Graphical Abstract

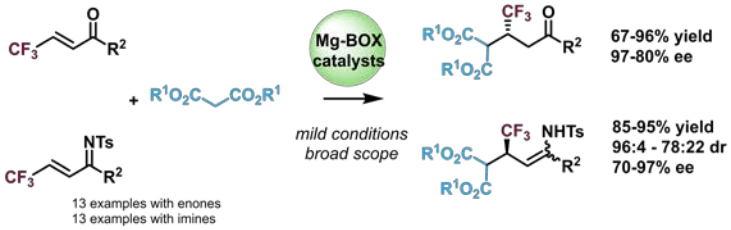
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Mg/BOX Complexes as Efficient Catalysts for the Enantioselective Michael Addition of Malonic Esters to β-Trifluoromethyl-α,β-Unsaturated Ketones and their N-Tosyl Imines

Leave this area blank for abstract info.

Miguel Espinosa, Antonio Iborra-Torres, Amparo Sanz-Marco, Gonzalo Blay,* Luz Cardona, Isabel Fernández and José. R. Pedro,*

Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, 46100-Burjassot, Spain.



Tetrahedron
journal homepage: www.elsevier.com

Mg/BOX Complexes as Efficient Catalysts for the Enantioselective Michael Addition of Malonic Esters to β-Trifluoromethyl-α,β-Unsaturated Ketones and their N-Tosyl Imines

Miguel Espinosa[a], Antonio Iborra-Torres[a], Amparo Sanz-Marco[a], Gonzalo Blay[a,*], Luz Cardona[a], Isabel Fernández[a] and José. R. Pedro[a,*]

[a] *Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, 46100-Burjassot, Spain. Fax: +(34)963544328; Tel:+(34)962544336; E-mail: jose.r.pedro@uv.es; gonzalo.blay@uv.es.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Enantioselective Michael Addition
Mg/BOX catalyst
Malonic Esters
β-Trifluoromethyl-α,β-Unsaturated Ketones
N-Tosyl Imines

ABSTRACT

Magnesium(II)-BOX complexes catalyze the enantioselective Michael addition of malonic esters to β-trifluoromethyl enones and their N-sulfonyl imines to give ketones or (*E*)-enamines bearing a trifluoromethylated stereogenic center, respectively, with good yields and high enantiomeric excesses. Magnesium complexes proved to be more active and stereoselective than zinc and copper analogues in these reactions.

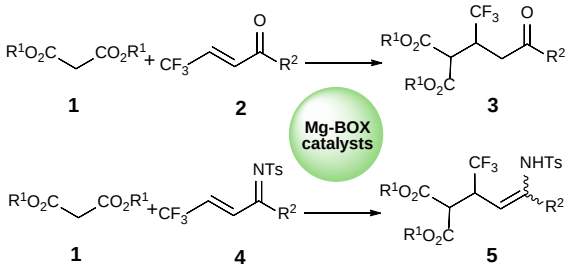
1. Introduction

Molecules containing the trifluoromethyl group have gained great importance in the fields of medicinal, agricultural and material chemistry, due to the significant changes that the introduction of fluorine atoms causes in the physicochemical features and biological properties of these molecules [1]. The trifluoromethyl group attached to a stereogenic centers is a structural motif present in a number of pharmaceutilcals and drug candidates [2], and chiral reagents [3]. Consequently, increasing efforts have been dedicated to the development of asymmetric methodologies for the generation of stereogenic centers attached to a trifluoromethyl group, among which, those involving the nucleophilic addition to prochiral trifluoromethylated carbons are particularly useful [4]. Besides the addition of nucleophiles to trifluoromethyl ketones [5] or trifluoromethyl imines [6] to give trifluoromethyl alcohols or imines, respectively, the conjugate addition to β-trilfuoromethyl alkenes conjugated with electron-withdrawing groups such as β-trifluoromethyl-α,β-unsaturated carbonyl compounds [7] or β-trifluoromethyl nitroalkenes [8] permits the generation of trifluoromethylated stereogenic centers not attached to heteroatoms.

Malonic esters have been frequently used as nucleophiles in enantioselective Michael additions as a way to prepare chiral acids bearing a stereogenic center at the β-position [9]. However, examples of enantioselective conjugate addition of malonate esters to β-trifluoromethyl-α,β-unsaturated carbonyl compound, which generate a trifluoromethylated stereocenter, are very scarce. Thus, Zhao reported in 2016 the addition of dimethyl malonate to 4,4,4-trifluoro-1-phenylbut-2-en-1-one (single example) using a dipeptide-derived multifunctional phosphonium salt catalyst [10]. Moreover, Liu and Zhang described in 2017 the enantioselective addition of 2-substituted malonic esters to a variety of β-trifluoromethyl enones catalyzed by a chiral biamide−phosphine multifunctional catalyst in the presence of competing methyl acrylate and an inorganic base [11]. Furthermore, our group has developed recently a procedure for the diastereo- and enantioselective conjugate addition of malonate esters to imines derived from β-trifluoromethyl enonas [12].

On the other hand, metal-bis(oxazoline) (BOX) complexes are privileged catalysts in asymmetric synthesis which have catalyzed a large number of reactions with high levels of stereoselectivity [13]. Although much less explored than other metal-BOX complexes, Mg-BOX complexes have found some successful applications in asymmetric catalysis, such as in Strecker and Mannich reactions [14], Diels-Alder [15], 1,3-dipolar cycloadditions [16], addition of isothiocyanate esters to aldehydes or imines [17], and the nitro-Michael reaction [18].

In this paper we describe a new application of Mg-BOX complexes as catalysts in the scarcely explored enantioselective addition of malonic esters to β-trifluoromethyl enones and their *N*-tosyl imines (Scheme 1).

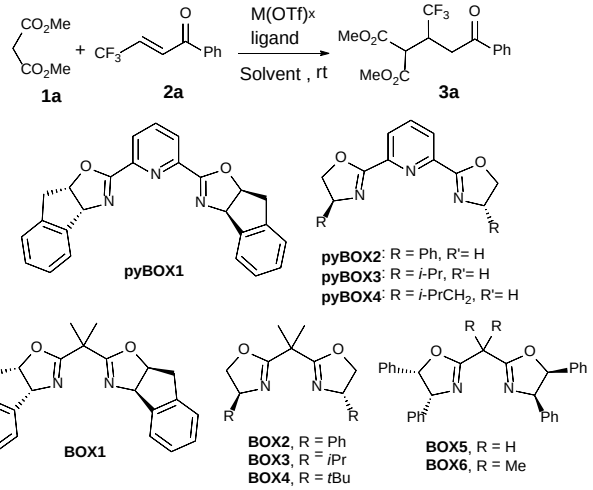


Scheme 1. Addition of malonate esters to β-trifluoromethyl enones **2** and their *N*-Tosyl imines derivate **4**.

2. Results and discussion

2.1. Michael addition to β-trifluoromethyl enones

Table 1. Enantioselective conjugate addition of dimethyl malonate (**1a**) to enone **2a**. Screening of catalysts and solvents.[a]

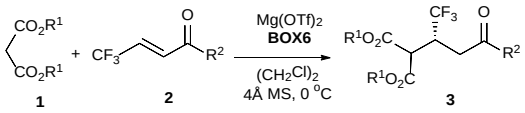


Entry	$M(OTf)_x$	Ligand	Solvent	t (h)	Yield (%)[b]	ee (%)[c]
1	$La(OTf)_3$	**PyBOX1**	CH_2Cl_2	24	92	rac
2	$La(OTf)_3$	**PyBOX2**	CH_2Cl_2	18	89	24
3	$La(OTf)_3$	**PyBOX3**	CH_2Cl_2	26	41	-47
4	$La(OTf)_3$	**PyBOX4**	CH_2Cl_2	18	95	rac
5	$Cu(OTf)_2$	**BOX1**	CH_2Cl_2	41	22	rac
6	$Zn(OTf)_2$	**BOX1**	CH_2Cl_2	41	18	rac
7	$Mg(OTf)_2$	**BOX1**	CH_2Cl_2	24	99	79
8	$Mg(OTf)_2$	**BOX2**	CH_2Cl_2	17	99	-75
9	$Mg(OTf)_2$	**BOX3**	CH_2Cl_2	18	99	-80
10	$Mg(OTf)_2$	**BOX4**	CH_2Cl_2	17	35	rac
11	$Mg(OTf)_2$	**BOX5**	CH_2Cl_2	17	99	75
12	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	36	91	89
13	$Mg(OTf)_2$	**BOX6**	$(CH_2Cl)_2$	18	99	90
14	$Mg(OTf)_2$	**BOX6**	$CHCl_3$	89	61	31
15	$Mg(OTf)_2$	**BOX6**	toluene	42	76	87
16	$Mg(OTf)_2$	**BOX6**	THF	41	48	Rac
17	$Mg(OTf)_2$	**BOX6**	EtOAc	89	62	17
18	$Mg(OTf)_2$	**BOX6**	CH_3CN	41	64	74
19[d]	$Mg(OTf)_2$	**BOX6**	$(CH_2Cl)_2$	44	85	93

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.25 mmol), ligand (0.025 mmol), M(OTf)x (0.025 mmol), solvent (2.1 mL). [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Reaction carried out at 0 ºC in the presence of 4 Å MS.

