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Alkylidene β-Ketoesters in Asymmetric Catalysis: Recent Developments

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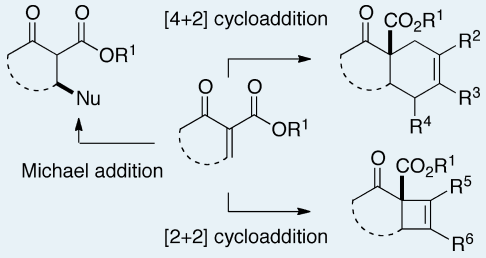
ABSTRACT: Although alkylidene β-ketoesters have been known since the beginning of the 20th century, they have only recently attracted the attention of the synthetic organic community. In these versatile electrophiles, the enone double bond is strongly polarized because of the presence of the ester moiety as a second electron-withdrawing group. The resulting increase in reactivity has recently opened the way to a number of challenging transformations in the field of enantioselective catalysis, but is also responsible for their high sensitivity toward acids, bases, and high temperature, which hampered their application in organic synthesis for a long time. The saturated β-ketoester moiety generated in these reactions has been used for diverse functionalization reactions, some of which lead to quaternary stereocenters. This perspective highlights the origins of alkylidene β-ketoester chemistry and focuses on recent developments of the quickly evolving field of asymmetric catalytic reactions of these substrates. After their general properties and preparations, recent developments are discussed, which mainly involve cycloaddition and conjugate addition reactions. A special class of unsaturated β-ketoesters, ester-substituted divinyl ketones, has been used in Nazarov cyclization reactions.



KEYWORDS: *asymmetric catalysis, β-ketoesters, bidentate ligands, Lewis acids, Michael addition, Diels–Alder, cycloaddition, Nazarov cyclization*

INTRODUCTION

As a general substrate class, β-ketoesters are synthetically important as they give access to quaternary stereocenters, which are present in numerous natural products and biologically relevant molecules.[1−10] However, these are particularly challenging targets for enantioselective catalytic reactions because of the steric repulsion between the carbon substituents. Saturated β-ketoesters are among the most exploited substrates to achieve the asymmetric formation of quaternary stereocenters, mostly via enolate chemistry as nucleophiles in Michael addition reactions, as selected, recent examples from our[11,12] and other groups show.[13−16] In principle, alkylidene β-ketoesters have even more potential than their saturated analogues, as they can form up to two quaternary stereocenters diastereoselectively in one step.[17,18] However, they have been scarcely applied in organic synthesis for a long time and have become only recently increasingly popular, especially in stereoselective catalysis.

In general, the enantioselective formation of carbon stereocenters is a very important goal for the synthesis of biomolecules, as two different enantiomers of the same molecule can have a very different effect in biological systems. The use of catalytic methods to achieve this goal is preferential to the use of chiral auxiliaries because small amounts of the chiral catalyst can produce large amounts of the chiral product and no additional steps are required for the removal of the chiral auxiliary.[7] This feature makes a catalytic reaction more atom- and time-efficient. Moreover, both enantiomers of a product are commonly available by using the two different enantiomeric forms of the catalyst. Usually, this target cannot be achieved by using chiral auxiliaries or enzyme chemistry, as they generally derive from nature and thus are only available in one enantiomeric form. These advantages have made catalytic enantioselective reactions one of the most dynamic aspects of chemistry today.[19−21]

The scarcely exploited synthetic potential of alkylidene β-ketoesters in asymmetric catalysis provided the motivation for this perspective. First, we will discuss the special properties of alkylidene β-ketoesters, which explain in part the slow progress on this field, and present different methods for their preparation. The following section gives some background on early, mostly nonstereoselective reactions of alkylidene β-ketoesters, after which we discuss recent developments that increasingly involve asymmetric catalysis.

