkyl chains at 6 and 6' positions. Poor selectivity in the reaction could be attributed to the PTC if either the phase-transfer event and/or the PTC's chiral environment were unsatisfactory.

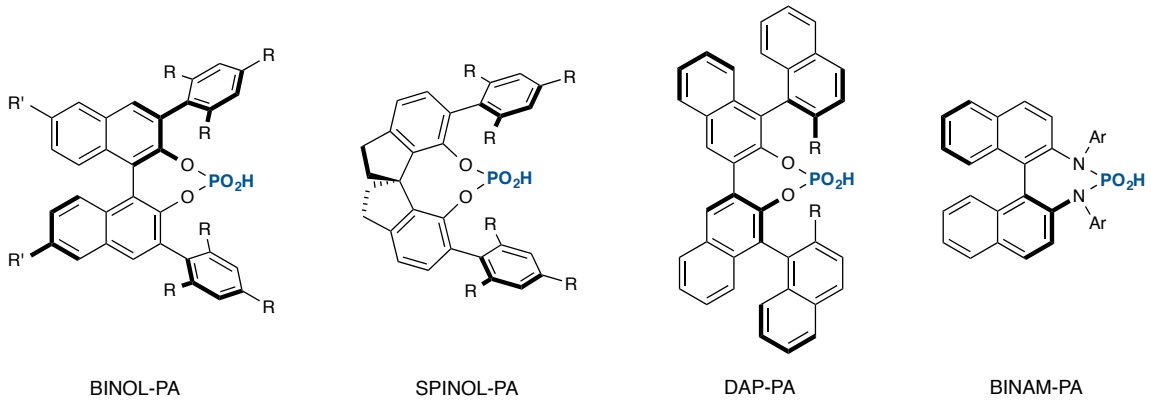
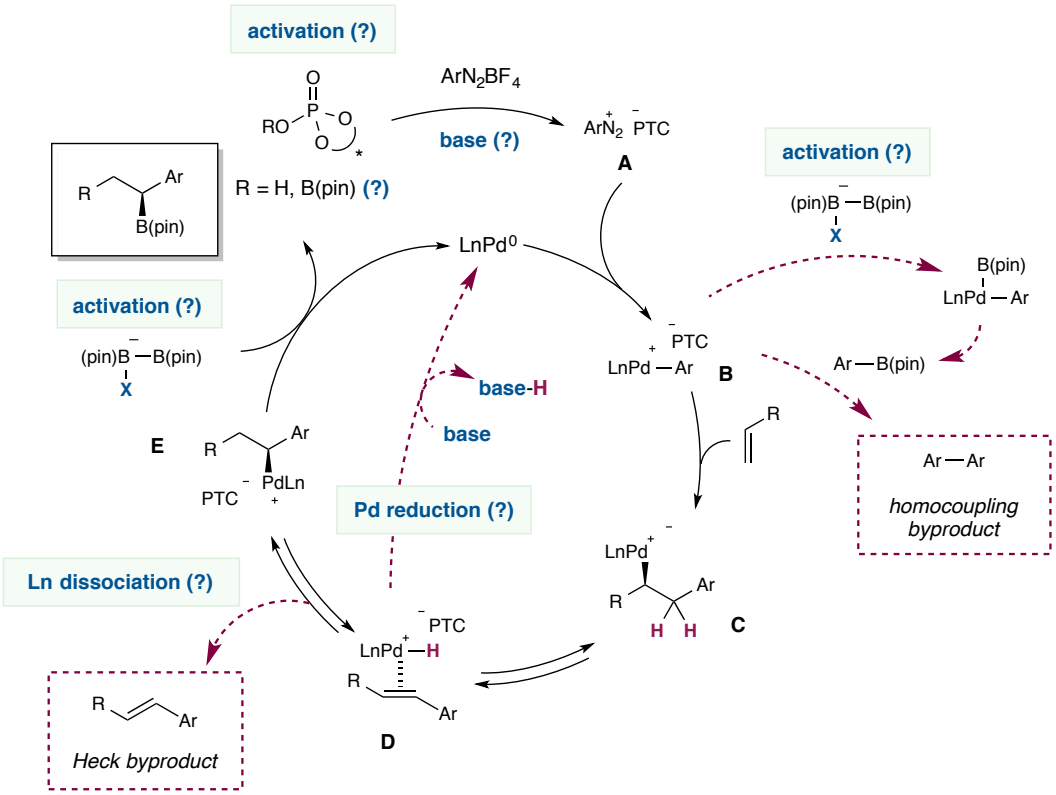


Figure 3.5. Phase-Transfer Catalyst (PTC) scaffolds.

-*Electrophile*. Presumably, electronics and sterics on the diazonium coupling partner will affect the stability of the π-benzyl palladium intermediate species. The identity of the diazonium counterion might be significant too, as it is directly correlated with salt's solubility.

-*Base*. In CAPT protocols, the PTC is commonly added to the reaction as a protonated phosphoric acid; thus, a base is required for deprotonation to generate the active anionic phase-transfer agent. However, an excess of base may be displaying alternative roles (*Scheme 3.9*), such as activating the nucleophilic boryl source, or facilitating PTC turnover by hydrolysis of the "chelated" (borylated) phase-transfer catalyst that may result after transmetalation. Additionally, base may be responsible of termination via β-hydride elimination through deprotonation of the cationic palladium hydride **D**, producing the Heck byproduct by ligand dissociation. Because of the envisioned multifaceted nature of base, we posited that the judicious choice of base and/or additive(s) would be crucial for the success on the attempted aim. An extensive base screening was conducted exploring the effect of pK_a, counterion (i.e. Na, K, Cs), as well as the equivalency of base.



Scheme 3.9. Plausible role(s) of base.

-*Transmetalating agent*. Differences in steric bulk and hydrogen bonding between e.g. R–B(pin) and R–B(OH), are likely to affect transmetalation and, thus, selectivity and/or efficiency.

-*Olefin*. Hydrogen-bonding interactions were reported to be highly beneficial for CAPT[161] and thus may lead to further enantioinduction (*Figure 3.6*).

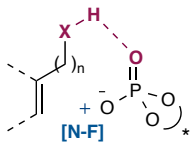


Figure 3.6. Reported H-boding model.

-*Solvent*. A general trend in CAPT catalysis is that nonpolar solvents tend to afford higher levels of enantioinduction than more polar solvents. This observation is consistent with the proposed mode of chirality transfer. A chiral ion pair is likely to be disrupted in solvents with greater polarity. With the knowledge of this CAPT trend, solvent screenings focused on hydrophobic aprotic solvents.

-*Other parameters*. Parameters such as stirring rate, equivalents of the coupling components or concentration had resulted really impactful in previous reported transformations operating under phase-transfer principle, and were considered as well.

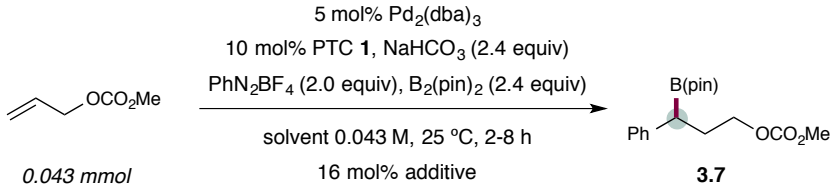
Thus, utilizing again allyl methyl carbonate and a non-biased coupling partner such as phenyl diazonium tetrafluoroborate,[195] an extensive study of reaction conditions was undertaken. A summary data is compiled in *Table 3.2*.[196]

Initial experiments showed that nonpolar solvents such as hexanes provided poor conversion (*entry 1*), whereas THF allowed for excellent conversion albeit with poor enantioselectivity (*entry 2*). After further solvent screening, Et_2O was identified as optimal, furnishing the product in 45% yield and 67:33 er (*entry 3*).[197] Examination of several PTCs identified PTC **2**, TCyP-PA, as superior in terms of enantioselectivity, providing desired product in 94:6 er (*entry 5*). Among different tested bases, Na_3PO_4 provided the highest yield, furnishing the product in 26% yield (*entry 7*). Notably, with stronger bases such as ^{t}BuOK, borylation of the aryl diazonium salt was observed, presumably due to boron species' activation (see *Scheme 3.9*). Finally, we noticed the addition of exogenous dibenzylideneacetone-type ligands improved the efficiency of the reaction. Among different tested ligands, 3,3'-CF_3-dba enabled to increase yield up to 39%, with retention of enantioselectivity (*entry 9*).[198] While the actual role of dba-type ligand improving the efficiency of the process was not

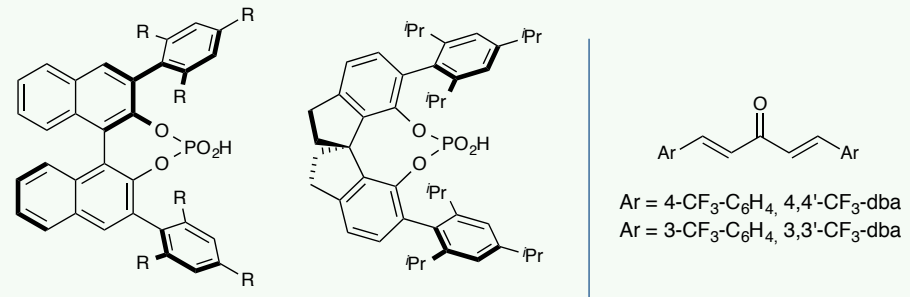
[195] Notably, PF_6 salts were tested as well in Et_2O achieving high yields but poor ee, probably due to their higher solubility (avoiding counterion exchange, and thus, chirality transfer).
[196] For further details see *Experimental Section 3.5.2.*
[197] Combination of solvents (e.g. Et_2O/THF) provided better yields, but at the expense of er. On the other hand, addition of increasing amounts of water resulted in loss of enantioinduction.
[198] We also prepared and tested Pd_2(3,3'-CF_3-dba)$_3$ complex, but it did not provide better results. Kapdi, A. R.; Whitwood, A. C.; Williamson, D. C.; Lynam, J. M.; Burns, M. J.; Williams, T. J.; Reay, A. J.; Holmes, J.; Fairlamb, I. J. S. *J. Am. Chem. Soc.* **2013**, *135*, 8388.

rigorously investigated, we attributed this effect to the stabilization of palladium intermediate species along the catalytic cycle.

Table 3.2. Optimization of the enantioselective 1,1-arylborylation reaction.



entry	conditions	additive	solvent	yield[a]	er[b]
1	as shown	-	hexanes	<5%	-
2	as shown	-	THF	72%	53:47
3	as shown	-	Et_2O	45%	67:33
4	PTC **3**	-	Et_2O	14%	53:47
5	PTC **2**	-	Et_2O	25%	94:6
6	PTC **2**, K_2CO_3	-	Et_2O	25%	97:3
7	PTC **2**, Na_3PO_4	-	Et_2O	26%	97:3
8	PTC **2**, Na_3PO_4	4,4'-CF_3-dba	Et_2O	40%	85:15
9	PTC **2**, Na_3PO_4	3,3'-CF_3-dba	Et_2O	39%	96:4



[a] Yield determined by ^1H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

In addition to protected allylic alcohols, α,β-unsaturated esters were utilized as alternative olefinic coupling partners for the enantioselective transformation. A similar screening was carried out for the acrylate system, with similar reaction conditions rendering the best results.[199] Notably, with acrylate coupling partners, use of 3,3'-CF_3-dba did not improve efficiency nor selectivity.

In order to determine the efficiency of phase-transference, we carried out a qualitative ^{19}F NMR study (*Figure 3.7*) consisting on comparing the solubility of the 4-fluoro-phenyl diazonium salt

[199] For further details, see *Experimental Section 3.5.4*.

4-F–$C_6H_4N_2BF_4$ in different solvents, with and without the sodium salt of the PTC **2** (**TCyP-PA-Na**). In tetrahydrofuran-d^8, the solvent selected for the racemic reaction, without the PTC, aryl diazonium salt was soluble, providing a ^{19}F NMR signal around -88 ppm. However, no fluorine signal was detected in diethyl ether-d^{10}. Addition of increasing amounts of the PTC, provided a signal. These results showcased the operability of a phase-transfer event under optimized conditions.

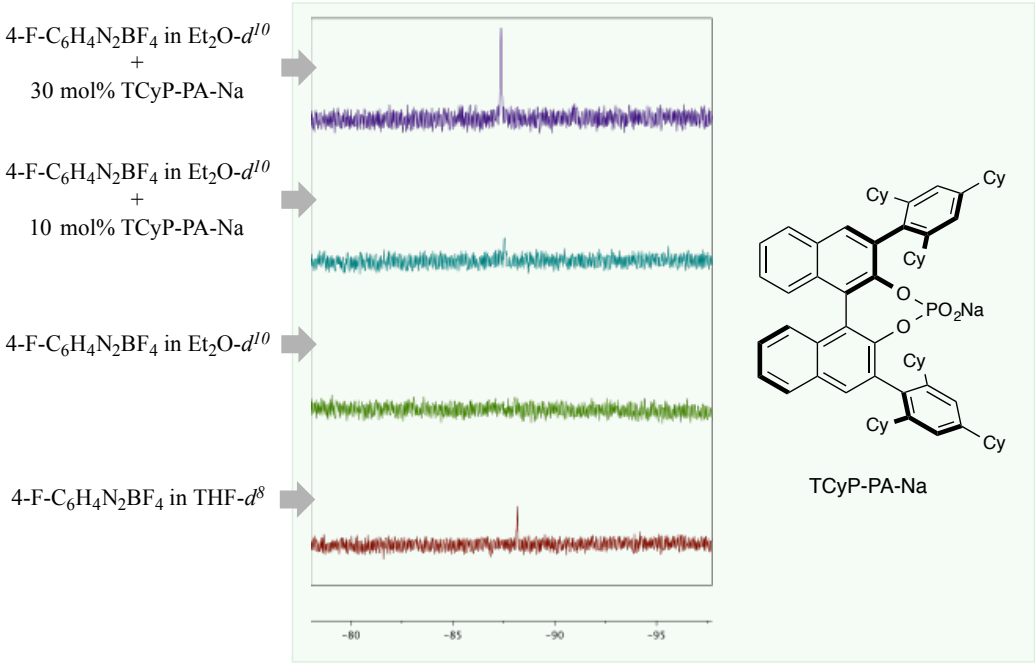
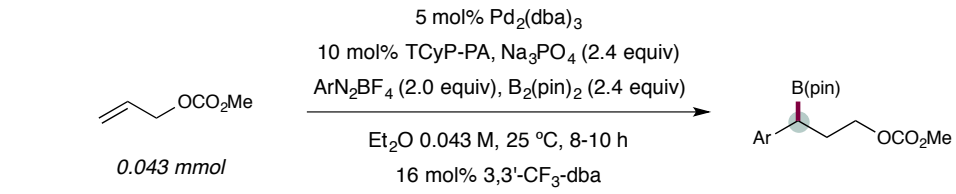


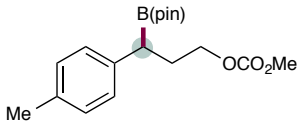
Figure 3.7. ^{19}F NMR experiments.

With optimized conditions in hand, we examined the aryl diazonium scope (*Table 3.3*).[200] In general, the developed methodology provided benzylic boronic esters in synthetically useful yields and good to excellent enantioselectivities.

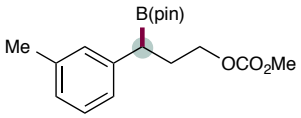
[200] In order to get isolated yields, an oxidative work-up was required. See *Experimental Section 3.5.3 & 3.5.5*.

Table 3.3. Enantioselective scope.[a,b]

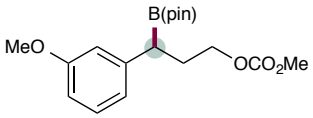




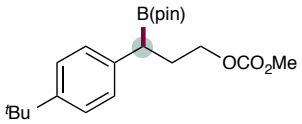
3.21, *46% yield, 93:7 er*



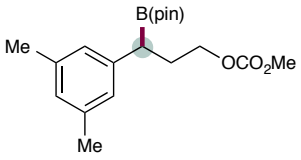
3.8, *50% yield, 94:6 er*



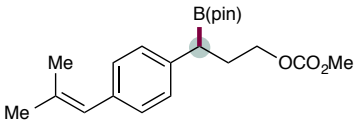
3.22, *58% yield, 94:6 er*



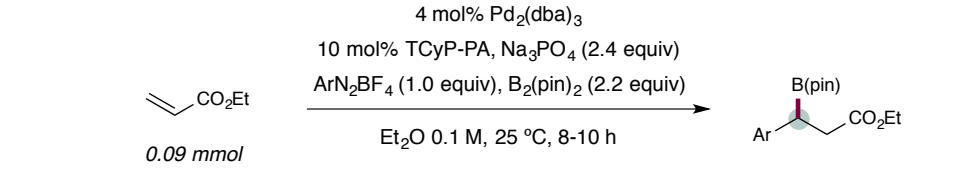
3.23, *32% yield, 98:2 er*

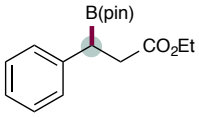


3.24, *50% yield, 93:7 er*

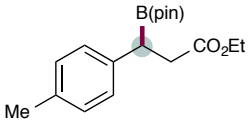


3.25, *40% yield, 99:1 er*

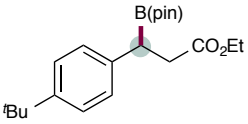




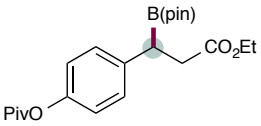
3.18, *47% yield, 95:5 er*



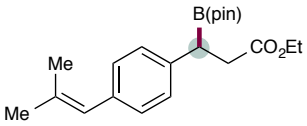
3.26, *44% yield, 92:8 er*



3.27, *33% yield, 99:1 er*



3.28, *40% yield, 99:1 er*



3.29, *29% yield, 99:1 er*

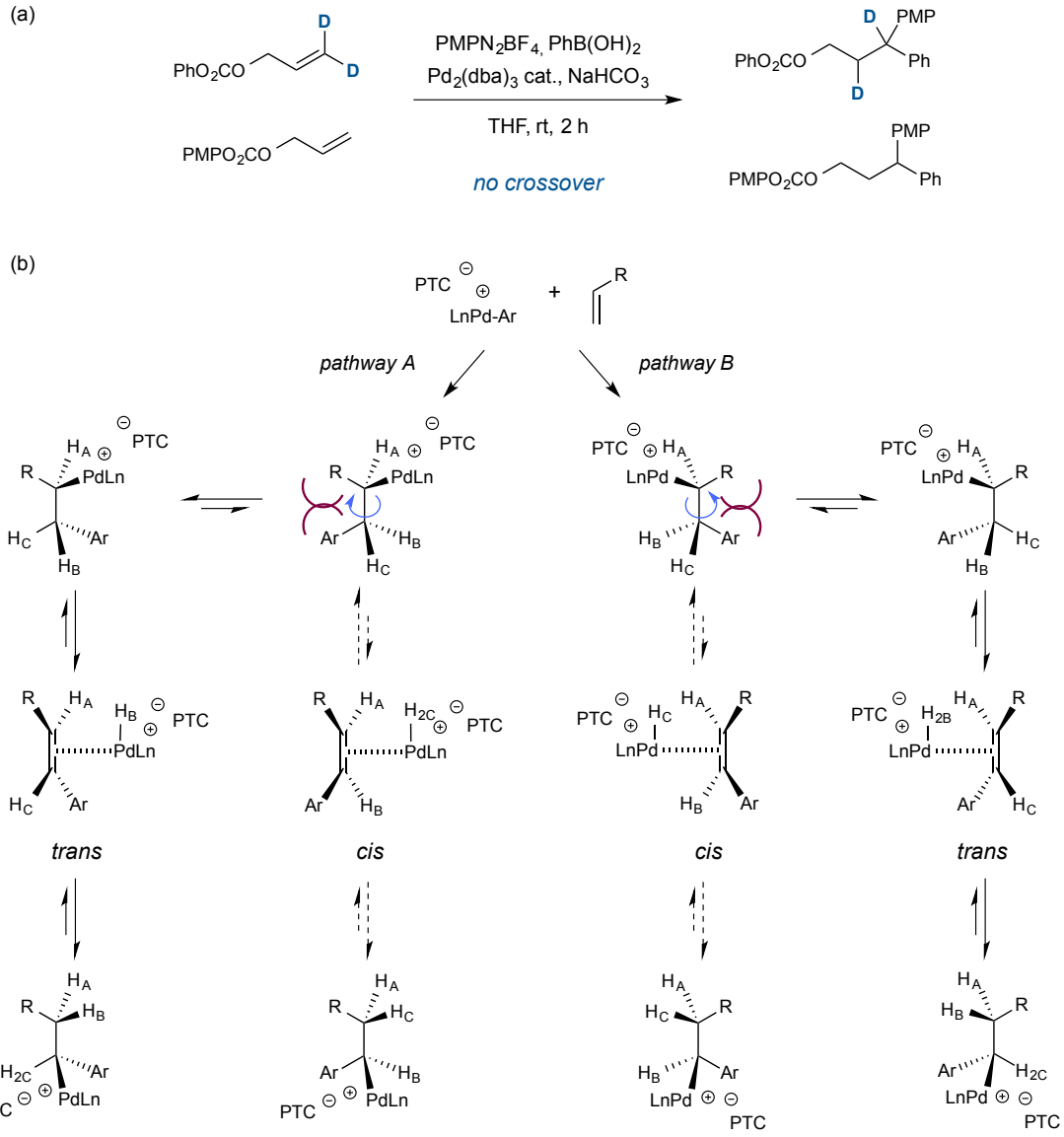
[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

Whereas *para*- and *meta*-substituents were well tolerated (see *Table 3.3*), the stereoselective process was highly sensitive to *ortho*- substitution, providing very low yields. As regards to

electronics, the stereoselective process was amenable applicable over non-highly electronically biased aryl diazonium salts. On the one hand, when substituted with electron-withdrawing groups, the efficiency of the process was harshly affected. We assume this is related with the stabilization of the π-benzyl palladium intermediate species (**E**, *Scheme 3.8*). According to its cationic character, its stability would be presumably compromised by electron-withdrawing groups. On the other hand, electron-rich aryl diazonium salts adversely affected selectivity. We hypothesize electron-donating properties of the aryl group contribute to disrupt the tight ion pair with the chiral phosphate counterion. However, the aryl moiety of the diazonium salt was tolerant of substitution of the *meta*- and *para*-positions with less-activating heteroatoms (**3.22**, **3.28**) or alkyl functional groups (**3.8**, **3.23**-**3.24**, **3.26**-**3.27**), providing a variety of 1,1-arylborylated esters in excellent enantioselectivities. Finally, substitution with a vinyl group at the *para*-position also afforded enriched boronic esters **3.25** and **3.29** in 99:1 er for both cases.

Despite moderate yields, conversions for both carbonate and acrylate systems were completed, detecting the corresponding Heck-product as the major byproduct. Unlike the non-stereoselective reaction in THF, the use of Et_2O and a phase-transfer catalyst resulted in significant termination via β-hydride elimination.

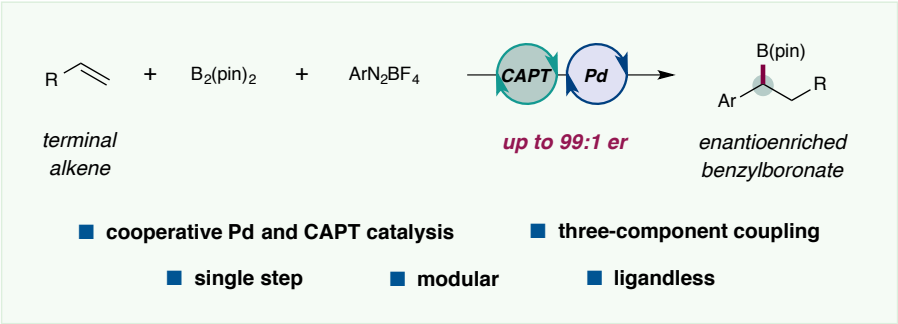
Finally, an interesting mechanistic insight might be inferred from Sigman's previous results. Attending to crossover experiments, which resulted in non-crossover products (*Scheme 3.10a*), we can assume an inner-sphere mechanism wherein the styrene does not dissociate prior transmetalation. Thereby, considering *syn*-stereoespecificity of both β-hydride elimination and insertion steps, we hypothesize chirality is established in the first insertion step. Then, stereospecificity of subsequent steps, besides kinetically prompted inner-sphere character, preserve chiral environment determined in the first migratory insertion step, in what might be considered as an illustration of "memory of chirality". As depicted in *Scheme 3.10b*, chiral PTC would favor migratory insertion over one of the enantiotopic faces of the olefin (pathway A vs pathway B). Then, *syn*-β-hydride elimination would take place over less energetic alternate conformation rather than over an eclipsed one. This is supported by the experimental detection of *trans*-styrene. *Cis*-styrene was never observed. Finally, an inner-sphere mechanism guarantees a stereospecific reinsertion.



Scheme 3.10. (a) Crossover experiments (Sigman). (b) Mechanistic hypothesis.

3.4. Conclusions.

Chapter 3 discloses a single-step method for the ready preparation of enantioenriched benzyl boronates from terminal alkenes.[201] This process was rendered highly enantioselective by means of the unprecedented "ligand-less" combination of CAPT and transition metal catalysis (*Scheme 3.11*). Though this methodology provides moderate yields, the modularity and step economy in this three-component coupling protocol can compensate for this limitation.



Scheme 3.11. Cooperative CAPT-Pd catalysis.

This strategy emerges as a feasible strategy to achieve enantioinduction in reaction manifolds where chiral ancillary ligands have a deleterious effect, such as in the Heck-Matsuda reaction. The significance of the developed transformation is implemented by the synthetic relevance of the accessed motifs, providing the basis for scaffold diversity. Novel applications of the developed strategy have been already reported.[202]

[201] Nelson, H. M.; Williams, B. D.; Miró, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213.
[202] (a) Yamamoto, E.; Hilton, M. J.; Orlandi, M.; Saini, V.; Toste, F. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 15877. (b) Tao, Z.-L.; Adili, A.; Shen, H.-C.; Han, Z.-Y.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 4322. (c) Yang, K.; Song, Q. *Org. Lett.* **2016**, *18*, 5460.

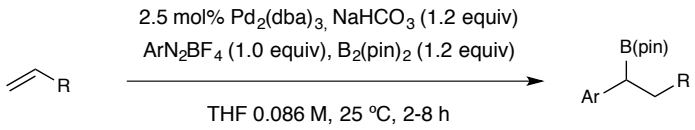
3.5. Experimental section.

General remarks: Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Chiral anion phase-transfer (CAPT) reactions were performed in 1-dram (0.5" x 1.75") vials equipped with a screw cap and stirred using a magnetic Teflon stir bar (1/2" x 5/16"), placed on the surface of a magnetic stir plate. Due to the heterogeneous nature of these reactions, it is important that fast and efficient stirring be maintained over the course of the reaction in order to obtain optimal results. Diethyl ether (Et_2O) was used as purchased from Fischer Scientific. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates, and visualized under UV or by staining with ceric ammonium molybdate or $KMnO_4$. Column chromatography was performed on Merck Silica Gel 60 Å, 230 X 400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV-600, AV-500, DRX-500, AVQ-400, AVB-400 and AV-300 spectrometers. ^1H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CHCl_3$, δH = 7.27 ppm and δC = 77.23 ppm; DMSO, δH = 2.50 and δC = 39.5 ppm; CH_2Cl_2, δH = 5.32 and δC = 53.8 ppm). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, app t = apparent triplet, m = multiplet, br = broad resonance. Solvent abbreviations are reported as follows: $B_2(pin)_2$ = bis(pinicaloato)diboron, MTBE = methyl *tert*-butyl ether, EtOAc = ethyl acetate, hex = hexanes, DCM = dichloromethane, Et_2O = diethyl ether, MeOH = methanol, ^{i}PrOH = isopropanol, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide, Et_3N = triethylamine. Mass spectral data were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley or by usage of an Agilent Time of Flight (Q-TOF) mass spectrometer in ESI mode. Enantiomeric excesses were measured on a Shimadzu VP Series Chiral HPLC using Chiralpak IA, IB, or IC columns. The syntheses of chiral phosphoric acids, e.g. TRIP-PA, H_8-TCyP-PA, TCyP-PA, STRIP-PA, have been previously reported.[152] Dibenzylideneacetone (dba) derivatives were prepared under basic conditions by aldol reaction between acetone and the corresponding benzaldehyde according to reported procedures.[203] **Caution:** Although we have not experienced any problems during the preparation and handling of the aryldiazonium tetrafluoroborates reported herein, appropriate safety precautions should be taken due to the explosive nature of diazonium salts, including the use of a blast shield.[204] Racemic products were synthesized utilizing homogeneous conditions in the absence of phase-transfer catalyst with THF as a solvent.

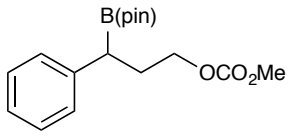
[203] Zhou, X.; Li, X.; Zhang, W.; Chen, J. *Tetrahedron Lett.* **2014**, *55*, 5137.

[204] Aryldiazonium salts were prepared according to general procedure reported in ref. 164b: Nelson, H. M.; Reisberg, S. H.; Shunatona, H. P.; Patel, J. S.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5600.

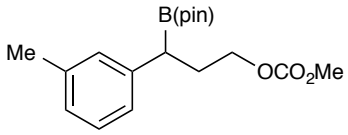
3.5.1. General procedure A: Racemic three-component 1,1-arylborylation reaction.



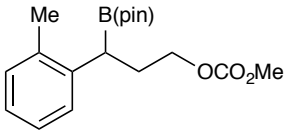
A 1 dram vial was charged with $B_2(pin)_2$ (1.2 equiv), Pd_2dba_3 (2.5 mol%), $NaHCO_3$ (1.2 equiv), the ArN_2BF_4 (1.0 equiv). To the solid reagents was added a solution of the appropriate olefin (1.0 equiv, 0.10 mmol) in THF (0.086 M). The headspace of the reaction vessel was sparged with N_2 for ca. 0.5 min, and then the vial was capped and the heterogeneous reaction mixture was stirred vigorously. The reaction progress monitored *via* TLC analysis. Upon completion the reaction was concentrated *in vacuo* and the crude reactions were purified by flash column chromatography (EtOAc/hexanes) to provide pure boronic esters.



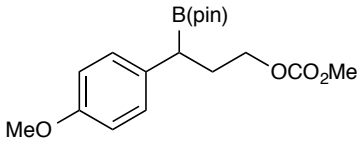
Methyl (3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl) carbonate. Following the general procedure A, **3.7** was obtained in 72% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.29-7.23 (m, 2H), 7.23-7.17 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 4.14 (dt, *J* = 10.6, 6.3 Hz, 1H), 4.05 (dt, *J* = 10.7, 6.9 Hz, 1H), 3.77 (s, 3H), 2.44 (t, *J* = 7.9 Hz, 1H), 2.24 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.02 (tt, *J* = 14.1, 6.4 Hz, 1H), 1.20 (d, *J* = 13.5 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) 156.02, 142.05, 128.69, 128.56, 125.76, 83.74, 67.62, 54.80, 31.43, 24.77. HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{17}H_{25}BKO_5$ 359.1427, found 359.1429.



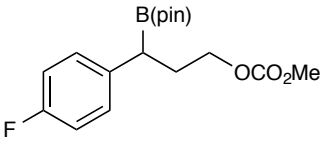
Methyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*m*-tolyl)propyl) carbonate. Following the general procedure A, **3.8** was obtained in 90% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.15 (t, *J* = 7.5 Hz, 1H), 7.03 – 6.94 (m, 3H), 4.14 (ddd, *J* = 10.6, 6.8, 5.8 Hz, 1H), 4.05 (dt, *J* = 10.6, 6.9 Hz, 1H), 3.77 (s, 3H), 2.39 (t, *J* = 7.9 Hz, 1H), 2.31 (s, 3H), 2.22 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.99 (ddt, *J* = 14.1, 8.2, 6.2 Hz, 1H), 1.20 (d, *J* = 11.0 Hz, 12H).^{13}C NMR (126 MHz, $CDCl_3$) δ 156.02, 141.90, 138.16, 129.43, 128.55, 126.55, 125.50, 83.70, 67.69, 54.81, 31.49, 24.79, 21.66. HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{18}H_{27}BKO_5$ 373.1583, found 373.1582.



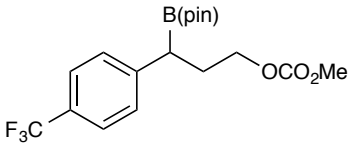
Methyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*o*-tolyl)propyl) carbonate. Follo-wing the general procedure A, **3.9** was obtained in 89% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.20 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.15 (tt, *J* = 5.5, 1.5 Hz, 2H), 7.08 (td, *J* = 7.2, 1.5 Hz, 1H), 4.18 (dt, *J* = 10.7, 6.3 Hz, 1H), 4.07 (dt, *J* = 10.5, 6.9 Hz, 1H), 3.79 (s, 3H), 2.66 (t, *J* = 7.8 Hz, 1H), 2.35 (s, 3H), 2.27 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.02 (ddt, *J* = 14.0, 7.9, 6.2 Hz, 1H), 1.22 (d, *J* = 12.1 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.03, 140.49, 136.31, 130.54, 127.95, 126.27, 125.60, 83.65, 67.75, 54.82, 31.01, 24.88, 24.77, 20.29. HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{18}H_{27}BKO_5$ 373.1583, 373.1584.



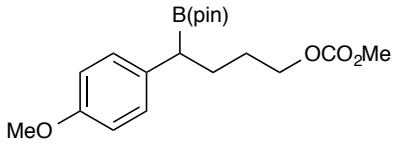
3-(4-Methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl methyl carbonate. Following the general procedure A, **3.10** was obtained in 90% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.17 – 7.05 (m, 2H), 6.87 – 6.75 (m, 2H), 4.13 (ddd, *J* = 10.6, 6.8, 5.8 Hz, 1H), 4.04 (dt, *J* = 10.6, 7.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.38 (t, *J* = 7.9 Hz, 1H), 2.19 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.96 (ddt, *J* = 14.2, 8.5, 6.2 Hz, 1H), 1.20 (d, *J* = 10.7 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.75, 156.02, 133.91, 129.46, 114.13, 83.68, 67.58, 55.39, 54.82, 31.63, 24.82, 24.78. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{27}BNaO_6$ 373.1793, found 373.1797.



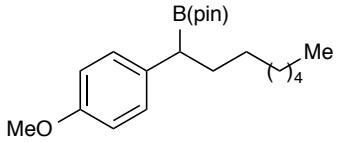
3-(4-Fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl methyl carbonate. Fo-llowing the general procedure A, **3.11** was obtained in 94% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.08 (dd, *J* = 9.0, 6.0 Hz, 2H), 6.87 (t, *J* = 9.0 Hz, 2H), 4.09 – 3.91 (m, 2H), 3.68 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 1H), 2.13 (td, *J* = 14.1, 7.4 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 12H). ^{13}C NMR (75.5 MHz, $CDCl_3$) 161.09 (d, J_{CF} = 243.1 Hz), 155.75, 137.39 (d, J_{CF} = 3.0 Hz), 129.61 (d, J_{CF} = 7.6 Hz), 115.20 (d, J_{CF} = 21.1 Hz), 83.59, 67.15, 54.59, 31.29, 24.57, 24.52. ^{19}F NMR (282 MHz, $CDCl_3$) -118.58 (tt, *J* = 8.8, 5.4 Hz). HRMS (ESI) *m/z* $[M+H]^+$ calcd. for $C_{17}H_{25}BFO_5$ 339.1774, found 339.1785.



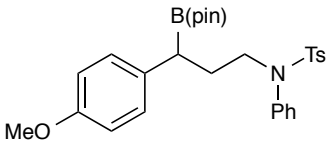
Methyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(4-(trifluoromethyl)phenyl)propyl) carbonate. Following the general procedure A, **3.12** was obtained in 71% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.14 (dt, *J* = 10.8, 6.2 Hz, 1H), 4.03 (ddd, *J* = 10.7, 7.3, 6.2 Hz, 1H), 3.76 (s, 3H), 2.52 (t, *J* = 7.9 Hz, 1H), 2.25 (dq, *J* = 14.2, 7.2 Hz, 1H), 2.02 (ddd, *J* = 14.0, 8.1, 6.0 Hz, 1H), 1.20 (d, *J* = 10.5 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.96, 146.52, 128.80, 128.24, 128.03, 125.61 (q, *J* = 7.5 Hz), 123.71, 84.05, 67.29, 54.87, 31.18, 24.83, 24.79. HRMS (EI) *m/z* $[M]^+$ calcd. for $C_{18}H_{24}BF_3O_5$ 388.1669, found 388.1665.