Following our previously work [19], in the onset of our research we tested several complexes of $La(OTf)_3$ and pyridine-bis-oxazoline (pyBOX) ligands in the reaction between dimethyl malonate **1** and the β-trifluoromethyl α,β-unsaturated ketone **2a** (Table 1, entries 1-4). In the view of these results, we decided to perform the reaction using complexes of divalent metal salts and bis-oxazoline (BOX) ligands as catalysts (Table 1, entries 5-12). The complexes of $Cu(OTf)_2$ and $Zn(OTf)_2$ with **BOX1** showed poor activity and provided racemic product **3a** with low yield in both cases (Table 1, entries 5 and 6). Gratifyingly, the $Mg(OTf)_2$ complex with **BOX1** lead to a quantitative yield of **3a** with 79% ee (Table 1, entry 7). Further research was performed by testing several catalytic complexes of magnesium triflate and different BOX ligands. High yields were obtained in almost all the cases. The best enantiomeric excess was obtained with the **BOX6** ligand obtaining the corresponding addition product in 91% yield and 89% ee (Table 1, entry 12). The influence of the reaction solvent was also studied with the $Mg(OTf)_2$-**BOX6** complex. The best result was obtained using dichloroethane, the Michael adduct **3a** obtained in quantitative yield and 90% enantiomeric excess (Table 1, entry 13). Other solvents provided worse results compared with dichloroethane. A first attempt to improve the enantiomeric excess by reducing the temperature to 0 ºC led to a very slow reaction. Fortunately, the reaction could be speeded up by adding 4 Å MS. In this way **3a** could be obtained in 85% yield and 93% ee (Table 1, entry 19). Under these conditions we studied the addition of dimethyl malonate 1 to several β-trifluoromethyl enones **2** (Table 2).

Table 2. Enantioselective conjugate addition of malonates **1** to enones **2**. Substrate scope.[a]



Entry	**2**	R^1	R^2	t (h)	**3**	Yield (%)[b]	ee (%)[c]
1	**2a**	Me	Ph	44	**3a**	85	93
2	**2b**	Me	4-MeC_6H_4	48	**3b**	90	90
3	**2c**	Me	4-ClC_6H_4	46	**3c**	96	96
4	**2d**	Me	4-BrC_6H_4	48	**3d**	73	97
5	**2e**	Me	4-$NO_2C_6H_4$	46	**3e**	96	96
6	**2f**	Me	4-$MeOC_6H_4$	48	**3f**	66	86
7	**2g**	Me	3-MeC_6H_4	46	**3g**	90	90
8	**2h**	Me	3-ClC_6H_4	54	**3h**	71	90
9	**2i**	Me	3-$NO_2C_6H_4$	46	**3i**	69	94
10	**2j**	Me	3-$MeOC_6H_4$	46	**3j**	68	80
11	**2k**	Me	2-$MeOC_6H_4$	48	**3k**	87	87
12	**2l**	Me	2- naphthyl	48	**3l**	96	85
13[d]	**2a**	Et	Ph	72	**3m**	67	85

[a] Reaction conditions: **1** (0.6 mmol), **2** (0. 25 mmol), **BOX6** (0.025 mmol), $Mg(OTf)_2$ (0.025 mmol), 4 Å MS (220 mg), $(CH_2Cl)_2$ (2.1 mL). [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Reaction carried out at room temperature.

The reaction could be carried out with different trifluoromethyl enones **2** bearing an aromatic ring attached to the carbonyl group. Both, electron-donating or electron-withdrawing substituents on this aromatic ring were allowed where excellent enantioselectivities were obtained in most of the cases. In general, for a same substituent the enantioselectivity decreased from *para* to *meta* and *ortho* substitution (entries 2 *vs* 7, entries 3 *vs* 8, entries 5 *vs* 9 and entries 6 *vs* 10 and 11). Also, the presence of electron-withdrawing groups gave better results than electron-donating groups (entry 5 *vs* 6 and entry 9 *vs* 10). A bulky naphthyl substituent in the carbonyl group led to a small decrease in the enantioselectivity of the reaction (entry 12). Substitution of the methoxy group in the malonate by a bulkier ethoxy group caused a noticeable decrease of reactivity and the reaction needed to be

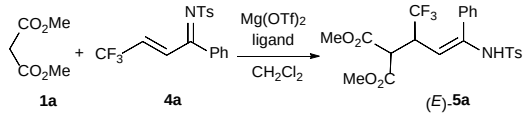
performed at room temperature to give the addition product in moderate yield and high enantiomeric excess (entry 13, 85% ee).

This procedure could also be performed in a 1.25 mmol scale (250 mg) providing the Michael addition adduct **3a** in 99% yield but with a slight erosion in the optical purity (86% ee).

2.2. Michael addition to β-trifluoromethyl α,β-unsaturated N-tosyl imines

Previously, we have described the addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines catalyzed by copper [12]. In the view of the results obtained with the Mg-BOX catalyst in the Michael addition with β-trifluoromethyl enones, we decided to study the application of the Mg-BOX system in the Michael addition with the corresponding *N*-tosyl imines. The performance of different complexes of BOX ligands and $Mg(OTf)_2$ was explored (Table 3).

Table 3. Enantioselective conjugate addition of dimethyl malonate (**1a**) to α,β-unsaturated imine **4a**. Screening of catalysts and solvents.[a]



1a **4a** (*E*)-**5a**

Entry	Ligand	T (°C)	t (h)	Yield (%)[b]	dr (*E*/*Z*)[c]	ee (%)[d]
1	**BOX1**	rt	20	99	92/8	86
2	**BOX2**	rt	20	82	92/8	-51
3	**BOX3**	rt	15	99	88/12	-74
4	**BOX4**	rt	46	40	65/35	0
5	**BOX5**	rt	5	99	91/9	68
6	**BOX6**	rt	50	63	91/9	59
7[e]	**BOX1**	0	40	99	96/4	89
8[f]	**BOX1**	0	16	98	96/4	89
9[g]	**BOX1**	0	4d	56	89/11	91
10[e]	**BOX1**	-10	41	93	96/4	91

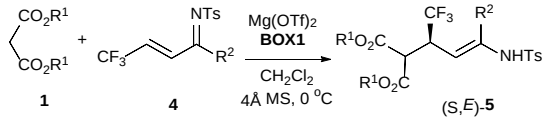
[a] Reaction conditions: **1a** (0.3 mmol), **4a** (0.125 mmol), **BOX** (0.0125 mmol), $Mg(OTf)_2$ (0.0125 mmol), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] ee for the major *E* diastereomer, determined by HPLC with chiral stationary phases; opposite sign indicates opposite enantiomers. [e] 4 Å MS was used. [f] 3 Å MS was used. [g] 5 Å MS was used.

In this case, the complex of $Mg(OTf)_2$ with **BOX1**, instead of **BOX 6**, provided the best result in terms of yield, diastereo- and enantioselectivity (Table 3, entry 1). A decrease of temperature to 0 °C almost completely stopped the reaction, which required the addition of 4 Å MS to proceed. In this way (Table 3, entry 7), compound **5a** was obtained with slightly improved enantiomeric excess (89%) and diastereomeric ratio (96:4). 3 Å MS led to similar results (Table 3, entry 8). On the other hand, the reaction in the presence of 5 Å MS was notably slower and, although a slight increase of ee (91%), was observed, product **5a** was obtained with low yield and poorer dr (Table 3, entry 9). Other solvents ($CHCl_3$, DCE, acetonitrile or EtOAc) were tested but none of them improved the results obtained in dichloromethane (Table S1, see SI).

Further decrease of temperature in the presence of 4 Å MS allowed increasing the ee up to 91% (Table 3, entry 10). Unfortunately, this low temperature was not compatible with many substrates, and therefore the study of the reaction scope was performed at 0 °C (Table 4).

The reaction showed broad scope, being of application to imines having a variety of aromatic rings attached to the azomethinic carbon. These aromatic rings could bear either electron-withdrawing or electron-donating groups at either position of the ring. The best enantioselectivities were observed with imines having *para* substitution in the aromatic ring attached to the imine (Table 4, entries 2-6), especially in the cases of a 4-Cl or a 4-MeO substituent. Good diastereomeric *E*/*Z* ratios above 90:10 were obtained in all the cases except with imines having nitrophenyl substituents (Table 4, entries 5 and 9). The reaction of diethyl malonate and imine **4a** was also carried out to give the corresponding enamine with good dr and ee (Table 4, entry 13), although these results were inferior to those obtained with dimethyl malonate. Notably, copper-BOX complexes could not catalyze the reaction with diethyl malonate.

