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Mukaiyama–Michael reaction: enantioselective strategies and applications in total synthesis

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The Mukaiyama–Michael (M–M) reaction is a powerful approach for carbon–carbon bond formation and can provide access to all-carbon quaternary centers and vicinal stereocenters. The use of chiral catalysts for this transformation has enabled the development of efficient asymmetric methods in which the reaction proceeds with high enantioselectivity in the presence of only a substoichiometric amount of the chiral promoter. Both chiral Lewis acid catalysts and organocatalysts have been employed. These catalytic methods have afforded improvements in reactivity, selectivity, and substrate scope for the M–M reaction and have enabled the synthesis of complex molecular targets including natural products. In this review, enantioselective M–M methods are surveyed along with their applications in the total synthesis of natural products.

1. Introduction

The Mukaiyama–Michael reaction, first reported in 1974 by Mukaiyama,[1] is a useful carbon–carbon bond forming transformation with a variety of applications in organic synthesis. The reaction involves the conjugate addition of a silyl enol ether or silyl ketene acetal to an α,β-unsaturated electrophile, such as an enone, enal, or enoate. Numerous enantioselective variants have been reported, and the development of new asymmetric methods for this transformation continues to be an active area of research.[2–5] The Mukaiyama–Michael reaction provides a powerful strategy for the construction of multiple stereocenters, including all-carbon quaternary centers, in a single step. The synthetic utility of the Mukaiyama–Michael reaction is particularly highlighted by its use in the total synthesis of natural products, where it has featured as a key step in various synthetic campaigns.

Conceptually and historically, the Mukaiyama–Michael reaction[1] follows from the Mukaiyama aldol reaction[6–8] and the Michael reaction (Fig. 1).[9] The Mukaiyama–Michael reaction, like the Mukaiyama aldol, employs a silyl enol ether or silyl ketene acetal as a latent nucleophile. This strategy can provide a stable enolate equivalent with defined stereochemistry. Instead of undergoing 1,2-addition in the Mukaiyama aldol reaction, the enolate equivalent can react *via* Michael addition (1,4-addition)

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Dr Quinlyn Waulters-Kline earned her Doctorate in Organic Chemistry from North Dakota State University in Fargo, North Dakota, in 2023 from Professor Mukund Sibi's group. Her doctoral research focused on the selective synthesis of three contiguous chiral centers using a Mukaiyama–Michael reaction. This work involved the use of various solvents, catalysts, ligands, and auxiliary groups to achieve the selective products. Since completing her PhD, Dr Waulters-Kline has transitioned from academia to pursue a career in the industrial sector.

Dr Gangadurai Chinnakuzhanthai was born in Navappalayam, a hamlet in Tiruvannamalai district, Tamil Nadu, India. He received his B.Sc from University of Madras and M.Sc (Organic Chemistry) from VIT University, Vellore, India. He earned his Ph.D under the supervision of Prof. S. Muthusamy from Bharathidasan University, India. After working as a CSIR-Research associate with Dr D. Srinivasa Reddy at CSIR-National Chemical Laboratory, Pune, India, he transitioned to industry and worked till 2024. Currently, he is working as Post-Doctoral associate with Professor Mukund. P. Sibi at North Dakota State University, USA. His current research focuses on synthesis of monomers for polymer materials from biomass, and enantioselective catalytic reactions.

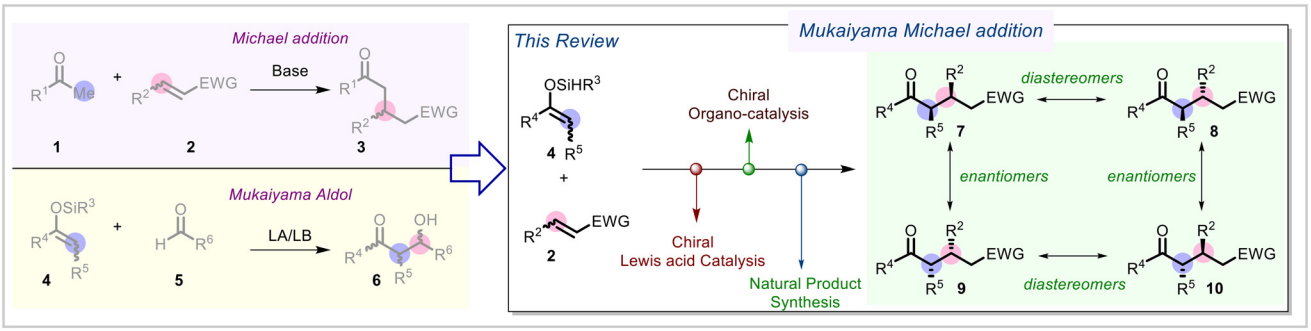
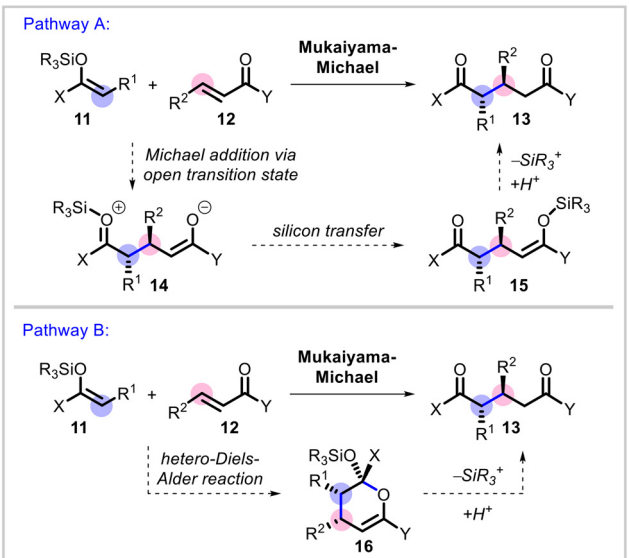


Fig. 1 Evolution of the Mukaiyama–Michael reaction from the Michael and Mukaiyama aldol reactions.

to an unsaturated electrophile, hence the term for this transformation, Mukaiyama–Michael. Relative to the base-mediated Michael reaction, the Mukaiyama–Michael reaction is a complementary approach offering mild reaction conditions and avoiding side reactions that may occur in the presence of base.[1]

The Mukaiyama–Michael reaction may proceed through either of two general mechanisms. In one possible mechanism (Scheme 1, pathway A), carbon–carbon bond formation occurs *via* 1,4-addition of the nucleophile to the unsaturated electrophile through an open (extended) transition state.[10] In the other possible mechanism (Scheme 1, pathway B), a [4 + 2] cycloaddition between the reactants (a hetero-Diels–Alder reaction) results in a cyclic adduct **16**, which can subsequently break down into the same product obtained in the other mechanism (Michael addition *via* an open transition state).[11] In literature reports, the responsible mechanism has often not been conclusively identified.[12–15] In a few cases, some mechanistic evidence is available.[11,16–20] For example, in the Cu(II)-catalyzed Mukaiyama–Michael addition of a pyrrole enolsilane to a crotyloxazolidinone, experimental results (including the isolation of a cyclic adduct as a minor product) were consistent with a mechanism involving a hetero-Diels–Alder reaction.[11] On the other hand, an uncatalyzed Mukaiyama–Michael addition of a silyl enol ether to a cyclic α-alkylidene β-oxo imide appeared not to involve a hetero-Diels–Alder mecha-



Scheme 1 Possible mechanistic pathways in the Mukaiyama–Michael reaction.

Dr Sagar Sudam Thorat was born in 1992 in Chinchani (Ambak), Maharashtra, India. He earned his post-graduate degree in Organic Chemistry from the School of Chemistry at PAH Solapur University in 2014. In 2021, he successfully defended his PhD thesis at the CSIR-National Chemical Laboratory in Pune, India, under the mentorship of Dr Ravindar Kontham. Following this, he served as a postdoctoral research associate in Prof. Mukund Sibi's research group at North Dakota State University in Fargo. His scientific interests encompass the total synthesis of biologically active natural products, transition metal salt-catalyzed domino reactions, and the synthesis of biobased monomers for polymer chemistry applications. He is currently a Senior Research Investigator at Syngene International Ltd in Bangalore, India.

Dr Anna C. Renner is originally from Fargo, North Dakota, and obtained her B.S. degree in chemistry from North Dakota State University. For her graduate studies, she worked in the research group of Professor Andrew Myers at Harvard University, where she synthesized structurally modified tetracyclines with anticancer activity. After earning her Ph.D. from Harvard, Anna joined the group of Professor Mukund Sibi at North Dakota State University as a postdoctoral researcher. Her current research in the Sibi group focuses on the development of enantioselective catalytic reactions and the synthesis of biobased monomers for applications in polymer science.

nism, as indicated by ^{1}H and ^{13}C NMR studies in which no cyclic adduct was detected.[16]

Mukaiyama originally employed a stoichiometric amount of titanium tetrachloride to promote addition of trimethylsilyl enol ethers to ketones or aldehydes.[1] In later research, the transformation was performed catalytically, without the need for a stoichiometric promoter. Further advances included the use of chiral catalysts to achieve enantioselectivity. Chiral Lewis acid catalysis was pioneered by researchers including Evans, who notably developed enantioselective Mukaiyama–Michael reactions catalyzed by copper(II)–bisoxazoline complexes.[11,18,21,22] The use of chiral organocatalysts in the Mukaiyama–Michael reaction was another significant development. Organocatalyzed enantioselective Mukaiyama–Michael reactions were first developed by MacMillan with the use of an imidazolidinone-based organocatalyst.[23] Over the five decades since the Mukaiyama–Michael reaction was introduced, many other researchers have developed enantioselective catalytic methods that have expanded the scope and versatility of the transformation.

Enantioselective methods for the Mukaiyama–Michael reaction typically involve activation of the electrophile with a chiral catalyst, generally either a Lewis acid or an organocatalyst. In many cases, these catalysts operate with low turnover numbers and are employed at fairly high catalyst loadings, such as 5–30 mol%. In general, chiral Lewis acid catalysts have been used with substrates capable of bidentate coordination, and the Lewis acids employed have been predominantly metals in the 2+ and 3+ oxidation states. In contrast, organocatalysts have often been used with aldehyde and ketone substrates that would not be capable of bidentate coordination to a Lewis acid but instead can be activated through interactions with an organocatalyst (such as iminium ion formation).[24] Apart from these general trends, enantioselective Mukaiyama–Michael methods also encompass other strategies that involve activation of the nucleophile instead of the electrophile, the use of lower catalyst loadings (<5 mol%), or alternative catalyst/substrate combinations.

The vinylogous Mukaiyama–Michael reaction[4,23–26] is closely related to the simple Mukaiyama–Michael reaction as well as the vinylogous Mukaiyama aldol[24,26–29] and vinylogous Mukaiyama–Mannich reactions.[24,26,30] In the vinylogous Mukaiyama–Michael reaction, a silyl dienol ether serves as the nucleophile. Due to the presence of two nucleophilic sites (α and γ) in this reaction component, the vinylogous Mukaiyama–Michael reaction presents the potential to yield multiple regioisomeric products and thus entails a higher level of complexity. Nevertheless, enantioselective methods for the vinylogous Mukaiyama–Michael reaction have been developed.

Over the past decade, a few reviews on asymmetric Mukaiyama–Michael reactions have been published. In 2018, Frías *et al*. reviewed organocatalyzed, asymmetric Mukaiyama–Michael and vinylogous Mukaiyama–Michael reactions.[24] Organocatalyzed, asymmetric vinylogous Mukaiyama–Michael reactions were also reviewed in 2017 by Yin and Jiang[31] and in 2021 by Hoppmann and García Mancheño.[26] These articles were limited to reactions promoted by organocatalysts and did not include those catalyzed by metal complexes.

In our review, we comprehensively cover enantioselective methods for Mukaiyama–Michael and vinylogous Mukaiyama–Michael reactions, encompassing not only organocatalytic methods but also those involving other catalyst types. Our discussion of various methods is organized according to the types of catalysts employed, broadly divided between chiral Lewis acids (comprising metal- and metalloid-based catalysts) and organocatalysts. We summarize enantioselective catalytic methods (excluding examples that are diastereoselective but not enantioselective) and highlight their applications in total synthesis. Throughout the review, we present the scope, synthetic utility, and limitations of enantioselective Mukaiyama–Michael methodology in a manner that emphasizes general trends in catalyst structures and mechanisms. In this way, we aim to provide a clear, accessible, and comprehensive review for researchers working toward new applications or methods for the Mukaiyama–Michael reaction.

2. Enantioselective Mukaiyama–Michael reaction using chiral Lewis acids: metal and metalloid-based catalysts

A variety of enantioselective methods for the Mukaiyama–Michael reaction have been developed using Lewis acid catalysis to activate the electrophile and control the stereochemical outcome of the reaction. This has typically involved the use of a chiral ligand together with a Lewis-acidic metal ion. Another strategy involves silylium Lewis acid catalysis using a chiral imidophosphorimidate counterion to achieve enantioselectivity. In this section of the review, we summarize different methods and organize our discussion according to the type of Lewis acid employed: complexes of Cu^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, and Fe^{2+} (sections 2.1–2.5); other Lewis acid–chiral ligand complexes based on B, Al, Sc, Fe, La, Ce, Eu, or Ti (section 2.6); chiral-at-metal rhodium complexes (section 2.7);

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and chiral imidophosphorimidates for catalysis with silicon as the Lewis acid (section 2.8).

In Lewis acid catalyzed Mukaiyama–Michael reactions, the α,β-unsaturated substrates employed as electrophiles often have structural features that allow for bidentate coordination to a metal ion, ensuring effective activation of the substrate and aiding stereocontrol *via* the chiral catalyst. Substrate structures commonly consist of an enoyl group appended to an achiral template containing a Lewis-basic heteroatom, such as an oxazolidinone, imidazole, or pyrazole template.

Ligand structure is also a noteworthy consideration in most Lewis acid catalyzed Mukaiyama–Michael (M–M) reactions. Ligands discussed in this review are shown in Fig. 2. The structure of a ligand should generally match the size and possible coordination geometry of a given metal ion. For example, bidentate bisoxazoline ligands are suitable for ions such as Cu^{2+} and Zn^{2+} and have been employed in numerous Mukaiyama–Michael methods using Cu^{2+} or Zn^{2+} as a Lewis acid. On the other hand, tridentate PyBOX-type ligands have been used in methods involving catalysis with Sc^{3+}, In^{3+}, La^{3+}, or Eu^{3+} since they can better chelate these metal ions.

Additional reaction components such as solvent and additives, such as hexafluoroisopropanol (HFIP), can also play important roles in these asymmetric transformations. Throughout our discussions of individual methods, we highlight these and other important factors contributing to the achievement of high yields and enantioselectivities in Mukaiyama–Michael reactions.

2.1. Copper catalyzed enantioselective Mukaiyama–Michael reaction

In one of the earliest reports on enantioselective M–M additions, Bernardi and co-workers demonstrated the use of a chiral Cu(II) complex mediated reaction between silylketene acetal **42** and 2-carbomethoxy cyclopentenone **43** (Scheme 2).[32] Reactions in dichloromethane using copper(II) triflate and ligand **18** in stoichiometric amount gave products **44** and **46** with good diastereoselectivity and modest ee. In contrast, reactions with catalytic amounts of the chiral Lewis acid gave the products in low yield and similar ee. A large amount of a racemic product arising from activation of the substrate by TBDMSOTf was observed. Changing the solvent to toluene gave lesser amounts of the racemic product. One of the highlights of this work was that the absolute configuration of the product could be controlled by varying the copper counterion. Reactions with $Cu(SbF_6)_2$/**18** gave the enantiomer **46** in good ee. The hydrolysis of **44** and **46** under acidic conditions yielded ketoacids **45** and **47**.

In 1999, Evans and co-workers reported the use of Cu(II) bisoxazoline (box) catalyst **17** as a chiral Lewis acid, and examined the asymmetric variants of Mukaiyama–Michael reactions between silyl thioketene acetal **48** with alkylidene malonates **49** accessing differentiated glutarate esters **51** (Scheme 3a).[21] Similar to observations described above, the use of catalytic amounts of the chiral Lewis acid led to inefficient reactions.

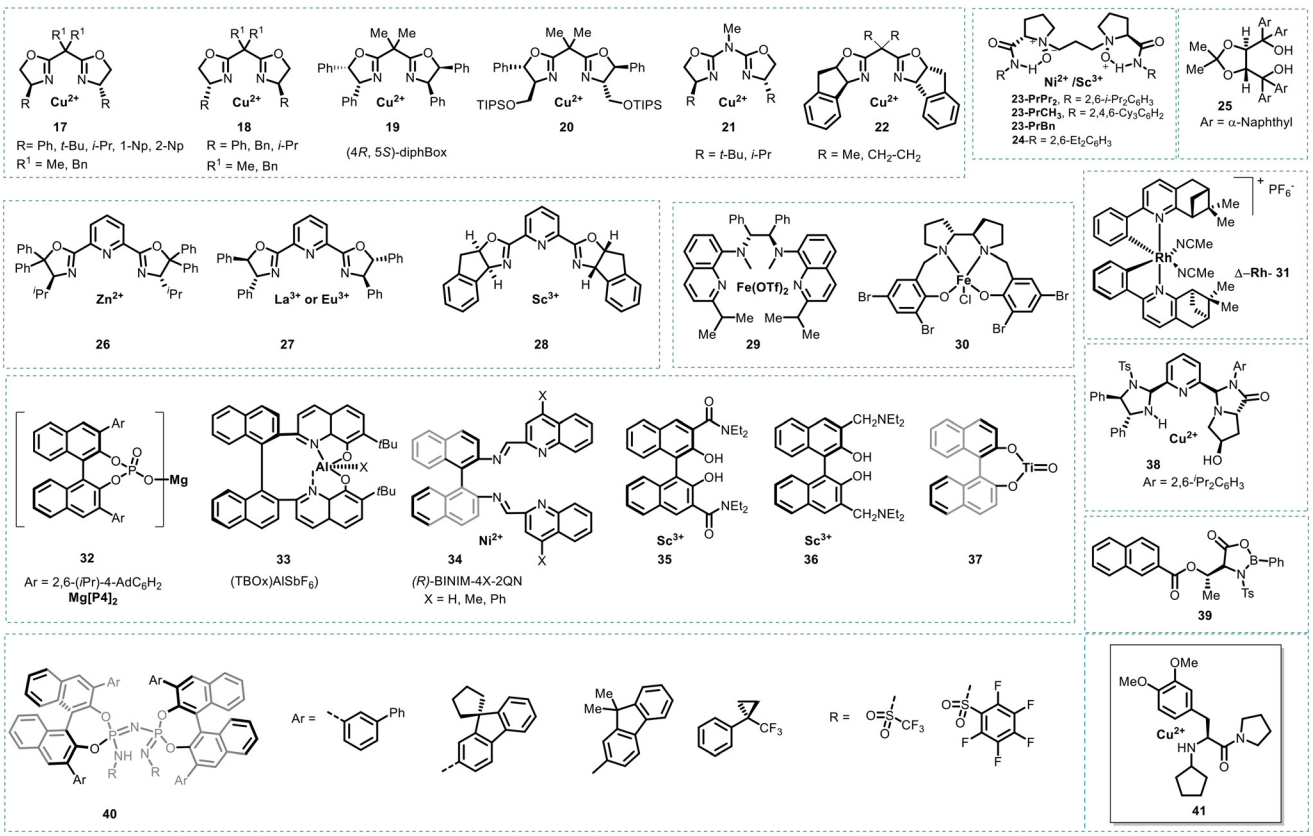
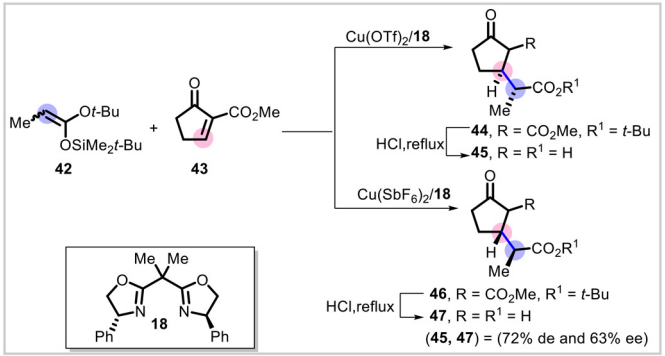
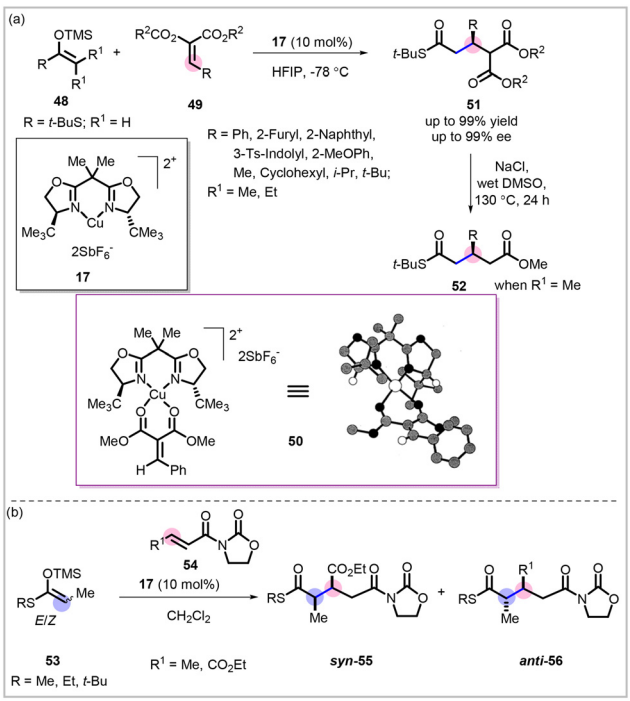


Fig. 2 Chiral ligands for Mukaiyama–Michael reactions.



