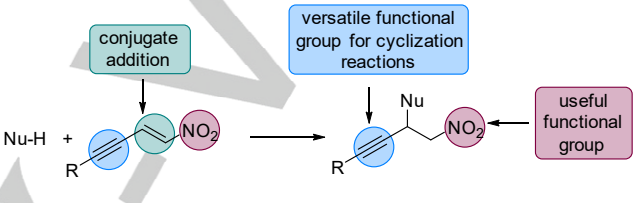
Nitroenynes as electrophiles in organocatalysis and its application in the synthesis of chiral heterocycles

Carlos Vila,*[a] Francisco Cernicharo-Toledo,[a] Gonzalo Blay[a] and José R. Pedro*[a]

[a] Dr. C. Vila, F. Cernicharo-Toledo, Prof. Dr. G. Blay, Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química,
Universitat de València
Dr. Moliner 50, 46100 Burjassot, València (Spain)
E-mail: jose.r.pedro@uv.es; carlos.vila@uv.es; https://www.uv.es/uvweb/college/en/directory/research-teams/basic-experimental-sciences/grup-1285956904846.html?p2=GIUV2013-125; https://www.carlosviladescals.com/

Abstract: Nitroenynes are a particular class of nitroalkenes, that have been recently used in organocatalysis. This review covers the recent examples in asymmetric catalysis using nitroenynes as electrophiles. The majority of the examples are enantioselective Michael additions, that have been categorized depending on the nucleophile, with representative examples providing insightful mechanistic details. Moreover, their applications to the synthesis of chiral heterocylces has also been discussed.



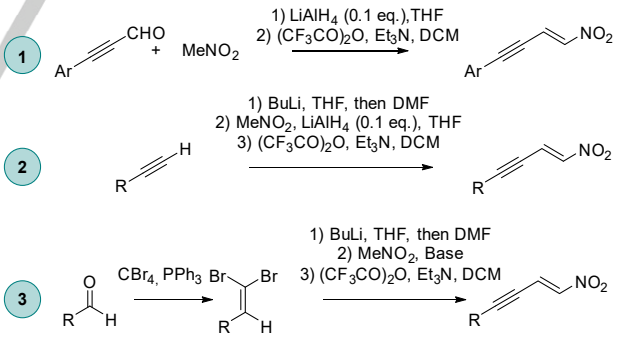
Scheme 1. Versatility of nitroenynes as electrophiles in asymmetric synthesis.

1. Introduction

The asymmetric conjugate addition of nucleophiles to α,β-unsaturated nitroalkenes[1] is a remarkable and useful tool for the construction of highly functionalized synthetic building blocks. The Nitro functional group in the resulting product can be converted into a variety of other useful functional groups.[2] Numerous examples of organocatalytic enantioselective reactions using nitroalkenes have been described in the literature for the synthesis of chiral nitro compounds.[3] In this context, the conjugate addition to polyconjugated substrates[4] have received increasing attention in the last years, and nitroenynes are a very attractive class of Michael acceptors.

The corresponding 1,4-addition product, homopropargylic nitro compounds, could enjoy the rich chemistry of functional-group transformations associated with the nitro[2] and alkynyl[5] moieties (Scheme 1). In all the examples discussed in this review, only 1,4-addition was observed. The 1,6-addition products that could be obtained using nitroenynes as electrophiles were not detected in any of the examples described. Therefore, all the examples presented are completely regioselective for the Michael reaction. In this review, an overview of the use of nitroenynes in organocatalysis is shown, discussing the reaction conditions and the stereoselectivity. But also, we will focus on the use of the corresponding chiral homopropargylic nitro compounds for the synthesis of chiral heterocycles. This kind of compounds are present in many biologically important molecules, like natural products or drugs.[6] They are particularly important in pharmaceutical industry and chemical synthesis and countless approaches have been established to prepare them. In this context, the functionalized homopropargylic nitro derivatives are excellent precursors for the synthesis of chiral heterocycles, due to the presence of the triple bond, that could be activated using metal catalyzed cyclizations.

There are three general methods for the synthesis of nitroenynes derivatives (Scheme 2), depending on the availability of the starting materials.[7] In all the cases, the final step is the Henry reaction of the corresponding propargylic aldehyde and nitromethane, and subsequent dehydratation of the nitroalcohol product using trifluoroacetic anhydride and a base.



Scheme 2. Synthesis of Nitroenynes.

Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from Valencia University. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling

reactions with organolithium reagents and asymmetric catalysis. In 2017, he was appointed as a 'Ramón y Cajal' researcher at the Organic Chemistry Department, Valencia University. His current research interests are asymmetric catalysis and photocatalysis.

Francisco Cernicharo-Toledo graduated in chemistry (2019) from the University of Valencia. In 2020 received his Master's degree in Organic Chemistry and conducting his Master Thesis under the supervision of Dr. Carlos Vila and Prof. Dr. José Ramón Pedro at the same university.

Gonzalo Blay (Real de Gandia, Valencia, 1964) received his degree in chemistry (1987) and his Ph.D. (1992) from the University of Valencia. He has been a Marie Curie postdoctoral fellow at the Agricultural University of Wageningen, The Netherlands, with Professor A. de Groot (1993–94) and visiting researcher at Aarhus University, Denmark, with Professor K. A. Jørgensen (2005). In 1996, he became Associate Professor at the Department of Organic Chemistry of the University of Valencia and was appointed Full Professor in 2012. His research interest includes organic synthesis and the development of catalytic methodologies, in particular asymmetric catalysis.

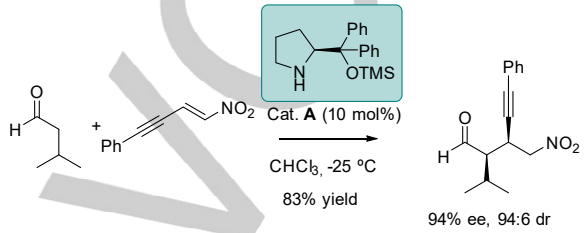
José R. Pedro graduated in chemistry from Valencia University, Spain, in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at Valencia University. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at Valencia University (AsymCat, GIUV-2013-125).

2. Reactions Using Carbonyl Compounds

Chiral γ-nitrocarbonyl compounds are synthetic precursors for a vast number of bioactive molecules, and their synthesis has received growing attention from the organic chemists over the last decades. Among all the methodologies described, the asymmetric Michel addition of carbonyl compounds to nitroolefins, is one of the most direct approach to provide such compounds. In this context, nitroenynes represent a valuable Michael acceptor, due to the presence of a triple bond in the corresponding Michael adducts. Several carbonyl compounds have been used as nucleophiles in the organocatalytic 1,4-addition to nitroenynes. We have divided this section, regarding the carbonyl compound used as nucleophile: aldehydes, ketones and malonate derivatives.

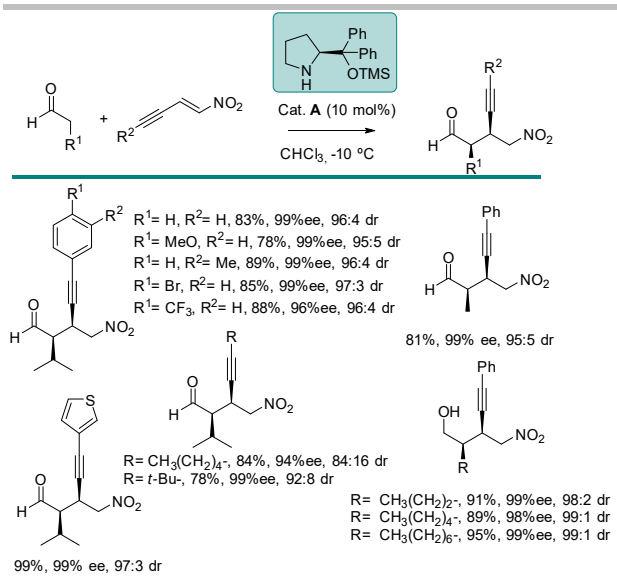
2.1. Aldehydes as nucleophiles

Alexakis and coworkers in 2008, described for the first time the use of phenylnitroenyne in asymmetric organocatalysis (Scheme 3).[8] His research group described the enantioselective addition of aldehydes to policonjugated substrates (nitrodienes) catalysed by (S)-diphenylprolinol silyl ether (Cat. **A**).[9] In this report, they described the enantioselective conjugate addition of isovaleraldehyde to phenylnitroenyne, obtaining the corresponding γ-nitrocarbonyl compound bearing two stereocenters, one of them propargylic, with good yield (83%) and excellent stereoselectivity (94:6 dr and 94% ee).



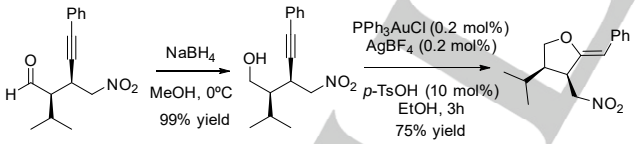
Scheme 3. The first example using a phenylnitroenyne in asymmetric organocatalysis (Alexakis, 2008).

Later, in 2010, Alexakis and Krause expanded the scope of this reaction to other aliphatic aldehydes and nitronenynes derivatives, and they also studied the synthetic possibilities of the corresponding chiral products.[10] In this article, the reported optimized reaction conditions are slightly different (-10 ºC) to the previous example, but using the same organocatalyst (cat. **A**). The described 12 examples (Scheme 4) all of them with good yields and stereoselectivities (excellent enantiomeric excesses and diastereomeric ratios). First they studied the reaction of isovaleraldehyde with aromatic nitroenynes, bearing electron-rich (MeO, Me) or electrondeficient (Br, CF_3), in *meta* or *para* position. The reaction also tolerates heteroaromatic (97:3 dr, 99% ee) and aliphatic nitroenynes. Finally, other aliphatic aldehydes were tested under the optimized reaction conditions, obtaining excellent results. In the case of *n*-valeraldehyde, heptanal and nonanal, the reaction products were obtained with excellent diastereo- (99:1) and enantioselectivities (>98% ee), which were determined after *in situ* reduction to the corresponding alcohols.