Table 4. Enantioselective conjugate addition of malonate esters **1** to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines **4**. Substrate scope.[a]



1 **4** (S,*E*)-**5**

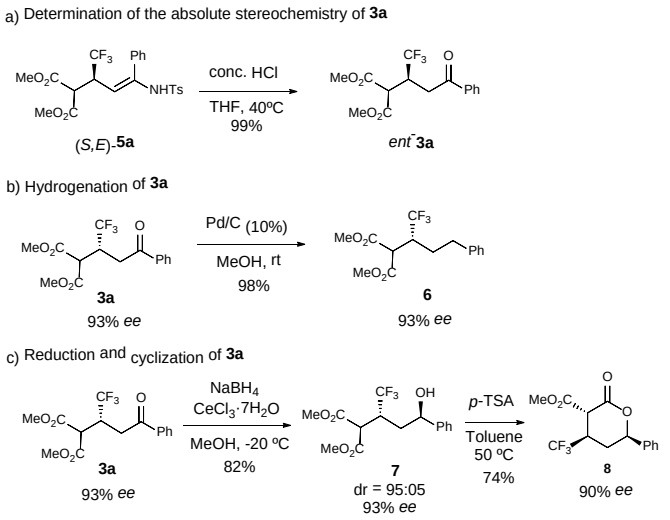
Entry	**4**	R^1	R^2	t (h)	**5**	Yield (%)[b]	dr (*E*/*Z*)[c,e]	ee (%)[d,e]
1	**4a**	Me	Ph	68	**5a**	95	96:4 (90:10)	89 (95)
2	**4b**	Me	4-MeC_6H_4	16	**5b**	96	95:5 (89/11)	89 (94)
3	**4c**	Me	4-ClC_6H_4	18	**5c**	93	95:5 (87/13)	97 (97)
4	**4d**	Me	4-BrC_6H_4	72	**5d**	85	95:5 (89/11)	91 (95)
5	**4e**	Me	4-$NO_2C_6H_4$	17	**5e**	97	84:16 (74:26)	89 (90)
6	**4f**	Me	4-$MeOC_6H_4$	40	**5f**	92	93:7 (84/16)	93 (94)
7	**4g**	Me	3-MeC_6H_4	16	**5g**	91	95:5 (87/13)	86 (94)
8	**4h**	Me	3-ClC_6H_4	19	**5h**	97	93:7 (82/18)	83 (91)
9	**4i**	Me	3-$NO_2C_6H_4$	16	**5i**	97	78:22 (60/40)	79 (83)
10	**4j**	Me	3-$MeOC_6H_4$	16	**5j**	95	93:7 (83/17)	86 (87)
11	**4k**	Me	2-$MeOC_6H_4$	72	**5k**	91	94:6 (72/28)	92 (89)
12	**4l**	Me	2- naphthyl	20	**5l**	96	94:6 (87/13)	88 (93)
13	**4a**	Et	Ph	100	**5m**	94	88:12	70

[a] Reaction conditions: **1a** (0.3 mmol), **11** (0.125 mmol), **BOX1** (0.0125 mmol), $Mg(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL), 0 °C. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Ee for the major *E* diastereomer, determined by HPLC with chiral stationary phases. [e] In brackets, values obtained with the $Cu(OTf)_2$-**BOX1** catalyst taken from ref. 12.

Compared with the **BOX1**-$Cu(OTf)_2$ catalyst previously used by our group [12], the **BOX1**-$Mg(OTf)_2$ system delivered compounds **5** with better diastereomeric ratios and only slightly lower enantiomeric excesses. The magnesium catalyst also showed higher activity and the reactions were completed within shorter times and with better yields.

The configuration of the stereogenic center and the geometry of the double bond for the major enamines **5** (Table 4) was assigned as *S* and *E*, respectively, by comparison with the data of the same products previously prepared in our laboratory by copper catalysis [12]. Hydrolysis of compound **5a** upon treatment with concentrated hydrochloric acid in THF at 40 °C gave the corresponding (*S*)-keto*ne ent*-**3a** [10], which showed identical spectroscopic features as the compound obtained from the Michael addition to enone **2a** catalyzed by $Mg(OTf)_2$-**BOX6** but with inverted retention times in HPLC (Scheme 2a). This result corroborated that the configuration of the stereogenic center in ketones **3** (Table 2) was *R*. Furthermore, compound **3a** was subjected to several synthetic transformations. The carbonyl group was successfully removed through catalytic hydrogenation on Pd/C achieving product **6** in quantitative yield (Scheme 2b). Additionally, the carbonyl group could be reduced using $NaBH_4$ to give alcohol **7** in high yields almost as a single diastereomer. Moreover, the treatment of **7** with *p*-toluenesulfonic acid gave the

corresponding lactone **8** (Scheme 2c). Remarkably, the reactions afforded the desired products without any loss of optical purity.



Scheme 2. Synthetic transformations of **3a** and **5a**.

3. Conclusions

In conclusion, we have found that magnesium(II)-BOX complexes are excellent catalysts for the enantioselective Michael addition of malonic esters to β-trifluoromethyl enones, a reaction that has been scarcely studied, so far. The reaction provided the expected ketones bearing a trifluoromethylated stereogenic center in the γ position with good yields and high enantiomeric excesses for a range of trifluoromethyl enones. Furthermore, the Mg(II)-BOX complexes have catalyzed the Michael addition of malonic esteres to β-trifluoromethyl-α,β-unsaturated *N*-tosyl imines to give β-trifluoromethyl (*E*)-enamines. Compared to a previous example catalyzed by copper, the magnesium-catalyzed reaction provided higher reaction rates, better *E/Z*-enamine diastereoselectivity and similar or slightly lower enantiomeric excesses. Both reaction provide access to chiral building blocks bearing a trifluoromethylated stereogenic center, which are interesting for the pharmaceutical industry. This work also shows the synthetic potential of the magnesium-BOX complexes as Lewis acids in asymmetric catalysis, which has been little explored compared with other metal-BOX complexes, such as those of copper or zinc.

4. Experimental section

Reactions were carried out under nitrogen in round bottom flasks oven-dried overnight at 120 ºC. Commercial reagents were used as purchased. Dichloromethane was distilled from CaH_2. 4 Å molecular sieves (8-12 mesh, beads Aldrich 208604) were dried at the flame under vacuum (oil pump) and stored in a closed flask and used before a week. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as internal standard (δ 7.26 and 77.0 ppm, respectively), and at 282 MHz for ^{19}F NMR using $CFCl_3$ as internal standard. Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or from Phenomenex. β-trifluoromethyl enones **2** and their *N*-sulfonyl imines **4** were prepared according to procedures described in the literature [7c,12,20].

*4.1. General procedure for the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl enones **2***

Anhydrous $Mg(OTf)_2$ (8.1 mg, 0.025 mmol) and **BOX6** (12.2 mg, 0.025 mmol) were introduced in a Schlenk tube that was filled with nitrogen. Dry dichloroethane (1.1 mL) was added via syringe and the mixture was stirred for 30 min. The reaction mixture was introduced in an ice bath and a solution of enone **2** (0.25 mmol) in dry dichloroethane (1.0 mL) was added via syringe, followed by dimethyl malonate 1a (69 μL, 0.6 mmol) and 4 Å MS (220 mg). The mixture was stirred at 0-4 ºC for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**.

Racemic compounds **3** were prepared in a similar manner using $La(OTf)_3$ in the absence of any ligand at room temperature.

*4.1.1. Dimethyl (R)-2-(1,1,1-trifluoro-4-oxo-4-phenylbutan-2-yl)malonate (**3a**)*

Obtained 71 mg (85%). The enantiomeric excess (93%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 90:10, 1 mL/min. Minor enantiomer tr = 9.3 min, major enantiomer tr = 10.1 min. Phenomenex-cellulose 2 hexane:isopropyl alcohol 90:10, 1 mL/min. Major enantiomer tr = 11.6 min, minor enantiomer tr = 12.7 min (HPLC for *ent*-**3a** see ref. 10). White solid; M.p. 86.4-87.5 ºC; $[\alpha]_D^{20}$ = +2.0 (*c* = 1.0, $CHCl_3$);, $[\alpha]_D^{26}$ = –1.9 for the (*S*)-enantiomer; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.60 (tt, *J* = 7.8, 1.2, 1H), 7.48 (m, 2H), 4.04 (m, 1H), 3.88 (d, *J* = 4.9 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.66 (dd, *J* = 18.6, 5.1 Hz, 1H), 3.37 (dd, *J* = 18.6, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.2 (C), 167.5 (C), 167.3 (C), 136.1 (C), 133.5 (CH), 128.7 (CH), 128.2 (CH), 126.6 (q, $J_{C\text{-}F}$ = 275 Hz, CF_3), 53.2 (CH_3), 52.9 (CH_3), 49.1 (q, $J_{C\text{-}F}$ = 2.3 Hz, CH), 38.2 (q, $J_{C\text{-}F}$ = 27.5 Hz, CH), 34.4 (q, $J_{C\text{-}F}$ = 2.3 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.6 (s, CF_3); HRMS (ESI) *m/z*: 333.0957 $[M+H]^+$, $C_{15}H_{16}F_3O_5^+$ requires 333.0944.