Scheme 2 Cu(II)-Catalyzed formation of products with vicinal stereocenters.

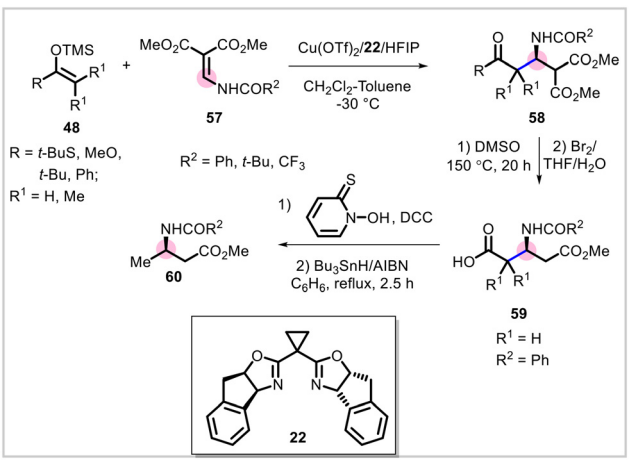


Scheme 3 Synthesis of an enantioenriched 1,5-dicarbonyl compound from an alkylidene malonate.

However, addition of hexafluoroisopropanol (HFIP) and use of a low dielectric constant solvent mixture (DCM and toluene) gave excellent conversion using catalytic amounts of the chiral Lewis acid. Mechanistic investigations[22] showed that HFIP acts as a proton source and also as a silicon acceptor. A variety of β-substituted alkylidene malonates were utilized as electrophiles in reactions with ketone derived enolsilane **48**. High selectivities were achieved with aromatic and heterocyclic β-substituents. The authors found that *ortho* subtitution on the aromatic ring was well-tolerated and afforded the addition products with the highest selectivity (99% ee). Similarly, reactions with cyclohexyl, isopropyl, and *tert*-butyl alkylidene malonates provided the addition products in enantioselectivities of 95, 93, and 90% respectively, while the corresponding methyl-substituted substrate yielded the product in only 43% ee with opposite facial selectivity. The authors were able to obtain a crystal structure of the substrate-Lewis acid complex **50** which showed that the substrate binds to copper in a distorted square planar geometry. Addition to the less hindered face of the complex is consistent with the observed absolute stereochemistry. The decarboxylation of glutarate esters **51** under Krapcho conditions provided enantioenriched 1,5-dicarbonyl compounds **52**, which are useful chiral synthons for many organic transformations. The Evans group carried out a detailed study on the scope of this reaction, which demonstrated that yields (>90%) and high ees (90–99%) can be obtained for a variety of substrates.

The use of oxazolidine-based fumarates (acrylimides) **54** as acceptors in the M–M reaction was also investigated by Evans and co-workers using Cu(II)–bisoxazoline complex **17** (Scheme 3b).[11,18,33] Once again, the use of hexafluoroisopropanol (HFIP) was essential for a successful outcome. Several interesting results emerged from these studies. This reaction revealed that the enantioselection was stereoregular while the diastereoselection is directly related to geometry of the thioester enolsilanes **53**: (*E*) enolsilanes delivered *anti* adducts *anti*-**56** and (*Z*) enolsilanes gave *syn* adducts *syn*-**55**. The authors suggest that HFIP aids in catalyst turnover but is not involved in the stereochemical outcome of the reaction.

In 2002, Sibi and co-workers reported the $Cu(OTf)_2$ and bisoxazoline (box) catalyzed enantioselective conjugate addition of silyl ketene thioacetals **48** to enamidomalonates **57** with excellent chemical efficiency and good selectivity (Scheme 4).[34] They also examined the effect of nucleophiles, *N*-acyl group, and ligands on selectivity. Both benzoyl and pivaloyl groups were equally effective with respect to yield and selectivity. Of the different ligands investigated, ligand **22** provided excellent chemical yield and high selectivity in the addition of neutral nucleophiles to enamidomalonates. Decarboxylation of **58** furnished useful β-amino acid deriva-

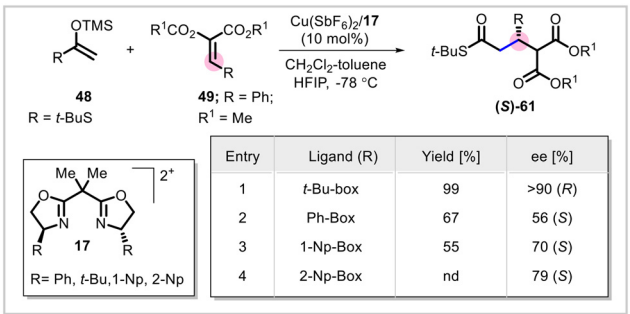


Scheme 4 Synthesis of chiral β-amino acid precursors.

tives **59**. The absolute stereochemistry was established on decarboxylated desymmetrized glutarate **60**.

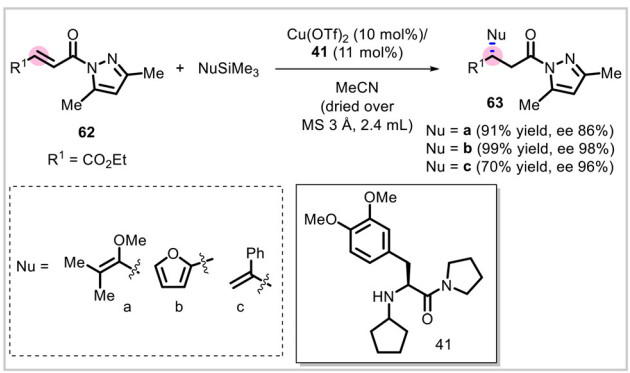
In 2005, Rutjes and co-workers reported asymmetric catalytic M–M reactions using a combination of copper salt and bulky aryl-substituted box ligands.[35] Addition of silyl ketene acetal **48** to arylidene malonate **49** in the presence of HFIP led to good yields of the M–M product **61**. Both 1-Np and 2-Np-box ligands delivered the addition product with similar selectivities of 70% and 79% *ee*, respectively, whereas the Ph-box ligand gave lower selectivity of 56% *ee* (Scheme 5). It is interesting to note that aryl-substituted box ligands and the *t*-Bu-box ligand gave opposite enantiomers of the product. The highest enantioselectivity (90% *ee*) was obtained using ligand **17** (R = *t*-Bu-box).

In 2006, Ishihara and co-workers reported the first example of Mukaiyama–Michael reaction using enoates with a 3,5-dimethylpyrazole template **62** and different silyl enol ethers (Scheme 6).[36] A new type of artificial metalloenzyme catalyst prepared from a L-DOPA-derived monopeptide ligand (*S*)-**41** and $Cu(OTf)_2$ was used in the conjugate addition. The reactions proceeded efficiently and gave the addition products **63a–c** in high yields and high enantioselectivities. Low catalyst loadings (2–10 mol%) were highly effective for the enantioselective M–M reactions of α–β-unsaturated acyl-3,5-dimethylpyrazoles. The authors postulated that a cation–π interaction



Entry	Ligand (R)	Yield [%]	ee [%]
1	*t*-Bu-box	99	>90 (*R*)
2	Ph-Box	67	56 (*S*)
3	1-Np-Box	55	70 (*S*)
4	2-Np-Box	nd	79 (*S*)

Scheme 5 Enantioselective Mukaiyama–Michael reaction of a Knoevenagel adduct.

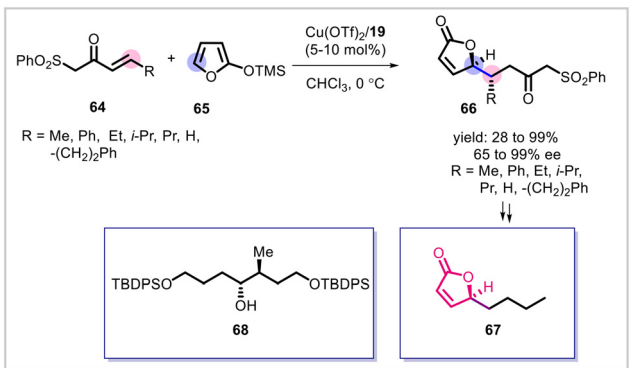


Scheme 6 M–M reaction of α,β-unsaturated 1-acylpyrazoles catalyzed by an artificial metalloenzyme catalyst.

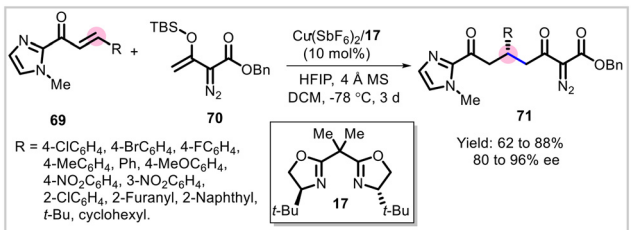
may be responsible for controlling the conformation of the chiral ligand.

Kim and co-workers carried out M–M reactions for synthesizing γ-butenolides **67** from readily available and cost effective 2-(trimethylsilyloxy)furan **65** and α′-phosphoric enones **64** as Michael acceptors (Scheme 7).[37] These reactions proved difficult to optimize. In contrast, reactions with α′-phenylsulfonyl enones **64** as the acceptor were efficient using densely substituted bis(oxazoline)–copper(II) complex **19** as the chiral catalyst (5–10 mol%). The butenolides were produced in high enantio- and diastereoselectivity. When the β-substituent on the enone was a bulky isopropyl group, reactions were less efficient and higher catalyst loading (20 mol%) was needed. The authors converted the γ-butenolide **66** (R = Me) to natural product **67** and **68** (an enantiomer of a previous known product[38] based on its optical rotation) by known protocols.

Doyle and co-workers reported the synthesis of a broad class of chiral multifunctional diazoacetoacetates through the catalytic, highly enantioselective M–M addition of 3-(trialkylsilanoxy)-2-diazo-3-butenoate **70** to unsaturated acceptors (Scheme 8).[39] Interestingly, the M–M reaction with an α,β-unsaturated oxazolidinone as the acceptor did not provide any product. Reactions with α,β-unsaturated 2-acylimidazoles **69** and diazoester **70** in the presence of a catalytic amount of chiral copper Lewis acid **17** gave the addition product in good yields and selectivity. The authors varied the ester substituent of the nucleophile (Me, *t*-Bu, and Bn) and the benzyl ester was optimal for both yield and selectivity of **71**. This method



Scheme 7 Synthesis of a γ-butenolide natural product.

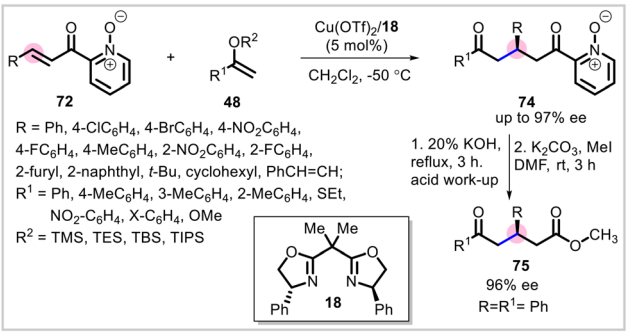


Scheme 8 Synthesis of chiral diazoesters.

offered convenient and easy access to chiral 1,5-diesters. The product chiral diazoacetoacetates are useful synthetic building blocks.

In 2012, Faita *et al*. reported the use of 2-acylpyridine *N*-oxide **72** as an acceptor in asymmetric M–M reactions (Scheme 9).[40] The oxygens of the *N*-oxide and the 2-acyl group coordinate a chiral Lewis acid in a bidentate fashion and provide the necessary activation for conjugate addition. Reactions with **72** and 2-trimethylsilyloxyfuran **65** proceeded effectively using a chiral Lewis acid formed by the combination of copper triflate and a bisoxazoline. Addition of **65** to **72** using 10 mol% of $Cu(OTf)_2$/**18** complex (HFIP, CH_2Cl_2) at −20 °C gave the product butenolide as a single diastereomer in good yield and high enantioselectivity. Interestingly, $Cu(OTf)_2$/**20** complex gave the same enantiomer of the product. The authors report a rare example of a crystal structure of a ternary complex between the chiral Lewis acid and the substrate, and the absolute stereochemistry of **73** is consistent with this structure. The authors also investigated reactions with cyclic enol ethers derived from cyclohexanone and tetralone. These reactions gave products in modest yield as a mixture of diastereomers. A product arising from a hetero-Diels–Alder reaction between **72** and the enol silyl ether of tetralone was also observed.

In the following year, Subba Reddy and co-workers reported the enantioselective M–M reaction of 2-enoylpyridine *N*-oxides **72** with acyclic silyl enol ethers **48** using a simple bis(oxazoline)-copper complex (Scheme 10).[41] A variety of bisoxazolines ranging from simple ones to more complex, sugar-based ligands were evaluated. Of these, the bisoxazoline **18**, derived from phenylglycinol, gave the best results. A variety of silyl enol ethers were evaluated in the reaction and delivered the corresponding Michael adducts **74** in high yields with high enantioselectivities. Higher enantioselectivity for product **74** (80%–96%) was observed when reactions were carried out at −50 °C rather than at room temperature. The acylpyridine fragment in compound **74** could be easily converted to an ester **75** in two simple steps.

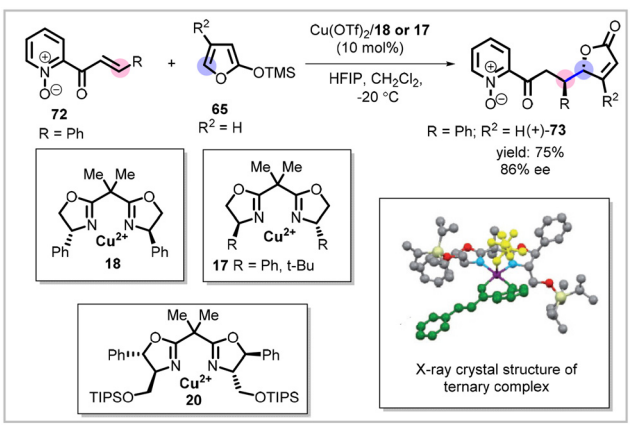


Scheme 10 Enantioselective Mukaiyama–Michael reaction of 2-enoylpyridine *N*-oxides.

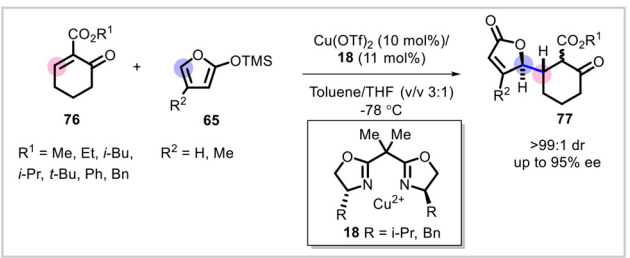
Guillou and co-workers reported the enantioselective vinylogous M–M reactions of 2-silyloxyfurans **65** and cyclic unsaturated oxo esters **76** (Scheme 11).[42] The C_2-symmetric box **18** copper(II) complex was optimal for this transformation and gave the product γ-butenolide **77** and its derivatives with high diastereoselectivity and good enantioselectivities. The authors also investigated the role of the ester group on the acceptor. Results from these studies revealed the significant role of the size of the ester group on enantioselectivity and reactivity. Reaction with the methyl ester of **76** gave good selectivity with ligand **18** (R = Bn), but ligand **18** (R = i-Pr) was optimal with other oxo esters. Reactions with cyclopentenone- and cycloheptenone-based substrates were also successful. The stereoselectivities with these two substrates were lower than with cyclohexenones.

In 2013, Fraile and co-workers reported vinylogous M–M reactions between 2-(trimethylsilyloxy)furan **65** and three different electron-deficient acceptors: alkylidene malonates **49**, enoyl oxazolidinones **54** and unsaturated ketones **78** (Scheme 12).[15] The goal of this study was to compare box ligands with azabox ligands in combination with a copper catalyst under homogeneous conditions. Additionally, the chiral Lewis acid catalysts were immobilized on LAPONITE® to provide a heterogeneous catalyst for evaluation and comparison of M–M reaction in two different phases.

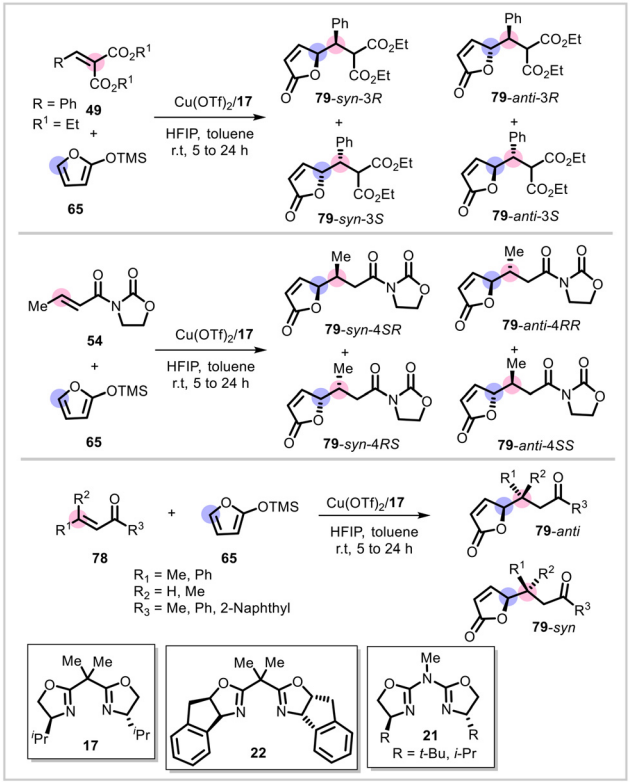
The authors studied the $Cu(OTf)_2$ catalyzed M–M reactions in both homogeneous and heterogeneous phases extensively. Under homogeneous conditions, *syn* isomers were obtained as



Scheme 9 A Cu-Catalyzed M–M reaction of a pyridine *N*-oxide and the X-ray crystal structure of a ternary Cu(II)/ligand/substrate complex.



Scheme 11 Synthesis of γ-butenolide-based products with vicinal stereocenters.