GENERAL PROPERTIES OF UNSATURATED β-KETOESTERS

Because of the possibility of separately addressing four different reactive sites, β-ketoesters are versatile synthetic building blocks in organic chemistry (Chart 1, a). The most exhaustive review on the topic[22] describes a large number of different reactions that illustrates the diverse and thoroughly explored applications of saturated β-ketoesters. Therein, the unsaturated analogues are barely mentioned and have not been subject to any review

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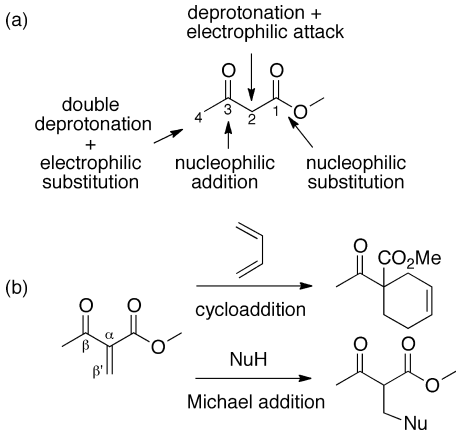
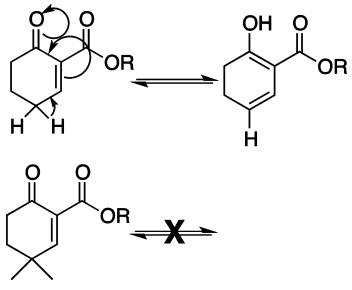
Chart 1. Reactive Sites of the β-Ketoester Moiety



articles since. This feature may be surprising, as alkylidene β-ketoesters are promising dienophiles in Diels–Alder chemistry as alternatives to the widely used α,β-unsaturated imides and α,β-unsaturated aldehydes,[23,24] and because they extend the broad portfolio of β-ketoester reactivity to nucleophilic addition onto the β′-position and cycloaddition (Chart 1, b). However, the use of alkylidene β-ketoesters has been restricted to a few specialized research fields because bulky alkylidene β-ketoesters tend to polymerize[25] and undergo significant keto–enol tautomerism.[26]

The strong polymerization tendency under acidic, basic, or high temperature conditions derives from the additional polarization of the enone by the ester moiety,[25] as reflected by the large deshielding of the vinyl proton, which generally appears at about δ 8.0 in the ^{1}H NMR spectrum. The polymerization tendency renders the isolation of these compounds difficult. In fact, they are usually not stable toward column chromatography and partially decompose at the elevated temperatures necessary for their distillation. However, if the distillation is rapidly performed under high vacuum, the purification of alkylidene β-ketoesters is relatively straightforward. The problem of keto–enol tautomerism has been avoided for a long time by using γ-*gem*-dialkyl substituted alkylidene β-ketoesters, which can no longer undergo this rearrangement (Scheme 1).[27,28] However, this approach limits

Scheme 1. Keto-Enol Tautomerism in Alkylidene β-Ketoesters



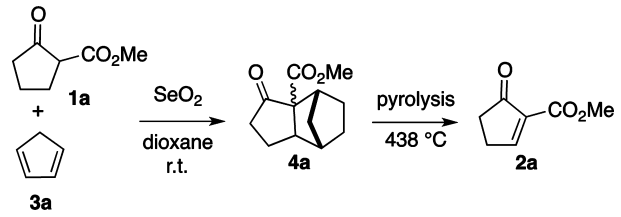
the synthetic applicability of the reaction products, as it is usually not possible to remove the geminal alkyl groups at a later point of the synthesis.

Besides the drawbacks mentioned above, alkylidene β-ketoesters offer many advantages. The strongly polarized double bond undergoes reactions that do not proceed with standard enones (see below). Moreover, the use of alkylidene β-ketoesters in enantioselective reactions avoids many of the problems associated with other conjugate electrophiles like acroleins, α,β-unsaturated ketones, and acrylates. In fact, as the ester moiety acts as an additional coordination site, unsaturated β-ketoesters are ideally suited as chelating ligands for catalysts with two adjacent coordination sites. The chelate formation improves the regioselectivity of substrate binding to the catalyst, which is a delicate issue with α,β-unsaturated ketones, as both sides of the carbonyl moiety are usually sterically and electronically very similar.[29] Moreover, the enone conformation is constrained to *s-trans*, which greatly simplifies mechanistic considerations counting on a defined organization of the dienophile in the transition state. For example, in Diels–Alder reactions, the exclusion of different conformers (s-cis or s-trans) avoids the sometimes elusive assumption of Curtin-Hammett conditions that is required when the stereochemical outcome does not match the expectations derived from the model of the catalyst-substrate adduct.[30]