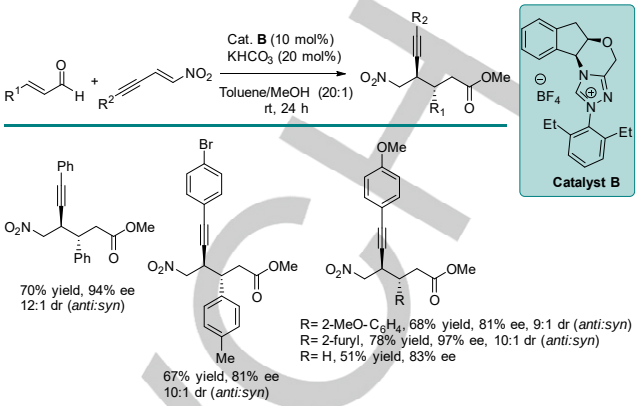
Scheme 4. Scope of the organocatalytic 1,4-addition of aldehydes to nitronenynes (Alexakis, 2010).

Alexakis, Krause and coworkers envisioned that the triple bond in the resulting chiral γ-nitrocarbonyl compounds could be converted into interesting chiral oxygen heterocycles using gold-mediated cyclization reactions.[11] Chiral tetrahydrofurans are widely occur in a large number of bioactive natural products and synthetic compounds.[12] Thus, considerable efforts have been dedicated to developing efficient methodologies for their synthesis. One way to synthesize this class of compounds is the cyclization of bis-homopropargylic alcohols catalyzed by gold (Scheme 5). First, they carried out the reduction of the Michael adduct with $NaBH_4$ in quantitative yield. The triple bond was subsequently activated with a mixture of gold and silver catalysts (PPh_3AuCl and $AgBF_4$), allowing the *5-exo dig* intramolecular attack of the hydroxyl group followed by a proto-deauration process, to finally give rise to the chiral tetrahydrofuran with good yield (75%) using only 0.2 mol% of gold catalyst.



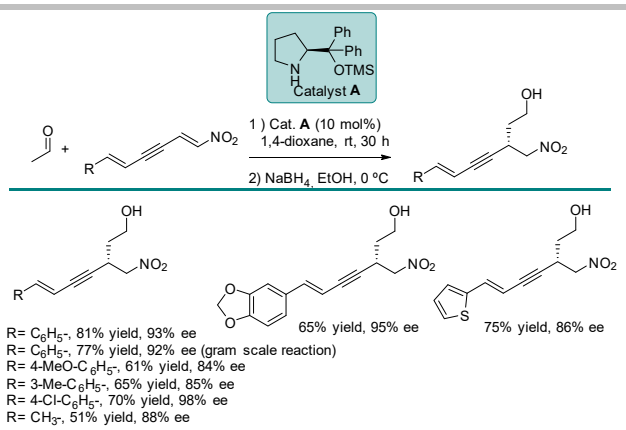
Scheme 5. Gold-catalyzed cyclization of bis-homopropargylic alcohol (Alexakis and Krause, 2009 and 2010).

Aldehydes can react with nitroenynes using other type of organocatalysis such as catalysis with *N*-heterocyclic carbenes "NHC".[13] Using this kind of catalysis, Liu's group described in 2011 the reaction between α,β-unsaturated aldehydes and polyconjugated nitroalkenes *via* homoenolate addition,[14] including 5 examples using nitroenynes as electrophiles (Scheme 6). Several enals, including aromatic and heteroaromatic, afford the corresponding products with good yields (67-78%), high enantioselectivity (81-97% ee) and diastereoselectivity (9:1-12:1). Additionally, acrolein was used as nucleophile, obtaining the corresponding δ-nitroester with lower yield and enantioselectivity (51% yield, 83% ee).



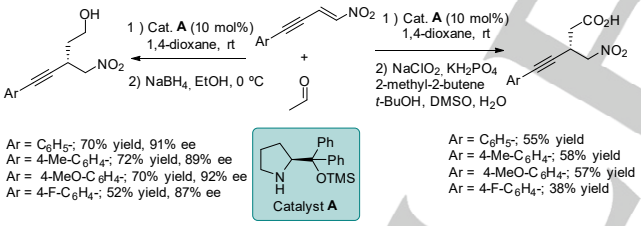
Scheme 6. Scope of homoenolate addition of enals to nitroenynes (Liu, 2012).

In the field of the asymmetric conjugate addition of carbonyl compounds to electron-deficient alkenes, the use of acetaldehyde, the simplest enolizable carbonyl compound, as nucleophile remains a challenge. Acetaldehyde acts as both a highly reactive nucleophile and electrophile, thus leading to its rapid consumption by self-aldolization. There are less examples of the direct conjugate addition reaction of acetaldehyde comparing with other enolizable aldehydes.[15] In this context, Shao, Peng and coworkers, in 2014 described the organocatalytic Michael addition of acetaldehyde to nitroenynes and nitrodienynes catalyzed by TMS-protected prolinol **A**.[16] The authors optimized the organocatalytic reaction using ((1*E*,5*E*)-6-nitrohexa-1,5-dien-3-yn-1-yl)benzene as electrophile and acetaldehyde as nucleophile using several protected prolinol catalysts. Catalyst **A** in dioxane at room temperature afforded the 1,3-enyne product, bearing a propargylic stereogenic center, with 81% yield amd 93% ee (Scheme 7). The catalytic asymmetric conjugate addition could be performed on a gram scale, obtaining similar results to the small scale reaction. The authors studied the scope of the reaction testing 6 different nitrodienynes. Aryl-substituted nitrodienynes bearing both electron-rich and -deficient aryl groups as well as heteroaromatic group gave highly functionalized 1,3-enyne products in good yields (61-77%) with high enantioselectivity (84-98% ee). Methyl-substituted nitrodienyne was also tested, obtaining the corresponding product in good enantioselectivity (88% ee), albeit in moderate yield (51%).



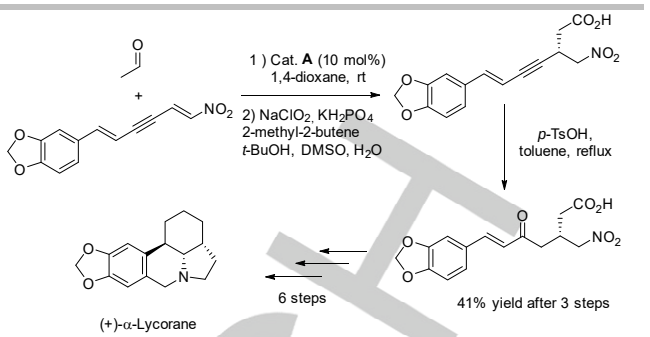
Scheme 7. Scope of the organocatalytic conjugate addition of acetaldehyde with nitrodienynes (Peng and Shao, 2014).

The authors extended their methodology using nitroenynes as electrophiles. They tested four different aromatic nitroenynes, obtaining moderate to good yields and high enantioselectivities, independently of the electronic character of the substituents of the aromatic ring (Scheme 8). Chiral β-alkynyl acids represent an important class of pharmaceutical compounds with diverse biological activities,[17] therefore their asymmetric synthesis is the great interest for the pharmaceutical industry and medicinal chemistry. In order to apply their methodology for the synthesis of β-alkynyl acids, the authors performed the Pinnick oxidation[18] with the Michael adducts furnishing the corresponding chiral β-alkynyl acids with moderate yields. The enantiomeric excesses of the corresponding chiral β-alkynyl acids were not determined, although they could measure their optical rotation.



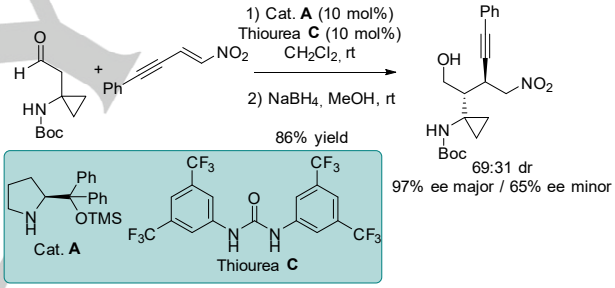
Scheme 8. Scope of the organocatalytic conjugate addition of acetaldehyde with nitroenynes (Peng and Shao, 2014).

Moreover, they could apply their methodology for the synthesis of the natural product (+)-α-Lycorane in 9 steps (Scheme 9). (+)-α-Lycorane is an alkaloid isolated from plants of the *Amaryllidaceae* family,[19] which has different pharmacological activities. The key step for the enantioselective synthesis of (+)-α-Lycorane, in which the chiral center was generated, was the conjugate addition of acetaldehyde to the nitrodienyne. The yield of the total synthesis was 7% after 9 steps.



Scheme 9. Organocatalytic enantioselective total synthesis of (+)-α-Lycorane (Peng and Shao, 2014).

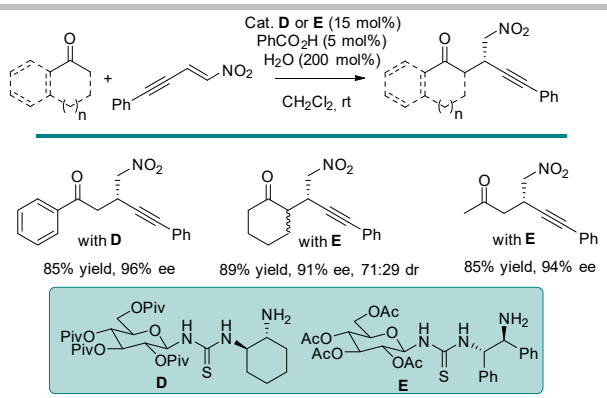
Kanger and coworkers, in 2015, described one example of organocatalytic conjugate addition of a cyclopropylacetaldehyde derivative to phenylnitroenyne (Scheme 10).[20] Cyclopropane-containing amino acids are important pharmaceuticals and biologically active compounds. The authors developed an organocatalytic methodology for the conjugate addition of cyclopropylaldehydes to different nitroalkenes. In this report, they also tested the phenylnitroenyne as electrophile, obtaining moderate diastereoselectivity, but high enantioselectivity (97% ee) for the major diastereoisomer.