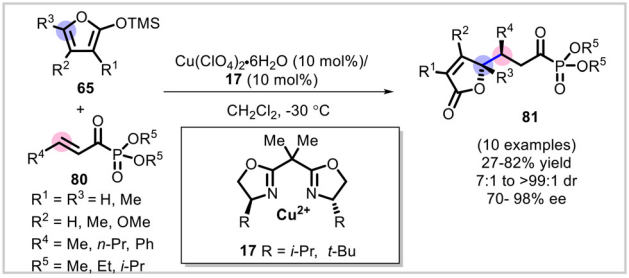
Scheme 12 Vinylogous M–M reactions catalyzed by homogeneous and immobilized Cu complexes.

major products with arylidene malonates in good enantioselectivity when ligand **22** was used. In general, box ligands gave higher selectivity than analogous azabox ones. In contrast, reactions with immobilized catalyst gave *syn* product as the major isomer in high yields but with no enantioselectivity.

Reactions with enoyl oxazolidinones under homogeneous catalysis gave the *anti* diastereomer as the major product while the *syn* diastereomer was the major product using immobilized catalyst. Interestingly, homogeneous reactions with azabox ligands **21** gave higher enantioselectivity than those with box ligands. Thus the ligand and nature of the acceptor are both important for realizing optimal outcomes.

Reactions with α,β-unsaturated enones were also examined under both homogeneous conditions and using an immobilized catalyst. M–M reactions proceeded in near quantitative yields under homogeneous conditions but with very minimal enantioselectivity. Interestingly, an immobilized chiral Lewis acid prepared from **17** gave 64% ee for the minor *syn* isomer. A similar outcome was also seen with an azabox ligand **21** (71% ee). The chemical yields of the products using immobilized catalysts were also very high.

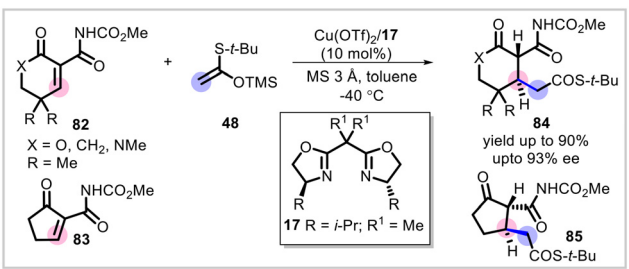
The Bolm group, in 2015, investigated the addition of a variety of trimethylsilyloxy furans **65** to α-keto phosphonates **80** using a complex derived from copper salts and bisoxazoline ligands (Scheme 13).[43] Of the different chiral Lewis acids investigated, copper triflate, copper hexafluoroantimonate,



Scheme 13 Conversion of α-keto phosphonates to γ-butenolide derivatives featuring vicinal stereocenters.

and copper perchlorate all gave products with high efficiency and enantioselectivity. The best results were obtained using 10 mol% copper perchlorate and **17** (R = *t*-Bu). Interestingly, the user-friendly copper perchlorate hexahydrate was better than the anhydrous salt. The *anti* diastereomers of the products, α-keto phosphonate containing γ-butenolides **81**, were formed with high selectivity. A variety of nucleophiles and electrophiles were well tolerated and gave the products with good stereoselectivities. Reaction with nucleophile **65** with $R^1 = R^2 =$ H and R^3 = Me gave a product with a hindered chiral center. The reaction efficiency was low but the ee for the product was high.

An enantioselective M–M reaction of cyclic α-alkylidene β-oxo imides **82**, **83** has been successfully carried out by Nakada and co-workers using a Box-Cu(OTf)$_2$ catalytic system, leading to the corresponding Michael adducts (Scheme 14).[16] Extensive optimization of the experimental conditions, especially concerning the choice of additive and solvent, finally yielded the desired product **84**, **85** in high yield and ee (yield up to 90%, up to 93% ee). Toluene was identified as the optimal solvent and reaction with 3 Å MS at −40 °C gave the M–M adducts with increased ee by retarding the background reaction. The scope of the reaction was quite good, and the M–M products were generally obtained with good enantioselectivity. Reactions with sterically hindered cyclic imides (X = CH_2 and R = CH_3) proceeded slowly and required higher catalyst loading (50 mol%) and a higher reaction temperature. The authors noticed lower enantioselectivity with cyclopentenone **83** compared to six-membered analog (X = CH_2 and R = H) due



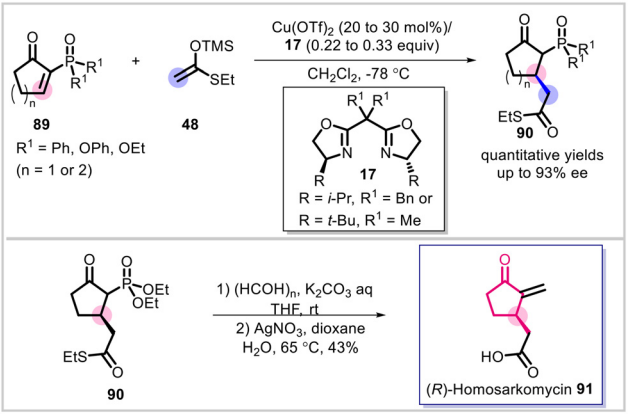
Scheme 14 Catalytic asymmetric Mukaiyama–Michael reactions of cyclic α-alkylidene β-oxo imides with a silyl ketene thioacetal.

to the weak intramolecular hydrogen bond and smaller ring size. The use of bulky ligands **17** (R = *t*-Bu, R^1 = Me; R = i-Pr; R^1 = Bn) decreased the yield and ee. The use of hexafluoroisopropanol (HFIP) as an additive delivered poor results. This is because the weakly acidic and protic HFIP impacts the intramolecular hydrogen bonding of imide **83**, resulting in low enantioselectivity.

In 2015, Wang and co-workers devised a novel cascade vinylogous M–M annulation reaction of 2-silyloxyfurans **86** as nucleophiles and azoalkenes **87** as electrophiles using a Cu(II)/*t*-Bu-Box complex (Scheme 15).[44] This approach provides access to a variety of biologically important and structurally complex fused butyrolactones **88** in high yield (up to 90% yield) and excellent diastereoselectivity (>20 : 1 dr) and excellent enantioselectivity (up to 99% ee). The authors proposed a stepwise mechanism based on ^{13}C NMR studies.

The substrate scope of the reaction was examined with α-chloro- or α-bromo-*N*-benzoyl hydrazones as the azoalkene precursors. Both electron rich and electron poor substituents on the phenyl ring of hydrazones gave the fused butyrolactones (78–88% yield) in excellent stereoselectivities (>20 : 1 dr, 91–97% ee).

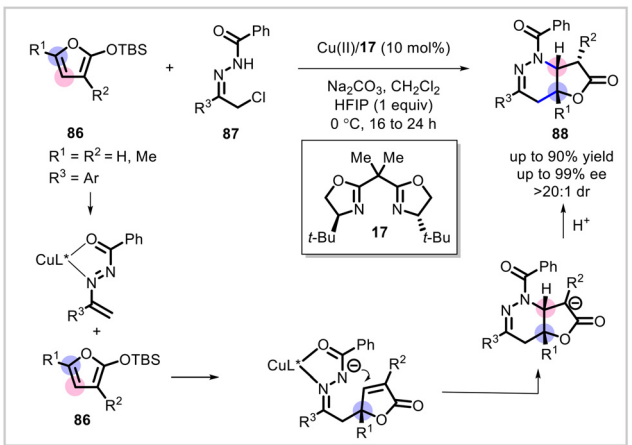
Nakada's group in 2017 reported the asymmetric M–M reaction of cyclic α-alkylidene β-oxo phosphates and phosphine oxides **89**, a new class of acceptors (Scheme 16).[45] A variety of ligands and copper salts were explored for the addition of a simple silyl enol ether. The substituent on the phosphorus impacted reactivity as well as selectivity, and a smaller ethoxy group proved optimal. Copper triflate (30 mol%) in combination with **17** (either R = i-Pr, R^1 = Bn or R = *t*-Bu, R^1 = Me) gave good chemical efficiency and high enantioselectivity. The sense of stereoinduction depended on the ligand structure: **17** with R = i-Pr and R^1 = Bn gave the opposite enantiomer relative to that obtained using **17** with R = *t*-Bu and R^1 = Me. The authors applied their methodology to the synthesis of (*R*)-homosarkomycin **91** from one of the products **90**.



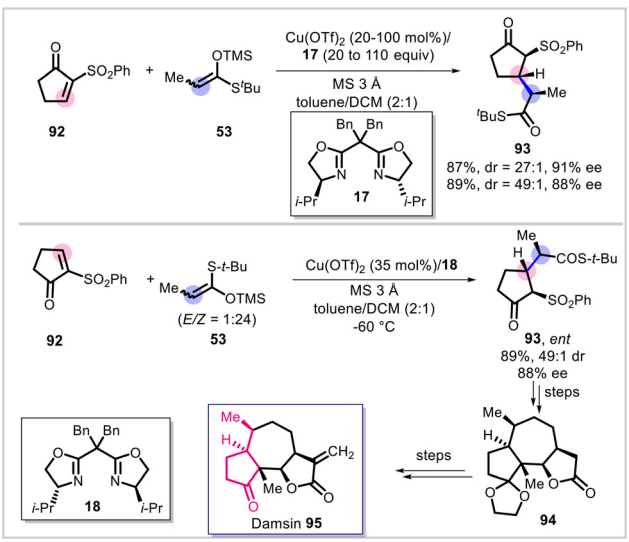
Scheme 16 M–M reactions of cyclic α-alkylidene β-oxo phosphonates and phosphine oxides and an application in the synthesis of (*R*)-homosarkomycin.

The above conjugate addition was extended to include a more complex nucleophile: the enol silyl ether of *tert*-butyl thiopropionate **53**. Addition of **53** to 2-(phenylsulfonyl)cyclopent-2-en-1-one **92** establishes three contiguous chiral centers of the products **93** (Scheme 17).[46] The sizes of the enol silyl ether substituent (TMS *vs.* TBS) and of the sulfur substituent (Et *vs.* *t*-Bu) impacted reaction outcome. A smaller silicon substituent (TMS) and a bigger substituent on sulfur (*t*-Bu) were optimal. A variety of reaction conditions were also evaluated for optimization: solvent, catalyst loading, temperature, and ligand. The best outcome was obtained using $Cu(OTf)_2$/**17** (25 mol%) as the catalyst in a toluene/DCM mixture at −60 °C (89% yield, 49 : 1 dr, and 88% ee).

Using the intermediate formed in this reaction, Nakada and Sugiyama reported the total synthesis of damsin.[47] Epimerization of compound **93** under basic conditions was



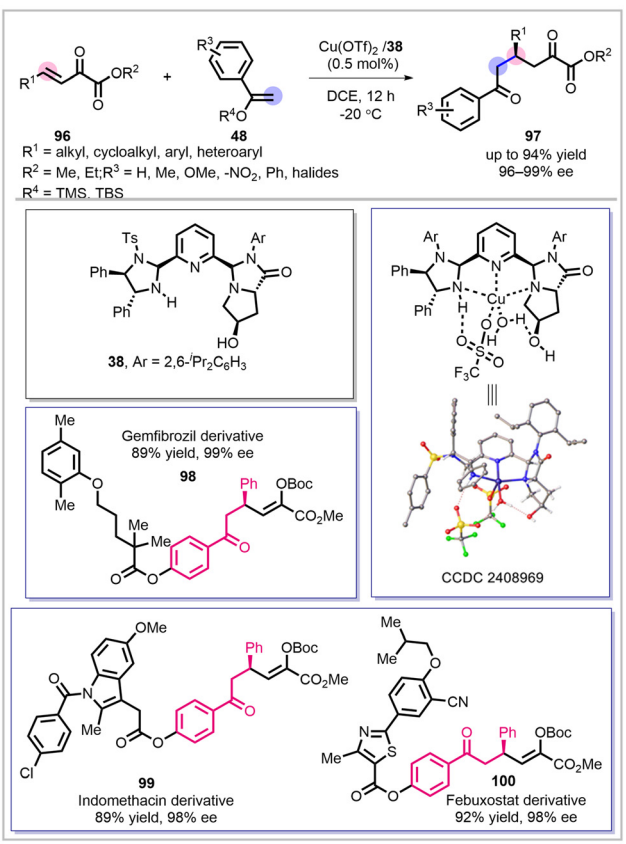
Scheme 15 Cu(II)-Catalyzed cascade reaction of silyloxydienes with hydrazones.



Scheme 17 Total synthesis of damsin *via* an asymmetric catalytic M–M reaction.

followed by a sequence of reactions that furnished intermediate **94**, which was then utilized for the synthesis of damsin **95**. This total synthesis was achieved in 21 steps *via* the catalytic M–M approach as a key step in contrast to a previously reported synthesis in 36 steps.

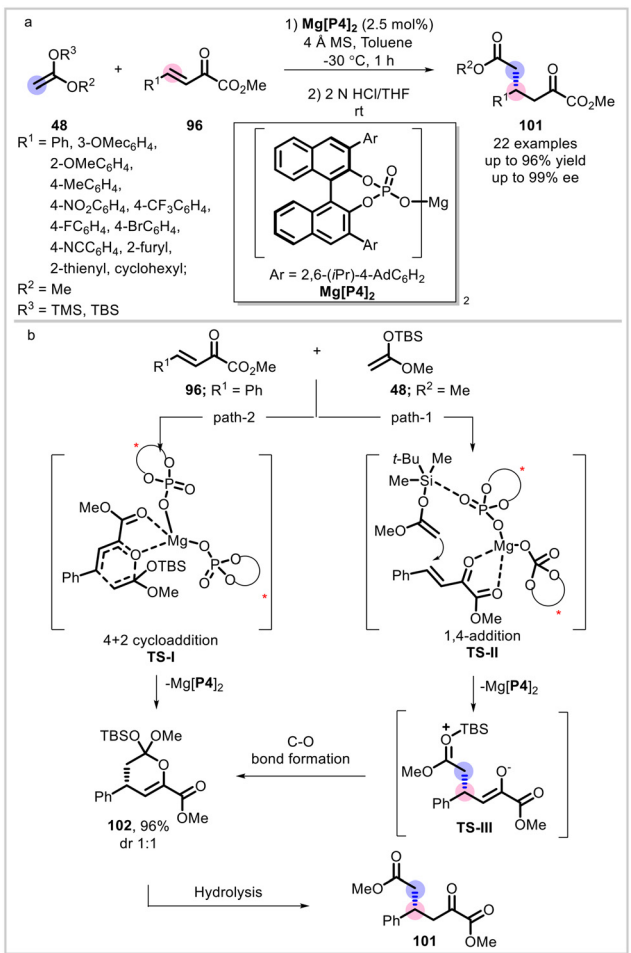
Xie, Guo and their co-workers reported a new class of chiral ligands, imidazolidine–pyrroloimidazolone pyridine (PyIPI), for M–M reactions using copper Lewis acids.[2] Conjugate additions of enol silyl ethers to β,γ-unsaturated α-keto esters **96**, keto amides and phenylvinylsilanes **48** were investigated (Scheme 18). The authors evaluated several different Lewis acids and copper(II) triflate proved to be optimal. One of the highlights of this work is the low catalyst loading. Reactions of ketoesters were efficient with 0.5 mol% of the catalyst at −20 °C. The reaction delivered 1,5-dicarbonyl compounds **97** in good yields (up to 94%) and high enantioselectivities (96–99% ee). Reactions with the less reactive ketoamides at 0 °C required 10 mol% of the catalyst. The products were obtained in high yield and selectivity. The synthetic utility of the methodology was demonstrated in the addition of drug-based complex silyl enol ethers derived from gemfibrozil, indomethacin, and febuxostat to ketoesters, which furnished products **98–100** in 89–92% yields and 98–99% ee.



Scheme 18 M–M reaction catalyzed by Cu(II) with a PyIPI ligand. Synthesis of derivatives of the drugs gemfibrozil, indomethacin, and febuxostat.

2.2. Mg-Catalyzed enantioselective Mukaiyama–Michael reaction

As discussed above, copper Lewis acids have played a major role in the development of enantioselective M–M reactions. Although not as prominent as copper, other 2+ Lewis acids have also been used. In 2023, Antilla's group described the use of chiral metal phosphates as catalysts for M–M reactions (Scheme 19).[13] Initial optimization for the addition of a silyl ether to β,γ-unsaturated α-keto ester **96** included the chiral phosphoric acid, metal, solvent, temperature and the nature of the silicon substituent. The best conditions for this transformation were a magnesium chiral Lewis acid prepared from a bulky chiral phosphoric acid (2.5 mol%) in toluene at −30 °C with 4 Å molecular sieves (MS). Reactions with a ketomethyl ester were more effective than the corresponding ethyl ester and substituents on the nucleophile were crucial for attaining high levels of efficiency and stereoselectivity: TBS ether was more effective than TMS ether and TBDPS ether did not yield the product. The reaction shows a broad scope for the β-substituent of the acceptor and various substituted arenes with diverse electronic properties could be employed.



Scheme 19 M–M reactions catalyzed by a chiral Mg Brønsted acid complex.

Interestingly, a β-alkyl substituent (cyclohexyl) was found to be unreactive. The reactions gave high chemical yields (90–96%) and the products were obtained with high enantioselectivity (90–98% ee).

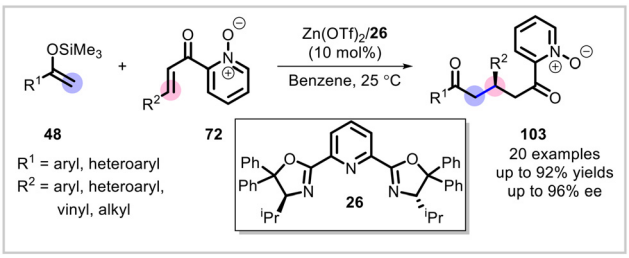
The authors have investigated the plausible mechanism for the reaction. It could proceed either through a 1,4-addition or a hetero Diels–Alder [4 + 2] pathway. To lend support for the Diels–Alder pathway, the authors were able to isolate intermediate **102** and characterize it structurally. Although 1,4-addition cannot be ruled out, the authors prefer the Diels–Alder pathway for the reaction.

2.3. Zn-Catalyzed enantioselective Mukaiyama–Michael reaction

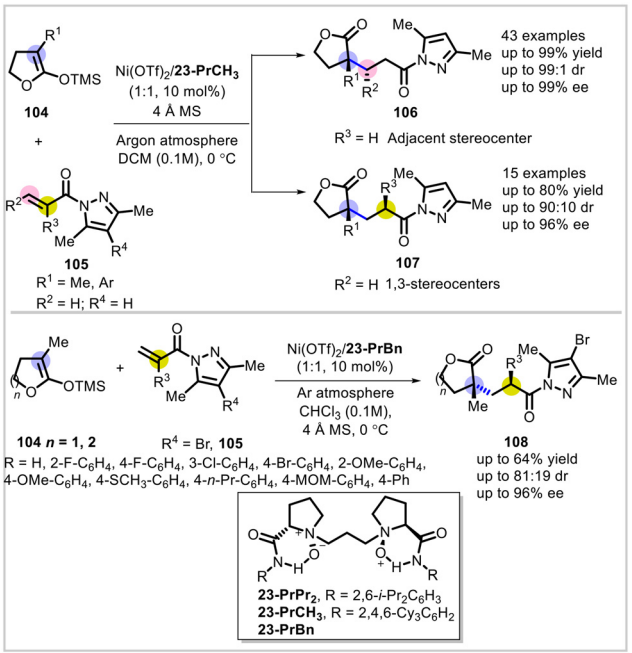
Similar to magnesium, zinc salts are also excellent Lewis acids.[48] Generally they generate well-organized complexes with bidentate ligands such as bisoxazolines. In 2013, Singh and co-workers reported the combination of zinc triflate and PyBox ligands in enantioselective M–M reaction of acyclic silyl enol ethers **48** with 2-enoylpyridine *N*-oxides **72** (Scheme 20).[49] As discussed earlier, 2-enoylpyridine *N*-oxides are excellent acceptors in M–M reactions. In this study, the addition of acyclic enol silyl ethers to **48** was investigated using zinc triflate as a Lewis acid. Reaction optimization showed that 10 mol% of the chiral Lewis acid **26** gave products **103** in high yield and enantioselectivity. Even 1 mol% of the catalyst was effective and gave the product with slightly lower ee. Highlights of this work are high yield and enantioselectivity for the products, reactions at ambient temperature, broad substrate scope for the acceptor, extention of the reaction to trisubstituted enol silyl ethers (less efficient) and that the reaction requires no additives. The authors proposed a 6-coordinated zinc complex to account for the observed selectivity.