SYNTHESIS OF ALKYLIDENE β-KETOESTERS

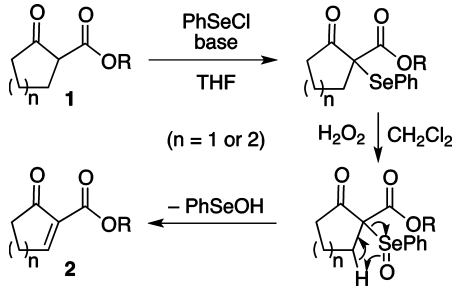
The first preparation of an unsaturated β-ketoester was reported in 1909 by Koetz and involved the elimination of hydrogen bromide from an α-bromo β-ketoester.[31] Another early example is the oxidation of 2-methoxycarbonyl cyclopentanone (**1a**) with selenium dioxide.[25] Because of the strong tendency toward polymerization, a pure sample of the unsaturated β-ketoester **2a** was only obtained by trapping with cyclopentadiene (**3a**) and subsequent pyrolysis of the Diels–Alder product **4a**, during which **2a** was isolated by condensation (Scheme 2).

Scheme 2. Early Preparation of Unsaturated β-Ketoester 1a[25]



Since then, the most widely applied method has become the selenide oxidation-elimination reaction, whose first step is a derivatization of a saturated β-ketoester (**1**) in the α-position by phenyl selenyl chloride in the presence of a base (Scheme 3).[32–34] In a common procedure, the β-ketoester is

Scheme 3. Preparation of Alkylidene β-Ketoesters (2) by the Selenide Oxidation-Elimination Reaction[32–34]



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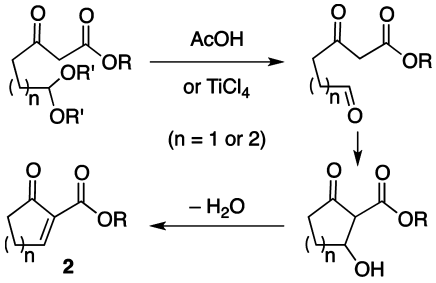
deprotonated with sodium hydride[32] or lithium diisopropylamide (LDA),[33] and the resulting enolate is quenched by the selenium reagent. Alternatively, pyridine is added directly together with phenyl selenyl chloride to give an activated, more electrophilic intermediate that readily reacts with the non-deprotonated form of the β-ketoester.[34] The second step is the oxidation of the phenyl selenyl group with hydrogen peroxide and the in situ *syn*-elimination of benzeneselenenic acid.

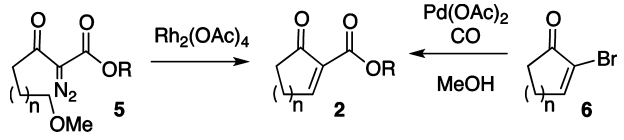
Also, β-ketoesters can be oxidized directly either by using $Pb(OAc)_4$ in the presence of catalytic amounts of $Cu(OAc)_2$[35] or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[36] but the reported yields are moderate at best. A further popular method is the Brønsted-[37] or Lewis acid-[38] catalyzed aldol condensation of a β-ketoester with an aldehyde (Scheme 4). The aldehyde can be introduced as an acetal group and deprotected in situ under the reaction conditions.