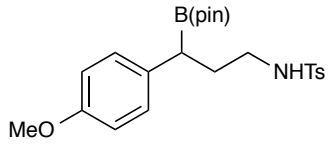
4-(4-Methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl methyl carbonate. Following the general procedure A, **3.13** was obtained in 74% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.17 – 7.02 (m, 2H), 6.88 – 6.73 (m, 2H), 4.12 (td, *J* = 6.6, 1.8 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.26 (t, *J* = 7.7 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.76 – 1.57 (m, 3H), 1.22 (d, *J* = 11.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.61, 156.01, 134.72, 129.43, 114.01, 83.54, 68.43, 55.37, 54.82, 28.95, 28.33, 24.84, 24.79. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{29}BNaO_6$ 387.1949, found 387.1951.



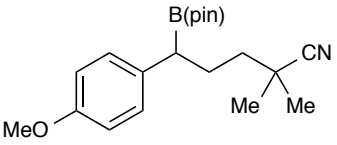
2-(1-(4-Methoxyphenyl)octyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Following the general procedure A, **3.14** was obtained in 90% yield. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 3H), 2.23 (t, *J* = 9.0 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.65 – 1.54 (m, 1H), 1.30 – 1.19 (m, 22H), 0.86 (t, *J* = 9.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) 157.21, 135.49, 129.15, 113.65, 83.13, 55.14, 32.86, 31.84, 29.58, 29.24, 29.21, 24.63, 24.57, 22.64, 14.09. HRMS (ESI) *m/z* $[M+NH_4]^+$ calcd. for $C_{21}H_{39}BNO_3$ 364.3029, found 364.3028.



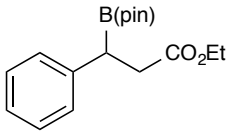
***N*-(3-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-methyl-*N*-phenylbenzenesulfonamide.** Following the general procedure A, utilizing deoxygenated THF, **3.15** was obtained in 84% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.46 – 7.38 (m, 2H), 7.27 (dt, *J* = 4.5, 3.1 Hz, 3H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.06 – 6.93 (m, 4H), 6.81 – 6.67 (m, 2H), 3.75 (s, 3H), 3.48 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.32 (t, *J* = 7.9 Hz, 1H), 1.94 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.71 (dq, *J* = 13.6, 7.6 Hz, 1H), 1.17 (d, *J* = 18.5 Hz, 12H).^{13}C NMR (151 MHz, $CDCl_3$) δ 157.61, 143.32, 139.51, 135.50, 134.18, 129.46, 129.38, 129.05, 128.95, 127.90, 127.84, 113.99, 83.61, 55.36, 50.11, 31.41, 24.85, 24.73, 21.73. HRMS (EI) *m/z* $[M]^+$ calcd. for $C_{29}H_{36}BNO_5S$ 521.2407, found 521.2399.



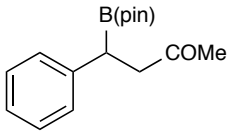
***N*-(3-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-methyl-benzenesulfonamide.** Following the general procedure A, utilizing deoxygenated THF, **3.16** was obtained in 91% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 9.8 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.63 (t, *J* = 6.2 Hz, 1H), 3.79 (d, *J* = 2.5 Hz, 3H), 2.99 – 2.76 (m, 2H), 2.44 (d, *J* = 2.5 Hz, 3H), 2.26 (t, *J* = 7.7 Hz, 1H), 1.95 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.79 (dq, *J* = 14.1, 7.0 Hz, 1H), 1.20 (dd, *J* = 12.8, 2.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.75, 143.40, 137.05, 133.81, 129.81, 129.41, 127.34, 114.14, 83.85, 83.34, 55.37, 42.73, 32.43, 24.81, 24.76, 21.71. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{23}H_{32}BNNaO_5S$ 468.1986, found 468.1985.



5-(4-Methoxyphenyl)-2,2-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentane-nitrile. Following the general procedure A, **3.17** was obtained in 99% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.23 (m, 10H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 2.41 – 2.30 (m, 2H), 2.28 (dd, *J* = 8.8, 6.7 Hz, 1H), 2.02 (ddd, *J* = 16.8, 13.7, 7.3 Hz, 1H), 1.87 – 1.73 (m, 1H), 1.21 (d, *J* = 10.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.67, 140.72, 140.06, 134.10, 129.47, 128.97, 128.96, 127.88, 127.05, 127.01, 122.63, 114.01, 83.60, 55.37, 51.85, 39.13, 28.43, 24.86, 24.76. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{30}H_{34}BNNaO_3$ 490.2524, found 490.2524.

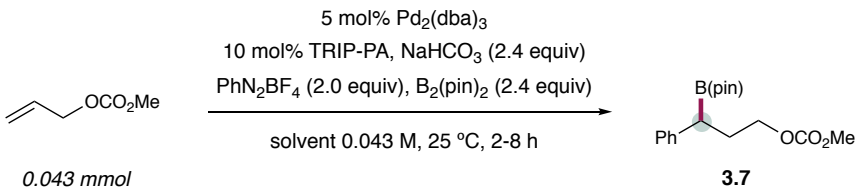


Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate. Following the general procedure A, **3.18** was obtained in 46% yield. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 4.24 – 4.06 (m, 2H), 2.92 (dd, *J* = 16.4, 10.2 Hz, 1H), 2.78 (dd, *J* = 10.2, 6.1 Hz, 1H), 2.70 (dd, *J* = 16.4, 6.1 Hz, 1H), 1.29 – 1.19 (m, 15H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.60, 141.60, 128.65, 128.40, 125.84, 83.74, 60.54, 37.53, 24.79, 24.70, 14.45. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{25}BNaO_4$ 343.1477, found 343.1479.

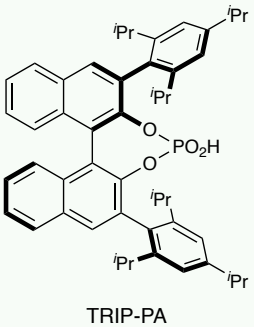


4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one. Following the general procedure A, **3.19** was obtained in 45% yield. Spectra matches previously reported spectra.[205]

3.5.2. Optimization of the enantioselective three-component 1,1-arylborylation reaction of methyl allyl carbonate. Summary data.



entry	solvent	yield[a]	ee[b]
1	hexanes	<5%	nd
2	THF	72%	6%
3	Et_2O	45%	34%
4	Et_2O/H_2O (50 μg)	<10%	80%
5	Et_2O/THF (1:1)	91%	<5%

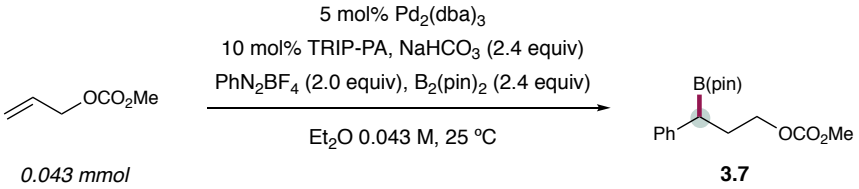


TRIP-PA

[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

[205] Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051.

·*Time study*



entry	time	yield[a]	ee[b]
1	2 h	5.7%	94%
2	4 h	6.6%	90%
3	6 h	21%	92%
4	14 h	19%	92%

[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

·*Others*

-$Pd_2(dba)_3$ loading (1.25-10 mol%) had no effect.

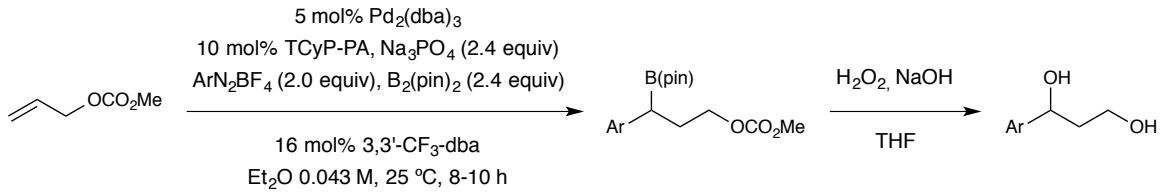
-Increasing equivalents of base had minor effect on ee.

-Increasing equivalents of ArN_2BF_4 had detrimental effect on yield.

-Decreasing equivalents of $B_2(pin)_2$ had detrimental effect on yield, while ee was unaffected. Increasing equivalents from standard conditions had positive effect on yield, but ee was reduced.

-Increasing equivalents of olefin had a detrimental effect on yield. Decreasing equivalents increased yield (ee was maintained).

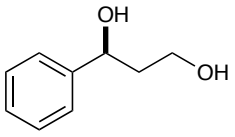
3.5.3. General procedure B: Enantioselective three-component 1,1-arylborylation reaction of allyl carbonate.



A 1 dram vial was charged with $B_2(pin)_2$ (2.4 equiv), Pd_2dba_3 (5 mol%), TCyP-PA (10 mol%), 3,3'-CF_3-dba (16 mol%), Na_3PO_4 (2.4 equiv), the ArN_2BF_4 (2.0 equiv). To the solid reagents was added a solution of allyl methyl carbonate (1.0 equiv, 0.043 mmol) in Et_2O (0.043 M in allyl methyl carbonate). The headspace of the reaction vessel was sparged with N_2 for ca. 10 seconds then the vial was capped and the heterogeneous reaction mixture was stirred vigorously. The reaction progress was monitored *via* TLC analysis. Upon completion the reaction was filtered through a plug of cotton to remove solid particulates and then concentrated *in vacuo*.

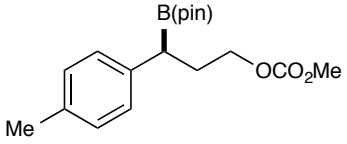
^{1}H NMR yield: The crude reaction mixture was dissolved in a solution of CD_2Cl_2 and dimethyl sulfone (1 equiv) to obtain the NMR yield.

Isolated yield of diol (over two steps): The crude reaction mixture was concentrated and purified *via* column chromatograph (EtOAc/hexanes) to obtain the boronic ester product contaminated with residual $B_2(pin)_2$. To this mixture was added THF (1.0 mL), 1 M NaOH (0.50 mL), and 30% v/v aq. H_2O_2 (0.25 mL) and then reaction mixture was stirred under a N_2 atmosphere. Reaction progress was monitored *via* TLC analysis. Upon complete conversion to the diol, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, concentrated, and then purified *via* column chromatography (40-60% EtOAc/hexanes) to provide pure diol.

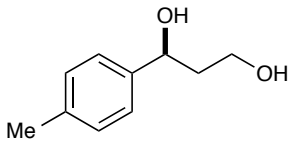


1-Phenylpropane-1,3-diol. Following the general procedure B, **3.30** was isolated in 23% yield over two steps. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 6.5 Hz, 3H), 7.33 – 7.22 (m, 2H), 4.98 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.88 (t, *J* = 5.5 Hz, 2H), 2.80 (s, 1H), 2.35 (s, 1H), 2.10 – 1.98 (m, 1H), 1.96 (dq, *J* = 14.2, 4.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.52, 128.76, 127.84, 125.86, 74.63,

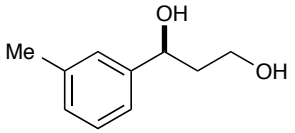
61.73, 40.75. Spectra matches previously reported spectra.[206] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (15.4 min), T_{minor} (11.8 min); 96:4 er (92% ee).



Methyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*p*-tolyl)propyl) carbonate. Following the general procedure B, **3.21** was provided in 46% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 – 7.02 (m, 4H), 4.15 (ddd, *J* = 10.6, 6.8, 5.8 Hz, 1H), 4.06 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.78 (s, 3H), 2.42 (t, *J* = 7.9 Hz, 1H), 2.32 (s, 3H), 2.23 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.00 (ddt, *J* = 14.2, 8.4, 6.2 Hz, 1H), 1.22 (d, *J* = 10.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.02, 138.83, 135.13, 129.41, 128.44, 83.67, 67.62, 54.80, 31.56, 24.82, 24.79, 21.20. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{27}BNaO_5$ 357.1844, found 357.1844.



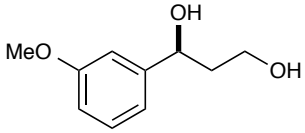
1-(*p*-Tolyl)propane-1,3-diol. Following the general procedure B, **3.31** was isolated in 35% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) = 7.29 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 4.97 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.89 (t, *J* = 5.5 Hz, 2H), 2.72 (s, 1H), 2.38 (s, 4H), 2.11-2.00 (m, 1H), 2.00-1.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) = 141.52, 137.55, 129.41, 125.80, 74.59, 61.80, 40.65, 21.33. Spectra matches previously reported spectra.[207] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (18.9 min), T_{minor} (14.2 min); 95:5 er (90% ee).



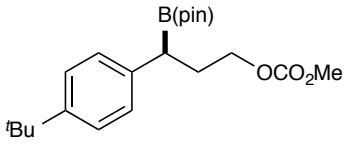
1-(*m*-Tolyl)propane-1,3-diol. Following the general procedure B, **3.32** was isolated in 30% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) 7.27 (d, *J* = 7.6 Hz, 1H), 7.23 (s, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 4.97 (dd, *J* = 8.9, 3.6 Hz, 1H), 3.90 (dd, *J* = 6.5, 4.6 Hz, 2H), 2.77 (s, 1H), 2.39 (s, 4H), 2.11-2.01 (m, 1H), 1.96 (dtd, *J* = 14.6, 5.2, 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) 144.44, 138.44, 128.65, 128.58, 126.54, 122.89, 74.75, 61.82, 40.65, 21.69. Spectra matches

[206] Borowiecki, P.; Wawro, A. M.; Winska, P.; Wielechowska, M.; Bretner, M. *Eur. J. Med. Chem.* **2014**, *84*, 364.
[207] Kim, J.; De Castro, K. A.; Lim, M.; Rhee, H. *Tetrahedron,* **2010**, *66*, 3995.

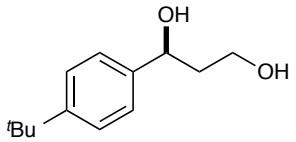
previously reported spectra.[208] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (18.2 min), T_{minor} (12.3 min); 94:6 er (88% ee).



1-(3-Methoxyphenyl)propane-1,3-diol. Following the general procedure B, **3.33** was isolated in a 37% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) 7.33-7.21 (m, 1H), 7.01-6.91 (m, 2H), 6.87-6.77 (m, 1H), 4.96 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.88 (dd, *J* = 6.6, 4.4 Hz, 2H), 3.83 (s, 3H), 2.82 (s, 1H), 2.33 (s, 1H), 2.10-1.99 (m, 1H), 1.99-1.88 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) 159.99, 146.23, 129.78, 118.11, 113.24, 111.32, 74.58, 61.76, 55.46, 40.64. Spectra matches previously reported spectra.[209] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (19.6 min), T_{minor} (11.1 min); 94:6 er (88% ee).



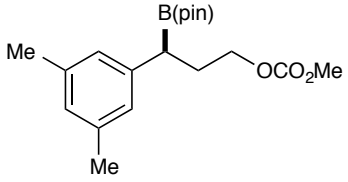
3-(4-(*Tert*-butyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl methyl carbonate. Following the general procedure B, **3.23** was provided in 32% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (600 MHz, Chloroform-*d*) 7.26 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 4.14 (dt, *J* = 10.6, 6.3 Hz, 1H), 4.05 (dt, *J* = 10.6, 6.9 Hz, 1H), 3.76 (s, 3H), 2.41 (t, *J* = 7.9 Hz, 1H), 2.25-2.14 (m, 1H), 1.99 (dq, *J* = 13.9, 6.3 Hz, 1H), 1.28 (s, 9H), 1.21 (d, *J* = 12.4 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) 156.06, 148.38, 138.77, 128.20, 125.58, 83.69, 67.73, 54.79, 34.51, 31.66, 31.62, 24.84. HRMS (ESI) *m/z* $[M+K]^{+}$ calcd. for $C_{21}H_{33}BKO_5$ 415.2053, found 415.2051.



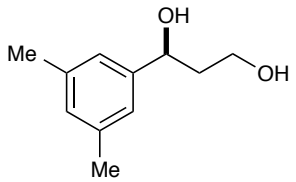
1-(4-(*Tert*-butyl)phenyl)propane-1,3-diol. Following the general procedure B, **3.34** was isolated in 32% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.99 (dd, *J* = 9.1, 3.6 Hz, 1H), 3.91 (s, 2H), 2.59 (s, 1H), 2.36 (s, 1H), 2.11-2.05 (m, 1H), 2.01-1.92 (m, 1H), 1.35 (s, 10H), 1.29 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) 150.87, 141.47, 125.68, 125.61, 74.58, 61.87, 40.56, 34.75, 31.57. Spectra matches previously reported

[208] Boyer, S. H.; Sun, Z.; Jiang, H.; Esterbrook, J.; Gómez-Galeno, J. E.; Craigo, W.; Reddy, K. R.; Ugarkar, B. G.; MacKenna, D. A.; Erion, M. D. *J. Med. Chem.* **2006**, *49*, 7711.
[209] Borowiecki, P.; Wawro, A. M.; Winska, P.; Wielechowska, M.; Bretner, M. *Eur. J. Med. Chem.* **2014**, *84*, 364.

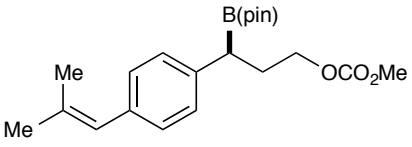
spectra.[210] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (14.9 min), T_{minor} (11.4 min); 98:2 er (96% ee).



3-(3,5-Dimethylphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl methyl carbonate. Following the general procedure B, **3.24** was provided in a 60% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (500 MHz, Chloroform-*d*) = 6.71 (s, 2H), 6.69 (s, 1H), 4.04 (ddd, *J* = 10.8, 6.9, 5.9 Hz, 1H), 3.96 (dt, *J* = 10.5, 6.9 Hz, 1H), 3.67 (s, 3H), 2.25 (t, *J* = 7.9 Hz, 1H), 2.17 (s, 6H), 2.11 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.91-1.83 (m, 1H), 1.11 (d, *J* = 10.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 156.01, 141.80, 137.97, 128.51, 127.48, 126.38, 83.64, 67.74, 54.77, 31.56, 24.74, 21.51. HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{19}H_{29}BKO_5$ 387.1740, found 387.1739.



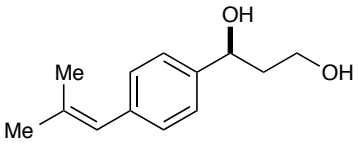
1-(3,5-Dimethylphenyl)propane-1,3-diol. Following the general procedure B, **3.35** was isolated in a 42% yield over two steps. ^{1}H NMR (600 MHz, Chloroform-*d*) = 6.99 (s, 2H), 6.94 (s, 1H), 4.91 (dd, *J* = 7.7, 4.5 Hz, 1H), 3.99-3.80 (m, 2H), 2.61 (s, 1H), 2.33 (s, 6H), 2.10-1.98 (m, 1H), 1.98-1.88 (m, 1H), 1.60 (s, 2H), 1.25 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) 144.50, 138.37, 129.48, 123.64, 74.74, 61.82, 40.74, 25.09, 21.55. Spectra matches previously reported spectra.[210] HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (18.1 min), T_{minor} (11.9 min); 93:7 er (86% ee).



Methyl 3-(4-(2-methylprop-1-en-1-yl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl carbonate. Following the general procedure B, **3.25** was provided in a 40% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.14 (s, 4H), 6.22 (t, *J* = 1.6 Hz, 1H), 4.14 (dt, *J* = 10.8, 6.3 Hz, 1H), 4.06 (dt, *J* = 10.6, 6.9 Hz, 1H), 3.76 (d, *J* = 0.8 Hz, 3H), 2.42 (t, *J* = 7.9 Hz, 1H), 2.22 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.89 (d, *J* = 1.3 Hz, 3H), 1.87 (d, *J* = 1.2 Hz, 3H),

[210] Reddy, K. R.; Matelich, M. C.; Ugarkar, B. G.; Gómez-Galeno, J. E.; DaRe, J.; Ollis, K.; Sun, Z.; Craigo, W.; Colby, T. J.; Fujitaki, J. M.; Boyer, S. H.; van Poelje, P. D.; Erion, M. D. *J. Med. Chem.* **2008**, *51*, 666.

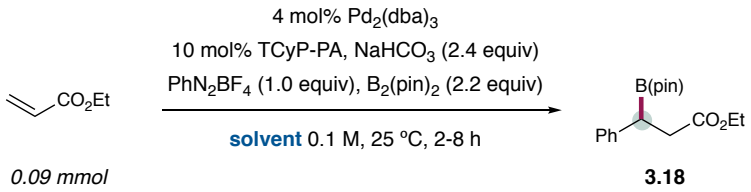
1.20 (d, J = 10.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.02, 139.42, 136.13, 134.99, 129.05, 128.22, 125.13, 83.72, 67.66, 54.81, 31.41, 27.18, 24.82, 24.77, 19.68. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{31}BNaO_5$ 397.2157, found 397.2160.



1-(4-(2-Methylprop-1-en-1-yl)phenyl)propane-1,3-diol. Following the general procedure B, **3.36** was isolated in a 37% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 6.26 (s, 1H), 5.04 – 4.87 (m, 1H), 3.89 (q, J = 5.3, 4.8 Hz, 2H), 2.65 (d, J = 2.7 Hz, 1H), 2.30 (s, 1H), 2.11 – 2.00 (m, 1H), 2.00 – 1.94 (m, 1H), 1.91 (d, J = 1.4 Hz, 3H), 1.87 (d, J = 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.82, 138.35, 135.97, 129.08, 125.59, 124.87, 74.63, 61.84, 40.59, 27.14, 19.65. HRMS (EI) *m/z* $[M]^+$ calcd. for $C_{13}H_{18}O_2$ 206.1307, found 206.1310. HPLC (ChiralPak IC column) 90:10 (hexane/^{i}PrOH) 1 mL/min; T_{major} (14.1 min), T_{minor} (11.8 min); 98:2 er (96% ee).

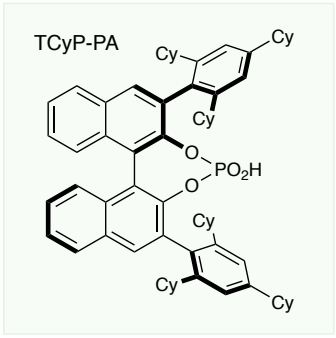
3.5.4. Optimization of the enantioselective three-component 1,1-arylborylation reaction of ethyl acrylate. Summary data.

·*Solvent screening*



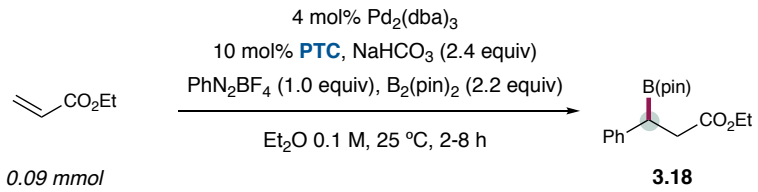
0.09 mmol **3.18**

entry	solvent	yield[a]	ee[b]
1	hexanes	33%	38%
2	toluene	73%	<5%
3	**Et_2O**	**47%**	**85%**
4	MTBE	55%	47%



[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

·*Catalyst screening*

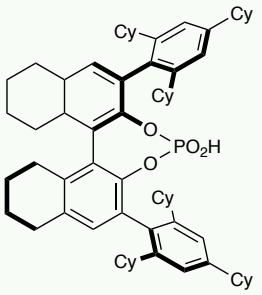


0.09 mmol

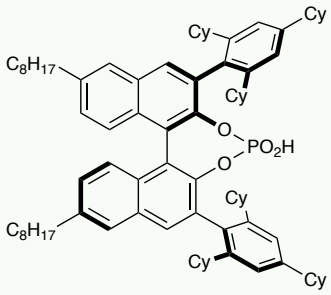
3.18

entry	PTC	yield[a]	ee[b]
1	**TCyP-PA**	**47%**	**85%**
2	H_8-TCyP-PA	35%	82%
3	C_8-TCyP-PA	46%	76%
4	TRIP-PA	54%	46%
5	STRIP-PA	52%	10%
6	9-Anthra-PA	24%	84%
7	4-CF_3-BINAM	29%	5%
8	3,5-diMe-BINAM	28%	21%
9	TRIP-NHTf	60%	<5%

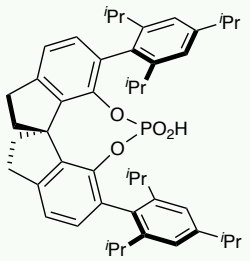
[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.



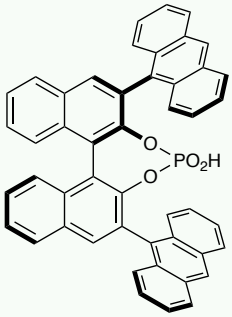
H_8-TCyP-PA



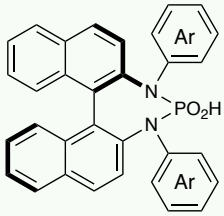
C_8-TCyP-PA



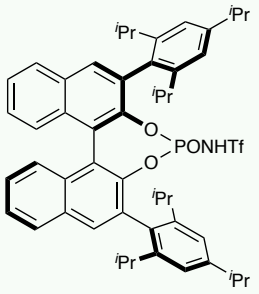
STRIP-PA



9-Anthra-PA

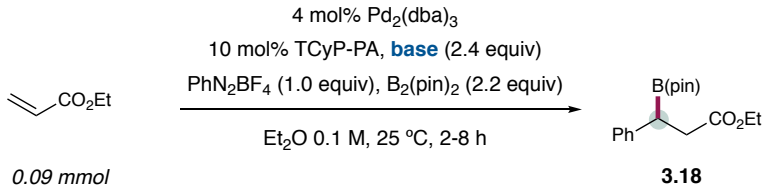


4-CF_3-BINAM (Ar = 4-CF_3-C_6H_4)
3,5-diMe-BINAM (Ar = 3,5-diMe-C_6H_4)



TRIP-NHTf

·*Base screening*

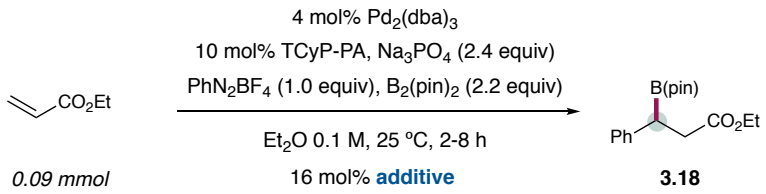


0.09 mmol **3.18**

entry	base	yield[a]	ee[b]
1	$NaHCO_3$	42%	86%
2	**Na_3PO_4**	**41%**	**89%**
3	K_3PO_4	<6%	nd
4	Na_2CO_3	36%	96%
5	K_2CO_3	32%	96%
6	Cs_2CO_3	not observed	-

[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

·*Additives*

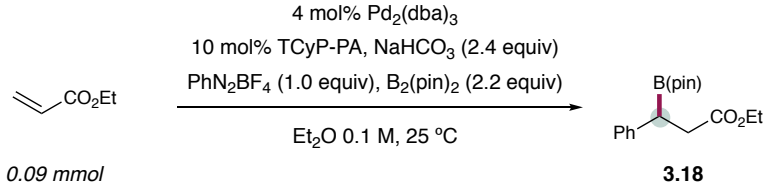


0.09 mmol **3.18**

entry	additive	yield[a]	ee[b]
1	-	41%	89%
2	dba	36%	93%
3	4-MeO-dba	38%	81%
4	4-CF_3-dba	39%	83%
5	3-CF_3-dba	34%	85%
6	3,5-diCF_3-dba	31%	66%

[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

·*Time study*

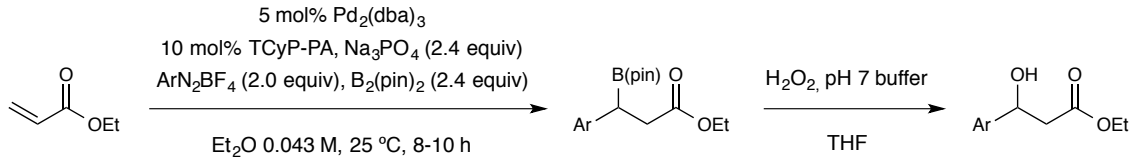


0.09 mmol **3.18**

entry	time	yield[a]	ee[b]
1	2 h	15%	76%
2	4 h	26%	81%
3	6 h	36%	80%
4	20 h	45%	86%

[a] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as internal standard. [b] Enantiomeric ratio determined by chiral phase HPLC.

3.5.5. General procedure C: Enantioselective three-component 1,1-arylborylation reaction of ethyl acrylate.

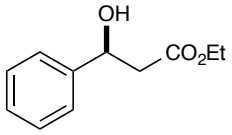


A 1 dram vial was charged with $B_2(pin)_2$ (2.2 equiv) , Pd_2dba_3 (4 mol%), TCyP-PA (10 mol%), Na_3PO_4 (2.4 equiv), the ArN_2BF_4 (1.0 equiv). To the solid reagents was added a solution of ethyl acrylate (1.0 equiv, 0.09 mmol) in Et_2O (0.1 M). The vial was capped and the heterogeneous reaction mixture was stirred vigorously. The reaction progress monitored *via* TLC analysis. Upon completion the reaction was filtered through a plug of Celite, and then concentrated *in vacuo*.

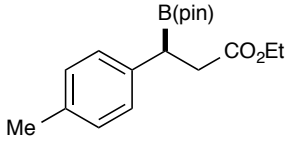
^{1}H NMR yield: The NMR yield was assessed by dissolving the crude reaction mixture in a solution of CD_2Cl_2 with dimethyl sulfone (1.0 equiv) as the internal standard.

Isolated yield of alcohol (over two steps): The crude reaction mixture (containing dimethyl sulfone) was purified *via* flash column chromatography (EtOAc/hexanes) to provide the boronic ester product that was contaminated with residual $B_2(pin)_2$. The mixture of product and byproduct was treated with THF (1 mL), pH 7 phosphate buffer solution (0.5 mL) was added, followed by the dropwise addition of 30% v/v aq. hydrogen peroxide (0.25 mL). After 0.5 h, stirring under a N_2 atmosphere, the reaction mixture was cautiously quenched with sat. aq. $Na_2S_2O_3$ (2 mL), and then diluted with H_2O. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over

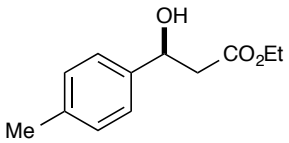
anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified *via* flash column chromatography (EtOAc/hexanes) to afford pure β-hydroxy ethyl esters as yellow oils.



Ethyl 3-hydroxy-3-phenylpropanoate. Following the general procedure C, **3.37** was isolated in a 46% yield over two steps. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 13.5, 6.2 Hz, 4H), 7.30 (t, *J* = 7.0 Hz, 1H), 5.15 (dt, *J* = 9.1, 3.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.28 (d, *J* = 3.4 Hz, 1H), 2.83 – 2.64 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.63, 142.72, 128.77, 128.02, 125.89, 70.56, 61.10, 43.55, 14.37. Spectra matches previously reported spectra.[211] HPLC (ChiralPak IC column) (hexane/^{i}PrOH) 1 mL/min; T_{major} (9.0 min), T_{minor} (8.2 min); 94:6 er (86% ee).

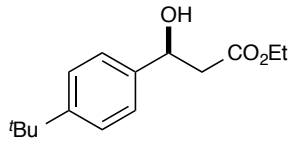


Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*p*-tolyl)propanoate. Following the general procedure C, **3.26** was provided in a 44% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (600 MHz, Chloroform-*d*) 7.12 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 4.21-4.01 (m, 2H), 2.86 (dd, *J* = 16.3, 10.1 Hz, 1H), 2.70 (dd, *J* = 10.1, 6.1 Hz, 1H), 2.63 (dd, *J* = 16.4, 6.1 Hz, 1H), 2.30 (s, 3H), 1.24-1.13 (m, 15H). ^{13}C NMR (151 MHz, $CDCl_3$) 173.66, 138.47, 135.22, 129.37, 128.29, 83.69, 60.50, 37.73, 24.81, 24.73, 21.18, 14.46. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{27}BNaO_4$ 341.1895, found 341.1894.

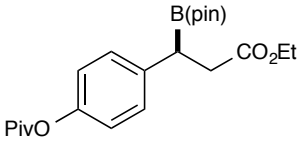


Ethyl 3-hydroxy-3-(*p*-tolyl)propanoate. Following the general procedure C, **3.38** was isolated in a 44% yield over two steps. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.34 – 7.22 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 5.11 (dd, *J* = 9.6, 3.4 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.21 (s, 1H), 2.76 (ddd, *J* = 16.3, 9.4, 1.1 Hz, 1H), 2.70 (ddd, *J* = 16.3, 3.7, 1.1 Hz, 1H), 2.35 (s, 3H), 1.28 (td, *J* = 7.2, 1.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.63, 139.80, 137.70, 129.41, 125.83, 70.41, 61.04, 43.55, 21.31, 14.37. Spectra matches previously reported spectra.[211] HPLC (ChiralPak IC column) (hexane/^{i}PrOH) 1 mL/min; T_{major} (9.0 min), T_{minor} (8.2 min); 92:8 er (84% ee).

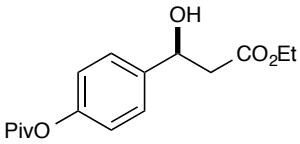
[211] Wolf, C.; Moskowitz, M. *J. Org. Chem.* **2011**, *76*, 6372.



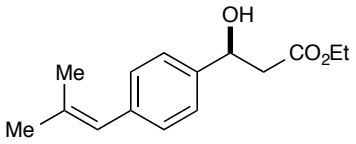
Ethyl 3-(4-(*tert*-butyl)phenyl)-3-hydroxypropanoate. Following the general procedure C, **3.39** was isolated in a 33% yield over two steps. ^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ 7.42 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 5.12 (dt, J = 7.3, 3.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.25 – 3.09 (bs, 1H), 2.80 – 2.66 (m, 2H), 1.35 (s, 8H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 172.65, 151.05, 140.17, 125.73, 125.68, 70.34, 61.10, 43.59, 34.74, 31.40, 14.30. Spectra matches previously reported spectra.[211] HPLC (ChiralPak IC column) (hexane/^{i}PrOH) 1 mL/min; T_{major} (21.4 min), T_{minor} (23.0 min); 99:1 er (98% ee).



4-(3-Ethoxy-3-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)phenyl pivalate. Following the general procedure C, **3.28** was provided in a 40% yield (*via* ^{1}H NMR analysis). ^{1}H NMR (500 MHz, Chloroform-*d*) 7.26-7.18 (m, 2H), 7.02-6.87 (m, 2H), 4.11 (qq, J = 10.8, 7.1 Hz, 2H), 2.86 (dd, J = 16.3, 10.0 Hz, 1H), 2.74 (dd, J = 10.0, 6.0 Hz, 1H), 2.65 (dd, J = 16.3, 6.0 Hz, 1H), 1.34 (s, 9H), 1.28-1.22 (m, 3H), 1.20 (app d, J = 20.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) 177.41, 173.52, 149.25, 138.84, 129.24, 121.57, 83.82, 60.65, 39.24, 37.57, 27.35, 24.79, 24.71, 14.46. HRMS (ESI) *m/z* $[M+K]^+$ calcd. for $C_{22}H_{33}BKO_6$ 427.2262, found 427.2266.

