REVIEW

Development and Application of Asymmetric Organocatalytic Mukaiyama and Vinylogous-Mukaiyama-Type Reactions

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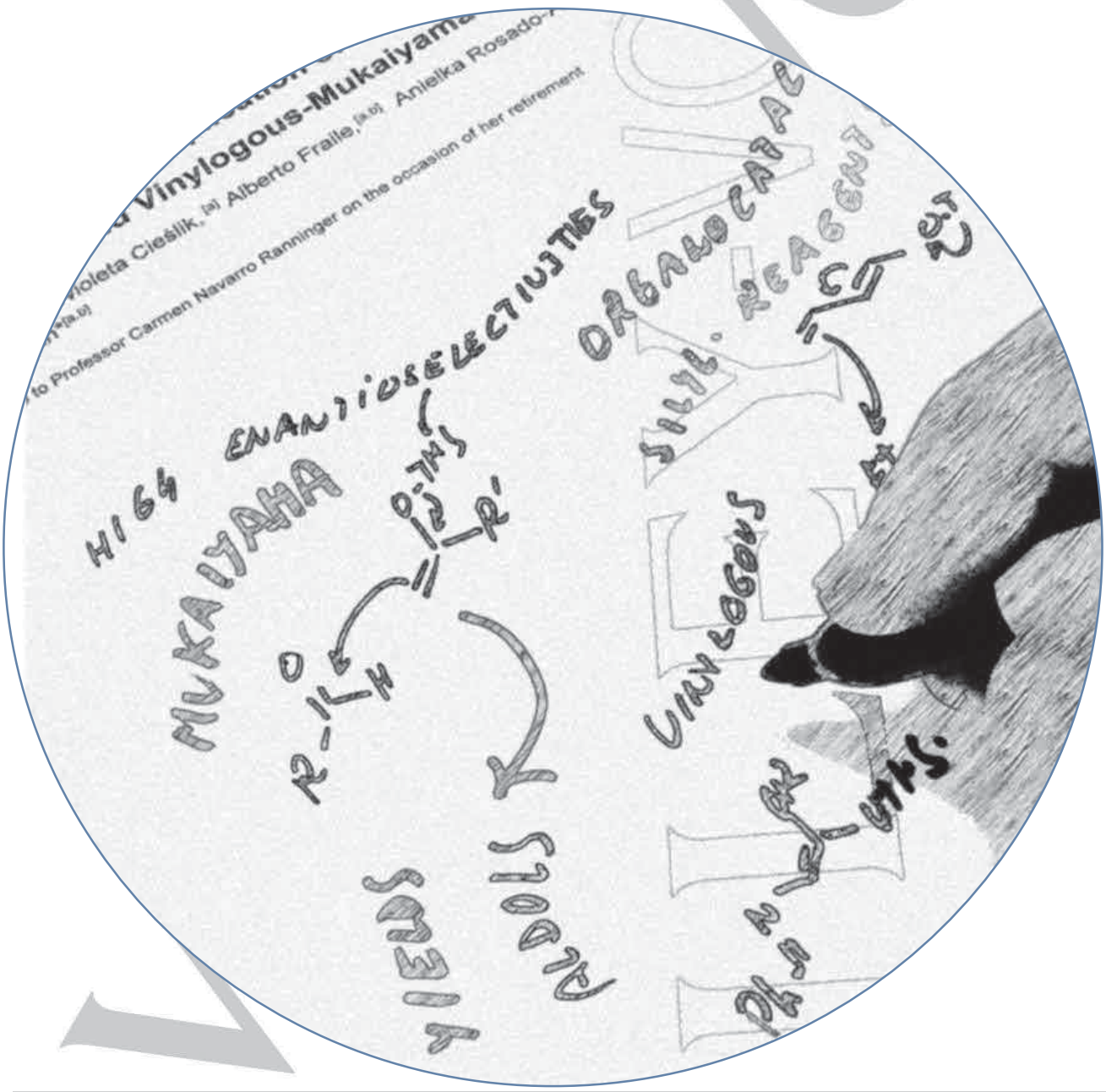

Abstract: Organocatalysis is a growing area that is benefiting from advances in many fields. Its implementation has begun in areas such as supramolecular chemistry, organic chemistry and natural product syntheses. While a considerable number of important publications in the field of organocatalytic Mukaiyama-type additions have been reported, they are yet to be fully covered in a review. Therefore, we would like to highlight the applications of various kinds of organocatalysts in Mukaiyama-type reactions, while also including the vinylogous Mukaiyama variant. Herein we describe and discuss the development and current state of the art of the organocatalytic Mukaiyama reaction, vinylogous Mukaiyama and related reactions.

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Alberto Fraile received his Ph.D. in 2003, focusing on asymmetric 1,3-dipolar cycloadditions to chiral vinyl sulfoxides at the Universidad Autónoma de Madrid (Madrid, 2003) under the supervision of Dr. Martín Ramos and Professor García Ruano. In 2011 he carried out postdoctoral stay at the Center for Catalysis in Aarhus (Denmark) with Professor Karl Anker Jorgensen. In 2000, he achieved a position as Assistant Professor at the Universidad Autónoma de Madrid and since 2013 he is an Associate Professor. His research involves asymmetric synthesis, sulfur chemistry and catalysis.

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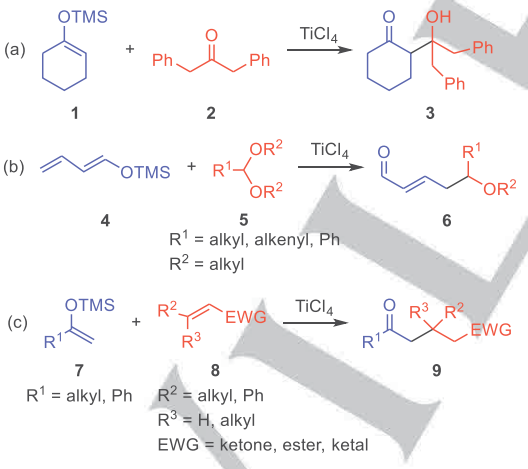
José Alemán obtained his PhD, working on sulfur chemistry, under the supervision of Prof. García Ruano in 2005. In 2003, he spent six months in the laboratory of Prof. Albert Padwa at Emory University, Atlanta, USA. Then, he carried out his post-doctoral stay (2006-2008) in the Center for Catalysis in Aarhus (Denmark) with Prof. Karl A. Jørgensen. He came back to Spain in 2009 as Ramón y Cajal Researcher and is currently an Associate Professor at the Universidad Autónoma de Madrid (Spain). In 2013 he received the Sigma-Aldrich prize for youth researchers from "Real Sociedad de Química Española". His research interests include asymmetric synthesis and catalysis. More recently, he has received a Consolidator Grant awarded by the European Research Council.

1. Introduction

The aldol reaction is one of the most versatile synthetic methods in organic synthesis available for the generation of β-hydroxy carbonyl compounds, also known as aldol derivatives, through C-C bond formation from two carbonyl precursors under basic or acidic conditions.[1] The reaction is however, frequently accompanied by undesired side reactions that give dehydration, self-condensation, and poly-condensation by-products. These limitations, as well as the frequent presence of the β-hydroxy carbonyl moiety in various natural products, and biologically active molecules, have prompted a search for improved and more convenient and efficient methods to effect cross-aldol reactions.[2]

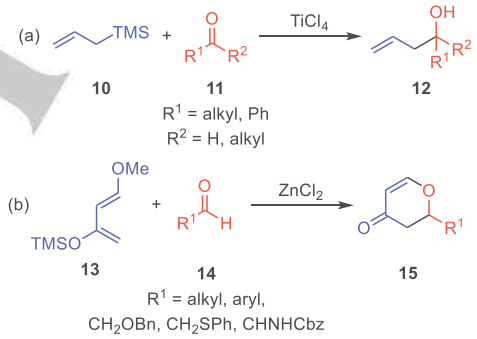


Scheme 1. Original, vinylogous and Mukaiyama-Michael reactions.

In 1973, Mukaiyama et al. reported the reaction of silyl enol ethers with ketones or aldehydes at room temperature in the presence of the Lewis acid titanium tetrachloride to give aldol products (equation a, Scheme 1).[3] Shortly thereafter, a vinylogous version of this reaction was developed by Mukaiyama et al. giving access to δ-alkoxy-α,β-unsaturated aldehydes (equation b, Scheme 1).[4] Later, the reaction between α,β-unsaturated ketones and silyl enol ethers leading to 1,5-dicarbonyl compounds was described.[5] This last transformation is frequently called the Mukaiyama–Michael reaction because it forms the same products as the traditional Michael reaction (equation c, Scheme 1).

Additionally, Mukaiyama disclosed several carbon-carbon bond forming reactions.[6] Thus, the reaction of ketene alkyl trialkylsilyl acetals, prepared from α–lithio esters and trialkylsilyl halides, with aldehydes and ketones at -78 ºC, in the presence of $TiCl_4$, produced the corresponding β-hydroxy esters and β-trialkylsilyloxy esters in good yields.[7] He also explored other nucleophiles different from silyl-reagents like the directed cross-aldol reaction mediated by boron enolates[8] and by tin (II) enolates,[9] and new organic reactions using titanium tetrachloride as Lewis acid.[10]

The Mukaiyama aldol reaction has stimulated the development of a variety of carbon-carbon bond formation reactions, such as the hetero-Diels-Alder reactions of Danishefsky's diene,[11] and the Hosomi-Sakurai allylation reaction[12] (Scheme 2). Moreover, it fostered the chemistry of Lewis acids in the field of chiral asymmetric synthesis.



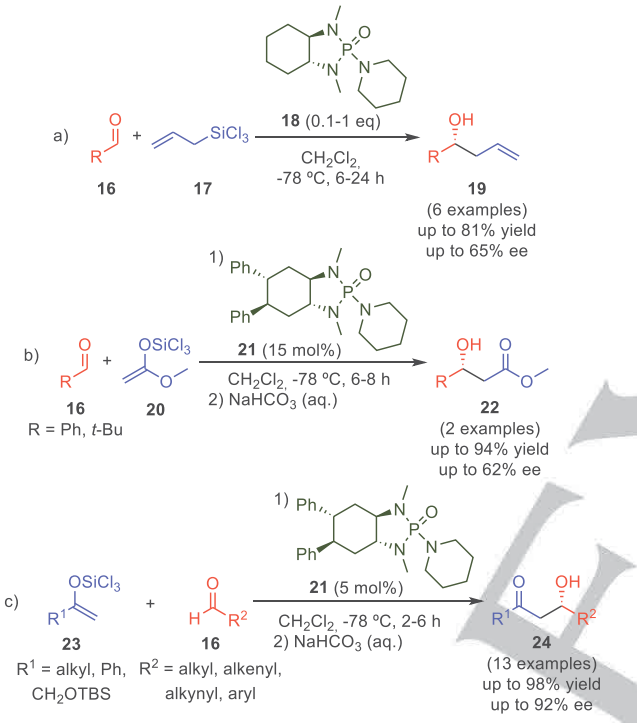
Scheme 2. Hosomi-Sakurai allylation and Danishefsky's diene reactions.

The plethora of new transformations pioneered in the 70s and 80s has allowed researchers to develop new concepts and reactivities. The significant challenge of the Mukaiyama reaction resided in the stereocontrol aspect of the process. Therefore, during the 1990-2000 period, a large number of asymmetric versions of the previously described reactions were developed using mainly metal- but also metal-free-based asymmetric catalytic methods.[13]

In this regard, Denmark's group made key contributions to the field based on Kobayashi's findings that DMF promotes allylations through coordination to allyl trichlorosilanes (equation a, Scheme 3).[14] Expansion of the role of Lewis base additives in allylation strategies led to remarkable activation and stereocontrol in aldol reactions through the key implementation of chiral phosphoramides, employing trichlorosilyl enol ethers as nucleophiles (equations b and c, Scheme 3).[15] Crucial coordination of the phosphoramide catalysts to the trichlorosilyl

enol ethers increases the Lewis acid character of the latter compounds, thus organocatalyzing the aldol processes. These ground-breaking reports by Denmark and co-workers constitute the first organocatalytic strategy deployed in enantioselective aldol reactions.

Nowadays, organocatalysis has been established as a new tool for the construction of chiral complex molecules in an easy, fast and economic way, which supposes important advantages for the synthesis of many compounds. Furthermore, the number of publications concerning the use of organocatalytic asymmetric Mukaiyama reactions, as well as the vinylogous version, has substantially increased since 2007.



Scheme 3. a) Initial asymmetric allylation employing chiral phosphoramides. b-c) Denmark's aldol reactions with trichlorosilyl enol ethers and chiral phosphoramides as Lewis base additives.

In the following years, diverse reactions were accomplished obeying this strategy, in which the vinylogous Mukaiyama reactions represent a pivotal development. The concept of vinylogy is, undeniably, a fundamental notion in organic chemistry established by R. C. Fuson in 1935.[16] Its importance relies on the propagation of nucleophilicity or electrophilicity throughout the conjugated double bond. When applied to enol ethers, the nucleophilicity inherent to these structures can be extended across the π system of a C5-enolizable carbonyl compound, rendering the C3-position less reactive than the C5-position of the final dienol ether.

Nevertheless, site selectivity has been a long-standing issue in which several factors play a key role in determining whether the dienol ether undergoes functionalization at the C3 or C5 position. For instance, metallodienolates and silyl dienol ethers, while being highly electron rich species, present different electronic properties at the C3 and C5 carbons of their structures, as described in Denmark's theoretical studies[17] following Fukui's accurate frontier-orbital density measurements (Figure 1).[18] By measuring the HOMO orbital coefficients (OCs) and electrophilic susceptibilities (ESs), Denmark proved that metallodienolates are prone to react through the C3 position (higher values for OC and ES at the C3-position), whereas silyl dienol ethers give rise to C5-addition products (higher OC and ES values at the C5 position). Additionally, reactivity and site selectivity can be modulated by surrounding the silyl dienol ethers with a certain steric environment, which can be achieved via organocatalysis.

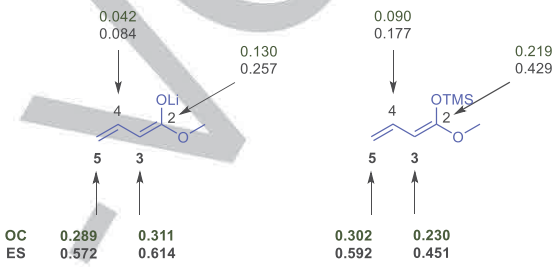


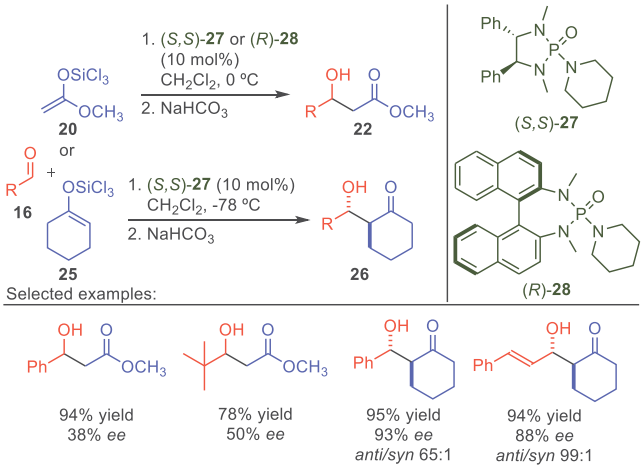
Figure 1. Computationally calculated OCs (green) and ESs (black) of a lithium dienolate (left) and a silyl ketene acetal (right).[17]

In this review, we will highlight how chemical researchers have turned their attention to the development of novel organocatalysts in Mukaiyama-type reactions, while also featuring the vinylogous version. It will cover all the publications describing organocatalytic asymmetric Mukaiyama-type processes and their application in the synthesis of important biological molecules. We have organized this review by the distinct kinds of developed reactions, including the aldol, Michael and Mannich variants of the highlighted Mukaiyama transformation.

2. Organocatalytic Mukaiyama aldol reactions

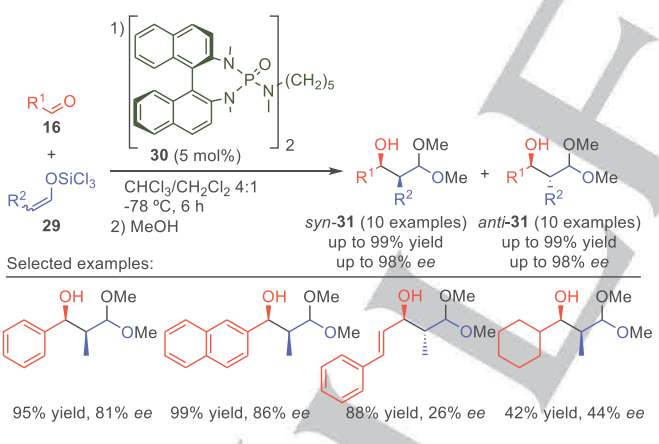
2.1. Phosphoramide, disulfonimide and phosphoric acid catalysts

Denmark's group reported the first trial of enantioselective organocatalysis in crossed-aldol reactions of aldehydes **16** and trichlorosilyl enolates **20** and **25** in 1996.[15a] A study of different phosphoramide catalysts **27** and **28** was conducted in up to four reactions of silyl enol ethers with aldehydes (Scheme 4), obtaining good yields and low to good enantioselectivities in the final aldol products.



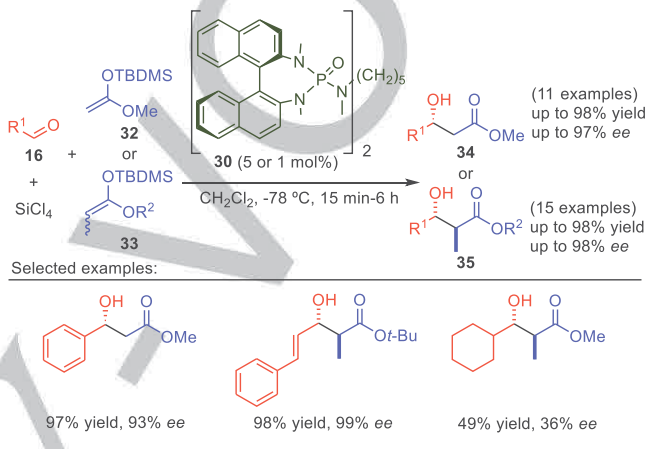
Scheme 4. The first organocatalytic asymmetric aldol reaction.

The same group similarly published the organocatalytic approach in crossed-aldol reactions of aldehydes **16** in the presence of dimeric phosphoramide **30** (Scheme 5).[19] They confirmed reactivity with a variety of pure trichlorosilyl enolates **29** and aldehydes **16**. The best results were achieved in a blend of $CHCl_3$ and CH_2Cl_2 (4:1) at -78 ºC with only 0.05 equiv of catalyst, namely the dimeric 1,1'-binaphthyl-2,2'-diamine-derived phosphoramide **30**. This catalyst gave satisfactory yields, excellent diastereomeric and moderate enantiomeric selectivity. In general, enantioselectivity with aromatic aldehydes was good, while unsaturated and aliphatic aldehydes gave poor results.