Scheme 4. Alkylidene β-Ketoester Preparation by Aldol Condensation[37,38]



Methods based on homogeneous catalysis have been scarcely explored. Examples thereof are the rhodium-catalyzed cyclization of diazo β-ketoesters **5** by C–H activation[39] and the palladium(II)-catalyzed coupling of 2-bromo-cyclopent-2-en-1-one (**6**) with carbon monoxide and methanol (Scheme 5).[40]

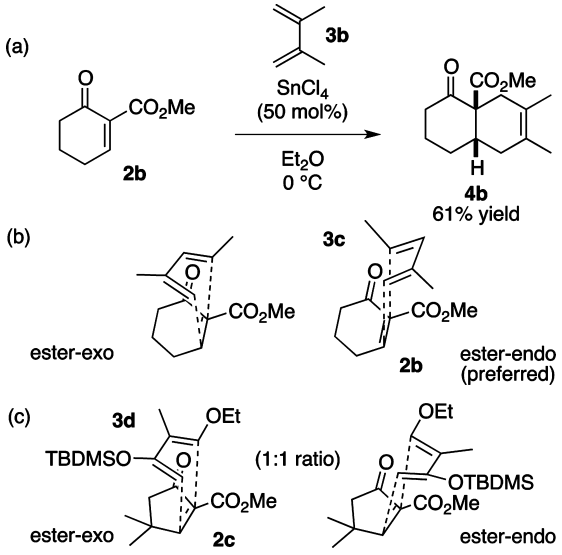
Scheme 5. Alkylidene β-Ketoesters by CH-Insertion and Carbonylation[39,40]



EARLY APPLICATIONS OF ALKYLIDENE β-KETOESTERS IN CATALYSIS

The first reactions featuring alkylidene β-ketoesters were [4 + 2] cycloadditions, as seen above in the early preparation of **2a**, which was trapped as the Diels–Alder product **4a** (Scheme 2).[25] The Diels–Alder chemistry of unsaturated β-ketoesters was thoroughly explored by Browne, who screened a broad variety of nonchiral Lewis acids for the reaction of cyclic alkylidene β-ketoester **2b** with 2,3-dimethylbutadiene (**3b**).[25,26,41] High catalyst loadings of $SnCl_4$ gave the best, but still only moderate, yield (Scheme 6, a). The reactions of unsaturated β-ketoesters that are not disubstituted in the γ-position were complicated by keto–enol tautomerization. Moreover, the strong Lewis acid $SnCl_4$ was reported to favor the decomposition of unsaturated β-ketoesters, which may also account for the moderate yields observed.[41]

Scheme 6. Diels–Alder Reaction on Cyclic Alkylidene β-Ketoester 2b and Transition States for 6- and 5-Membered Ring Substrates[25,26,41]



As for the stereochemical course of the reaction, Browne et al. discovered that alkoxycarbonyl cyclohexenones like **2b** usually react with dienes such as **3c** to give the ester-endo product (Scheme 6, b).[26] Reactions on the five-membered ring analogues were only performed with γ-*gem*-dimethyl-substituted derivatives such as **2c** (Scheme 6, c). Interestingly, no exo/endo selectivity was found in the reaction of this dienophile with (*E*)-*tert*-butyl((4-ethoxy-3-methylbuta-1,3-dien-2-yl)oxy)dimethylsilane (**3d**), although an unfavorable steric interaction would be expected between the two methyl groups of the cyclopentenone ring and the large silyloxy group of the diene in the ester-exo transition state.[41]

In 1997, Richardson and Welker reported a very elaborate approach to Diels–Alder reactions of alkylidene β-ketoesters based on stoichiometric diene-activation.[42] The highly electron-rich 2-cobaloxime-substituted 1-methylbuta-1,3-diene (**3e**) reacted with 2-ethoxycarbonyl-2-cyclohexen-1-one (**2d**, 4 equiv) in boiling tetrahydrofuran (THF) during 3 days to give the corresponding cycloaddition product **4c** in high yield and high ester-endo selectivity (Scheme 7).

As expected, the ester exo/endo selectivity changed toward the ester-exo product when the dienophile was the bulky *tert*-butyl-ester derivative **2e**. This selectivity is explained by the highly unfavorable interaction of the large *tert*-butyl group pointing toward the forming pericyclic ring in the ester-endo transition state. As both transition states are highly crowded, the reactivity was further reduced, and the yield dropped from 89% for the ethyl ester analogue **4c** to 60% for **4d**. Besides the lack of atom economy, a general problem of this approach is the necessity to remove the cobaloxime group from the Diels–Alder products **4c** and **4d** by using $AlMe_3$, which gave only moderate yields of **4e** and **4f**, and thus further diminished the overall yield of the protocol (62 and 38%, respectively).