Scheme 10. Organocatalytic conjugate addition of *tert*-butyl (1-(2-oxoethyl)cyclopropyl)carbamate to phenylnitroenyne.

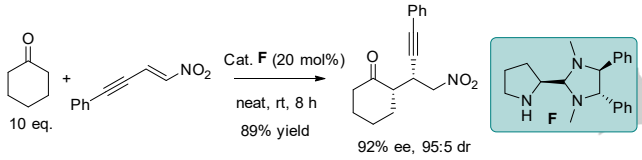
2.2. Ketones as nucleophiles

Ketones have also been used as nucleophiles in organocatalytic conjugate additions to nitroenynes, affording chiral γ-nitrocarbonyl compounds. In 2009, Ma and coworkers described the addition of 3 different ketones (acetophenone, cyclohexanone and acetone) to phenyl nitroenyne using saccharide-derived bifunctional thiourea catalysts (Scheme 11).[21,22] The corresponding Michael products were obtained with high yields and excellent enantioselectivities. However, when cyclohexanone was used as nucleophile moderate diastereoselectivity was observed (71:29 dr).



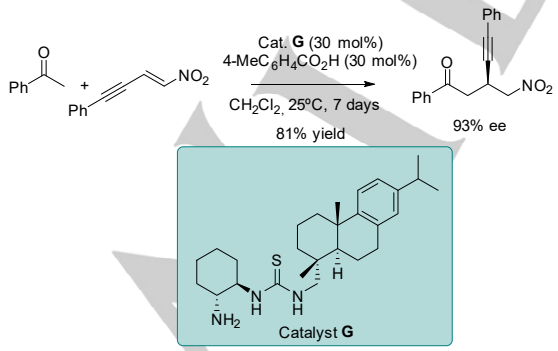
Scheme 11. Organocatalytic 1,4-addition of ketones to phenylnitroenyne (Ma, 2009).

In 2010, Alexakis's group described one example of the enantioselective addition of cyclohexanone to phenylnitroenyne using as organocatalyst a chiral secondary amine **F** (Scheme 12).[10] If we compare with the previously described reaction, the example of Alexakis is superior because the diastereoselectivity obtained was 95:5 with 92% ee.



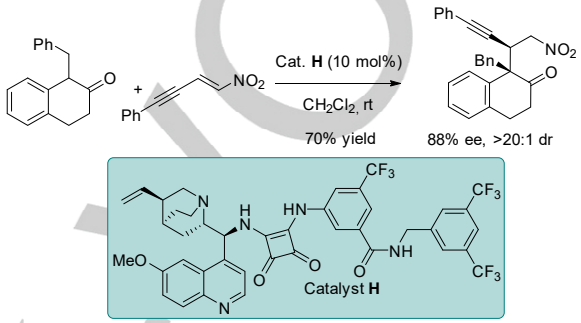
Scheme 12. Organocatalytic 1,4-addition of cyclohexanone to phenylnitroenyne (Alexakis, 2010).

In 2017, Wu and coworkers described the addition of aromatic ketones to polyconjugated nitrodienes.[23] In this report, they described one example using phenylnitroenyne as electrophile and acetophenone as nucleophile (Scheme 13). The corresponding chiral γ-nitro ketone was obtained with 81% yield and 93% ee. These results are slightly inferior to the ones reported by Ma and the reaction takes place for 7 days.



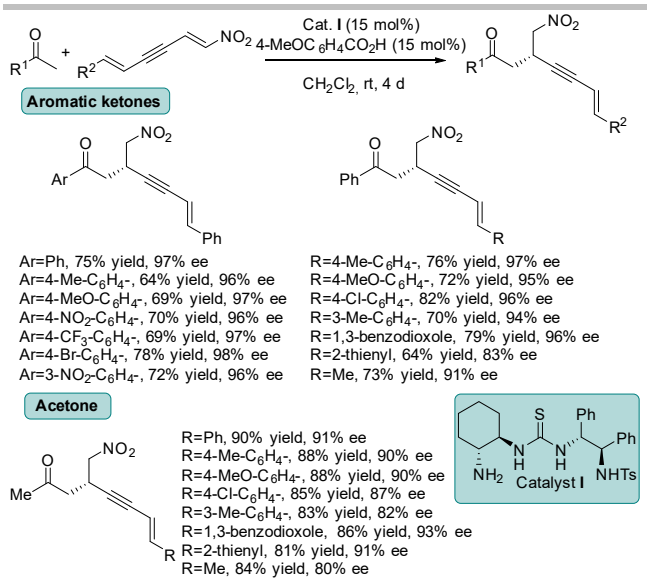
Scheme 13. Organocatalytic 1,4-addition of acetophenone to phenylnitroenyne (Wu, 2017).

In the same year, Palomo and collaborators performed the organocatalytic alkylation of a β-tetralone using as electrophile phenylnitroenyne (Scheme 14).[24] The corresponding chiral γ-nitroketone with two stereogenic center, one of them tetrasubstituted, was obtained with good yield (70%) high ee (88% ee) and excellent diastereoselectivity (>20:1) using as catalyst a bifunctional squaramide (catalyst **H**). Although the enantioselectivity is not excellent, this example is remarkable, due to the reaction is completely regioselective, both in the nucleophile and the electrophile, generating 2 chiral centers, one of them quaternary.



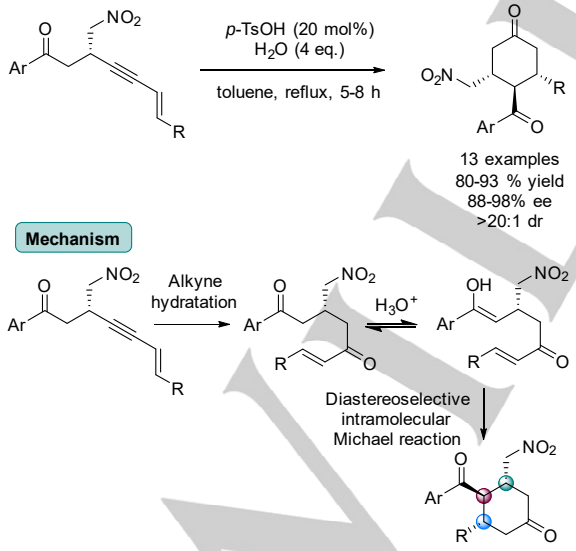
Scheme 14. Regio-, diastereo-, and enantioselective C_α-alkylation of β-tetralone and phenylnitroenyne (Palomo, 2017).

The last example using ketones as nucleophiles in asymmetric organocatalytic 1,4-addition to nitroenynes, was described by Peng and Sao in 2017.[25] They described the addition of aromatic ketones and acetone to nitrodienynes, using as catalyst a chiral thiourea-primary amine and 4-methoxybenzoic acid as co-catalyst (Scheme 15). This report is highly valuable, because the corresponding chiral γ-nitroketones are interesting building blocks, due to the existence of a carbonyl and nitro groups present in a 1,3-enyne compound. The authors described a broad substrate scope regarding aromatic ketones and nitrodienynes. Several aromatic nitrodienynes reacted smoothly with aromatic ketones, with good yields and excellent enantioselectivities (94-98% ee). Only when 2-thienyl substituted nitrodienyne was used, they observed lower enantioselectivity (83% ee). Moreover, an alkyl-substituted nitrodienynes was suitable compound for this enantioselective transformation obtaining the corresponding chiral 1,3-enyne in 73% yield and 91% ee. The authors extended their methodology to acetone, however the enantioselectivities were slightly lower (80-93% ee) comparing with aromatic ketones.



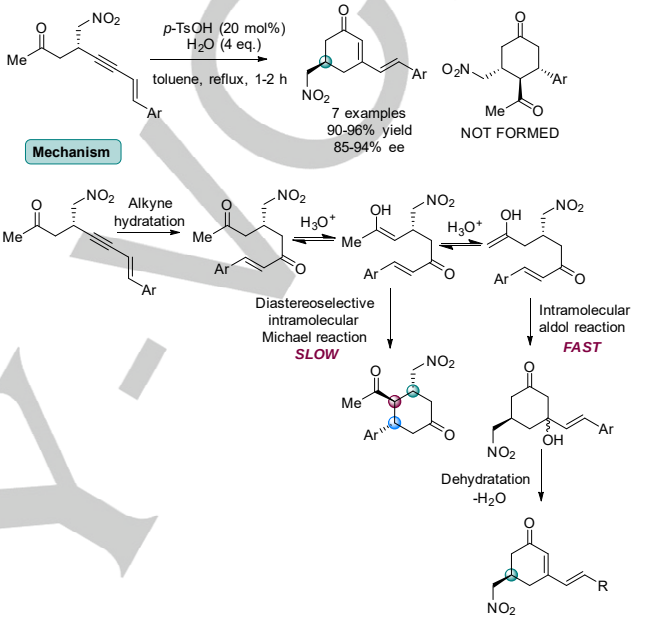
Scheme 15. Enantioselective conjugate addition of aromatic ketones and acetone to nitroenynes (Peng and Shao, 2017).