*4.1.2. Dimethyl (R)-2-(1,1,1-trifluoro-4-oxo-4-(p-tolyl)butan-2-yl)malonate (**3b**)*

Obtained 78 mg (90%). The enantiomeric excess (90%) was determined by HPLC, Chiralcel OD-H, hexane:isopropyl alcohol 98:02, 1 mL/min. Major enantiomer tr = 10.5 min, minor enantiomer tr = 12.9 min. Yellow pale solid; M.p. 57.5-60.5 ºC; $[\alpha]_D^{20}$ = +2.9 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 4.04 (m, 1H), 3.86 (d, *J* = 5.1 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.61 (dd, *J* = 18.4, 5.2 Hz, 1H), 3.34 (dd, *J* = 18.5, 6.9 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 194.7 (C), 167.5 (C), 167.3 (C), 144.4 (C), 133.6 (C), 129.4 (CH), 128.3 (CH), 126.3 (q, $J_{C\text{-}F}$ = 280.1 Hz, CF_3), 53.1 (CH_3), 52.8 (CH_3), 49.1 (q, $J_{C\text{-}F}$ = 2.4 Hz, CH), 38.2 (q, $J_{C\text{-}F}$ = 27.5 Hz, CH), 34.2 (q, $J_{C\text{-}F}$ = 1.8, CH_2), 21.6 (CH_3); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.6 (s, CF_3); HRMS (ESI) *m/z*: 347.1093 $[M+H]^+$, $C_{16}H_{18}F_3O_5^+$ requires 347.1101.

*4.1.3. Dimethyl (R)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)malonate (**3c**)*

Obtained 88 mg (96%). The enantiomeric excess (96%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 98:02, 0.7 mL/min. Major enantiomer tr = 13.8 min, minor enantiomer tr = 14.9 min. Oil; $[\alpha]_D^{20}$ = +6.0 (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* =

8.4 Hz, 2H), 4.00 (m, 1H), 3.86 (d, *J* = 4.9 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3,63 (dd, *J* = 18.5, 5.1 Hz, 1H), 3.37 (dd, *J* = 18.5, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 194.1 (C), 167.5 (C), 167.2 (C), 140.1 (C), 134.4 (C), 129.6 (CH), 129.0 (CH), 126.5 (q, J_{C-F} = 280.1 Hz, CF_3), 53.2 (CH_3), 52.9 (CH_3), 48.9 (q, J_{C-F} = 2.4 Hz, CH), 38.2 (q, J_{C-F} = 27.5 Hz, CH), 34.3 (q, J_{C-F} = 2.2 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.7 (s, CF_3); HRMS (ESI) *m/z*: 367.0560 $[M+H]^+$, $C_{15}H_{15}ClF_3O_5^+$ requires 367.0555.

*4.1.4. Dimethyl (R)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)malonate (**3d**)*

Obtained 75 mg (73%). The enantiomeric excess (97%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 95:05, 1 mL/min. Major enantiomer tr = 19.3 min, minor enantiomer tr = 20.5 min. Oil; $[\alpha]_D^{20}$ = +5.0 (c = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.85 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 4.05-3.97 (m, 1H), 3.87 (d, *J* = 4.8 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3,64 (dd, *J* = 18.6, 5.1 Hz, 1H), 3.31 (dd, *J* = 18.6, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 194.5 (C), 167.7 (C), 167.4 (C), 135.0 (C), 132.2 (CH), 129.8 (CH), 129.0 (C), 126.7 (q, J_{C-F} = 279.9 Hz, CF_3), 53.4 (CH_3), 53.1 (CH_3), 49.1 (q, J_{C-F} = 2.4 Hz, CH), 38.3 (q, J_{C-F} = 27.5 Hz, CH), 34.5 (q, J_{C-F} = 2.2 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.2 (s, CF_3); HRMS (ESI) *m/z*: 411.0052 $[M+H]^+$, $C_{15}H_{15}BrF_3O_5^+$ requires 411.0049.

*4.1.5. Dimethyl (R)-2-(1,1,1-trifluoro-4-(4-nitrophenyl)-4-oxobutan-2-yl)malonate (**3e**)*

Obtained 90 mg (96%). The enantiomeric excess (96%) was determined by HPLC, Chiralpak OD-H, hexane:isopropyl alcohol 98:02, 1 mL/min. Major enantiomer tr = 10.6 min, minor enantiomer tr = 12.3 min. Oil; $[\alpha]_D^{20}$ = +5.3 (*c* = 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.29 (d, *J* = 9.0 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 2H), 4.06-3.88 (m, 1H), 3.86 (d, *J* = 4.5 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.80-3.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 194.1 (C), 167.5 (C), 167.2 (C), 150.6 (C), 140.5 (C), 129.2 (CH), 126.4 (q, J_{C-F} = 280.1 Hz, CF_3), 123.9 (CH), 53.2 (CH_3), 53.0 (CH_3), 48.6 (q, J_{C-F} = 2.1 Hz, CH), 38.2 (q, J_{C-F} = 27.8 Hz, CH), 34.9 (q, J_{C-F} = 2.0 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): *δ* –70.8 (s, CF_3); HRMS (ESI) *m/z*: 378.0778 $[M+H]^+$, $C_{15}H_{15}F_3NO_7^+$ requires 378.0795.

*4.1.6. Dimethyl (R)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-oxobutan-2-yl)malonate (**3f**)*

Obtained 60 mg (66%). The enantiomeric excess (86%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 80:20, 0.7 mL/min. Major enantiomer tr = 19.1 min, minor enantiomer tr = 20.6 min. White solid; M.p. 79.1-80.8 ºC; $[\alpha]_D^{20}$ = +4.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.96 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.13-3.92 (m, 1H), 3.86 (s, 3H), 3.85 (d, *J* = 4.2 Hz, 1H) 3.74 (s, 3H), 3.72 (s, 3H), 3.58 (dd, *J* = 18.4, 5.3 Hz, 1H) 3.30 (dd, *J* = 18.4, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 193.6 (C), 167.5 (C), 167.2 (C), 163.8 (C), 130.4 (CH), 129.1 (C), 126.5 (q, J_{C-F} = 280.1 Hz, CF_3), 113.8 (CH), 55.4 (CH_3), 53.0 (CH_3), 52.8 (CH_3), 49.2 (q, J_{C-F} = 2.3 Hz, CH), 38.2 (q, J_{C-F} = 27.5 Hz, CH), 33.9 (q, J_{C-F} = 1.8 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ 70.6 (s, CF_3); HRMS (ESI) *m/z*: 363.1058 $[M+H]^+$, $C_{16}H_{18}F_3O_6^+$ requires 363.1050.

*4.1.7. Dimethyl (R)-2-(1,1,1-trifluoro-4-oxo-4-(m-tolyl)butan-2-yl)malonate (**3g**)*

Obtained 78 mg (90%). The enantiomeric excess (90%) was determined by HPLC, Lux cellulose-4, hexane:isopropyl alcohol 98:02, 1 mL/min. Major enantiomer tr = 13.9 min, minor enantiomer tr = 16.4 min. Oil; $[\alpha]_D^{20}$ = +2.7 (*c* = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.01-7.55 (m, 2H), 7.36 (d, *J* = 7.7 Hz, 2H), 4.04 (m, 1H), 3.86 (d, *J* = 5.0 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.62 (dd, *J* = 18.6, 5.1 Hz, 1H), 3.55 (dd, *J* = 18.6,6.1 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 195.4 (C), 167.5 (C), 167.3 (C), 138.5 (C), 136.1 (C), 134.3 (CH), 128.6 (CH), 128.6 (CH), 126.7 (q, J_{C-F} = 280.2 Hz, CF_3), 125.4 (CH), 53.2 (CH_3), 52.9 (CH_3), 49.1 (q, J_{C-F} = 2.2 Hz, CH), 38.2 (q, J_{C-F} = 27.7 Hz, CH), 34.4 (q, J_{C-F} = 2.2 Hz, CH_2), 21.30 (CH_3); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.6 (s, CF_3); HRMS (ESI) *m/z*: 347.1087 $[M+H]^+$, $C_{16}H_{18}F_3O_5^+$ requires 347.1101.

*4.1.8. Dimethyl (R)-2-(4-(3-chlorophenyl)-1,1,1-trifluoro-4-oxobutan-2-yl)malonate (**3h**)*

Obtained 66 mg (71%). The enantiomeric excess (90%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 98:02, 0.5 mL/min. Minor enantiomer tr = 36.7 min, major enantiomer tr = 40.3 min. Oil; $[\alpha]_D^{20}$ = +2.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.96-7.83 (m, 2H), 7.56 (ddd, *J* = 7.9, 2.1 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 4.01 (m, 1H), 3.87 (d, *J* = 4.8 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.65 (dd, *J* = 18.6, 5.0 Hz, 1H), 3.32 (dd, *J* = 18.7,6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 194.1 (C), 167.5 (C), 167.2 (C), 137.6 (C), 135.1 (C), 133.5.6 (CH), 130.0 (CH), 128.3 (CH), 126.5 (q, J_{C-F} = 279.4 Hz, CF_3), 126.2 (CH), 53.2 (CH_3), 53.0 (CH_3), 48.9 (q, J_{C-F} = 2.3 Hz, CH), 38.2 (q, J_{C-F} = 27.7 Hz, CH), 34.5 (q, J_{C-F} = 1.9 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.7 (s, CF_3); HRMS (ESI) *m/z*: 367.0563 $[M+H]^+$, $C_{15}H_{15}ClF_3O_5^+$ requires 367.0555.