Besides Diels–Alder reactions, early applications of alkylidene β-ketoesters are the [2 + 2] cycloaddition of alkynyl sulfanes and the Michael addition of heteroaromatic rings. For example, ethynyl(phenyl)sulfane (**7**) was used to prepare **8**, an intermediate in the synthesis of tricycloclavulone, an unusual prostanoid-related compound (Scheme 8).[43] The protocol is

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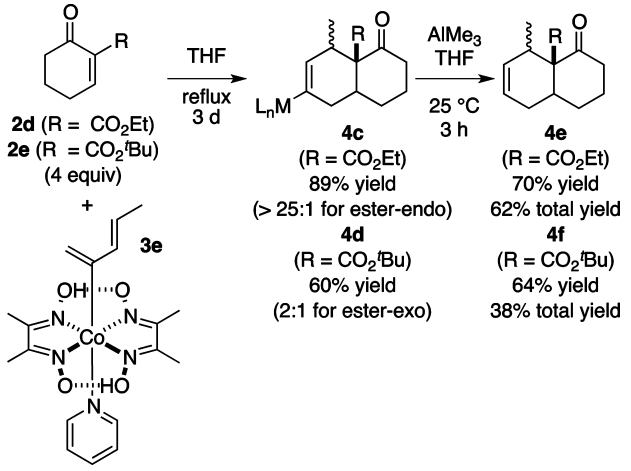
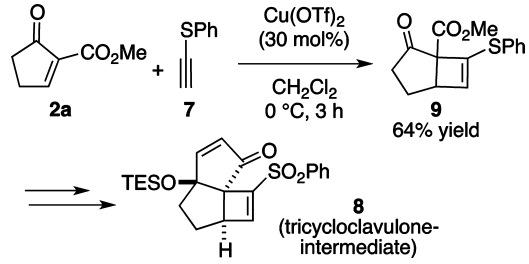
Scheme 7. Diene Activation Approach for Diels–Alder Reactions on Alkylidene β-Ketoesters[42]



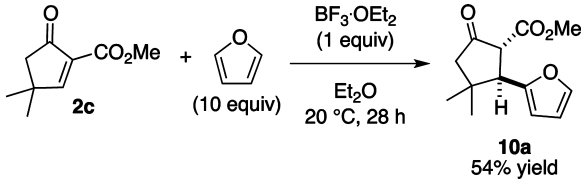
Scheme 8. [2 + 2] Cycloaddition Reaction with Ethynyl(phenyl)sulfane (7)[43]



not very efficient, as it features high catalytic loadings of copper(II) triflate (30 mol %), and gives moderate yields. The resulting [3.2.0]cyclohept-5-ene ring system **9** was subsequently transformed into the tricyclic system of the target molecule.

Heteroaromatic compounds can react with dienophiles in either Diels–Alder or Michael addition reactions. An example of the Michael addition of furan to γ-dimethyl substituted unsaturated β-ketoester **2c** was reported by Browne et al. in 1992 (Scheme 9).[41] Various Lewis acids were screened, and the

Scheme 9. Michael Addition Reaction with Furan[41]

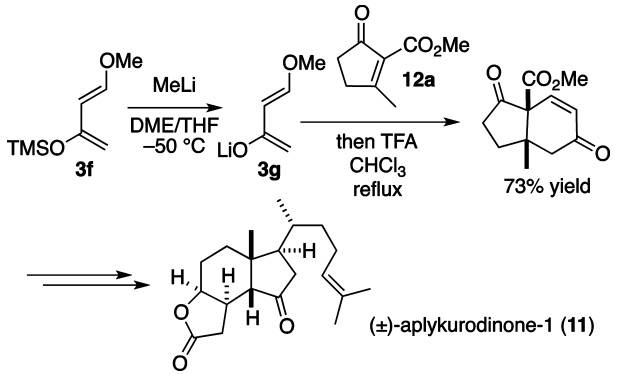


best results were obtained with stoichiometric amounts of $BF_3{\cdot}OEt_2$ over 28 h with a large excess of furan (10 equiv). However, even under these conditions, only a moderate yield of **10a** was obtained (54%). With stoichiometric amounts of $SnCl_4$, only substrate decomposition was observed, which shows that strong Lewis acids are not well suited for the generally sensitive unsaturated β-ketoesters. A recent example of this chemistry, the Michael addition of 2-(trialkylsilyloxy)-furans to cyclic enones and alkylidene β-ketoesters, will be discussed later.[44]