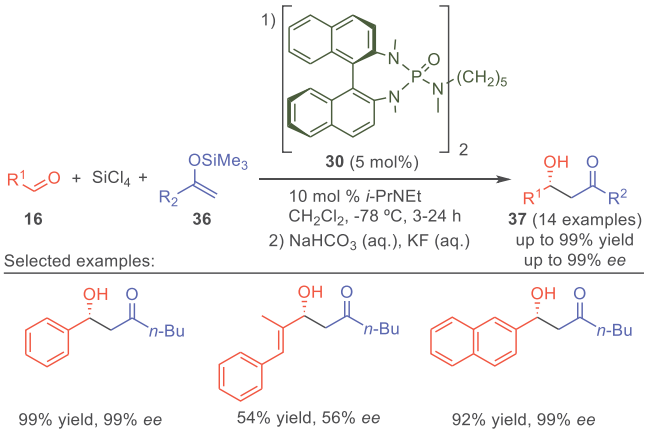
Scheme 5. Aldol reaction of trichlorosilyl enolates with various aldehydes catalyzed by a phosphoramide derivative.

Denmark's group continued to work on this topic, and in 2002 they fulfilled the addition of acetate and propanoate derived silyl ketene acetals **32** or **33** to aromatic, aliphatic and unsaturated aldehydes **16** with high enantio- and diastereoselectivity.[20] The reaction was completed in the presence of 5 or 1 mol% of the dimeric phosphoramide **30** and 1.1 equiv of $SiCl_4$ at -78 ºC in short reaction times (15 min - 6 h) (Scheme 6). The use of $SiCl_4$ as a Lewis acid removed the nucleophile-related restrictions since the preparation of the trichlorosilyl nucleophile is no longer required, hence expanding the range of the reaction to the other main functional group organometallic nucleophiles. In contrast to the previous method, aliphatic aldehydes underwent the transformation successfully, leading to products with good yields and enantioselectivities but over slower reaction times. These results are particularly noteworthy since aliphatic aldehydes are generally unreactive when combined with other trichlorosilyl-based nucleophiles.



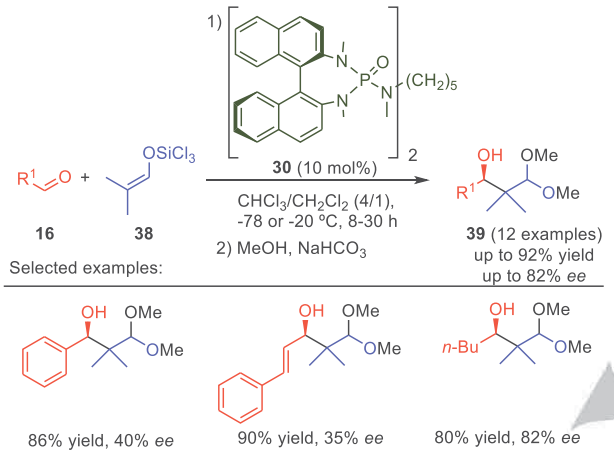
Scheme 6. Addition of silyl ketene acetals to aldehydes.

In 2003, Denmark's group developed the enantioselective addition of silyl enol ethers **36**, derived from simple methyl ketones, to various aldehydes **16** (Scheme 7).[21] The reaction was performed with 5 mol% of bisphosphoramide catalyst **30** and 1.5 equiv of $SiCl_4$ in CH_2Cl_2 at -78 ºC. The process was highly enantioselective, and addition of Hünig's base (*i*-Pr_2EtN) increased reaction efficiency. Excellent *ee*s were found with electron-rich and electron-poor aromatic aldehydes and different heteroaromatic aldehydes. However, α-branched substituted aldehydes showed low yield and enantioselectivity, while aliphatic aldehydes were found to be completely unreactive.



Scheme 7. Aldol additions of various ketone enolates **36** to aldehydes **16**.

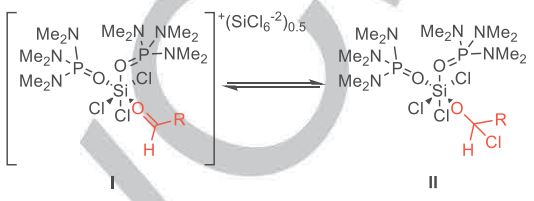
As another example of this approach, organocatalysis has been employed to conduct the addition of isobutyraldehyde trichlorosilyl enolate (**38**) to a wide range of aldehydes **16** (Scheme 8).[22] The reaction proceeded in the presence of 10 mol% bisphosphoramide **30** without any addition of $SiCl_4$ or base, giving dimethyl acetals **39** in high yields with moderate enantiomeric purity. In general, the rate of the reaction with electron-poor aromatic aldehydes was faster than with electron-rich aromatic aldehydes, as well as more enantioselective. Addition to olefinic aldehydes displayed low enantioselectivity, whereas aliphatic aldehydes required higher temperatures and longer reaction times to afford products with good selectivity and yields.



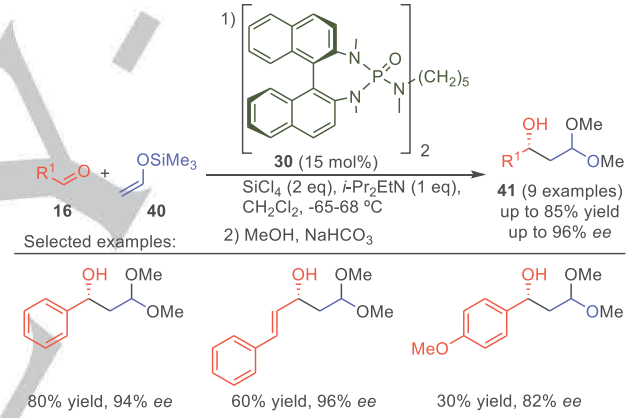
Scheme 8. The aldol addition of isobutyraldehyde trichlorosilyl enolate (**38**) to various aldehydes **16**.

In 2005 the aldol addition of acetate-, propanoate-, and isobutyrate-derived silyl ketene acetals to various aldehydes was described.[23] The reaction was promoted by 5 or even 1 mol% of the dimeric phosphoramide catalyst **30** with addition of $SiCl_4$, yielding products with high levels of regio-, diastereo- and enantiocontrol. In the series of different alkoxy substituents, an increase of enantioselectivity was observed from a methyl to the sterically more demanding *tert*-butyl ester. However, no differences were perceived between reactions with electron-withdrawing and electron-donating aromatic aldehydes. Nevertheless, aliphatic aldehydes were obtained with moderate yields and poor enantioselectivity. The authors attributed this trend to the rapid transformation of aliphatic aldehydes into unreactive α-chloro trichlorosilyl ethers **II**, obtained from the silyl cation complex of the aldehyde **I** via attack of the ionized chlorine to the carbonyl moiety (Scheme 9).

Later on, the same group reported the reaction of acetaldehyde-derived trimethylsilyl enol ether (**40**) with various aldehydes **16** in the presence of 15 mol% of chiral phosphoramide **30** (Scheme 10).[24] In order to improve the yield and selectivity of the reaction, 1.0 equiv of Hünig's base was used. Electron-deficient aromatic aldehydes underwent aldol addition, providing the desired products in good yields and enantioselectivities. Electron-rich aromatic aldehydes afforded products with moderate selectivities and rather low yields, whereas aliphatic and unsaturated aldehydes proved to be unreactive. Higher temperatures and different concentrations did not improve the results significantly. Nonetheless, the researchers disclosed the first example of stereoselective carbon-carbon bond formation by trapping an aldolate intermediate *in situ* with *tert*-butyl isocyanide to form an α-hydroxy lactone in a "one-pot reaction". These findings highlight the synthetic utility of this methodology.



Scheme 9. Transformation of the silyl cation complex of aldehyde **I** into unreactive α-chloro trichlorosilyl ether **II**.

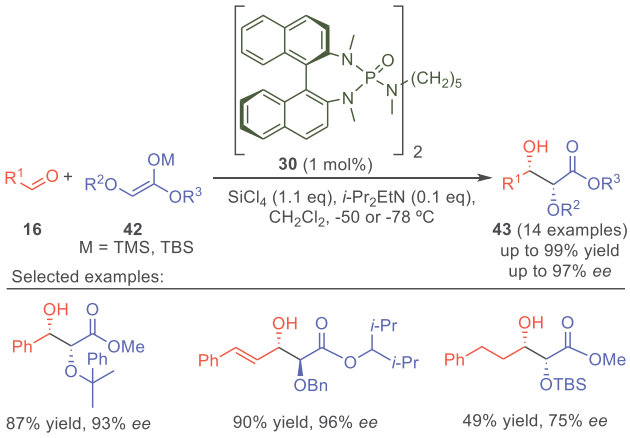


Scheme 10. Enantioselective addition of silyl enol ether **40** to aldehydes **16**.

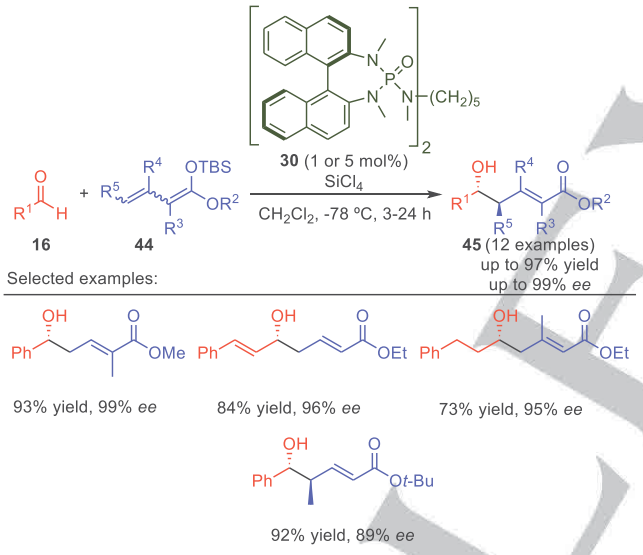
Organocatalytic enantioselective glycolate aldol reactions were described by Denmark and Chung in 2008.[25] In this case, the reaction was carried out with different aldehydes **16** in the presence of $SiCl_4$, *i*-Pr_2EtN and only 1 mol% of chiral phosphoramide catalyst **30**, in short times (0.5 h) and at -50 or -78 ºC (Scheme 11). The aldol products **43** were obtained in high yields and also elevated diastereo- and enantioselectivities. Reaction times increased (9-20 h) when aromatic aldehydes with a higher level of steric hindrance were used (e.g. 2-methylbenzaldehyde). Unfortunately, the reaction did not proceed with aliphatic aldehydes.

It was Denmark and Beutner who reported the first trial of an enantioselective vinylogous aldol reaction catalyzed by a chiral bisphosphoramide.[26] The reaction exclusively afforded the γ-addition products with *E* configuration in the presence of $SiCl_4$ and only 1 mol% of catalyst **30** (Scheme 12). The researchers studied various aldehydes and dienol ethers, obtaining γ-hydroxy enones in good yields and high enantio- and diastereoselectivities. Reactions with aliphatic aldehydes, which

are generally unreactive while displaying poor enantioselectivity, were also successful. Under this catalytic system however, high enantioselectivities were reached, although 5 mol% of catalyst was required to achieve better yields.



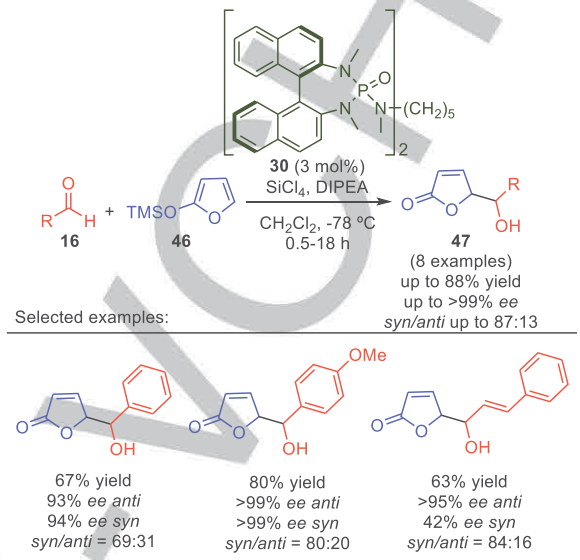
Scheme 11. Selective glycolate aldol reaction with aldehydes.



Scheme 12. Vinylogous aldol reaction of ester-derived dienolates **45** and aldehydes **16**.

In a related work, the authors examined the reaction with acyclic and cyclic ketone-derived silyl enol ethers.[27] The reaction was carried out at higher temperatures (-50 ºC) coupled with addition of *i*-Pr_2NEt and 5 mol% of bisphosphoramide catalyst **30**. All these reactions proceeded exclusively with γ-selectivity and high enantio- and diastereoselectivity. On the other hand, reactions with cyclic dienolates displayed a slightly lower selectivity than acyclic reagents. In these reactions, the studies have shown the lack of reactivity with aliphatic aldehydes.

Palombi et al. described the enantioselective vinylogous aldol γ-addition of 2-trimethylsiloxyfuran (**46**) to various aldehydes **16**. The best results were obtained with bisphosphoramide catalyst **30** (Scheme 13).[28]

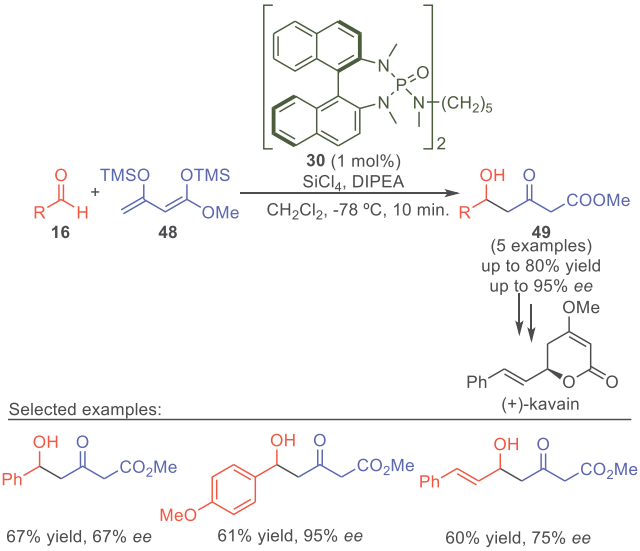


Scheme 13. $SiCl_4$/bisphosphoramide-promoted enantioselective vinylogous aldol reaction.

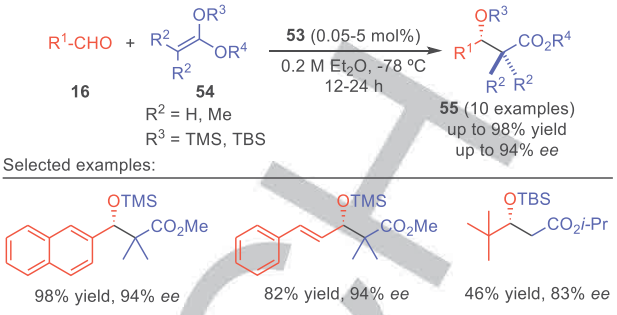
In general, δ-hydroxy butenolides **47** were obtained with moderate yields and diastereoselectivities, and in most cases high enantioselectivities were found with aromatic and α,β-unsaturated aldehydes. This methodology favors the *anti*-diastereoselective approach, opposite to the classical method catalyzed by a Ti(IV) or Sn(IV)-based Lewis acid.[29]

Another example where the $SiCl_4$/bisphosphoramide catalytic system is applied in the enantioselective vinylogous aldol reaction is the addition of silyloxydiene **48** to aldehydes **16** (Scheme 14).[30] The reaction was carried out under the same conditions as before, in the presence of only 1 mol% of catalyst **30** and very short reaction times (10 min). The resulting products, δ-hydroxy-β-ketoesters **49**, were obtained in moderate yields and from moderate to high enantioselectivities. No data regarding reactions with aliphatic aldehydes was reported. Strikingly, the method was conveniently used for the rapid preparation of (+)-kavain, a natural bioactive compound.

List's group proved that the catalytic activity of the disulfonimide **53** was much higher than the other Brønsted acids such as phosphoric acids, phosphoramides or disulfonic acids (**50-52**, Figure 2) in the Mukaiyama aldol reaction, managing to lower the catalytic loading even further while still reaching full conversion.[31] Reaction of aromatic and aliphatic aldehydes **16** with ketene acetals **54** was carried out successfully with 0.05-5 mol% of disulfonimide catalyst **53** after 12-24 h at -78 ºC (Scheme 15). The desired aldol products **55** were obtained with high efficiency and good enantioselectivity.



Scheme 14. The enantioselective vinylogous reaction of silyloxydiene **48** and its application.



Scheme 15. Scope of the disulfonimide-catalyzed Mukaiyama aldol reaction.

The proposed catalytic cycle begins with the formation of *N*-silyl imide **III**, product of the initial reaction between catalyst **53** and ketene acetal **54** (Scheme 16). Afterwards, the aldehyde is activated through a silyl transfer from imide **III** to generate oxonium ion **IV**. The subsequent reaction between the ion pair **IV** (consisting of the disulfonimide anion and *O*-silylated oxonium cation) and ketene acetal **54** produces the ion pair intermediate **V**, which provides the desired aldol product **55**.

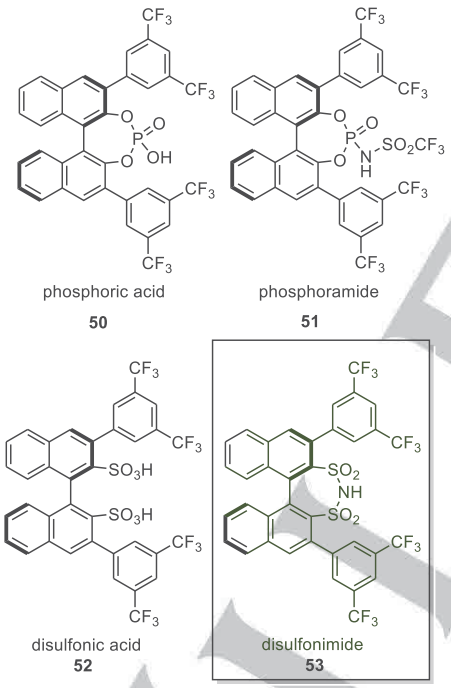
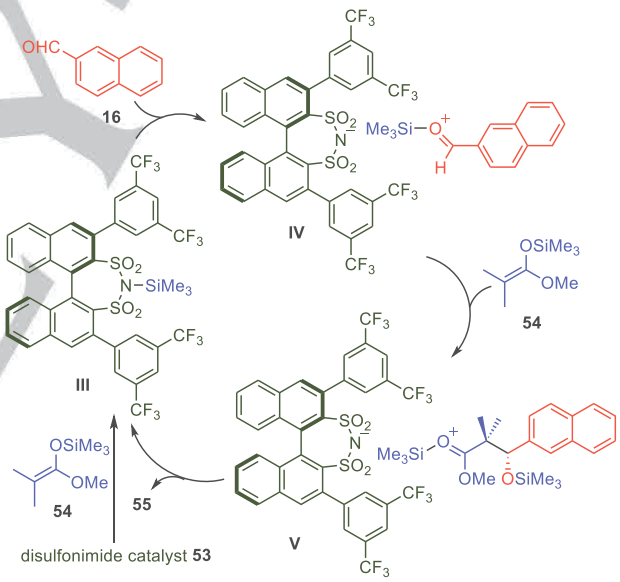


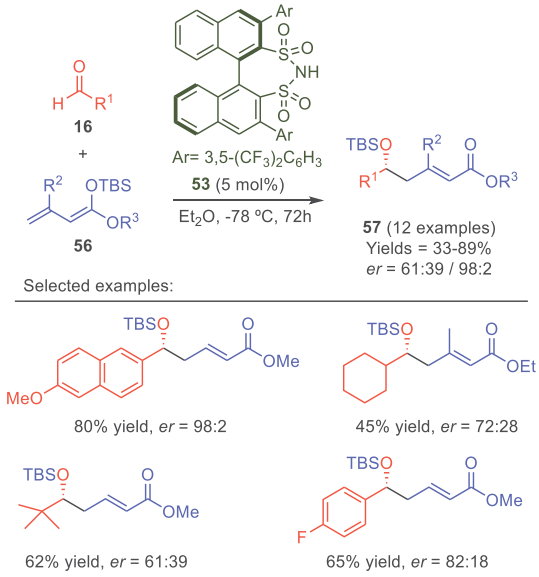
Figure 2. Evaluation of different chiral acid catalysts in the Mukaiyama aldol reaction.