2.4. Ni-Catalyzed enantioselective Mukaiyama–Michael reaction

In 2024, a nickel catalyzed asymmetric M–M reaction of silyl ketene acetals (SKAs) **104** and α,β-unsaturated pyrazolamides **105** was demonstrated by Feng *et al.* (Scheme 21).[3] Unlike in most reported enantioselective experiments, the authors use a nucleophile which provides butyrolactones as the products. A proline-derived *N*,*N*′-dioxide ligand popularized by the author was effective for the M–M reaction. Initial reaction optimization was carried out with SKA **104** and the 3,5-dimethylpyrazole cinnamate. Of the different Lewis acids investigated, $Ni(OTf)_2$ (10 mol%) in DCM and 4 Å MS gave the best results. The reaction shows very broad substrate scope for the acceptor (substituted aryl, heterocyclic, and alkyl) and the products are obtained in high yield, excellent *anti* diastereoselectivity and high enantioselectivity for the major diastereomer. Both five and six-membered SKAs also worked well. The authors also investigated the addition of SKA's to α-substituted acrylates **105** (R^4 = Br) to produce butyrolactones **108** with 1,3-quaternary/tertiary stereocenters. Five membered SKA's worked very well whereas the six-membered SKA gave the δ-lactone in low yield and low selectivity.

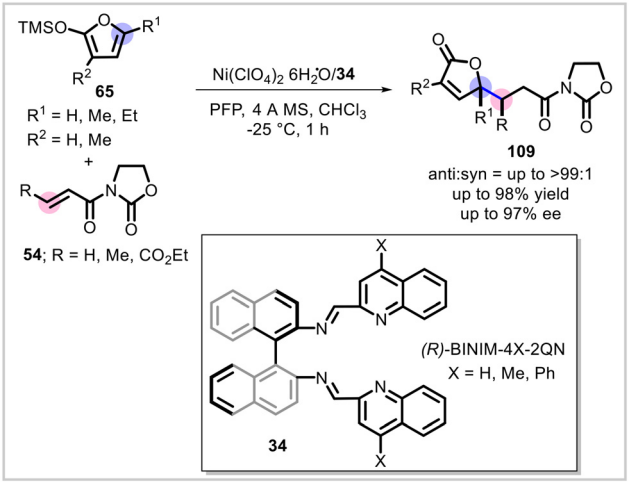


Scheme 20 Zn(II)-Catalyzed M–M reactions of 2-enoylpyridine *N*-oxides.



Scheme 21 M–M reactions of cyclic silyl ketene acetals and α,β-unsaturated pyrazolamides, providing products with two stereocenters.

Chiral nickel complexes prepared from chiral BINIM-2QN or its derivatives and $Ni(ClO_4)_2{\cdot}6H_2O$ have also been effectively used in enantioselective M–M reactions. In 2004, Suga *et al.* developed an effective procedure for the synthesis of chiral γ-butenolides from 2-silyloxyfurans **65** and 3-alkenoyl-2-oxazolidinones **54** catalyzed by BINIM–Ni complex **34** (Scheme 22).[50] This protocol yielded γ-butenolides **109** with high yield and enantioselectivities (up to 98% yield, up to 97% ee). The chemistry worked best when $CHCl_3$ was used as a solvent. Generally HFIP worked better than pentafluorophenol (PFP) as an additive. Reactions with the parent acryloyl oxazolidinone gave product butenolide in high enantioselectivity and thus estab-

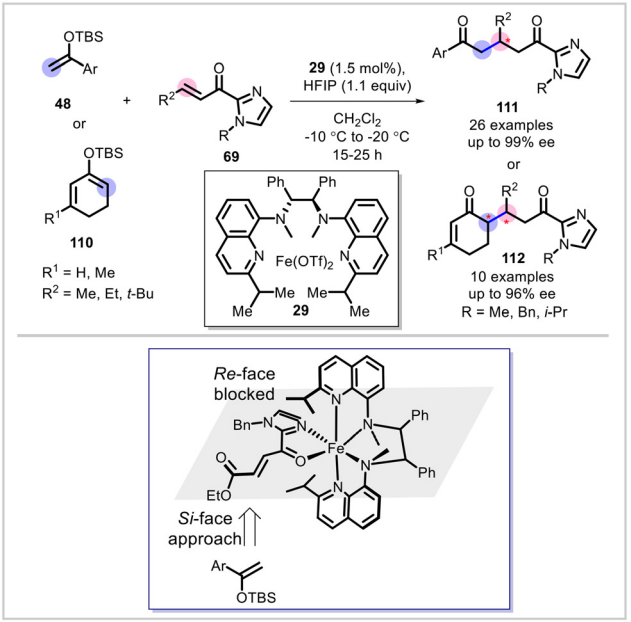


Scheme 22 Ni(II)-Catalyzed synthesis of γ-butenolide-containing products with vicinal stereocenters.

lished a remote chiral center. When 5-substituted-2-silyloxyfuran was used as the nucleophile, reactions with β-substitued acceptor furnished products with two contiguous chiral centers (one all carbon quaternary center) in high efficiency with high diastereoselectivity and good enantioselectivity. Another noteworthy feature of this work is the use of very low catalyst loading (5 mol%). Even 1 mol% of the catalyst was effective, albeit with slightly diminished selectivity.

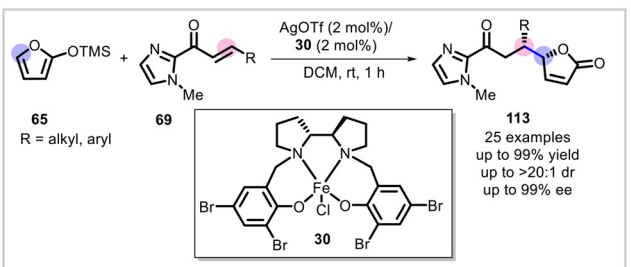
2.5. Iron catalyzed enantioselective Mukaiyama–Michael reaction

In comparison to the extensive use of Lewis acids such as Mg, Cu, Ni, *etc.* in asymmetric transformations, iron salts have not received the same level of scrutiny. There is significant interest in the development of asymmetric transformations using earth abundant metals such as Fe, Ni, Co, *etc.*[51] In 2021, Che and co-workers reported the use of chiral Lewis acids prepared from $Fe(OTf)_2$ and tetradentate ligands (for example, (*R*,*R*)-*N*,*N*′-bis (2-isopropylquinolin-8-yl)-1,2-diphenylethane-1,2-diamine) **29** for the enantioselective M–M reactions of acyclic and cyclic silyl enol ethers **48**, **110** with α,β-unsaturated 2-acyl imidazoles **69** (Scheme 23).[52] It should be noted that these catalysts are chiral at metal and also possess ligand-centered chirality. Initial optimization studies showed that **29**, a chiral Lewis acid derived from $Fe(OTf)_2$ and bulky tetradentate (*R*,*R*)-bis-(quinolyl)diamine ligand (3 mol%) in DCM, and HFIP as an additive gave high yields for the addition of **48** to acceptor **69**. Of the three different silyl substituted acyclic nucleophiles, the TBS enol ether gave the best results. Addition of molecular sieves had a negative impact on the reaction. The reaction exhibited a large substrate scope, with a variety of acceptors (aryl, alkyl) and nucleophiles, and provided the conjugate addition products in high yield (83–98%) and high enantioselectivity (74–99% ee). The conjugate addition was equally efficient with cyclic enol silyl ethers. The authors' stereochemical model for explaining the sense of stereoinduction is shown (Scheme 23).



Scheme 23 Iron catalyzed M–M reactions of silylenol ethers with acyl imidazoles.

In continuation of their work on the use of Fe(II) catalysts, Che and co-worker investigated the addition of cyclic enol ethers **65** to acyl imidazoles **69** using a chiral Lewis iron acid (Scheme 24).[5] The stable (isolable) chiral Lewis acid can be prepared from iron chloride and a salan ligand. This compound was treated with a silver salt to generate a more reactive catalyst during the reaction. Of the different silver salts tested, the triflate gave the best results. Under optimized conditions, the reaction using 5 mol% of the catalyst in DCM at room temperature gave the γ-butenolide **113** in high yield (90 to 98%), excellent diastereoselectivity (8 : 1 to 20 : 1) and high enantioselectivity (96–99% ee) for the major isomer. It is interesting to note that a complex prepared from $Fe(OTf)_3$ and the chiral ligand was equally effective. Of the different ligands investigated, bipyrrolidine ligands worked better than the corresponding bipiperidine ligands. The reaction showed broad substrate scope for the acceptor. Reactions using 5-substituted 2-silyloxyfurans gave products with hindered chiral centers in high yield and selectivity. The authors have pro-



Scheme 24 Vinylogous M–M reactions catalyzed by an Fe(III) complex.

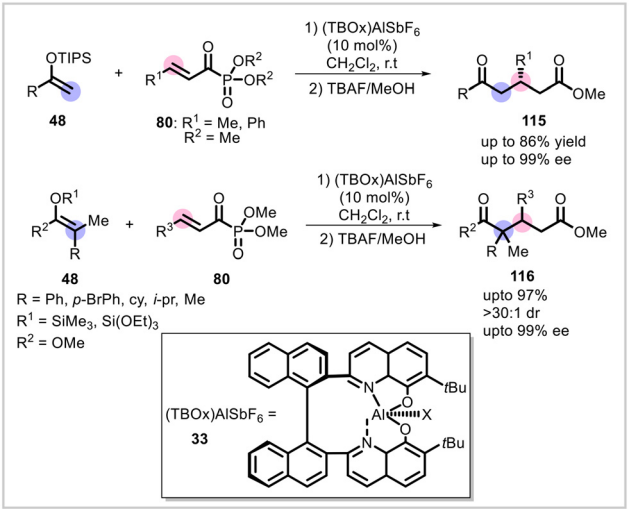
posed an octahedral iron complex to account for the observed selectivity.

2.6. B,Al,Sc,La,Ce,Eu,Ti-Catalyzed enantioselective Mukaiyama–Michael reaction

Boron halides are some of the strongest Lewis acids known. The preparation of chiral boron Lewis acids by incorporation of appropriate chiral frameworks has been well established and one class of catalysts which has received significant attention are the oxazaborolidines.[53,54] One of the key features of oxazaborolidines is their ability to activate aldehydes and ketones (single point donors).[53,54] Harada and co-workers have developed enantioselective M–M reaction of acyclic enones **78** with TBS ketene *S*,*O*-acetal **48** using a boron catalyst prepared from *allo*-threonine, *O*-(2-naphthoyl)-*N*-tosyl-L-*allo*-threonine-derived β-phenyloxazaborolidinone (Scheme 25).[55] Under optimized reaction conditions (40 mol% catalyst of **39**, DCM, −78 °C), product **114** ($R^1 = R^2 = Me$) was obtained in good yield and 84% ee. TBS ketene acetals **48** performed better than the corresponding TMS ether. 2,6-Diisopropylphenol as an additive improved the reaction characteristics by diminishing the racemic pathway (M–M reaction with achiral silicon compounds).

Two years later, the same group reported investigations on the use of a threonine-based boron Lewis acid.[56,57] The scope of the M–M reaction was extended to include a number of alkenyl methyl ketones as Michael acceptors, providing the addition products with high enantioselectivities (85–90% ee). The catalyst loading for these experiments was 10 mol%, and a combination of 2,6-diisopropylphenol and *t*-BuOMe as additives was essential to achieve high enantioselectivity.

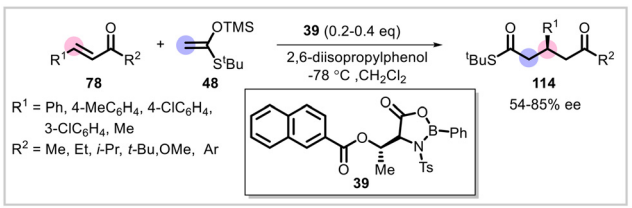
Chiral aluminum Lewis acids have also been extensively used in asymmetric synthesis.[58] Based on their work on novel chiral binaphthyl tethered bis(8-quinolinoato) ligands (TBOx), Yamamoto and co-workers developed aluminum catalysts **33**, derived from TBOx, for M–M reactions (Scheme 26).[59] The reaction comprised the addition of silyl enol ethers **48**, derived from alkyl methyl or aryl methyl ketones, to unsaturated ketophosphonates **80** using reactive aluminum triflates or hexafluoroantimonates (10 mol%) in DCM. The product 1,5-dicarbonyl compounds **115** were obtained in good yields (66–86% yield) and very high enantioselectivities (96–99% ee). The use of tetrasubstituted silyl enol ethers derived from cyclic methyl ketones was also efficient in the M–M reaction, generating products **116** with two adjacent chiral centers, with one of them



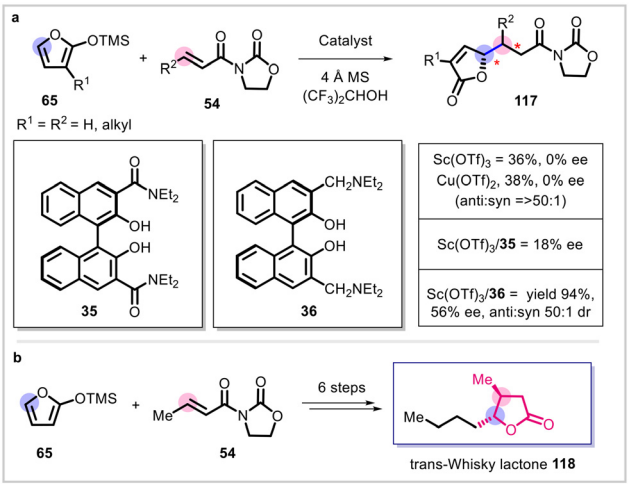
Scheme 26 (TBOx)AlX catalyzed Mukaiyama–Michael reactions affording 1,5-dicarbonyl compounds, including products with adjacent chiral centers and all-carbon quaternary centers.

being an all carbon quaternary center, in good to high yields (54–97%), good to high diastereoselectivity (2 : 1 to 30 : 1) and high enantioselectivity (96–99% ee).

Pre-lanthanide 3+ Lewis acids, scandium and yttrium trifluoromethanesulfonates, are stable solids and have been extensively used in catalysis as well as asymmetric synthesis.[60–63] These two small Lewis acids generally form 6-coordinate complexes with both N and O donors. Katsuki and co-workers investigated an asymmetric Michael addition of trimethylsilyloxyfurans **65** to 3[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one **54** in the presence of $Sc(OTf)_3$ and a ligand derived from BINOL (Scheme 27, entry a).[38,64] Reaction using ligand **35** proceeded smoothly but gave only low ee (18%) for the product. When the reactions were carried with **36** as a chiral source and $Sc(OTf)_3$ (5 mol%), the product was produced with



Scheme 25 Organoboron catalyzed enantioselective M–M reaction.

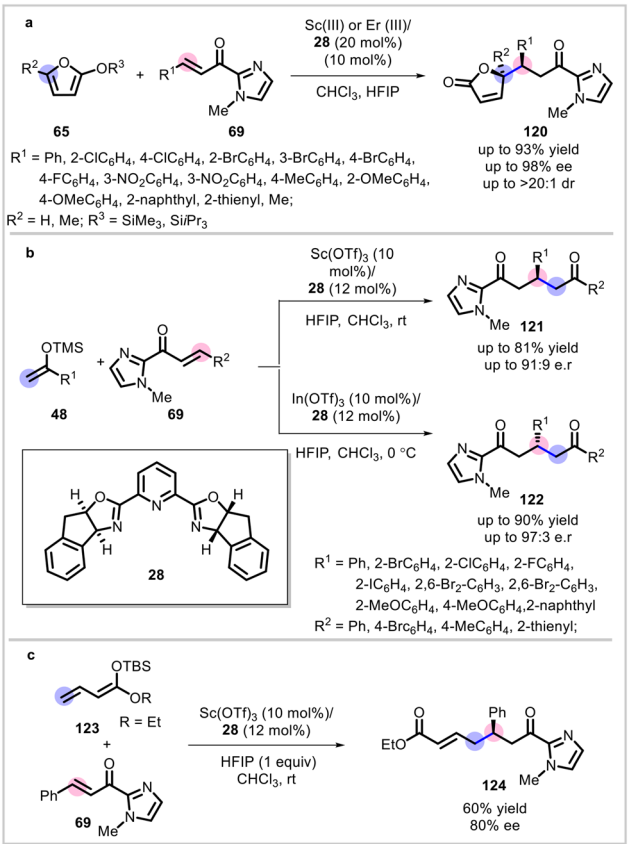


Scheme 27 Synthesis of *trans*-whisky lactone *via* a M–M reaction.

high diastereoselectivity and good enantioselectivity (yield 44%, 73% ee, *anti* : *syn* 50 : 1). Addition of HFIP gave significant improvement in yield (80%) with a slight decrease in enantioselectivity (65% ee). Later in 1998, the authors utilized their protocol and demonstrated the enantioselective synthesis of *trans*-whisky lactone **118** in six steps starting from **65** (Scheme 27, entry b).[65]

Feng and co-workers have developed a novel class of chiral ligands derived from linked proline amides. The ligands are versatile and have found several applications.[66–68] Building on their previous work they reported the use of scandium(III)-bis-*N*-oxide complex for asymmetric vinylogous M–M reaction of 2-silyloxyfuran **86** with chalcones **78** (Scheme 28).[69] Initial studies showed that the scandium salt was superior in the transformation in comparison to reactions with lanthanum and yttrium salts, which mainly yielded side products. The size of the amide substituent in the ligand played a critical role in the outcome of the reaction. Under optimal conditions, a $Sc(OTf)_3$-proline amide catalyst (10 mol%) in a solvent mixture comprising of ethyl propiolate and *t*-BuOH gave the best results for addition of **86** to a variety of chalcones to furnish **119** in very high yield (92–99%), as a single diastereomer with high enantioselectivity (82–99% ee). An octahedral stereochemical model was proposed to account for the observed stereoselectivity based on an X-ray crystal structure of the ligand–$Sc(OTf)_3$ complex.

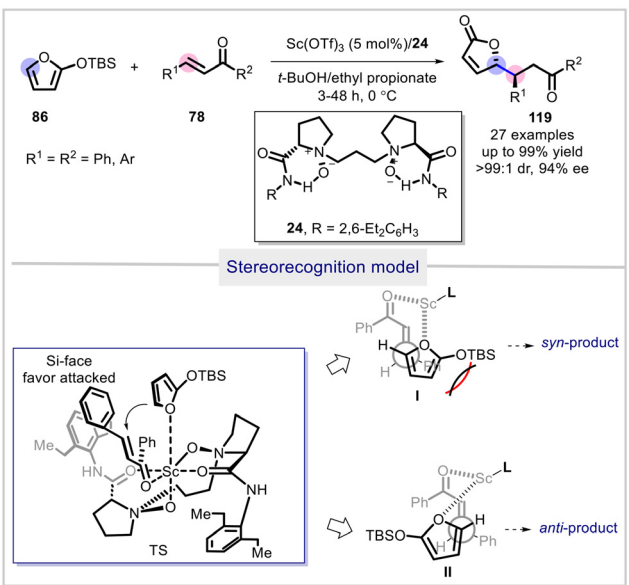
In a series of articles,[4,70,71] Singh and co-workers reported the first enantio- and diastereoselective vinylogous M–M reactions of silyloxyfurans **65** with α,β-unsaturated 2-acyl imidazoles **69** using $Sc(OTf)_3$-PyBox complexes (Scheme 29, entry a). During reaction optimization, a variety of pre-lanthanide and lanthanide Lewis acids and chiral ligand combinations (PyBox and Box ligands) were explored.[70] Of these, scandium triflate with an aminoindanol-derived PyBox ligand (10 mol%) in chloroform gave the best results. HFIP as an additive improved reaction times and enantioselectivity. A large number of substrates with aryl substituents were competent in the addition of 2-silyloxyfuran and gave butenolides in high yield (88–93%), diastereoselectivity (20 : 1) and enantioselectivity (92–98% ee). The conjugate addition was equally efficient with 5-methyl-2-silyloxy furan (80–88% yield, 20 : 1 dr, and 80–96% ee). Interestingly, an erbium triflate-Pybox combination also worked well and gave results similar to those obtained with scandium.