*4.1.9. Dimethyl (R)-2-(1,1,1-trifluoro-4-(3-nitrophenyl)-4-oxobutan-2-yl)malonate (**3i**)*

Obtained 65 mg (69%). The enantiomeric excess (94%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 90:10, 1 mL/min. Major enantiomer tr = 14.9 min, minor enantiomer tr = 15.9 min. White solid; M.p. 64.7-67.1 ºC; $[\alpha]_D^{20}$ = +8.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 8.77 (t, *J* = 2.0 Hz, 1H), 8.42 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.30 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 4.00 (m, 1H), 3.87 (d, *J* = 4.8 Hz, 1H), 3.79-3.73 (m, 1H) 3.75 (s, 3H), 3.74 (s, 3H), 3.37 (dd, *J* = 18.7, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 193.4 (C), 167.5 (C), 167.2 (C), 148.5 (C), 137.3 (C), 133.7 (CH), 130.0 (CH), 128,3 (CH), 127.7 (q, J_{C-F} = 280.1 Hz, CF_3), 123.0 (CH), 53.2 (CH_3), 53.0 (CH_3), 48.6 (q, J_{C-F} = 2.5 Hz, CH), 38.2 (q, J_{C-F} = 27.7 Hz, CH), 34.7 (q, J_{C-F} = 2.1 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.8 (s, CF_3); HRMS (ESI) *m/z*: 378.0790 $[M+H]^+$, $C_{15}H_{15}F_3NO_7^+$ requires 378.0795.

*4.1.10. Dimethyl (R)-2-(1,1,1-trifluoro-4-(3-methoxyphenyl)-4-oxobutan-2-yl)malonate (**3j**)*

Obtained 62 mg (68%). The enantiomeric excess (80%) was determined by HPLC, Lux cellulose-4, hexane:isopropyl alcohol 98:02, 1 mL/min. Major enantiomer tr = 15.8 min, minor enantiomer tr = 18.2 min. Oil; $[\alpha]_D^{20}$ = –0.4 (*c* = 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.58-7.48 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.03 (m, 1H), 3.86 (d, *J* = 5.1 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.62 (dd, *J* = 18.3, 5.1 Hz, 1H), 3.34 (dd, *J* = 18.6, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 195.1 (C), 167.5 (C), 167.3 (C), 159.9 (C), 137.4 (C), 129.7 (CH), 126.6 (q, J_{C-F} = 280.1 Hz, CF_3), 120.7 (CH), 120.0 (CH), 112.4 (CH), 55.4 (CH_3), 53.1 (CH_3), 52.9 (CH_3), 49.1 (q, J_{C-F} = 2.3 Hz, CH), 38.2 (q, J_{C-F} = 27.6 Hz, CH), 34.5 (q, J_{C-F} = 2.2 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): *δ* –70.6 (s, CF_3); HRMS (ESI) *m/z*: 363.1062 $[M+H]^+$, $C_{16}H_{18}F_3O_6^+$ requires 363.1050.

*4.1.11. Dimethyl (R)-2-(1,1,1-trifluoro-4-(2-methoxyphenyl)-4-oxobutan-2-yl)malonate (**3k**)*

Obtained 79 mg (87%). The enantiomeric excess (87%) was determined by HPLC, AD-H, hexane:isopropyl alcohol 80:20, 1 mL/min. Major enantiomer tr = 6.9 min, minor enantiomer tr = 7.6

min. Oil; $[\alpha]_D^{20}$ = +6.5 (*c* = 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.02-6.95 (m, 2H), 4.05-4.00 (m, 1H), 3.91 (s, 3H), 3.82 (d, *J* = 5.5 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.55 (dd, *J* = 18.7, 5.6 Hz, 1H), 3.43 (dd, *J* = 19.1, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.0 (C), 167.4 (C), 158.8 (C), 134.0 (CH), 130.7 (CH), 127.0 (C), 126.8 (q, $J_{C\text{-}F}$ = 280.1 Hz, CF_3), 120.7 (CH), 111.6 (CH), 55.5 (CH_3), 53.0 (CH_3), 52.7 (CH_3), 49.5 (q, $J_{C\text{-}F}$ = 2.3 Hz, CH), 39.6 (q, $J_{C\text{-}F}$ = 1.8 Hz, CH_2), 38.2 (q, $J_{C\text{-}F}$ = 27.3 Hz, CH); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.0 (s, CF_3); HRMS (ESI) *m/z*: 363.1057 $[M+H]^+$, $C_{16}H_{18}F_3O_6^+$ requires 363.1050.

*4.1.12. Dimethyl (R)-2-(1,1,1-trifluoro-4-(naphthalen-2-yl)-4-oxobutan-2-yl)malonate (**3l**)*

Obtained 92 mg (96%). The enantiomeric excess (85%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 80:20, 1 mL/min. major enantiomer tr = 9.8 min, minor enantiomer tr = 11.8 min. White Solid; M.p. 91.9-92.9 ºC; $[\alpha]_D^{20}$ = +20.6 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.51 (d, *J* = 1.7 Hz, 1H), 8.16-7.81 (m, 4H), 7.65-7.49 (m, 2H), 4.04 (m, 1H), 3.93 (d, *J* = 4.9 Hz, 1H), 3.86-3.78 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.53 (dd, *J* = 18.5, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.1 (C), 167.6 (C), 167.3 (C), 135.7 (C), 133.5 (C),132.4 (C), 129.9 (CH), 129.6. (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 126.9 (CH), 126.4 (q, $J_{C\text{-}F}$ = 280.1 Hz, CF_3), 123.7 (CH), 53.1 (CH_3, 52.9 (CH_3), 49.1 (q, $J_{C\text{-}F}$ = 2.4 Hz, CH), 38.3 (q, $J_{C\text{-}F}$ = 27.5 Hz, CH), 34.4 (q, $J_{C\text{-}F}$ = 2.2 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.6 (s, CF_3); HRMS (ESI) *m/z*: 383.1119 $[M+H]^+$, $C_{19}H_{18}F_3O_5^+$ requires 383.1101.

*4.1.13. Diethyl (R)-2-(1,1,1-trifluoro-4-oxo-4-phenylbutan-2-yl)malonate (**3m**)*

Obtained 61 mg (67%). The enantiomeric excess (85%) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 90:10, 1 mL/min. Minor enantiomer tr = 8.9 min, major enantiomer tr = 9.7 min, minor enantiomer tr = 11.8 min. White solid; M.p. 51.9-52.8 ºC; $[\alpha]_D^{20}$ = –3.1 (c = 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.58 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.47 (tt, *J* = 8.4, 1.5 Hz, 2H), 4.24-4.16 (m, 4H), 4.12-3.92 (m, 1H), 3.83 (d, *J* = 5.1 Hz, 1H), 3.64 (dd, *J* = 18.6, 4.8 Hz, 1H), 3.38 (dd, *J* = 18.6, 6.3 Hz, 1H), 1.29-1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.2 (C), 167.1 (C), 166.9 (C), 136.01 (C), 133.5 (CH), 128.7 (CH), 128.1. (CH), 126.7 (q, $J_{C\text{-}F}$ = 280.1 Hz, CF_3), 62.3 (CH_2), 52.0 (CH_2), 49.5 (q, $J_{C\text{-}F}$ = 2.1 Hz, CH), 38.0 (q, $J_{C\text{-}F}$ = 27.5 Hz, CH), 34.4 (q, $J_{C\text{-}F}$ = 1.9, CH_2), 14.0 (CH_3), 13.8 (CH_3); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –70.4 (s, CF_3); HRMS (ESI) *m/z*: 361.1265 $[M+H]^+$, $C_{17}H_{20}F_3O_5^+$ requires 361.1257.

*4.2. General procedure for the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl α,β-usaturated N-sulfonylimines **4***

Anhydrous $Mg(OTf)_2$ (8.0 mg, 0.025 mmol) was dried in a Schlenk tube under vacuum. **BOX1** (8.9 mg, 0.025 mmol) was added and the tube was filled with nitrogen. Dry CH_2Cl_2 (1.1 mL) was added via syringe and the mixture was stirred for 30 min. A solution of imine **4** (0.25 mmol) dissolved in dry CH_2Cl_2 (1.0 mL), was added via syringe, followed by 4 Å MS (220 mg) and dimethyl malonate (68 μL, 0.6 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **5**. Compounds 3 were characterized by 1H NMR to determine de diastereomeric ratio and by HPLC to determine the enantiomeric excess of each diastereomer. For full characterization data of compounds **5** see ref 12.

Racemic compounds for comparative purpose were prepared by following the same procedure, using $La(OTf)_3$-pyBOX (rac) at 40 °C.

*4.2.1. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenylbut-3-en-2-yl)malonate (**5a**)*

Obtained 115.2 mg (95%), *Z:E* = 96:4 (^1H NMR), Chiral HPLC analysis: Chiralpak AD-H, hexane-isopropyl alcohol 80:20, 1 mL/min, *E*-diastereomer (89% ee): *major enantiomer (S)* tr = 8.4 min, *minor enantiomer (R)* tr = 14.0 min; *Z*-diastereomer (75% ee): *major enantiomer* tr = 12.4 min, *minor enantiomer* tr = 9.4 min.

*4.2.2. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(p-tolyl)but-3-en-2-yl)malonate (**5b**)*

Obtained 120 mg (96%); *E:Z* = 95:5 (^1H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 85:15, 1 mL/min, *E*-diastereomer (89% ee): *major enantiomer (S)* tr = 13.5 min, *minor enantiomer (R)* tr = 16.2 min; *Z*-diastereomer (61% ee): *major enantiomer* tr = 14.7 min, *minor enantiomer* tr = 12.0 min.