Scheme 16. Proposed catalytic cycle for the disulfonimide-catalyzed Mukaiyama reaction.

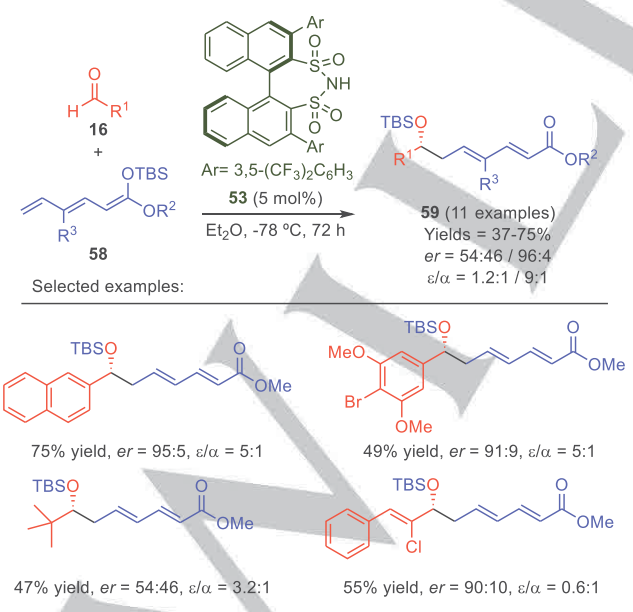
In 2011, List made use of these chiral disulfonimides as effective catalysts to perform the asymmetric vinylogous and bisvinylogous Mukaiyama aldol reactions. The aldol products were prepared with high regio- and enantioselectivities (Scheme 17).[32] Optimal reaction conditions involved silyl dienol ethers **56** in Et_2O at -78 ºC loading 5 mol% of chiral disulfonimide catalyst **53**. Regarding the scope of this reaction, List's group studied different silyl groups at the nucleophile, observing few changes in reactivity. However, in the case of the *tert*-butyl group on the final ester moiety, the yields decreased in comparison with the methyl ester. The reaction was amenable to a large number of

aromatic groups with EWGs and EDGs, while also working with alkyl branched aldehydes, albeit with lower yields and *ees* (Scheme 17).



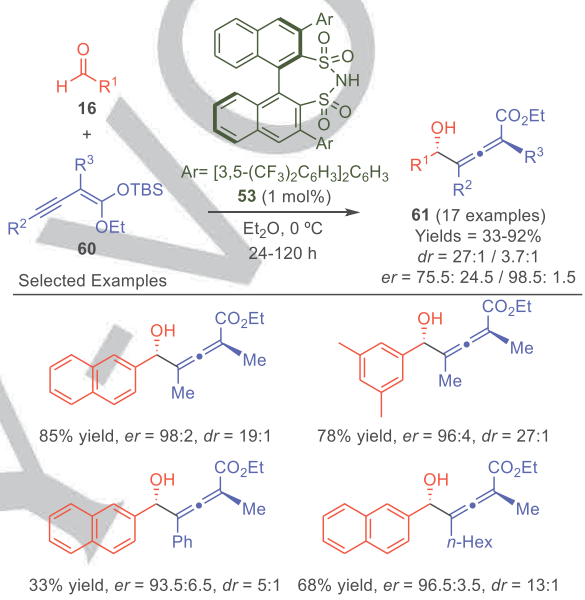
Scheme 17. Asymmetric vinylogous and bisvinylogous Mukaiyama aldol reactions.

Furthermore, List and co-workers went on to describe the first asymmetric bisvinylogous aldol reaction with aldehydes **16** catalyzed by the same chiral disulfonimide **53**. The reaction proceeds with exclusive ε-regioselectivity. They studied the scope of the reaction with different aromatic and aliphatic aldehydes, obtaining the desired products with good enantioselectivities and moderate yields (Scheme 18).



Scheme 18. First asymmetric bisvinylogous aldol reaction with aldehydes.

Meanwhile, due to their interesting properties and versatile reactivity, many research groups have focused their attention on finding new methodologies for the synthesis of chiral allenes. In this regard, List's group published the use of the chiral disulfonimide catalyst **53** in the asymmetric Mukaiyama aldol reaction between alkynyl-substituted ketene acetals **60** and aldehydes **16**, in order to obtain allenes **61** with high diastereo-, enantio-, and complete γ-regioselectivity.[33] The best results were obtained when 5 mol% of the chiral disulfonimide **53** was used and Et_2O acted as solvent at 0 ºC (Scheme 19).

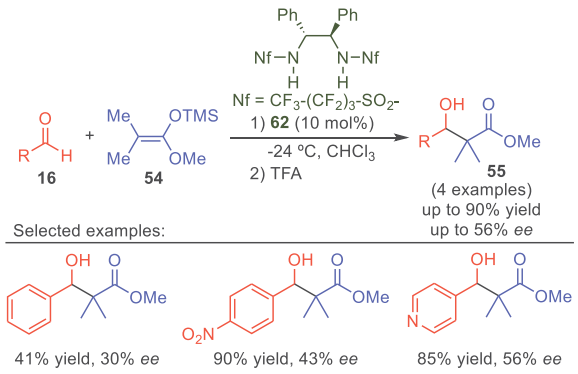


Scheme 19. Asymmetric Mukaiyama aldol reaction between alkynyl-substituted ketene acetals and aldehydes.

A wide range of aromatic aldehydes were responsive under these conditions. However, aliphatic aldehydes never yielded the desired product. Different substitutions at the alkynyl ketene acetals were also studied. A phenyl group at the terminal position resulted in a decrease in reactivity and selectivity when compared with a methyl group at the same position. A benzyl group, however, led to tetrasubstituted allenes **61** in moderate yields, high *dr*s and *ees* (Scheme 19). The researchers established the value of their methodology by turning chiral allenes into valuable substrates such as dihydrofuranes and lactones with good yields and excellent enantioselectivities.

In 2006, Boxer and Yamamoto found triflimide ($HNTf_2$) to be a very good catalyst for the racemic Mukaiyama cross-aldol reaction of bulky tris(trimethylsilyl)silyl (TTMSS) enol ethers derived from acetaldehyde and propionaldehyde.[34] Triflimide catalyzes the reaction with a loading of 0.05 mol%, giving the 1:1 adduct mixture in high yields. The authors established that the TTMSS group gives rise to β-hydroxy aldehydes with high yield starting from a broad range of aldehydes. The same reagents can be used for Sequential Aldol-Grignard reactions (SA-Grignard reactions) and 4-component Sequential Aldol-Aldol-Grignard reactions (SA-A-Grignard reactions).[35] These

one-pot methodologies give access to complex molecules,[36] and have been used for the synthesis of different natural products.[37] Nonetheless, the aforementioned syntheses with bis-sufonamides in a catalytic role continue to afford racemic mixtures. Recognizing this limitation, Jørgensen's group pioneered the use of chiral bis-sulfonamides for the asymmetric Mukaiyama reaction (Scheme 20).[38]

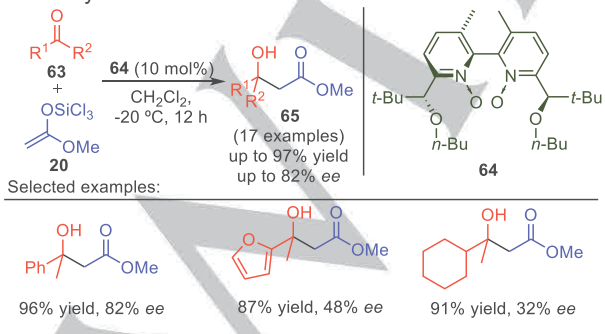


Scheme 20. The enantioselective Mukaiyama aldol reaction performed in the presence of *bis*-nonaflamide **62** as catalyst.

The best results were obtained with *bis*-nonaflamide **62** as a catalyst, although the resulting enantioselectivities were rather low. This report suggests that both sulfonamide groups form a chelating structure wherein the catalyst interacts with the carbonylic oxygen through two hydrogen bonds.[39]

2.2. *N*-oxide catalysts

The first enantioselective aldol addition of ester trichlorosilyl enolates to ketones catalyzed by chiral bis-*N*-oxides was reported by Denmark and Fan in 2002.[40] Different *N*-oxides were studied as catalysts, achieving the best results with *P*-isomers of **64** (Scheme 21). The reaction was carried out with 10 mol% of catalyst for 12 h at -20 ºC in CH_2Cl_2, tolerating various ketones. By and large, the corresponding products were obtained in good yields, although with low to moderate enantioselectivities (8-82% *ee*). The highest enantioselectivities were found with aromatic ketones, whereas aliphatic ketones gave nearly racemic form.[41]



Scheme 21. The Mukaiyama reaction catalyzed by a chiral bis-*N*-oxide catalyst.

Nakajima's group employed chiral *N,N'*-dioxides and monodentate *N*-oxides as catalysts (**66-69**, Figure 3) for the enantioselective Mukaiyama aldol reaction of trichlorosilyl enol ethers with aldehydes.[42]

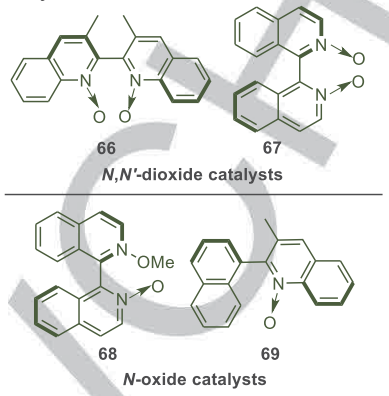
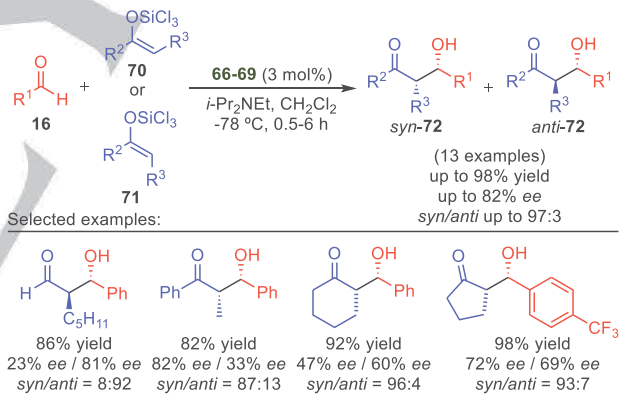


Figure 3. The structure of a chiral *N,N'*-dioxides and monodentate *N*-oxides.

It so happens that in the reaction of acyclic enols, *N,N'*-dioxides **66** and **67** gave *anti*-adducts from (*E*)-enol ethers **71**, and *syn*-adducts from (*Z*)-enol ethers **70** (see Scheme 22). However, the reaction of cyclic (*E*)-enol ethers using *N,N'*-monooxides **68** or **69** gave only the *syn*-adducts.

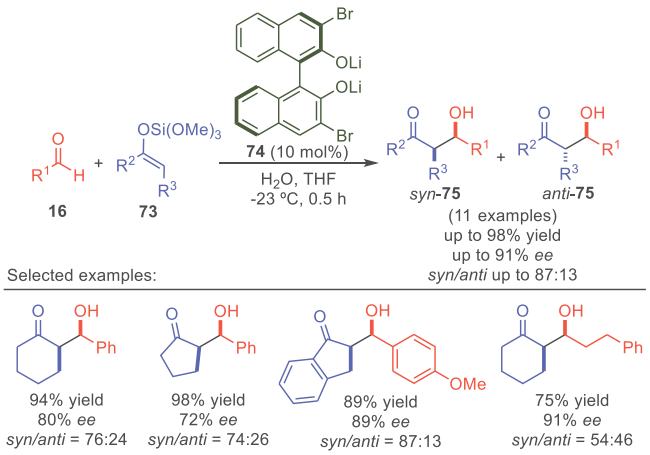


Scheme 22. The enantioselective aldol reaction catalyzed by chiral *N,N'*-dioxides and monodentate *N*-oxides.

2.3. Lithium binaphtholate catalysts

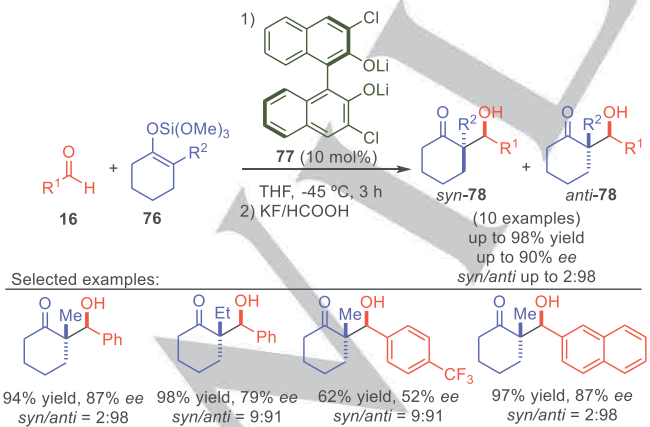
The remaining example regarding an enantioselective Mukaiyama-type reaction catalyzed by a chiral base was reported by Nakajima's group in 2004.[43] The aldol reaction of trimethoxysilyl enol ethers **73** was catalyzed by 10 mol% of dilithium salt of 3,3'-dibromobinaphthol (**74**), prepared *in situ* from the corresponding binaphthol and BuLi. The addition of water into the reaction medium appeared to play an important role in increasing diastereo- and enantioselectivity, probably due to the strong coordinate bonds that can be established between water and silicon. Reactions with different ethers and aldehydes

were tested, obtaining the corresponding products with good yields, low to moderate diastereoselectivities and low to good enantioselectivities (Scheme 23).



Scheme 23. Enantioselective aldol reaction catalyzed by a chiral base.

The influence of various chiral bases, such as the lithium salts of chiral alcohols, amines and binaphthol with different substituents at the 3,3'-positions were also studied.[44] However, the best selectivity was still obtained with the previously used catalyst **74** - dilithium salt of 3,3'-dibromobinaphthol. They also expanded the scope of the reaction using other trimethoxysilyl enol ether derivatives and aldehydes, producing the desired adducts with good yields. Unfortunately, the diastereoselectivity continued to be unsatisfactory (*syn/anti* from 54:46 to 76:24), while the enantioselectivity ranged between low and good values (from 8 to 97% *ee*). Nakajima's group continued to work on this topic, looking for better diastereo- and enantioselectivity. As a result, they presented an analogous aldol reaction with 2,2-disubstituted trimethoxysilyl enol ethers **76** (Scheme 24)[45] improving the disappointing stereoselectivity shown in their previous work (Scheme 23).

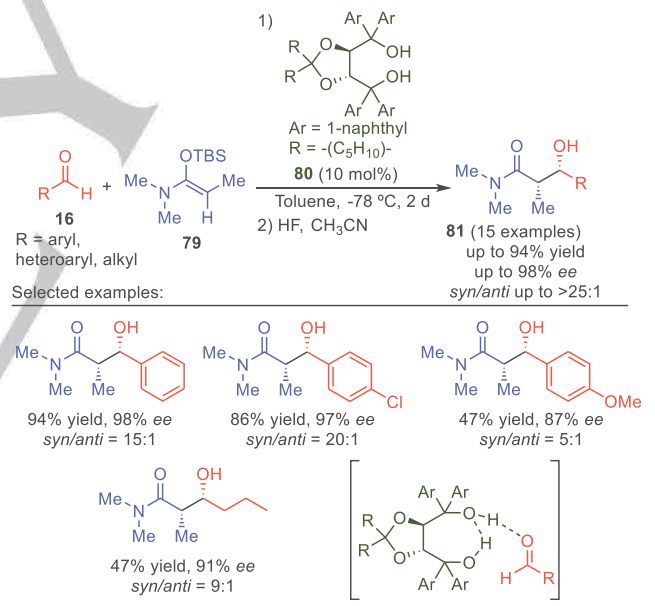


Scheme 24. The aldol reaction of 2,2-disubstituted trimethoxysilyl enol ethers with aldehydes.

They found the workup conditions to be a key factor, suppressing the isomerization process attached to the retro-aldol reaction by use of an aqueous solution of potassium fluoride/formic acid. The authors also examined two catalysts with bromo- and chloro- substituents at the 3,3'-positions of binaphthol. Much higher *anti*-selectivity was obtained with the chloro-catalyst than in the case of the bromo-substituted catalyst. Diverse trimethoxysilyl enol ethers and aldehydes were examined during the scope studies. Introducing an electron-donating or electron-withdrawing group on the aldehydic phenyl ring diminished the stereoselectivity. Aliphatic aldehydes displayed a similar behavior.

2.4. TADDOL catalysts

In a previous report, Rawal displayed the effectiveness of simple diols as catalysts in enantioselective reactions, e.g. TADDOL (α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol).[46] Moreover, by evaluating up to a dozen different catalysts, they concluded that cyclohexylidene-TADDOL derivative **80** was the best catalyst for the aldol reaction. Therefore, Rawal and co-workers decided to study the Mukaiyama aldol reaction with this TADDOL derivative **80** as catalyst (Scheme 25).[47]

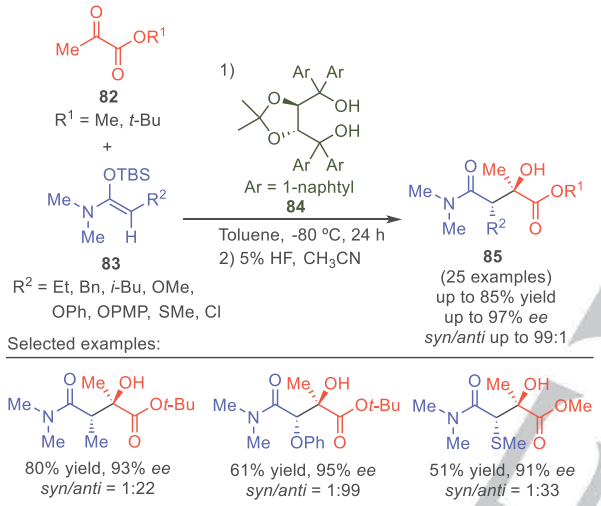


Scheme 25. Asymmetric Mukaiyama aldol reaction catalyzed by a TADDOL derivative.

The results showed that aldol products are generally obtained in good yields and high diastereo- and enantioselectivities. A crystal structure obtained from complexation between a TADDOL derivative and an aldehyde displayed an intermolecular hydrogen bond linking the carbonylic oxygen and a hydroxy group, as well as an intramolecular hydrogen bond between the latter and the additional hydroxy group. Both interactions were thus proven to be responsible for the catalytic activity of **80** (bottom-right,

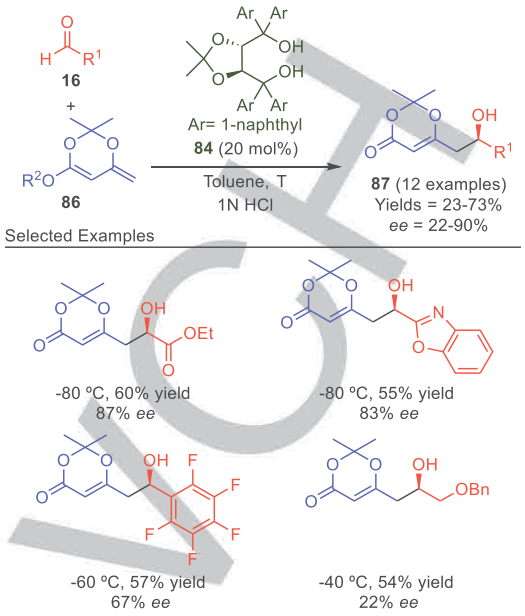
Scheme 25). This complex confirms the authors' hypothesis concerning the activation mode of the carbonyl group through a single-point hydrogen-bonding interaction.