The authors demonstrated the versatility and utility of the obtained chiral Michael adducts. The treatment of 1,4-adducts prepared from aromatic ketones with H_2O in the presence of *p*-TsOH (20 mol%) in refluxing toluene, produced chiral 1,5-diketones bearing three contiguous stereogenic centers with high yields and excellent diastereoselectivity, maintaining the optical purity (Scheme 16). This transformation represents a tandem process, with first a regioselective hydratation of the triple bond, and then a diastereoselective intramolecular Michael reaction yielding the cyclic compound.



Scheme 16. Tandem hydratation/intramolecular Michael cyclization.

Remarkably, when the authors test the same reaction conditions with the chiral 1,4-adducts prepared from acetone, a different chiral product was formed. Using H_2O, *p*-TsOH and refluxing toluene, a chiral cyclic dienone was obtained. The authors provided a different mechanism to explain the different reactivity (Scheme 17). First, the regioselective hydration of the triple bond takes place affording a chiral enone as a product. Then, two enol tautomeric forms can be proposed. The more substituted enol form is the responsible for the diastereoselective intramolecular Michael addition, that the authors suggest that this reaction could be slow. While the less substituted enol form, could react with the carbonyl group of the enone by an intramolecular aldol reaction (faster than other Michael cyclization), followed by a dehydration to form the corresponding chiral dienone.

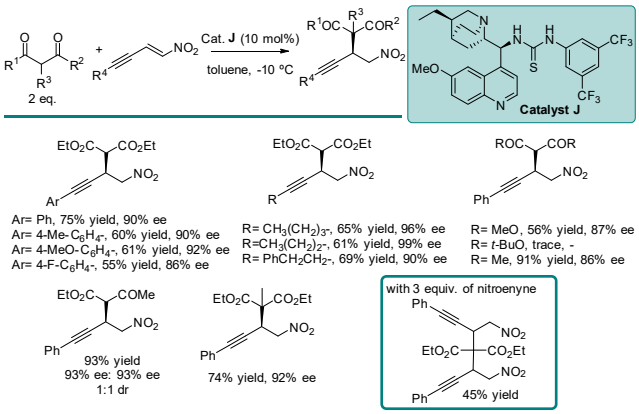


Scheme 17. Tandem hydratation/intramolecular aldol cyclization/ dehydratation.

2.3. 1,3-dicarbonyl compounds as nucleophiles

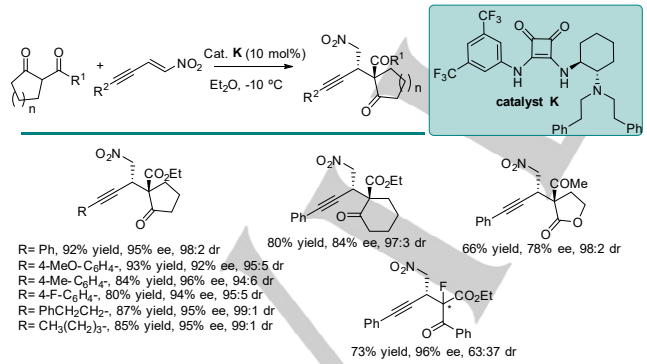
Other carbonyl compounds that have been used as nucleophile for the organocatalytic Michael addition to nitroenynes are dialkyl malonates.[26] This represent a straightforward manner to obtain chiral β-alkynyl acids derivatives, which constitute a class of building blocks as well as biologically active compounds.[17] The first authors that described the use of malonates as nucleophiles were Shao and coworkers (Scheme 18).[27] They studied different bifunctional organocatalysts, being the best catalyst a squaramide derived from dihydroquinine. Using diethylmalonate as nucleophile, they studied the scope of the reaction regarding the nitroenyne. The corresponding chiral Michael adducts were obtained with moderate to good yields (55-75%) and high enantioselectivities (86-99% ee), using aromatic and aliphatic nitroenynes. Interestingly, alkyl-substituted nitroenynes afforded the products with higher enantioselectivity. After, the authors studied the scope using other 1,3-dicarbonyl compounds. Dimethyl malonate gave lower yield and enantiomeric excess than diethyl malonate, while di-*t*-Butyl malonate did not react under the optimized reaction conditions. Acetyl acetone gave the corresponding product with 91% yield and 86% ee. Remarkably, diethyl 2-methylmalonate was tested as nucleophile obtaining good results (74% yield, 92% ee). It is interesting to note that if three equivalents of nitroenyne were used, the bis-addition

product of malonate to two nitroenyne molecules was the major product.



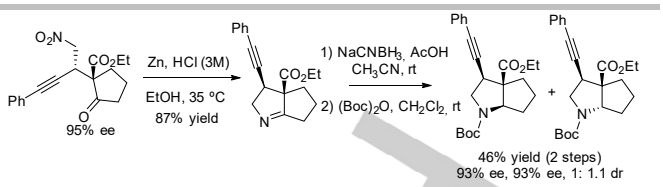
Scheme 18. Enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroenynes (Shao, 2011).

Furthermore, in 2012, Peng, Shao and coworkers developed the asymmetric Michael addition to nitroeynes of α-substituted β-ketoesters catalyzed by a bifunctional squaramide (Scheme 19).[28] The corresponding products are very interesting due to the presence of two contiguous stereogenic centers with several functional groups. First they studied the scope of the reaction using ethyl 2-oxocyclopentane-1-carboxylate and 6 different substituted nitroenynes, obtaining in all cases high yields (80-93%), excellent enantiomeric excess (92-95% ee) and excellent diastereoselectivity (94:6-99:1), for aromatic and aliphatic nitroenynes. Ethyl 2-oxocyclohexane-1-carboxylate and 2-acetylbutyrolactone afforded the corresponding Michael adducts with lower enantiomeric excess (84% ee and 78% ee respectively). Finally, the authors tested an acyclic α-fluorinated β-keto ester, affording high enantioselectivity (96% ee) but moderate diastereoselectivity (63:37 dr).



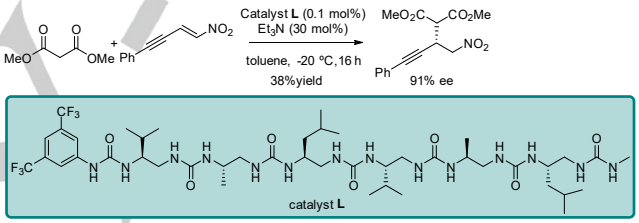
Scheme 19. Enantioselective Michael addition of α-substituted β-ketoesters to nitroenynes (Shao, 2012).

Furthermore, the authors developed the synthesis of conformationally constrained bicyclic γ^2-amino acid derivative, starting from the organocatalytic 1,4-addition product showing the aplicability of the developed methodology (Scheme 20).



Scheme 20. Synthetic transformation of the chiral β-ketoesters (Shao, 2012).

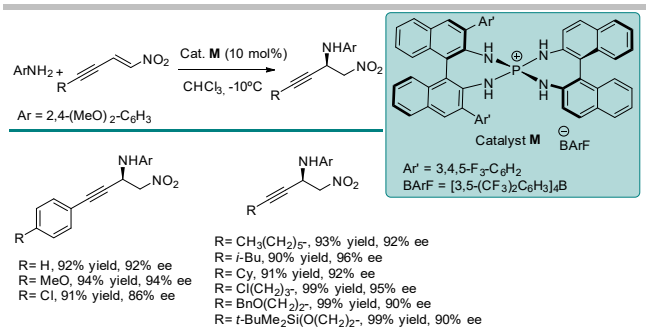
Additionally, in 2017, Guichard, Palomo and coworkers developed the Michael addition of diethyl malonate to different nitroalkenes using chiral oligo-ureas as bifunctional catalysts.[29] These molecules are of considerable size and present multiple hydrogen bond donors and acceptors bonds, for which the authors formulated the hypothesis of that a network of intramolecular hydrogen bonds is established that allow the catalyst to adopt a helix shape, making it a highly active organocatalyst. With the oligo-urea catalyst **L** (0.1 mol%), the Michael reaction of diethyl malonate to phenylnitroenyne was tested, obtaining similar enantiomeric excess (91% ee) than Shao's report, but with lower yield (38%) (Scheme 21).



Scheme 21. Organocatalytic addition of dimethyl malonate to phenylnitroenyne catalyzed by a helical oligo-urea foldamer (Guichard and Palomo 2017).

3. Reactions Using Amines

The previous examples were focused on the study of carbon nucleophilic species. However, there are very few studies based on the use of heteroatomic nucleophilic compounds in combination with nitroenynes as electrophiles, despite their important potential in organic chemistry for the synthesis of chiral β-propargylic nitroalkanes. Ooi *et al*. published in 2011 the enantioselective addition reaction of 2,4-dimethoxyaniline to different nitroenynes, using chiral arylaminophosphonium barfates as organocatalysts (Scheme 22).[30] The authors studied the scope of the reaction with 9 different substituted nitroenynes (aromatic and aliphatic) with different electronic and steric characteristics. Using electron-donor groups (MeO) at the *para*-position of the aromatic group obtained the corresponding chiral propargylic amine with higher yield and enantiomeric excess than with an electron-withdrawing group. On the other hand, the use of acyclic and cyclic alkyl groups did not affect the effectiveness of the reaction. Additionally, the system is compatible with alkyl chlorides as substituents, obtaining the addition product quantitatively with an enantiomeric excess of 95% ee. Finally, the bulky *tert*-butyl dimethyl silyl ether group was tolerated under the optimized reaction conditions affording good results.