RECENT APPLICATIONS OF ALKYLIDENE β-KETOESTERS

Cycloaddition Reactions. As described in the previous section, alkylidene β-ketoesters have proven to be challenging substrates in cycloaddition reactions. This behavior is probably due to the sterically difficult generation of a quaternary stereocenter in the α-position of the β-ketoester, which seems to overcompensate the beneficial effect of the additional conjugation to the ester moiety. This effect is even more pronounced when the C–C double bond of the alkylidene β-ketoester is fully substituted, as recently demonstrated by Danishefsky during the synthesis of (±)-aplykurodinone-1 (**11**) (Scheme 10).[17] As two contiguous quaternary stereocenters

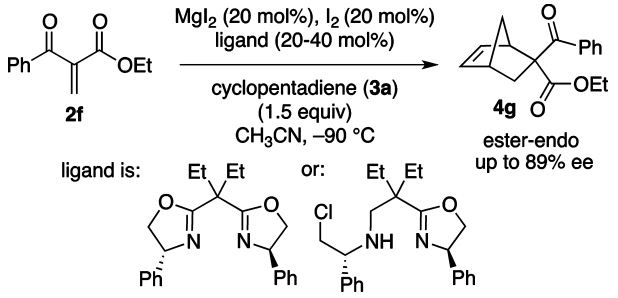
Scheme 10. Diels–Alder Reaction of Fully-Substituted Alkylidene β-Ketoester 12a[17]



had to be formed, the reaction of the tetrasubstituted enone **12a** with the highly reactive Danishefsky's diene (**3f**) was unsuccessful under a number of standard conditions. The nonenantioselective reaction proceeded only after generation of the extremely reactive lithium salt **3g**. It was not investigated whether the reaction is still a concerted [4 + 2] cycloaddition or a 2-step, double Michael addition reaction.[17]

Because of the intrinsic low reactivity of alkylidene β-ketoesters toward cycloaddition, the development of enantioselective reactions has been very slow.[45] Yamauchi et al. developed the first enantioselective Diels–Alder reaction of an unsaturated β-ketoester.[23] The catalytic system contained magnesium salts in combination with mono- or bisoxazoline ligands and employed ethyl 2-benzoylacrylate (**2f**) as dienophile, which is sterically less demanding than cyclic unsaturated β-ketoesters. The reaction with cyclopentadiene (**3a**) gave good yield and enantioselectivity, as well as excellent selectivity in favor of the ester-endo product **4g** (Scheme 11).

Scheme 11. First Enantioselective Diels–Alder Reaction of Alkylidene β-Ketoesters[23,24]



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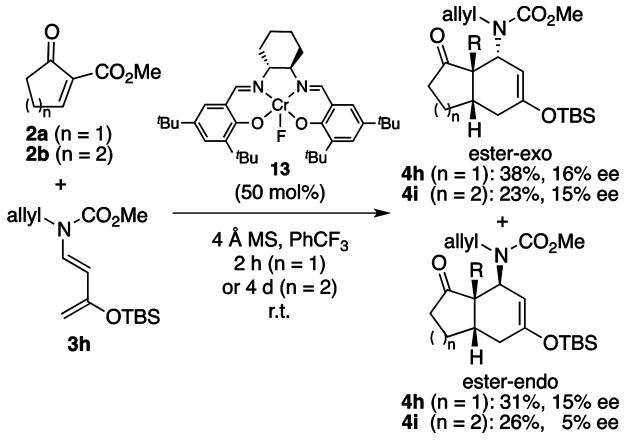
The drawbacks of the protocol are the high catalyst loading (20−40 mol % based on the ligands, as they are the most expensive component) and the necessity for extremely low temperatures (−90 °C) to achieve high enantioselectivity. Moreover, the fact that it was not possible to isolate a catalyst-substrate adduct for X-ray crystallography hinders the investigation of a possible transition state. However, calculations have been performed in a more extensive report on the system[24] that contained also a comparison to a titanium TADDOL catalyst, one of the most exploited systems for Diels−Alder reactions on chelating dienophiles.[30] However, this benchmark system is not suitable for unsaturated β-ketoesters, as only moderate yields, low enantio-, and poor selectivity were observed.