In addition, Rawal's group studied the Mukaiyama aldol reaction of α-ketoesters promoted by hydrogen-bonding, focusing their efforts on the transformation that takes place between various pyruvate esters and several ketene acetals in the presence of the commercially available naphthyl-TADDOL **84**, giving the corresponding aldol products with excellent diastereo- and enantioselectivities (Scheme 26).[48] The high enantioselectivity can be explained through a transition state model similar to the mechanism for the Mukaiyama aldol reaction of aldehydes catalyzed by TADDOL, wherein the ketone carbonyl group is activated by the TADDOL catalyst through a single-point hydrogen bond.



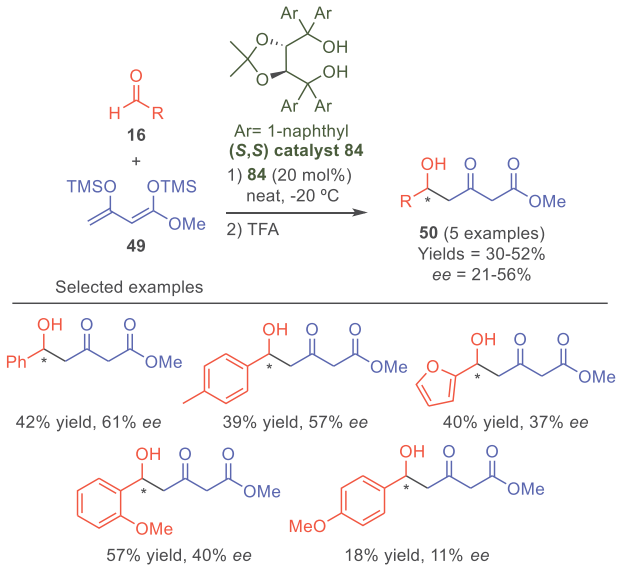
Scheme 26. Enantioselective Mukaiyama aldol reactions of *N,O*-ketene acetals.

Regarding the vinylogous version, in 2005 Rawal et al. described the addition of trialkylsilyldienol ethers **86** to aldehydes under hydrogen bond catalysis.[49] Different chiral alkaloids and diols were studied as catalysts in the reaction of trimethylsilyldienol ether of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and 2-nitrobenzaldehyde, obtaining the best results with TADDOL-based catalysts. A combination of 1-naphthyl-TADDOL as catalyst and ethyl glioxalate as the chosen aldehyde led to the highest enantioselectivity (87% *ee*) when the temperature was decreased to -80 ºC and the TMS group of the nucleophile was replaced by a TBS group. Various substituted aldehydes were found to perform well in the reaction. The vinylogous aldol products were obtained with moderate yields and moderate to good *ee*s, and γ-selectivity was observed in all cases (Scheme 27).

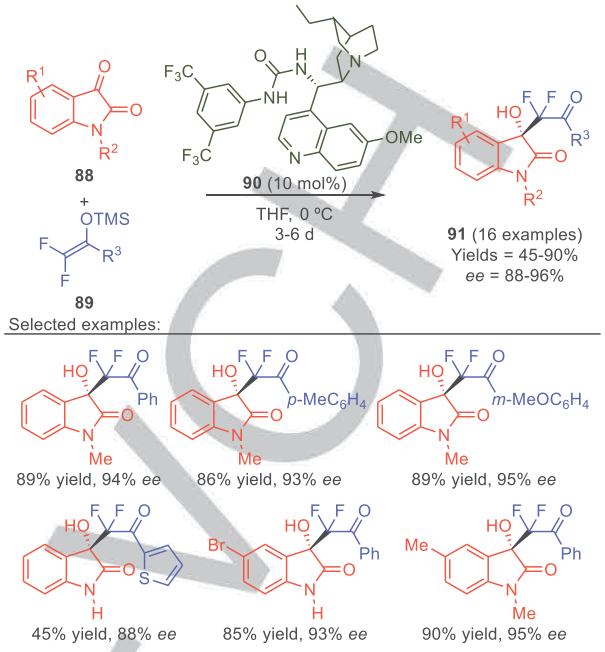


Scheme 27. Addition of trialkylsilyldienol ethers **88** to aldehydes **16** under TADDOL catalysis.

In 2007, Scettri and co-workers published the vinylogous aldol reaction between aromatic aldehydes **16** and Chan's diene catalyzed by a TADDOL derivative (*S,S*-**84**).[50] A difference in reactivity between Chan's and Brassard's dienes in the presence of aldehydes had already been established in metal catalysis; the former would lead to chiral polyketide derivatives, while hetero-Diels-Alder products would be obtained when the latter was involved. With these precedents in mind, Scettri's group decided to study the reaction between Chan's diene **49** and benzaldehyde **16** under catalyst **84**, giving rise exclusively to the corresponding vinylogous aldol product **50** with moderate yield and enantioselectivity. The scope of the reaction included aromatic as well as heteroaromatic aldehydes, obtaining vinylogous aldol-type products in all examples (Scheme 28). However, when the aldehyde contained an electron withdrawing group in its structure (*p*-NO_2, *o*-NO_2), a change in the reactivity was observed, leading to a mixture of the vinylogous aldol product and the pyrone with moderate *ee*s (51-60%). The group carried out a mechanistic analysis, establishing a model for the TADDOL derivatives.[51] As previously mentioned, TADDOL catalysts display an intramolecular hydrogen bond between their hydroxy groups. Therefore, an intermolecular hydrogen bond can be formed between the free hydroxy group and the oxygen of the aldehyde, effectively lowering the LUMO energy, and hence making the carbonyl activation possible. Finally, the enantioselectivity is described as a result of a π-π* interaction between the naphthyl core of the catalyst and the carbonyl group of the electron poor aldehyde.



Scheme 28. Vinylogous aldol reaction between aldehydes **16** and Chan's diene **49**.

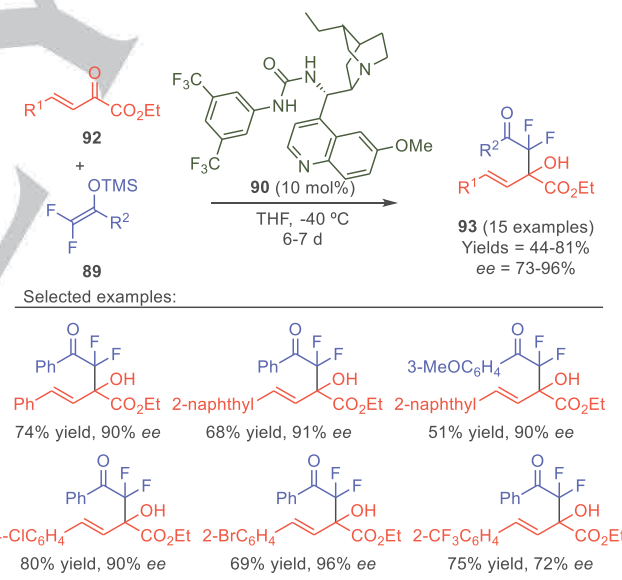


Scheme 29. Addition of difluorosilyl enol ether **89** to differently substituted isatins **88** under bifunctional catalysis.

2.5. Bifunctional organocatalytic cinchona derivatives

The use of bifunctional catalysts has been described in a large number of asymmetric reactions.[52] However, they have been circumscribed to the reactions of fluorosilyl enol ethers to isatins (Schemes 29-32) and sulfonyl ketimines (see later). The first example of a Mukaiyama aldol reaction under bifunctional urea catalysis was carried out by Zhou et al., who studied the catalyzed addition of difluorosilyl enol ethers **89** to differently substituted isatins **88** under catalyst **90** (Scheme 29).[53] They determined that the tertiary amine was necessary since it is acting as a Lewis base, activating trimethylsilyl nucleophile **89**. The reaction took place in high yields and high enantioselectivities regardless of substitution at the aromatic ring of difluoroenoxysilane **89** or isatin **88**.

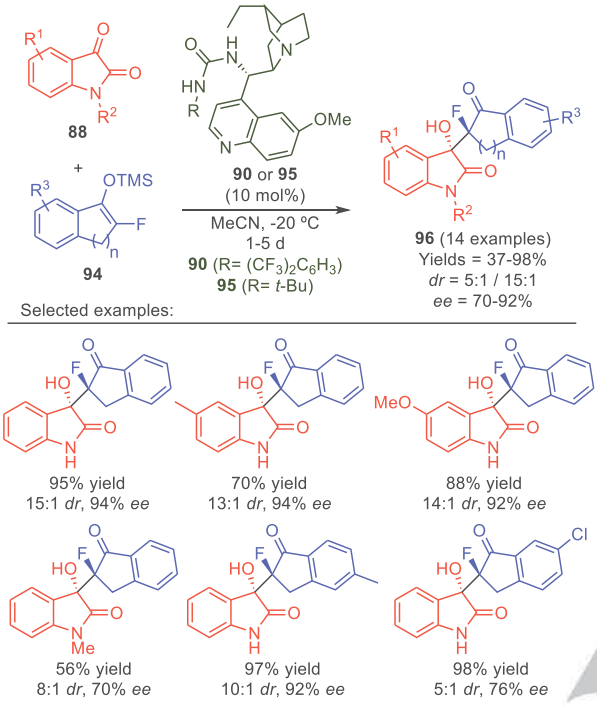
Zhou successively studied the Mukaiyama reaction of difluorosilyl enol ethers **89** with α,β-unsaturated ketoesters **92** catalyzed by urea **90**, obtaining the corresponding Mukaiyama aldol adducts **93** in moderate to good yields and high enantioselectivities (Scheme 30).[54] The reaction took place in chemoselective fashion, solely achieving addition to the ketone moiety.



Scheme 30. Addition of difluorosilyl enol ethers **89** to α,β-unsaturated ketoesters **92** under bifunctional catalysis.

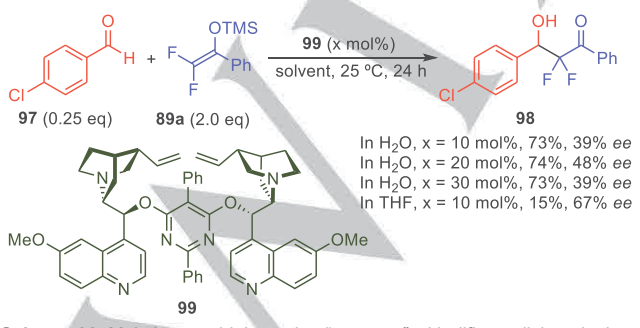
In addition to the Mukaiyama aldol reaction studies performed with the acyclic difluorosilyl enol ethers **89**, Zhou and co-workers have described the addition of cyclic monofluorinated silyl enol ethers **94** to isatins **88**, which afforded bicyclic structures **96** with two quaternary stereocenters in excellent yields, good enantioselectivities, and high diastereoselectivities (Scheme 31).[55] Once again, urea derivative **90** proved to be the most efficient catalyst for this

process. In some cases, isatins with electron-withdrawing substituents such as halogens required a slight modification in the structure of cinchona alkaloid **90**, replacing an aromatic ring with a *tert*-butyl group (**95**).



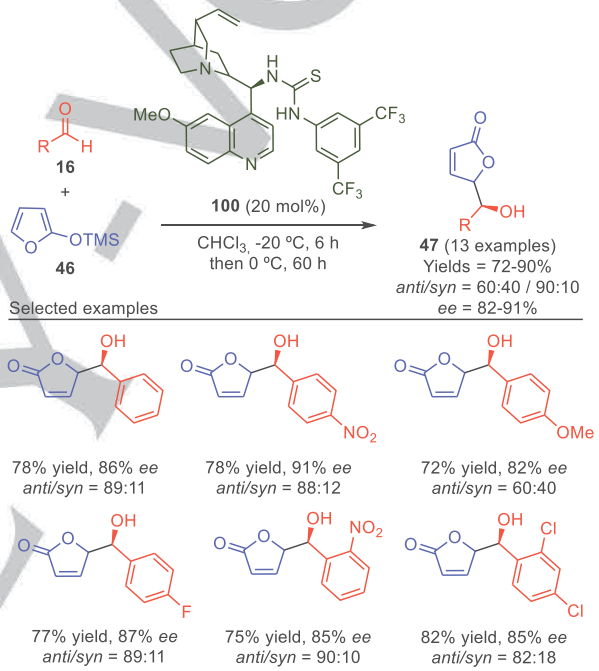
Scheme 31. Addition of cyclic monofluorinated silyl enol ethers to isatins.

Lastly, an interesting work was described by Zhou's group in which they carried out the Mukaiyama aldol reaction "on water" with difluorosilyl enol ether **89a** and *p*-chlorobenzaldehyde (**97**), using quinine dimer derivative **99** as a chiral catalyst (Scheme 32).[56] Water would play a dual role in this case, activating both the aldehyde and the silyl enol ether through hydrogen bonding. In fact, when the reaction was performed in THF it only afforded a 15% yield. As for the steric aspect of this transformation, the nitrogen at the quinuclidine moiety activates difluoroenoxysilane reagent and controls the stereoselectivity. However, the enantiomeric excesses were rather low in water due to the background reaction.



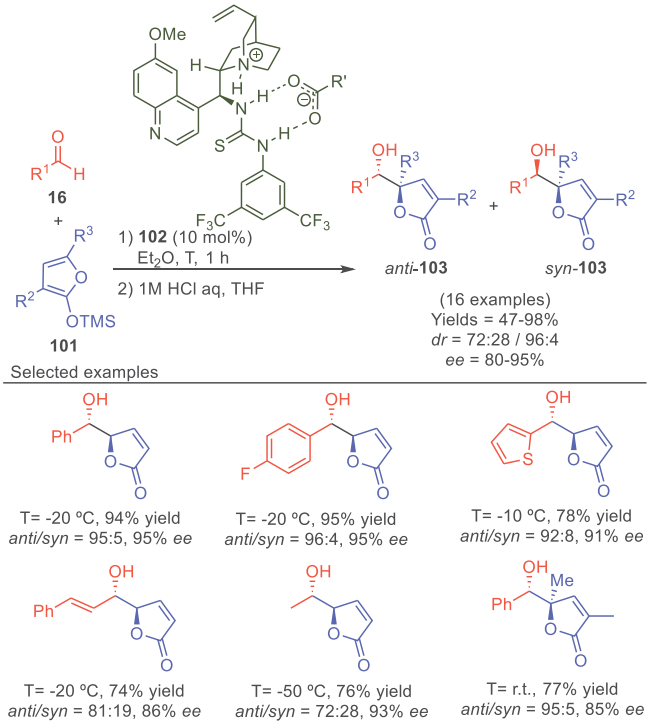
Scheme 32. Mukaiyama aldol reaction "on water" with difluorosilyl enol ether.

With respect to the vinylogous systems, in 2010, Wang's group described the first methodology employing a bifunctional alkaloid thiourea catalyst in the vinylogous Mukaiyama aldol reaction between 2-trimethyl-siloxyfuran (**46**) and aldehydes **16**.[57] The best results were obtained with 20 mol% of the bifunctional catalyst **100**, in $CHCl_3$ at -20 ºC for 6 h and then at 0 ºC for 60 h (78% yield, 91% *ee*, 88/12 *dr*). The authors also studied the influence of different additives such as water and alcohols. By adding 10 mol% of water, the yield could increase up to 90%, although there was a small decrease in the diastereo- and enantioselectivities. Ultimately, they concluded that a small amount of additive could transform the TMS species into a silanol or a silyl ether, regenerating the bifunctional catalyst and increasing the yield (Scheme 33).



Scheme 33. Vinylogous Mukaiyama aldol reaction between 2-trimethyl-siloxyfuran **46** and aldehydes **16**.

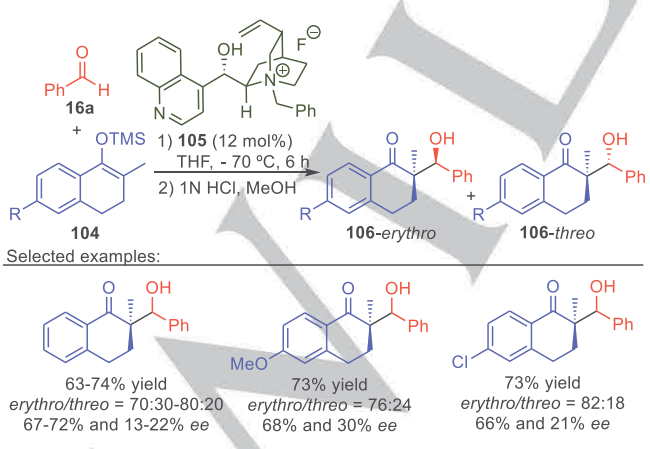
Deng's group established in 2010 a new synthetic approach for the synthesis of chiral butenolides under the influence of a chiral trifluoroacetic acid derived organic salt **102** (resulting from a mixture of amine-thiourea and carboxylic acid) (Scheme 34).[58] The screening of the optimal conditions was carried out with 2-trimethylsiloxyfuran (**46**) and benzaldehyde (**16a**) in the presence of 10 mol% of the catalyst at -20 ºC in CH_2Cl_2. These conditions led to products *anti*-**103** and *syn*-**103** with 96% of conversion, 95:5 of diastereoselectivity and *ee* values of 95%. The authors proposed a catalytic cycle in which the carboxylate moiety reacts with the siloxyfuran in order to form the trimethylsilylester and the 2-furoxy anion. Ensuing activation of the aldehyde by the thiourea through hydrogen bonding would allow the reaction to proceed in high enantio- and diastereoselective fashion (Scheme 34).



Scheme 34. Synthesis of chiral butenolides under a chiral trifluoroacetic acid derived organic salt **102**.

2.6. Ammonium salt catalysts

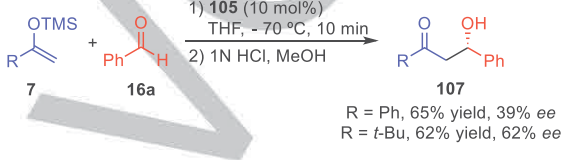
The high demand for enantiomerically enriched compounds in industry led to a pioneering study carried out by a research group from Merck in 1984, which is recognized as the first application of asymmetric phase transfer catalysis.[59] More than twenty years ago, Shioiri et al. reported the first Mukaiyama aldol reaction of cyclic and acyclic silyl enol ethers with benzaldehyde (**16a**) catalyzed by a chiral quaternary ammonium fluoride cinchonine derivative **105** (Scheme 35).[60]



Scheme 35. Mukaiyama aldol reaction of silyl enol ethers catalyzed by a chiral quaternary ammonium fluoride cinchonine.