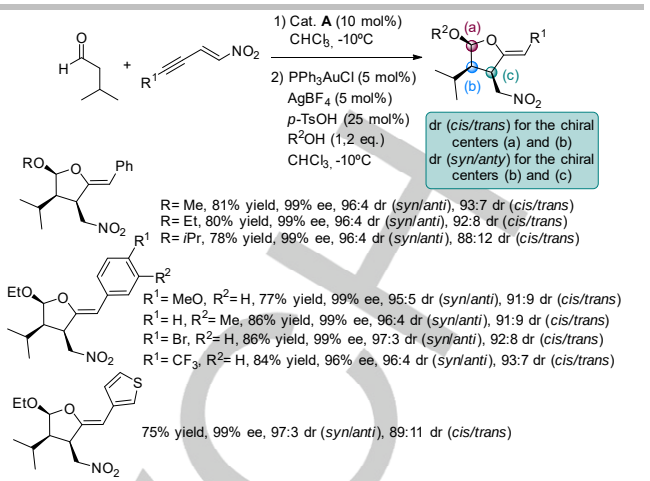


Scheme 22. Aza-Michael reaction with nitroenyne derivatives (Ooi, 2011).

4. Examples using Relay/Sequential Metal-organocatalysis

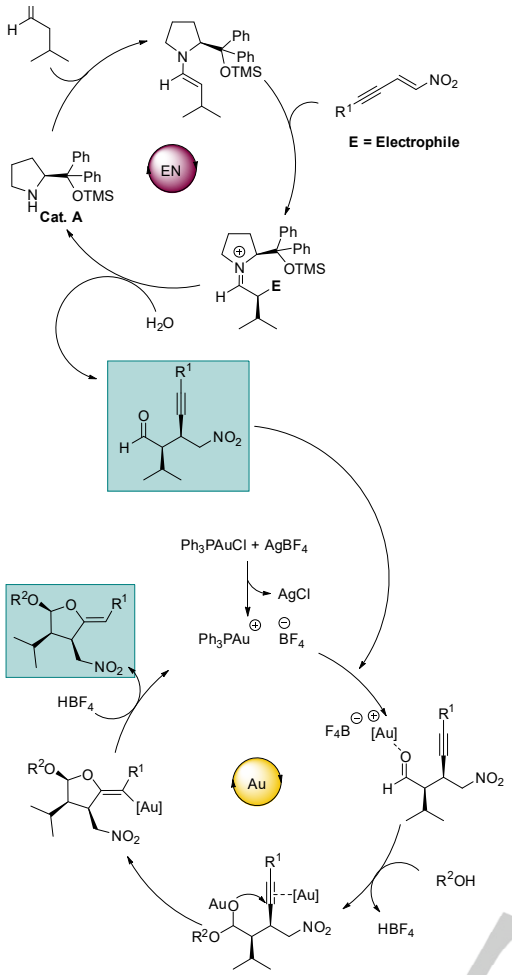
Asymmetric metal/organo combined catalysis, applying a metal complex and a chiral organocatalyst in a one-pot cascade or tandem reaction, has emerged as a promising strategy to build up molecular complexity from simple materials.[31] Such type of catalysis merges the advantages of both metal catalysis and organocatalysis, providing step-economy, and, more importantly, the potential to achieve inaccessible reactivity by a single catalyst. Based on the behaviors of the distinct catalysts, combined catalysis can be classified into cooperative, relay and sequential catalysis. In cooperative catalysis all the catalysts are involved in bond-breaking or forming events individually and simultaneously, while relay catalysis refers to a one-pot cascade process in which individual reactions are independently promoted by distinct catalysts in a cascade manner. Finally, in sequential catalysis some of the catalysts or reagents must be added in a stepwise manner, due to that some catalysts become significantly incompatible with each other, or with reaction conditions. In this part of the review, several examples of sequential (one-pot) and relay catalysis combining metal/organocatalysis involving nitroenynes are described.

The first authors that described the combination of metal and organocatalysis in a one-pot process using nitroenynes as electrophiles were Alexakis, Krause and coworkers. With the chiral γ-nitrocarbonyl compounds obtained through the organocatalytic conjugate addition of aldehydes to nitroenynes, they decided to investigate the gold-catalyzed tandem acetalization/cyclization[32] of the homopropargylic aldehyde affording chiral tetrahydrofuranyl ethers bearing three stereogenic centers (Scheme 23).[33]. After some optimization process, they could develop the one-pot reaction consisting in the enantioselective organocatalytic Michael addition of aldehydes to nitroenyne derivatives followed by a subsequent gold-catalyzed acetalization/cyclization, enabling them to obtain eight nitrosubstituted tetrahydrofuranyl ethers in high diastereo- and enantioselectivities and with excellent yields (Scheme 23).



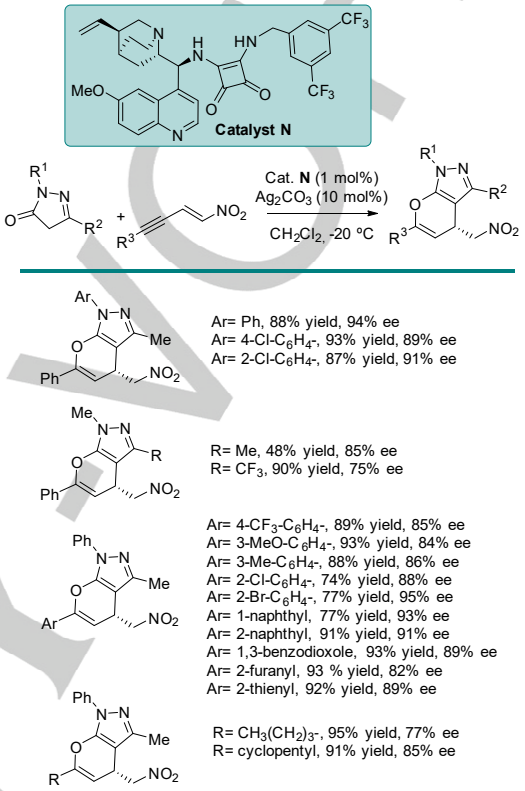
Scheme 23. Scope of the one-pot enantioselective Michael/acetalization/gold-catalyzed cyclization (Alexakis and Krause, 2009 and 2010).

The organocatalytic cycle (Scheme 24) begins with the previous formation of an enamine intermediate between the carbonyl compound (isovaleraldehyde) and the chiral amine **A** that acts as catalyst (Jørgensen-Hayashi catalyst). This enamine intermediate, which is more nucleophilic than the initial carbonyl species, reacts stereoselectively with the electrophile (nitroenyne). Finally, the hydrolysis of the resulting iminium ion takes place, with the consequent release of the addition product and the recovery of the catalyst. On the other hand, the metal cycle begins with the reaction between the gold and silver precursors, forming a new gold complex whose positive charge is more accessible that in the initial precursor. This catalyst activates the carbonyl oxygen of the Michael adduct, increasing the electrophilicity of the carbonyl group and allowing the attack of alcohol. Then, the gold complex activates the triple bond allowing the 5-*endo* attack by the hemiacetal oxygen. Finally, the proto-deauration process takes place affording the highly functionalized tetrahydrofuran product.



Scheme 24. Proposed mechanism for the one-pot process for the synthesis of chiral tetrahydrofuranyl ethers (Alexakis and Krause, 2009).

pyrazolone as nucleophile had to be carried out at room temperature, due to the low solubility of the compound, thus obtaining the cyclization product with a low yield (48% yield) but a high enantiomeric excess (85% ee). Finally, the reaction tolerates the use of nitroenynes with aliphatic substituents, although the enantioselectivity decreases (77-85% ee).

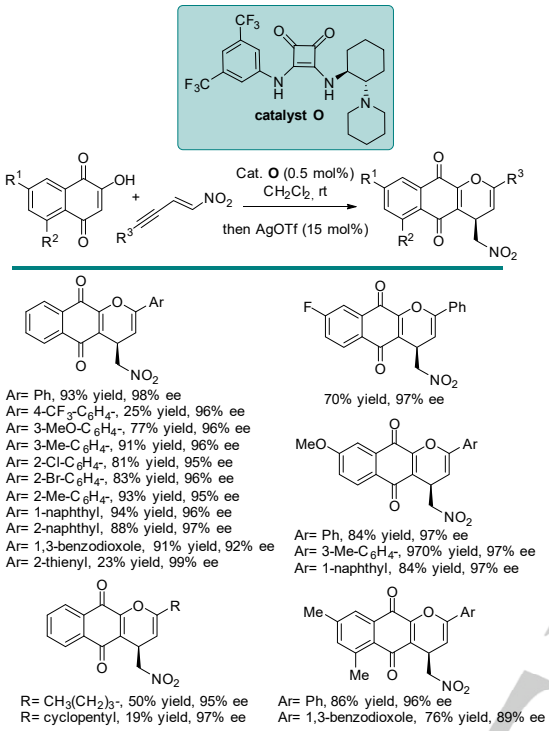


Scheme 25. Asymmetric tandem Michael/hydroalkoxylation cyclization combining silver and organocatalysis (Enders, 2015).