Recently, Nishida and Ohfusa have published a detailed report about the reactivity of 1-amino-3-siloxy-butadienes **3h** with cyclic dienophiles, including alkylidene β-ketoesters **2a** and **2b**, using the Cr-salen complex **13** (Scheme 12).[46] Despite

Scheme 12. Diels−Alder Reactions with 1-Amino-3-siloxy-butadienes[46]

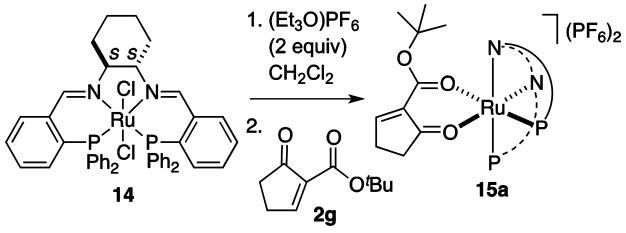


the very high catalyst loading (50 mol %), **4h** and **4i** were obtained in moderate yields and with poor enantio- and exo/endo selectivity. The above examples show that enantioselective cycloaddition reactions on alkylidene β-ketoesters are by far not a trivial task, and that a suitable catalytic system has to balance opposite requirements such as the strong activation of the double bond and mild conditions to avoid the decomposition of the substrate, while simultaneously providing an efficient chiral environment for enantioselection.

A system that has recently proven to be highly successful in this regard is based on structurally characterized, dicationic Ru/PNNP complexes, which have previously found application as chiral Lewis acids for electrophilic transformations of saturated β-ketoesters such as fluorination,[47] hydroxylation,[48] and Michael addition[11,12] reactions (PNNP is the chiral tetradentate ligand (*S*,*S*)-*N*,*N*′-bis[o-(diphenylphosphino)-benzylidene]cyclohexane-1,2-diamine). The catalyst is prepared by double chloride abstraction with $(Et_3O)PF_6$ (2 equiv) from the stable and readily available dichloro complex $[RuCl_2(PNNP)]$ (**14**). Addition of **2g** gives the corresponding adduct **15a**, in which the alkylidene β-ketoester acts as a chelating ligand (Scheme 13).

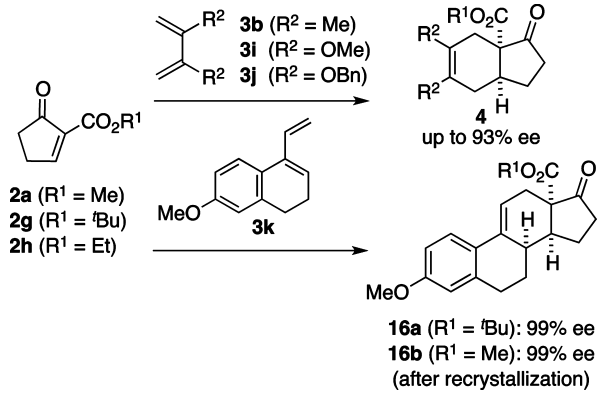
The enone moiety of unsaturated β-ketoesters like **2a**, **2g**, and **2h** is activated by coordination to the dicationic Ru/PNNP fragment. Thus, catalytic amounts of **14** (after activation as in

Scheme 13. Preparation of an Alkylidene β-Ketoester Complex of Ruthenium(II)[49,50]



Scheme 13) readily promote Diels−Alder reactions with dienes **3b**, **3i**, and **3j** to form bicyclic products in high yields and up to 93% enantiomeric excess (ee) (Scheme 14).[49,50] With Dane's