*4.2.3. Dimethyl (S,E)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl)-sulfonamido)-but-3-en-2-yl)malonate (**5c**)*

Obtained 121 mg (93%); *E:Z* = 95:5 (^1H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 95:05, 1 mL/min, *E*-diastereomer (97% ee): *major enantiomer (S)* tr = 38.1 min, *minor enantiomer (R)* tr = 47.1 min; *Z*-diastereomer (63% ee): *major enantiomer* tr = 48.2 min, *minor enantiomer* tr = 31.3 min.

*4.2.4. Dimethyl (S,E)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (**5d**)*

Obtained 120 mg (85%); *E:Z* = 95:5 (^1H NMR). Chiral HPLC analysis: Chiralpak IC, hexane-isopropyl alcohol 95:05, 1 mL/min, *E*-diastereomer (91% ee): *major enantiomer (S)* tr = 48.8 min, *minor enantiomer (R)* tr = 58.5 min; *Z*-diastereomer (43% ee): *major enantiomer* tr = 32.2 min, *minor enantiomer* tr = 41.0 min.

*4.2.5. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(4-nitrophenyl)but-3-en-2-yl)malonate (**5e**)*

Obtained 129 mg (97%); *E:Z* = 84:16 (^1H NMR). Chiral HPLC analysis: Chiralpak IC, hexane-isopropyl alcohol 90:10, 1 mL/min, *E*-diastereomer (89% ee): *major enantiomer (S)* tr = 60.1 min, *minor enantiomer (R)* tr = 68.5 min; *Z*-diastereomer (78% ee): *major enantiomer* tr = 50.1 min, *minor enantiomer* tr = 95.4 min.

*4.2.6. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (**5f**)*

Obtained 119 mg (92%); *E:Z* = 93:7 (^1H NMR). Chiral HPLC analysis: Chiralpak IC, hexane-isopropyl alcohol 90:10, 1 mL/min, *E*-diastereomer (93% ee): *major enantiomer (S)* tr = 44.2 min, *minor enantiomer (R)* tr = 63.8 min; *Z*-diastereomer (69% ee): *major enantiomer* tr = 38.0 min, *minor enantiomer* tr = 50.9 min.

*4.2.7. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(m-tolyl)but-3-en-2-yl)malonate (**5g**)*

Obtained 102 mg (91%); *E:Z* = 95:5 (^1H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-

diastereomer (86% ee): *major enantiomer (S)* tr = 7.3 min, *minor enantiomer (R)* tr = 11.2 min; *Z*-diastereomer (58% ee): *major enantiomer* tr = 10.0 min, *minor enantiomer* tr = 8.0 min.

*4.2.8. Dimethyl (S,E)-2-(4-(3-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (**5h**)*

Obtained 126 mg (97%); *E:Z* = 93:7 (^{1}H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 80:20, 1 mL/min, *E*-diastereomer (83% ee): *major enantiomer (S)* tr = 7.0 min, *minor enantiomer (R)* tr = 10.8 min; *Z*-diastereomer (96% ee): *major enantiomer* tr = 9.7 min, *minor enantiomer* tr = 8.3 min.

*4.2.9. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(3-nitrophenyl)but-3-en-2-yl)malonate (**5i**)*

Obtained 129 mg (97%); *E:Z* = 78:22 (^{1}H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 95:05, 2 mL/min, *E*-diastereomer (79% ee): *major enantiomer (S)* tr = 43.3 min, *minor enantiomer (R)* tr = 80.9 min; *Z*-diastereomer (62% ee): *major enantiomer* tr = 52.3 min, *minor enantiomer* tr = 35.0 min.

*4.2.10. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-(3-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (**5j**)*

Obtained 122 mg (95%); *E:Z* = 93:7 (^{1}H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 90:10, 1 mL/min, *E*-diastereomer (86% ee): *major enantiomer (S)* tr = 20.6 min, *minor enantiomer (R)* tr = 32.9 min; *Z*-diastereomer (62% ee): *major enantiomer* tr = 28.7 min, *minor enantiomer* tr = 22.5 min.

*4.2.11. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-(2-methoxyphenyl)-4-((4-methylphenyl)-sulfonamido)but-3-en-2-yl)malonate (**5k**)*

Obtained 117 mg (91%); *E:Z* = 94:6 (^{1}H NMR). Chiral HPLC analysis: Chiralpak AD-H, hexane-isopropyl alcohol 90:10, 1 mL/min, *E*-diastereomer (92% ee): *major enantiomer (S)* tr = 22.9 min, *minor enantiomer (R)* tr = 50.2 min; *Z*-diastereomer (11% ee): *major enantiomer* tr = 34.9 min, *minor enantiomer* tr = 41.5 min.

*4.2.12. Dimethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(naphthalen-2-yl)but-3-en-2-yl)malonate (**5l**)*

Obtained 129 mg (96%); *E:Z* = 94:6 (^{1}H NMR). Chiral HPLC analysis: Lux Amylose-1, hexane-isopropyl alcohol 80:20, 1 mL/min, *E*-diastereomer (88% ee): *major enantiomer (S)* tr = 11.6 min, *minor enantiomer (R)* tr = 14.1 min; *Z*-diastereomer (49% ee): *major enantiomer* tr = 12.7 min, *minor enantiomer* tr = 9.2 min.

*4.2.13. Diethyl (S,E)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenylbut-3-en-2-yl)malonate (**5m**)*

Obtained 83 mg (94%); *E:Z* = 88:12 (^{1}H NMR). Chiral HPLC analysis: Chiralpak AD-H, hexane-isopropyl alcohol 80:20, 1 mL/min, *E*-diastereomer (70% ee): *major enantiomer (S)* tr = 7.5 min, *minor enantiomer (R)* tr = 12.1 min; *Z*-diastereomer (70% ee): *major enantiomer* tr = 10.8 min, *minor enantiomer* tr = 9.2 min. **Major *E*-diastereomer:** Oil; $[\alpha]_D^{20}$ +10.2 (c = 1.0, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.35-7.31 (m, 5H), 7.09-7.06 (m, 2H), 6.07 (s, 1H), 5.65-5.61 (m, 1H), 4.29-4.10 (m, 4H), 3.67-3.64 (m, 2H), 2.45 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C), 166.9 (C), 143.9 (C), 142.0 (C), 137.1 (C), 134.3 (C), 129.8 (CH), 129.7 (CH), 129.0 (CH), 128.2 (CH), 127.2 (CH), 125.0 (C, q, $J_{C\text{-}F}$ = 278 Hz), 111.7 (CH), 63.2 (CH_2), 62.7 (CH_2), 51.7 (CH), 42.0 (CH, q, $J_{C\text{-}F}$ = 27.8 Hz), 21.6 (CH_3), 14.2 (CH_3), 14.0 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ –69.7 (s, CF_3) ppm; HRMS (ESI) m/z 514.1509 $[M+H]^+$, $C_{24}H_{27}F_3NO_6S^+$ requires 514.1506. **Minor *Z*-diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixture: δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.44-7.41 (m, 2H), 5.20 (d, *J* = 10.8 Hz, 1H), 2.39 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ –69.2 (s, CF_3) ppm.

*4.3. Synthetic transformations of **3a** and **5a***

*4.3.1. Hydrolysis of compound **5a** to give **ent-3a**. Determination of the absolute configuration of **3a**.*

Compound (*S,E*)-**5a** (30 mg, 0062 mmol, *E/Z* = 90:10, % ee = 89/75) dissolved in THF (2.5 mL) was treated with 35% aqueous HCl (7 drops) and heated at 40 °C for 22 hours. The solvent was removed under reduced pressure, most water was removed after azeotropic distillation with dichlorometane and the mixture was chromatographed eluting with hexane:EtOAc to give 21 mg (97%) of ketone (*S*)-**3a**. The ketone obtained in this way showed identical spectroscopic features as the compound obtained from the Michael addition to enone 2a catalyzed by $Mg(OTf)_2$-**BOX6** but with inverted retention times in HPLC. The enantiomeric excess (87% ee) was determined by HPLC, Chiralpak AD-H, hexane:isopropyl alcohol 90:10, 1 mL/min. Major enantiomer tr = 9.7 min, minor enantiomer tr = 10.7 min.

*4.3.2. Dimethyl (R)-2-(1,1,1-trifluoro-4-phenylbutan-2-yl)malonate (**6**)*

A solution of **3a** (30 mg, 0.09 mmol, 93% *ee*) in methanol (2 mL) was stirred under hydrogen atmosphere in presence of 10% Pd/C (5 mg) for 3 h at room temperature. Then, the reaction mixture was filtered through a short pad of Celite® eluting with CH_2Cl_2. The solvent was removed under reduced pressure to give **6** (28 mg, 98%). Enantiomeric excess (94%) was determined by chiral HPLC (chiralpak AY-H), hexane-isopropyl alcohol 90:10, 1 mL/min, major enantiomer tr = 22.9 min, minor enantiomer tr = 32.6 min. Oil; $[\alpha]_D^{20}$ = +13.0 (c = 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.33-7.27 (m, 2H), 7.23-7.16 (m, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.10-3.03 (m, 1H), 2.80-2.72 (m, 2H), 2.09-1.93 (m, 2H), 1.70-1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 167.7 (C), 167.3 (C), 140.9 (C), 128.7 (CH), 128.6 (CH), 127.2 (q, $J_{C\text{-}F}$ = 280.6 Hz, CF_3), 126.4 (CH), 53.2 (CH_3), 53.0 (CH_3), 50.7 (q, $J_{C\text{-}F}$ = 2.6 Hz, CH), 42.8 (q, $J_{C\text{-}F}$ = 26.3 Hz, CH), 33.9 (CH_2), 28.6 (CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –68.4 (s, CF_3); HRMS (ESI) *m/z*: 319.1157 $[M+H]^+$, $C_{15}H_{18}F_3O_4^+$ requires 319.1152.