The Enders group has developed various methodologies in which organocatalysis and metal catalysis converge. Among them, the use nitroenins as electrophiles has been discussed and applied for the catalytic synthesis of chiral furans or pyrans. In 2015, Enders and coworkers described the asymmetric synthesis of pyrano-annulated pyrazoles using pyrazolones as nucleophiles and nitroenynes as electrophiles in a relay metal/organocatalysis methodology employing a squaramide as organocatalyst (Cat. **N**) and a silver salt (Ag_2CO_3) (Scheme 25).[34] Pyrazoles and their derivatives represent an important class of nitrogen heterocycles found widely in pharmaceutical and agrochemical.[35] Therefore, their asymmetric synthesis is highly important. In this context, pyrano-annulated pyrazoles have shown interesting biological properties. [36] Enders studied the scope and limitations of his Michael/hydroalkoxylation reaction with 18 different examples, obtaining good results in terms of yield and enantioselectivity for a wide variety of pyrazolones and nitroenynes, regardless of their electronic characteristics. The observed product is a pyrano-annulated pyrazole resulting from the *6-endo dig* attack of the enol form of the pyrazolone to the triple bond. It should be noted that when nitroenynes substituted with bulky groups are used, such as 1-naphthyl, 2-BrPh or 2-ClPh, they observed a decrease in yield but maintaining the enantioselectivity, possibly due to steric hindrance. On the other hand, the reaction using 2,5-dimethyl

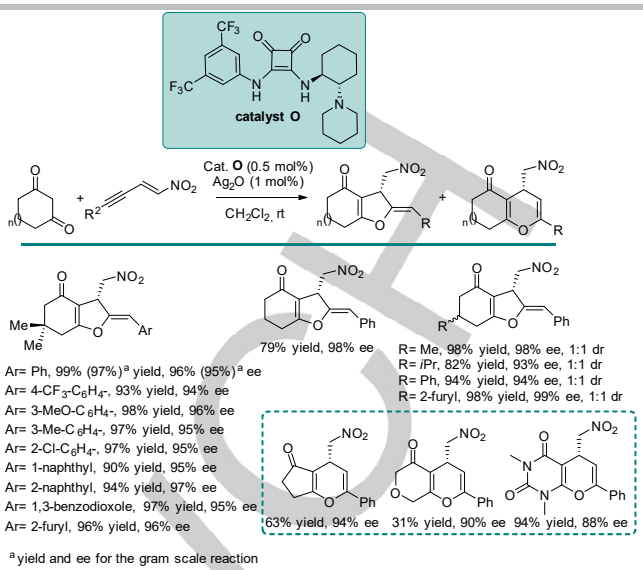
1,4-Naphthoquinone skeleton is present in a wide range of natural products that show several biological activities.[37] Therefore, the synthesis of chiral compound bearing this particular skeleton is interesting for the synthetic community. Enders group published, in 2016, a study using 2-hydroxy-1,4-naphthoquinones as nucleophiles and nitroenynes in the synthesis of chiral pyranonaphthoquinones.[36] In this article, the authors develop a sequential catalytic process that uses a chiral squaramide **O** (0.5 mol%), that catalyzed the Michael addition, and a silver salt (AgOTf) that catalyzed the hydroalkoxylation cyclization (Scheme 26). The scope of the reaction was widely investigated with 19 examples, using several substituted nitroenynes and several substituted hydroxynaphthoquinones. Using 2-hydroxy-1,4-naphthoquinone as nucleophile and phenylnitroenyne as electrophile, the cyclization product was obtained in excellent yield (93%) and excellent enantiomeric excess (98% ee) after the one-pot reaction. When nitroenynes with bulky substituents such as 1-naphthyl, 2-ClPh or 2-Br-Ph or with electron-donating groups (MeO, Me) the results were excellent both in conversion and enantioselectivity. However, the use of substrates with strong electron-withdrawing group such CF_3 at *para* position or heteroaromatic groups, was deleterious for the yield (23-25%), although the enantioselectivity was still high (96-99% ee).

Additionally, the reaction tolerates nitroenynes bearing aliphatic substituents leading to the products with excellent enantioselectivity (95-97% ee) although with low yields (19-50%). Finally, the authors studied the reaction using hydroxynaphthoquinone substituted with electron-donating and electron-withdrawing groups at the aromatic ring, observing good results for the final products.



Scheme 26. Asymmetric sequential one-pot Michael/hydroalkoxylation cyclization combining silver and organocatalysis (Enders, 2016).

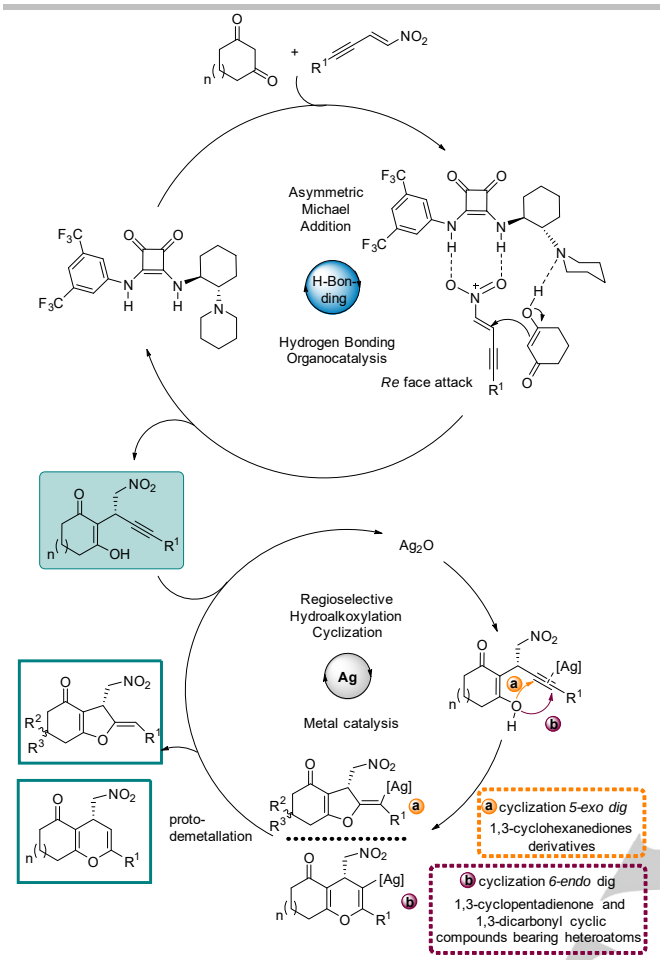
Additionally, the Enders group described in 2016, another one-pot enantioselective addition of Michael/ hydroalkoxylation cyclization. In this case cyclic 1,3-dicarbonyl compounds and different nitroenynes were reacted, using relay catalysis: the combination of squaramide organocatalyst (0.5 mol% of cat. **O**) and Ag_2O (1 mol%) (Scheme 27).[38] In this article, the authors describe 17 examples, obtaining in some cases chiral furans and in other cases chiral pyrans depending on the 1,3-dicarbonyl compound used. First, they studied the addition of dimedone and different aromatic nitroenynes affording the chiral tetrahydrobenzofurans with excellent yields (90-99% yield) and enantioselectivities (94-97% ee). In these cases, after the Michael addition of the cyclic 1,3-dicarbonyl compound to the nitroenyne, a selective *5-exo dig* cyclization takes places catalyzed by Ag_2O. After, different cyclic 1,3-dicarbonyl compounds were tested using phenylnitroenyne as electrophile. 1,3-cyclohexanedione gave the chiral tetrahydrofuran product with lower yield (79%) but excellent enantiomeric excess (98% ee). The authors also tested several 5-substituted 1,3-cyclohexanediones to introduce another stereocenter via desymmetrization in the final cyclization products. The desired tetrahydrobenzofurans were obtained in very good yields and enantioselectivities, but the diastereomeric ratio was virtually 1:1 in all the examples studied.



Scheme 27. Asymmetric sequential one-pot Michael/hydroalkoxylation cyclization with cyclic 1,3-diketones and nitroenynes combining silver and organocatalysis (Enders, 2016).

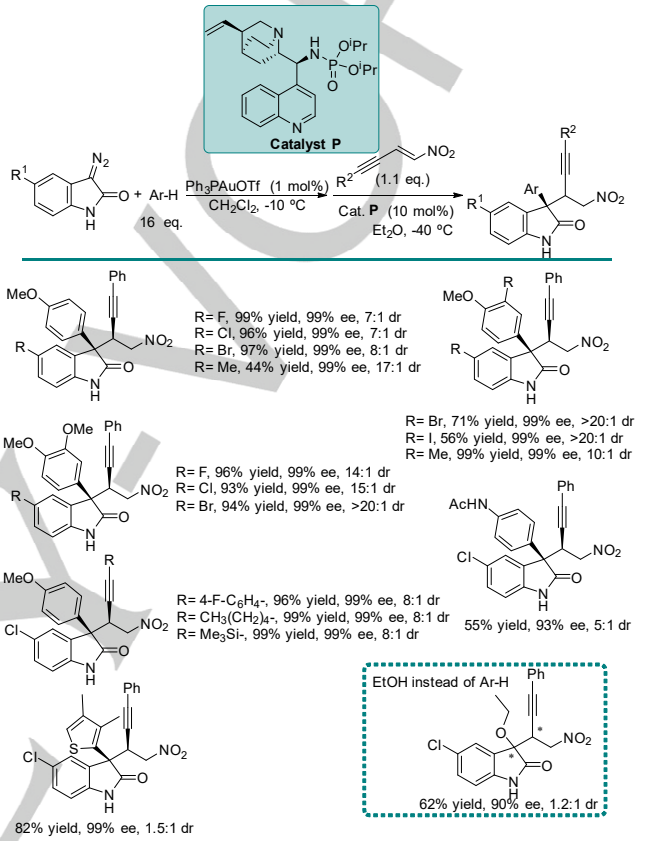
Interestingly, when the reaction was performed with 1,3-cyclopentanedione afforded a chiral dihydropyran with moderate yield (63%) and excellent enantiomeric excess (94% ee). In this case, after the Michael addition of the cyclic 1,3-dicarbonyl compound to the phenylnitroenyne, a selective *6-endo dig* cyclization takes places catalyzed by Ag_2O. In a similar way, when cyclic 1,3-dicarbonyl compounds with heteroatoms were used, the dihydropyran were also obtained with slightly lower enantioselectivity (88-90% ee). Moreover, the authors could apply their enentioselective methodology at one-gram scale reaction, obtaining the chiral tetrahydrobenzofuran with a 97% yield (3.41 mmol, 1.07 grams) and the same enantioselectivity (95 %ee).