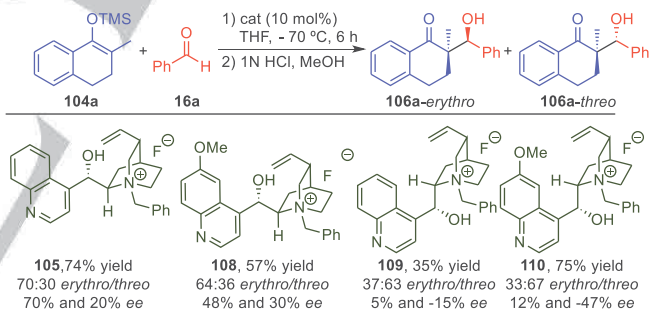
They studied the Mukaiyama aldol reaction with several cyclic silyl enol ethers (**104**) (Scheme 35), obtaining good yields and diastereoselectivities. The enantioselectivities were good for the **106** *erythro*-isomers (66-72% *ee*) but very low for the **106** *threo* ones (less than 30% *ee*).

The same group studied the reaction with acyclic silyl enol ethers **7** obtaining similar yields to those obtained previously with cyclic silyl enol ethers **104** (Scheme 36). However, the enantioselectivities depended on the substituent at the nucleophile. Consequently, when a more sterically hindering group, such as *tert*-butyl, was present in enol ether **7**, the enantioselectivity was higher than when a phenyl derivative was used.



Scheme 36. Addition of acyclic silyl enol ethers **7** to benzaldehyde (**16a**).

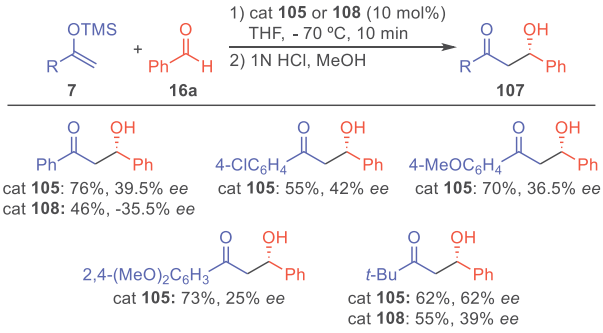
Shioiri's group also investigated the importance of the hydroxymethyl-quinuclidine fragment in the asymmetric Mukaiyama aldol reaction, using quaternary ammonium fluorides derived from cinchona alkaloids (Scheme 37).[61]



Scheme 37. Reaction of silyl enol ether **104a** with benzaldehyde (**16a**) under different fluoride ammonium salts derivatives.

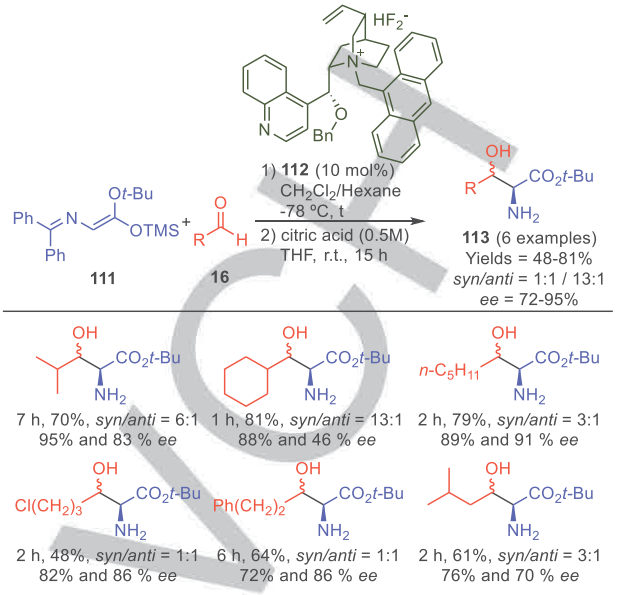
In this work, Shioiri and co-workers synthesized 13 ammonium fluoride cinchona derivatives (**105, 118-110**) and the ensuing study was focused on the ability to control the stereoselectivity of the reaction of silyl enol ether **104a** with benzaldehyde (**16a**) (Scheme 37). The authors established that the stereoselectivity mainly depended on the stereochemistry of the hydroxymethyl-quinuclidine unit, which indicated that hydrogen bonding between the enolate intermediate and the hydroxy group of the catalyst was taking place. The most efficient catalysts are shown in Scheme 37, where cinchonine **105** and quinidine **108** derivatives can be found to afford the *erythro*-**106a** isomer as a major product while the *threo*-**106a** isomer was primarily obtained when cinchonidine **109** and quinine **110** derivatives were used. In most of the cases, the enantioselectivities were moderate. With the best catalysts in

hand, Shioiri studied the reaction of acyclic enol ether **7** with benzaldehyde (**16a**) (Scheme 38). Thus, when cinchonine derivative **105** was used, the *S* isomer was obtained as the major adduct, while cinchonidine derivative **108** led to the *R* isomer. The reaction afforded the desired compounds **107** in moderate to good yields and moderate enantioselectivities at best. In fact, the most sterically hindered *tert*-butyl group and catalyst **105** yielded aldol **107** in only 62% *ee*.



Scheme 38. Reaction of acyclic enol ether **7** with benzaldehyde (**16a**).

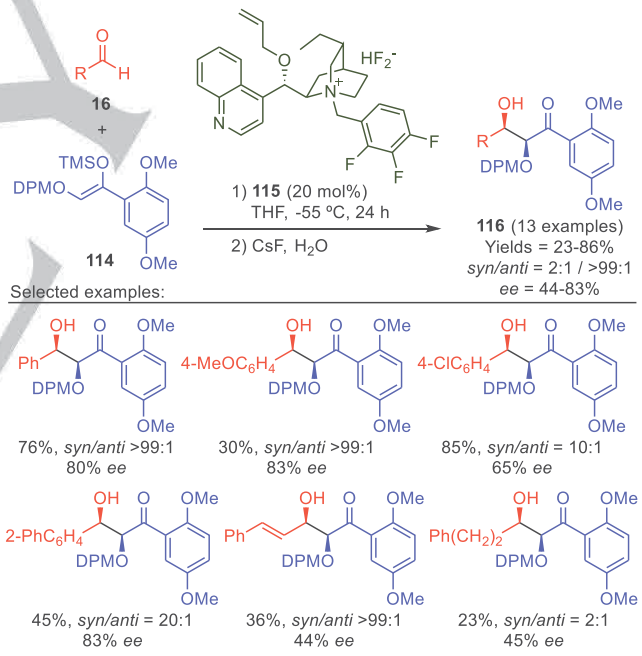
In 1999, Corey et al. also utilized cinchonidine derivative bifluoride salt **112** to synthesize β-hydroxy-α-aminoesters **113** via a Mukaiyama aldol reaction between several aldehydes **16** and the trimethylsilyl enol ether of the *tert*-butylglycinate-benzophenone Schiff base **111** (Scheme 39).[62] Reactions afforded a mixture of *syn*/*anti* isomers of β-hydroxy-α-aminoesters **113** following hydrolysis of primary aldol products in good yields. Actually, *syn*/*anti* selectivity depends on the aldehyde being utilized. Therefore, no diastereoselectivity was observed when unbranched aldehydes were used. However, branched aldehydes displayed higher *syn*/*anti* selectivity, reaching a 13:1 ratio for the cyclohexyl derivative. These results suggest that attraction-based Van der Waals interactions take place between the cyclohexyl group of the aldehyde and the *tert*-butyl and *E*-phenyl groups of the enolate, which are in contact with the catalyst.



Scheme 39. Synthesis of β-hydroxy-α-aminoesters derivatives **113**.

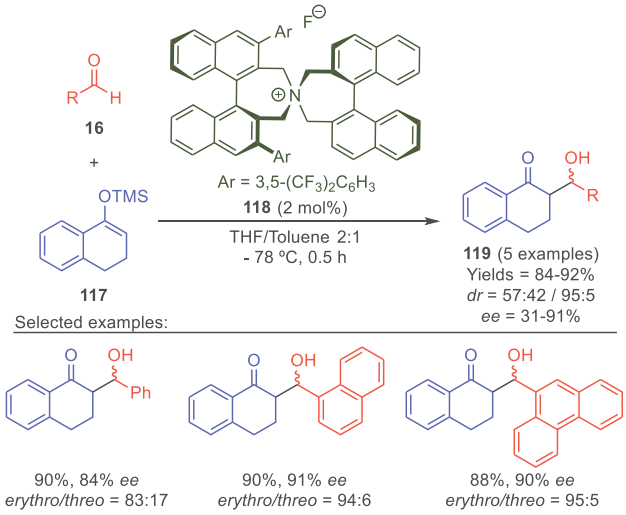
More recently, Andrus and co-workers have reported the asymmetric synthesis of 1,2-diols **116** by means of a Mukaiyama aldol reaction of silyl enol ether **114** with aldehydes **16** catalyzed by the dihydrocinchonium hydrofluoride **115** (Scheme 40).[63]

Andrus carried out an extensive screening of catalysts, solvent and silyl enol ethers differently substituted at the aromatic ring. Interestingly, the use of reagent grade THF afforded better yield and lower reaction time than dry THF, which indicates that the presence of a catalytic amount of water is necessary. The reaction worked well with aromatic aldehydes, obtaining the *syn*-isomer as the main product in good *ee*s. However, alkyl and α,β-unsaturated aldehydes delivered low yield and selectivity.

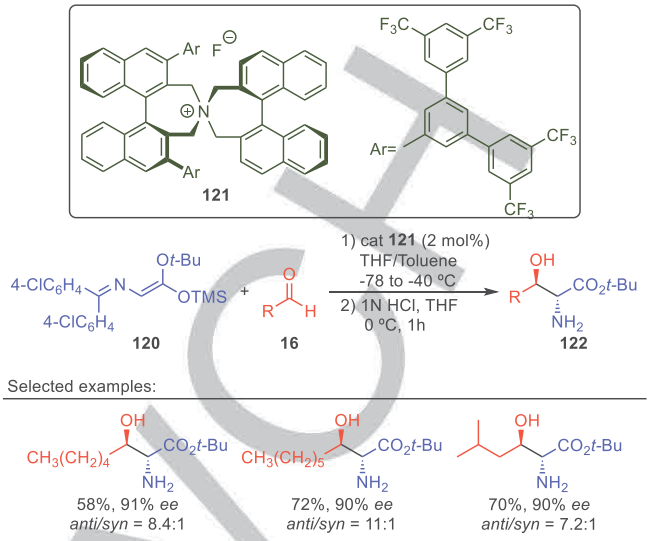


Scheme 40. Synthesis of 1,2-diols **116** by means of a Mukaiyama aldol reaction of silyl enol ether **114** with aldehydes **16.**

Maruoka et al. have also studied quaternary ammonium catalysts in Mukaiyama-type reactions by means of *in situ* generation of the corresponding fluoride derivative **118**.[64] Firstly, the reaction of silyl enol ether **117** with benzaldehyde (**16a**) was studied (Scheme 41) in order to find the best catalyst.



Scheme 41. Reaction of silyl enol ethers with aldehydes in the presence of Maruoka's catalyst.



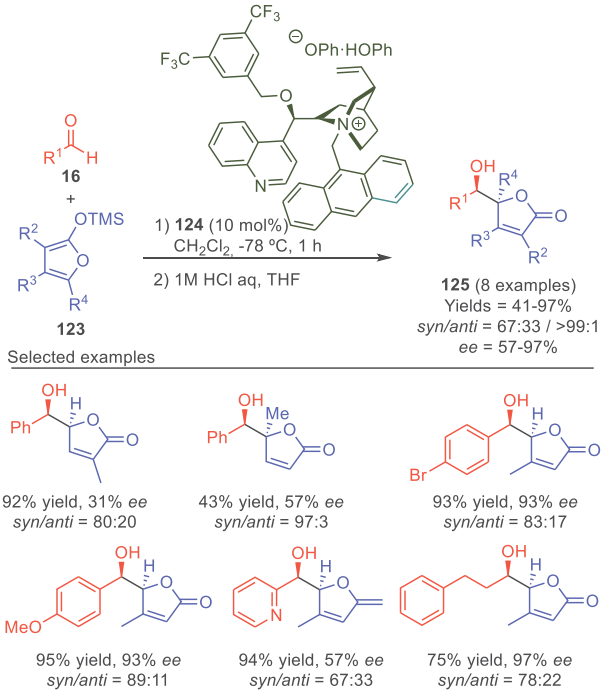
Scheme 42. Synthesis of *anti*-β-hydroxy-α-amino esters **122.**

Switching the 2-naphthyl group with a 3,5-di-CF_3-phenyl in the catalyst increased the *erythro/threo* ratio up to 83:17, which indicates that the presence of electron withdrawing groups at the aromatic ring stimulates the ionic interaction between the ammonium moiety and the enolate. Once the reaction conditions were optimized, the authors carried out the reaction with two more aldehydes obtaining the desired products **119** in high yields and very high stereoselectivities (Scheme 41).

Later, Maruoka and co-workers reported the synthesis of *anti*-β-hydroxy-α-amino esters **122** by reaction of aliphatic aldehydes **16** with ketene silyl acetal **120** catalyzed by quaternary ammonium fluorides **121** (Scheme 42).[65] The catalyst was generated *in situ* from the ammonium hydrogen sulfate catalyst in the presence of potassium fluoride. To obtain high selectivities, the synthesis of catalyst **121** with bulkier substituents at the binaphthyl moiety was necessary, as shown in Scheme 42. Moreover, the presence of an electron withdrawing substituent at the *para* position of the aromatic ring of silyl enol ether **120** also increased the selectivity. The reaction proceeded accordingly with both branched and unbranched aldehydes, always obtaining the *anti*-isomer as the major product. It should be noted that the observed diastereoselectivity is the opposite of the one achieved with cinchonium catalyst derivatives (*syn*-isomers are the major products in this case).

Along these lines, a similar work was reported by Wiskur et al. in 2009, in which they also carried out a mechanistic investigation regarding Mukaiyama aldol reactions catalyzed by chiral acetate quaternary ammonium salt cinchona derivatives.[66] In this study, the authors concluded that the silylation step induces the enantioselectivity of the reaction, instead of the Mukaiyama aldol step.

On the other hand, and because of their importance as versatile building blocks and their presence in many natural products, several research groups have focused their attention towards the asymmetric synthesis of butenolides. Therefore, Mukaiyama's group reported an organocatalytic vinylogous aldol reaction between silyloxyfurans **123** and aldehydes **16** under chiral ammonium salt catalysis **124** (Scheme 43).[67] The reaction was studied at first with benzaldehyde and 2-(trimethylsilyloxy)furan in the presence of 10 mol% of the chiral salt. The best results were obtained in CH_2Cl_2 at -78 ºC, with a moderate enantioselectivity (76% *ee*), further improved by changing the silyloxyfuran substituents. Substitution at the 3 or 5 positions lowered the enantioselectivity, whereas substitution at the 4 position increased the *ee* up to 93%, with excellent yield and diastereoselectivity (*syn*/*anti* = 93:7). The scope of the reaction was studied with different aliphatic and aromatic aldehydes. In all cases, the desired product **125** was obtained with good yields and excellent diastereo- and enantioselectivities.

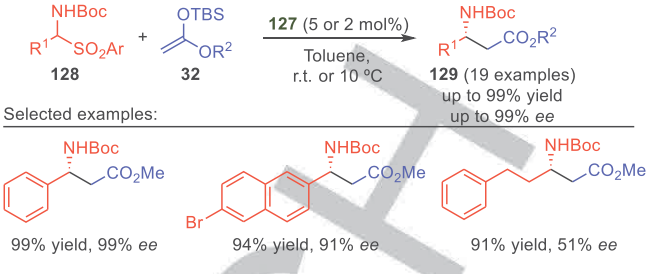


Scheme 43. Organocatalytic vinylogous aldol reaction between silyloxyfurans **123** and aldehydes **16** under a chiral ammonium salt catalyst.

3. Organocatalytic Mukaiyama-Mannich reactions

3.1. Disulfonimide and phosphoric acid catalysts

In 2013, List et al. developed the first disulfonimide-catalyzed asymmetric Mukaiyama-Mannich reaction of *N*-Boc-amino sulfones **128** with silyl ketene acetals **32** (Scheme 44).[68] Optimal reactivity was found when reactions were performed in toluene during 36-72 h at room temperature or 10 ºC. The authors tested three different disulfonimide catalysts (**53, 126-127**, Figure 4) and different catalytic loadings. The best results were obtained with catalyst **127**. Additionally, yields and enantioselectivities remained equal when adding 2 or 5 mol% of catalyst. Furthermore, in order to shed light upon the enantiodiscriminating step of the reaction, different sulfone groups (SO_2Ar) were studied, although they proved to be non-factors at this stage. The alkoxy group (OR^2) of the silyl ketene acetals was also investigated. If extended, the aliphatic chain decreased enantioselectivity. The scope of the reaction of the *N*-Boc-amino sulfones (R^1) showed excellent yields (92-99%) and very good enantioselectivities (90-99%) with naphthyl and phenyl substituents, regardless of substitution (electron-donating or electron-withdrawing groups). Lower enantioselectivities were achieved when heterocyclic (72%) or aliphatic (51%) substrates were employed. Notwithstanding, this was the first-ever reported example of a catalytic asymmetric Mukaiyama-Mannich reaction with aliphatic *N*-Boc-protected substrates.



Scheme 44. Scope of the asymmetric Mukaiyama-Mannich reaction.

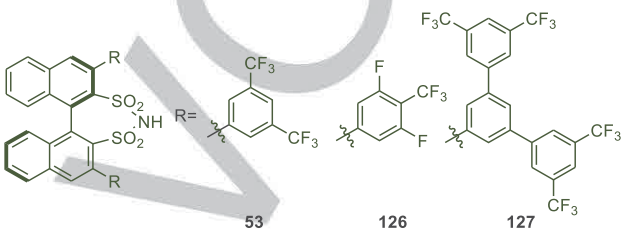
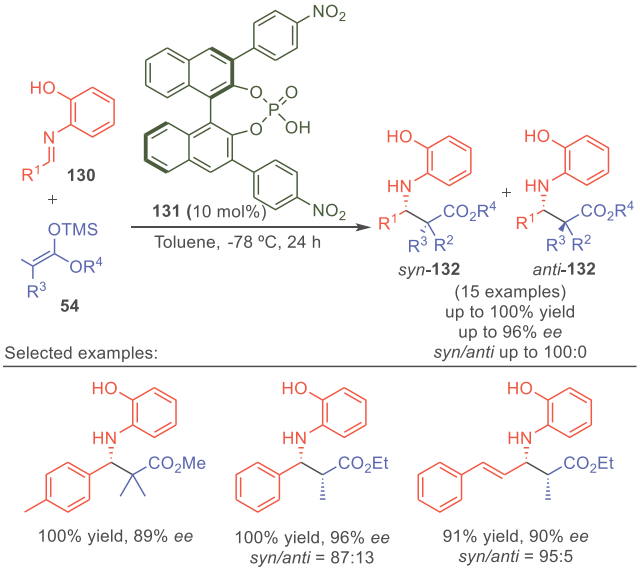


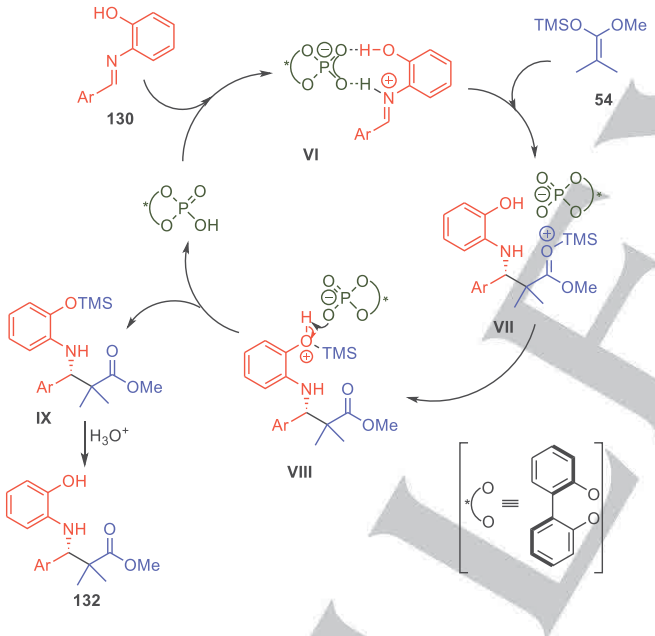
Figure 4. Disulfonimide catalysts used in the Mukaiyama-Mannich reaction of Scheme 13.