Scheme 29 Vinylogous M–M reactions of α,β-unsaturated 2-acyl imidazoles catalyzed by Sc-, Er-, and In-based Lewis acids.

Building upon their previous work, the same authors reported the use of α,β-unsaturated 2-acyl imidazoles as acceptors in enantioselective M–M reaction using chiral Lewis acids derived from $Sc(OTf)_3$ or $In(OTf)_3$ and indapybox ligand (Scheme 29, entry b).[71] Both reactions gave products **121** and **122** with high efficiency. A point of note is that scandium and indium triflates gave enantiomeric products while using the same chiral ligand, with high yields and ee in each case. The authors proposed an octahedral complex with scandium and a pentagonal bipyramidal complex (7-membered complex) with indium to account for the switch in face selectivity.

Recently, the same authors extended their study to the addition of vinyl ketene silyl acetals (linear dienolate) to



Scheme 28 Scandium Lewis acid catalyzed vinylogous M–M reactions of silyloxyfurans and chalcones.

α,β-unsaturated 2-acyl imidazoles (Scheme 29, entry c).[4] The addition can occur in a 1,2 or a 1,4 pathway. The vinylogous M–M reaction was highly selective towards the 1,4-pathway using a chiral Lewis acid derived from $Sc(OTf)_3$ and IndapyBox (10 mol%) in chloroform (82% yield and 78% ee). The use of HFIP as an additive led to improvements in both yield and selectivity. The product was converted to a carboxylic acid, with removal of the imidazole template, in a straightforward manner without compromising enantioselectivity.

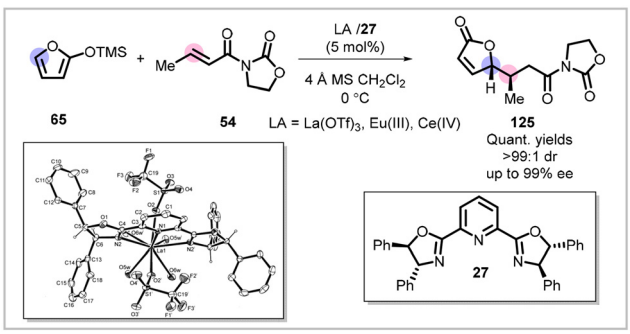
Desimoni and co-workers screened a series of optically active chiral Box and PyBox based ligands and metal cations for the enantioselective M–M reactions of (*E*)-3-crotonyl-1,3-oxazolidin-2-one **54** and 2-trimethylsilyloxyfuran **65** (Scheme 30).[72] Initial experiments using $Sc(OTf)_3$/Box ligand (5 mol%) as the catalyst in DCM at 0 °C with 4 Å MS gave the addition product in 80% yield as a racemate. Changing the ligand to PyBox improved efficiency, and the optimal ligand was (*R*,*R*)-diPh-Pybox. Reaction with $Sc(OTf)_3$/PyBox **127** gave *anti* product **125** in quantitative yield and 93% ee. Other lanthanide (La, Eu, Yb and Ce) triflates also gave **125** in even higher selectivity (98–99% ee). The authors obtained a crystal structure of $Sc(OTf)_3$/**27** which shows coordination of **54** with a 1 : 1 ligand/metal complex.

Mukaiyama first introduced the use of [(*R*)-1,1′-bi-2-naphthalenediolato(2-)-*O*,*O*′]oxotitanium catalyst **37** in asymmetric Michael reactions of silylenol ethers **126** with cyclic enones and chalcones **78** (Scheme 31).[73] The reactions were carried out in toluene at −78 °C and afforded the corresponding 1,5-dicarbonyl products **127** in good yields (76%), and high ee (90%). Among the three cyclic enones investigated, systems including cyclopentenone gave the highest selectivity (90% ee) followed by 2-cyclohexenone (70% ee) and 2-cyloheptenone (40% ee). In contrast, reactions with chalcones were less effective and gave products in low ee.

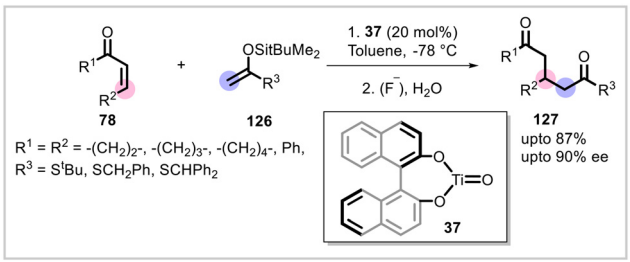
Bernardi and Scolastico and their co-workers reported the use of *in situ* generated TADDOL-derived $TiCl_2$ catalysts in enantioselective M–M reactions of silyl ketene acetals and 2-carboxyalkyl cyclopentenones.[74] The conjugate additions proceeded in generally low yields and low ee. The reaction of silyl ketene acetal **42** (R = Me) with 2-carboxyalkyl cyclopentenone **43** gave the *syn* adduct **128** (98 : 2 *syn*/*anti*) with fair ee (47%) (Scheme 32).

2.7. Chiral-at-metal Lewis acids: rhodium catalyzed enantioselective Mukaiyama–Michael reaction

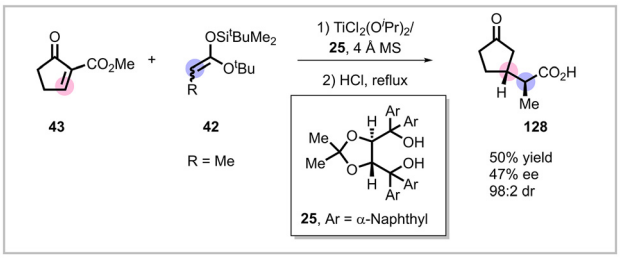
In the past decade, chiral-at-metal Lewis acids have received increased attention for applications in asymmetric synthesis.[75] Kang and co-workers reported the synthesis of a modified chiral pinene–pyridine based rhodium catalyst and its applications in enantioselective M–M reactions (Scheme 33).[76] These catalysts are fairly Lewis acidic because of the ionic nature of the catalyst. Initial reaction optimization using 2-cinnamoylimidazole and enol silyl ether as substrates and 2 mol% of the catalyst, with THF as the solvent, gave the 1,5-dicarbonyl product **129** in high yield (85%) and excellent



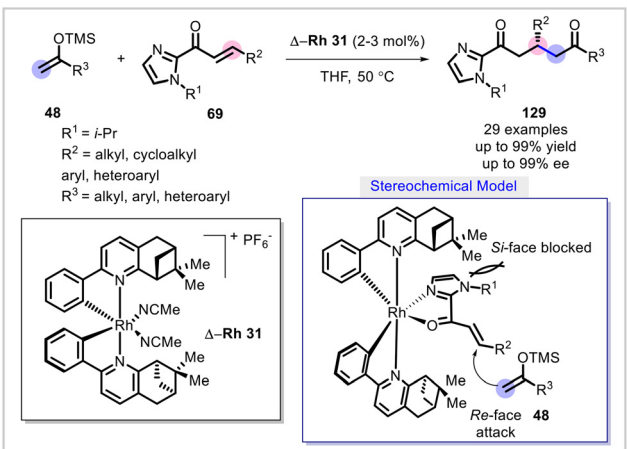
Scheme 30 M–M reactions catalyzed by lanthanide salts.



Scheme 31 M–M reactions catalyzed by a chiral Ti(IV) catalyst.



Scheme 32 TADDOL–TiCl catalyzed M–M reaction.



Scheme 33 M–M reactions of 2-acylimidazoles catalyzed by a chiral-at-metal rhodium complex.

enantioselectivity (98% ee). The reaction showed very broad substrate scope for the acceptor (aryl, heterocyclic, and alkyl) and gave the products in excellent yields (up to 99%) with excellent enantioselectivities (up to 99% ee). Similarly, a variety of enol silyl ethers derived from aryl methyl ketones, heteroaryl methyl ketones, and alkyl methyl ketones also gave the products with excellent selectivities. An octahedral stereochemical model of **48** based on the observed face selectivity was proposed by the authors.

2.8. Silicon Lewis acids: BINOL-derived imidodiphosphorimidates

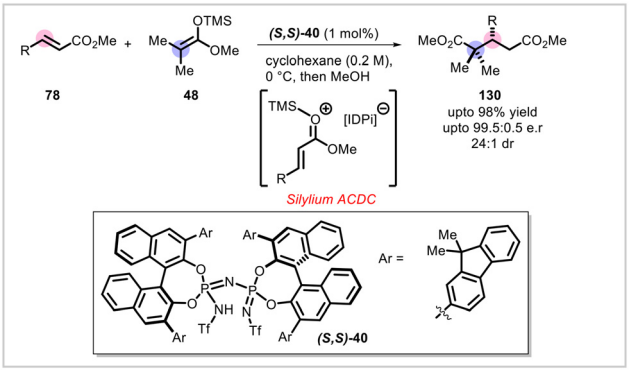
A new concept called "Silylium ACDC" was introduced by the List group in which a Lewis acidic silyl cation is coordinated to a chiral imidodiphosphorimidate (IDPi) counterion and the complex can participate very efficiently in asymmetric transformations.[77–80] The silicon Lewis acid can activate a variety of acceptors for addition of a nucleophile. Typically, α,β-unsaturated esters are very weak acceptors. In this work, List and co-workers developed an effective protocol for a silylium imidodiphosphorimidate (IDPi) Lewis acid catalyzed enantioselective M–M reaction of silyl ketene acetals with α,β-unsaturated methyl esters **78** (Scheme 34).[81] Initial optimization studies involved the addition of commercial SKA **48** to methyl cinnamate using 3 mol% of different IDPi acids. The IDPis are strong acids, and the product anion is C_2-symmetric. Cyclohexane as a solvent and **40** as a catalyst at 0 °C gave the product in 100% conversion and 94% ee. Use of freshly prepared and pure SKA led to better results and required only 1 mol% of the catalyst. Under the optimal conditions, a variety of β-aryl methyl esters and β-alkyl methyl esters underwent conjugate additions to produce **130** in high yields and excellent selectivities. γ-Branched substrates were found to be highly unreactive with these optimal conditions. It is also interesting to note that an ethyl ester gave lower ee (relative to the corresponding methyl ester) and methyl *cis*-cinnamate gave low conversion and ee. A variety of SKAs were competent in conjugate additions to methyl cinnamate. The authors have carried out control experiments and NMR studies to arrive at a mechanism for the transformation.

List and co-workers extended their studies to the addition of a tetrasubstituted SKA **48** to cyclopentenone **78** using 0.1 mol% of the catalyst to provide **131** in 95% yield and 96% ee (Scheme 35).[82] In 2021, the group presented an unprecedented enantioselective synthesis of (+)-2-*epi*-ziza-6(13)en-3-one (**132**), an active smelling principle of vetiver oil, with asymmetric organocatalytic M–M addition as a crucial step. (+)-2-*epi*-Ziza-6(13)en-3-one was accessed in 10 steps from the M–M product **131**.

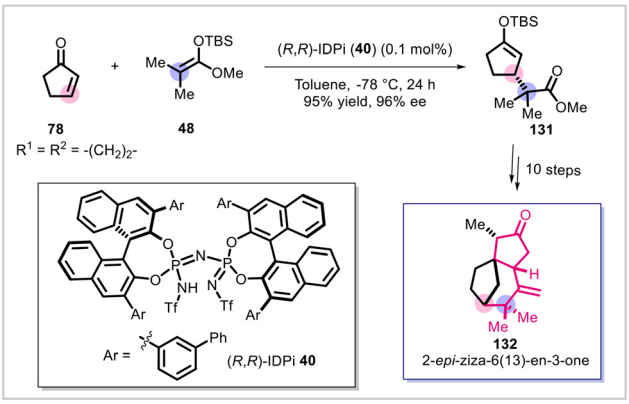
List and co-workers also reported a catalytic asymmetric approach to nitroso acetals **134** from readily available silyl nitronates **133** with silyl ketene acetals **48** and **123**, catalyzed by imidodiphosphorimidate catalysts (Scheme 36).[83] Silyl nitronates are ambiphilic and can react with both nucleophiles and electrophiles. In this work, the authors have demonstrated their electrophilic character by adding SKAs using silylium Lewis acids. For initial optimization studies, the authors treated four different silyl nitronates with SKA in the presence of an IDPi catalyst (2.5 mol% catalyst in toluene/pentane (1 : 1) at 100 °C). Six different IDPis were evaluated and catalyst **40** gave the best results (99% ee for product **134**). A variety of silyl nitronates (R = alkyl, aryl, and heterocyclic) were excellent substrates and gave the products in modest to high yields (53–96%) and high enantioselectivities (90–99% ee). Reaction with (*Z*) and (*E*) SKAs derived from methyl propionate gave *anti* (9 : 1 dr) and *syn* (3 : 1) diastereomers, respectively, with high ees for both major and minor diastereomers. The product nitroso acetals could be easily converted into *N*-Boc-β^3-amino acid esters in a single step.

3. Enantioselective Mukaiyama–Michael reaction using chiral organocatalysts

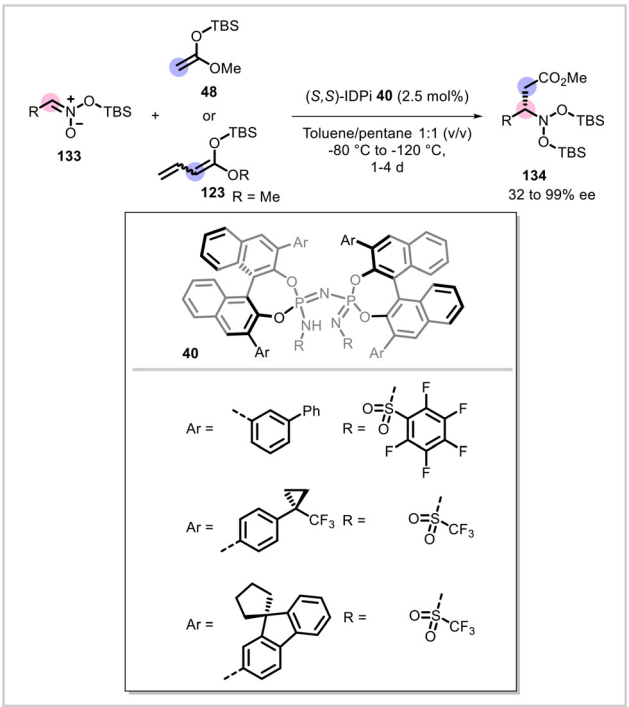
A variety of structurally diverse chiral organocatalysts (Fig. 3) have been used to catalyze the Mukaiyama–Michael transformation. Chiral amine catalysts (section 3.1), prolinol-based cata-



Scheme 34 Silylium-IDPi catalyzed reaction of silyl ketene acetals with α,β-unsaturated methyl esters.



Scheme 35 Enantioselective total synthesis of 2-*epi*-ziza-6(13)-en-3-one *via* M–M reaction.



Scheme 36 M–M reactions of silyl nitronates using IDPi catalysts.

lysts (section 3.2), and MacMillan's imidazolidinone catalysts (section 3.3) promote Mukaiyama–Michael addition by forming an electrophilic iminium ion from aldehydic substrates. Squaramides (section 3.4) also activate the electrophile but do so through hydrogen-bonding. Cinchonidinium catalysts (section 3.5) function by forming a chiral ion pair in phase-transfer catalysis. Finally, a chiral phosphoramide (section 3.6) has also been reported as an effective catalyst for the transformation, acting as a Lewis base and serving to activate the nucleophile.

Relative to Lewis acid catalysis, organocatalysis[24] is a complementary approach for achieving highly enantioselective Mukaiyama–Michael reactions. For example, Lewis acid catalysis and organocatalysis can be suitable for different substrate types: Lewis acid catalysis is more often used with substrates capable of chelating a metal ion while organocatalysis is more frequently employed with other substrates, such as aldehydes that can readily undergo iminium ion catalysis. Additionally, some organocatalysts[84–86] feature bifunctional structures—containing two functionalities that play important catalytic roles—whereas no enantioselective methods involving bifunctional catalysis with Lewis acids have been reported. Both organocatalysis and Lewis acid catalysis have demonstrated significant synthetic utility in various contexts, including the total synthesis of natural products.

3.1. Chiral amine catalysts

As discussed in the previous section, a majority of substrates which are typically used as acceptors in M–M reactions generally form a chelate with Lewis acids for activation. In contrast, substrates which are typically suitable for activation with organocatalysts are aldehydes or ketones. Two approaches for activating the acceptor have been explored for enantioselective M–M reactions. They are (1) formation of iminium ions using

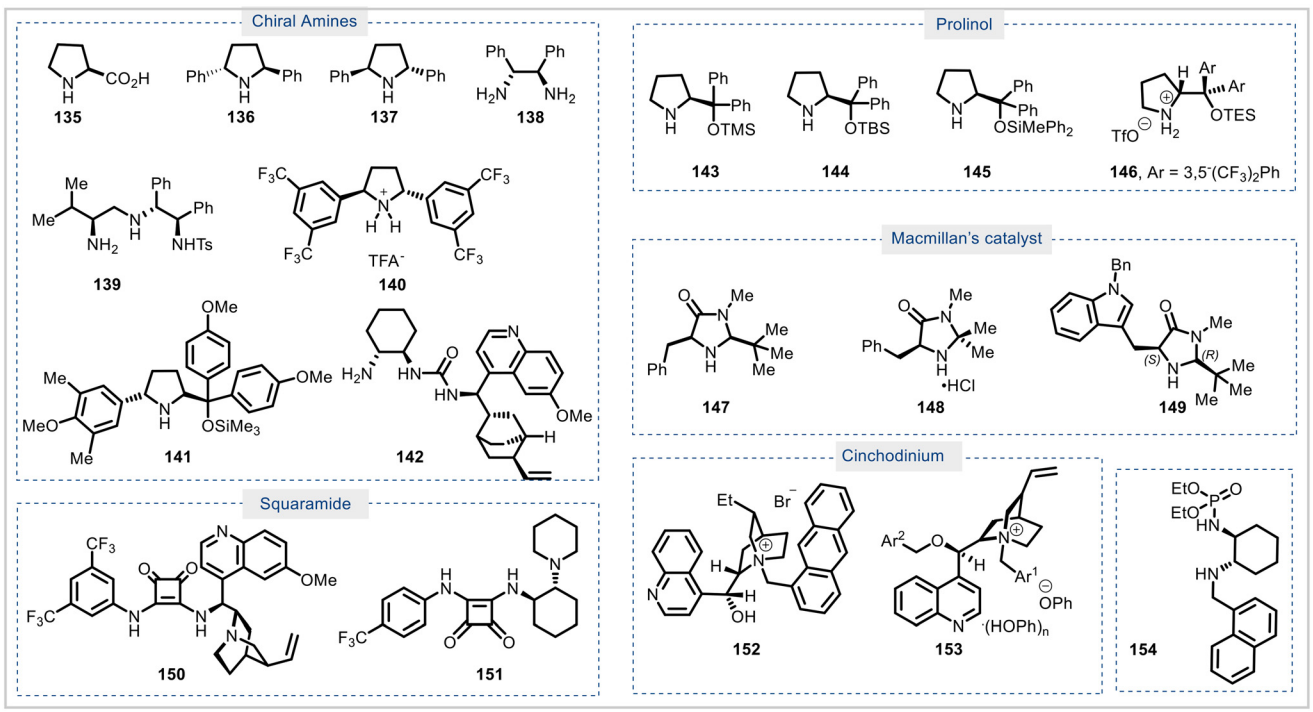


Fig. 3 Chiral organocatalysts for Mukaiyama–Michael reactions.

different chiral amines and (2) activation of acceptors through hydrogen bonding. Alternatively, the nucleophile can be activated using H-bonding or phase transfer catalysts.