The authors proposed a reaction mechanism for their one-pot procedure (Scheme 28). In the first cycle, the squaramide catalysts acts as a bifunctional catalyst. Nitroenyne is activated due to the formation of hydrogen bonds between the nitro group and the squaramide. Simultaneously, the nucleophile is activated by establishing an analogous interaction of the hydroxyl group of the enol form with the tertiary amine. Thanks to the interaction of both substrates, plus the chiral environment provided by the catalyst backbone, the enantiomerically enriched Michael addition product is obtained. In the second cycle the Ag (I) species, activated electrophilically the triple bond via a π-complex, facilitating the intramolecular hydroalkoxylation cyclization reaction, which occurs via *5-exo dig* or *6-endo dig* depending on the nature of the 1,3-dicarbonyl compound. Finally, the process of protodeargentation of the vinyl silver intermediate takes place, giving rise to the chiral tetrahydrobenzofuran or dihydropyran derivatives. The authors did not give an explanation for the different cyclization mechanisms.



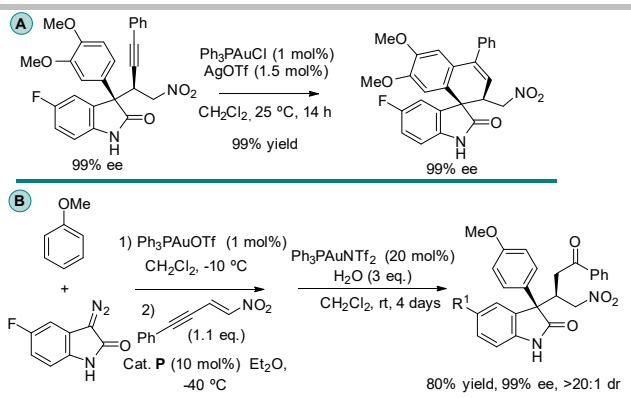
Scheme 28. Proposed mechanism for the one-pot Michael addition/hydroalkoxylation cyclization (Enders, 2016).

Another example using a combination of metal catalysis and organocatalysis was described by Zhou and coworkers in 2016.[39] They reported the sequential Au(I)/hydrogen bonding organocatalysis for a tandem gold mediated C-H functionalization of anisoles and thiophenes with diazooxindoles and subsequent Michael addition reaction for the synthesis of chiral oxindoles products bearing two stereogenic centers (Scheme 29). The first step is the gold catalyzed C-H insertion of the electron-rich arene in the diazooxindole derivative. After this reaction, they removed the CH_2Cl_2, dissolved in Et_2O, added the organocatalyst **P** (10 mol%), cooled to -40 ºC and followed with the addition of nitroenyne. It was found that by catalysis with gold (I) complexes, all nucleophiles reacted effectively with the diazooxindole derivatives, and subsequently the Michael addition to nitroenyne allow the formation of the oxindole with a quaternary stereocenter. The authors described 15 examples, using nucleophiles and electrophiles with different degrees of substitution. It should be noted that when using slightly electron-donating groups (Me) in the diazocompound, the yield decreases, but good results are obtained in terms of enantioselectivity and diastereoselectivity (44% yield, 99% ee, 17:1 dr). Additionally, when electron-withdrawing groups are used in the diazocompound the yields, enantiomeric excess and diastereoselectivity were excellent. The reaction tolerates substituted nitroenynes with aliphatic chains or TMS group. Finally, changing the anisole nucleophile for 3,4-dimethylthiophene or acetanilide, good yields and excellent enantioselectivities were obtained, but the diastereoselectivity decreased (1.5:1 and 5:1 dr). The authors also extended their methodology for O-H insertion/Michael addition sequence obtaining the 3-alkoxy-oxindole with good yield (62%) and high enantioselectivity (90% ee), but poor diastereoisomeric ratio (1.2:1 dr).



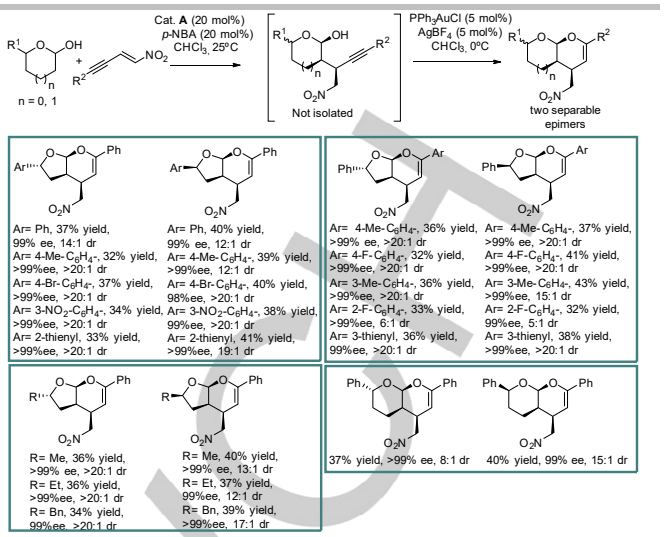
Scheme 29. Sequential C-H functionalization of arenes/asymmetric Michael addition using the combination of gold/organocatalysis (Zhou, 2016).

Moreover, the authors showed the synthetic versatility of the functionalized chiral oxindoles with the propargylic stereocenter obtained with their sequential methodology (Scheme 30 A). The cyclization of the Michael product gave the corresponding spirocyclic oxindole using 1 mol% of $Ph_3PAuOTf$ maintaining the enantiomeric purity of the compound. Furthermore, the authors described the gold catalyzed regioselective hydratation of the triple bond of the Michael adduct through a one-pot triple sequential reaction to prepare the γ-nitroketone bearing an oxindole moiety.



Scheme 30. Synthetic transformations of the propargylic chiral compounds (Zhou, 2016).

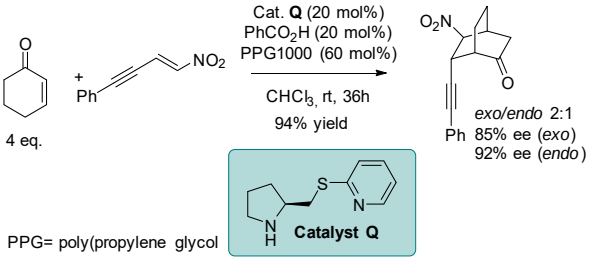
Chiral bicyclic acetals are important structures in synthetic organic chemistry, as they can serve as building blocks for the construction of complex oxygen containing heterocycles. In this context, Liu's group studied the addition of various racemic hemiacetals to aromatic nitroenynes, by a one-pot reaction using organocatalysis/gold-catalysis (Scheme 31) taking advantage of the propargylic stereocenter.[40] This case is an example of sequential catalysis. The authors studied 14 examples with different degrees of substitution, in which two separable epimers with several chiral centers were obtained from the racemic lactols precursors. In all cases, the gold catalyzed cyclization occurs through a *6-endo dig* attack. Using cyclic five-membered hemiacetals substituted with neutral aromatic rings, or with electron-attracting groups or heteroaromatic rings, the cyclization products were obtained with good yields (total yield), excellent enantiomeric excesses (99% ee in most of the cases) and excellent diastereoselectivities (20:1 in most of the cases). On the other hand, when nitroenynes substituted with aromatic rings with electron-donating or electron-withdrawing groups or heteroaromatic rings were used, similar yields, enantiomeric excesses or diastereoselectivities were observed. Only in the case of *orto*-fluorobenzene derivative the diastereoselectivities observed were lower (6:1 and 5:1). Finally, the use of a six-membered racemic lactol also shows the formation of the *6-endo dig* cyclization product, with yield and enantioselectivity similar to the other cases, but with a slight decrease on the diasteresolectivity. The absolute configuration of the products was determined by single-crystal X-ray analysis and NOE experiments.



Scheme 31. Scope of the organocatalytic addition of racemic lactols and aromatic nitroenynes (Liu, 2017).

5. Other reactions

In the last part of this review other organocatalytic reactions different from Michael addition using nitrenynes are discussed. Looking at the literature examples, phenylnitroenyne had been used also in an organocatalytic Diels-Alder. The grup of Xu developed a Diels-Alder reaction of cyclohexenones with nitro polyconjugated compounds in excellent chemo-, regio- and enantioselectivities using supramolecular organocatalysis.[41] The authors claim that this chiral supramolecular catalysts, self-assembles from chiral secondary amine (catalyst **Q**) with readily available achiral poly(alkene glycol)s through weak noncovalent interactions. In this article, they report one example using phenylnitroenyne. The corresponding Diels-Alder product is obtained in 94% yield, 2:1 *exo/endo* ratio and 85% ee for the major *exo* product (Scheme 32).



Scheme 32. Organocatalytic Diels-Alder reacttion of cyclohexanone and phenylnitroenyne using supramolecular organocatalysis (Xu, 2012).

7. Conclusions

In summary, in this review we have presented an overview of the use of nitroenynes and derivatives in organocatalytic reactions that have been reported in the last years. Several successful organocatalytic methodologies for the Michael addition of different nucleophiles to this particular kind of electrophile have been described. Moreover, the versatility of Michael adducts with a propargylic stereocenter have been discussed with the different

applications that have been described in the literature. The triple bond represents a powerful functional group for subsequent cyclizations catalyzed by gold or silver, providing an extensive variety of chiral heterocycles. We hope that this review will serve as a handy reference for synthetic chemists interested in developing new organocatalytic protocols using nitroenynes as electrophile.

Acknowledgements ((optional))

Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (CTQ2017-84900-P) is acknowledged. C.V. thanks the Agencia Estatal de Investigación (AEI, Spanish Government) for RyC contract (RYC-2016-20187).

Keywords: organocatalysis • asymetric catalysis • nitrocompounds • alkynes • heterocycles

[1] a) *Catalytic Asymmetric Conjugate Reactions*, (Ed. A. Córdova), Wiley-VCH: Weinheim, **2010**; b) *Conjugate Addition Reactions in Organic Synthesis*; Pergamon, (Ed. P. Perlmutter), Oxford, **1992**; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877-1894.

[2] a) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**; b) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017-1047.