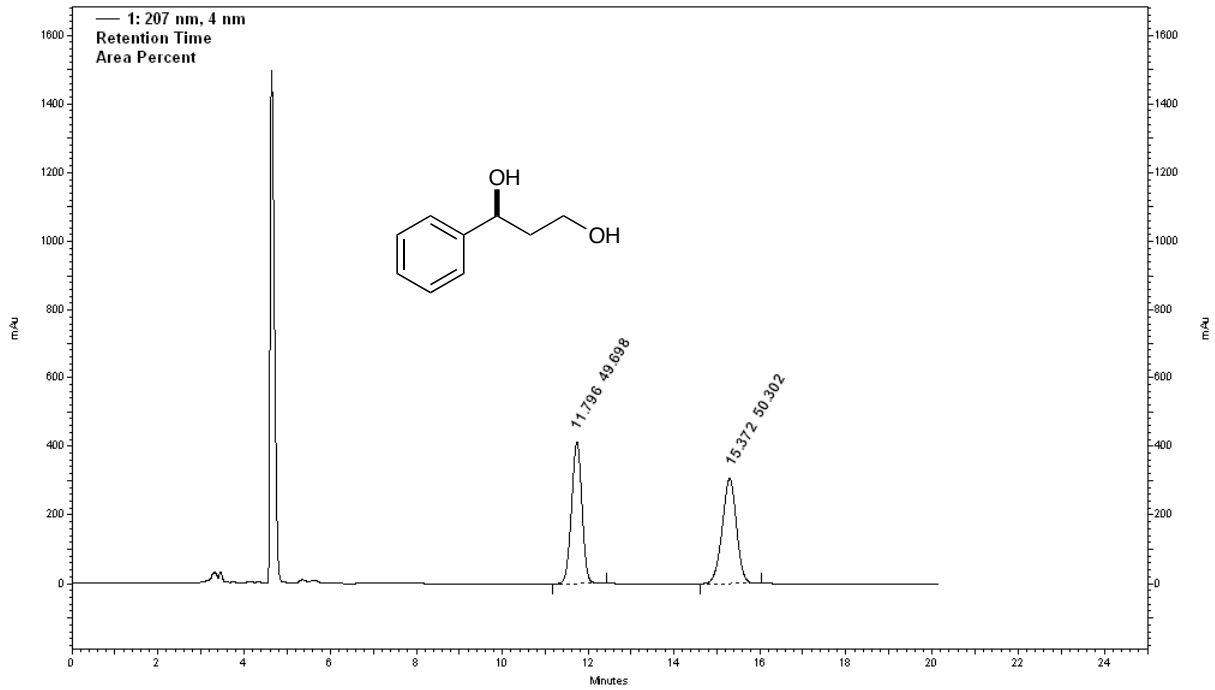


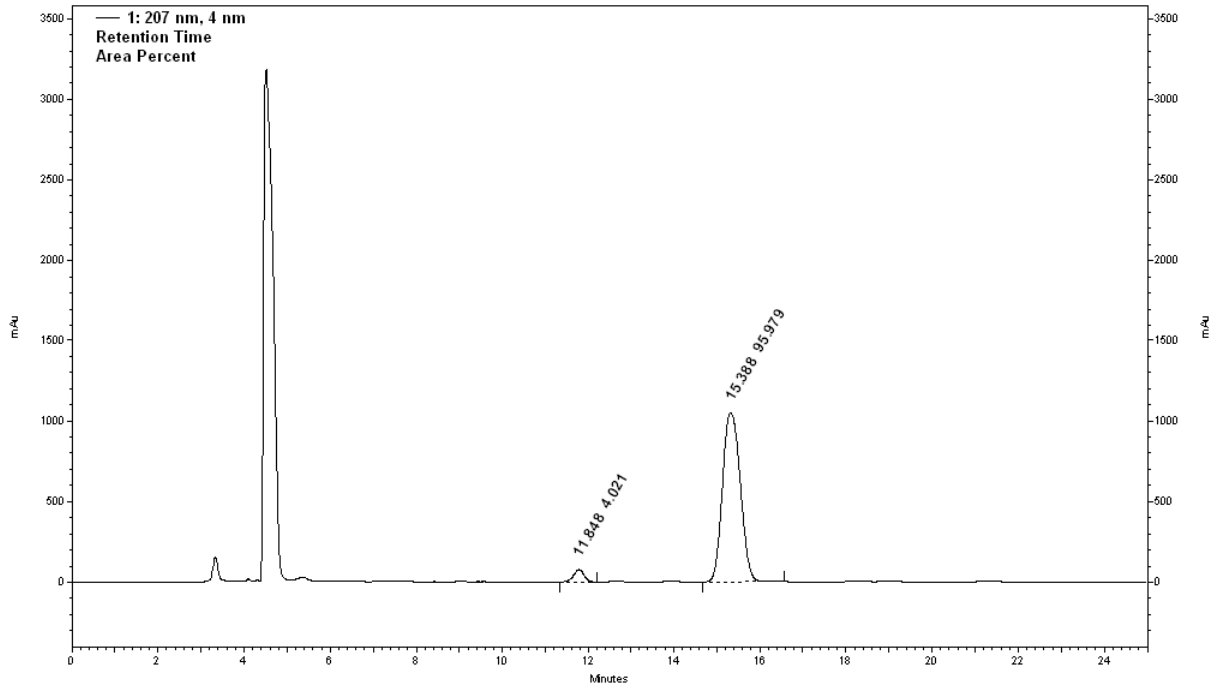
4-(3-Ethoxy-1-hydroxy-3-oxopropyl)phenyl pivalate. Following the general procedure C, **3.40** was isolated in a 37% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 5.15 (dt, J = 7.9, 3.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.33 (d, J = 3.3 Hz, 1H), 2.81 – 2.63 (m, 2H), 1.36 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.34, 172.61, 150.76, 140.00, 126.92, 121.79, 70.04, 61.18, 43.50, 39.28, 27.34, 14.37. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{16}H_{22}NaO_5$ 317.1359, found 317.1357. HPLC (ChiralPak IC column) (hexane/^{i}PrOH) 1 mL/min; T_{major} (32.8 min), T_{minor} (38.8 min); 96:4 er (92% ee).



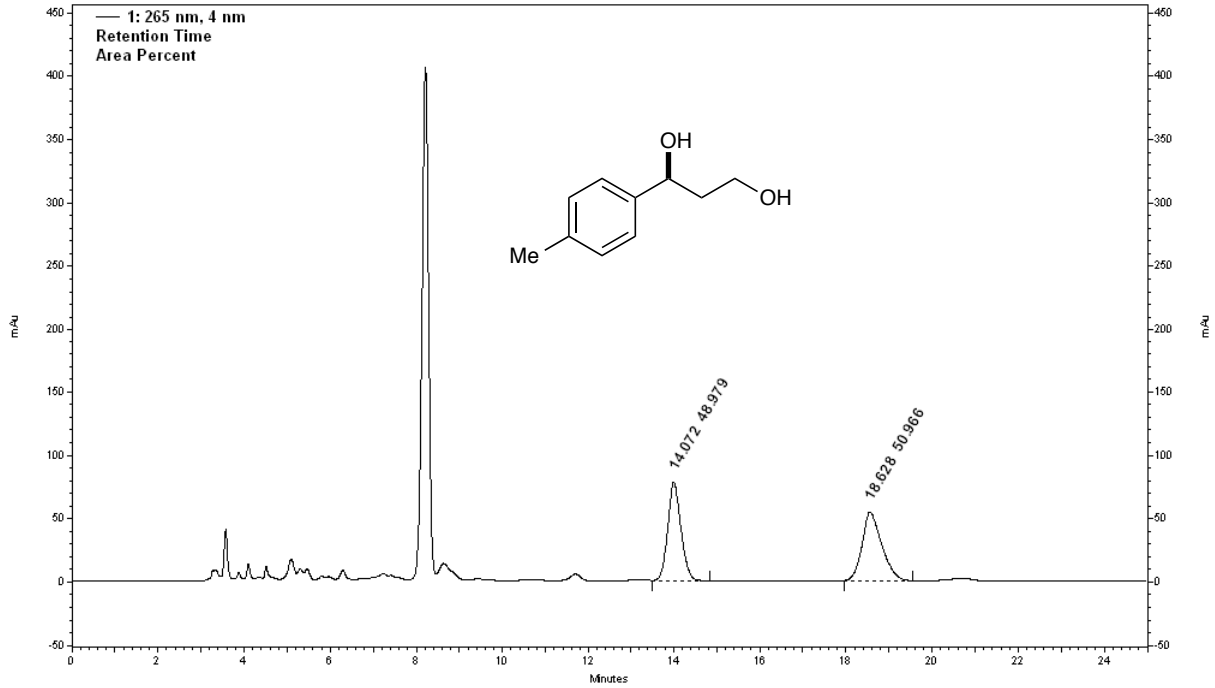
Ethyl 3-hydroxy-3-(4-(2-methylprop-1-en-1-yl)phenyl)propanoate. Following the general procedure C, **3.41** was isolated in a 27% yield over two steps. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.26 (s, 1H), 5.13 (dt, *J* = 9.3, 3.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.24 (d, *J* = 3.4 Hz, 1H), 2.84 – 2.64 (m, 2H), 1.91 (d, *J* = 1.4 Hz, 3H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.27 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.72, 140.00, 138.50, 136.03, 129.08, 125.62, 124.86, 70.42, 61.10, 43.42, 27.13, 19.63, 14.38. HRMS (ESI) *m/z* $[M+Na]^+$ calcd. for $C_{15}H_{20}NaO_3$ 271.1305, found 271.1306. HPLC (ChiralPak IC column) (hexane/^{i}PrOH) 1 mL/min; T_{major} (21.0 min), T_{minor} (22.3 min); 98:2 er (96% ee).

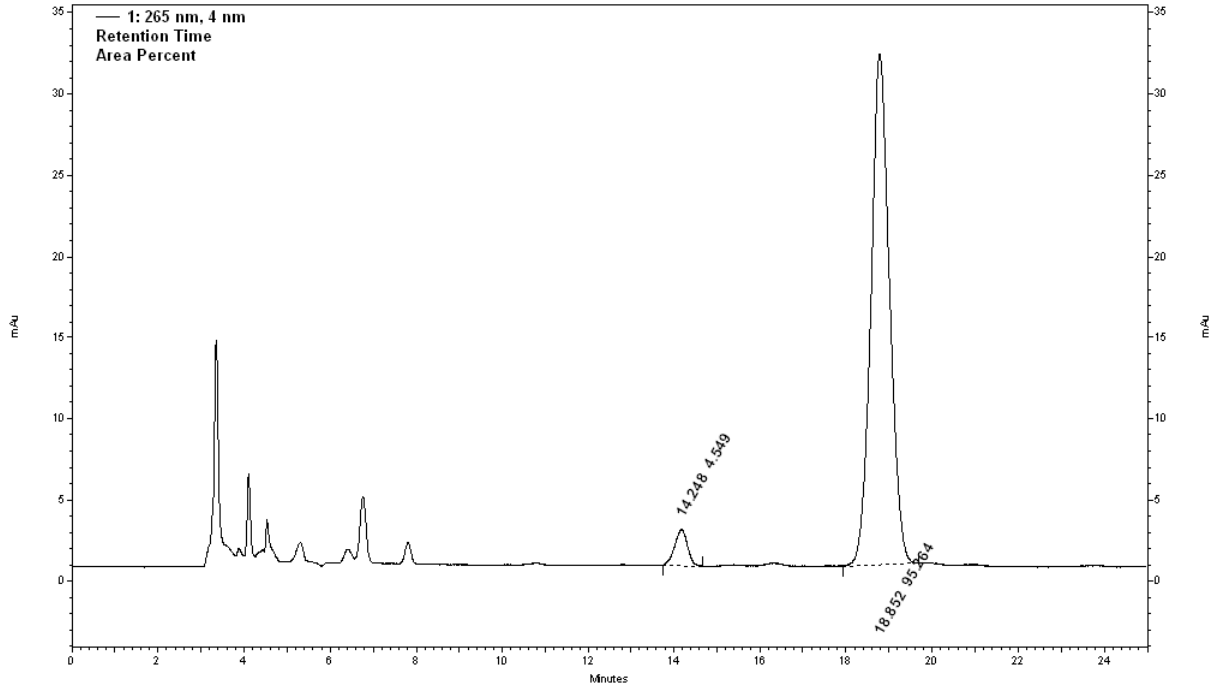
3.5.6. HPLC data.



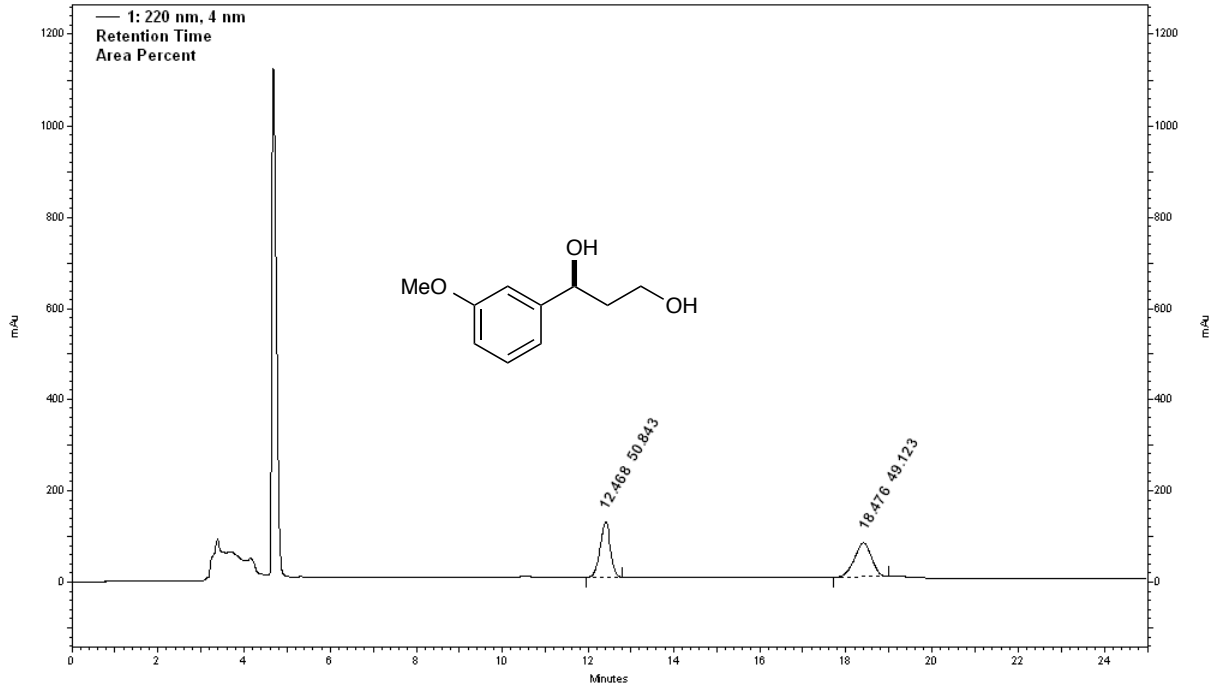


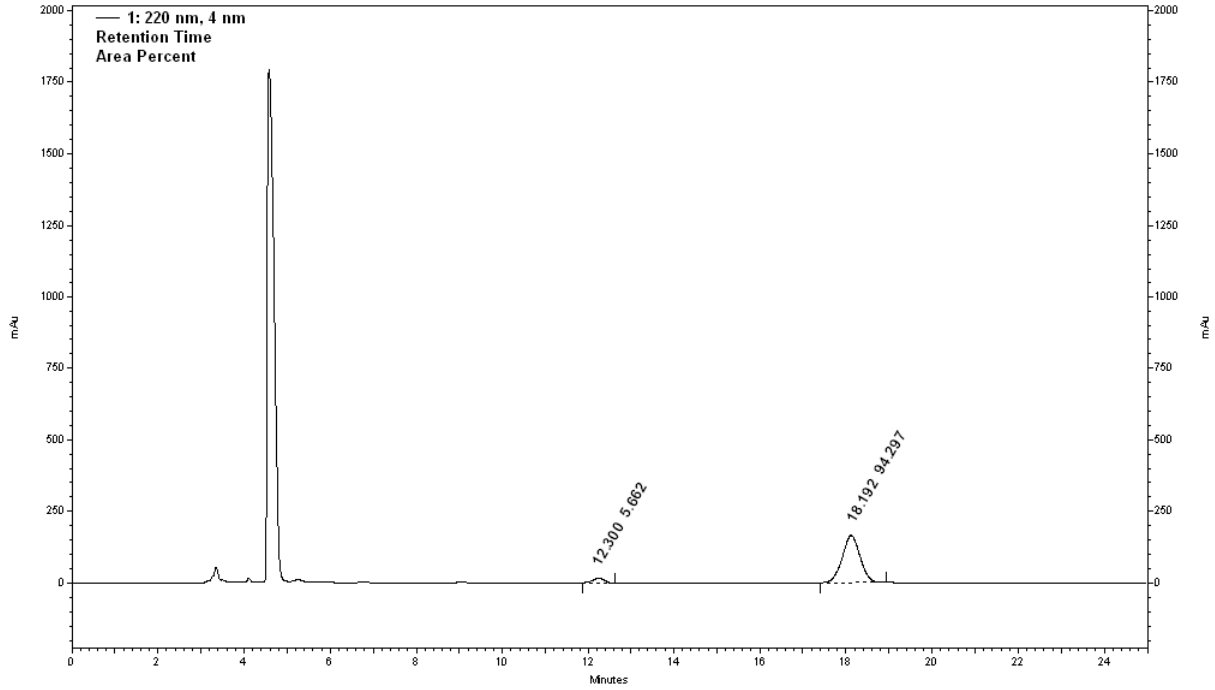
retention time	area
11.8 min	4.0%
15.4 min	96.0%





retention time	area
14.2 min	4.5%
18.9 min	95.3%





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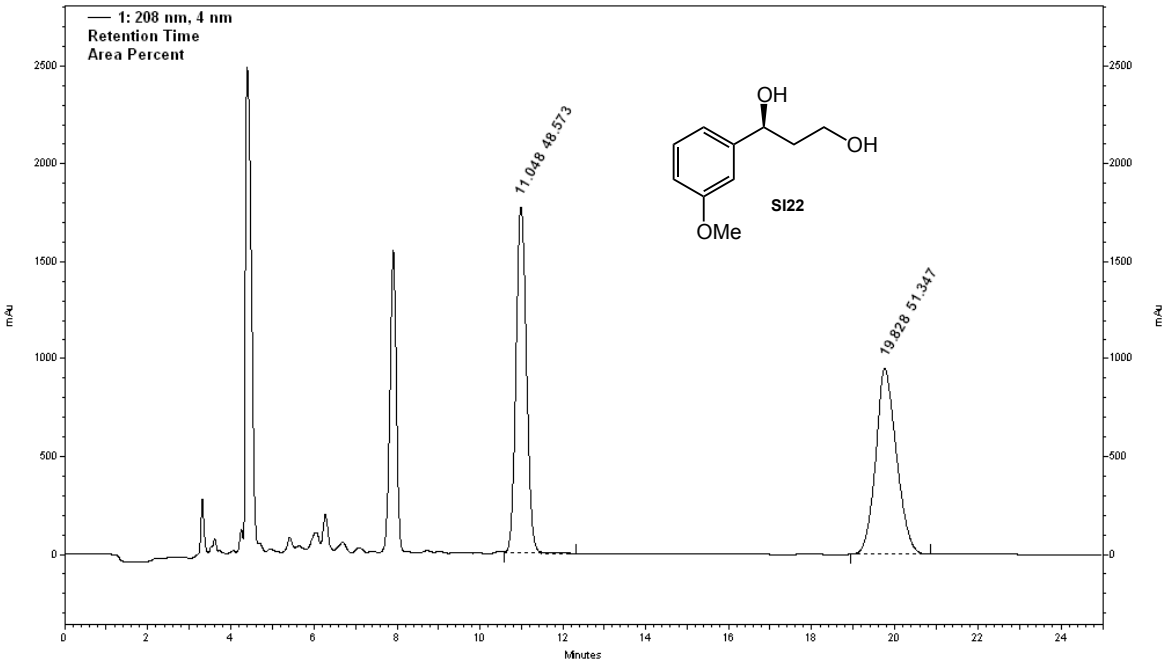
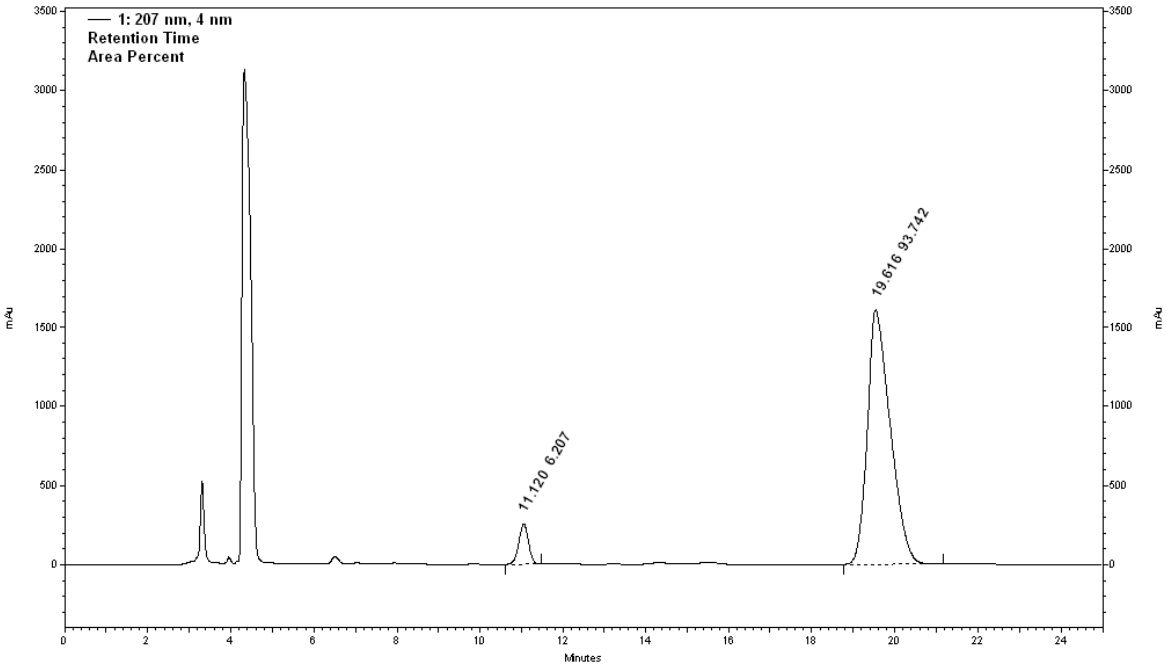
18.2 min	94.3%





retention time	area
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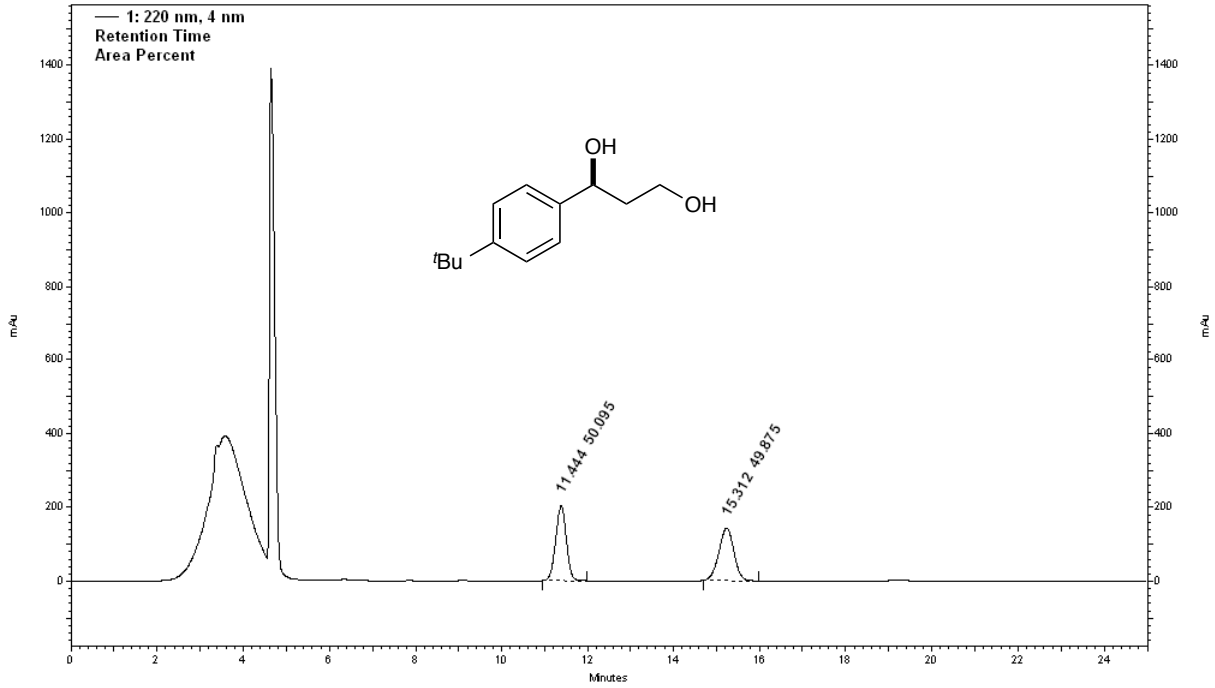
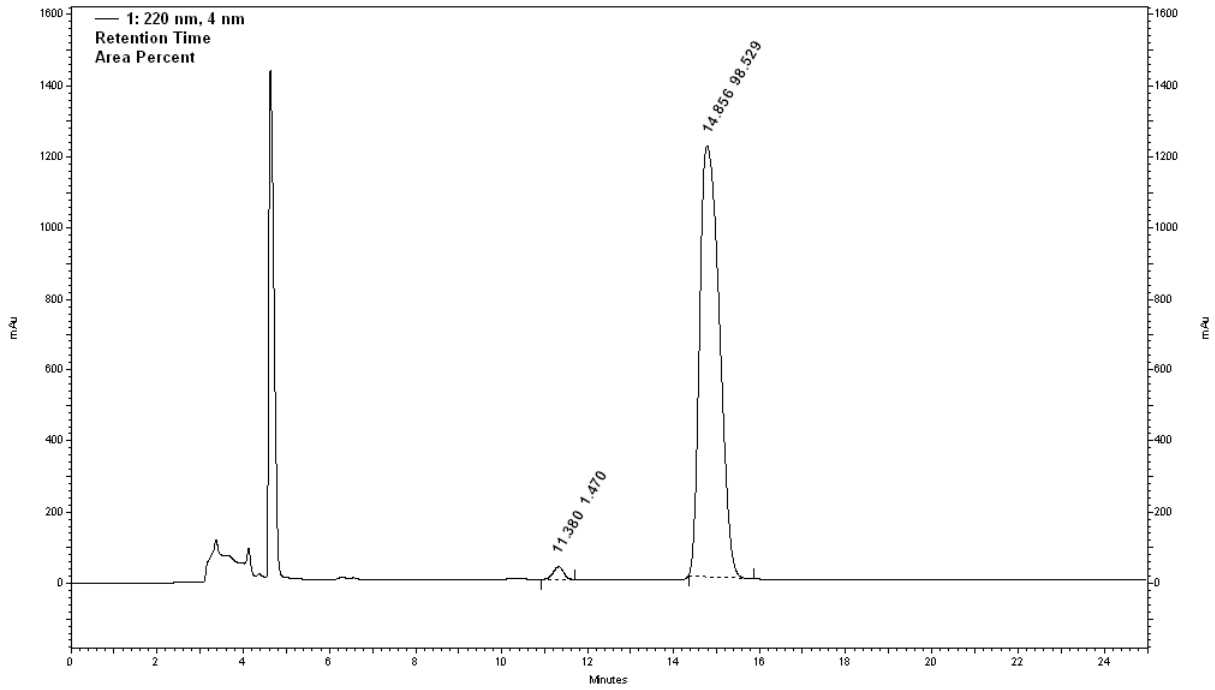
19.6 min	93.7%





retention time	area
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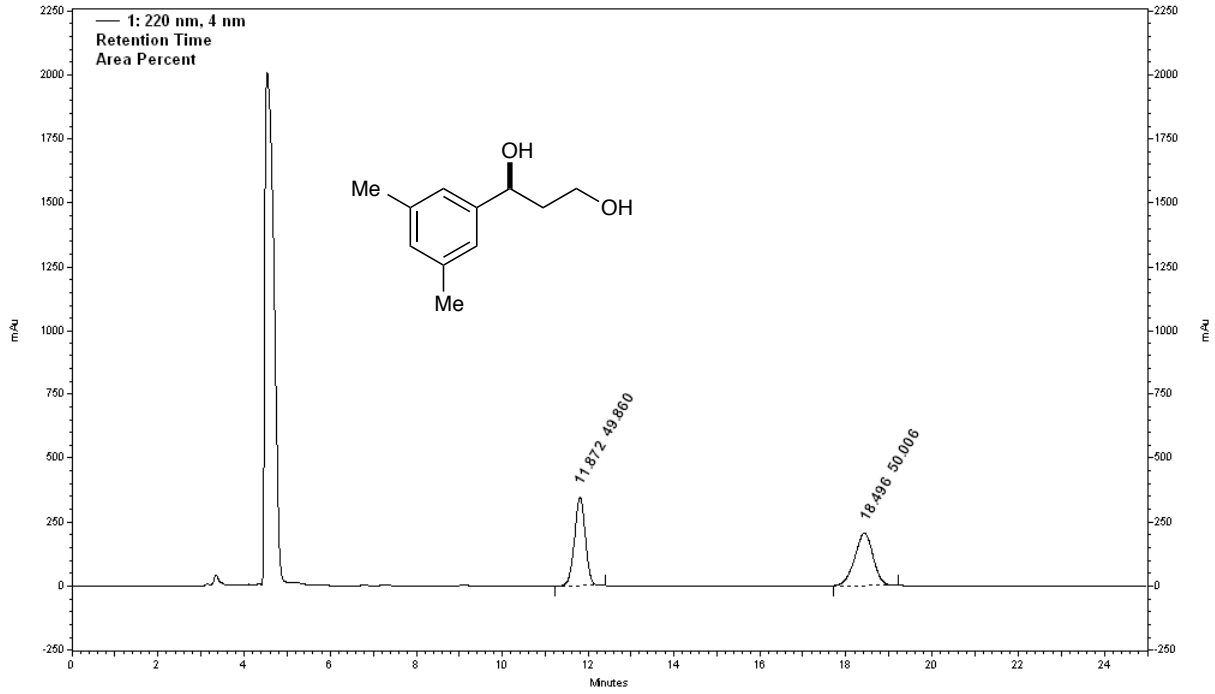
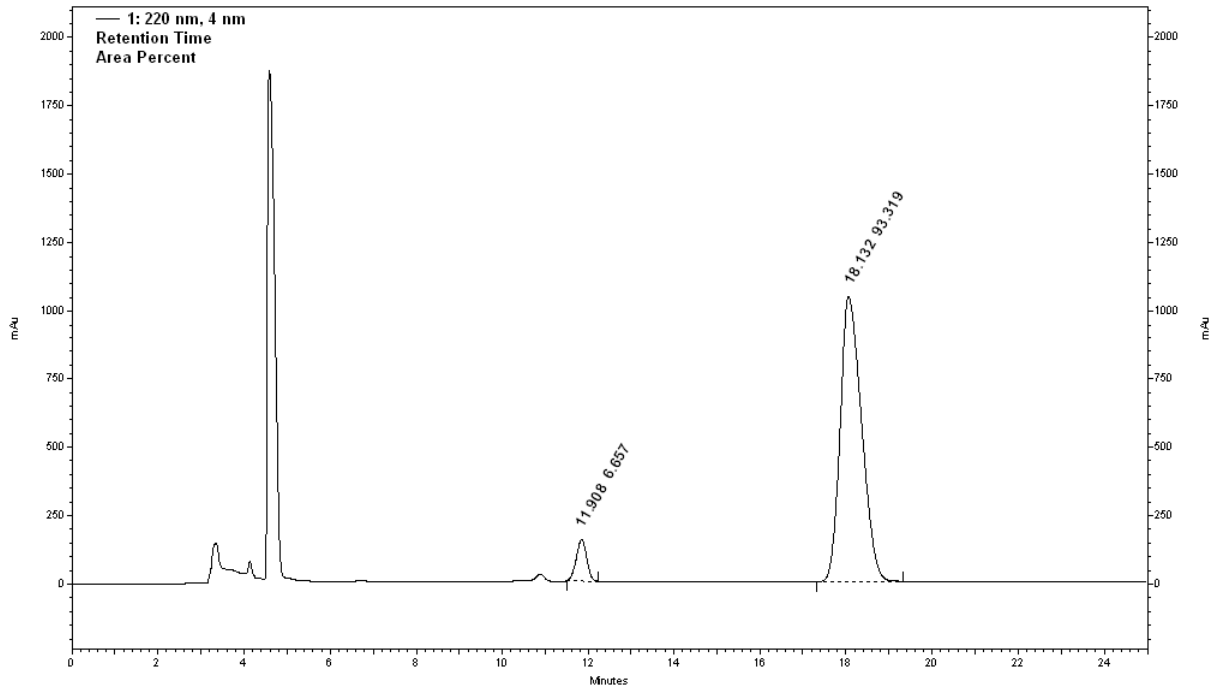
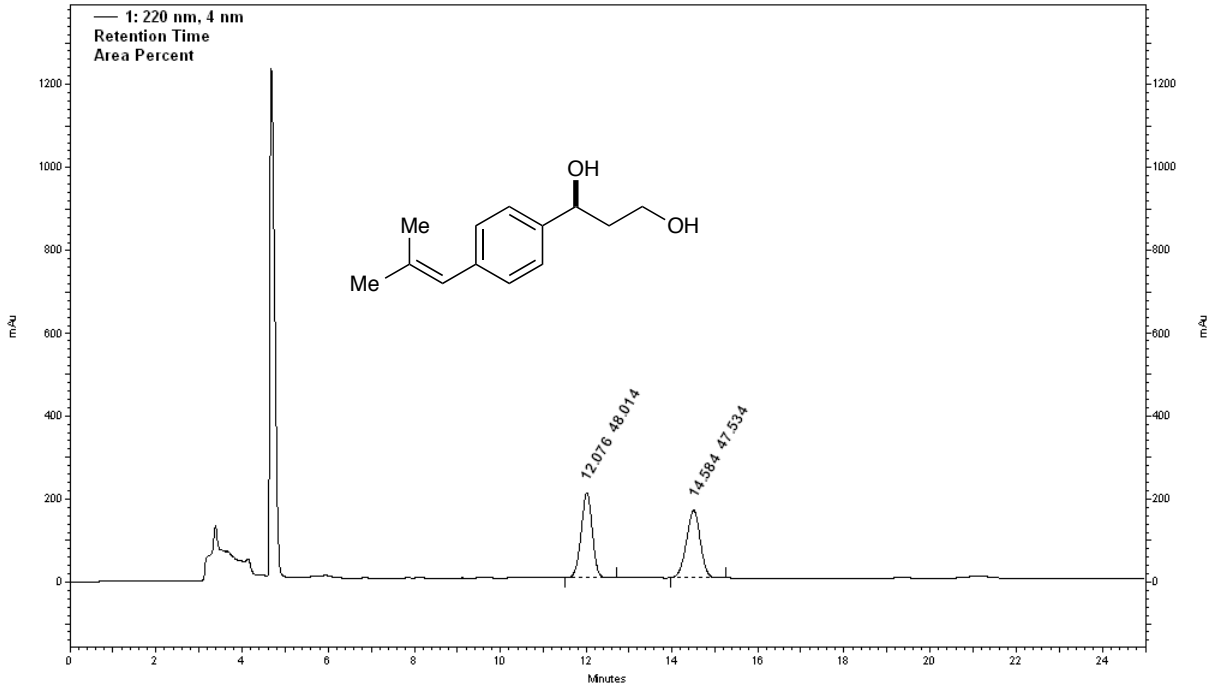
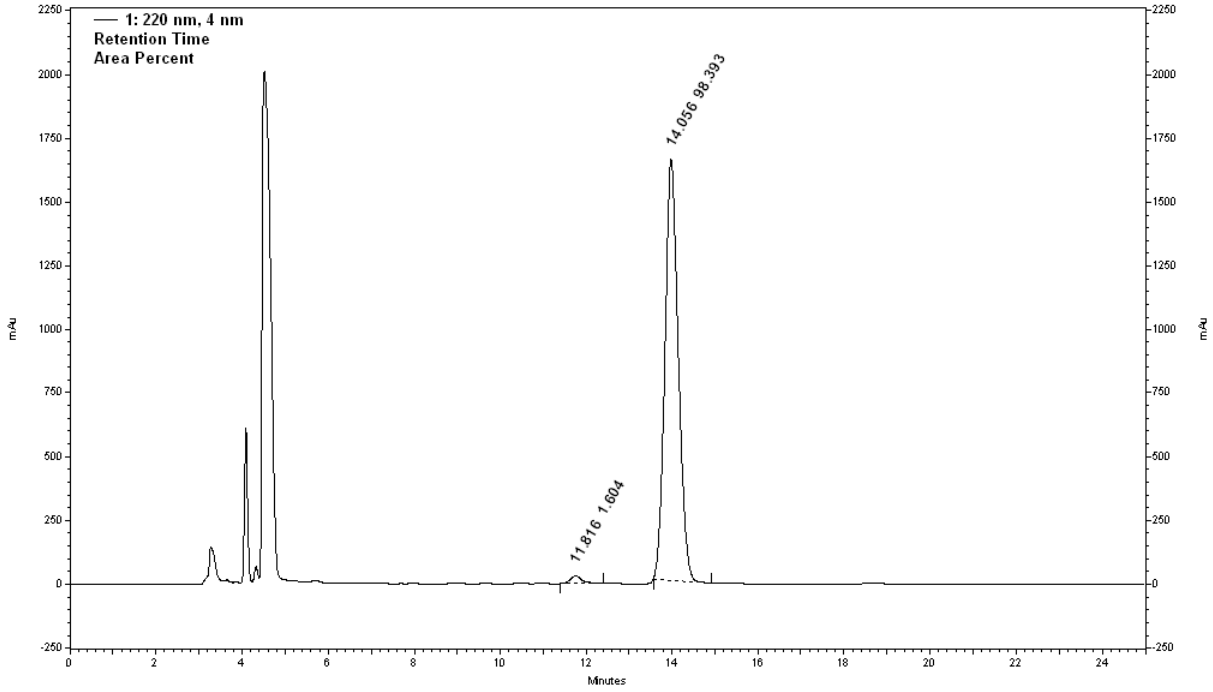
14.9 min	98.5%