Akiyama's group accomplished an enantioselective Mukaiyama-Mannich type reaction between aldimines **130** and silyl enolates **54** (Scheme 45).[69] The reaction was catalyzed by chiral phosphate derivatives with different aromatic groups at the 3,3'-positions. The highest enantioselectivity was obtained with 4-nitrophenyl phosphate derivative **131**, requiring a 10 mol% catalyst loading in toluene at -78 ºC to complete the reaction after 24 h. A variety of ketene silyl acetals and aldimines are tolerated in the reaction, and all β-aminoesters **132** were obtained with excellent yields and good enantioselectivities. Interestingly, chiral Brønsted acids had been previously engaged in enantioselective Mukaiyama-Mannich reactions, yet this was the first example of such a reaction in which the carbon-nitrogen double bond is activated by a metal-free chiral Brønsted acid.

Subsequently, Akiyama and co-workers described a mechanistic proposal for this reaction based on DFT calculations in 2007,[70] indicating that the dicoordination pathway through the zwitterionic species was the most plausible mechanism (Scheme 46). In the following years, Akiyama's group investigated the scope of this reaction, giving rise to a wide array of derivatives.[71]



Scheme 45. Catalytic enantioselective Mukaiyama-Mannich-type reactions.



Scheme 46. Plausible mechanism for the Mukaiyama-Mannich reaction.

Following Akiyama's work, Yamamoto and Zhou studied the same reactions in terms of the application of other chiral phosphoric acid derivatives as catalysts by modifying the aromatic substituents at the 3,3'-positions in the catalyst structure (Figure 5).[72]

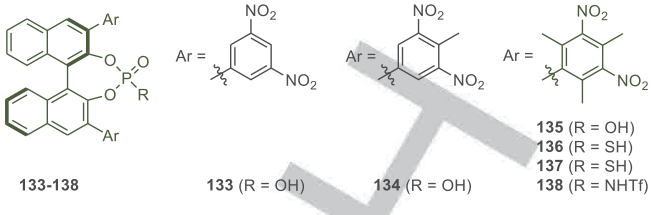
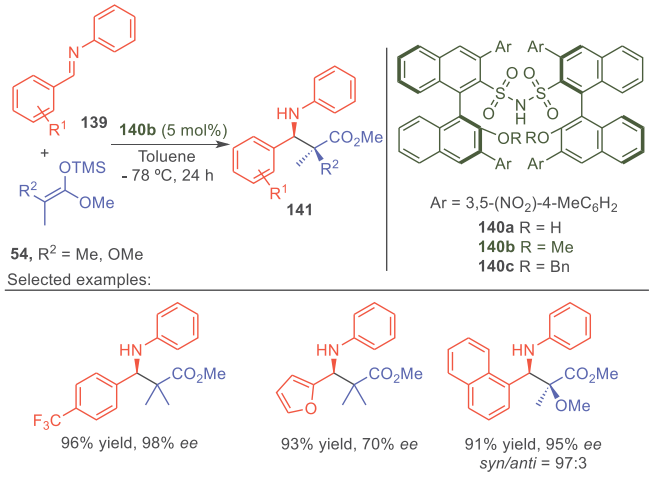


Figure 5. Chiral phosphoric acid derivatives used as catalysts in Mukaiyama-Mannich reactions.

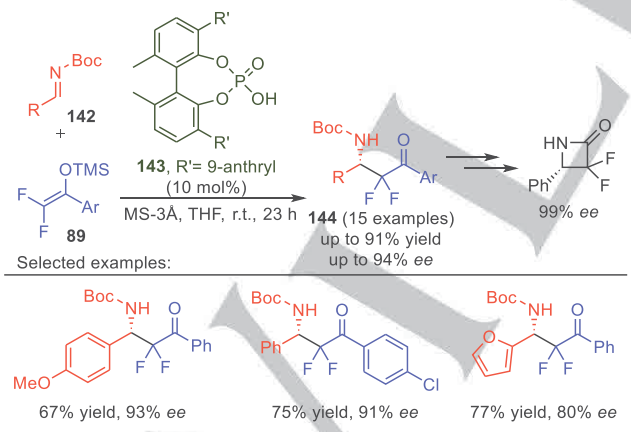
In spite of the high yields achieved with 4-nitrophenyl catalyst derivatives **133** and **134**, the enantioselectivity was moderate at best and always lower than Akiyama's reported results (see Scheme 45). To increase the enantioselectivity, a hydrogen atom at the *para* position of the 3,5-dinitrophenyl ring was replaced by a methyl group. Catalyst **134** displayed a slight improvement over Akiyama's work, and an even better outcome was observed when catalyst **135** was used (2,4,6-trimethyl-3,5-dinitrophenyl derivative). The authors also studied different analogues of catalyst **135** in which the hydroxy group had been replaced with other functionalities (**136-138**). However, these catalysts gave lower enantioselectivities than **135**. In the presence of organocatalyst **135**, a broad substrate scope (38 examples) was shown. Both aromatic and aliphatic imines gave products in good yields (up to 99%) and high enantioselectivities (up to 99%). As they continued to gain insight into this approach, Yamamoto and Zhou similarly employed various ketene silyl acetals under the same conditions, obtaining excellent enantioselectivities (up to 99%) and moderate to high diastereoselectivities (*syn/anti* up to 99:1).

In their ensuing work, Yamamoto and Zhou rendered the 2-hydroxyphenyl moiety in aldimines unnecessary in order to reach good enantioselectivities.[73] They developed a new assortment of chiral disulfonimide catalysts, including those with 4-methyl-3,5-dinitrophenyl substituents (Scheme 47), which gave access to high enantiocontrol. The best results were obtained with 5 mol% of catalyst **140b** at -78 ºC after 24 h. All the aromatic aldimines containing electron-withdrawing or electron-donating groups underwent the reaction smoothly, giving their corresponding products in good yields and excellent enantio- and diastereoselectivities. However, reactions with heterocyclic aldimines gave good yields, but much lower *ee*s. The authors did not examine reactions with aliphatic aldimines.



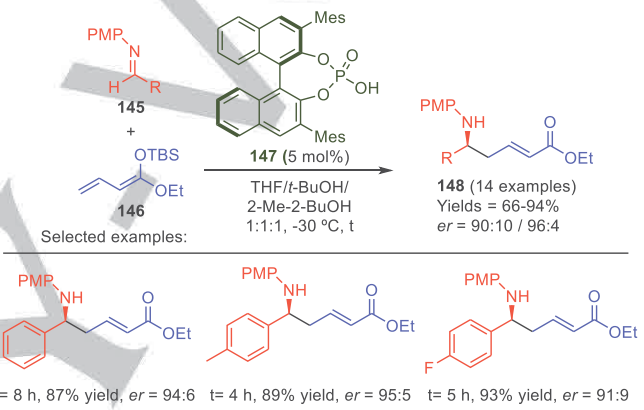
Scheme 47. The disulfonimide-catalyzed enantioselective Mukaiyama-Mannich reaction.

In 2011 Akiyama et al. developed a similar reaction of *N*-Boc aldimines **142** with difluoroenol silyl ethers **89** employing a biphenyl-derived chiral phosphoric acid **143** as catalyst, which contains 9-anthryl groups at the 3,3'-positions (Scheme 48).[74] The researchers found that the addition of Molecular Sieves (MS-3Å) and THF as solvent significantly improved the yield. Aromatic substituents with both electron-withdrawing and electron-donating groups, as well as substrates with a bulky group at the imine produced good enantioselectivities. However, heteroaromatic aldimines gave the corresponding adduct in lower *ee*s, and aliphatic aldimines did not afford the desired product. The authors demonstrated that the resulting adduct could be transformed into optically pure 3,3-difluoroazetidin-2-one.



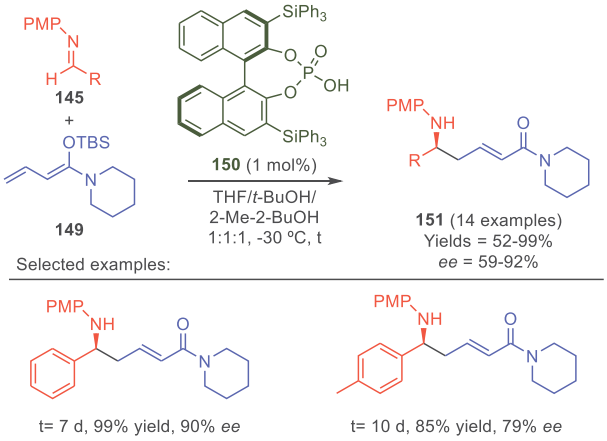
Scheme 48. Reaction of *N*-Boc imine **142** with difluoroenol silyl ether **89** catalyzed by chiral phosphoric acid **143**.

We can also find several examples of the vinylogous version of these reactions in the literature. In 2008, Schneider et al. reported the novel organocatalytic asymmetric vinylogous Mukaiyama-Mannich reaction between acyclic silyl dienol ethers **146** and *p*-methoxyphenyl imines **145** under BINOL-based phosphoric acid catalysis **147**.[75] The optimal conditions featured 5 mol% of the chiral phosphoric acid bearing the 3,3'-bismesityl groups, a mixture of THF, *t*-BuOH and 2-Me-BuOH as solvent, and 1 equiv. of water as additive at -30 ºC. These conditions led to the desired γ-regioisomer products with good yields and enantioselectivities. The reaction tolerated aromatic, heteroaromatic and aliphatic aldimines, producing good yields and enantiomeric ratios up to 96:4. Schneider also highlighted the utility of the methodology with a three-component reaction between the corresponding aldehyde, amine and silyl dienol ether, obtaining the desired product with a slight increase in yield in comparison to the reaction between the corresponding imine and silyl dienol ether (Scheme 49).



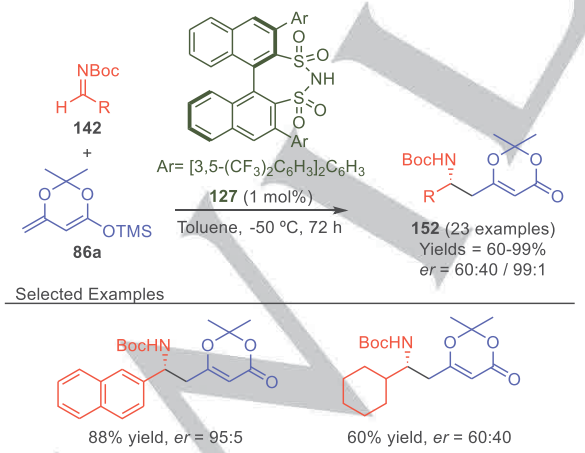
Scheme 49. Asymmetric vinylogous Mukaiyama-Mannich developed by Schneider.

Months later, Schneider's group also published the asymmetric vinylogous Mukaiyama-Mannich reaction of vinylketene silyl *N,O*-acetals **149** and *p*-methoxyphenyl imines **145** employing chiral phosphoric acid **150**.[76] In this case, 3,3'-bistriphenylsilyl groups were incorporated to the phosphoric acid to obtain better results. The catalytic loading could be decreased to 1 mol%, giving rise to δ-amino-α,β-unsaturated amines **151** with good yields and enantioselectivities after 7 days of reaction. Different vinylketene silyl *N,O*-acetals were studied, reaching the best results (91% yield, 90% *ee*) with the piperidide vinylketene silyl *N,O*-acetal derivative. Once the best conditions and nucleophile were chosen, the authors focused their attention on the scope of the reaction. Their findings showed that it tolerated a wide range of different aldimines, delivering the γ-regioisomer in good yields and enantioselectivities up to 90% (Scheme 50).



Scheme 50. Vinylogous Mukaiyama-Mannich reaction of vinyl-ketene silyl *N,O*-acetals **149** and imines **145**.

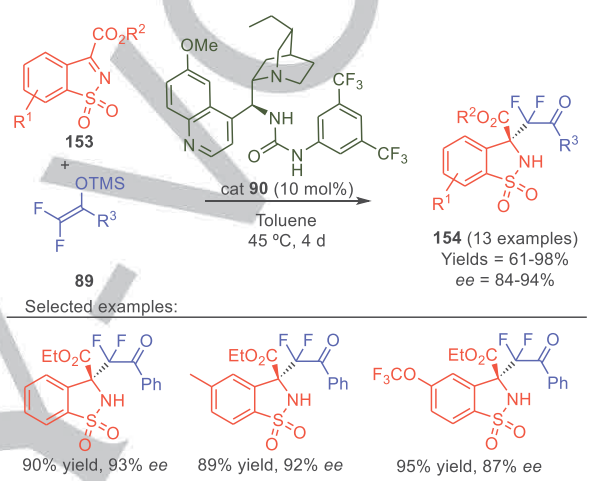
In 2011, List made use of the chiral disulfonimides described previously as effective catalysts to perform the asymmetric vinylogous Mukaiyama-Mannich reaction between *N*-Boc imines **142** and silyl dienol ethers **86a** with high yields and *ee*s (Scheme 51).[77] The optimization of the reaction began with the search for the most effective disulfonimide (1 mol% of **127**). Toluene would be used as solvent at -50 ºC. The scope of the reaction allowed the use of differently aryl- and naphthyl-substituted *N*-Boc imines. Surprisingly, the *meta*-methyl-phenyl-*N*-Boc imine presented higher enantioselectivity in comparison with the analogous *ortho*- and *para*-methylphenyl imine derivatives. The reaction was also compatible with imines containing halide-substituted aromatic groups, disubstituted phenyls and heterocyclic *N*-Boc imines. High yields and moderate to good *ee*s were achieved following this methodology (Scheme 51). The Mukaiyama-Mannich products **152** were used for further transformations in order to obtain enantiomerically enriched α-amino-β-ketoesters, highly useful compounds in the synthesis of piperidine and pyrrolidine alkaloid derivatives.



Scheme 51. Asymmetric vinylogous Mukaiyama-Mannich reaction between *N*-Boc imines **142** and silyl dienol ethers **86a**.

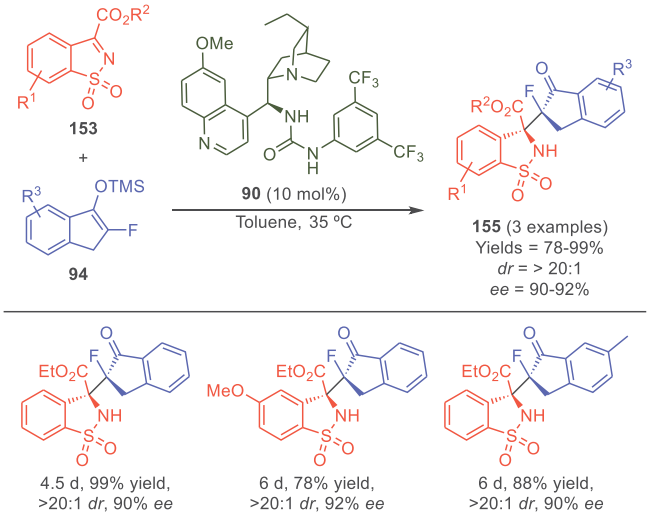
3.2. Bifunctional organocatalytic cinchona derivatives

Recently, Zhou's group has improved the applicability of fluoro silyl enol ethers by carrying out Mukaiyama-Mannich reactions with *N*-sulfonyl ketimines, giving rise to α-aminoacid derivatives with up to two quaternary stereocenters in a controlled manner.[78] At first, the reactions of acyclic difluoro silyl enol ethers **89** with *N*-sulfonyl ketimines **153** were evaluated in the presence of catalyst **90**, obtaining the corresponding benzosultam **154** in good to high yields and enantioselectivities regardless of the nature and position of the substitution at the ketimine or the enol ether (Scheme 52).



Scheme 52. Addition of fluoro silyl enol ethers to *N*-sulfonyl ketimines.

However, aliphatic difluoroenoxysilanes did not undergo this reaction, possibly due to their low reactivity. Accordingly, the reaction of cyclic monofluoro derivatives **94** with *N*-sulfonyl ketimines **153** using the same bifunctional organocatalyst **90** was studied (Scheme 53). Lower temperature (35 ºC) than reactions with acyclic difluoro derivatives afforded the desired benzosultam **155** with two quaternary stereocenters in great yields, high *ee*s and excellent diastereomeric ratios. Considering the absolute configuration of the final products **154**, elucidated by X-ray analysis, the authors proposed a transition state (Figure 6) in which *N*-sulfonyl ketimine **153** is activated by hydrogen-bonding interaction with the urea moiety while the difluoroenoxysilane reagent **90** is activated by means of an interaction between the nitrogen of the quinuclidine moiety and the silicon atom. At this juncture, the nucleophilic attack takes place on the *Re*-face of the ketimine to afford the (*S*)-enantiomer as the major product.



Scheme 53. Cyclic monofluoro derivative **94** addition to cyclic sulfonyl ketimines **153**.

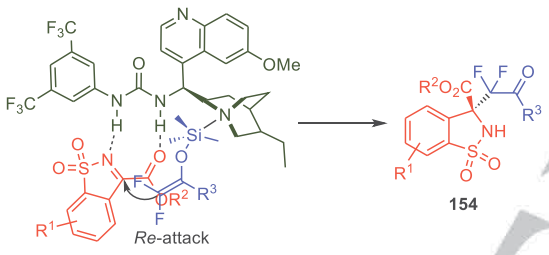
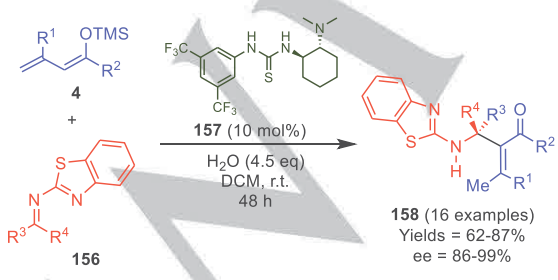


Figure 6. Proposed transition state of the reaction of fluorosilyl reagents with ketimines shown in Scheme 52.

Very recently, our group for the first time and in contrast with all the precedents described in the literature, has shown the 1,3 functionalization in the reaction between silyl dienol ethers **4** and benzothiazolimines **156**.[79] We have provided a general method for the synthesis of a wide range of aza-Baylis-Hillman-type products with excellent enantioselectivities, which are difficult to obtain by other methodologies. The regioselectivity presented in this work is a main novelty that is a consequence of the structure of the bifunctional catalyst.



Scheme 54. Frustrated vinylogous Mukaiyama-Mannich reaction.

4. Organocatalytic Mukaiyama-Michael Reactions

4.1. Imidazolidinone and pyrrolidine catalysts

Previous work by MacMillan's group disclosed the use of chiral imidazolidinones as effective catalysts for the 1,4-addition of electron rich aromatic systems to α,β-unsaturated aldehydes.[80] These catalyst types, by condensation with the α,β-unsaturated aldehyde, generate an α,β-unsaturated iminium ion (Figure 7) which is inert to nucleophilic 1,2-addition on the basis of steric constraints imposed by the catalyst framework. Moreover, the bulky substituents at the catalyst lead to high stereoselectivities. In addition, the formation of this ion iminium intermediate induces a decrease of the LUMO energy of the conjugated system favoring the nucleophilic addition.