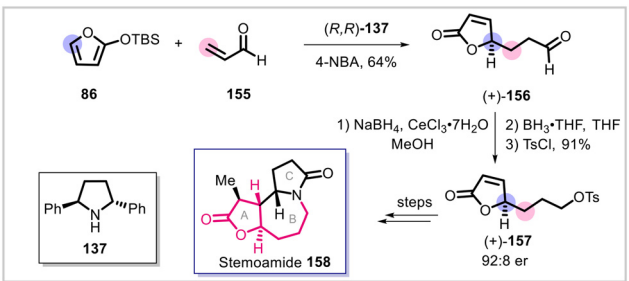
C_2 symmetric chiral amines have played a key role in iminium ion catalysis. Pihko and co-workers investigated the addition of silyl enol ether **86** to acrolein **155** using a chiral amine catalyst (Scheme 37).[87] The addition of 2-OTBS furan to acrolein using 10 mol% of (*R*,*R*)-2,5-diphenylpyrrolidine **137**, 4-nitrobenzoic acid (4-NBA, 10 mol%), and water (2 equiv.) in DCM at 0 °C gave the product butenolide **156** in 56% yield and 91% ee. The silicon substituent plays a role in the outcome of the reaction. Use of the corresponding 2-OTIPS furan gave the product in 71% yield and 92% ee. Reaction with 5-methyl-2-OTBS furan with acrolein gave a butenolide in 65% yield and 93% ee. Compound **156** was converted to stemoamide **158**, a member of the *Stemona* alkaloid family, in several steps.

Pihko and co-workers have also investigated the addition of silyl enol ethers to methacrolein (Scheme 38).[88] Three distinct class of organocatalysts were investigated: (1) chiral pyrrolidines, (2) prolinols, and (3) imidazolidinones (MacMillan catalysts). The efficacy of the reaction was evaluated using 10 mol% of the catalyst, 10 mol% of 4-nitrobenzoic acid, and 2 equivalents of water in DCM at room temperature. Interestingly, both prolinol and imidazolidinone catalysts gave the product with good conversion but with nearly 1 : 1 diastereoselectivity and low enantioselectivity. In contrast, reaction with 2,5-diphenyl pyrrolidine gave the product in >95% conversion as a 1 : 1 mixture of diastereomers with high enantioselectivity (93% ee for both diastereomers). The diastereomers were easily separated and compound **159** served as a key building block for the synthesis of **161**, the C17–C28 fragment of pectenotoxin **162**, a marine natural product.

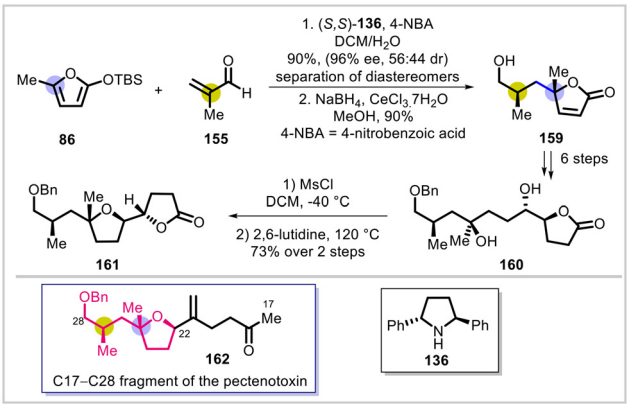
In a separate report,[89] the authors carried out a detailed investigation on the above reaction. Several reaction parameters were optimized. Large excess of the starting acrolein was necessary to obtain high reaction rate and complete conversion of the starting material. The nature of the acid co-catalyst was also investigated and it was found that a good balance of acid strength and lipophilicity was required and 4-nitrobenzoic was optimal. Pyrrolidines with different aryl substituents (size) were also investigated and 2,5-diphenylpyrrolidine gave the best results. Several different α-substituted acroleins gave products with good efficiency, high enantioselectivity (70–92% ee), and modest diastereoselectivity (Scheme 39). Similarly, reactions of acroleins with different β-alkyl substituents **165** were also successful, furnishing products in high diastereoselectivites and high ees. The authors performed detailed DFT calculations which revealed that the enantioselectivity was induced by stabilizing noncovalent interactions between the reacting partners, and not due to steric hindrance.

The products obtained from the M–M reaction are excellent precursors for synthesizing biologically active natural products. Pihko and co-workers described a short synthesis of (+)-Greek tobacco lactone using the product from the M–M reaction between acr7olein **155** and silyloxyfuran **86** using (***R*, *R*)-13** as the catalyst.[90] Compound **167** was converted to the target **168** in 4 steps (Scheme 40).

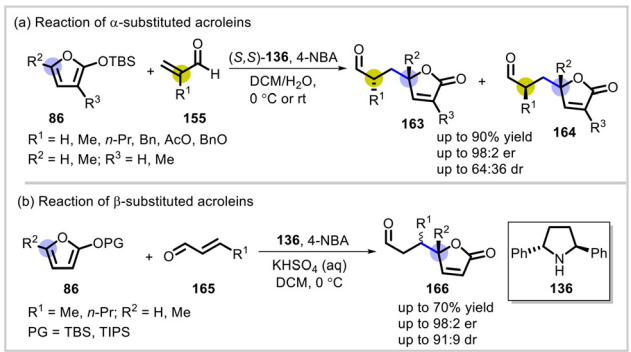
Lycoperdic acid is a biologically active natural product isolated from mushrooms and its structure is similar to glutamic acid.[91,92] Pihko and co-workers have developed a short enantioselective synthesis of lycoperdic acid using organocatalysts.[93] The key step in the synthesis was the formation of butenolide **169** in enantioenriched form using a M–M reaction. To this end they optimized the M–M reaction of 5-carbomethoxy-2-silyloxyfuran **65** with acrolein (Scheme 41). A prior report on this transformation using MacMillan's catalyst gave



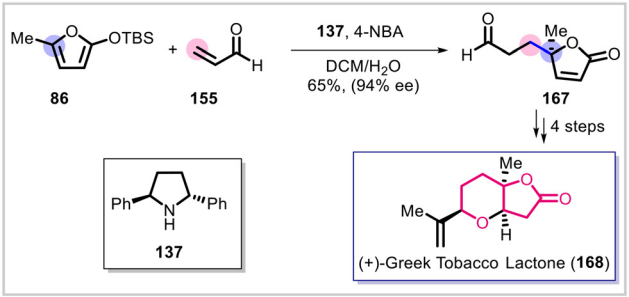
Scheme 37 Asymmetric synthesis of stemoamide *via* organocatalyzed M–M reaction.



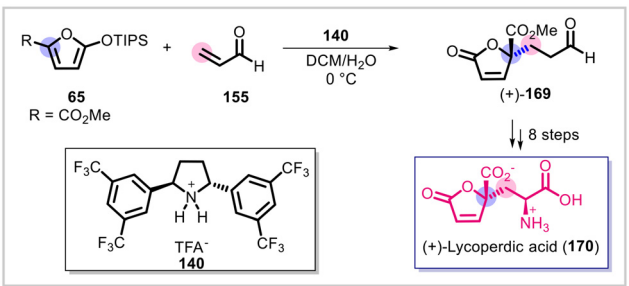
Scheme 38 Synthesis of the C17–C28 fragment of pectenotoxin.



Scheme 39 M–M reactions of α- and β-substituted acroleins.



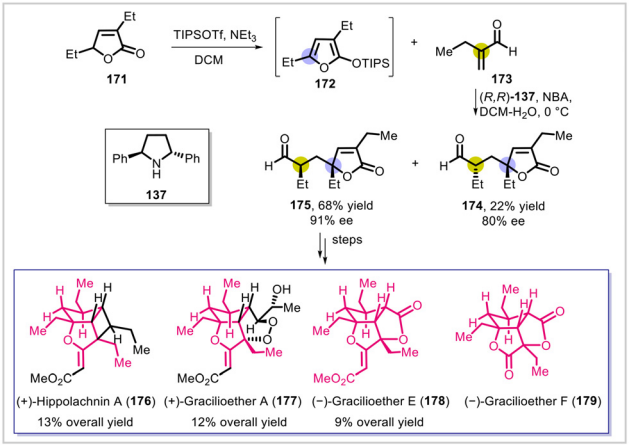
Scheme 40 Enantioselective M–M reaction as a key step in the total synthesis of Greek tobacco lactone.



Scheme 41 Enantioselective synthesis of (+)-lycoperdic acid.

the desired product in low yield and good enantioselectivity. An initial screen of different types of catalysts (MacMillan, Hayashi–Jørgensen, chiral amines) gave products in low yields and moderate enantioselectivites. Modification of the 2,5-pyrrolidine structure by introducing electron withdrawing groups and their impact on efficiency and selectivity was investigated. These optimization studies led to the identification of the best pyrrolidine catalyst (**140**) and TFA as the acid co-catalyst (DCM, H_2O (2 eq.) at 0 °C). This gave the butenolide product in 47% yield and 88% ee. The butenolide (+)-**169** was transformed to (+)-lycoperdic acid **170** in 8 steps.

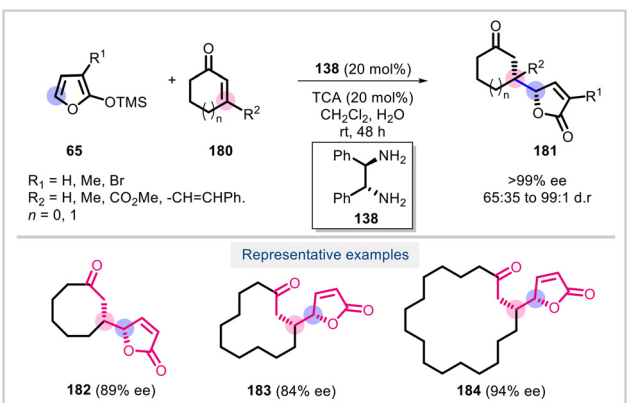
The use of highly substituted furan silyl ethers in enantioselective M–M remains a significant challenge. The products from these reactions are functionalized butenolides with multiple chiral centers. As part of a program to synthesize complex natural products containing the butyrolactone substructure, Enders and co-workers investigated the M–M reactions of furan silyl ethers with α-substituted acroleins (Scheme 42).[94] Addition of *in situ* generated silyl ether **172** to 2-ethyl acrolein **173** using organocatalysts was undertaken. The use of Hayashi–Jørgensen catalyst gave the product in good yield but with low ee. Other well-known catalysts such as MacMillan's catalyst gave no reaction. On the other hand, use of 2,5-diphenylpyrrolidine as a catalyst (15 mol%) with 4-nitrobenzoic acid as a co-catalyst (15 mol%) in DCM/H_2O gave a diastereomeric mixture of the product (*syn* : *anti* = 3 : 1) in 88% combined yield with 91% ee for the *syn* isomer. The major *syn* isomer was transformed to (+)-hippolachnin A **176** in 5 steps. The



Scheme 42 Enantioselective biomimetic total synthesis of (+)-hippolachnin A and (+)-gracilioethers A, E, F.

intermediate **175** was also converted to other natural products: gracilloethers A (**177**), E (**178**), and F (**179**).

The degree of substitution of the acceptor has a significant impact on yield and selectivity in conjugate additions of carbon nucleophiles. The products from these reactions are important because of the potential to incorporate all-carbon quaternary center(s). Generally, conjugate additions to cyclic enones proceed with good efficiency, and the literature has many successful examples.[95] However, development of highly selective methods for the addition of carbon nucleophiles to 3-substituted enones remains a challenge. Given the significant importance of bioactive cycloalkane-bound γ-butenolides, Singh and co-workers have developed a primary diamine-catalyzed *syn*-selective vinylogous M–M reaction of 2-silyloxyfurans **65** and cyclic enones **180** (Scheme 43).[96] Preliminary investigations on the addition of 2-silyloxyfuran to cyclohexanone with chiral phenethyl amine (a primary monoamine) as a catalyst (20 mol%) and TFA as a co-catalyst (20 mol%) gave poor yields and good selectivity (77% ee). Based on the hypothesis that a diamine can activate both the acceptor and the donor,



Scheme 43 Asymmetric M–M reactions of silyloxyfurans with cyclic enones.

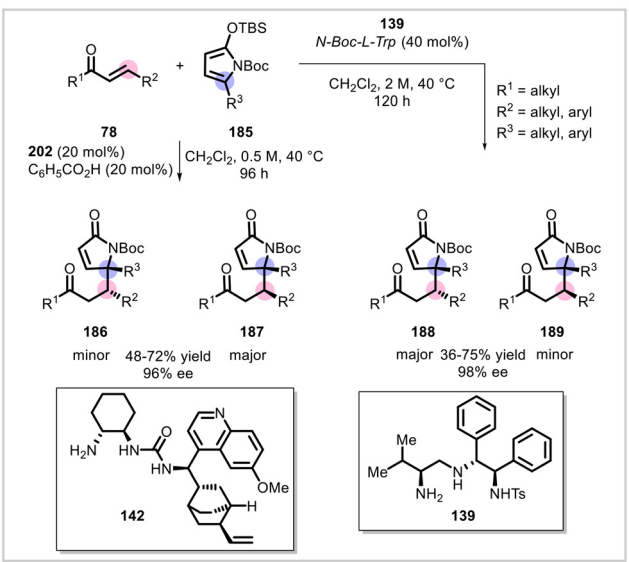
several chiral diamines were evaluated. Of these, 1,2-diphenylethylene diamine **138** (20 mol%) in combination with trichloroacetic acid (20 mol%) in DCM at room temperature gave the addition product in 85% yield as a mixture of diastereomers (*syn* : *anti* = 4 : 1) and with 96% ee for the major isomer **181**. The reaction showed excellent substrate scope and cycloalkenones of different ring sizes (5, 6, 8, 12, and 15) were competent and gave the products in modest yields but high selectivities. The authors investigated several 3-substituted cycloalkenones as substrates, and the vinylogous adducts were obtained in moderate to good yields (51–82%), high diastereoselectivities (96 : 4 to 99 : 1) and high enantioselectivities (98–99% ee).

The ability to overcome the inherent substrate-controlled diastereoselectivity of a reaction and enable the formation of other diastereomers is important.[97–100] A desirable outcome for this type of diastereodivergence is the identification of catalysts which can provide each diastereomer with high selectivity. Dixon and co-workers have designed bifunctional catalysts with structural units capable of strong and weak H-bonding interactions to activate the nucleophile in addition to a primary amine group which can form an iminium ion from the acceptor. A diastereodivergent Mukaiyama–Michael was identified as an optimal reaction to test the hypothesis (Scheme 44).[101]

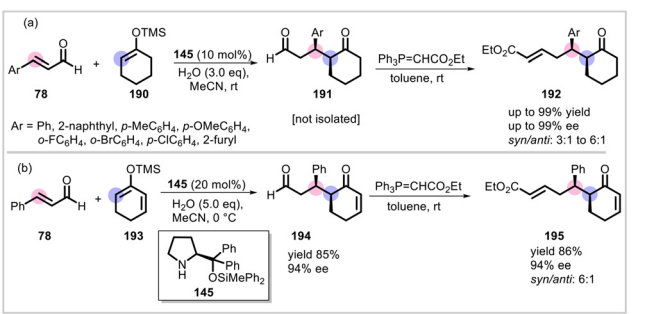
To establish optimal reaction conditions, the authors carried out detailed work on the Michael addition of γ-phenylbutenolide to 3-hepten-2-one using different catalysts.[101] The chemistry was then extended to M–M reactions between 5-substituted-2-OTBS pyrroles and enones (Scheme 44). The reaction of benzalacetone **78** (R^1 = Me, R^2 = Ph) with γ-methyl-*N*-Boc-2-(*tert*-butyldimethylsilyl)oxypyrrole **185** (R^3 = Me) was performed using a bifunctional amine/sulfonamide catalyst **139** capable of forming strong H-bonding with the nucleophile and an iminium ion with the electrophile. Under optimal conditions (20 mol% catalyst and 40 mol% *N*-Boc tryptophan as a co-catalyst in DCM at 40 °C), the reaction gave predominantly the *anti* diastereomer (5 : 1 *anti* : *syn*) in 75% yield and 98% ee. The reaction showed good scope for both components and gave *anti* products (1.2 : 1 to 7 : 1 *anti* : *syn*) in modest yields (38–64%) with high enantioselectivites (94–98% ee). In contrast, the same substrates with a bifunctional primary amine-thiourea catalyst derived from a cinchona alkaloid was able to provide the *syn* diastereomer selectively. The reaction (20 mol% catalyst, 20 mol% benzoic acid as a co-catalyst in DCM at 40 °C) showed good substrate scope and gave the *syn* isomer (1.2 to 13 : 1 *syn* : *anti*) in modest to good yields (48–72%) and high enantioselectivities (91–96% ee).

3.2. Prolinol-based catalysts

Proline and its derivatives are another class of organocatalysts with broad applications in organic synthesis.[102,103] Diarylprolinol silyl ether catalysts show promise in both enamine and iminium ion reactions.[104,105] A variety of silyl enol ethers have successfully been used in Mukaiyama–Michael reactions. One class which has received sparse attention is that of cyclic enol and dienol silyl ethers. Hayashi and co-workers have conducted a detailed study on the asymmetric catalytic M–M reaction between α,β-unsaturated aldehydes **78** and silyl enol ether of cyclic ketones **190** using diphenylprolinol silyl ether **145** as a catalyst (Scheme 45).[106] Reactions of 1-silyloxycyclohexene with several α,β-unsaturated enones gave addition products in high yield and selectivity using catalyst **145** (10 mol% **145** in MeCN and 3 eq. of H_2O at rt): 85–97% yield, *syn* : *anti* = 2 : 1 to 6 : 1, 96–99% ee. Reactions with enol silyl ethers derived from cyclopentanone and cycloheptanone also gave products in high yield, modest diastereoselectivity and high enantioselectivity. Reaction of the more labile silyl dienol ether of cyclohexenone **193** (3 eq.) with cinnamaldehyde **78** using the prolinol catalyst **145** (20 mol%, in MeCN with 5 eq. of H_2O) gave the product in 85% yield as a mixture of diastereomers (*syn* : *anti* = 6 : 1) and 94% ee. The reaction showed good substrate scope for the aldehyde and gave products in high yields and high enantioselectivities.



Scheme 44 Catalyst controlled diastereoselectivity in the Mukaiyama–Michael reaction.

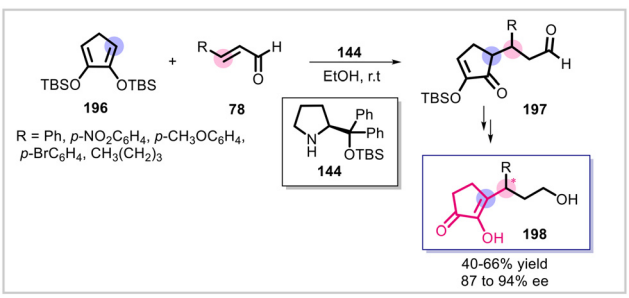


Scheme 45 Asymmetric Michael reactions of α,β-unsaturated aldehydes and silyl enol ethers derived from cyclic ketones.