retention time	area
11.9 min	6.7%
18.1 min	93.3%





retention time	area
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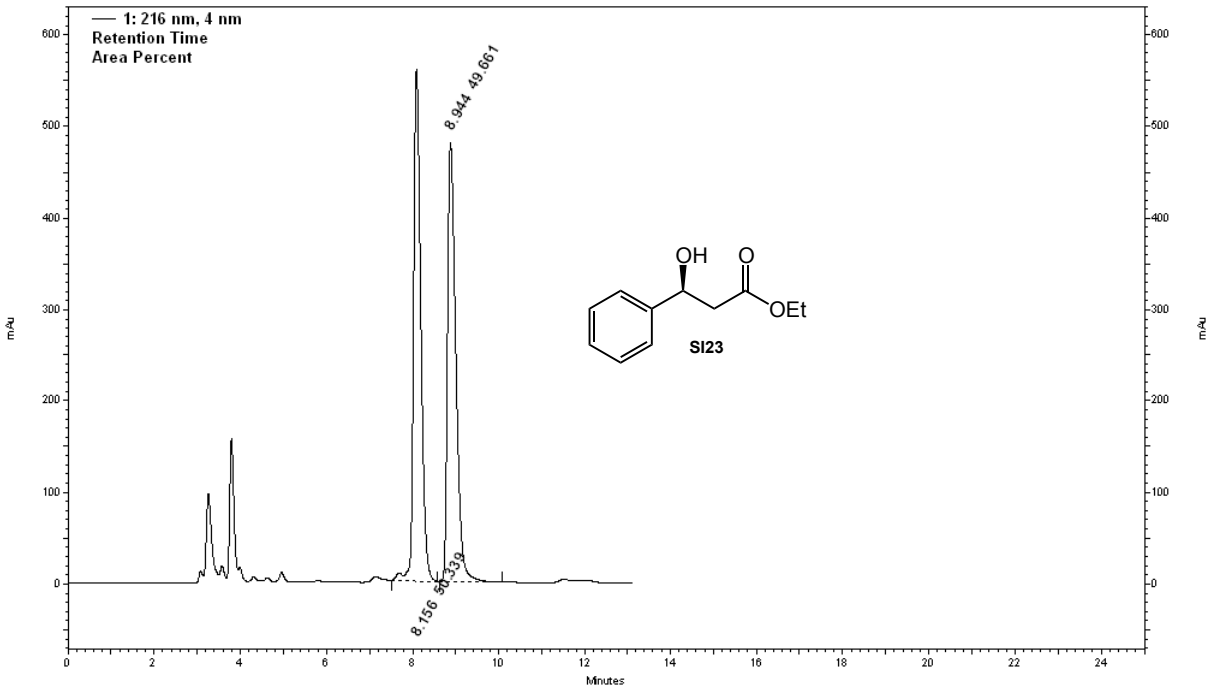
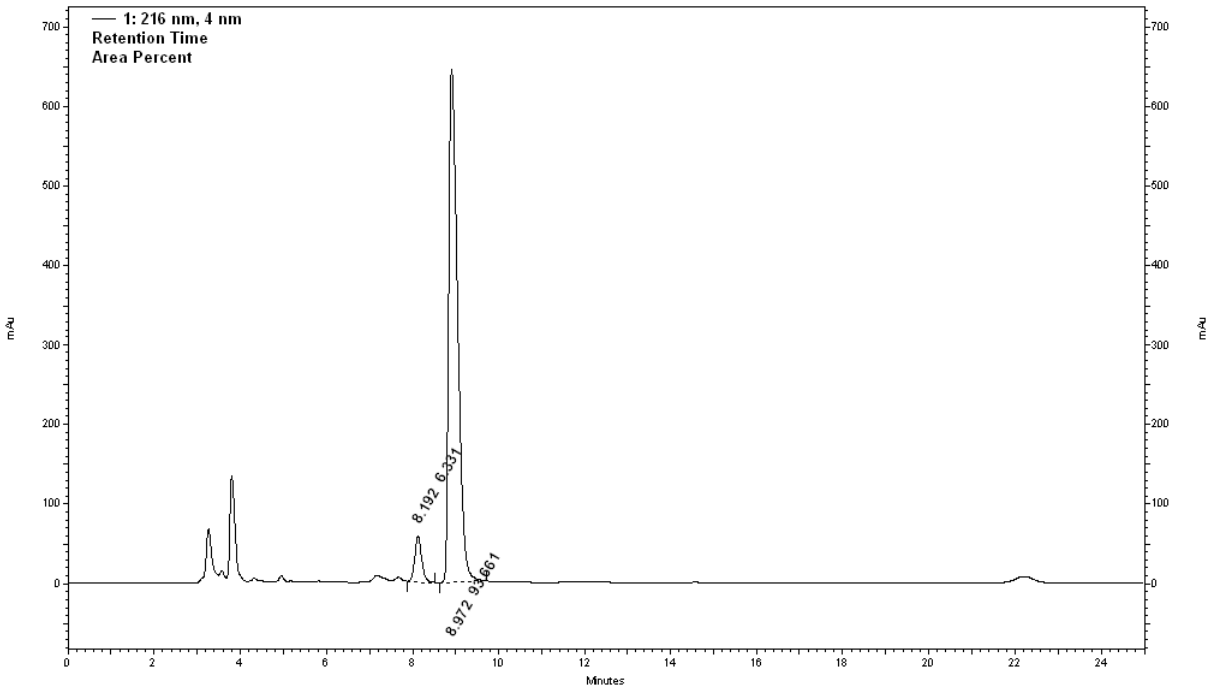
14.1 min	98.4%





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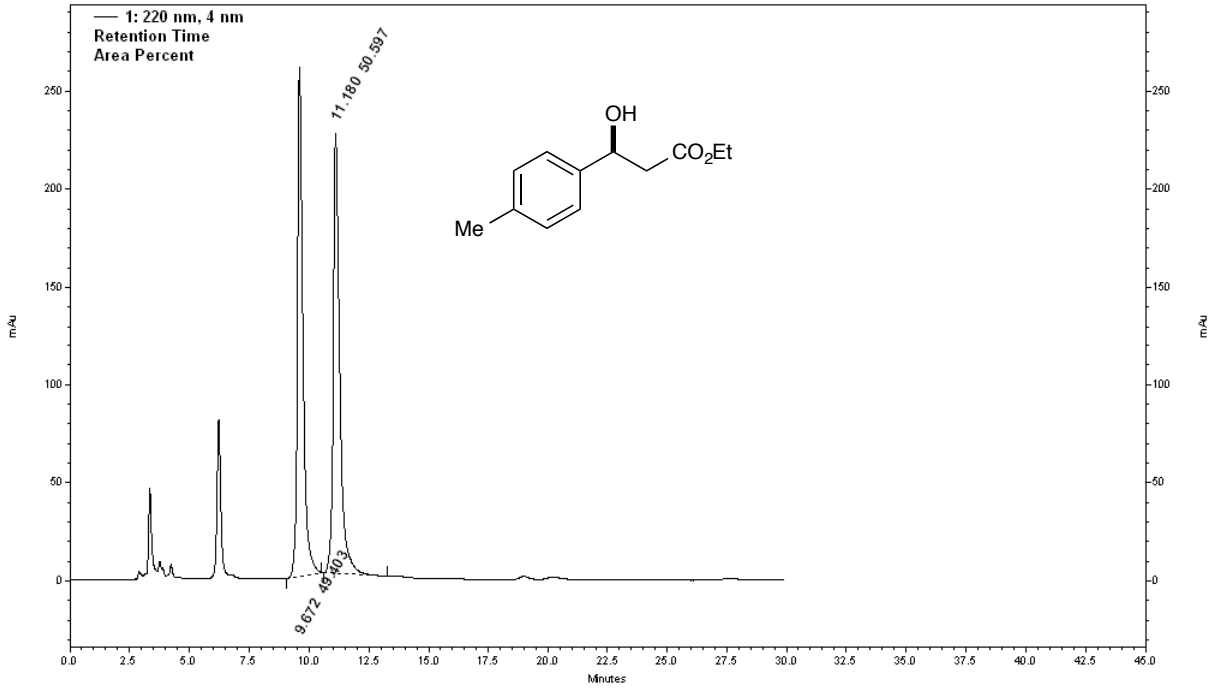

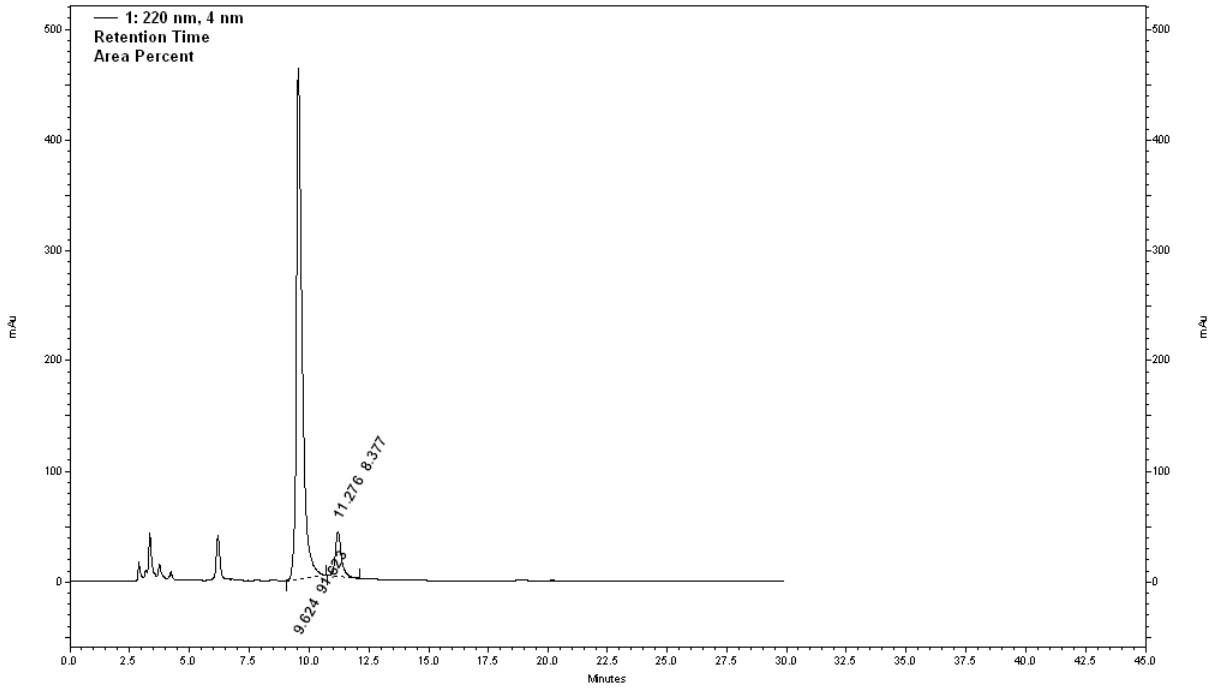

retention time	area
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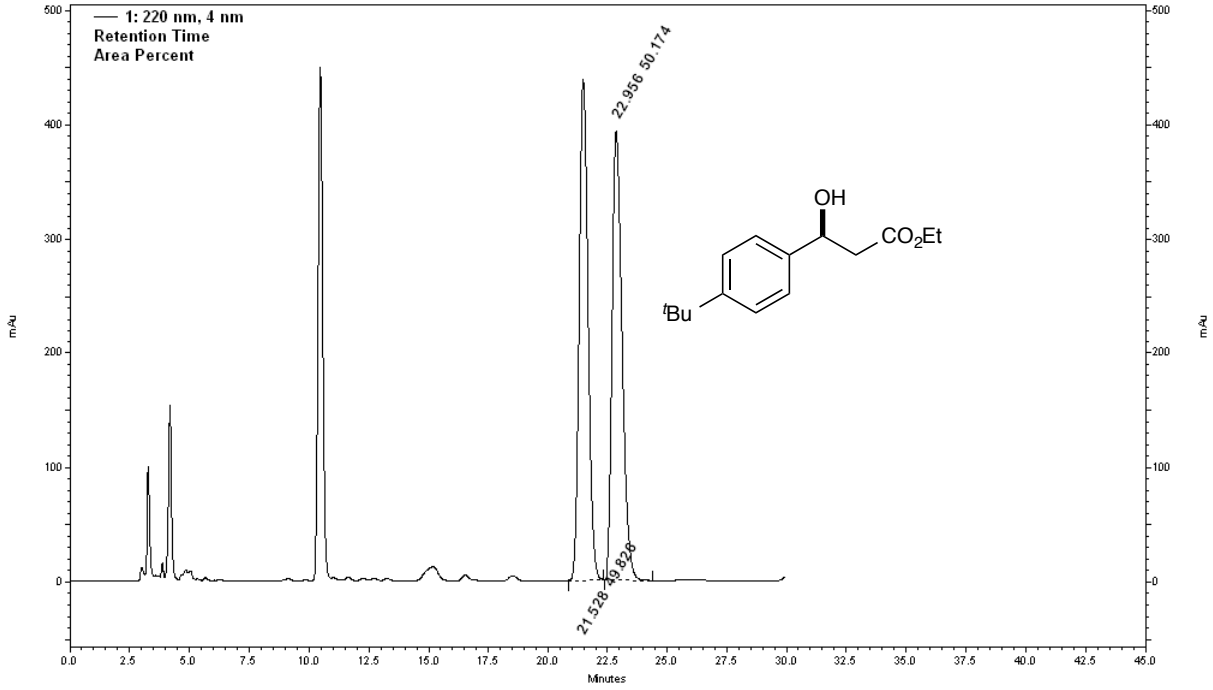
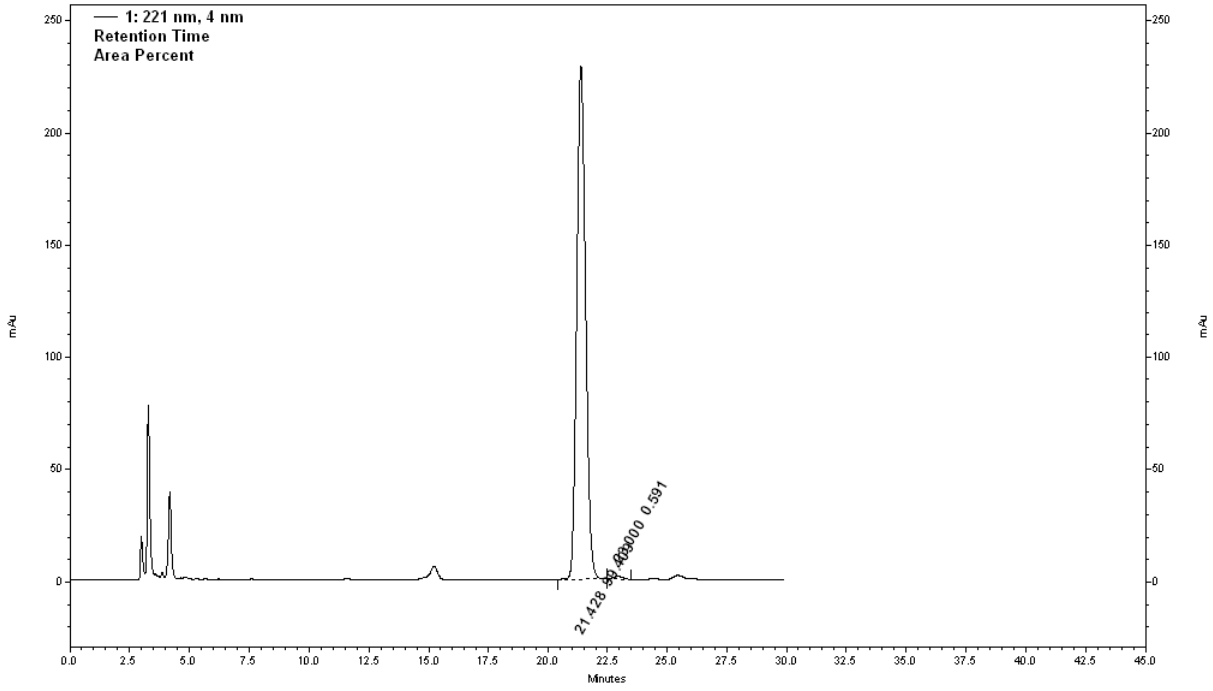
11.3 min	8.4%





retention time	area
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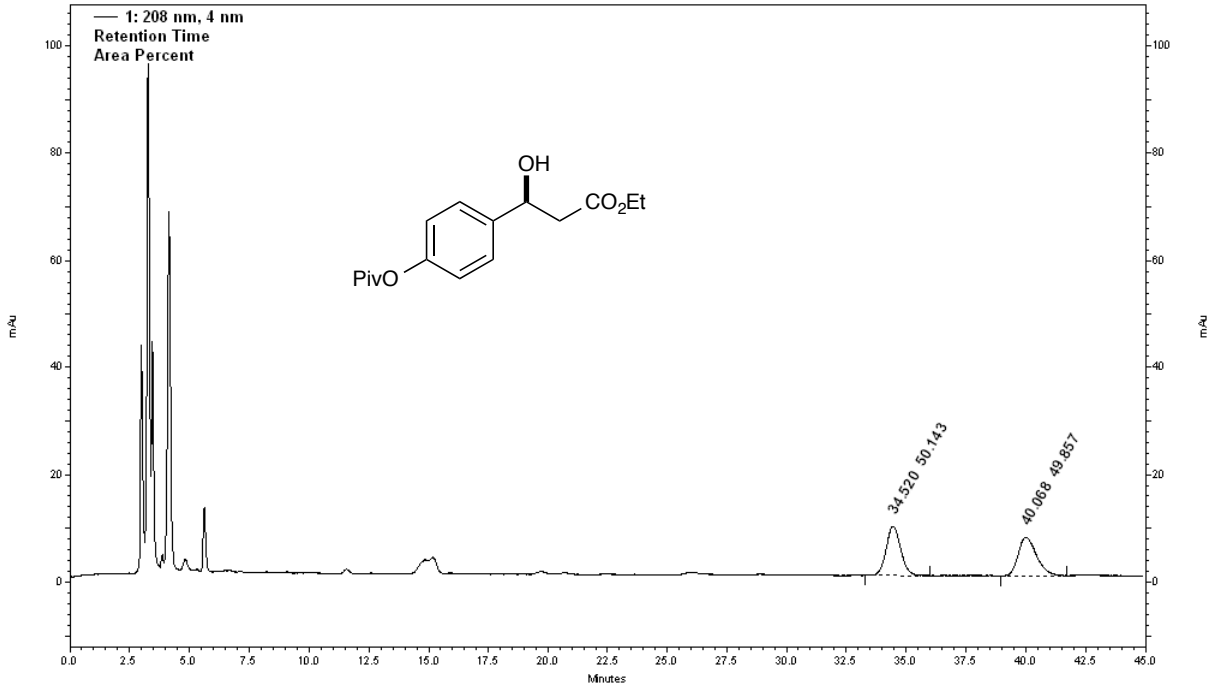
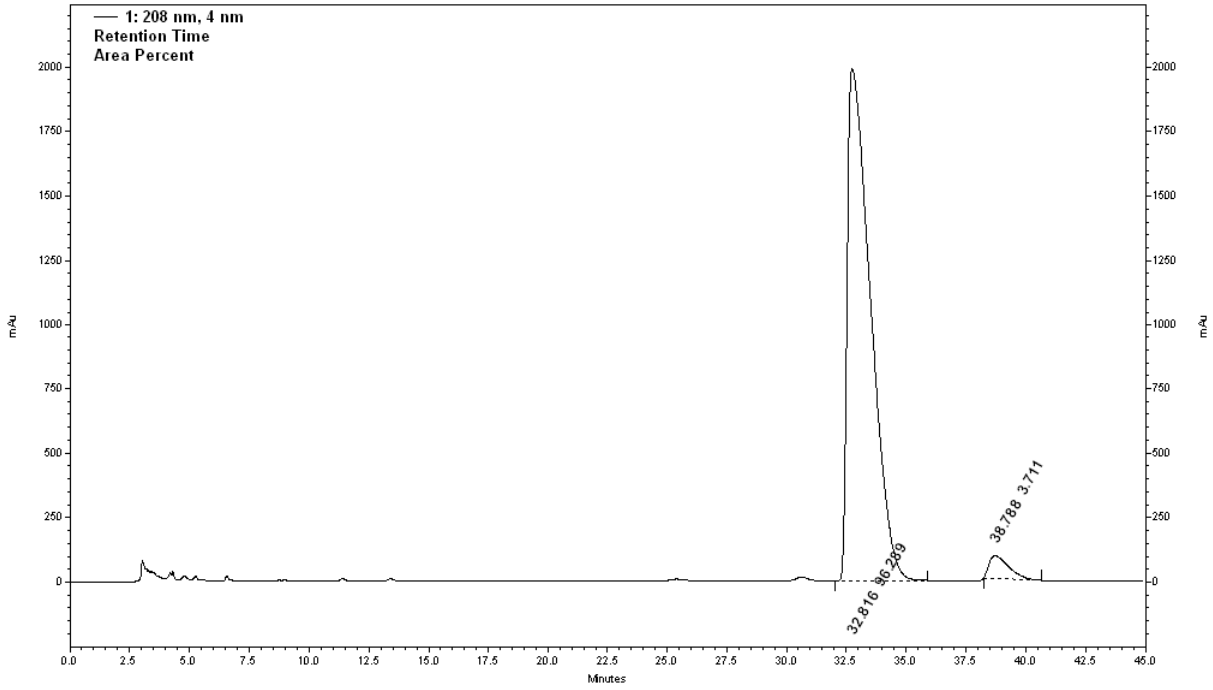
23.0 min	0.6%





retention time	area
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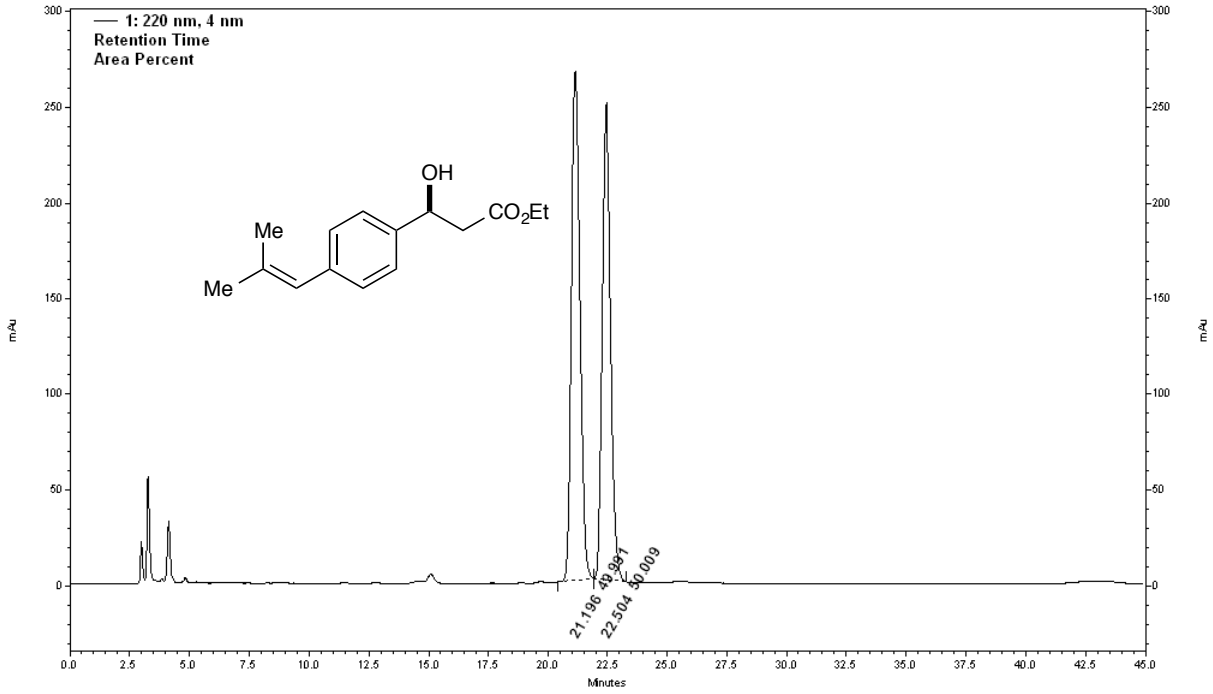
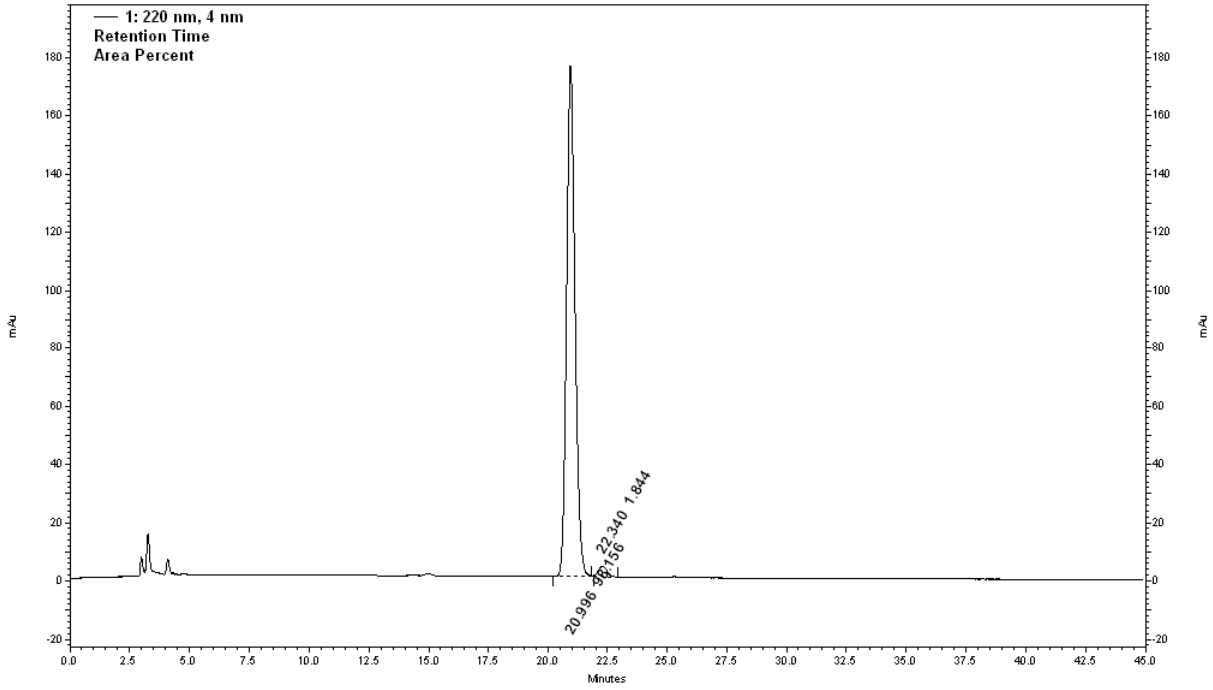
38.8 min	3.7%





retention time	area
21.0 min	98.2%
22.3 min	1.8%

Chapter 4

Enantioselective palladium-catalyzed oxidative β,β-fluoroarylation of α,β-unsaturated carbonyl derived systems

4.1. Introduction and current state-of-the-art.

The pivotal role displayed by fluorine in the growth and development of medicinal chemistry is firmly established, providing remarkable breakthroughs in this arena.[212] Despite its widespread distribution in nature, the presence of fluorine in natural organic molecules is scarce, and most of the fluorine-containing organic molecules are synthetic.[6d] Given this reality, the development of new methodologies that gain access to new fluorinated derivatives is always in great demand, particularly those enabling selective fluorination at specific positions of an organic framework.

Among current strategies for the asymmetric construction of sp^3 C–F bonds,[7a,7b] α-fluorination of carbonyl derivatives is the strategy most commonly exploited. Distinct approaches, including organocatalytic methods,[213] ring-opening of strained heterocycles,[214] and transition metal-catalyzed fluorinations,[215] have been developed. Compared to the other approaches, transition metal-catalyzed fluorinations remain the most challenging. Despite the high C–F bond energy (the strongest made with carbon at 456-486 $KJ \cdot mol^{-1}$, exceeding that of C–H bond), reductive elimination from transition metal complexes is extremely challenging.[216] While the strength of the C–F bond offers a thermodynamic

[212] (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.

[213] Selected examples: (a) Kwiatkowsky, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738. (b) Lozano, O.; Blessley, G.; Martínez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105. (c) Ref. 155: Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science*, **2011**, *334*, 1681. (d) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4157.

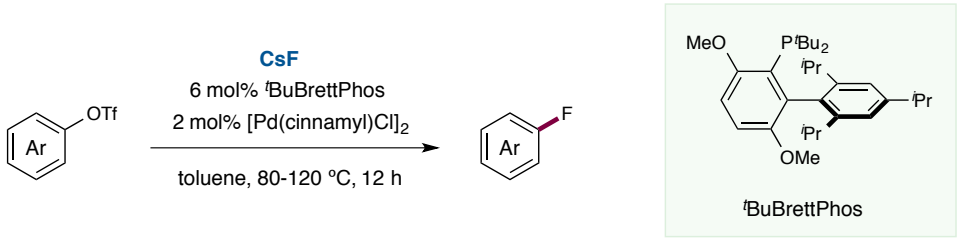
[214] (a) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268. (b) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 16001. (c) Zhu, J.; Tsui, G. C.; Lautens, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 12353. (d) Kalow, J. A.; Doyle, A. G. *Tetrahedron*, **2013**, *69*, 5702.

[215] Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530.

[216] (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (b) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (c) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342. (d) Grushin, V. V.; Marshall, W. J.

driving force for elimination, the metal-fluoride bond is also strong, providing a certain degree of ground-state stabilization that limits the kinetic feasibility of C–F reductive elimination. Grushin's in-depth research in this area revealed the formation of stable, thus unreactive, $[LnPdAr(F)]_2$ dimeric species as one of the key factors compromising reductive elimination.

Nonetheless, in 2009, Buchwald and coworkers accomplished C–F reductive elimination from a Pd(II) fluoride complex through careful ligand design (*Scheme 4.1*).[217] A sterically demanding, electron-rich biaryl monophosphine ligand, **^{t}BuBrettPhos**, was able to promote reductive elimination. Due to its large size, the formation of the aforementioned dimeric Pd(II) species was prevented, enabling fluorination of aryl triflates.



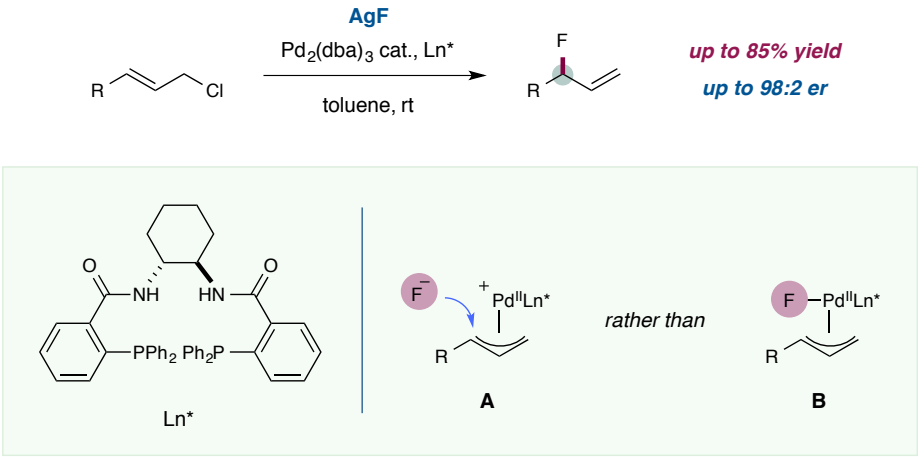
Scheme 4.1. C-F reductive elimination from a Pd(II) fluoride (Buchwald, 2009).

Alternatively, Doyle and coworkers proposed a complementary pathway to achieve C–F bond formation from a Pd(II) fluoride species. They accomplished the enantioselective fluorination of allylic chlorides with silver fluoride in a Pd(0)/Pd(II) redox cycle.[218] However, authors point out that an outer-sphere nucleophilic attack of fluoride to an electrophilic π-allyl Pd(II) intermediate (**A**), rather than reductive elimination (**B**), is likely to be operating. They argue that precipitation of AgCl provides the driving force for the C–F bond formation.

Organometallics, **2007**, *26*, 4997. (e) Grushin, V. V. *Chem. Eur. J.* **2002**, *8*, 1007.

[217] Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science*, **2009**, *325*, 1661.

[218] (a) Katcher, M. H.; Norrby, P.-O.; Doyle, A. G. *Organometallics*, **2014**, *33*, 2121. (b) Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902. (c) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.



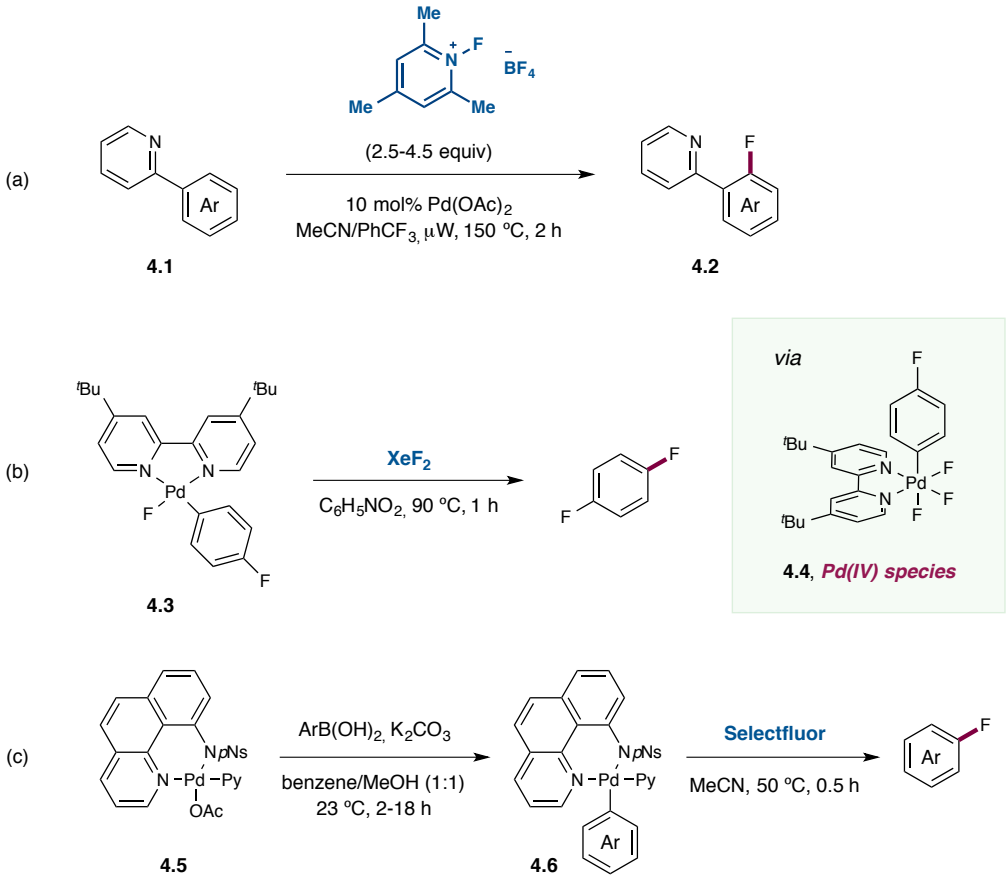
Scheme 4.2. Outer-sphere attack rather than reductive elimination (Doyle, 2010).