*4.3.3. Dimethyl 2-((2R,4R)-1,1,1-trifluoro-4-hydroxy-4-phenylbutan-2-yl)malonate (**7**)*

A solution of **3a** (30 mg, 0.09 mmol, 93% *ee*) in methanol (2 mL) was stirred in presence of $NaBH_4$ (8 mg, 0.2 mmol) and $CeCl_3{\cdot}7H_2O$ (75 mg, 0.2 mmol) for 5 h at –20 ºC. Then, the reaction mixture was diluted in CH_2Cl_2 (20 mL) and was extracted with HCl 1 M (10 mL) and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (90:10) gave **7** (25 mg, 82%). Enantiomeric excess (94%) was determined by chiral HPLC (chiralpak AD-H), hexane-isopropyl alcohol 90:10, 1 mL/min, major enantiomer tr = 13.1 min, minor enantiomer tr = 14.2 min. Oil; $[\alpha]_D^{20}$ = –2.0 (c = 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.39-7.25 (m, 5H), 4.84 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.92 (d, *J* = 4.2 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.32-3.23 (m, 1H), 2.64 (br s, 1H), 2.19-2.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 168.8 (C), 167.5 (C), 143.6 (C), 128.7 (CH), 127.9 (CH), 127.0 (q, $J_{C\text{-}F}$ = 280.0 Hz, CF_3), 125.8 (CH), 70.7 (CH), 53.6 (CH_3),

53.1 (CH_3), 49.7 (q, J_{C-F} = 2.4 Hz, CH), 40.2 (q, J_{C-F} = 26.8 Hz, CH), 35.7 (q, J_{C-F} = 1.9 Hz, CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –69.4 (s, CF_3); HRMS (ESI) *m/z*: 335.1107 $[M+H]^+$, $C_{15}H_{18}F_3O_5^+$ requires 335.1101.

*4.3.4. Methyl (3R,4R,6R)-2-oxo-6-phenyl-4-(trifluoromethyl)tetrahydro-2H-pyran-3-carboxylate (**8**)*

A solution of compound **7** (15 mg, 0.045 mmol, 93% *ee*) in toluene (1 mL) was stirred in presence of *p*-toluenesulfonic acid (5 mg, 0.03 mmol) for 1 h at 50 ºC. Then, the reaction mixture was diluted in OEtAc (20 mL) and was extracted with $NaHCO_3$ sat. (10 mL) and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography eluting with hexane:EtOAc (90:10) gave **8** (10 mg, 74%). Enantiomeric excess (90%) was determined by chiral HPLC (Lux Cellulose-3), hexane-isopropyl alcohol 90:10, 1 mL/min, major enantiomer tr = 23.3 min, minor enantiomer tr = 52.2 min. Oil; $[\alpha]_D^{20}$ = +17.3 (c = 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.43-7.36 (m, 5H), 5.43 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.88 (s, 3H), 3.80 (d, *J* = 9.9 Hz, 1H), 3.49-3.39 (m, 1H), 2.33-2.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 167.6 (C), 166.1 (C), 137.1 (C), 129.3 (CH), 129.1 (CH), 127.0 (q, J_{C-F} = 280.0 Hz, CF_3), 126.0 (CH), 78.7 (CH), 53.6 (CH_3), 45.9 (q, J_{C-F} = 2.3 Hz, CH), 37.2 (q, J_{C-F} = 28.3 Hz, CH), 29.9 (CH_2); ^{19}F NMR ($CDCl_3$, 289 MHz): δ –73.1 (s, CF_3); HRMS (ESI) *m/z*: 303.0836 $[M+H]^+$, $C_{14}H_{14}F_3O_4^+$ requires 303.0839.

Declaration of competing interest

The authors declare that they have no known competingfinancial interests or personal relationships that could haveappeared to influence the work reported in this paper.

Acknowledgments

Financial support from the Agencia Estatal de Investigación (AEI-MINECO) and FEDER (CTQ2017-84900-P) is ackowledged. A. S.-M. thanks the Generalitat Valenciana and FEDER-EU for a post-doctoral grant (APOST/2016/139) and the Spanish government for a Juan de la Cierva Contract (IJC2018-036682- I). We also thank the SCSIE-UV for providing access to NMR and MS facilities.