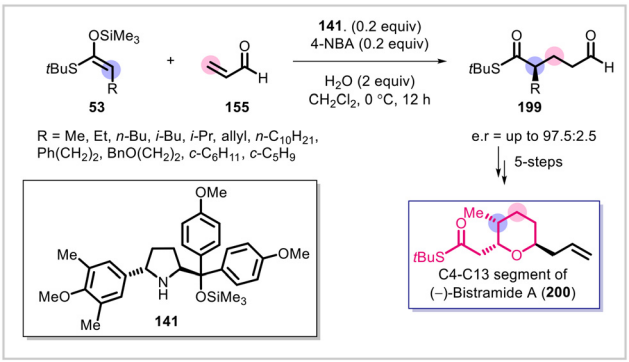
Lopp and co-workers investigated the M–M reaction between cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether **196** with α,β-unsaturated aldehydes **78**.[107] The products **197** were converted to the alcohol **198** (R = Ph) for ease of analysis and reproducibility (Scheme 46). A variety of catalysts were evaluated, and catalyst **144** (10 mol%) proved to be optimal. A protic solvent was required and ethanol at room temperature gave the best results. Under the optimal conditions using cinnamaldehyde as the acceptor, the product **197** (R = Ph) was formed in 54% yield with 92% ee. Reactions with different acceptors were also investigated, which gave products in modest yields but with high selectivity.

Pihko and co-workers have developed several organocatalyst mediated M–M reactions. In continuation of their work with acrolein as an acceptor, they investigated the addition of silylketene thioacetals using amine catalysts.[108] Initial screening with different catalysts (2,5-diphenylpyrrolidine, Hayashi–Jørgensen-type catalysts, and second generation MacMillan catalyst) under well-established protocols gave the product in modest enantioselectivity. To improve face selectivity, the authors prepared new pyroglutamic acid derived 2,5-disubstituted pyrrolidines (with 3 points of structural variation) as potential iminium catalysts. The M–M of **53** and acrolein **155** using the newly designed iminium catalysts (15 different variants) showed that catalyst **141** was optimal, providing the product **199** (R = Me) in 90% ee. A variety of alkylated silyl ketene thioacetals were compatible and gave products in high enantiomeric purity (up to 97.5 : 2.5 er). This approach enabled access to chiral thioesters, amides, aldehydes, and ketones bearing an α-methyl stereocenter with excellent enantioselectivities, and allowed rapid access to the C4–C13 segment of (−)-bistramide A **200** (Scheme 47).

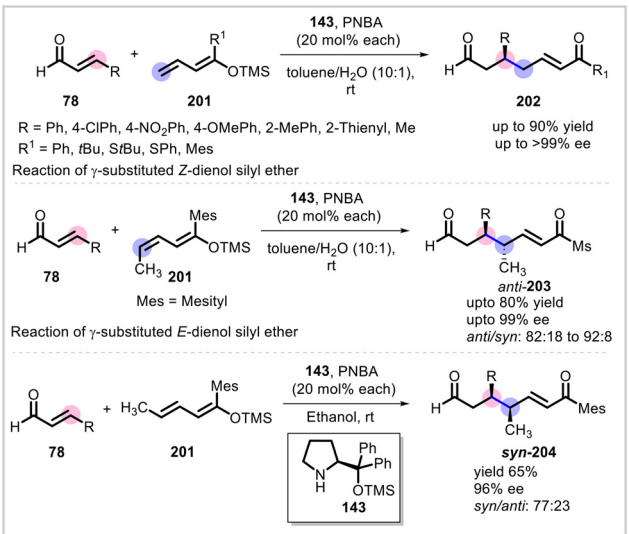
Acyclic dienol silyl ethers are interesting nucleophiles for M–M reactions. They have two sites for reaction with an acceptor and thus controlling site and face selectivity becomes important. Schneider and co-workers investigated in some detail reactions of dienol silyl ethers with unsaturated aldehydes using chiral iminium catalysis.[25] Preliminary experiments investigated the addition of dienol silyl ethers or silylketene thioacetals (**201**) to crotonaldehyde (**78**, R = Me) using a catalyst (20 mol%), 2,4-dinitrobenzenesulfonic acid (20 mol%) in DCM/water (10 : 1) at 0 °C (Scheme 48). Second generation



Scheme 46 Organocatalytic M–M addition of cyclopentane-1,2-dione bis(*tert*-butyldimethylsilyl) enol ether with α,β-unsaturated aldehydes.



Scheme 47 Enantioselective synthesis of the C4–C13 segment of (−)-bistramide A using an M–M reaction promoted by a chiral pyrrolidine catalyst.



Scheme 48 Vinylogous M–M reactions catalyzed by a prolinol-based organocatalyst.

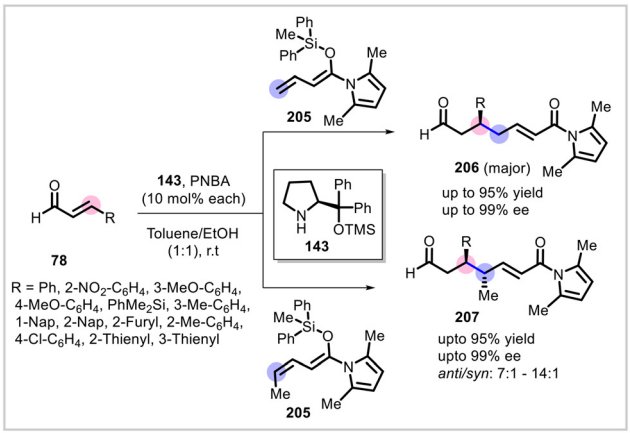
MacMillan catalyst with different silyl ethers gave the 1,4-addition product (**202**, R = Me) predominantly in modest yield and selectivity. In contrast, α,α-diphenylprolinol silyl ether **143** gave the γ-product **202** in 40% yield and 98% ee along with some 1,2-addition product. The optimal conditions were reactions using a dienol silyl ether with a sterically demanding mesityl group (**201**, R^1 = Mes) which partially blocks addition at the α-carbon and thus enhances the yield of the γ-product **202** (R = Me, R^1 = Mes, 74% yield and 99% ee). The method gave excellent results with a variety of α,β-unsaturated aldehydes (**78**, R = aryl, heterocyclic, alkyl, and trialkylsilyl), favoring the 1,4-addition product **202** (50–90% yield and 71–99% ee).

Reactions with stereochemically defined γ-substituted dienol silyl ethers with cinnamaldehyde (**78**, R = Ph) were also investigated: the dienol with 3*Z* configuration gave the *anti* vinylogous product *anti*-**203** (*anti* : *syn* = 92 : 8, 70% yield and 99% ee) and the dienol with 3*E* configuration gave the *syn* vinylogous product *syn*-**204** (*syn* : *anti* = 77 : 23, 65% yield and 96% ee).

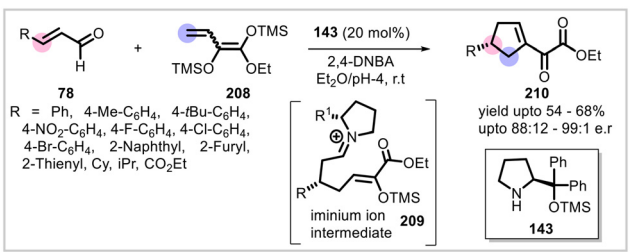
Schneider and co-workers extended their work on dienol silyl ethers to reactions of silyl dienol ether *N*,*O*-acetals **205** with α,β-unsaturated aldehydes **78** promoted by catalyst **143**, with a set of improved conditions including lower catalyst loading and enhanced substrate scope (Scheme 49).[109] Reactions with vinylketene silyl *N*,*O*-acetals bearing different silyl groups showed that a small TMS gave a mixture of γ and α products in nearly equal amounts, and the γ product was produced with very high enantioselectivity (95% ee). The optimal silicon substituent was the bulky diphenylmethylsilyl group, which gave the γ isomer (**206**, R = Ph) in 80% yield and 98% ee. The reaction was efficient with a variety of unsaturated aldehydes and gave the product in good yields (61–80% yield of the γ-product in 96–98% ee). Reactions with a γ-methyl-substituted dienolate (*Z*-isomer) with a variety of unsaturated aldehydes were also successful and gave the *anti* diastereomers (*anti* : *syn* = 7 : 1 to 14 : 1) in good yields (54–82%) and high enantioselectivities (96–99% ee).

The Schneider group also investigated M–M reactions with bis-silyl-1,3-dienediolate **208** as a nucleophile with unsaturated aldehydes **78** using iminium catalysis (Scheme 50).[110] Reaction of **208** with cinnamaldehyde using catalyst **143** (20 mol%) and 2,4-dinitrobenzoic acid (1 equiv.) as co-catalyst in EtOH/H_2O (pH 4) gave a cyclopentene (a γ 1,4 addition product) **210** along with minor amounts of the uncyclized 1,4-addition product. The cyclopentene was formed in good yield and high enantioselectivity (92% ee). This reaction can be viewed as an enantioselective [3 + 2]-cycloannulation of **208** with α,β-unsaturated aldehydes. The iminium ion **209** formed from the aldehyde and the catalyst undergoes a vinylogous Michael reaction with the dienediolate followed by a Knoevenagel-type condensation of the silyl enol ether and the intermediate iminium ion, resulting both in ring-closure and regeneration of the chiral catalyst. The reactions showed very good substrate scope, and a variety of unsaturated aldehydes (**78**, R = aryl, alkyl, and heterocyclic) were effective and gave the cyclopentene as a major product in good yields and high selectivities.

As part of a route to the ABCDE ring system of rubriflordilactone B, Xie and co-workers needed access to the M–M product of 5-substituted 2-silyloxyfuran **211** and α,β-unsaturated aldehyde **212** (Scheme 51).[111] Towards this end, they investigated the addition of 5-propargyl-2-OTBS furan with β-substituted acrolein **212**. Several catalysts (20 mol%) were screened along with 2,4-dinitrobenzoic acid as a co-catalyst (20 mol%) in DCM/H_2O. Proline, diphenylprolinol, a second generation MacMillan catalyst, and Hayashi–Jørgensen-type catalysts were screened and catalyst **143** gave the *anti* diastereomer (20 : 1) product in 68% yield and 97% ee. Interestingly, reaction with the (*Z*)-isomer of the aldehyde also gave the same *anti* diastereomer. The product butenolide **213** was transformed to the ABCDE ring system of rubriflordilactone B (**214**) in several steps.



Scheme 49 Enantioselective vinylogous M–M reactions using silyl dienol ether *N*,*O*-acetals, catalyzed by a prolinol-based catalyst.

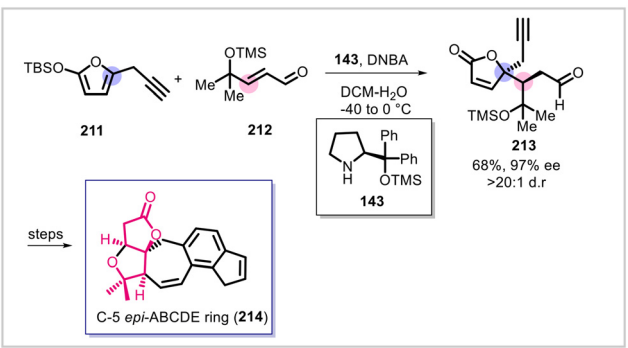


Scheme 50 [3 + 2]-Cycloannulations of a bis-silyl-1,3-dienediolate with enals.

3.3. MacMillan's imidazolidinone catalysts

The introduction of the concept of "iminium ion activation" by MacMillan[112] has had an enormous impact on the field of organocatalysis.[113,114] This area has seen tremendous growth in the past two decades. In recognition of his ground breaking contributions, MacMillan received the Nobel Prize in Chemistry in 2021. Macmillan introduced imidazolidinones,[115,116] compounds readily synthesized from amino acids, as catalysts for a variety of asymmetric transformations. Many of the imidazolidinones now known as 'MacMillan catalysts' are commercially available.

The MacMillan group, in 2003, reported the first enantioselective M–M reaction using imidazolidinone catalysts.[23] The



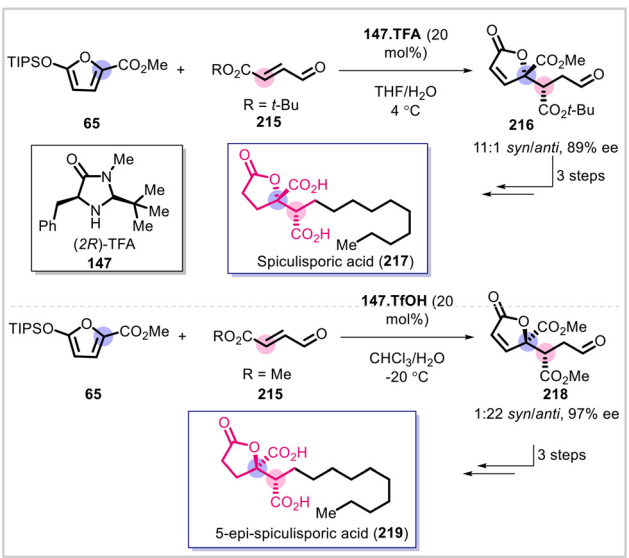
Scheme 51 Synthesis of the C5-*epi*-ABCDE ring of rubriflordilactone B.

authors examined the addition of silyloxy furan **65** to α,β-unsaturated aldehydes **215** using chiral imidazolidinones **147** to construct chiral γ-butenolides **216** (Scheme 52).

Preliminary studies using crotonaldehyde and 5-methyl-2-silyloxyfuran and catalyst **147** showed that the conjugate addition product was formed and no 1,2-addition product was observed (20 mol% of **147**, 20 mol% of dinitrobenzoic acid in DCM/H_2O at −60 °C). The reaction gave the butenolide product with excellent *syn* diastereoselectivity and enantioselectivity but in low yield. Addition of excess water improved the efficiency of the reaction by better catalyst turnover and gave the product in 84% yield, 22 : 1 *syn* : *anti* selectivity and 92% ee for the major isomer.

The reaction showed excellent substrate scope and a variety of unsaturated aldehydes (R = Me, Pr, i-Pr, Ph, CH_2OBz, and CO_2Me) underwent conjugate addition to furnish **216** in high yields (77–86%) and high selectivity (1 : 6 to 30 : 1 *syn* selectivity; 84–99% ee). Reactions with more highly substituted silyloxyfurans were investigated with crotonaldehyde as an acceptor. These reactions also worked well and gave the butenolide product in good yields and high diastereoselectivity.

During the reaction between crotonaldehyde and 5-carbomethoxy-2-OTIPS furan **65**, the authors noticed a change in diastereoselectivity depending on the nature of the acid additive. When **147**·TFA salt (20 mol%) was used, the *syn* isomer (6 : 1) was formed as the major product with 98% ee. Interestingly, when **147**·TfOH salt (20 mol%) was used as the catalyst, the *anti* isomer (7 : 1) was formed as the major product in 98% ee. Reaction of 3-*t*-butylcarboxylate-acrolein **215** with **65** using **147**·TFA salt (20 mol%, THF-H_2O) gave the *syn* product **216** (*syn* : *anti* = 11 : 1) in 89% ee. Reaction of **65** with 3-carboxymethylacrolein **215** using **147**·TfOH salt (20 mol%) gave the *anti* product **218** (*syn* : *anti* = 1 : 22) in 97% ee. Compound **216** was converted to spiculisporic acid[117–119] **217** in 3 steps in 54% overall yield. Similarly, compound **218** was converted to 5-*epi*-spiculisporic acid **219** over 3 steps.

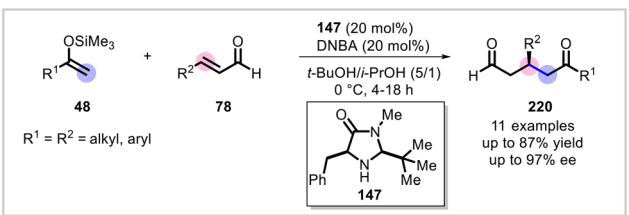


Scheme 52 Total synthesis of spiculisporic acid and 5-*epi*-spiculisporic acid.

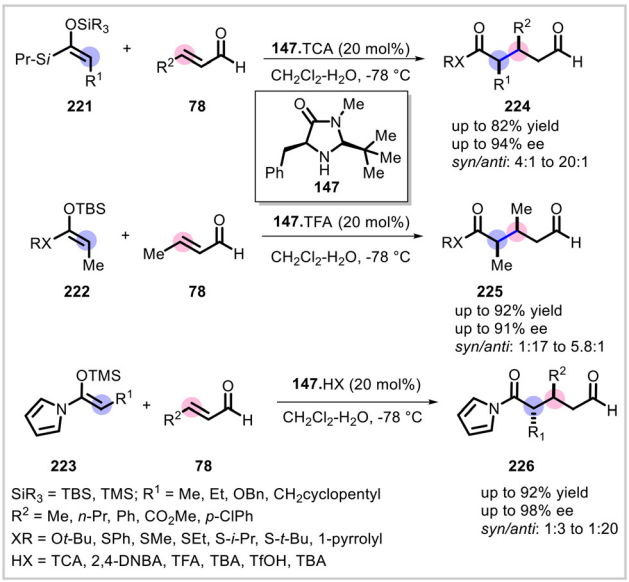
Wang *et al.* reported the organocatalyzed enantioselective M–M reaction of silyl ethers **48** and α,β-unsaturated aldehydes **78** using an imidazolidinone catalyst (Scheme 53).[120] Silyl enol ethers derived from methyl ketones are quite labile and not tolerant to highly acidic/aqueous conditions. Initial optimization studies examined the addition of an acetophenone-derived enol TMS ether to cinnamaldehyde using different amine catalysts (20 mol% catalyst, 20 mol% acid co-catalyst, solvent 0 °C or rt). Of the different catalysts investigated (imidazolidinones, proline, and 2-methylaminopyrrolidines), catalyst **147** proved optimal. Solvent and the nature of the acid co-catalyst also impact the reaction significantly. A solvent mixture of *t*-BuOH and i-PrOH (5 : 1 v : v) at 0 °C gave the best results. Of the different acid co-catalysts investigated, 2,4-dinitrobenzoic acid was the most effective. Under the optimal conditions, the 1,5-dicarbonyl product **220** was obtained in 75% yield and 90% ee. The reaction showed good scope for the acceptor as well as the nucleophile. A variety of enol silyl ethers and substituted acroleins were competent in the reaction and gave products in 56 to 87% yields and high enantioselectivity (85–97% ee).

MacMillan and co-workers have examined addition of *S*-alkyl (*Z*)-silyl enolethers to crotonates (Scheme 54).[121] These reactions furnished products **224** and **225** with good conversion, modest *syn* diastereoselectivity and high enantioselectivity. The S–i-Pr substituted silyl ketene thioacetal was optimal and gave the *syn* product (5.6 : 1) with high selectivity (90% ee). Interestingly, the *E*-silyl enolate of pyrrole amides gave the *anti* isomer (20 : 1) with good enantioselectivity (83% ee). A variety of substituted acroleins underwent conjugate addition with S–i-propyl TBS silyl ketene thioacetal (20 mol% **147**·TCA salt, DCM/H_2O, −78 °C) and gave the *syn* isomer (4 : 1 to 20 : 1) in good to high yields (50–82%) and high enantioselectivities (90–94% ee). Similarly, a variety of substituted acroleins reacted with the (*E*)-silyl enolate of pyrrole amide (20 mol% of **147**·HX, solvent/H_2O, −78 °C) and gave the *anti* isomer (3 : 1 to 20 : 1) in high yields (55–92%) and high enantioselectivities (83–98% ee). Thus, both diastereoisomeric products can be accessed with high selectivity.

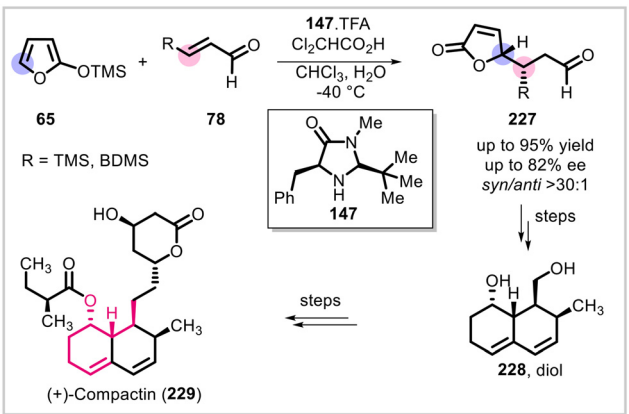
Robichaud and co-workers described the synthesis of compactin[122] using a key building block prepared from an enantioselective M–M reaction (Scheme 55).[123] The authors explored two β-silylacroleins in enantioselective M–M reaction using



Scheme 53 Iminium catalysis approach to 1,5-dicarbonyl compounds.