As a hard base, fluoride is also well suited for stabilizing highly oxidized metal centers,[219] and as Sanford and Ritter demonstrated, reductive elimination can be accomplished from high valent electron-deficient palladium species generated by oxidative fluorination (*Scheme 4.3*).[220]

In 2006, the Sanford group reported a Pd-catalyzed C-H fluorination of 2-aryl pyridine derivatives **4.1** in the presence of 2,4,6-Me_3-NFPy·BF_4 under microwave irradiation conditions (*Scheme 4.3a*).[221] Three years later, they demonstrated the intermediacy of a high-valent Pd(IV) species **4.4** in a related oxidative Pd-mediated fluorination reaction (*Scheme 4.3b*).[222] Species **4.4** constitutes the first characterized example of a Pd(IV) bifluoride.

[219] S. Riedel, M. Kaupp, *Coord. Chem. Rev.* **2009**, *253*, 606.
[220] (a) Racowski, J. M.; Sanford, M. S. *Top. Oranomet. Chem.* **2011**, *35*, 61. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (c) Xu, L.-M.; Li, J.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712.
[221] Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
[222] Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796.

Similarly, in 2008, Ritter and coworkers published a stoichiometric Pd-mediated fluorination of boronic acids using Selectfluor, affording aryl fluorides in moderate to good yields (*Scheme 4.3c*).[223] The intermediacy of an aryl Pd(IV) fluoride could be later demonstrated.[224]

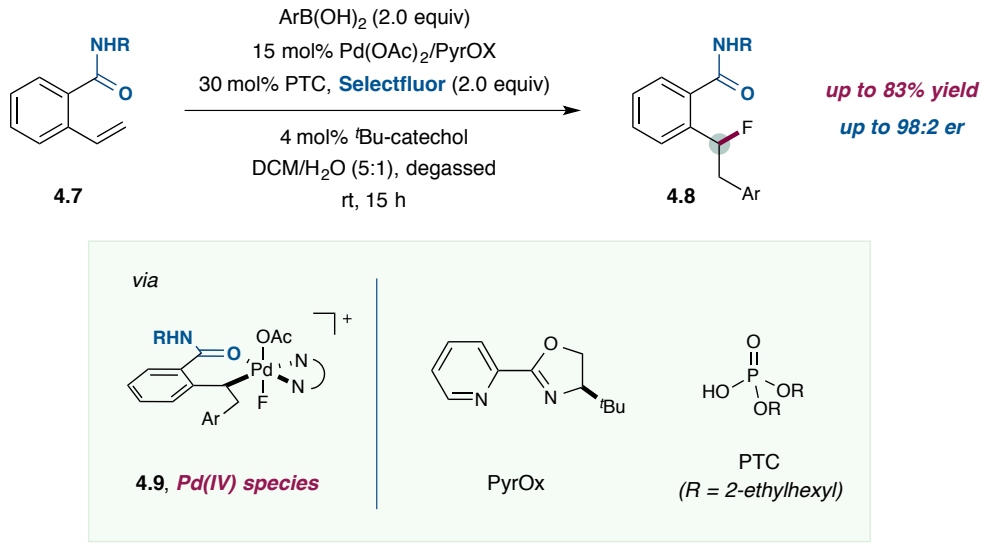


Scheme 4.3. C–F reductive elimination from high-valent Pd species (Sanford & Ritter).

These seminal contributions set a foundation for the development of new catalytic transition metal-catalyzed fluorination reactions.

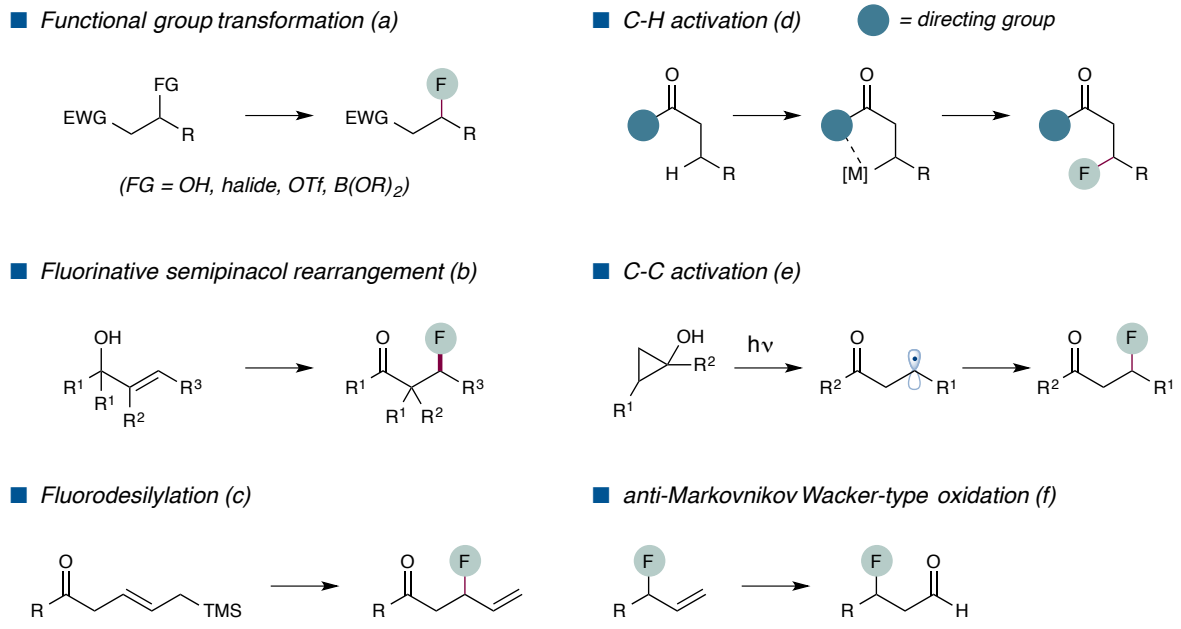
In a more recent example, Toste and coworkers disclosed a palladium-catalyzed 1,2-fluoroarylation of styrenes **4.7** with aryl boronic acids in the presence of Selectfluor, generating secondary benzyl fluorides **4.8** in good yields and good selectivities (*Scheme 4.4*).[225] The authors believe the reaction is directed by the *ortho*-amide group, which can be removed in subsequent steps.

[223] (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5993. (b) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060.
[224] Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.
[225] Talbot, E. P. A.; Fernandes, T. A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101.



Scheme 4.4. Pd-catalyzed oxidative 1,2-fluoroarylation of styrenes (Toste, 2014).

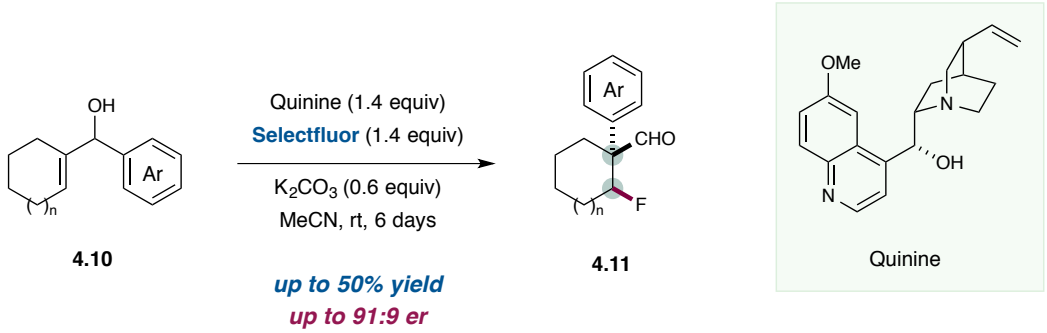
As previously mentioned, while great progress has been made in the assembly of C–F bonds adjacent to an electron-withdrawing group, very few protocols that incorporate fluorine at the β-position of a carbonyl derivative have been reported to date, and most of them are racemic (*Scheme 4.5*).



Scheme 4.5. Approaches to β-fluoro carbonyl systems.

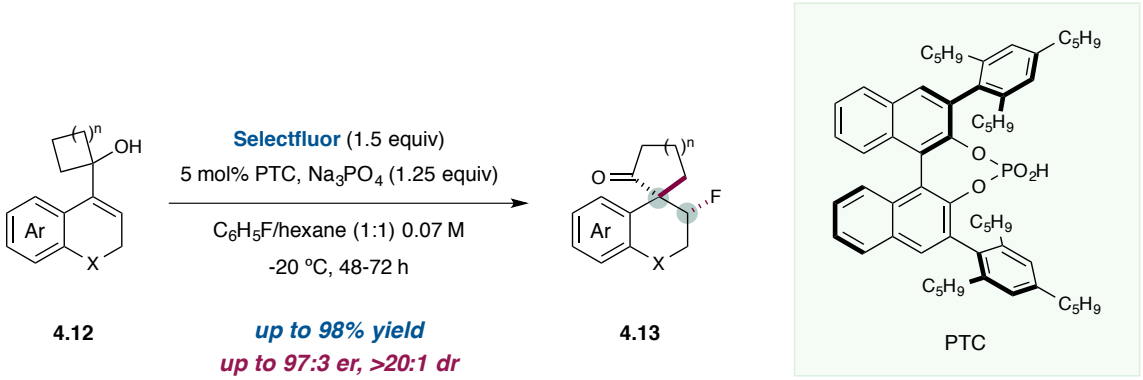
Early contributions entailed prior installation of a functional group, e.g. alcohols, halides, sulfonates, or boronates, and further conversion into the corresponding β-fluorinated carbonyl compound using either nucleophilic or electrophilic fluorinating reagents (*Scheme 4.5a*).[226]

Enantioselectivity was only achieved in fluorinative Wagner-Meerwein rearrangements on allylic alcohols **4.10** (*Scheme 4.5b*). In 2005, Tu and coworkers reported the combination of chiral alkaloids and Selectfluor as a means to induce an asymmetric semipinacol rearrangement (*Scheme 4.6*).[227]



Scheme 4.6. Fluorinative semipinacol rearrangement (Tu, 2005).

More recently, the Alexakis group successfully applied CAPT technology to render these types of rearrangements highly enantioselective (*Scheme 4.7*).[228]



Scheme 4.7. Asymmetric Wagner-Meerwein transposition via CAPT (Alexakis, 2013).

[226] (a) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439. (b) Zhang, M.; Gong, Y.; Wang, W. *Eur. J. Org. Chem.* **2013**, 7372. (c) Bonacorso, H. G.; Porte, L. M. F.; Navarini, J.; Paim, G. R.; Luz, F. M.; Oliveira, L. M.; Whietan, C. W.; Martins, M. A. P.; Zanatta, N. *Tetrahedron Lett.* **2011**, *52*, 3333. (d) Kim, K.-Y.; Kim, B. C.; Lee, H. B.; Shin, H. *J. Org. Chem.* **2008**, *73*, 8106.

[227] Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C.-A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. *Chem. Commun.* **2005**, 5580.

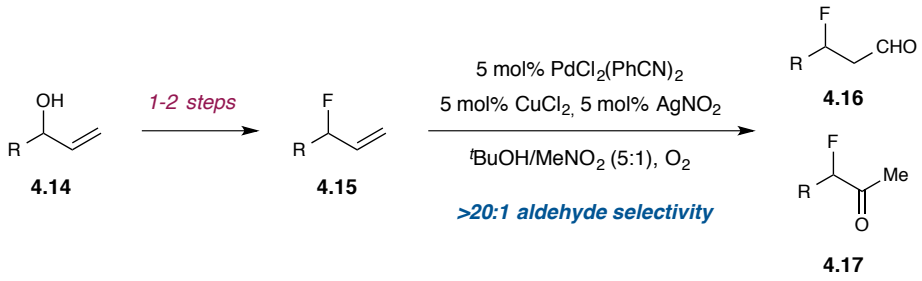
[228] (a) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9266. (b) Romanov-Michailidis, F.; Pupier, M.; Guénée, L.; Alexakis, A. *Chem. Commun.* **2014**, *50*, 13461.

Previously, Gouverneur and coworkers accomplished the preparation of β-fluoro carboxylic acid derivatives through an electrophilic fluorodesilylation reaction in the presence of Selectfluor (*Scheme 4.5c*).[229]

Recently reported methods explored selective C–H[230] and C–C activation[231] as a means to guide C(sp^3) fluorination. In this sense, the groups of Shi, Yu, Ge and Xu recently reported a palladium-catalyzed *anti*-selective β-fluorination of valuable chiral α-amino acid derivatives by ligand-enabled C(sp^3)–H activation (*Scheme 4.5d*).[232] Mechanistic studies were consistent with direct C–F reductive elimination from a Pd(IV) fluoride intermediate.

More recently, Leckta and coworkers disclosed a tandem ring-opening of conformationally strained cyclopropanols and successive site-selective β-fluorination towards the preparation of β-fluoro ketones in moderate to good yields (*Scheme 4.5e*).[233] This protocol, which relies on a photoinduced C–C bond activation, employs 1,2,4,5-tetracyanobenzene (TCB) as a photosensitizer, along with Selectfluor.

Finally, the Grubbs group discloses the preparation of achiral β-fluoro aldehydes **4.16** by an *anti*-Markovnikov Wacker-type oxidation of allylic fluorides **4.15** (*Scheme 4.5f & 4.8*).[234] The observed regioselectivity is determined by the inductive withdrawing effects imparted by the fluoride.



Scheme 4.8. Nitrite-modified Wacker oxidation (Grubbs, 2016).

[229] Tredwell, M.; Tenza, K.; Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 4495.

[230] Selected examples: (a) Xia, J.-B; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014**, *1*, 468. (b) Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. *Org. Lett.* **2013**, *15*, 1722. (c) Bloom, S.; Sharber, A.; Holl, M. G.; Knippel, J. L.; Lectka, T. *J. Org. Chem.* **2013**, *78*, 11082. Metal-free C(sp^3)-H fluorinations: (d) Pitts, C. R.; Ling, B.; Woltornist, R.; Liu, R.; Lectka, T. *J. Org. Chem.* **2014**, *79*, 8895. (e) S. Bloom, J. L. Knippel, T. Lectka, *Chem. Sci.* **2014**, *5*, 1175. (f) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 4690. (g) Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C.-H. *Chem. Commun.* **2014**, *50*, 8211. (h) Bloom, S.; McCann, M.; Lectka, T. *Org. Lett.* **2014**, *16*, 6338. (i) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494.

[231] (a) Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. *Chem. Eur. J.* **2015**, *21*, 8060. (b) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654.

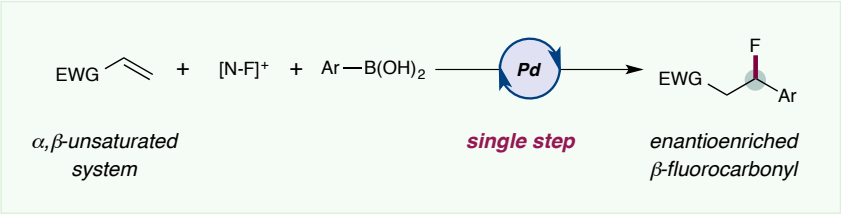
[232] (a) Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067. (b) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219. For other closely-related examples, see: (c) Zhu, Q.; Ji, D.; Liang, T.; Wang, X.; Xu, Y. *Org. Lett.* **2015**, *17*, 3798. (d) Miao, J.; Yang, K.; Kurek, M.; Ge, H. *Org. Lett.* **2015**, *17*, 3738.

[233] Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. *Chem. Eur. J.* **2015**, *21*, 8060.

[234] Chu, C. K.; Ziegler, D. T.; Carr, B.; Wickens, Z. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8435.

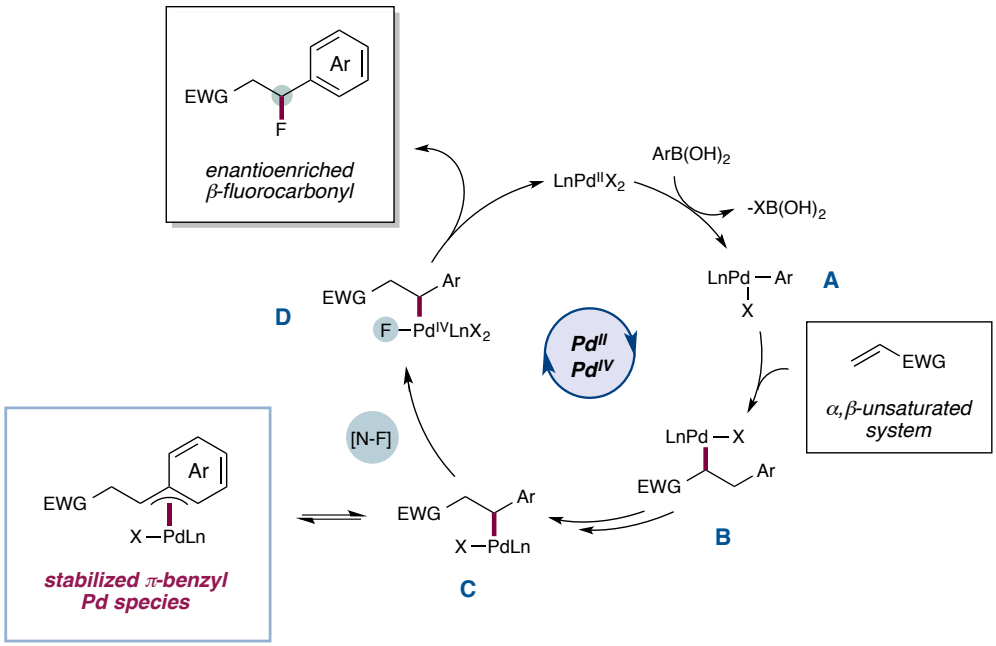
4.2. Enantioselective Pd-catalyzed β,β-fluoroarylation reaction.

On the basis of the limited reports of oxidative transition metal-catalyzed fluorinations and inspired by recent examples of palladium-catalyzed 1,1-difunctionalizations from Sanford, Sigman and Toste,[235] we envisioned accessing β-fluorinated carbonyl derivatives via a single-step three-component Heck arylation-oxidative fluorination cascade (*Scheme 4.9*).



Scheme 4.9. Our proposal: Heck arylation-oxidative fluorination.

Our attempted catalytic cycle is outlined in *Scheme 4.10*.

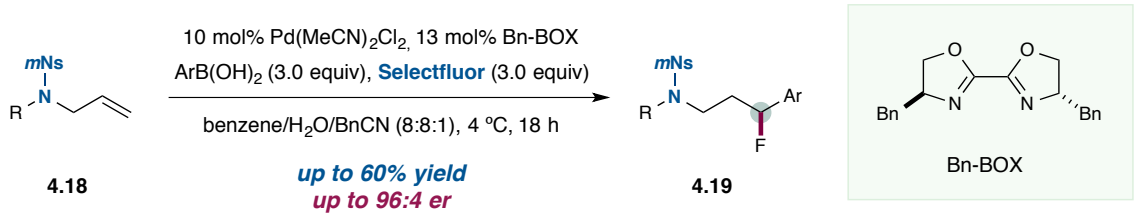


Scheme 4.10. Proposed catalytic cycle.

[235] (a) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 8419. (b) Kalyani, D.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 2150. (c) Ref. 165: Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008. (d) Ref. 194b: Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372. (e) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133, 5784.* (f) Ref. 201: Nelson, H. M.; Williams, B. D.; Miró, J. Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3213. (g) He, Y.; Yang, Z.; Thornbury, R. T.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 12207.

Starting from a suitable Pd(II) species, transmetalation with an aryl boronic acid and subsequent migratory insertion, would generate a β-arylated-α-Pd(II) intermediate **B**. Thereafter, sequential β-hydride elimination and reinsertion steps would yield a π-benzyl palladium complex **C**. Oxidation by an appropriate electrophilic fluorine source, [N-F], would give rise to a high-valent Pd(IV)-fluoride **D**, which is poised to undergo reductive elimination yielding the final β-fluorocarbonyl derivative and completing the catalytic cycle.

During the realization of this work, the Toste group published an enantioselective palladium-catalyzed 1,1-fluoroarylation of unactivated allyl amines **4.18** (*Scheme 4.11*),[235g] showcasing the feasibility of the attempted 1,1-difunctionalization. As for the previously reported 1,2-fluoroarylation reaction (see *Scheme 4.4*),[225] chiral bidentate diimine BOX-type ligands were used to render the process enantioselective. Once again, the presence of a directing group (in this case nosyl) was critical prompting insertion.

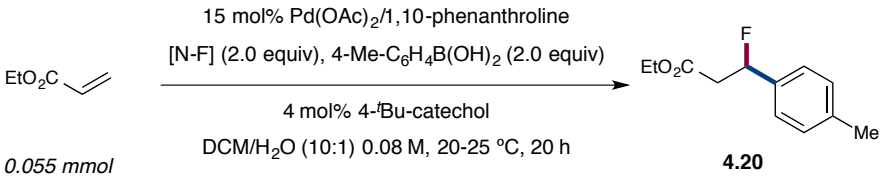


Scheme 4.11. 1,1-Fluoroarylation of allyl amines (Toste, 2015).

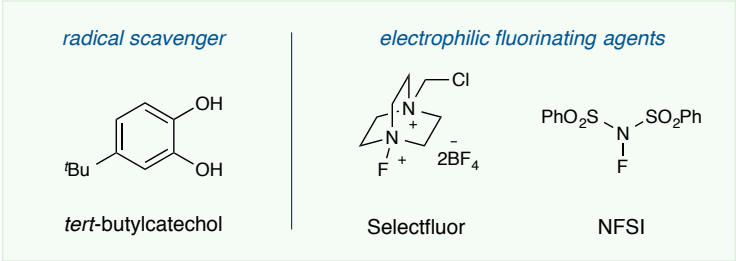
4.3. Results and discussion.

Under this scenario, we decided to test our hypothesis by examining the fluoroarylation of ethyl acrylate with 4-tolyl boronic acid as a model reaction. The optimization process is summarized in *Table 4.1*. Initially, the reaction was performed under similar conditions to those previously employed in the 1,2-fluoroarylation of styrenes.[225] Thus, ethyl acrylate was treated with 2.0 equiv of the aryl boronic acid, 15 mol% of $Pd(OAc)_2$, 15 mol% of 1,10-phenanthroline, and 4 mol% of 4-*tert*-butylcatechol, in a 0.08M mixture DCM:H_2O (10:1), using Selectfluor (2.0 equiv) as both the electrophilic fluorine source and the oxidant. However, after 20 hours, only trace amounts of the desired β-fluoroester **4.20** were detected, with the major product resulting from the competing Heck reaction (*entry 1*).

Table 4.1. Optimization of reaction conditions.[a]



entry	variation from standard conditions	yield[b]
1	[N-F] = Selectfluor	trace
2	[N-F] = NFSI	95%
3	w/o degassing	-
4	w/o water	-
5	w/o 1,10-phenanthroline	-
6	w/o 4-^{t}Bu-catechol	trace



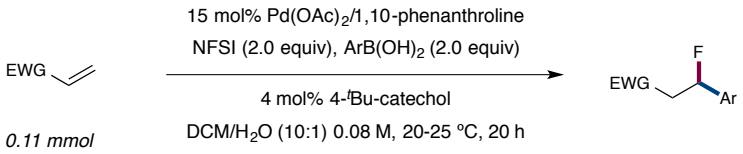
[a] Conditions: all reactions were run on 0.055 mmol scale with respect to α,β-unsaturated system. [b] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard.

Pleasingly, switching [N-F] source to NFSI had a dramatic effect, giving rise to the exclusive formation of 1,1-fluoroarylated product **4.20** in excellent yield (*entry 2*), with complete exclusion of

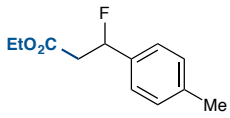
styrene formation.[236] Notably, degassing of the system was necessary to avoid oxidation of the boronic acid coupling partner (*entry 3*). Moreover, the reaction did not proceed in the absence of water (*entry 4*), which is potentially responsible for initiating transmetalation. Even though water may result in having a more active, tetracoordinated, negatively charged boronate $[ArB(OR)_2(OH)]^-$ as the actual species undergoing transmetalation, mechanistic studies suggest that nucleophilic palladium hydroxo complexes are likely operative.[237] Aryl boronic ester 4-Me–C_6H_4B(pin) was found inactive under these conditions. The presence of a bipyridine-type ligand is crucial to achieve the desired fluorinative reaction manifold (*entry 5*). Therefore, an *N*,*N*-ligated Pd(II) complex is most likely the catalytically active species. Likewise, the presence of a radical scavenger to prevent either alternative radical pathways involving the aryl boronic acid or polymerization of starting alkenes (*entry 6*), was critical.[238] Remarkably, the product derived from the 1,2-fluoroarylation of ethyl acrylate was not observed.

With these optimized conditions in hand, the scope of the β,β-fluoroarylation protocol was next evaluated (*Table 4.2*).

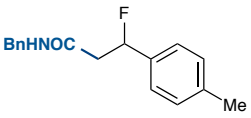
Table 4.2. Non-enantioselective substrate scope.[a,b,c]



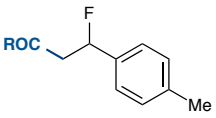
Olefin scope



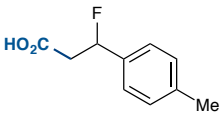
4.20, *95% yield (83%)*



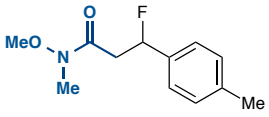
4.21, *91% yield (80%)*



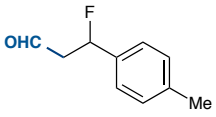
4.22, *R = Me, 49% yield*
4.23, *R = PMP, 84% yield (61%)*



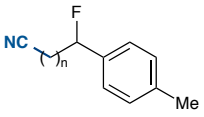
4.24, *32% yield*



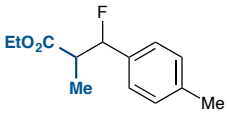
4.25, *98% yield (80%)*



4.26, *69% yield*[d]



n = 1, not observed
4.27, *n = 2, 52% yield (36%)*



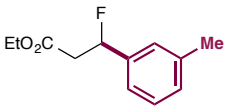
4.28, *78% yield (69%), 3:1 dr*

[236] Outstandingly, this electrophilic fluorine source was inefficient in previously reported 1,2- and 1,1-fluoroarylation of alkenes reported by the Toste group: (a) Ref. 225: Talbot, E. P. A.; Fernandes, T. de A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101. (b) Ref. 235g: He, Y.; Yang, Z.; Thornbury, R. T.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 12207.

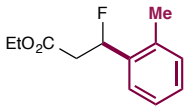
[237] (a) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. (c) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5156.

[238] Martínez, C.; Muñiz, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 7031.

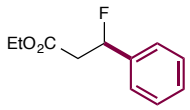
ArB(OH)$_2$ scope



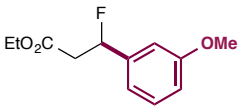
4.29, *85% yield (78%)*



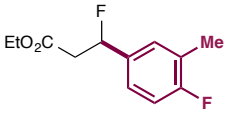
4.30, *76% yield (61%)*



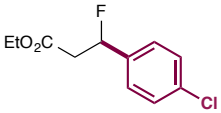
4.31, *86% yield (67%)*



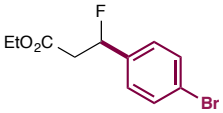
4.32, *70% yield (56%)*



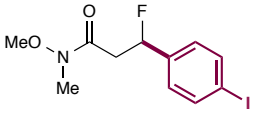
4.33, *85% yield (54%)*



4.34, *57% yield (47%)*



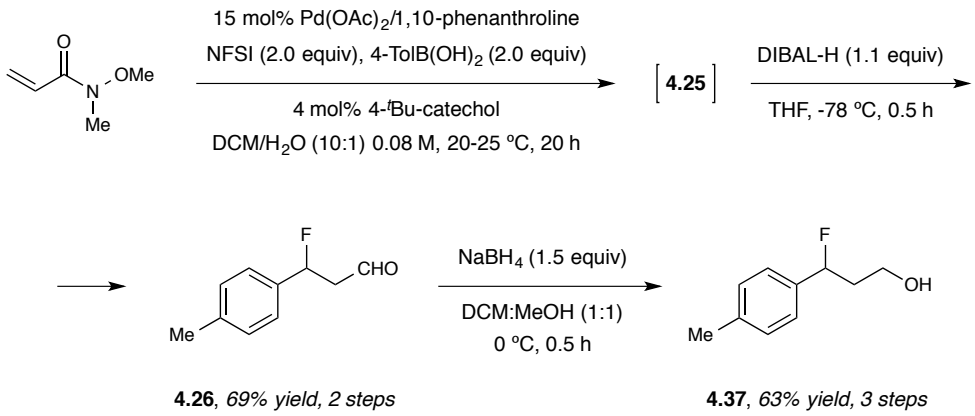
4.35, *52% yield (47%)*



4.36, *67% yield (43%)*

[a] Conditions: all reactions were run in 0.11 mmol scale with respect to starting α,β-unsaturated system. [b] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [c] Isolated yields in brackets. [d] Yield over two steps: (1) β,β-fluoroarylation of *N*-methoxy-*N*-methylacrylamide and (2) reduction of **4.25**.

We were pleased to observe that, under optimized conditions, acrylic esters, amides, and ketones smoothly provided racemic β-fluoro derivatives **4.20**-**4.23** in good to excellent yields. Nevertheless, acrylic acid furnished benzyl fluoride **4.24** in diminished yields, despite increased equivalents of aryl boronic acid. Diminished yields obtained for methyl vinyl ketone (**4.22**) offers an interesting mechanistic insight into the reaction manifold. We hypothesized that this result was an indication of the likely role displayed by the chelating carbonyl group, prompting insertion, while backing up the stabilization of the palladium intermediate species. In agreement with this hypothesis, highly activated 4-methoxyphenyl vinyl ketone, afforded β-fluoroketone **4.23** in a satisfactory 84% yield. Moreover, a Weinreb amide underwent smooth β,β-fluoroarylation in 98% yield. This result, in addition to widening the ketone scope, opened access to aldehyde derivatives (**4.26**), and in turn, to over-reduced 3,3-fluoroaryl alcohols **4.37** (*Scheme 4.12*).



4.26, *69% yield, 2 steps*

4.37, *63% yield, 3 steps*

Scheme 4.12. Weinreb amide derivables.

Furthermore, the use of a nitrile-substituted substrate provided γ-fluoro nitrile **4.27** in modest yields, however the nitrile moiety had to be placed at a more distant position. α-Substituted ethyl methacrylate provided the corresponding product **4.28** in good yield and modest diastereoselectivity, while β-substituents were not tolerated.

Likewise, a range of aryl boronic acids was subjected to oxidative conditions. As shown in *Table 4.2*, this procedure was efficient with non-electronically-biased aryl boronic acids. β-Fluoro esters **4.29** and **4.30** were formed in 85% and 76% yields, respectively, indicating that steric hindrance did not significantly impact the reaction. Electron-rich 4-methoxyphenyl boronic acid gave trace amounts of the desired product, most likely because of the incompatibility of the anisole ring with strongly oxidizing species such as NFSI.[239] The less activated 3-methoxyphenyl boronic acid afforded the desired product **4.32** in good yield. On the other hand, highly deactivated aryl boronic acids such as 4-trifluoromethyl phenyl boronic acid, failed to provide the desired β-fluoro carbonyl adducts, but formed the Heck coupled product instead. Presumably, electron-withdrawing substituents difficult oxidation of palladium species **C** (see *Scheme 4.10*). Likewise, the reaction was amenable to halogen substitution (**4.33**-**4.36**), leaving chlorine, bromine and iodine moieties intact for further transformations.

[239] (a) Qian, D.; Zhang, J. *Beilstein. J. Org. Chem.* **2011**, *7*, 808. (b) Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 5519. (c) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3112.

The regiochemistry of 1,1-difunctionalization was confirmed by two-dimensional NMR studies on substrate **4.25**. A heteronuclear multiple bond correlation (HMBC) experiment showed a correlation between the methylene and carbonyl groups, but not with the CHF proton, confirming 1,1-regiochemistry (*Figure 4.1*).

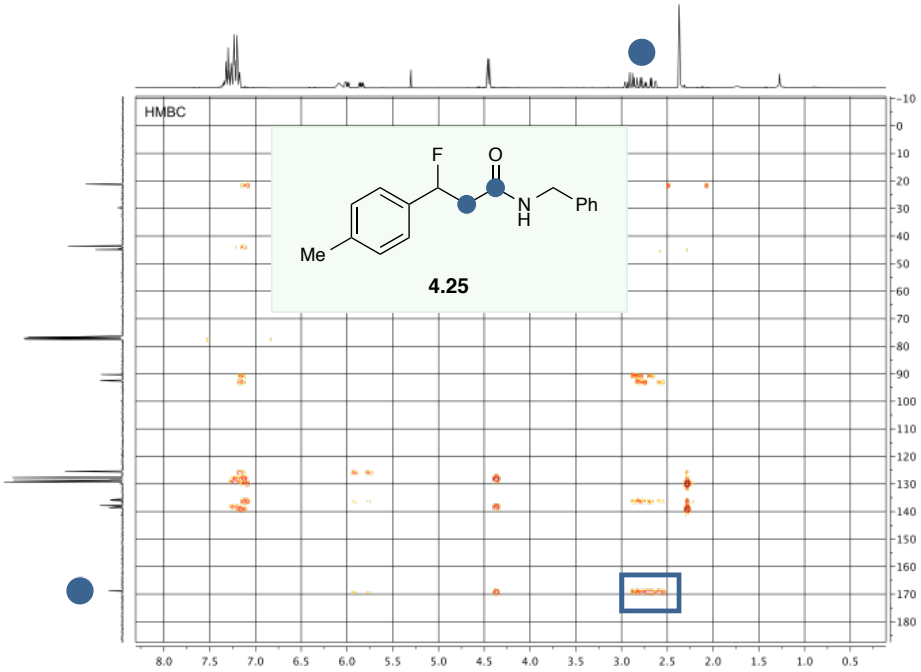
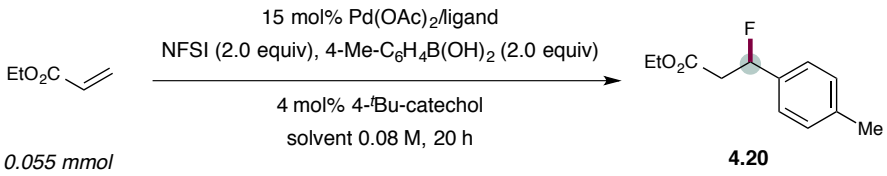


Figure 4.1. HMBC of substrate **4.25**.

Having provided proof-of-principle for the β,β-fluoroarylation reaction, the enantioselective variant was next examined using ethyl acrylate as a model substrate (*Table 4.3*). To this end, we undertook the evaluation of a range of different bidentate diimine chiral ligands, e.g. those indicated in *Table 4.3*, *entries 1-4*.[240] Among them, **BOX 3a** was identified as the most encouraging ligand, affording **4.20** in 72:38 er and quantitative yield (*entry 3*). Unfortunately, attempts at increasing the er by cooling proved unfruitful (*entry 5*). We then proceeded to survey solvent effects. Switching to nonpolar solvents, such as toluene, resulted in the erosion of yield without increasing selectivity (*entry 6*). Pleasingly, further examination led us to identify that coordinating solvents, such as EtOAc, EtOH, and acetone, are superior in terms of enantioselectivity (*entries 7-9*), providing the desired product **4.20** in up to 96:4 er (*entry 8*). However, this improvement in selectivity was obtained at the expense of yield, as previously observed in the reported Heck-Matsuda arylation-Miyaura borylation cascade reaction.[201] Attempts to increase yield by combining solvents, were unsuccessful (*entry 10*). Finally, acetone was the solvent of choice, providing a good compromise in terms of selectivity and yield (*entry 9*).