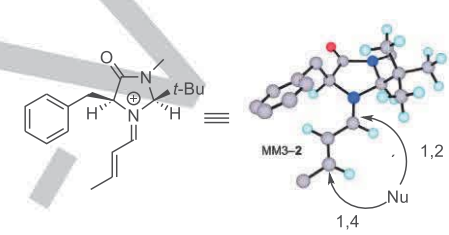
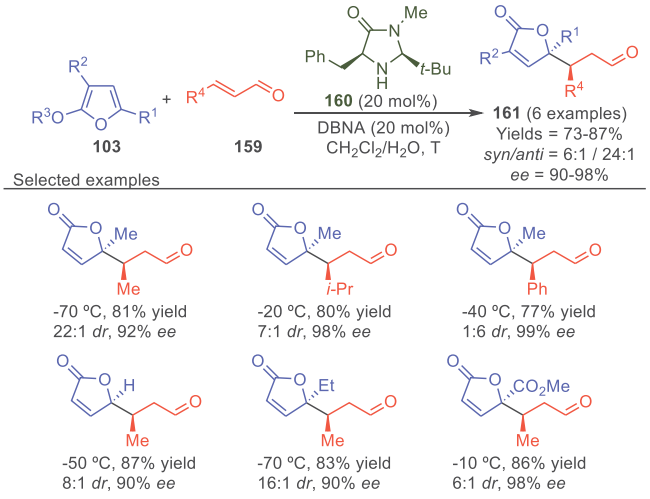


Figure 7. Formation of the α,β-unsaturated iminium ion.

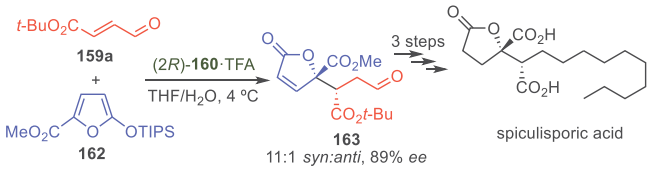
Subsequently, the search for new imidazolidinone-based chiral molecules capable of catalyzing carbon-carbon bond-forming reactions took place. Thus, in 2003, MacMillan and co-workers developed an enantioselective vinylogous Mukaiyama-Michael reaction via chiral imidazolidinone-catalysis, in which α,β-unsaturated aldehydes **159** were transformed into γ-butenolide derivatives **161** (Scheme 55) in high yields, diastereo- and enantioselectivities.[81]



Scheme 55. Enantioselective Mukaiyama-Michael reaction with α,β-unsaturated aldehydes.

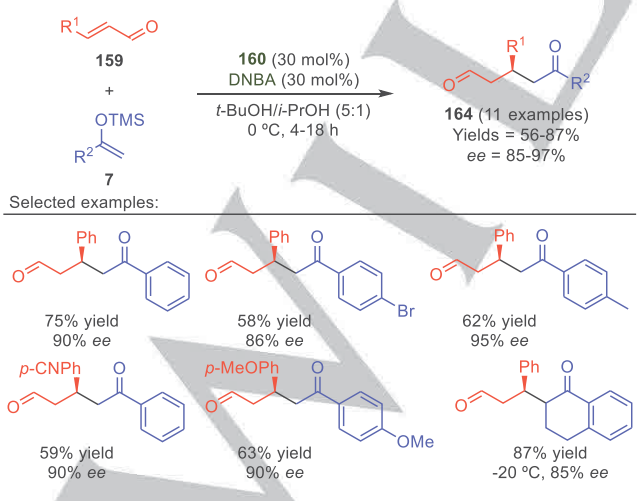
The best results were obtained by use of the amine salt **160**·2,4-dinitrobenzoic acid (DBNA) in a mixture of CH_2Cl_2–H_2O (the presence of water is required to avoid the inhibition of catalytic cycle). The reactions work well with aliphatic and aromatic aldehydes but the diastereoselectivity depends on the nature of the aldehyde. Thus, *syn*-isomers were obtained as major compounds when aliphatic aldehydes were used while an aromatic aldehyde (R^3=Ph) delivered the *anti*-isomer as the major one. Moreover, it is remarkable how the change of cocatalyst reversed the diastereoselectivity when the reaction was carried out with the methyl (*E*)-4-oxobut-2-enoate (*syn*-isomer was obtained when TFA was used as cocatalyst and *anti*-isomer when TfOH was used).

The authors demonstrated the utility of this reaction in the γ-butenolide system construction across the synthesis of the spiculisporic acid (Scheme 56),[82] a *Penicillium spiculisporum* fermentation adduct[83] which is used commercially as a biosurfactant for metal decontamination.[84]



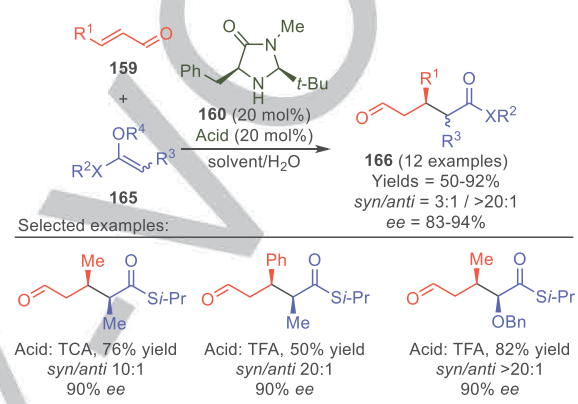
Scheme 56. Synthesis of spiculisporic acid.

Two years later, Wang described the first organocatalytic Mukaiyama-Michael addition of acyclic silyl enol ethers **7** with α,β-unsaturated aldehydes **159** via ion iminium, affording δ-keto aldehydes **164** in high yields and enantioselectivities (Scheme 57).[85] The authors tested the reaction with five different chiral aminocatalysts (pyrrolidines and imidazolidinones), determining that MacMillan's imidazolidinone (**160**) was the best. The nature of the acid co-catalyst was very important. Thus, strong acids such as HCl or TFA caused decomposition of **7**. However, 2,4-dinitrobenzoic acid (DNBA) afforded high yields.



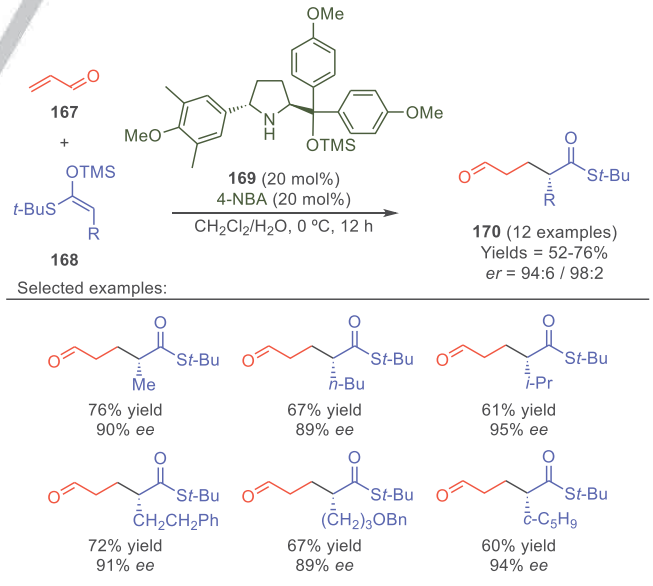
Scheme 57. Reaction of silyl enol ethers **7** with α,β-unsaturated aldehydes **159** via iminium ion.

In 2009, MacMillan et al. studied the Mukaiyama-Michael reaction between a variety of α,β-unsaturated aldehydes **159** and *Z*- and *E*-silyl ketene acetals **165** using imidazolidinone **160** as catalyst. *Syn*- and *anti*-products **166** could be easily obtained with good levels of diastereo- and enantioselectivity depending on the starting silyl ketene acetals, and without any enol hydrolysis (Scheme 58).[86] The reaction tolerated both electron-withdrawing and electron-donating substituents in silyl ketene acetals **165**. However, the presence of electron-withdrawing substituents in aldehydes **159** provided lower diastereoselectivities.



Scheme 58. Mukaiyama-Michael reaction between α,β-unsaturated aldehydes **159** and *Z*- and *E*-silyl ketenes **165**.

Recently, Pihko et al. have also described the reactions of acrolein **167** with silyl ketene thioacetals **168** in the presence of a chiral pyrrolidine **169** to give α-alkyl substituted thioesters **170** (Scheme 59).[87]



Scheme 59. Aminocatalytic reactions of silyl ketene thioacetals **168** with acrolein.

In order to obtain high levels of enantioselectivity, the authors designed a new pyrrolidine catalyst **169** which bears an aryl substituent at the C5 position since the use of other aminocatalysts such as MacMillan's (**160**), or a *C2*-symmetric 2,5-diphenylpyrrolidine catalyst, afforded lower values. Catalyst **169**, containing electron-donating substituents at the aryl groups, gave the best results from an enantioselectivity and conversion standpoint. The reaction worked well with different alkyl chains or cyclic substituents at the silyl ketene thioacetals **168**. Moreover, the presence of the *E* isomer in the starting nucleophile **168** did not affect the final enantioselectivity value, although the yield was lower possibly due to the lower reactivity of the *E* isomer. In addition, the authors used this reaction to synthesize the C4-C13 fragment of (-)-bistramide A.

Authors carried out DFT calculations for transition states of the C-C bond formation between the iminium intermediate and silyl ketene thioacetal to try to explain the observed stereoselectivities (Figure 8). These calculations indicate that the TS-*R* is more favored than TS-*S*, due to combinations of steric and attractive effects, which is in accordance with the stereoselectivities obtained.

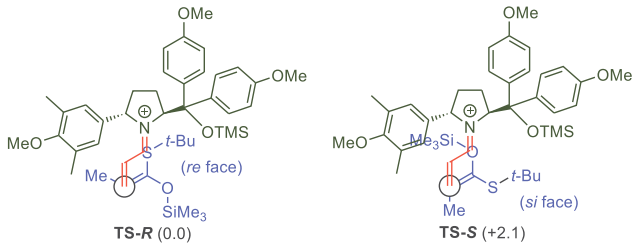
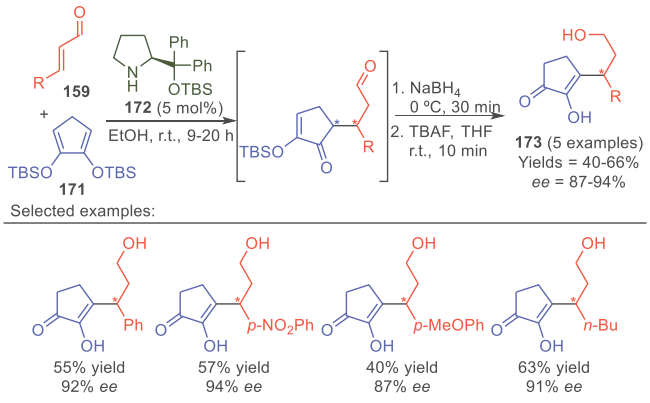


Figure 8. Transition states of the C-C bond formation.

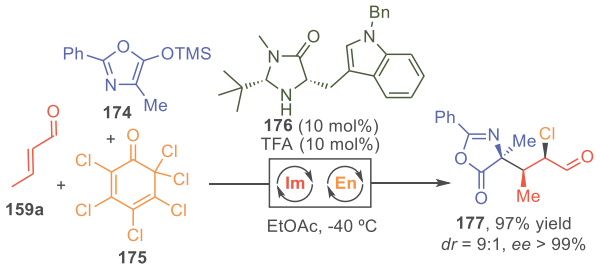
Afterwards, Lopp and co-workers described the synthesis of cyclopentane-1,2-diketones **173** (in mono-enolic form) by means of a Mukaiyama-Michael reaction of α,β-unsaturated aldehydes **159** with cyclopentane-1,2-diones bis-silyl enol ethers **171** in the presence of organocatalyst **172**, affording good yields and high enantiomeric excesses in most cases (Scheme 60).[88]



Scheme 60. Mukaiyama-Michael reaction of cyclopentane-1,2-diones bis-silyl enol ethers with α,β-unsaturated aldehydes.

The reaction proceeded adequately with both aromatic and aliphatic aldehydes, but aldehydic aromatic rings bearing an electron-donating substituent (e.g. methoxy group) caused lower yields and moderate enantioselectivity. The primary adducts obtained in these reactions were isolated after reduction of the carbonyl group and subsequent deprotection to afford the stable alcohol **173** with only one stereocenter, whose absolute configuration was not elucidated.

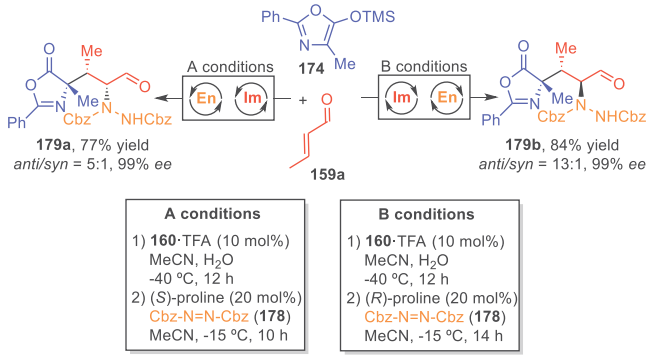
In addition to the examples shown before, MacMillan and co-workers reported a tandem reaction in which iminium and enamine cycles are involved. Specifically, MacMillan described in 2005 the reaction of crotonaldehyde **159a** with silyloxyoxazole **174** in which chlorinated quinone **175** was employed in concert with the catalytically-active imidazolidinone **176** (Scheme 61).[89] The reaction afforded the corresponding azalactone **177** in high yield and diastereomeric ratio, and excellent enantiomeric excess.



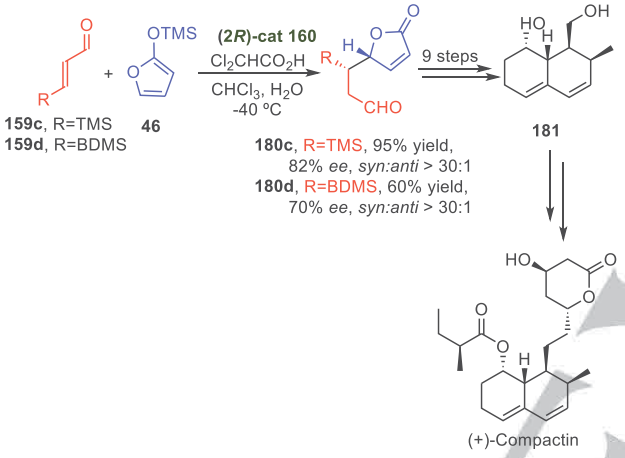
Scheme 61. Tandem reaction involving iminium and enamine cycles with silyloxyoxazole **174.**

Later on, the same authors described the tandem reaction of silyloxyoxazole **174** with dibenzylazodicarboxylate **178** as aza-Michael acceptor (Scheme 62).[90] In this process, the combination of imidazolidinone and proline catalysts was necessary, providing the corresponding adducts **179a-b** in high *anti/syn* ratio and complete enantioselectivity. The imidazolidinone controls the Michael addition of silyloxyoxazole **174** to crotonaldehyde **159a** via iminium while the proline catalyzes the reaction with aza-Michael acceptor **178** via enamine. The *anti/syn* diastereoselectivity of the final product is controlled by the stereochemistry of the proline catalyst.

Robichaud and Tremblay have also reported the synthesis of butenolides **180** by means of MacMillan's organocatalytic Mukaiyama-Michael reaction (Scheme 65).[91] In addition, they established these diols as key intermediates for the synthesis of (+)-compactin, a metabolite previously isolated from *Penicillium brevicompactum* strains.[92] This work highlighted the role the β substituent in the aldehyde plays in order to reach an optimal stereoselectivity. Therefore, when a silyl substituent is present at the starting aldehyde, the final γ-butenolide **180** is obtained in good *ee*s (82 and 70%) and excellent *dr*s. The incorporation of other bulky substituents, such as thioethers (R = S*t*-Bu or SPh) also afforded the desired products, albeit with low diastereoselectivities (~3:1).



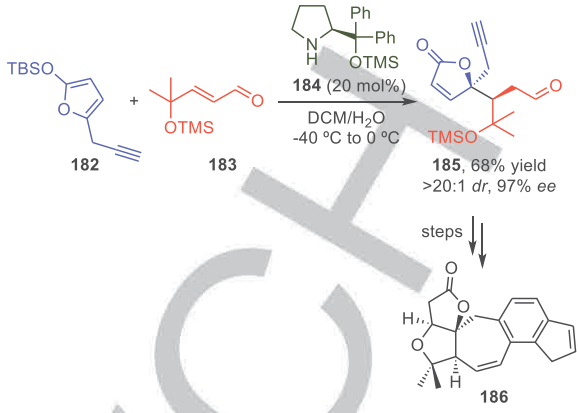
Scheme 62. Combination of iminium and enamine cycles involving two different aminocatalysts.



Scheme 65. Synthesis of (+)-compactin.

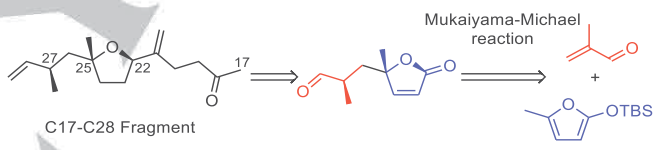
As stated above, they also reported a novel enantioselective approach to the advanced intermediate **181** and established this diol as a key intermediate for the synthesis of (+)-compactin, a metabolite previously isolated from *Penicillium brevicompactum* strains.[93] The important biological activity of (+)-compactin has led to the publication of several synthesis.[94]

Very recently, the Xie group has described the highly stereoselective construction of the C5-epi ABCDE ring system **186** of Rubriflordilactone B using an organocatalytic vinylogous Mukaiyama-Michael reaction as the key step (Scheme 66).[95] The authors carried out a screening of known iminium/enamine type catalysts (proline derivatives and MacMillan catalyst **160**). The best results were achieved with catalyst **184**. Surprisingly, MacMillan's catalyst **160** did not work, perhaps due to its steric hindrance. Nevertheless, the stereochemistry obtained in the Mukaiyama-Michael reaction was appropriate to synthesize the C5-epi ABCDE ring system (no epimerization step was necessary).



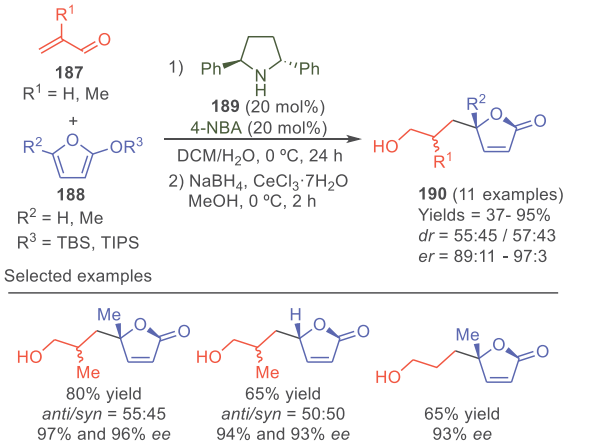
Scheme 66. Synthesis of Rubriflordilactone B **191**.

The excellent control over the selectivity at the 5 position of the γ-butenolide in the Mukaiyama-Michael reaction has been used by Pihko et al. to synthesize the C17-C28 fragment of Pectenotoxin-2 (Scheme 67), which bears a thermodynamically unstable "non-anomeric" spiroketal (C25).[96] In addition, another stereocenter must be generated at C27. For that purpose, methacrolein had to be involved in the procedure, and therefore this process had to be studied thoroughly because it is a non-common substrate in iminium organocatalysis.