References and notes

1. (a) I. Ojima, Fluorine in Medicinal Chemistry and Chemical Biology, Wiley-Blackwey, Chichester, 2009. (b) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.* 116 (**2016**) 422. (c) J. Wang, M. Sanchez-Rosello, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.* 114 (**2014**) 2432. (d) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.* 40 (**2010**) 3496. (e) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.* 37 (**2008**) 320. (f) K. Müller, C. Faeh and F. Diederich, *Science* 317 (**2007**) 1881. (g) M. Bassetto, S. Ferla and F. Pertusati, *Future Med. Chem.* 7 (**2015**) 527.
2. (a) M. Kulke, T. O'Dorisio, A. Phan, E. Bergsland, L. Law, P. Banks, J. Freiman, K. Frazier, J. Jackson, J. C. Yao, L. Kvols, P. Lapuerta, B. Zambrowicz, D. Fleming and A. Sands, *Endocr. Relat. Cancer* 21 (2014) 705. (b) S. P. Brown, P. J. Dransfield, M. Vimolratana, X. Y. Jiao, L. Zhu, V. Pattaropong, Y. Sun, J. Liu, J. Luo, J. Zhang, S. Wong, R. Zhuang, Q. Guo, F. Li, J. C. Medina, G. Swaminath, D. C.-H. Lin and J. B. Houze, *ACS Med. Chem. Lett.* 3 (**2012**) 726. (c) S. Vadivelan, T. N. Deeksha, S. Arun, P. K. Machiraju and R. Gundia, *Eur. J. Med. Chem.* 46 (**2011**) 851. (d) G.-H. Kuo, T. Rano, P. Pelton, K. T. Demarest, A. C. Gibbs, W. V. Murray, B. P. Damiano and M. A. Connelly, *J. Med. Chem.* 52 (**2009**) 1768. (e) N. Zhang, S. Ayral-Kaloustian, T. Nguyen, J. Afragola, R. Hernandez, J. Lucas, J. Gibbons and C. Beyer, *J. Med. Chem.* 50 (**2007**) 319. (f) S. Caron, N. M. Do, J. E. Sieser, P. Arpin and E. Vazquez, *Org. Process Res. Dev.* 11 (**2007**) 1015.
3. (a) J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem. 34 (**1969**) 2543. (b) E. Francotte, R. W. Lang and T. Winkler, *Chirality* 3 (**1991**) 177. (c) L. Yang, T. Wenzel, R. T. Williamson, M. Christensen, W. Schafer and C. J. Welch, *ACS Cent. Sci.* 2 (**2016**) 332. (d) W. H. Pirkle and D. J. Hoover, *Top. Stereochem.* 13 (**1982**) 263.
4. (a) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.* 111 (**2011**) 455. (b) M. Tredwell, V. Gouverneur in Comprehensive Chirality, Eds. H. Yamamoto, E. M. Carreira, Elsevier Science, Amsterdam, **2012**, vol. 1, pp 70.
5. Selected examples: (a) D. Park, C. I. Jette, J. Kim, W.-O. Jung, Y. Lee, J. Park, S. Kang, M. S. Han, B. M. Stoltz and S. Hong, *Angew. Chem. Int. Ed.* 59 (**2020**) 775. (b) D. C. Fager, K. A. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.* 141 (**2019**) 16125. (c) J. H. Park, J. H. Sim and C. E. Song, *Org. Lett.* 21 (**2019**) 4567. (d) P. Martinez-Pardo, G. Blay, C. Vila, A. Sanz-Marco, M. C. Munoz and J. R. Pedro, *J. Org. Chem.* 84 (**2019**) 314. (e) T. Neves-Garcia, A. Velez, J. M. Martinez-Ilarduya and P. Espinet, *Chem. Commun.* 54 (**2018**) 11809. (f) H. Noda, F. Amemiya, K. Weidner, N. Kumagai and M. Shibasaki, *Chem. Sci.* 8 (**2017**) 3260. (g) A. M. Cook and C. Wolf, *Angew. Chem. Int. Ed.* 55, (**2016**) 2929. (h) C. Wang, J. Qin, X. Shen, R. Riedel, K. Harms and E. Meggers, *Angew. Chem. Int. Ed.* 55 (**2016**) 685. (i) M. Montesinos-Magraner, C. Vila, G. Blay, I. Fernandez, M. C. Munoz and J. R. Pedro, *Adv. Synth. Catal.* 357 (**2015**) 3047. (j) E. Sanchez-Diez, M. Fernandez, U. Uria, E. Reyes, L. Carrillo and J. L. Vicario, *Chem. Eur. J.* 21 (**2015**) 8384. (k) G. Blay, I. Fernandez, A. Monleon and J. R. Pedro, C. Vila, *Org. Lett.* 11 (**2009**) 441.
6. Selected examples: (a) J. Zhu, L. Huang, W. Dong, N. Li, X. Yu, W.-P. Deng and W. Tang, *Angew. Chem. Int. Ed.* 58 (**2019**) 16119. (b) X. Wang, Y. Gao, Z. Wei, J. Cao, D. Liang, Y. Lin and H. Duan, *Org. Chem. Front*. 6 (**2019**) 3269. (c) M. Miyagawa, M. Yoshida, Y. Kiyota and T. Akiyama, *Chem. Eur. J.* 25 (**2019**) 5677. (d) B. M. Trost, C-I. Hung, M. J. Scharf, *Angew. Chem. Int. Ed*. 57 (**2018**) 11408. (e) H. Lou, Y. Wang, E. Jin and X. Lin, *J. Org. Chem.* 81 (**2016**) 2019. (f) D. Zhou, Z. Huang, X. Yu, Y. Wang, J. Li, W. Wang and H. Xie, *Org. Lett.* 17 (**2015**) 5554. (g) M.-X. Zhao, H.-L. Bi, R.-H. Jiang, X.-W. Xu and M. Shi, *Org. Lett.* 16 (**2014**) 4566. (g) F.-G. Zhang, X.-Y. Zhu, S. Li, J. Niea and J.-A. Ma, *Chem. Commun*. 48 (**2012**) 11552.
7. Friedel–Crafts reactions: (a) H. Liu, A. M. Z. Slawin and A. D. Smith, *Org. Lett.* 22 (**2020**) 1301. (b) Y. Zhu, Z. Dong, X. Cheng, X. Zhong, X. Liu, L. Lin, Z. Shen, P. Yang, Y. Li, H. Wang, W. Yan, K. Wang and R. Wang, *Org. Lett.* 18 (**2016**) 3546. (c) G. Blay, I. Fernandez, M. C. Muñoz, J. R. Pedro and C. Vila, *Chem. Eur. J.* 16 (**2010**) 9117. Nitro-Michael addition: (d) Z. Jia, X. Hu, Y. Zhao, F. G. Qiu, A. S. C. Chan and J. Zhao, *Org. Lett.* 21 (**2019**) 9584. (e) P. Kwiatkowski, A. Cholewiak and A. Kasztelan, *Org. Lett.* 16 (**2014**) 5930. (f) H. Kawai, Z. Yuan, T. Kitayama, E. Tokunaga and N. Shibata, *Angew. Chem. Int. Ed.* 52 (**2013**) 5575. Alkynylation: (g) A. Sanz-Marco, G. Blay, M. C. Muñoz and J. R. Pedro, *Chem. Commun.* 51 (**2015**) 8958. (h) A. Sanz-Marco, G. Blay, C. Vila and J. R. Pedro, *Org. Lett.* 18 (**2016**) 3538. Enolate-addition: (i) X. Xu, Y. He, J. Zhou, X. Li, B. Zhu and J. Chang, *J. Org. Chem.* 85 (**2020**) 574. (j) C. Shu, H. Liu, A. M. Z. Slawin, C. Carpenter-Warren and A. D. Smith, *Chem. Sci*. 11 (**2020**) 241. (k) M.-X. Zhao, H.-K. Zhu, T.-L. Dai and M. Shi, *J. Org. Chem.* 80 (**2015**) 11330. Alkylation (l) G.-L. Chai, A.-Q. Sun, D. Zhai, J. Wang, W.-Q. Deng, H. N. C. Wong and J. Chang, *Org. Lett.* 21 (**2019**) 5040. Cycloadditions: (m) X.-C. Yang, Jin-Yu Liu, Zhen Liu, Xiu-Qin Hu and Peng-Fei Xu, *J. Org. Chem.* 84 (**2019**) 13871. (n) Y. You, W.-Y. Lu, Z.-H. Wang, Y.-Z. Chen, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett.* 20 (**2018**) 4453. (n) B. Xu, Z.-M. Zhang, L. Zhou and J. Zhang, *Org. Lett*. 20 (**2018**) 2716.
8. Friedel–Crafts reaction: (a) W. Xu, X. Shen, Q. Ma, L. Gong and E. Meggers, *ACS Catal.* 6 (**2016**) 7641. (b) H. Wu, R.-R. Liu, C. Shen, M.-D. Zhang, J. Gao and Y.-X. Jia, *Org. Chem. Front.* 2 (**2015**) 124. (c) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han and Y.-X. Jia, *J. Am. Chem. Soc.* 135 (**2013**) 2983. Enolate addition: (d) X. Lai, G. Zha, W. Liu, Y. Xu, P. Sun, T. Xia and Y. Shen, *Synlett* 27 (**2016**) 1983. (e) X. Hou, H. Ma, Z. Zhang, L. Xie, Z. Qin and B. Fu, *Chem. Commun.* 52 (**2016**) 1470. Cycloadditions: (f) L. Tang, B. Zhao, L. Dai, M. Zhang, Z Zhou, *Chem. Asian J.* 11 (**2016**) 2470. (g) X. Yuan, S.-J. Zhang, W. Du, Y.-C. Chen, *Chem. Eur. J.* 22 (**2016**) 11048.
9. (a) G. Romeder, Diethyl malonate in e-EROS Encyclopedia of Reagents for Organic Synthesis, **2001**, p. 1. (b) M. Yamaguchi,

Catalytic Conjugate Addition of Stabilized Carbanions in Comprehensive Asymmetric Catalysis, Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Springer-Verlag, **1999**, vol. 3, p. 1121. (c) B. N. Nguyen, K. K. Hii, W. Szymanski and D. B. Janssen, Conjugate Addition Reactions in Science of Synthesis, Stereoselective Synthesis, Eds. J. G. De Vries, G. A. Molander, D. A. Evans, Georg Thieme-Verlag, Sttutgart, **2011**, vol. 1, p. 571. (d) E. Reyes, U. Uria, J. L. Vicario and L. Carrillo, The catalytic, enantioselective Michael reaction in Organic Reactions, Ed. S. E. Denmark, John Wiley and Sons, Hoboken, **2016**, vol. 90, p. 1.

10. D. Cao, G. Fang, J. Zhang, H. Wang, C. Zheng and G. Zhao, *J. Org. Chem.* 81 (**2016**) 9973.
11. B. Huang, C. Li, H. Wang, C. Wang, L. Liu and J. Zhang, *Org. Lett.* 19 (**2017**) 5102.
12. M. Espinosa, J. Herrera, G. Blay, L. Cardona, M. C. Muñoz and J. R. Pedro, *Org. Biomol. Chem.* 15 (**2017**) 3849.
13. (a) G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.* 106 (**2006**) 3561. (b) G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.* 111 (**2011**) PR284.
14. (a) S. Nakamura, H. Nakashima, H. Sugimoto, N. Shibata and T. Toru., *Tetrahedron Lett.* 47 (**2006**) 7599. (b) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, and T. Toru., *Chem. Eur. J.* 14 (**2008**) 2145.
15. (a) M. Takacs, E. C. Lawson, M. J. Reno, M. A. Youngman and D. A. Quincy., *Tetrahedron: Asymmetry* 8 (**1997**) 3073. (b) S. Crosignani, G. Desimoni, G. Faita and P. P. Righetti, *Tetrahedron* 54 (**1998**) 15721. (c) H. Wang, X. Liu, H. Xia, P. Liu, J. Gao, P. Ying, J. Xiaoa and C. Li, *Tetrahedron* 62 (**2006**) 1025.
16. (a) K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.* 61 (**1996**) 346. (b) K. V. Gothelf, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.* 63 (**1998**) 5483.
17. (a) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin and M. P. John Dr., *Angew. Chem. Int. Ed.* 44 (**2005**) 1543. (b) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn and M. C. Willis, J. Am. Chem. Soc. 129 (2007) 10632. (c) M. Espinosa, G. Blay, L. Cardona, M. C. Muñoz and J. R. Pedro, *Chem. Eur. J.* 23 (**2017**) 14707.
18. C. Palomo, R. Pazos, M. Oiarbide and J. M. García., *Adv. Synth. Catal.* 348 (**2006**) 1161.
19. (a) M. Espinosa, G. Blay, L. Cardona and J. R. Pedro, *Chem. Eur. J.* 19 (**2013**) 14861. (b) M. Espinosa, G. Blay, L. Cardona and J. R. Pedro, *Chem. Eur. J.* 19 (**2013**) 17632 (correction). (c) M. Espinosa, G. Blay, L. Cardona and J. R. Pedro, *Org. Chem. Front.* 6 (**2019**) 2907. (d) M. Espinosa, G. Blay, L. Cardona, I. Fernandez, M. C. Muñoz and J. R. Pedro, *J. Coord. Chem.* 71 (**2018**) 864.
20. (a) W. Wang, X. Lian, D. Chen, X. Liu, L. Lin and X. Feng, *Chem. Commun*. 47 (**2011**) 7821. (b) D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M.Z. Slawin, T. J. C. O'Riordan, A. D. Smith, *Angew. Chem. Int. Ed.* 52 (**2013**) 11642.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.