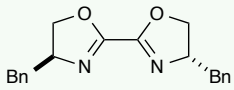
[240] For further details on the optimization, see *Experimental Section 4.5.2.*

Table 4.3. Optimization of enantioselective β,β-fluoroarylation.[a]

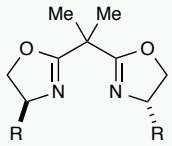


entry	ligand	solvent	temperature	yield[b]	er[c]
1	**PyrOX 1**	DCM/H_2O (10:1)	20-25 ºC	>99%	52:48
2	**BOX 2**	DCM/H_2O (10:1)	20-25 ºC	39%	62:38
3	**BOX 3a**	DCM/H_2O (10:1)	20-25 ºC	>99%	72:28
4	**BOX 3b**	DCM/H_2O (10:1)	20-25 ºC	>99%	68:32
5	**BOX 3a**	DCM/H_2O (10:1)	10 ºC	96%	72:28
6	**BOX 3a**	toluene/H_2O (10:1)	20-25 ºC	43%	78:22
7	**BOX 3a**	AcOEt/H_2O (10:1)	20-25 ºC	37%	95:5
8	**BOX 3a**	EtOH/H_2O (10:1)	20-25 ºC	53%	96:4
9	**BOX 3a**	acetone/H_2O (10:1)	20-25 ºC	61%	93:7
10	**BOX 3a**	acetone/DCM/H_2O (6:3:1)	20-25 ºC	62%	91:9

PyrOX 1



BOX 2

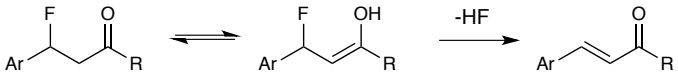


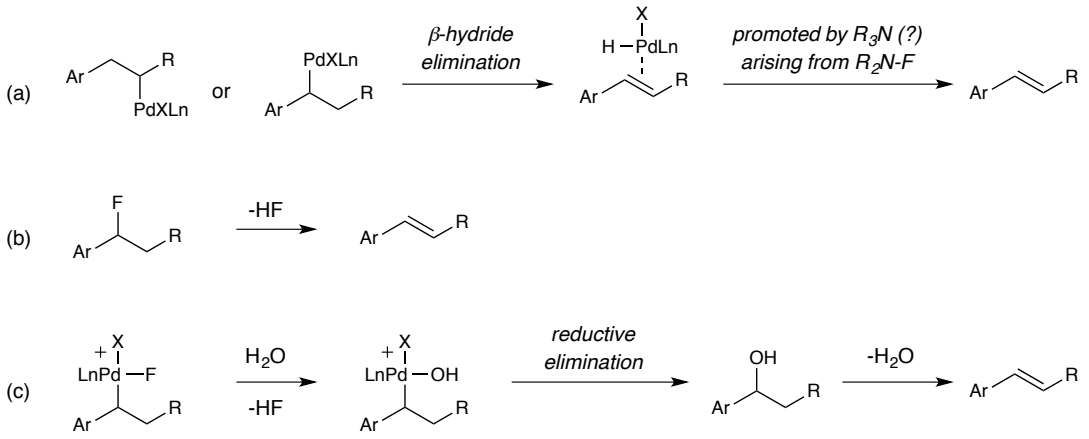
BOX 3a (R = ^{i}Pr)
BOX 3b (R = Ph)

[a] Conditions: all reactions were run on 0.055 mmol scale with respect to ethyl acrylate. [b] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [c] Enantiomeric ratio determined by chiral phase HPLC.

Notably, the major byproduct in the asymmetric reactions was the corresponding styrene, i.e. selected conditions resulted in significant termination via β-hydride elimination (*Scheme 4.13a*). Alternatively, styrene formation might be ascribed to either HF elimination on the final products (*Scheme 4.13b*)[241] or C–OH reductive elimination and subsequent dehydration as a result of F/OH exchange on the metal center (*Scheme 4.13c*).

[241] As it was mentioned above, this pathway was significant just for certain ketones under acidic conditions, via keto-enol tautomerism.





Scheme 4.13. Plausible pathways to Heck byproduct.

Additionally, amides were also evaluated for the enantioselective transformation. In this case, a combination of **PyrOX 1** ligand and ^{i}PrOH as solvent provided the best results.[242]

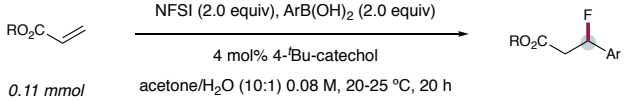
With optimized conditions in hand, a range of boronic acids were evaluated (*Table 4.4*). To our delight, the desired β-fluoroesters and amides were obtained in synthetically useful yields and good enantiomeric ratios. As for the racemic reaction, this procedure was efficient with non-electronically-biased aryl boronic acids. While steric effects did not have a deleterious effect on the efficiency of the process (**4.29**, **4.47**), 3-substituted aryl boronic acids provided higher er. 3-Methoxyphenyl boronic acid afforded the desired products **4.32** and **4.41** in comparably good yields and good er. Again, the reaction was amenable to the presence of halogens (**4.33**-**4.35**, **4.40**). The protocol was even compatible with heteroaryl boronic acids, rendering product **4.48** in 46% yield and 88:12 er. Notably, the ester group did not have a dramatic effect on the enantioselectivity (**4.39**), providing good levels of stereoselectivity even when more challenging steroid-derived acrylates (**4.43**) were used.

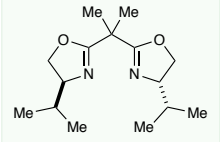
Molecular complexity was also tolerated in the aryl coupling partner (**4.44**), showcasing that this chemistry may add to the repertoire of late-stage functionalization methods and even to the ready generation of fluoro-bioconjugates (**4.45**). Moreover, the protocol was applicable to primary (**4.50**), secondary (**4.49**), and tertiary amides (**4.25**). Notably, the stereochemical integrity of the products was preserved after several weeks of storage at room temperature. Furthermore, when this protocol was scaled up ten fold, the catalytic charge (5 mol%) and the amount of $ArB(OH)_2$ (2.0 equiv) were reduced without affecting neither the yield nor er (**4.20**, **4.39**).

[242] For further details on the optimization, see *Experimental Section 4.5.3.*

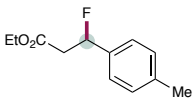
Table 4.4. Enantioselective substrate scope.[a,b,c,d]

(a)

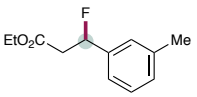




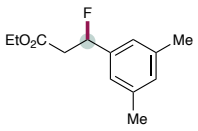
BOX 3a



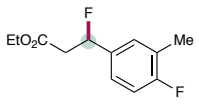
4.20, *61% yield (52%), 93:7 er*
(x10)[e] *69% yield (53%), 93:7 er*



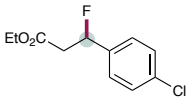
4.29, *61% yield (54%), 92:8 er*



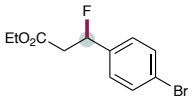
4.38, *66% yield (47%), 95:5 er*



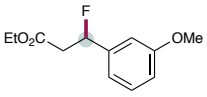
4.33, *63% yield (56%), 92:8 er*



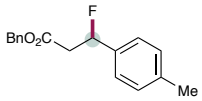
4.34, *54% yield (42%), 92:8 er*



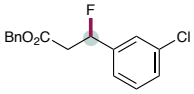
4.35, *55% yield (49%), 93:7 er*



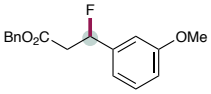
4.32, *62% yield (50%), 96:4 er*



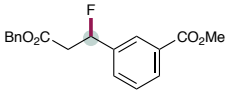
4.39, *60% yield (43%), 95:5 er*
(x10)[e] *66% yield (55%), 94:6 er*



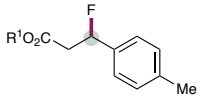
4.40, *61% yield (52%), 95:5 er*



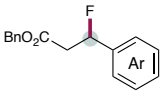
4.41, *88% yield (73%), 97:3 er*



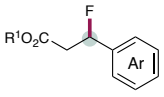
4.42, *59% yield (41%), 93:7 er*



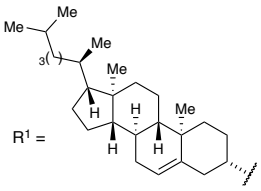
4.43[g]
70% yield , 11:1 dr in acetone
55% yield , 20:1 dr in EtOAc

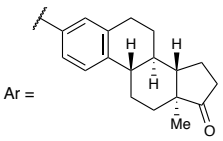


4.44,[g,h] *70% yield , 13:1 dr*

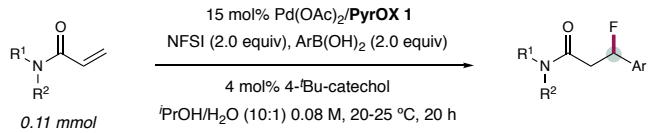


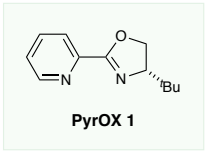
4.45,[g,h] *76% yield , 7:1 dr*



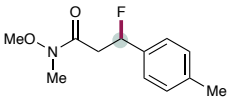


(b)

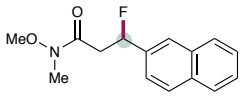




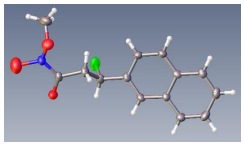
PyrOX 1

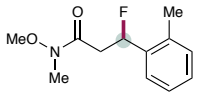


4.25, *55% yield (48%), 90:10 er*

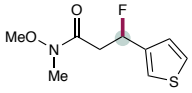


4.46, *56% yield (41%), 92:8 er*

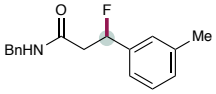




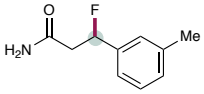
4.47, *45% yield (32%), 84:16 er*



4.48, *46% yield (37%), 88:12 er*



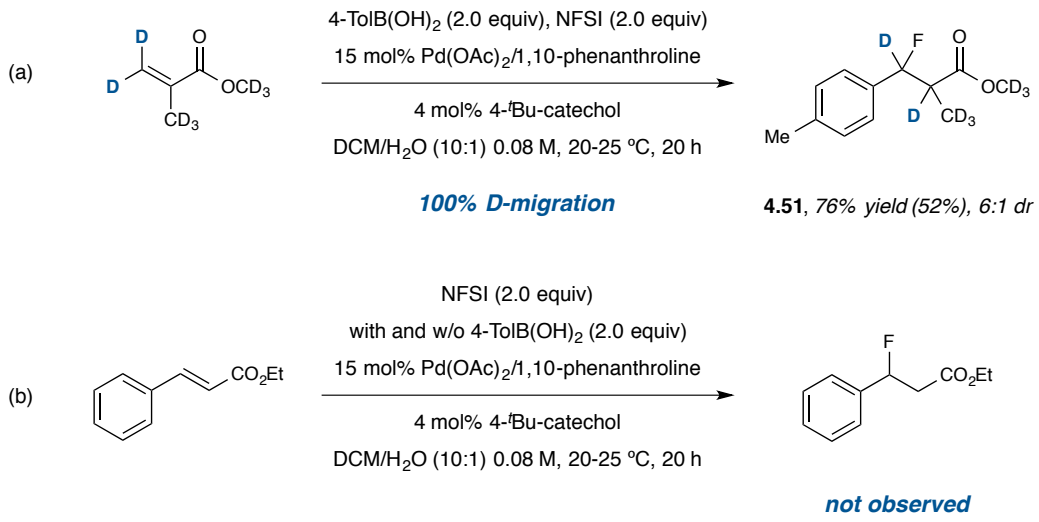
4.49, *85% yield (72%), 90:10 er*



4.50, *64% yield (51%), 90:10 er*

[a] Conditions: all reactions were run in 0.11 mmol scale with respect to starting α,β-unsaturated system. [b] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [c] Isolated yields in brackets. [d] Enantiomeric ratio (er) determined by chiral phase HPLC. [e] Absolute configuration assigned by analogy to that of **4.46**, which was determined to be (*R*) by single-crystal X-ray diffraction. [f] 5 mol% $Pd(OAc)_2$/**BOX 3a**. [g] Diastereomeric ratio (dr) determined by ^{19}F NMR. [h] 0.04 M.

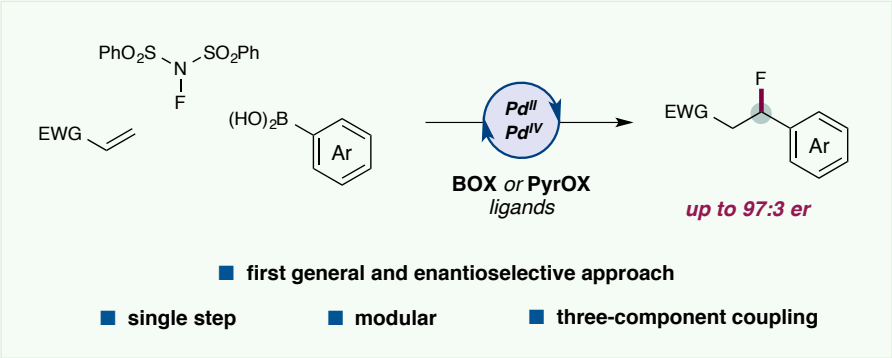
Finally, deuterium labeling experiments carried out with d^8-labelled methyl methacrylate, corroborated the proposed 1,1-difunctionalization mechanism disclosed above, i.e. β-deuteride elimination and subsequent Pd-deuteride reinsertion (*Scheme 4.14a*). Additionally, the β-fluoride ester was not observed when the reaction conditions were examined with the Heck-type byproduct ethyl cinnamate, eliminating a pathway involving β-fluoride addition to the unsaturated ester (*Scheme 4.14b*).



Scheme 4.14. Mechanistic experiments.

4.4. Conclusions.

In conclusion, we have disclosed a novel strategy to access β-fluoro-carbonyl derived systems via the mild catalytic and direct 1,1-difunctionalization of α,β-unsaturated systems (*Scheme 4.15*).[243] In agreement with previously reported transformations, the reaction is likely to proceed through the intermediacy of a high valent Pd(IV)-fluoride species in an oxidative Heck-type mechanism. The developed methodology establishes a general, modular, and step-economical approach that broadens the limited number of reported strategies for the still challenging enantioselective construction of $C(sp^3)$–F bonds β to electron-withdrawing groups.



Scheme 4.15. Heck arylation-oxidative fluorination.

[243] Miró, J.; del Pozo, C.; Toste, F. D.; Fustero, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9045.

4.5. Experimental section.

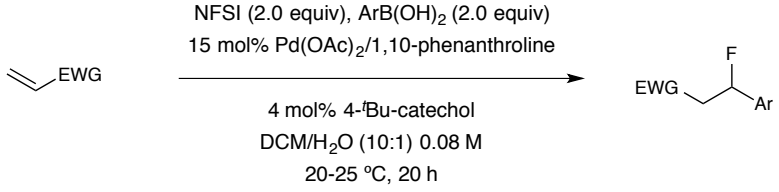
General remarks: Unless otherwise noted, reactions were carried out under argon atmosphere and all reagents were purchased from commercial suppliers and used without further purification. 4-Methoxyphenyl vinyl ketone, Weinreb amide, cholesterol-derived acrylate and estrone-derived boronic acid were prepared according to procedures previously described in the literature.[244] Non-commercially available BOX ligands were prepared according to previously reported procedures.[245] The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). Melting points were measured on Büchi B-540 apparatus. ^{1}H, ^{13}C and ^{19}F spectra were recorded on 300 MHz and 500 MHz Bruker spectrometers. Chemical shifts (δ) are given in ppm relative to the residual solvent signals (chloroform, 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Coupling constants (*J*) are given in Hertz (Hz). Letters m, s, d, t and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. Letters br indicate that the signal is broad. High-resolution mass spectra were carried out on an AB SCIEX TripleTOF™ 5600 LC/MS/MS system in ESI mode [*Conditions: Ion source gas 1 (GC1): 35 psi; Ion source gas 2 (GC2): 35 psi; Curtain gas 1: 25 psi; Temperature: 450 ºC; Ion Spray Voltage (ISVF): 5500; Infusion positive mode*] by the University of Valencia Mass Spectrometry Service. Enantiomeric ratios were determined with the aid of HPLC analysis with ChiralPak OD-H, ChiralPak IC, ChiralPak AD or Amylose-1 columns (25 cm x 0.46 cm).

Note: It is worthy to note that, for both general procedures **A** and **B**, employed organic solvents, as well as water, were previously degassed using an argon stream for ca. 30 minutes under stirring.

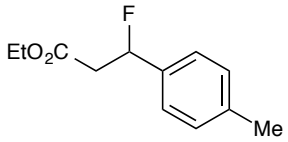
[244] (a) Hellmuth, T.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788. (b) Commare, B.; Rigault, D.; Lemasson, I. A.; Deschamps, P.; Tomas, A.; Roussel, P.; Brabet, I.; Goudet, C.; Pin, J.-P.; Leroux, F. R.; Colobert, F.; Acher, F. C. *Org. Biomol. Chem.* **2015**, *13*, 1106. (c) Laskar, P.; Samanta, S.; Ghosh, S. K.; Dey, J. *J. of Colloid and Interface Science*, **2014**, *430*, 305. (d) Baek, Y.; Kim, S.; Jeon, B.; Lee, P. H. *Org. Lett.* **2016**, *18*, 104.

[245] (a) Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron*, **1996**, *52*, 13649. (b) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron Asymmetry*, **2002**, *13*, 1651. (c) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Synlett*, **2005**, 2321. (d) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932.

4.5.1. General procedure A: Racemic three-component β,β-fluoroarylation reaction.

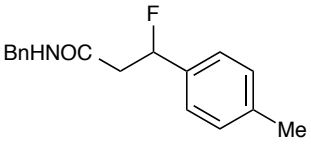


A 1 dram vial was charged of palladium catalyst (15 mol%), 1,10-phenanthroline (15 mol%) and 1/3 of DCM. The headspace of the reaction vessel was sparged with Ar for ca. 10 seconds, and then vial was capped and the mixture was stirred for 15-20 min. A separate 1 dram vial was charged with aryl boronic acid (2.0 equiv) and NFSI (2.0 equiv). To the solid reagents, 2/3 of DCM were added; then, 4 mol% of 4-*tert*-butylcatechol (stock solution), the corresponding alkene (0.11 mmol, 1.0 equiv) and H_2O. The palladium complex was then transferred to the reaction mixture *via* syringe. Once again, the headspace of the reaction vessel was sparged with Ar for ca. 10 seconds, vial was capped and the mixture was vigorously stirred for 20 hours. After the reaction was complete, the mixture was diluted with DCM and filtered through a pad of Celite eluting with DCM. The organic phase was evaporated and yield was determined, firstly, by ^{19}F-NMR.[246] Then, the crude was purified by column chromatography over silica gel using a mixture of hexanes/DCM/EtOAc as eluent to give the desired products.

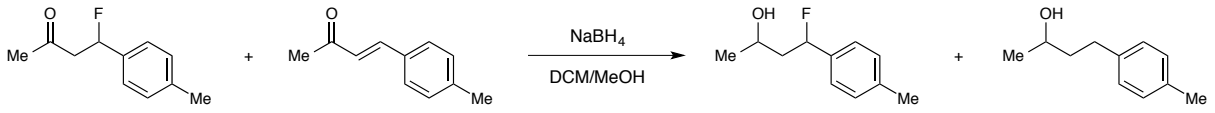


Ethyl 3-fluoro-3-(*p*-tolyl)propanoate. Following the general procedure A, **4.20** was obtained in 83% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 6.0 Hz, 3H), 2.36 (s, 3H), 2.77 (ddd, *J* = 33.0, 15.0, 6.0 Hz, 1H), 3.03 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 4.19 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.88 (ddd, *J* = 45.0, 9.0, 3.0 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 21.2, 42.4 (d, *J* = 27.2 Hz), 60.9, 90.6 (d, *J* = 171.4 Hz), 125.7 (d, *J* = 6.0 Hz), 129.3, 135.7 (d, *J* = 19.6 Hz), 138.7 (d, *J* = 2.3 Hz), 169.7 (d, *J* = 5.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -171.6 (ddd, *J* = 48.0, 33.0, 12.0 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{15}FNaO_2$: 233.0948; found: 233.0944.

[246] **^{19}F NMR yield:** The crude reaction mixture was dissolved in $CDCl_3$ and 0.25 equivalents of fluorobenzene were added to obtain the NMR yield.



***N*-benzyl-3-fluoro-3-(*p*-tolyl)propanamide.** Following the general procedure A, **4.21** was obtained in 80% yield as a white solid (mp = 113-115 ºC). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H), 2.71 (ddd, *J* = 33.0, 15.0, 3.0 Hz, 1H), 2.90 (dt, *J* = 15.0, 9.0 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 5.92 (ddd, *J* = 45.0, 9.0, 6.0 Hz, 1H), 6.08 (br s, NH), 7.17-7.35 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.2, 43.6, 44.8 (d, *J* = 24.9 Hz), 91.4 (d, *J* = 170.6 Hz), 125.5 (d, *J* = 6.0 Hz), 127.5, 127.7, 128.6, 129.3, 135.8 (d, *J* = 19.6 Hz), 137.8, 138.6 (d, *J* = 2.3 Hz), 168.8 (d, *J* = 3.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -172.2 (ddd, *J* = 47.7, 33.0, 15.2 Hz); HRMS (ES) calc. for (M^++1) $C_{17}H_{18}NOF$: 272.1445; found: 272.1445.



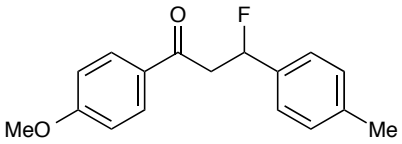
Via (a) Heck arylation and/or (b) HF elimination

4.52 (dr 1:0.6)

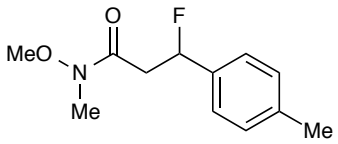
4.53

Inseparable mixture

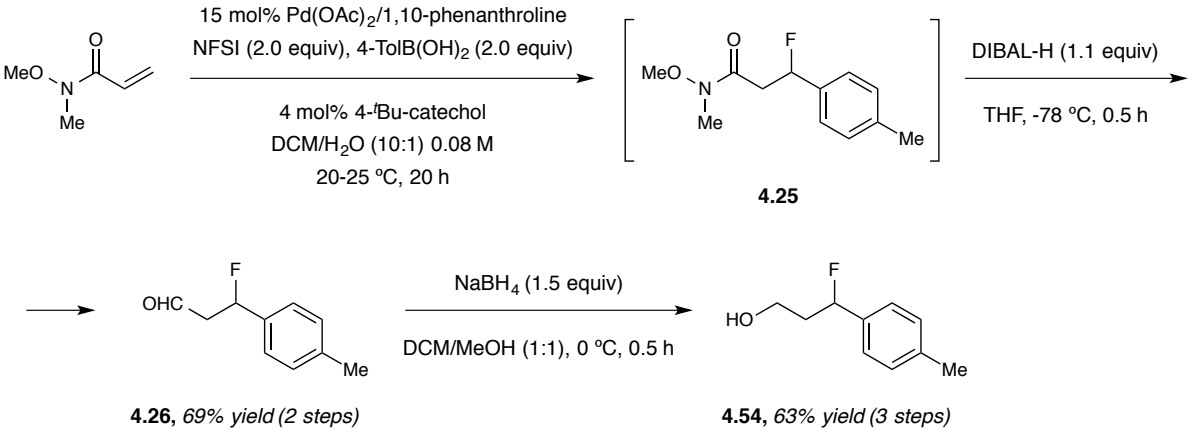
Following the general procedure A, **4.22** was obtained in 49% NMR yield. Attempts of chromatographic purification on silica gel lead majorly to elimination product. Alternatively, the crude reaction mixture was placed under inert atmosphere, redissolved in DCM/MeOH (1:1) and cooled to 0 ºC. Solid $NaBH_4$ (5.0 equiv) was added and the reaction was stirred vigorously for 2 hours at room temperature. Then, solvents were removed under reduced pressure. The crude reaction mixture was quenched with H_2O and extracted into DCM. Combined organic extracts were dried with anhydrous Na_2SO_4, filtered through a pad of Celite and concentrated by rotary evaporation. ^{19}F-NMR of the crude indicates dr prior to isolation. Alcohol **4.52** was isolated as an inseparable mixture of diastereoisomers (dr 1:0.6), besides over-reduced elimination product **4.53**, by column chromatography on silica gel, using a mixture hexanes/DCM/EtOAc as eluent. **4.52** + **4.53**: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (d, *J* = 6.0 Hz, 3H), 1.28 (d, *J* = 9.0 Hz, 1.8H), 1.81-2.28 (m, 3+1.8H), 2.36 (s, 3+1.8H), 3.93-4.04 (m, 1H), 4.10-4.21 (m, 0.6H), 5.62 (ddd, *J* = 48.0, 6.0, 3.0 Hz, 1H), 5.70 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 0.6H), 7.10 (m, 4+2.4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.0, 21.2, 23.6, 24.1, 31.7, 41.0, 45.9 (d, *J* = 21.9 Hz), 46.4 (d, *J* = 23.4 Hz), 64.3 (d, *J* = 3.0 Hz), 66.0 (d, *J* = 4.5 Hz), 67.5, 91.7 (d, *J* = 168.4 Hz), 94.1 (d, *J* = 167.6 Hz), 125.5 (d, *J* = 6.0 Hz), 125.7 (d, *J* = 6.8 Hz), 128.2, 129.1, 129.2, 129.2, 135.2, 136.7 (d, *J* = 19.6 Hz), 137.2 (d, *J* = 20.4 Hz), 138.1 (d, *J* = 2.3 Hz), 138.4 (d, *J* = 2.3 Hz), 138.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -172.6 (ddd, *J* = 45.1, 31.0, 14.1 Hz, 1F), -176.6 (ddd, *J* = 47.9, 36.7, 14.1 Hz, 0.6F); HRMS (ES) calc. for **4.22** (M^+-F) $C_{11}H_{13}O$: 161.0961; found: 161.0955.



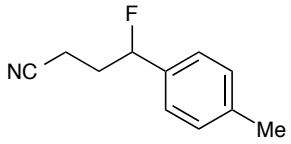
3-Fluoro-1-(4-methoxyphenyl)-3-(*p*-tolyl)propan-1-one. Following the general procedure A, **4.23** was obtained in 61% yield as a yellowish oil. In this case, HF elimination on silica gel was not as fast and ketone **4.23** could be purified by column chromatography. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 3.26 (ddd, *J* = 30.0, 18.0, 6.0 Hz, 1H), 3.76 (ddd, *J* = 18.0, 15.0, 6.0 Hz, 1H), 3.87 (s, 3H), 6.13 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 6.0 Hz, 2H), 7.95 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.2, 45.5 (d, *J* = 26.4 Hz), 55.5, 90.5 (d, *J* = 169.9 Hz), 113.8, 120.9, 123.0, 125.7 (d, *J* = 6.0 Hz), 129.3, 130.6, 138.5 (d, *J* = 2.3 Hz), 163.8, 194.7 (d, *J* = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -172.6 (ddd, *J* = 47.9, 31.0, 16.9 Hz); HRMS (ES) calc. for (M^+-F) $C_{17}H_{17}O_2$: 253.1223; found: 253.1228.



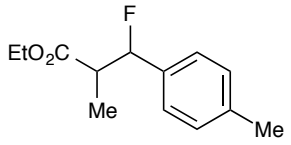
3-Fluoro-*N*-methoxy-*N*-methyl-3-(*p*-tolyl)propanamide. Following the general procedure A, **4.25** was obtained in 80% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 2.76 (ddd, *J* = 33.0, 18.0, 6.0 Hz, 1H), 3.21 (s, 3H), 3.24-3.41 (m, 1H), 3.67 (s, 3H), 5.99 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 21.2, 32.1, 39.7 (d, *J* = 26.4 Hz), 61.4, 90.7 (d, *J* = 169.9 Hz), 125.7 (d, *J* = 6.0 Hz), 129.2, 136.4 (d, *J* = 19.6 Hz), 138.5 (d, *J* = 2.3 Hz), 170.2 (d, *J* = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -172.5 (ddd, *J* = 45.2, 31.0, 11.3 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{16}FNNaO_2$: 248.1057; found: 248.1052.



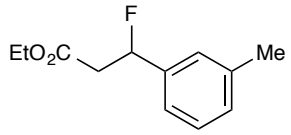
Following the general procedure A, vinyl Weinreb amide was submitted to β,β-fluoroarylation protocol. Crude reaction mixture was filtered through a pad of silica gel to obtain Weinreb amide **4.25** slightly contaminated. Aldehyde **4.26** was prepared from **4.25** by treatment of a solution of **4.25** in THF 0.1 M cooled at -78 ºC with 1.1 equiv of DIBAL-H for 0.5 h. After completion, reaction mixture was quenched with a 1.0 M HCl solution and extracted with EtOAc. Collected organic fractions were dried with anhydrous Na_2SO_4 and filtered. Attempts of chromatographic purification on silica gel lead majorly to elimination product. However, crude reaction mixture was pure enough for characterization. **3-Fluoro-3-(*p*-tolyl)propanal** (**4.26**): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 2.88 (dddd, *J* = 30.0, 20.0, 5.0, 5.0 Hz, 1H), 3.17 (ddd, *J* = 25.0, 15.0, 10.0 Hz, 1H), 5.97 (ddd, *J* = 50.0, 10.0, 5.0 Hz, 1H), 7.21 (d, *J* = 10.0 Hz, 2H), 7.26 (d, *J* = 10.0 Hz, 2H), 9.84 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 21.2, 50.4 (d, *J* = 25.1 Hz), 89.1 (d, *J* = 170.4 Hz), 125.5 (d, *J* = 6.3 Hz), 129.4, 135.5 (d, *J* = 20.0 Hz), 138.9 (d, *J* = 2.5 Hz), 198.6 (d, *J* = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -172.7 (ddd, *J* = 47.9, 31.0, 16.9 Hz); HRMS (ES) calc. for (M^+-F) $C_{10}H_{11}O$: 147.0804; found: 147.0803. Alcohol **4.54** was obtained by reduction with 1.5 equivalents of $NaBH_4$ in an equimolar mixture of DCM/MeOH 0.1M. After 0.5 h, solvents were removed under reduced pressure. Crude reaction mixture was treated with water and extracted with DCM. Collected organic fractions were washed with brine, then dried with anhydrous Na_2SO_4, filtered and distilled to remove solvents, rendering alcohol **4.54** pure enough for characterization. **3-Fluoro-3-(*p*-tolyl)propan-1-ol** (**4.54**): ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.72 (br s, OH), 1.99-2.12 (m, 1H), 2.20-2.30 (m, 1H), 2.37 (s, 3H), 3.78-3.82 (m, 1H), 3.85-3.90 (m, 1H), 5.65 (ddd, *J* = 50.0, 10.0, 5.0 Hz, 1H), 7.20 (d, *J* = 10.0 Hz, 2H), 7.26 (d, *J* = 5.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 21.2, 39.2 (d, *J* = 22.6 Hz), 59.2 (d, *J* = 3.8 Hz), 92.4 (d, *J* = 166.6 Hz), 125.5 (d, *J* = 6.3 Hz), 129.2, 136.9 (d, *J* = 20.0 Hz), 138.3 (d, *J* = 2.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -175.8 (ddd, *J* = 47.9, 33.8, 16.9 Hz); HRMS (ES) calc. for (M^+-F) $C_{10}H_{13}O$: 149.0961; found: 149.0961.



4-Fluoro-4-(*p*-tolyl)butanenitrile. Following the general procedure A, **4.27** was obtained in 36% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.04-2.35 (m, 2H), 2.37 (s, 3H), 2.41-2.62 (m, 2H), 5.54 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 7.22 (s, 4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.4 (d, *J* = 5.3 Hz), 21.2, 32.8 (d, *J* = 25.7 Hz), 92.1 (d, *J* = 172.9 Hz), 118.8, 125.4 (d, *J* = 6.0 Hz), 129.4, 135.2 (d, *J* = 19.6 Hz), 138.9; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -178.1 (ddd, *J* = 45.1, 31.0, 16.9 Hz); HRMS (ES) calc. for (M^++Na) $C_{11}H_{12}FNNa$: 200.0846; found: 200.0848.

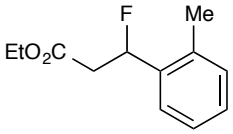


Ethyl 3-fluoro-2-methyl-3-(*p*-tolyl)propanoate. Following the general procedure A, **4.28** was obtained in 69% yield as a yellowish oil. Isolated as an inseparable mixture of diastereoisomers (3:1 dr). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.95 (d, *J* = 9.0 Hz, 3H), 1.07 (t, *J* = 6.0 Hz, 3/4H), 1.30 (t, *J* = 9.0 Hz, 3H), 2.28 (s, 3/4H), 2.36-2.38 (m, 3+3/4H), 2.72 (dd, *J* = 12.0, 9.0 Hz, 1/4H), 2.99 (m, 1H), 4.05 (q, *J* = 8.0 Hz, 1/2H), 4.23 (q, *J* = 7.0 Hz, 2H), 5.51 (dd, *J* = 45.0, 9.0 Hz, 1H), 5.55 (dd, *J* = 48.0, 9.0 Hz, 1/4H), 6.92-7.04 (m, 1H), 7.16-7.31 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 13.4 (d, *J* = 7.6 Hz), 14.0, 14.2, 21.0, 21.2, 34.2 (d, *J* = 6.0 Hz), 46.3 (d, *J* = 25.7 Hz), 54.5 (d, *J* = 24.2 Hz), 60.7, 60.9, 94.8 (d, *J* = 174.4 Hz), 95.6 (d, *J* = 172.9 Hz), 121.2, 126.8 (d, *J* = 6.0 Hz), 128.6, 129.0, 129.2, 129.4, 129.9, 134.0 (d, *J* = 19.6 Hz), 134.6, 136.0, 139.0 (d, *J* = 3.0 Hz), 139.1 (d, *J* = 3.0 Hz), 172.5 (d, *J* = 2.3 Hz), 173.9 (d, *J* = 2.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -166.8 (dd, *J* = 47.9, 8.5 Hz), -168.4 (dd, *J* = 47.9, 11.3 Hz); HRMS (ES) calc. for (M^++Na) $C_{13}H_{17}FNaO_2$: 247.1105; found: 247.1102.

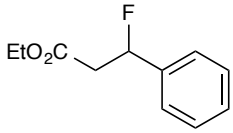


Ethyl 3-fluoro-3-(*m*-tolyl)propanoate. Following the general procedure A, **4.29** was obtained in 78% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 6.0 Hz, 3H), 2.37 (s, 3H), 2.78 (ddd, *J* = 33.0, 15.0, 3.0 Hz, 1H), 3.02 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 4.20 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.89 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 7.15-7.18 (m, 3H), 7.25-7.30 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 21.4, 42.5 (d, *J* = 27.2 Hz), 60.9, 90.7 (d, *J* = 172.1 Hz), 122.7 (d, *J* = 6.8 Hz), 126.3 (d, *J* = 6.0 Hz), 128.5, 129.5 (d, *J* = 2.3 Hz), 138.4, 138.6 (d, *J* = 19.6 Hz), 169.7 (d, *J* = 5.3 Hz); ^{19}F-

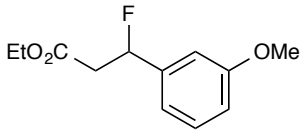
NMR ($CDCl_3$, 282 MHz): δ -173.3 (ddd, *J* = 45.1, 31.0, 11.3 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{15}FNaO_2$: 233.0948; found: 233.0944.



Ethyl 3-fluoro-3-(*o*-tolyl)propanoate. Following the general procedure A, **4.30** was obtained in 61% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, *J* = 9.0 Hz, 3H), 2.38 (s, 3H), 2.76 (ddd, *J* = 33.0, 15.0, 3.0 Hz, 1H), 2.99 (ddd, *J* = 18.0, 15.0, 12.0 Hz, 1H), 4.21 (qd, *J* = 9.0, 3.0 Hz, 2H), 6.15 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 1H), 7.16-7.28 (m, 3H), 7.38-7.44 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 18.9, 41.4 (d, *J* = 27.9 Hz), 61.0, 88.1 (d, *J* = 171.4 Hz), 125.3 (d, *J* = 8.3 Hz), 126.3, 128.6 (d, *J* = 2.3 Hz), 130.7, 134.6 (d, *J* = 4.5 Hz), 136.7 (d, *J* = 18.9 Hz), 169.8 (d, *J* = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -175.9 (ddd, *J* = 45.1, 33.8, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{15}FNaO_2$: 233.0948; found: 233.0945.

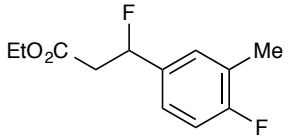


Ethyl 3-fluoro-3-phenylpropanoate. Following the general procedure A, **4.31** was obtained in 67% yield as a yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 6.0 Hz, 3H), 2.79 (ddd, *J* = 33.0, 15.0, 6.0 Hz, 1H), 3.04 (ddd, *J* = 18.0, 15.0, 9.0 Hz, 1H), 4.20 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.93 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 7.35-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 42.5 (d, *J* = 27.2 Hz), 60.9, 90.6 (d, *J* = 172.1 Hz), 125.6 (d, *J* = 6.8 Hz), 128.6, 128.8 (d, *J* = 2.3 Hz), 138.7 (d, *J* = 19.6 Hz), 169.6 (d, *J* = 5.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -173.6 (ddd, *J* = 47.9, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{11}H_{13}FNaO_2$: 219.0780; found: 219.0784.