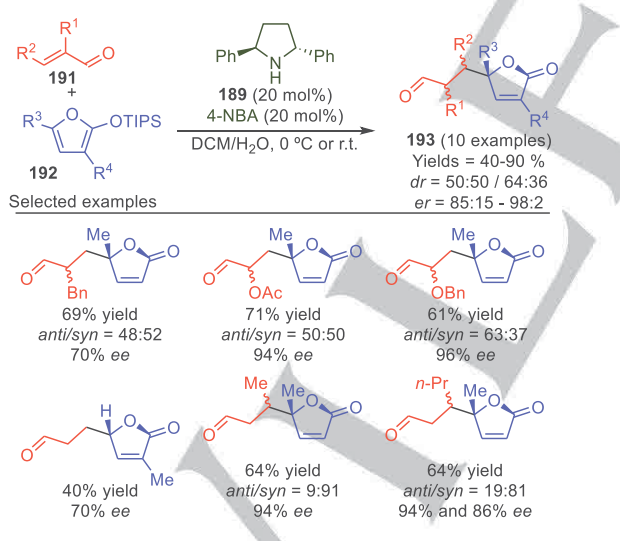
Scheme 67. Synthesis of the fragment C17-C28 of Pectenotoxin-2.

To reach a high level of selectivity with methacrolein, the authors carried out an extensive catalyst screening, evaluating MacMillan's imidazolidinones, prolinol derivatives and a *C2*-symmetric 2,5-diphenylpyrrolidine. The first two options turned in very low enantiomeric excesses and diastereoselectivities (Scheme 68). However, when the *C2*-symmetric 2,5-diphenylpyrrolidine catalyst (**189**) was used, the final Mukaiyama-Michael adduct was obtained in excellent *ee* (93%) but moderate diatereoselectivity (56:44), which indicates that stereochemical control over carbon C27 is not possible.



Scheme 68. Mukaiyama-Michael reaction using methacrolein as starting material.

Pihko and co-workers were able to separate both isomers by column chromatography and the *syn*-isomer was used to synthesize the C17-C28 fragment of Pectenotoxin. The authors also studied the reaction of several silyl enol ethers with acrolein and methacrolein. The reaction with both aldehydes afforded the corresponding γ-butenolides in good yields and high enantiomeric excesses, regardless of the presence or absence of a substituent at the silyl enol ether (R^2). Pihko also carried out a detailed study of the reaction conditions (catalyst, silyl protecting group, acid co-catalyst) of the vinylogous Mukaiyama-Michael reaction (Scheme 69).[97]



Scheme 69. Reaction scope with methacroleins and α,β-unsaturated aldehydes.

They determined that the best conditions were the same as the ones used in their previous work, and decided to increase the reaction scope using other methacroleins and α,β-unsaturated aldehydes. Interestingly, when a benzyl group is present in the starting methacrolein or a 3-methylsilylenol ether is used in the reaction with acrolein, the enantioselectivity decreased to 70%. The reaction also took place with β-substituted acroleins, obtaining good diastereoselectivities (*syn*-isomer is the major one) when the silyl enol ether was substituted at C5. Additionally, the authors carried out a complete theoretical study by means of DFT calculations to rationalize the observed stereoselectivities. These theoretical studies showed that, in addition to the steric effect, weak intermolecular van der Waals interactions between the furyl moiety and TBS group of the nucleophile and the phenyl substituent and pyrrolidine moiety at the catalyst play an important role in the stereoselectivity of the process (Figure 9). Finally, the authors published the protecting group-free total synthesis of (+)-Greek tobacco lactone following their methodology, starting from acrolein and *tert*-butyldimethyl((5-methylfuran-2-yl)oxy)silane to afford the natural lactone in four steps with a 34% overall yield.[98]

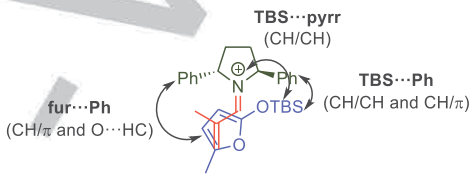
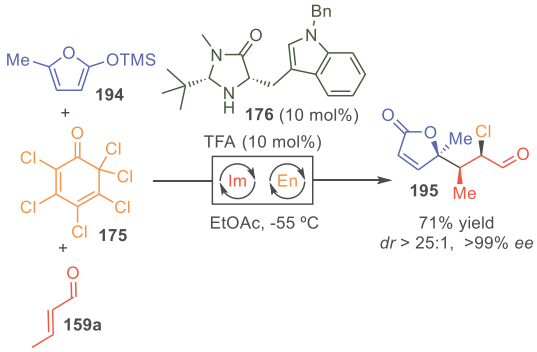


Figure 9. Intermolecular van der Waals interactions studied by Pihko's group.

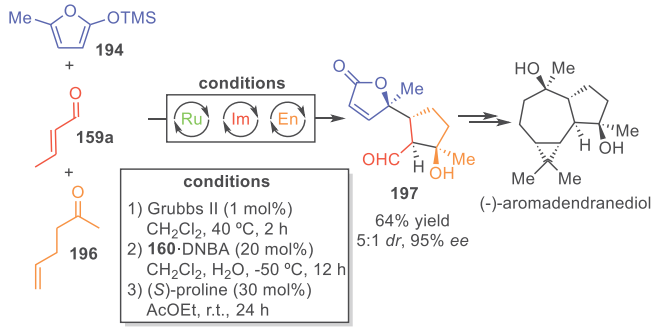
The silyloxyfuran derivative **194** has also been used in tandem reactions, in which iminium and enamine catalytic cycles are involved. MacMillan and co-workers described the reaction of silyloxyfuran **194** with crotonaldehyde **159a** in the presence of catalyst **176,** followed by reaction with the chlorinated quinone **175**, giving rise to difunctionalized aldehydes at the α and β positions (Scheme 70).[99] The reaction afforded the corresponding γ-butenolide **195** in good yield and with complete stereocontrol (only one stereoisomer was obtained).



Scheme 70. Tandem reaction developed by MacMillan using a Mukaiyama reaction.

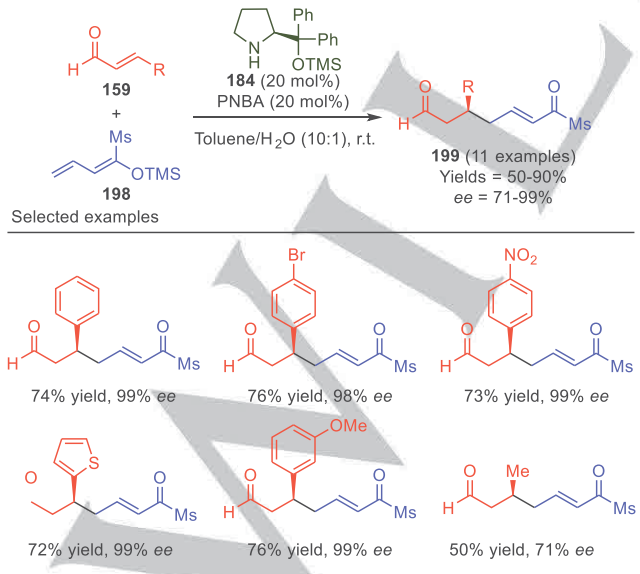
In a related work, MacMillan's group carried out the synthesis of (-)-aromadendranediol, a sesquiterpene whose bicycle structure presents six stereocenters. A triple-tandem-

catalytic procedure (metathesis/Vinylogous Mukaiyama-Michael/aldol reaction) was developed, highlighted by the key Mukaiyama-Michael transformation (Scheme 71).[100]



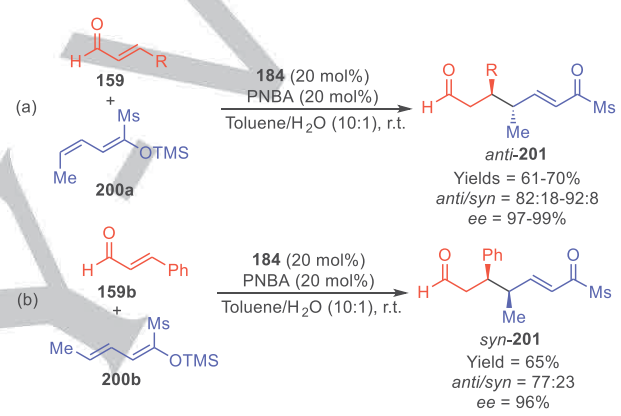
Scheme 71. Synthesis of (-)-aromadendranediol.

In 2012, Schneider reported a new protocol for the synthesis of enantiomerically enriched 1,7-dioxo compounds through a vinylogous Mukaiyama-Michael reaction between acyclic silyl dienol ethers **198** and α,β-unsaturated aldehydes **159** under iminium catalysis.[101] The most suitable catalyst for the reaction proved to be the Jørgensen-Hayashi pyrrolidine **184**. The optimal conditions that led to the γ-1,4 regioisomers **199** in good yields and excellent *ee*s were a combination of a 20 mol% loading of the Jørgensen-Hayashi catalyst and the same amount of PNBA as co-catalyst. The chosen solvent was a mixture of toluene/water (10:1). When the group carried out the reaction between the acyclic silyl dienol ether **198** and cinnamaldehyde under these conditions, they detected a small amount of the undesired α-1,4 regioisomer. By replacing the phenyl group in the nucleophile with a mesityl group, complete regiocontrol was achieved. The scope of the reaction was studied, employing different types of α,β-unsaturated aldehydes, and reaching excellent *ee* values in all cases (Scheme 72).



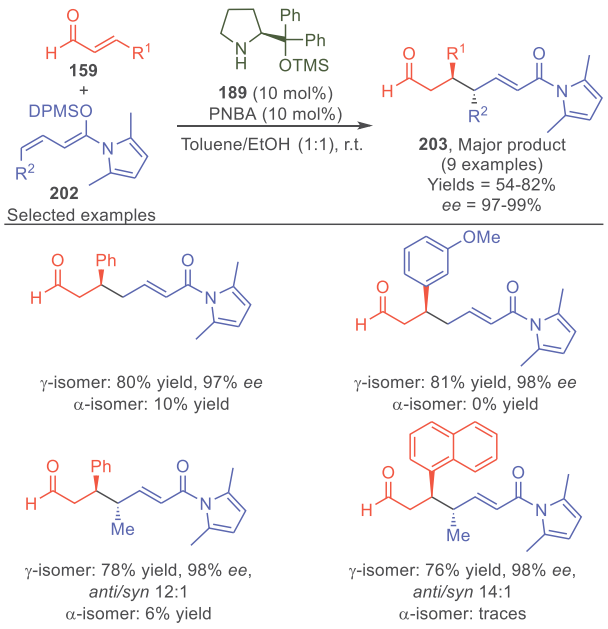
Scheme 72. Synthesis of enantiomerically enriched 1,7-dioxo compounds **204**.

They also wanted to study the effect of the double bond geometry. Accordingly, they synthesized the γ-methyl substituted silyl dienol ethers **200a** and **200b** (*Z* and *E* isomers, respectively) of the nucleophile and tested them in the reaction under the optimal conditions. When the **200a** *Z* isomer was used in the reaction, the *anti*-vinylogous Mukaiyama product *anti*-**201** was formed in 70% yield and 99% *ee*. The diastereoselectivity varies from 82:18 to 92:8 depending on the nature of the aldehyde brought into play, and no traces of the α-1,4 isomer were observed (equation a, Scheme 73). However, when the **200b** *E* isomer was present, the rate of the reaction decreased, obtaining desired products *syn*-**201** with moderate yields and diastereoselectivities (equation b, Scheme 73). Consequently, the relative configuration of the major vinylogous Mukaiyama diastereoisomer is entirely determined by the configuration of the starting silyl dienol ether (*Z* or *E* configuration).



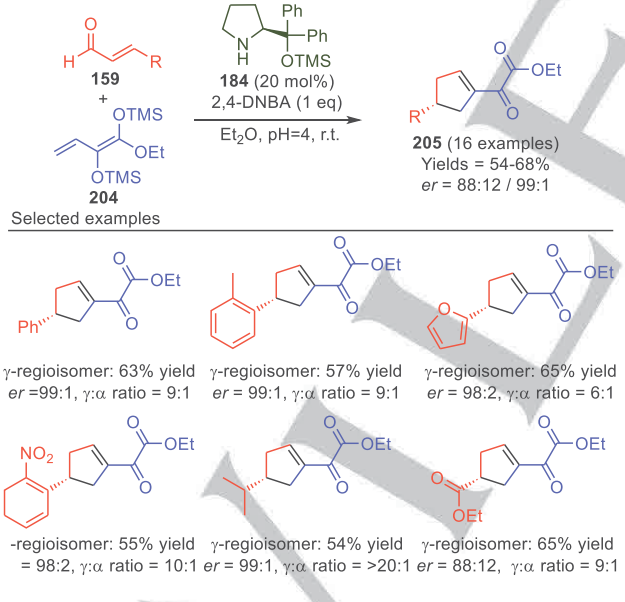
Scheme 73. *Anti*-vinylogous Mukaiyama reaction.

Two years later, Schneider's group published an improved methodology, with a lower catalyst loading and different derivatizations of the final products.[102] In this case, an asymmetric vinylogous Mukaiyama-Michael reaction between the silyl dienol ether *N,O*-acetal **202** and α,β-unsaturated aldehydes **159** under the Jørgensen-Hayashi catalyst **184** was presented, obtaining the desired products with good yields, excellent *ee*s and predominantly γ-regioselectivity. The influence on the regioselectivity inflicted by the steric bulkiness of the silyl group was studied, and the best results were achieved in the presence of the diphenylmethylsilyl (DMPS) dienolate, giving the major product, γ-regioisomer **203**, in 80% yield and 98% *ee*. Regarding the scope of the reaction, the protocol was compatible with a wide range of α,β-unsaturated aldehydes and also with γ-methyl-substituted silyl dienol ethers, generally reaching good yields and excellent *ee*s (Scheme 74).



Scheme 74. Asymmetric vinylogous Mukaiyama-Michael reaction between the silyl dienol ether *N,O*-acetal **202** and α,β-unsaturated aldehydes **159**.

In 2015, Schneider and co-workers reported a new [3+2]-cycloannulation reaction involving the bis-silyl-1,3-dienolate **204** and α,β-unsaturated aldehydes **159** under pyrrolidine catalysis (Scheme 75).[103]

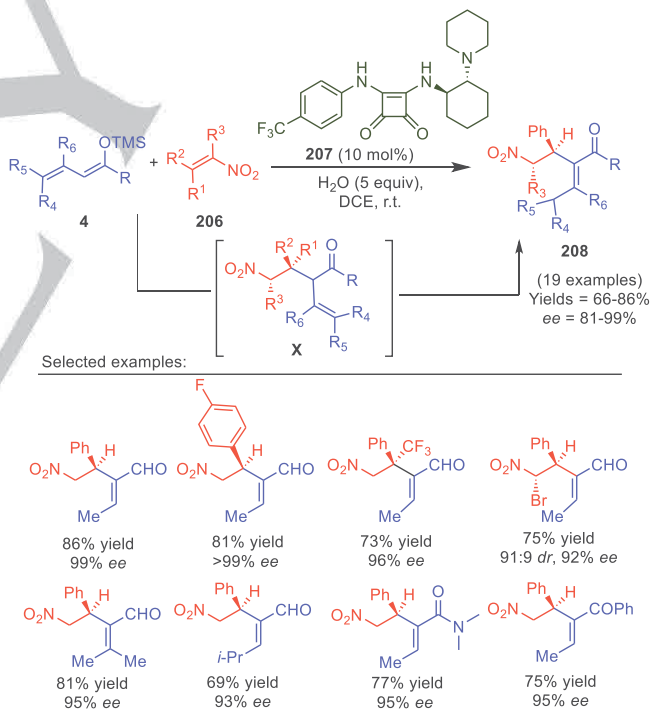


Scheme 75. Cycloannulation reaction involving the bis-silyl-1,3-dienolate **204** with α,β-unsaturated aldehydes **159** under pyrrolidine catalysis.

In this case, 20 mol% of Jørgensen-Hayashi catalyst **184** is required, along with 1 equivalent of 2,4-dinitrobenzoic acid. The reaction led to the desired product (γ-regioisomer **205** coupled with traces of the α-regioselectivity) in good overall yields and excellent enantioselectivities, while tolerating different α,β-unsaturated aldehydes. The cyclopentenyl-α-keto esters could also be derivatized into a wide range of interesting products by simple transformations.

4.2. Bifunctional catalysts

Recently, our group has reported a frustrated vinylogous reaction between silyl dienol ethers **4** and nitroalkenes under bifunctional squaramide catalysis (Scheme 76).[104] The use of this bifunctional catalyst **207** provokes a dramatic change in the regioselectivity, from the 1,5 to the 1,3-functionalization. The 1,3-reactivity is key in the synthesis of synthesis of tri- and tetra-substituted double bonds in Rauhut-Currier-type products **208** via isomerization reaction through intermediate **X**. The scope of the reaction was quite general, allowing the use of different nitroalkenes **206**, and different electron withdrawing groups at the double bond, like ketones, esters and amides, which are difficult to obtain by other methodologies. In this work, the authors showed a mechanistic pathway based on DFT calculations, where the important role played by water is portrayed (the reaction does not proceed without water).



Scheme 76. Synthesis of Rauhut-Currier-type products **208** via frustrated vinylogous type reaction.

4. Conclusions and Outlook

Organocatalysis has been established for over more than a decade in the synthetic field, proving to be a direct and asymmetric course to an extensive array of useful

enantioenriched products. Its quick ascendance as a valid activation pathway for diverse substrates has impacted many areas. As shown across this review, an impressive number of researchers have largely benefitted from this organocatalytic approach to develop asymmetric Mukaiyama reactions. Several activation modes and organocatalytic systems have been applied to activate silylenolate derivatives, including organocatalysts as wide-ranging as phosphoramides, disulfonimides, phosphonates, TADDOLs, imidazolidinones, pyrrolidines, ammonium salts and bifunctional aminocatalysts.

On the other hand, several challenges remain to be addressed in this area. For instance, new silyl-derived reagents should be studied, and will increase the impact of these Mukaiyama-type additions. Therefore, trimethylnitronates and allenoates silyl derivatives remain to be studied in Mukaiyama reactions. Additionally, aliphatic aldehydes have continued to lack reactivity under most of the organocatalytic activations, requiring new approaches for these substrates. On the other hand, for vinylogous Mukaiyama-type additions, the regioselectivity has been an issue, and some vinylogous Mukaiyama-Mannich reactions have displayed moderate enantioselectivity. New organocatalytic systems for vinylogous-type additions would be highly desirable.

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Keywords: Mukaiyama • Vinylogous • Silyl-reagents • Asymmetric • Organocatalysis

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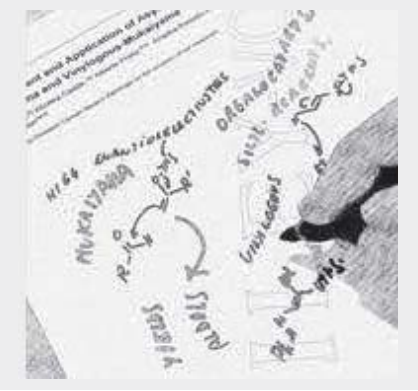
This review highlights the applications of several types of organocatalysts in Mukaiyama-type reactions, while also including the vinylogous Mukaiyama version.



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Development and Application of Asymmetric Organocatalytic Mukaiyama and Vinylogous-Mukaiyama-Type Reactions