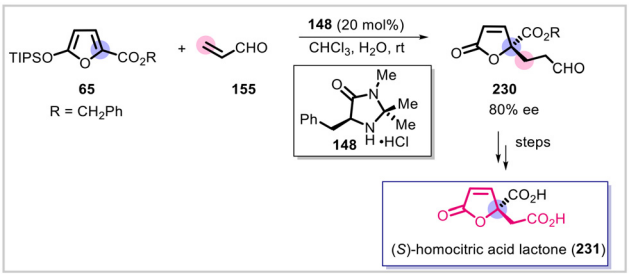
Scheme 54 Synthesis of *syn* and *anti* 1,5-dicarbonyl compounds.



Scheme 55 Synthesis of (+)-compactin *via* iminium ion catalysis.

MacMillan's catalyst. Addition of 2-OTMS furan **65** to 3-(trimethylsilyl)acrolein **78** (R = TMS) using catalyst **147** gave the *syn* isomer of **227** (R = TMS) in 95% yield and 82% ee. Reaction with 3-(benzyldimethylsilyl)acrolein was less successful and gave the *syn* product in 70% ee. Compound **228** was elaborated to **229** over several steps.

Pansare and co-workers investigated the M–M reaction of 5-substituted-2-silyloxyfuran **65** with acrolein to obtain a key intermediate for the synthesis of homocitric acid lactone (Scheme 56).[124] Reaction optimization using different catalysts showed that the 1st generation MacMillan catalyst (**148**) gave the best results. The ester substitutent in the nucleophile had a significant impact on reaction outcome. Reactions with the methyl ester (R = Me in **65**) afforded inferior results, giving the product in 24% yield and 73% ee, whereas reaction with the benzyl ester gave the product in 38% yield and 80% ee. This

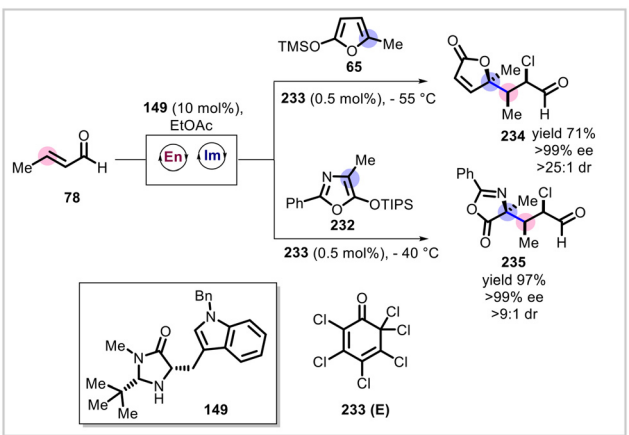


Scheme 56 Organocatalyzed synthesis of a butenolide intermediate *en route* to (*S*)-homocitric acid lactone.

intermediate was elaborated to (*S*)-homocitric acid lactone **231** in a few steps.

MacMillan and co-workers have shown that the M–M reaction can be part of a cascade. In this process two different catalytic cycles are integrated seamlessly, thus improving the overall efficiency of the process. The MacMillan catalyst can activate enones to form an iminium ion which undergoes the designed reaction with a nucleophile, and after completion the catalyst is released to provide a saturated aldehyde. The product then forms an enamine with the catalyst which can then react with an electrophile to provide the final product. The reactions can be conducted with all components from the beginning or sequentially by adding the electrophile after the completion of the first reaction. To obtain high enantioselectivity for the product, the stereochemistry in the second step should be under catalyst control, not under substrate control.

An example of effective cascade catalysis was demonstrated by MacMillan by conducting M–M reaction followed by trapping with a chlorine electrophile using optimized conditions developed for a Friedel–Crafts alkylation/chlorination cascade (Scheme 57).[125] The M–M reaction was conducted by mixing 5-methyl-2-OTMS, crotonaldehyde, the catalyst (2*S*,5*S*)-5-(1-benzyl-1*H*-indol-3-yl)-2-*tert*-butyl-3-methyl-imidazolidin-4-one



Scheme 57 Enantioselective organocatalytic cascade reactions of silyloxyfurans and α,β-unsaturated aldehydes.

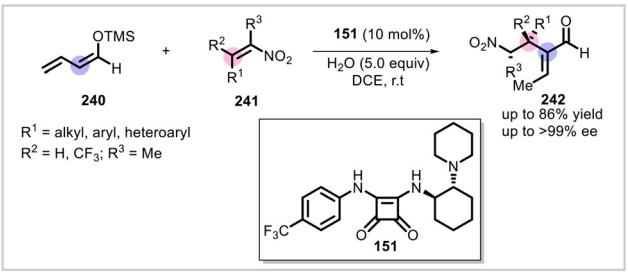
(10 mol%), TFA (10 mol%) as a co-catalyst, and the electrophile 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one in ethyl acetate at −55 °C. A sequential reaction (addition of the electrophile after consumption of the silyloxy furan) gave the product in higher yield of 71% as the *syn* isomer (>25 : 1 *syn* : *anti*) with high enantioselectivity (>99% ee). A similar reaction but using 4-methyl-2-phenyl-5-(triisopropylsilyloxy)-1,3-oxazole as the nucleophile and (2*R*)-2-*tert*-butyl-3-methyl-imidazolidin-4-one TCA salt as the catalyst gave the *syn* diastereomer (9 : 1) in 97% yield and >99% ee.

MacMillan and co-workers have extended their cascade catalysis to reactions which involve three independent catalytic cycles (Scheme 58).[126] The first step of this cascade is a cross metathesis reaction followed by a conjugate addition using iminium catalysis and the final step is an electrophile incorporation using an enamine reaction. For the iminium ion catalysis a second generation MacMillan catalyst is used and proline carries out the enamine catalysis. The cascade process using 5-hexene-2-one **236**, crotonaldehyde **78** and siloxyfuran **65** led to the formation of butenolide **238** with four contiguous chiral centers in 64% yield as 5 : 1 diastereomeric mixture with 95% ee. This cascade catalysis strategy was successfully applied to the total synthesis of (−)-aromadendranediol **239** *via* intermediate **238**.

3.4. Squaramides

Depending on its structure a typical catalyst used for organic transformations generally activates either the donor or the acceptor but rarely both. Hydrogen bonding catalysts (thioureas) have the ability to interact with both donor and acceptors and thus provide a pathway for bifunctional catalysts.[127,128] Unlike the single activators, the levels of activation with H-bond catalysts are generally modest.

In 2017, Alemán and co-workers demonstrated the synthesis of Rauhut–Currier type esters using squaramide bifunctional organocatalysts (Scheme 59).[84] Their initial working hypothesis, based on literature reports, was that the urea functionality could activate the acceptor and a basic site in the catalyst could activate an enol silyl ether by interaction with



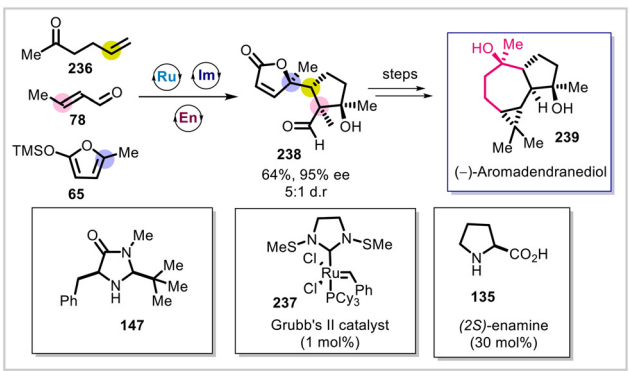
Scheme 59 Rauhut–Currier reaction under bifunctional organocatalysis.

the silicon group. They investigated the reaction between nitroalkenes and dienol silyl ethers with the goal of altering the favored 1,4-selectivity to a 1,2 pathway. Towards this end the addition of dienol silyl ethers to nitrostyrenes was performed using different catalysts. Thioureas derived from cinchona alkaloids gave the 1,2-addition product in low yield and low selectivity. Similarly, Takemoto's catalyst gave improved yields and ee. Use of a bifunctional squaramide catalyst **151** (10 mol%) in DCE/H_2O gave the 1,2-addition product in quantitative yield and 99% ee. The reaction shows good scope for both the nitroalkene and the dienol silyl ether. The products are formed in high yields and selectivity. Interestingly, a β,β-disubstituted nitroalkene **241** underwent 1,2 addition in high yield and selectivity. The authors did control experiments and DFT calculations, which suggested that the secondary amine activates the nucleophile and the protonated tertiary amine activates the nitro group.

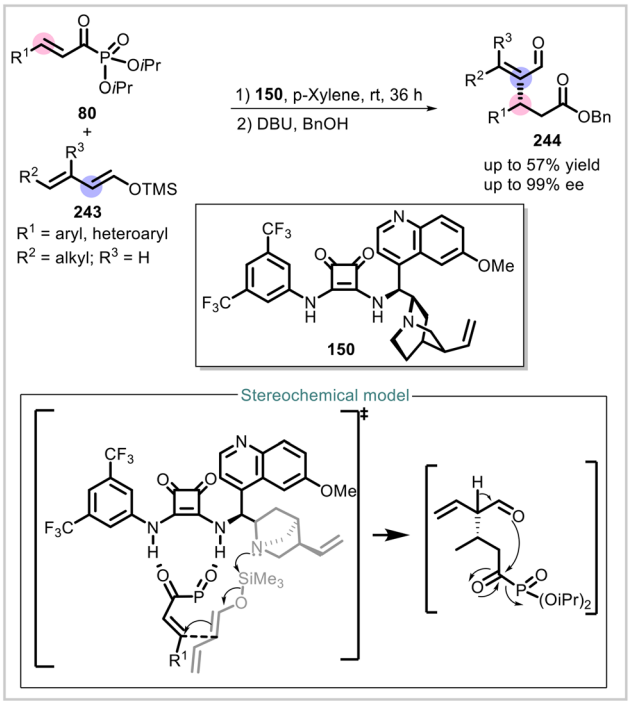
One year later, the same group investigated the addition of dienol silyl ethers **243** to ketophosphonates **80** using squaramide-derived catalysts (Scheme 60).[85] The authors carried out preliminary experiments with a dienol TMS ether ($R^2 = R^3 = H$) to a cinnamoyl ketophosphonate using different bifunctional catalysts (10 mol%) at rt. Of the different catalysts screened, a squaramide with an aminoquinine substituent gave the 1,2-addition product **244** in 57% yield and 97% ee. The reaction shows excellent substrate scope for the β-substituent of the acceptor as well as the substituted dienol silyl ether. The products were obtained in low to modest yields but with high selectivity. The authors propose that the quinuclinide nitrogen of the catalyst initiates the addition to the substrate activated by hydrogen bonding.

3.5. Cinchonidinium catalysts

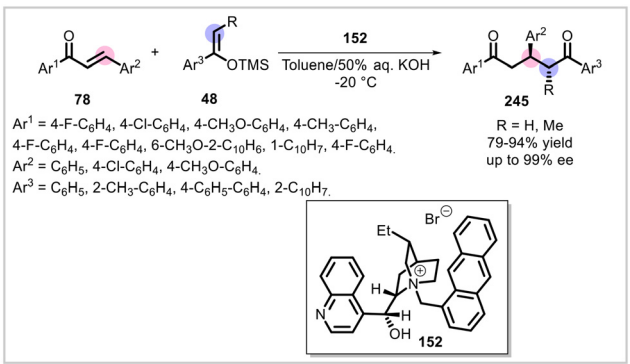
Chiral phase transfer reagents are another well investigated class of catalysts.[129] They are readily accessed and participate in a variety of asymmetric tranformations.[129] One feature of some phase transfer catalysts is that they can also participate as bifunctional catalysts.[129] Corey and co-workers investigated the use of chiral phase transfer catalysts for M–M reactions (Scheme 61).[130] The addition of the enol silyl ethers of aryl methyl ketones **48** to chalcones **78** was investigated using *N*-(9-anthracenylmethyl)dihydrocinchonidinium salt **152** as catalyst



Scheme 58 A three-catalyst cascade reaction, synthesis of (−)-aromadendranediol.

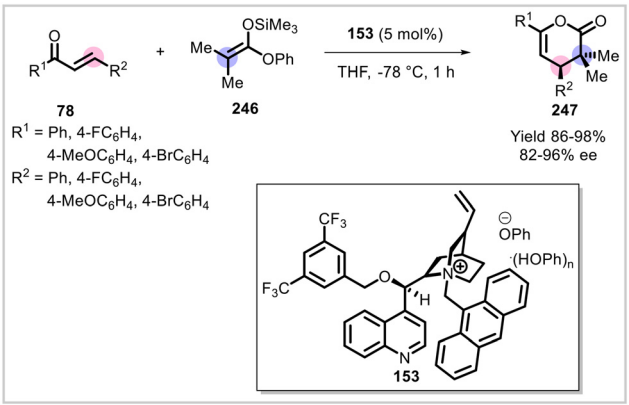


Scheme 60 Mukaiyama–Michael addition to acylphosphonates under bifunctional catalysis.



Scheme 61 Quaternary cinchonidinium salt catalyzed enantioselective M–M reaction.

in toluene/50% aqueous KOH at −20 °C. The reaction showed broad substrate scope and gave the 1,5-dicarbonyl product in high yields (80–92%) and high enantioselectivities (92–99% ee). Reactions using (*Z*)-1-phenyl-1-(trimethylsilyloxy)-1-propene with chalcones were also successful. The reaction furnished *anti* diastereomer predominantly (3 : 1 to 20 : 1 *anti* : *syn*) in good to high yields (65–82%) and with high enantioselectivities (92–99% ee). In these types of reactions, the counterion of the catalyst (or an additive) removes the silicon group and the resulting enolate forms a chiral complex with the catalyst. Depending on the catalyst, the OH group in **152** can potentially coordinate and activate the acceptor.



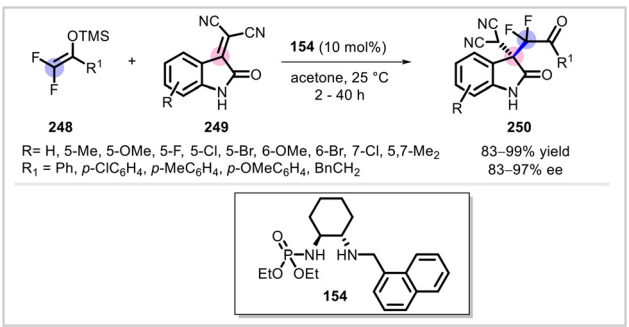
Scheme 62 Domino Michael addition and lactonization.

In 2007, Mukaiyama and co-workers screened a series of new cinchona-derived chiral quaternary ammonium phenoxides **153** in domino Michael addition and lactonization of α,β-unsaturated ketones **78** and ketene silyl acetal **246** (Scheme 62).[131] This approach furnished optically active 3,4-dihydropyran-2-one derivatives **247** in high yield (86–98%) and enantiomeric excess (up to 90%). Furthermore, the authors described the unique relationships between the structure of the catalyst and the absolute stereochemistry in this asymmetric domino reaction.

3.6. Lewis basic catalyst for nucleophile activation

Of the different methods for activation in M–M reaction, most of them have focused on the activation of the acceptors and there are limited number of examples where the nucleophile is activated by the chiral catalyst.

Zhou and co-workers have designed catalysts derived from *trans*-1,2-diaminocyclohexane in which one of the amino group is converted to a phosphoramide and the other alkylated to generated a secondary amine.[86] The working hypothesis was that the secondary amine can selectively activate enol silyl ethers and the phosphoramide can activate the acceptor by hydrogen bonding. The authors screened a series of chiral secondary amine phosphoramide catalysts for the enantio-



Scheme 63 Enantioselective M–M addition with Lewis base activation of the nucleophile.

selective M–M reaction between difluorinated enol silyl ethers **248** and isatylidene malononitriles **249** (Scheme 63). These experiments demonstrated that the conjugate addition is quite effective and provided the product, which contains an all carbon quaternary center, in high yields and high enantioselectivities. The reaction showed good scope for both the nucleophile as well as the acceptor to provide compounds **250** (yield up to 99%, 97% ee) using **154** as catalyst.

This method was also efficient with monofluorinated enol silyl ethers derived from α-fluoroindanone and benzofuranone, affording the corresponding M–M products with adjacent and/or fully substituted carbon stereocenters in excellent enantioselectivity.

4. Conclusion

The literature examples presented in this review highlight the wide variety of catalysts that have been employed for enantioselective Mukaiyama–Michael reactions. These catalysts include both chiral Lewis acids and organocatalysts, which are broadly complementary to each other in their mechanistic function and scope of compatible substrates. Most enantioselective catalytic methods using either mode of catalysis involve activation of the electrophile, but a few organocatalytic methods proceed *via* activation of the nucleophile. A general limitation common to both Lewis acid catalyzed and organocatalytic methods is that catalyst loadings at or above 5 mol% are often employed. However, several methods[2,5,13,52,76,81,83] have used lower catalyst loadings, and imidodiphosphorimidate catalysts are particularly notable in this respect, providing good catalytic activity even when used in quantities down to 0.1 mol%.[82]

Yield, enantioselectivity, and diastereoselectivity in Mukaiyama–Michael reactions can be strongly affected by multiple reaction parameters, including not only the catalyst but also additives, solvent, and temperature. Notably, hexafluoroisopropanol (HFIP),[21,52] pentafluorophenol (PFP),[50] and 2,6-diisopropylphenol[55–57] have been employed as additives in chiral Lewis acid catalyzed reactions. In organocatalyzed reactions involving iminium ion formation, acids (4-nitrobenzoic acid,[25,87–90,94,108,109] trifluoroacetic acid,[23,93,121,123] trichloroacetic acid,[96,121] benzoic acid,[101] 2,4-dinitrobenzoic acid,[110,111,120,121] *p*-toluenesulfonic acid,[23,121] and dichloroacetic acid[123]) have commonly been used as co-catalysts, and water has typically been added to accelerate turnover of the amine catalyst.

Enantioselective Mukaiyama–Michael methods feature significant structural diversity in electrophiles, encompassing variously substituted acyclic α,β-unsaturated substrates as well as cyclic substrates such as cyclopentenone- and cyclohexanone-based compounds. A notable limitation in electrophile scope is that few β,β-disubstituted α,β-unsaturated electrophiles have been used. The nucleophiles employed in enantioselective Mukaiyama–Michael reactions also exhibit considerable variation in structure (though less so than the electrophiles), including various acyclic silyl enol ethers, acyclic silyl dienol ethers, acyclic silyl ketene acetals, and silyloxyfurans.

Development of new enantioselective Mukaiyama–Michael methods holds promise for addressing limitations of existing methods. New methods using low catalyst loadings and inexpensive or easily accessible catalysts would improve the general practicality of the transformation. Additional methods for Mukaiyama–Michael reactions of β,β-disubstituted α,β-unsaturated electrophiles could provide new ways of constructing all-carbon quaternary centers in an enantioselective manner. Likewise, methods accommodating nucleophiles with greater structural diversity may expand the potential synthetic applications of the transformation.

The Mukaiyama–Michael reaction stands out as a versatile transformation that can yield products with vicinal stereocenters or all-carbon quaternary centers. The high degree of structural complexity that can be achieved has made the transformation an important strategy in the total synthesis of natural products. Numerous natural products have been synthesized with the aid of enantioselective Mukaiyama–Michael methodology. Against the backdrop of established methods and synthetic applications, the Mukaiyama–Michael reaction remains a promising subject for future research, offering opportunities to facilitate the construction of challenging synthetic targets.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No data is available for this document.

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