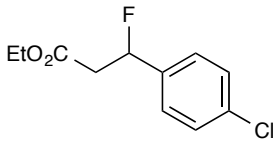


Ethyl 3-fluoro-3-(3-methoxyphenyl)propanoate. Following the general procedure A, **4.32** was obtained in 56% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 6.0 Hz, 3H), 2.78 (ddd, *J* = 33.0, 18.0, 6.0 Hz, 1H), 3.01 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 3.82 (s, 3H), 4.20 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.90 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 6.87-6.95 (m, 3H), 7.27-7.32 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 42.6 (d, *J* = 27.2 Hz), 55.3, 61.0, 90.5 (d, *J* = 172.9 Hz), 111.0 (d, *J* = 6.8 Hz), 114.3 (d, *J* = 2.3 Hz), 117.7 (d, *J* = 6.8 Hz), 129.7, 140.3 (d, *J* = 19.6 Hz), 159.8, 169.6 (d, *J*

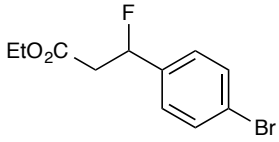
= 4.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -174.2 (ddd, *J* = 45.1, 31.0, 11.3 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{15}FNaO_3$: 249.0897; found: 249.0895.



Ethyl 3-fluoro-3-(4-fluoro-3-methylphenyl)propanoate. Following the general procedure A, **4.33** was obtained in 54% yield as a yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, *J* = 6.0 Hz, 3H), 2.29 (d, *J* = 3.0 Hz, 3H), 2.76 (ddd, *J* = 30.0, 15.0, 3.0 Hz, 1H), 3.02 (ddd, *J* = 15.0, 15.0, 9.0 Hz, 1H), 4.18 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.85 (ddd, *J* = 45.0, 9.0, 3.0 Hz, 1H), 7.00 (7.5), 7.13-7.21 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 14.6 (d, *J* = 3.0 Hz), 42.4 (d, *J* = 27.2 Hz), 61.0, 90.2 (172.1), 115.2 (d, *J* = 23.4 Hz), 124.8 (dd, *J* = 8.3, 6.0 Hz), 125.3 (d, *J* = 18.1 Hz), 129.0 (t, *J* = 6.0 Hz), 134.1 (dd, *J* = 19.6, 3.8 Hz), 161.4 (dd, *J* = 246.9, 3.0 Hz), 169.5 (d, *J* = 6.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -117.5 (m, 1F), -171.0 (dddd, *J* = 45.1, 31.0, 11.3, 2.8 Hz, 1F); HRMS (ES) calc. for (M^++Na) $C_{12}H_{14}F_2NaO_2$: 251.0854; found: 251.0851.

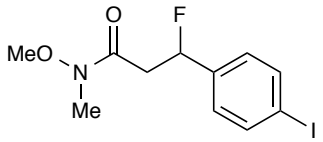


Ethyl 3-(4-chlorophenyl)-3-fluoropropanoate. Following the general procedure A, **4.34** was obtained in 47% yield as a yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, *J* = 6.0 Hz, 3H), 2.77 (ddd, *J* = 30.0, 15.0, 6.0 Hz, 1H), 3.01 (ddd, *J* = 15.0, 15.0, 9.0 Hz, 1H), 4.18 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.89 (ddd, *J* = 45.0, 9.0, 3.0 Hz, 1H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 42.4 (d, *J* = 26.4 Hz), 61.1, 89.9 (d, *J* = 172.9 Hz), 127.0 (d, *J* = 6.0 Hz), 128.9, 134.7 (d, *J* = 2.3 Hz), 137.2 (d, *J* = 19.6 Hz), 169.3 (d, *J* = 5.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -174.0 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{11}H_{12}ClFO_2$: 253.0402; found: 253.0402.



Ethyl 3-(4-bromophenyl)-3-fluoropropanoate. Following the general procedure A, **4.35** was obtained in 47% yield as a yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, *J* = 6.0 Hz, 3H), 2.76 (ddd, *J* = 30.0, 15.0, 3.0 Hz, 1H), 3.00 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 4.18 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.88 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR

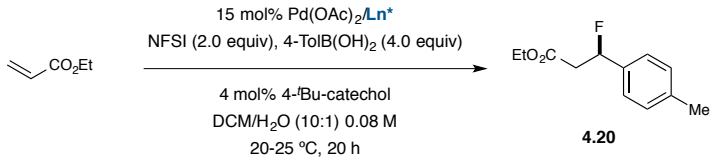
($CDCl_3$, 75.5 MHz): δ 14.1, 42.3 (d, *J* = 27.2 Hz), 61.1, 90.0 (d, *J* = 173.7 Hz), 122.8 (d, *J* = 3.0 Hz), 127.3 (d, *J* = 6.8 Hz), 131.8, 137.7 (d, *J* = 19.6 Hz), 169.3 (d, *J* = 5.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -174.5 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{11}H_{12}BrFNaO_2$: 296.9897; found: 296.9903.



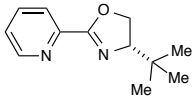
3-Fluoro-3-(4-iodophenyl)-*N*-methoxy-*N*-methylpropanamide. Following the general procedure A, **4.36** was obtained in 43% yield as a yellowish oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.76 (ddd, *J* = 30.0, 15.0, 3.0 Hz, 1H), 3.14-3.32 (m, 1H), 3.20 (s, 3H), 3.66 (s, 3H), 5.97 (ddd, *J* = 48.0, 9.0, 6.0 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.72 (d, *J* = 6.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 32.1, 39.7 (d, *J* = 27.2 Hz), 61.4, 90.2 (d, *J* = 172.1 Hz), 94.2 (d, *J* = 3.0 Hz), 127.5 (d, *J* = 6.8 Hz), 137.7, 139.2 (d, *J* = 20.4 Hz), 169.8; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -175.8 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^+-F) $C_{13}H_{11}INO_2$: 317.9997; found: 317.9988.

4.5.2. Optimization of the enantioselective three-component β,β-fluoroarylation reaction of ethyl acrylate. Summary data.

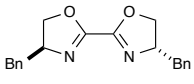
·*Catalyst screening*



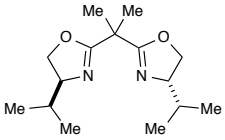
4.20



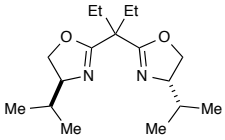
99% yield, 4% ee



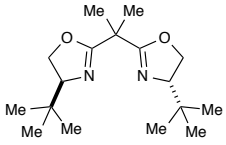
39% yield, 24% ee



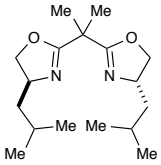
99% yield, 44% ee



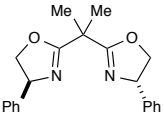
99% yield, 43% ee



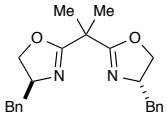
38% yield, <5% ee



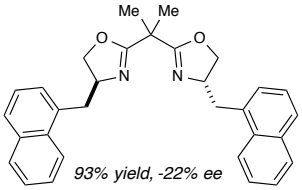
99% yield, 16% ee



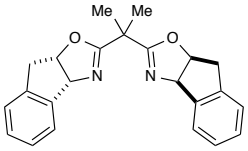
99% yield, 36% ee



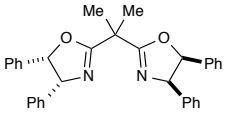
93% yield, <10% ee



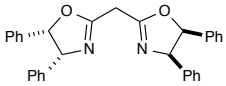
93% yield, -22% ee



99% yield, -12% ee

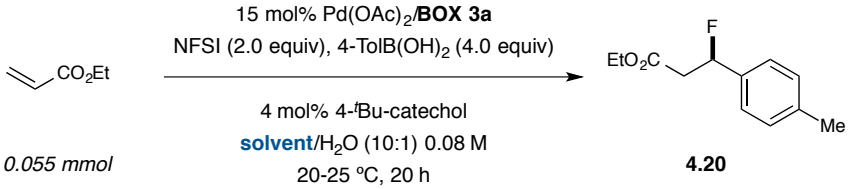


99% yield, -38% ee



54% yield, -54% ee

·*Solvent screening*

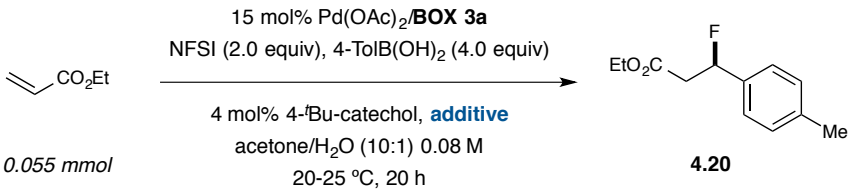


0.055 mmol **4.20**

entry	solvent	yield[a]	ee[b]
1	DCM	>99%	44%
2	DCM, 10ºC	96%	44%
3	1,2-DCE	97%	38%
4	$CHCl_3$	44%	60%
5	toluene	43%	56%
6	benzene	42%	58%
7	hexane	10%	nd
8	MeCN	18%	14%
9	$MeNO_2$	67%	65%
10	DMF	-	-
11	EtOAc	37%	90%
12	Et_2O	22%	73%
13	THF	31%	86%
14	dioxane	27%	84%
15	MeOH	47%	90%
16	EtOH	53%	92%
17	^{i}PrOH	35%	96%
18	**acetone**	**61%**	**86%**
19	acetone:DCM (2:1)	62%	82%

[a] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [b] Enantiomeric excess determined by chiral phase HPLC.

·*Additives*

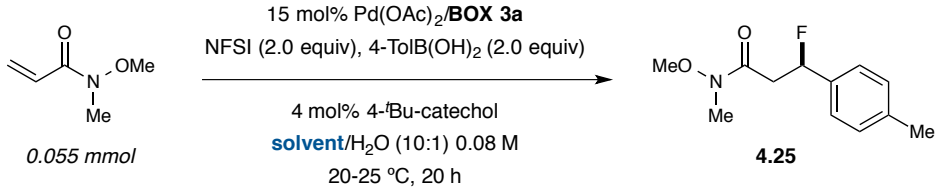


entry	additive	yield[a]	ee[b]
1	benzoquinone (1.0 equiv)	64%	86%
2	$Cu(OAc)_2$ (1.0 equiv)	43%	74%
3	Ag(OAc) (1.0 equiv)	55%	82%
4	Ag(TFA) (1.0 equiv)	24%	30%
5	AcOH (0.5 equiv)	61%	84%
6	TFA (0.5 equiv)	40%	70%
7	30 mol% $(BnO)_2PO_2H$	60%	86%
8	30 mol% 4-^{t}Bu-dba	58%	86%
9	30 mol% 4-MeO-dba	61%	86%
10	30 mol% 4-F-dba	62%	86%
11	30 mol% 3-CF_3-dba	64%	84%

[a] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [b] Enantiomeric excess determined by chiral phase HPLC.

4.5.3. Optimization of the enantioselective three-component β,β-fluoroarylation reaction of vinyl Weinreb amide. Summary data.

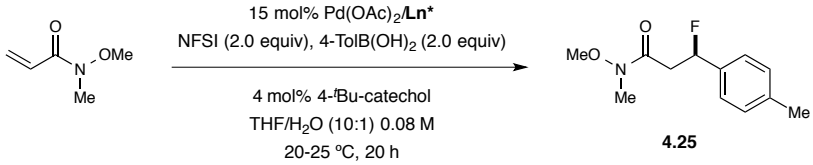
·Solvent screening

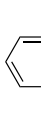


entry	solvent	yield[a]	ee[b]
1	acetone	83%	19%
2	DCM	99%	-24%
3	EtOAc	69%	36%
4	**THF**	**65%**	**44%**
5	EtOH	45%	42%

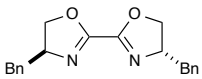
[a] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [b] Enantiomeric excess determined by chiral phase HPLC.

·Catalyst screening

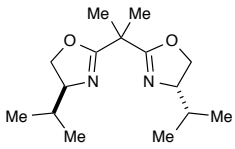




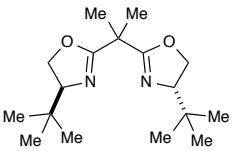
16% yield, 62% ee



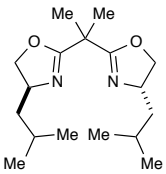
37% yield, 4% ee



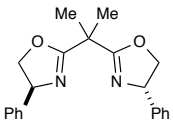
65% yield, 44% ee



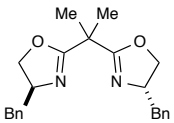
70% yield, 0% ee



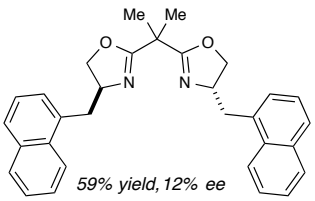
58% yield, 10% ee



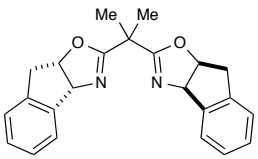
63% yield, 10% ee



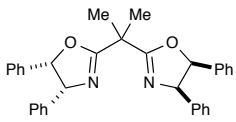
63% yield, -40% ee



59% yield, 12% ee

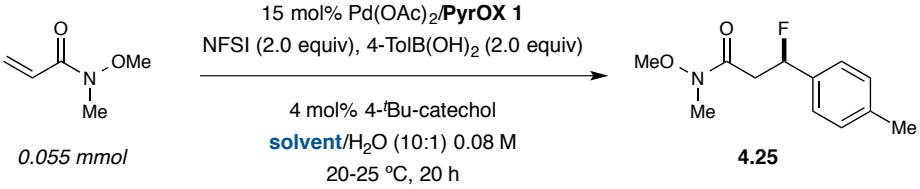


68% yield, 6% ee



56% yield, -14% ee

·*Solvent screening*



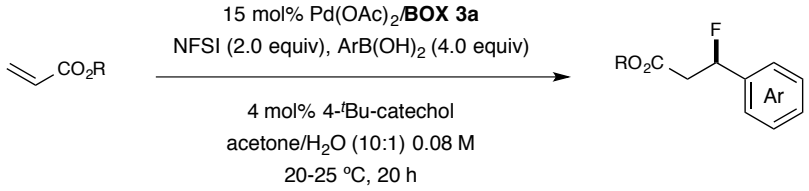
0.055 mmol

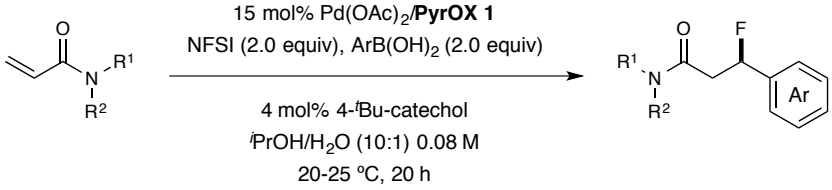
4.25

entry	solvent	yield[a]	ee[b]
1	THF	16%	62%
2	DCM	99%	38%
3	acetone	76%	70%
4	EtOAc	68%	68%
5	EtOH	55%	78%
6	Et_2O	<5%	nd
7	MeCN	19%	32%
8	MeOH	54%	74%
9	**^{i}PrOH**	**66%**	**80%**
10	^{t}BuOH	59%	78%

[a] Yield determined by ^{19}F NMR utilizing fluorobenzene as internal standard. [b] Enantiomeric excess determined by chiral phase HPLC.

4.5.4. General procedure B: Enantioselective three-component β,β-fluoroarylation reaction.

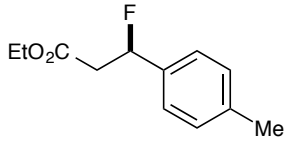




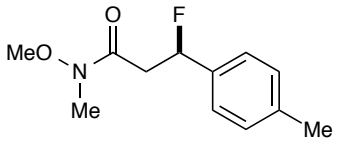
A 1 dram vial was charged of palladium catalyst (15 mol%), chiral ligand (15 mol%) and 1/3 of organic solvent (acetone or ^{i}PrOH). The headspace of the reaction vessel was sparged with Ar for ca. 10 seconds, and then vial was capped and the mixture was stirred for 15-20 min. A separate 1 dram vial was charged with aryl boronic acid (4.0 or 2.0 equiv) and NFSI (2.0 equiv). To the solid reagents,

2/3 of organic solvent were added; then, 4 mol% of 4-*tert*-butylcatechol (from a stock solution), ethyl acrylate or vinyl Weinreb amide (0.11 mmol, 1.0 equiv) and H_2O. The palladium complex was then transferred to the reaction mixture *via* syringe. Once again, the headspace of the reaction vessel was sparged with Ar for ca. 10 seconds, vial was capped and the mixture was vigorously stirred for 20 hours. After the reaction was complete, the mixture was diluted with DCM and filtered through a pad of Celite eluting with DCM. The organic phase was evaporated and yield was determined, firstly, by ^{19}F NMR.[247] Then, the crude was purified by column chromatography over silica gel using a mixture of hexanes/DCM/EtOAc as eluent to give the desired products. When necessary, preparative TLC was used for purification. Enantiomeric ratio (er) was determined by chiral phase HPLC using IC, AD, OD-H or Amylose-1 columns under indicated conditions.

Note: When the reaction was scaled up to 1.1 mmol (x10), it was run in a sealed tube using 2.0 equiv of the corresponding aryl boronic acid and 5 mol% of the catalytic system Pd(OAc)/Ln*. The work-up was modified in this case. After removal of solvents, the crude reaction mixture was diluted in DCM (20 mL) and poured onto a separatory funnel. Then, water was added (20 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. After removal of solvents, the crude reaction mixture was purified by flash column chromatography, rendering the corresponding fluorinated product slightly contaminated by the Heck byproduct. This mixture could be separated on a semi-preparative HPLC column.

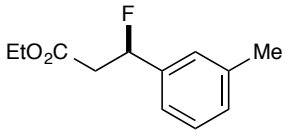


Ethyl (*R*)-3-fluoro-3-(*p*-tolyl)propanoate. Following the general procedure B, **4.20** was obtained in 52% yield. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (8.9 min), T_{minor} (10.1 min); 93:7 er (87% ee).

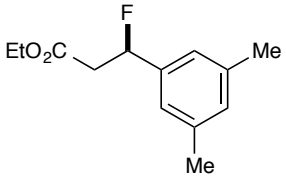


(*R*)-3-Fluoro-*N*-methoxy-*N*-methyl-3-(*p*-tolyl)propanamide. Following the general procedure B, **4.25** was obtained in 48% yield. HPLC (ChiralPak IC column) 70:30 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (10.5 min), T_{minor} (11.7 min); 90:10 er (80% ee).

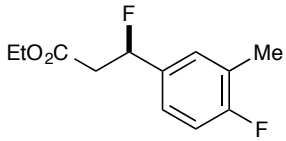
[247] **^{19}F NMR yield:** The crude reaction mixture was dissolved in $CDCl_3$ and 0.25 equivalents of fluorobenzene were added to obtain the NMR yield.



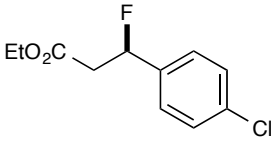
Ethyl (*R*)-3-fluoro-3-(*m*-tolyl)propanoate. Following the general procedure B, **4.29** was obtained in 54% yield as a colourless oil. HPLC (ChiralPak ODH column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (8.0 min), T_{minor} (9.0 min); 92:8 er (84% ee).



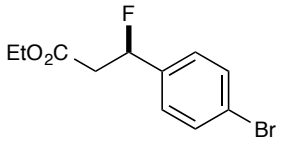
Ethyl (*R*)-3-(3,5-dimethylphenyl)-3-fluoropropanoate. Following the general procedure B, **4.38** was obtained in 47% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 6.0 Hz, 3H), 2.33 (s, 6H), 2.76 (ddd, *J* = 33.0, 18.0, 6.0 Hz, 1H), 3.01 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 4.20 (qd, *J* = 6.0, 3.0 Hz, 2H), 5.85 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 1H), 6.98 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 14.1, 21.3, 42.5 (d, *J* = 27.2 Hz), 60.9, 90.8 (d, *J* = 172.1 Hz), 123.4 (d, *J* = 6.0 Hz), 130.4 (d, *J* = 2.3 Hz), 138.3, 138.6 (d, *J* = 18.9 Hz), 169.8 (d, *J* = 5.3 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -173.0 (ddd, *J* = 47.9, 33.8, 14.1 Hz); HRMS (ES) calc. for (M^{+}+Na) $C_{13}H_{17}FNaO_2$: 247.1105; found: 247.1106. HPLC (ChiralPak IC column) 99:1 (Hexane/^{i}PrOH) 0.7 mL/min; T_{major} (16.5 min), T_{minor} (17.9 min); 95:5 er (90% ee).



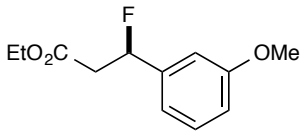
Ethyl (*R*)-3-fluoro-3-(4-fluoro-3-methylphenyl)propanoate. Following the general procedure B, **4.33** was obtained in 56% yield as a yellowish oil. HPLC (ChiralPak IC column) 99:1 (Hexane/^{i}PrOH) 0.7 mL/min; T_{major} (11.9 min), T_{minor} (13.0 min); 92:8 er (84% ee).



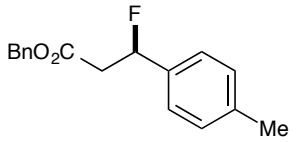
Ethyl (*R*)-3-(4-chlorophenyl)-3-fluoropropanoate. Following the general procedure B, **4.34** was obtained in 42% yield as a yellowish oil. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (7.2 min), T_{minor} (7.8 min); 92:8 er (84% ee).



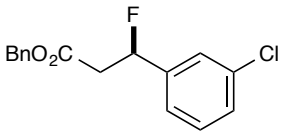
Ethyl (*R*)-3-(4-bromophenyl)-3-fluoropropanoate. Following the general procedure B, **4.35** was obtained in 49% yield as a yellowish oil. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (7.5 min), T_{minor} (8.1 min); 93:7 er (86% ee).



Ethyl (*R*)-3-fluoro-3-(3-methoxyphenyl)propanoate. Following the general procedure B, **4.32** was obtained in 50% yield as a colourless oil. HPLC (ChiralPak IC column) 99:1 (Hexane/^{i}PrOH) 0.7 mL/min; T_{major} (29.4 min), T_{minor} (27.9 min); 4:96 er (-92% ee).

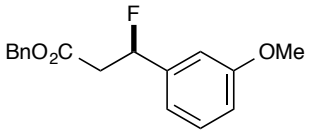


Benzyl (*R*)-3-fluoro-3-(*p*-tolyl)propanoate. Following the general procedure B, **4.39** was obtained in 43% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 2.84 (ddd, *J* = 30.0, 15.0, 3.0 Hz, 1H), 3.10 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 5.17 (s, 2H), 5.90 (ddd, *J* = 45.0, 9.0, 3.0 Hz, 1H), 7.18 (d, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.30-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 21.2, 42.4 (d, *J* = 27.6 Hz), 66.7, 90.5 (d, *J* = 171.7 Hz), 125.7 (d, *J* = 6.3 Hz), 128.2, 128.3, 128.6, 129.3, 135.5, 135.5 (d, *J* = 18.8 Hz), 138.8 (d, *J* = 2.5 Hz), 169.5 (d, *J* = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -171.4 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^{+}+NH_4^{+}) $C_{17}H_{21}FNO_2$: 290.1551; found: 290.1551. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (9.9 min), T_{minor} (11.0 min); 95:5 er (90% ee).

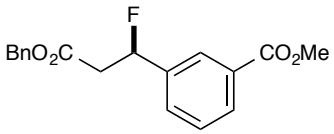


Benzyl (*R*)-3-(3-chlorophenyl)-3-fluoropropanoate. Following the general procedure B, **4.40** was obtained in 52% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.84 (ddd, *J* = 30.0, 15.0, 5.0 Hz, 1H), 3.07 (ddd, *J* = 15.0, 10.0, 5.0 Hz, 1H), 5.17 (s, 2H), 5.91 (ddd, *J* = 50.0, 10.0, 5.0 Hz, 1H), 7.21-7.23 (m, 1H), 7.29-7.39 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 42.3 (d, *J* = 27.6 Hz), 66.9, 89.7 (d, *J* = 172.9 Hz), 123.7 (d, *J* = 6.3 Hz), 125.8 (d, *J* = 7.5 Hz), 128.3, 128.4, 128.6, 129.0 (d, *J* =

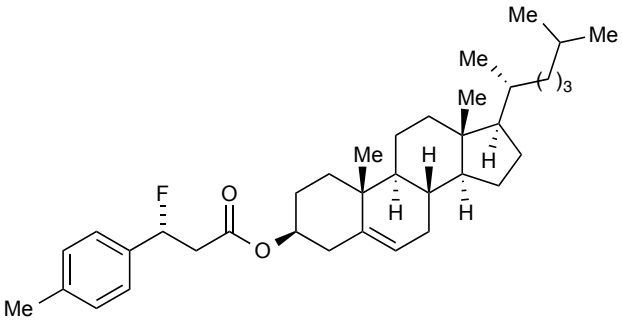
1.3 Hz), 130.0, 134.7, 135.4, 140.6 (d, J = 18.8 Hz), 169.1 (d, J = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -175.2 (ddd, J = 46.9, 32.8, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{16}H_{14}ClFNaO_2$: 315.0559; found: 315.0567. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (8.0 min), T_{minor} (8.5 min); 95:5 er (90% ee).



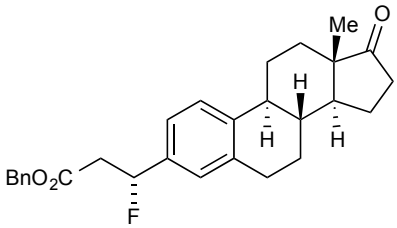
Benzyl (*R*)-3-fluoro-3-(3-methoxyphenyl)propanoate. Following the general procedure B, **4.41** was obtained in 73% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.85 (ddd, J = 35.0, 15.0, 5.0 Hz, 1H), 3.08 (ddd, J = 15.0, 10.0, 5.0 Hz, 1H), 3.81 (s, 3H), 5.18 (s, 2H), 5.92 (ddd, J = 50.0, 10.0, 5.0 Hz, 1H), 6.87-6.93 (m, 3H), 7.27-7.39 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 42.5 (d, J = 26.3 Hz), 55.3, 66.8, 90.4 (d, J = 172.9 Hz), 111.0 (d, J = 7.5 Hz), 114.4 (d, J = 2.5 Hz), 117.7 (d, J = 6.3 Hz), 128.2, 128.4, 128.6, 129.8, 135.5, 140.1 (d, J = 20.0 Hz), 159.8, 169.4 (d, J = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -174.0 (ddd, J = 46.9, 32.8, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{17}H_{17}FNaO_3$: 311.1054; found: 311.1055. HPLC (ChiralPak AD column) 99:1 (Hexane/^{i}PrOH) 0.5 mL/min; T_{major} (31.2 min), T_{minor} (33.0 min); 97:3 er (94% ee).



Methyl (*R*)-3-(3-(benzyloxy)-1-fluoro-3-oxopropyl)benzoate. Following the general procedure B, **4.42** was obtained in 41% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.88 (ddd, J = 30.0, 15.0, 5.0 Hz, 1H), 3.11 (ddd, J = 15.0, 10.0, 5.0 Hz, 1H), 3.93 (s, 3H), 5.17 (s, 2H), 5.98 (ddd, J = 45.0, 10.0, 5.0 Hz, 1H), 7.31-7.38 (m, 5H), 7.46 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 10.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 42.3 (d, J = 26.3 Hz), 52.3, 66.9, 90.0 (d, J = 172.9 Hz), 126.7 (d, J = 6.3 Hz), 128.3, 128.4, 128.6, 128.8, 130.0 (d, J = 1.3 Hz), 130.1 (d, J = 6.3 Hz), 130.7, 135.4, 139.0 (d, J = 20.0 Hz), 166.5, 169.1 (d, J = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -174.8 (ddd, J = 46.9, 32.8, 14.1 Hz); HRMS (ES) calc. for (M^++NH_4^+) $C_{18}H_{21}FNO_4$: 334.1449; found: 334.1455. HPLC (ChiralPak IC column) 98:2 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (35.2 min), T_{minor} (39.0 min); 93:7 er (86% ee).

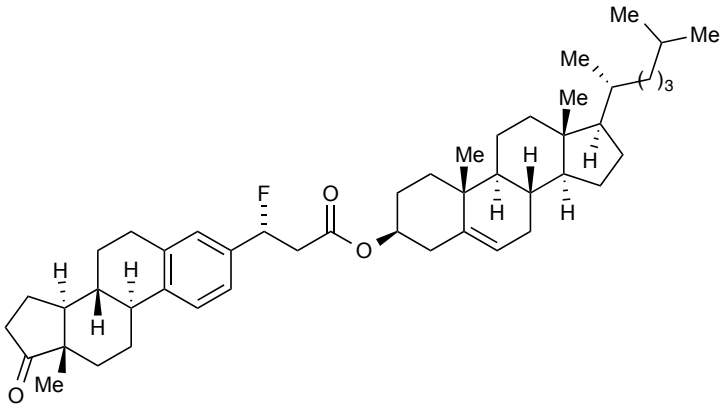


(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl (*R*)-3-fluoro-3-(*p*-tolyl)propanoate. Following the general procedure B, **4.43** was obtained in 55% yield and 20:1 dr (when using EtOAc as solvent) as a white solid (mp 103-105 ºC). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.68 (s, 3H), 0.87 (dd, *J* = 10.0, 5.0 Hz, 6H), 0.92 (d, *J* = 10.0 Hz, 3H), 0.94-1.20 (m, 11H), 1.02 (s, 3H), 1.22-1.42 (m, 5H), 1.43-1.64 (m, 5H), 1.80-1.88 (m, 3H), 1.95-2.03 (m, 2H), 2.29-2.39 (m, 2H), 2.36 (s, 3H), 2.76 (ddd, *J* = 30.0, 15.0, 5.0 Hz, 1H), 3.01 (ddd, *J* = 15.0, 10.0, 5.0 Hz, 1H), 4.63-4.70 (m, 1H), 5.38 (t, *J* = 5.0 Hz, 1H), 5.87 (ddd, *J* = 45.0, 10.0, 5.0 Hz, 1H), 7.19 (d, *J* = 10.0 Hz, 2H), 7.26 (d, *J* = 10.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 11.9, 18.7, 19.3, 21.0, 21.2, 22.6, 22.8, 23.8, 24.3, 27.7, 28.0, 28.2, 31.9, 31.9, 35.8, 36.2, 36.6, 36.9, 38.0, 39.5, 39.7, 42.3, 42.7 (d, *J* = 27.6 Hz), 50.0, 56.1, 56.7, 74.6, 90.7 (d, *J* = 170.4 Hz), 122.8, 125.7 (d, *J* = 6.3 Hz), 129.3, 135.7 (d, *J* = 20.0 Hz), 138.7 (d, *J* = 2.5 Hz), 139.5, 169.1 (d, *J* = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 468.9 MHz): δ -171.6, -171.6; HRMS (ES) calc. for (M^++NH_4^+) $C_{37}H_{59}FNO_2$: 568.4524; found: 568.4511.

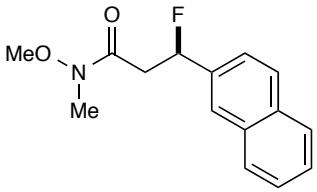


Benzyl (*R*)-3-fluoro-3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-deca-hydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)propanoate. Following the general procedure B, **4.44** was obtained in 70% NMR yield and 13:1 dr. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.91 (s, 3H), 1.41-1.68 (m, 6H), 1.96-2.19 (m, 4H), 2.28-2.32 (m, 1H), 2.41-2.45 (m, 1H), 2.51 (dd, *J* = 20.0, 10.0 Hz, 1H), 2.84 (ddd, *J* = 30.0, 15.0, 5.0 Hz, 1H), 2.91 (dd, *J* = 5.0, 5.0 Hz, 2H), 3.09 (ddd, *J* = 20.0, 15.0, 10.0 Hz, 1H), 5.17 (s, 2H), 5.88 (ddd, *J* = 45.0, 10.0, 5.0 Hz, 1H), 7.10 (s, 1H), 7.14 (d, *J* = 5.0 Hz, 1H), 7.34 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 13.8, 21.6, 25.7, 26.4, 29.4, 31.6, 35.8, 38.0, 42.3 (d, *J* = 26.3 Hz), 44.4, 47.9, 50.5, 66.7, 90.5 (d, *J* = 170.4 Hz), 123.1 (d, *J* = 6.3 Hz), 125.7 (d, *J* = 2.5 Hz), 126.4 (d, *J* = 8.8 Hz), 128.2, 128.3, 128.6, 135.5, 136.0 (d, *J* = 17.5 Hz), 136.9, 140.6, 169.5 (d, *J* =

5.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -171.4, -171.6; HRMS (ES) calc. for (M^++NH_4^+) $C_{28}H_{35}FNO_3$: 452.2595; found: 452.2595.



(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl (*R*)-3-fluoro-3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta-[*a*]phenanthren-3-yl)propanoate. Following the general procedure B, **4.45** was obtained in 76% NMR yield and 7:1 dr besides an inseparable impurity corresponding to the Heck byproduct. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.68 (s, 3H), 0.87 (dd, *J* = 6.0, 3.0 Hz, 6H), 0.91 (s, 6H), 1.02 (s, 3H), 0.96-2.56 (m, 41H), 2.77 (ddd, *J* = 33.0, 15.0, 6.0 Hz, 1H), 2.93 (dd, *J* = 6.0, 3.0 Hz, 2H), 3.01 (ddd, *J* = 15.0, 12.0, 9.0 Hz, 1H), 4.61-4.74 (m, 1H), 5.39 (dd, *J* = 12.0, 6.0 Hz, 1H), 5.85 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 1H), 7.11 (s, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 3.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 74.6, 90.6 (d, *J* = 164.1 Hz), 169.1 (d, *J* = 5.0 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -171.8, -172.1; HRMS (ES) calc. for (M^++NH_4^+) $C_{48}H_{73}FNO_3$: 730.5569; found: 730.5548.



(*R*)-3-Fluoro-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)propanamide. Following the general procedure B, **4.46** was obtained in 41% yield as a white solid (mp 68-70 ºC). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.88 (ddd, *J* = 30.0, 15.0, 3.0 Hz, 1H), 3.22 (s, 3H), 3.32-3.46 (m, 1H), 3.68 (s, 3H), 6.20 (ddd, *J* = 45.0, 9.0, 3.0 Hz, 1H), 7.46-7.54 (m, 3H), 7.82-7.89 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 32.1, 39.9 (d, *J* = 25.7 Hz), 61.4, 90.9 (d, *J* = 171.4 Hz), 123.1 (d, *J* = 5.3 Hz), 124.9 (d, *J* = 8.3 Hz), 126.4, 126.4, 127.7, 128.1, 128.5, 133.0, 133.3 (d, *J* = 0.8 Hz), 136.8 (d, *J* = 19.6 Hz), 170.1; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -174.3 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^+-F) $C_{15}H_{16}NO_2$: 242.1176; found: 242.1165. HPLC (ChiralPak IC column) 75:25 (Hexane/^{i}PrOH) 1.0

mL/min; T_{major} (12.6 min), T_{minor} (13.7 min); 92:8 er (86% ee). Absolute configuration was determined to be (*R*) by single-crystal X-ray diffraction (*Figure 4.2*).