[3] a) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. J. Ramón, *Molecules* **2017**, *22*, 895; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun*. **2007**, 3123-3135; c) D. Roca-López, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron Asymmetry* **2010**, *21*, 2561-2601; d) R. Somanathan, D. Chavez, F. A. Servin, J. A. Romero, A. Navarrete, M. Parra-Hake, G. Aguirre, D. P. C. Anaya, J. González, *Curr. Org. Chem*. **2012**, *16*, 2440-2461; e) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, *45*, 2627-2648; e) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065-2092.

[4] a) A. G. Csakÿ, G. de la Herrán, M. C. Murcia, *Chem. Soc. Rev*., **2010**, *39*, 4080-4102; b) R. Ballini, N. Araújo, M. V. Gil, E. Román, J. A. Serrano, *Chem. Rev*. **2013**, *113*, 3493-3515.

[5] a) *Acetylene Chemistry: Chemistry, Biology, and Material Science*, (Eds: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**; b) *Modern Acetylene Chemistry*, (Eds: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1995**.

[6] a) *Heterocycles in Natural Product Synthesis*, (Eds: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**; b) *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, (Eds. T. Eicher, S. Hauptmann, A. Speicher), Wiley-VCH, Weinheim, **2012**; c) *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, (Eds. A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky), John Wiley & Sons, Chichester, **2011**.

[7] For the first report in the use of nitroenynes in asymmetric catalysis: B. M. Trost, S. Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003-6005; For examples using chiral metal complexes, see: b) M. Tissot, D. Muller, S. Belot, A. Alexakis, *Org. Lett*. **2010**, *12*, 2770-2773; c) M. Tissot, A. Alexakis, *Chem. Eur. J.* **2013**, *19*, 11352-11363.

[8] S. Belot, A. Massaro, A. Tenti, A. Mordini, A. Alexakis, *Org. Lett*., **2008**, *10*, 4557-4560.

[9] a) A. Mielgo, C. Palomo, *Chem. Asian J*. **2008**, *3*, 922-948; b) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal*. **2010**, *352*, 243-279; c) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res*. **2012**, *45*, 248-264.

[10] S. Belot, A. Quintard, N. Krause, A. Alexakis, *Adv. Synth. Catal.* **2010**, *352*, 667-695.

[11] a) R. Dorel, A, M. Echevarren, *Chem. Rev*. **2015**, *115*, 9028-9072; b) M. Marín-Luna, O. Nieto Faza, C. Silva López, *Front. Chem*. **2019**, *7*, 296.

[12] For selected reviews on the synthesis of natural products with tetrahydrofuran skeletons, see: a) M. M. Faul, B. E. Huff, *Chem. Rev*. **2000**, *100*, 2407-2473; b) E. J. Kang, E. Lee, *Chem. Rev*. **2005**, *105*, 4348-4378; c) A. Goel, A. Kumar, A. Raghuvanshi, *Chem. Rev*. **2013**, *113*, 1614-1640; d) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Alvarez, *Chem. Rev*. **2013**, *113*, 4567-4610.

[13] a) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev*. **2008**, *37*, 2691-2698; b) V. Nair, R. S. Menon, A. T. Biju, C. R.Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev*. **2011**, *40*, 5336-5346; c) D. T. Cohen, K. A. Scheidt, *Chem. Sci*. **2012**, *3*, 53-57.

[14] B. Maji, L. Ji, S. Wang, S. Vedachalam, R. Ganguly, X.-W. Liu, *Angew. Chem. Int. Ed.* **2012**, *124*, 8401-8405.

[15] For the first examples of the conjugate addition of acetaldehyde to nitroalkenes, see: a) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem., Int. Ed*. **2008**, *47*, 4719-4721; b) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem., Int. Ed*. **2008**, *47*, 4722-4724.

[16] X.-L. Meng, T. Liu, Z.-W. Sun, J.-C. Wang, F.-Z. Peng, Z.-H. Shao, *Org. Lett.* **2014**, *16*, 3044−3047.

[17] a) T. Shimada, H. Ueno, K. Tsutsumi, K. Aoyagi, T. Manabe, S. Sasaki, S. Katoh, *Int. Appl. PCT, WO 2009054479*, **2009**; b) J. Houze, J. Liu, Z. Ma, J. C. Medina, M. J. Schmitt, R. Sharma, Y. Sun, Y. Wang, L. Zhu, *U.S. Patent 7,465,804*, **2008**; c) S. P. Brown, P. Dransfield, Z. Fu, J. Houze, X. Jiao, T. J. Kohn, V. Pattaropong, M. Vimolratana, M. J. Schmitt, *Int. Appl. PCT, WO 2008130514*, **2008**, d) J. N. Xiang, J. M. Karpinski, S. B. Christensen, *Int. Appl. PCT, WO 0009116*, **2000**.

[18] B. S. Bal, W. E. Jr. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091-2096.

[19] a) Z. Jin, *Nat. Prod. Rep*., **2005**, *22*, 111-126; b) Z. Jin, *Nat. Prod. Rep*., **2007**, *24*, 886-905.

[20] M. Kaasik, A. Noole, K. Reitel, I. Järving, T. Kanger, *Eur. J. org. Chem*. **2015**, 1745-1753.

[21] H. Ma, K. Liu, F.-G. Zhang, C.-L. Zhu, J. Nie, J.-A. Ma, *J. Org. Chem*. **2010**, *75*, 1402-1409.

[22] For the use of saccharide-derived bifunctional thiourea catalysts, see: a) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett*. **2007**, *9*, 923-925. (b) X.-J. Li, K. Liu, H. Ma, J. Nie, J.-A.Ma, *Synlett* **2008**, 3242-3246.

[23] X.-T. Guo, F. Sha, X.-Y. Wu, *Synthesis*, **2017**, *49*, 647-656.

[24] I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.*, **2017**, *56*, 2059-2063.

[25] T. Liu, M. Zhou, T. Yuan, B. Fu, X. Wang, F. Peng, Z. Shao, *Adv. Synth. Catal.* **2017**, *359*, 89-95.

[26] For enantioselective examples using metal complexes, see: a) Q. Zhu, H. Huang, D. Shi, Z. Shen, C. Xia, *Org. Lett.* **2009**, *11*, 4536-4539; b) X. Li, F. Peng, M. Zhou, M. Mo, R. Zhao, Z. Shao, *Chem. Commun.,* **2014**, *50*, 1745-1747; c) Z. Sun, M. Zhou, X. Li, X. Meng, F. Peng, H. Zhang, Z. Shao, *Chem. Eur. J*. **2014**, *20,* 6112-6119.

[27] X.-J. Li, F.-Z. Peng, X. Li, W.-T. Wu, Z.-W. Sun, Y.-M. Li, S.-X. Zhang, Z.-H. Shao, *Chem. Asian J*. **2011**, 6, 220-225.

[28] X. Li, X. Li, F. Peng, Z. Shao, *Adv. Synth. Catal*. **2012**, *354*, 2873-2885.

[29] D. Bécart, V. Diemer, A. Salaün, M. Oiarbide, Y. R. Nelli, B. Kauffmann, L. Fischer, C. Palomo, G. Guichard, *J. Am. Chem. Soc*. **2017**, *139*, 12524-12532.

[30] D. Uraguchi, N. Kinoshita, T. Kizu, T. Ooi, *Synlett.*, **2011**, 1265-1267.

[31] a) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.*, **2010**, *16*, 9350-9365; b) J. Zhou, *Chem. Asian J*., 2010, 5, 422-434; c) N. T. Patil, V. S. Shinde B. Gajula, *Org. Biomol. Chem*., **2012**, *10*, 211-224; d) Z. Du, Z. Shao, *Chem. Soc. Rev*., **2013**, *42*, 1337-1378; e) P.-S. Wang, D.-F. Chen, L.-Z. Gong, *Top Curr. Chem.,* **2020**, *378*, 9.

[32] a) V. Belting, N. Krause, *Org. Biomol. Chem*. **2009**, *7*, 1221-1225; b) T. Godet, C. Vaxelaire, C. Michel, A. Millet, P. Belmont, *Chem. Eur. J*. **2007**, *13*, 5632-5641.

[33] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed*. **2009**, *48*, 8923-8926.

[34] D. Hack, P. Chauhan, K. Deckers, Y. Mizutani, G. Raabe, D. Enders, *Chem. Commun*., **2015**, *51*, 2266-2269.

[35] S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev*. **2011**, *111*, 6984-7034.

[36] a) S. Prasanna, E. Manivannan, S. C. Chaturvedi, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 2097-2102; b) S. R. Berthensha, J. J. Talley , D. J. Rogier , M. J. Graneto, C. M. Koboldt , *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 2827-2830.

[37] U. Kaya, P. Chauhan, D. Hack, K. Deckers, R. Puttrenddy, K. Rissanen, D. Enders, *Chem. Commun*. **2016**, *52*, 1669−1672.

[38] U. Kaya, P. Chauhan, K. Deckers, R. Puttrenddy, K. Rissanen, G. Raabe, D. Enders, *Synthesis*. **2016**, *48*, 3207-3216.

[39] Z.-Y. Cao, Y.-L. Zhao, J. Zhou, *Chem. Commun*. **2016**, *52*, 2537-2540.

[40] Z.-H. You, Y.-H. Chen, X.-N. Wu, Y.-K. Liu, *Adv. Synth. Catal*., **2017**, *359*, 4260-4266.

[41] A.-B. Xia, D.-Q. Xu, C. Wu, L. Zhao, Z.-Y. Wu, *Chem. Eur. J.* **2012**, *18*, 1055-1059.

Entry for the Table of Contents

Insert graphic for Table of Contents here. ((Please ensure your graphic is in **one** of following formats))

Insert text for Table of Contents here.

Nitroenynes are an interesting electrophile in asymmetric organocatalysis, due to the versatility of the functional groups present in its structure. This review covers the organocatalytic examples using this electrophile and its application for the synthesis of chiral heterocycles.

Institute and/or researcher Twitter usernames: @cviladescals