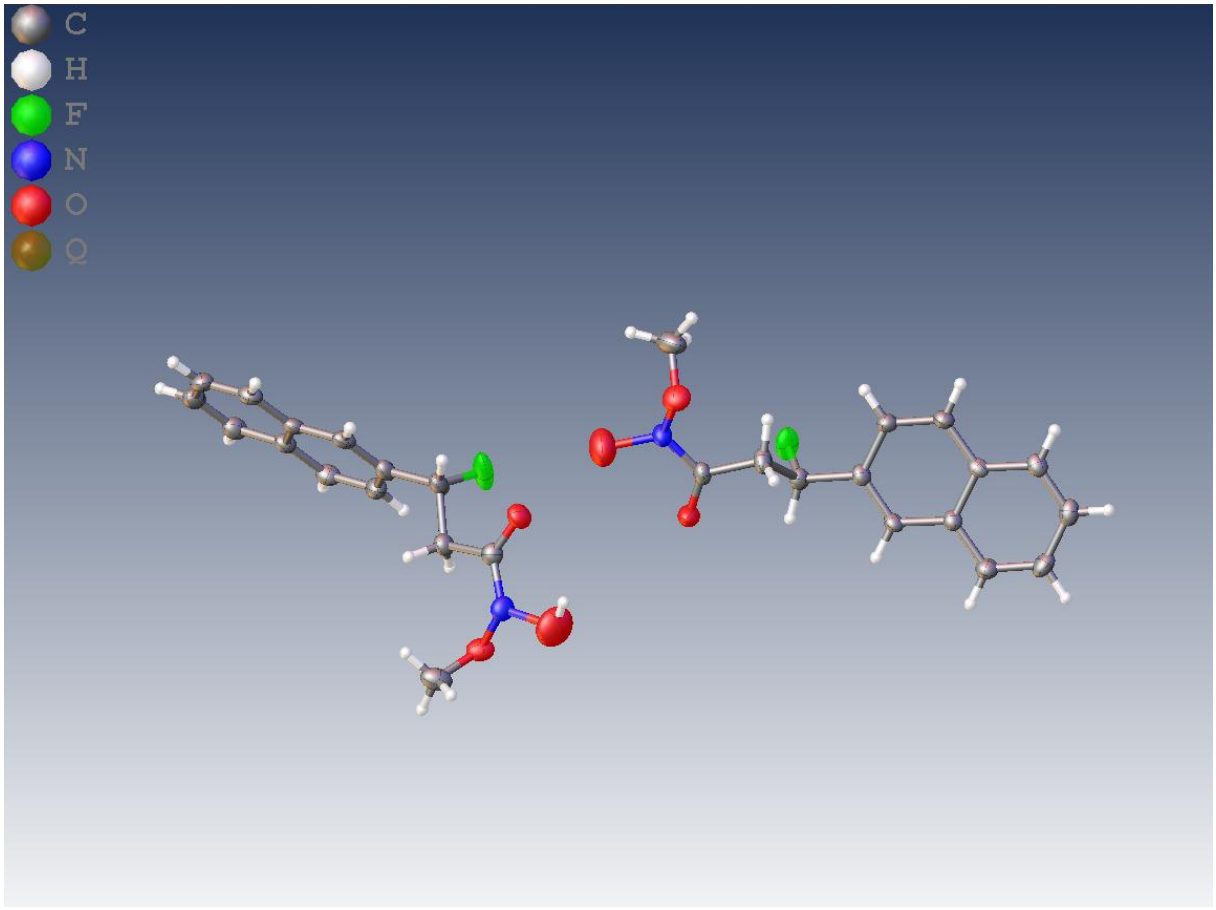
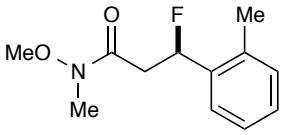
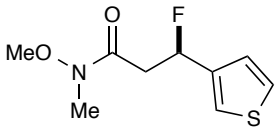


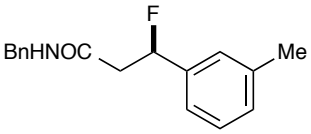
Figure 4.2. X-Ray ORTEP of compound (*R*)-**4.46**.



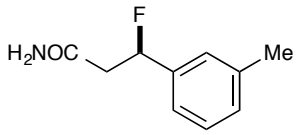
(*R*)-3-Fluoro-*N*-methoxy-*N*-methyl-3-(*o*-tolyl)propanamide. Following the general procedure B, **4.47** was obtained in 32% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.38 (s, 3H), 2.72 (ddd, *J* = 36.0, 18.0, 3.0 Hz, 1H), 3.21-3.35 (m, 1H), 3.23 (s, 3H), 3.70 (s, 3H), 6.25 (ddd, *J* = 48.0, 9.0, 3.0 Hz, 1H), 7.16-7.21 (m, 1H), 7.22-7.29 (m, 2H), 7.42-7.48 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 18.9, 32.1, 38.8 (d, *J* = 26.4 Hz), 61.4, 88.2 (d, *J* = 170.6 Hz), 125.2 (d, *J* = 8.3 Hz), 126.2, 128.4 (d, *J* = 2.3 Hz), 130.6, 134.6 (d, *J* = 4.5 Hz), 137.5 (d, *J* = 18.1 Hz), 170.2; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -176.5 (ddd, *J* = 47.9, 33.8, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_{12}H_{16}FNNaO_2$: 248.1057; found: 248.1052. HPLC (ChiralPak ODH column) 70:30 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (5.4 min), T_{minor} (5.9 min); 84:16 er (68% ee).



(*R*)-3-Fluoro-*N*-methoxy-*N*-methyl-3-(thiophen-3-yl)propanamide. Following the general procedure B, **4.48** was obtained in 37% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.84 (ddd, *J* = 30.0, 15.0, 5.0 Hz, 1H), 3.22 (s, 3H), 3.29-3.36 (m, 1H), 3.69 (s, 3H), 6.10 (ddd, *J* = 45.0, 10.0, 5.0 Hz, 1H), 7.12-7.14 (m, 1H), 7.33-7.35 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 32.1, 39.0 (d, *J* = 27.2 Hz), 61.4, 87.1 (d, *J* = 168.4 Hz), 122.5 (d, *J* = 8.3 Hz), 125.3 (d, *J* = 3.4 Hz), 126.5, 140.5 (d, *J* = 21.9 Hz), 170.0; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -168.9 (ddd, *J* = 45.1, 31.0, 14.1 Hz); HRMS (ES) calc. for (M^++Na) $C_9H_{12}FNNaO_2$: 240.0465; found: 240.0458. HPLC (ChiralPak IC column) 70:30 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (10.8 min), T_{minor} (11.6 min); 88:12 er (76% ee).



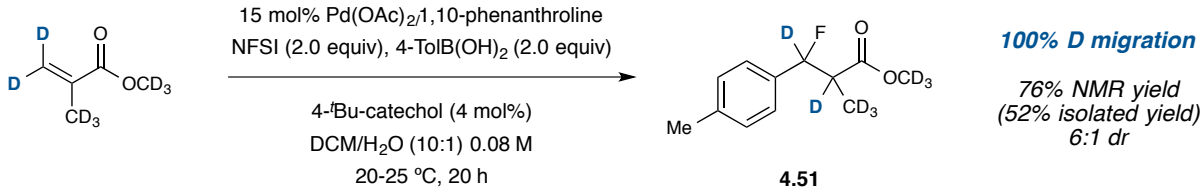
(*R*)-*N*-benzyl-3-fluoro-3-(*m*-tolyl)propanamide. Following the general procedure B, **4.49** was obtained in 72% yield as a white solid (mp 84-86 ºC). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.36 (s, 3H), 2.72 (ddd, *J* = 30.0, 15.0, 5.0 Hz, 1H), 2.88 (dt, *J* = 15.0, 10.0 Hz, 1H), 4.47 (t, *J* = 5.0 Hz, 2H), 5.93 (ddd, *J* = 50.0, 10.0, 5.0 Hz, 1H), 5.96 (br s, NH), 7.14-7.17 (m, 3H), 7.21-7.23 (m, 2H), 7.25-7.34 (m, 4H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 21.4, 43.7, 44.9 (d, *J* = 25.1 Hz), 91.5 (d, *J* = 170.4 Hz), 122.4, 122.5, 126.0, 126.1, 127.5, 127.7, 128.6, 128.7, 129.5, 129.5, 137.8, 138.4, 138.8 (d, *J* = 25.1 Hz), 168.7 (d, *J* = 3.8 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -173.9 (ddd, *J* = 47.9, 33.8, 16.9 Hz); HRMS (ES) calc. for (M^++H) $C_{17}H_{20}FNO$: 272.1445; found: 272.1446. HPLC (Lux® 5 mm Amylose-1 column) 90:10 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (14.7 min), T_{minor} (12.9 min); 90:10 er (80% ee).



(*R*)-3-Fluoro-3-(*m*-tolyl)propanamide. Following the general procedure B, **4.50** was obtained in 51% yield as a colourless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 2.70 (ddd, *J* = 35.0, 15.0, 5.0 Hz, 1H), 2.91 (dt, *J* = 15.0, 10.0 Hz, 1H), 5.56 (br s, NH), 5.70 (br s, NH), 5.89 (ddd, *J* = 50.0, 10.0, 5.0 Hz, 1H), 7.12-7.18 (m, 3H), 7.22-7.30 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125.3 MHz): δ 21.4, 44.1 (d, *J* = 25.1 Hz), 91.2 (d, *J* = 170.4 Hz), 122.4 (d, *J* = 6.3 Hz), 126.0 (d, *J* = 6.3 Hz), 128.6, 129.6 (d, *J* = 2.5 Hz), 138.5, 138.6 (d, *J* = 20.0 Hz), 171.1 (d, *J* = 2.5 Hz); ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -174.1 (ddd, *J* = 47.9, 33.8, 16.9 Hz); HRMS (ES) calc. for (M^++H) $C_{10}H_{13}FNO$: 182.0964; found: 182.0965.

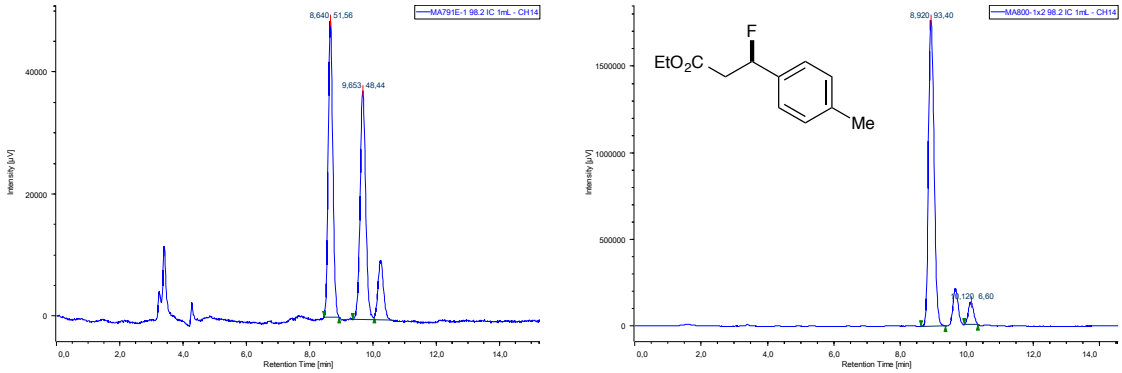
HPLC (ChiralPak ODH column) 95:5 (Hexane/^{i}PrOH) 1.0 mL/min; T_{major} (35.7 min), T_{minor} (40.9 min); 90:10 er (80% ee).

4.5.5. Deuterium labeling experiments.

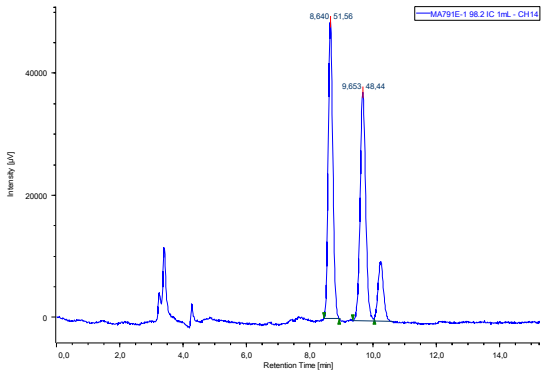


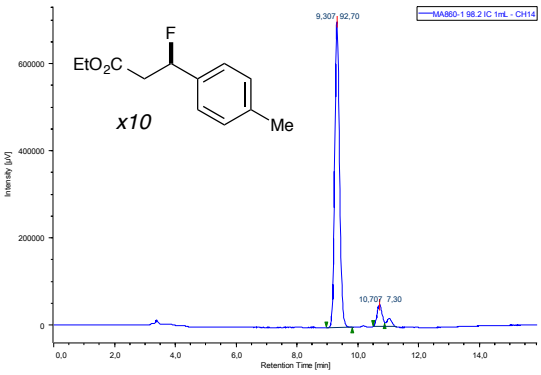
The reaction was carried out following the general procedure A described above over commercially available d^8-labeled methyl methacrylate. 100% deuterium migration from β to α-position bears out proposed 1,1-difunctionalization mechanism, i.e. β-deuteride elimination and subsequent Pd-deuteride reinsertion. Final β-fluoride carbonyl-derived systems would be rendered by oxidation and reductive elimination of the Pd(IV) intermediate **D** (*Scheme 4.10*). Compound **4.51** was isolated as a yellowish oil in 52% yield. Diastereomeric ratio (6:1) was determined by ^{19}F NMR over the crude reaction mixture. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.32-2.39 (m, 3H), 6.90-7.30 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 20.8, 21.2, 121.2, 126.7 (d, J = 6.0 Hz), 128.4, 129.2, 129.9, 133.9 (d, J = 19.6 Hz), 135.8 (d, J = 48.3 Hz), 139.0 (d, J = 3.0 Hz), 169.7, 174.3; ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -167.5 (t, J = 7.1 Hz), -168.9 (br s); HRMS (ES) calc. for (M^+-F) $C_{12}H_7D_8O_2$: 199.1569; found: 199.1565.

4.5.6. HPLC data.

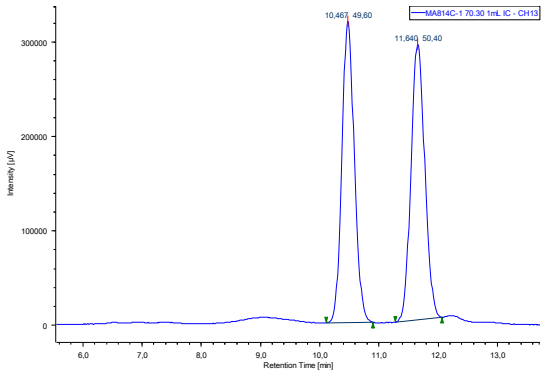


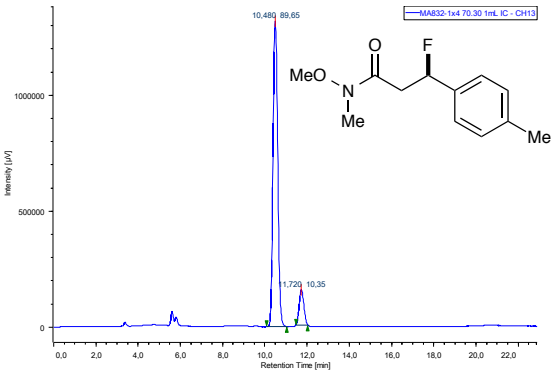
retention time	area
8.9 min	93.4%
10.1 min	6.6%





retention time	area
8.3 min	92.7%
10.7 min	7.3%





retention time	area
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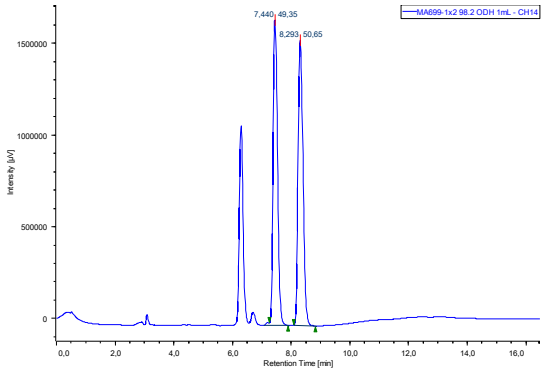
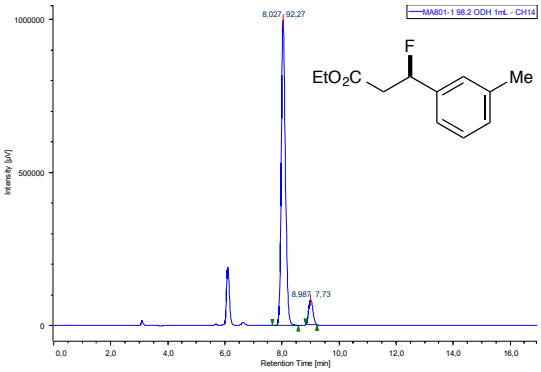
11.7 min	10.3%





retention time	area
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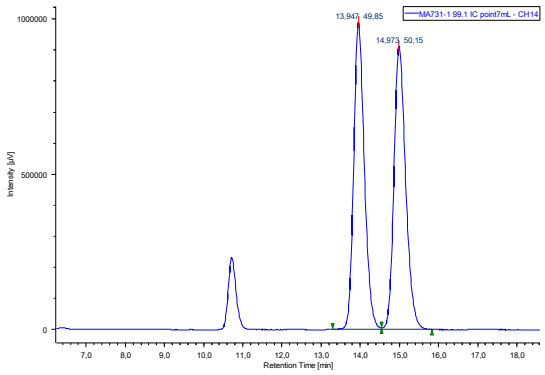
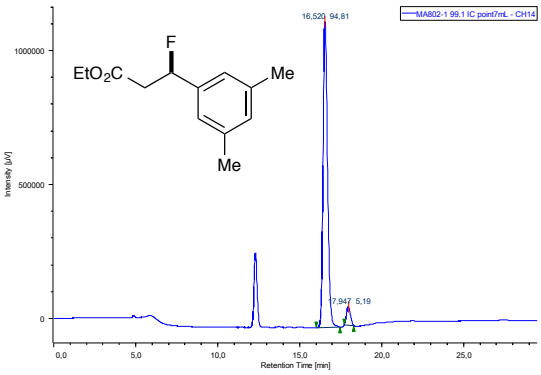
9.0 min	7.7%





retention time	area
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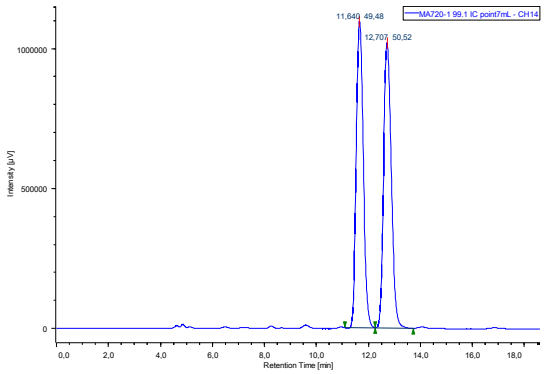

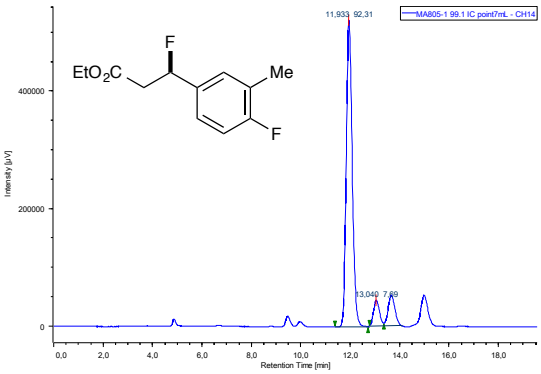

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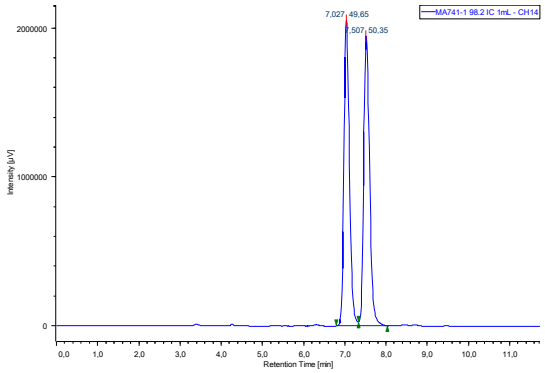
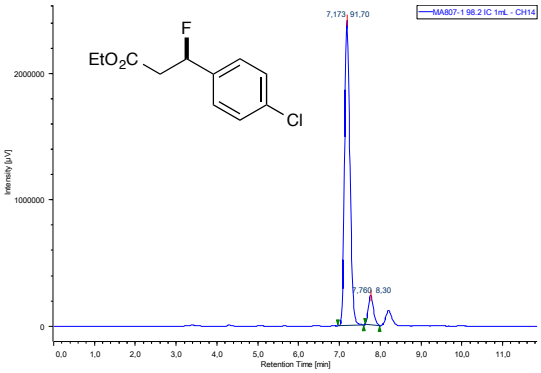
13.0 min	7.7%





retention time	area
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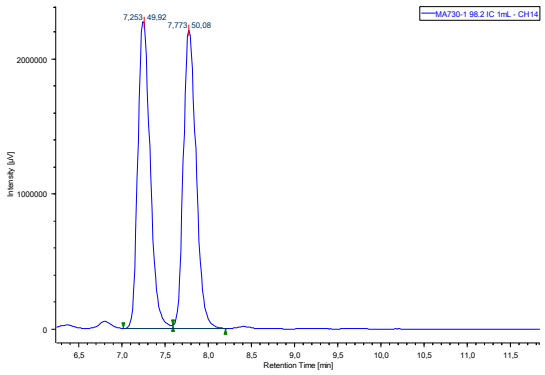
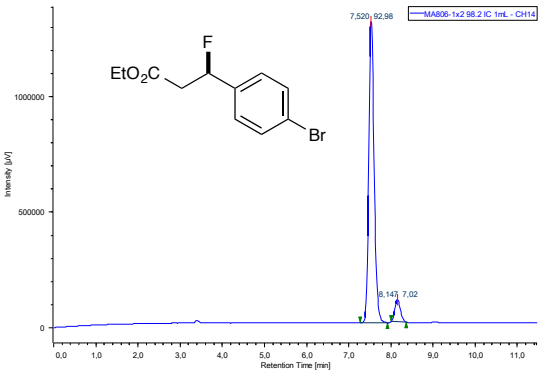
7.8 min	7.7%





retention time	area
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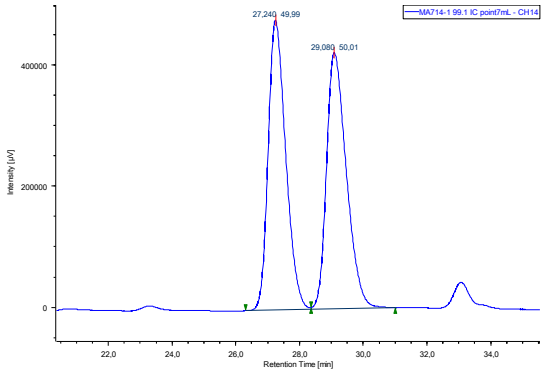
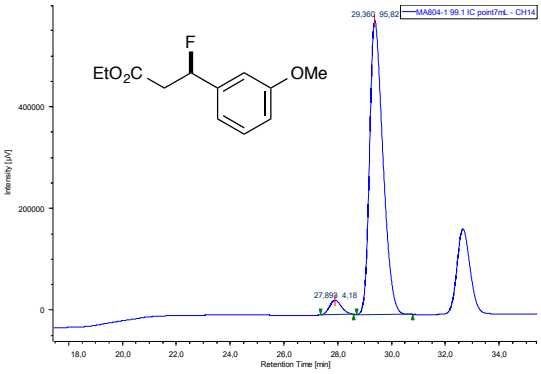
8.1 min	7.0%





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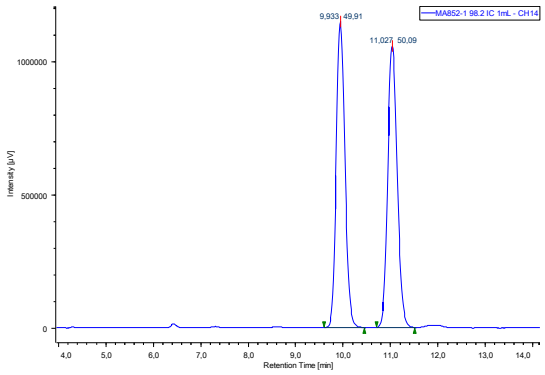
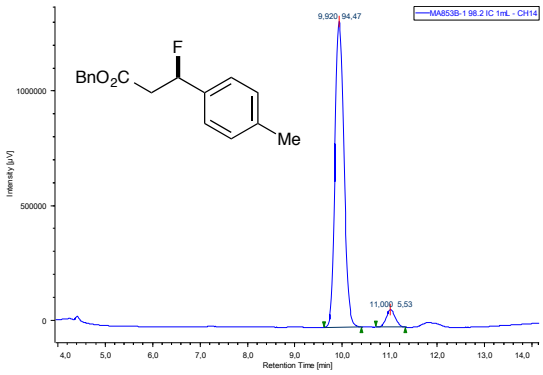
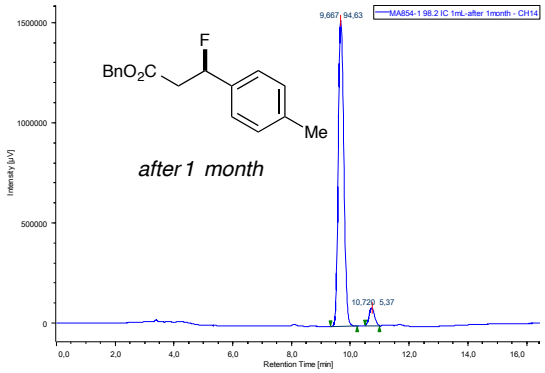
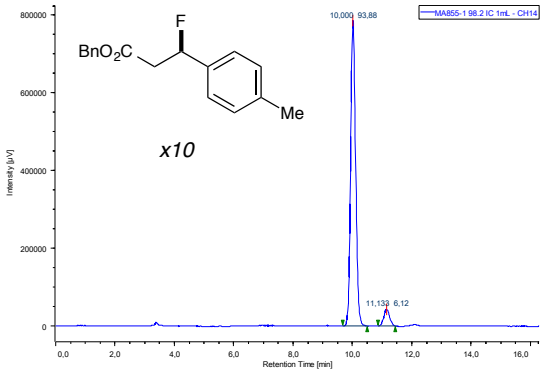
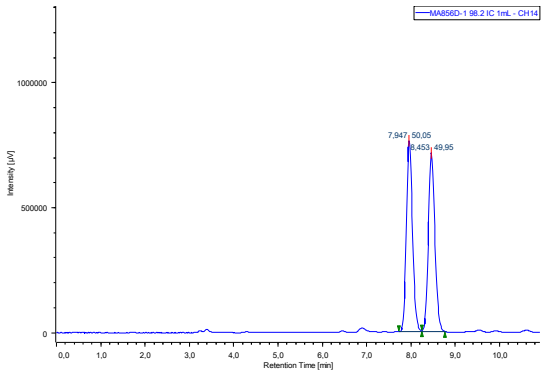


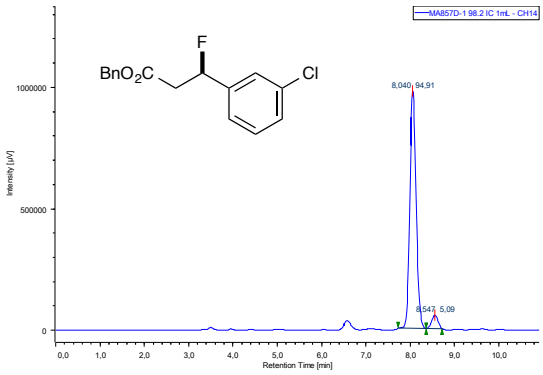






retention time	area
9.9 min	94.5%
11.0 min	5.5%





retention time	area
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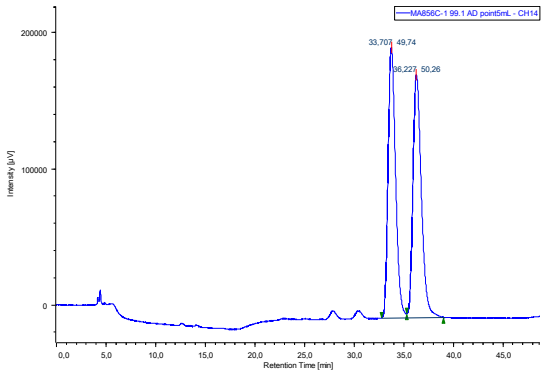
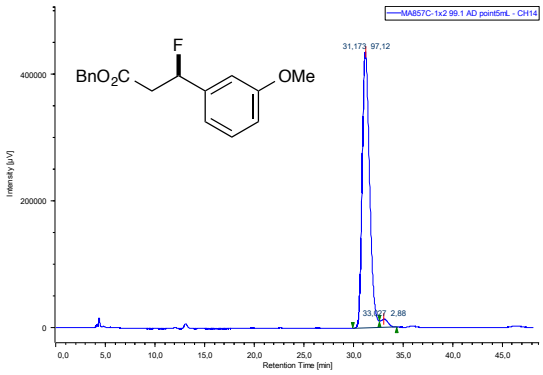
8.5 min	5.1%





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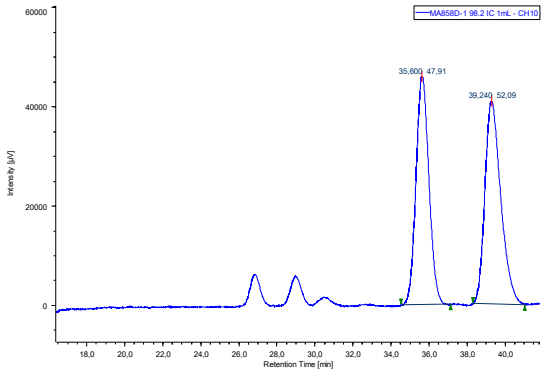

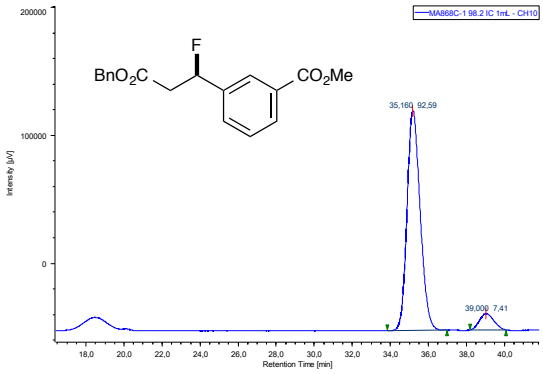

retention time	area
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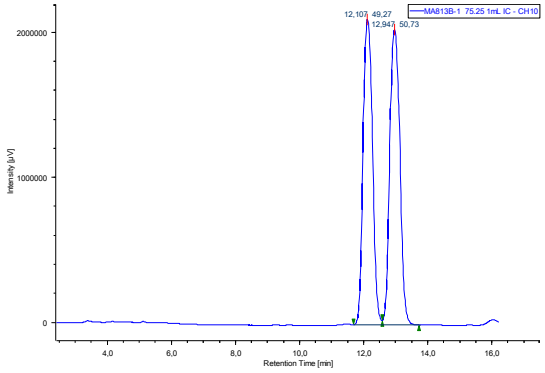
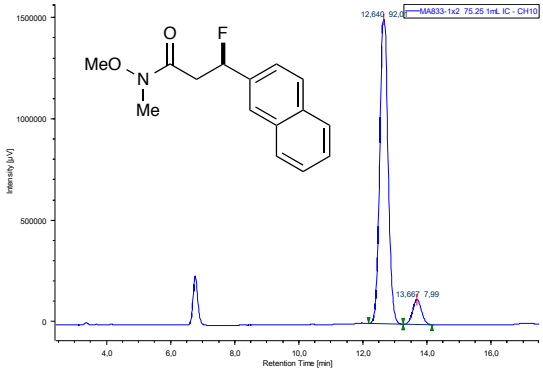
39.0 min	7.4%





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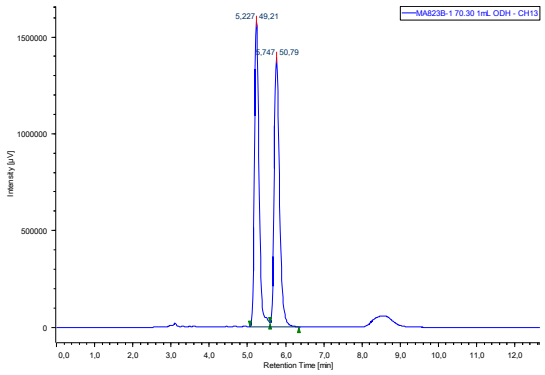
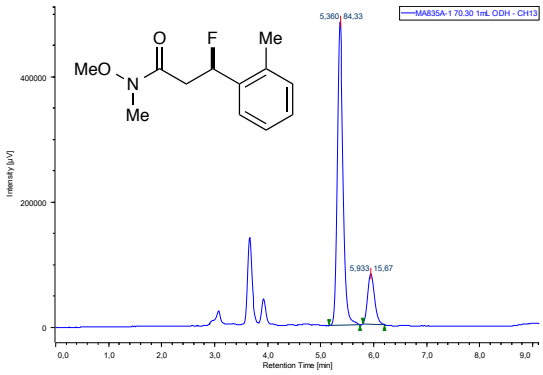
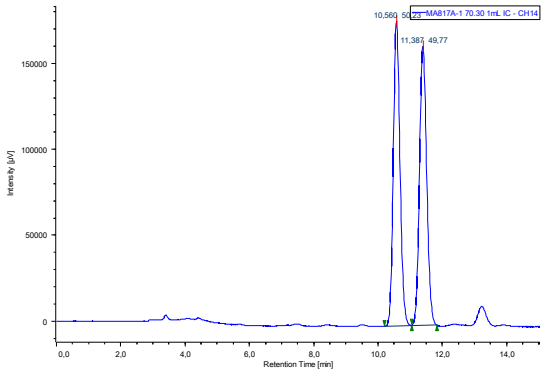
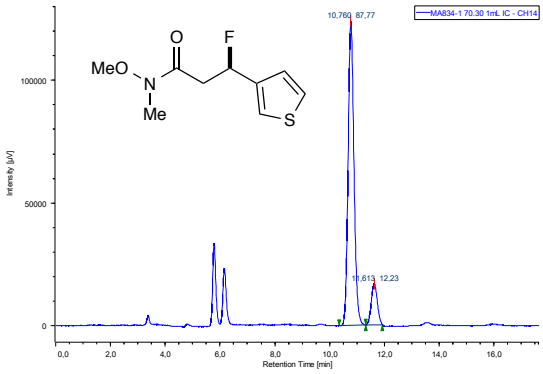
12.6 min	92.0%
13.7 min	8.0%





retention time	area
5.4 min	84.3%
5.9 min	15.7%





retention time	area
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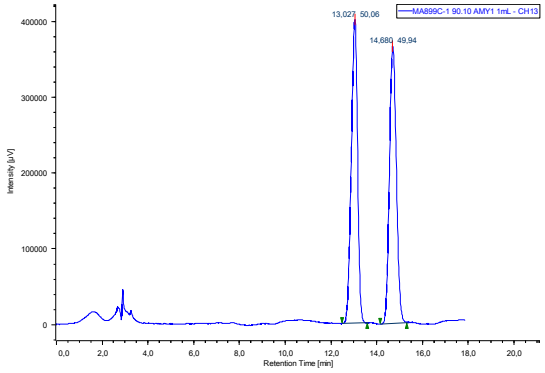
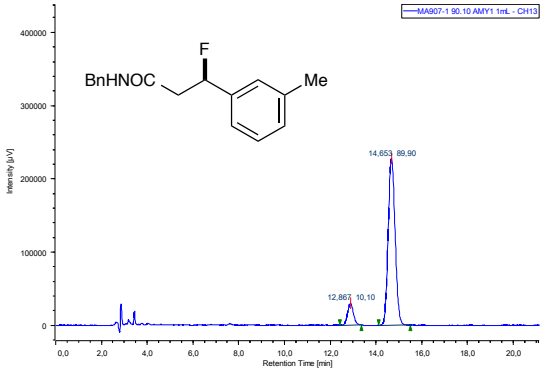
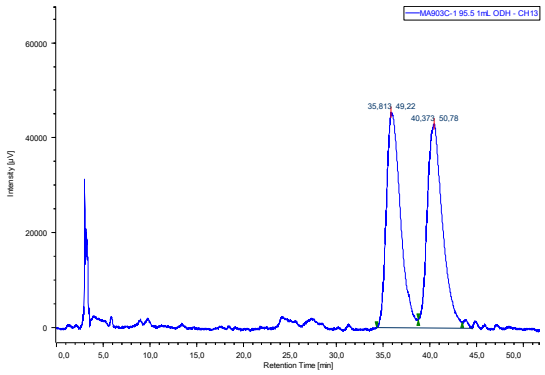
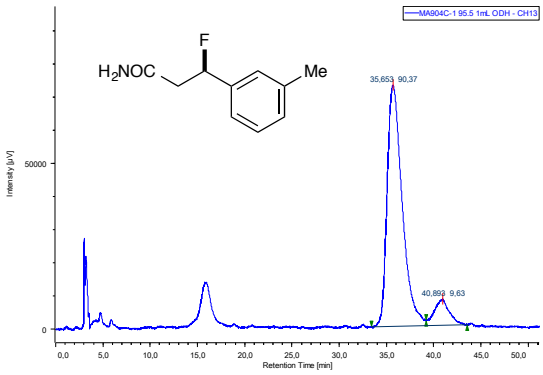




retention time	area
12.9 min	10.1%
14.7 min	89.9%





retention time	area
35.7 min	90.4%
40.9 min	9.6%

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(196) For further details see *Experimental Section 3.5.2.*

(197) Combination of solvents (e.g. Et_2O/THF) provided better yields, but at the expense of er. On the other hand, addition of increasing amounts of water resulted in loss of enantioinduction.

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