Scheme 14. Ru/PNNP Catalyzed Diels−Alder Reactions on Alkylidene β-Ketoesters[49]



diene (**3k**), the enantiomerically pure estrone derivatives **16** were obtained with an ester-exo:endo ratio of up to 145:1 (after recrystallization). These products are interesting in view of applications in medicinal chemistry, for example, for the treatment of hormone dependent breast cancer, where they act as inhibitors of steroidogenic enzymes[51−53] or as antimicrotubule agents.[54]

The absolute configuration of the estrone derivative **16a** and the structure of the catalyst-substrate adduct **15a** were determined by X-ray diffraction. In the latter complex, a phenyl ring of the PNNP ligand efficiently shields the lower face of the enone **2g** and directs the diene attack from above. This observation is in agreement with the absolute configuration of the products and accounts for the high enantioselectivity. In turn, the enantiofacial selectivity is determined by the diastereoselectivity of the coordination of the substrate. When the substrate substituent is the bulky *tert*-butyl derivative **2g**, a single diastereoisomer is formed, in which the ester group points away from the diphenylphosphine moiety. The pivotal role played by diastereoselective substrate coordination in enantiodifferentiation was confirmed by preparing the substrate adducts with the smaller methyl ester derivative **2a**, which forms the analogous substrate-catalyst adduct as a mixtures of diastereoisomers (**15b** and **15c**, Scheme 15).[55] These were prepared in pure form by separating a mixture of the corresponding enolato complexes **17b** and **17c** via column chromatography, followed by hydride abstraction.

The diastereoisomers **15b** and **15c**, which expose opposite enantiofaces of the coordinated alkylidene β-ketoester **2a**, do not interconvert in solution. Addition of a stoichiometric

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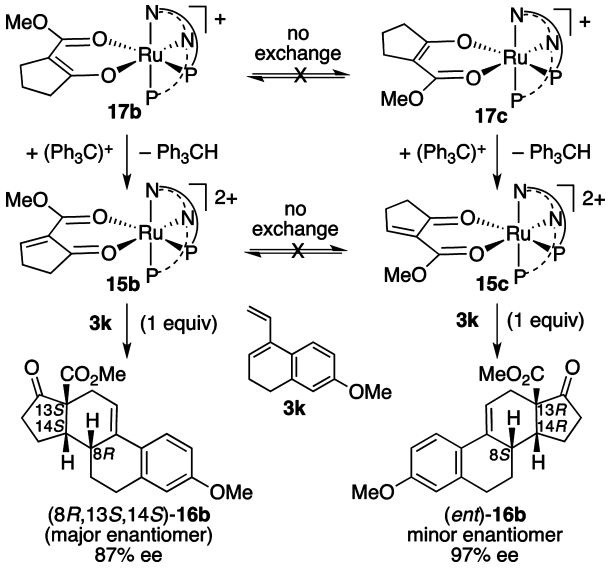
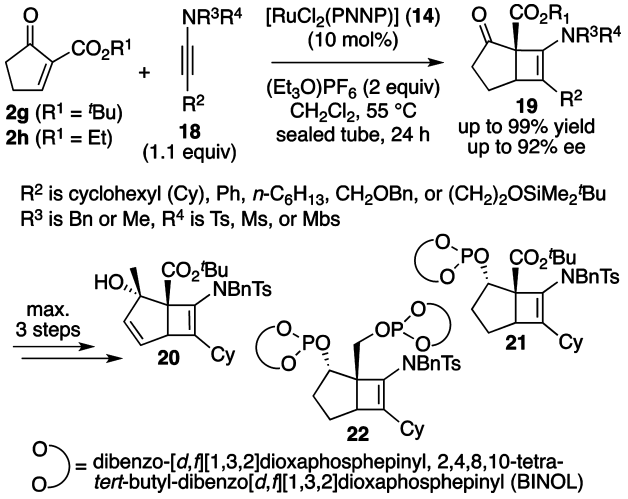
Scheme 15. Investigations on Substrate Coordination and Enantioselection with Ru/PNNP Catalysts[55]



amount of Dane's diene (**3k**) to **15b** gives the major enantiomer **16b** with 87% ee, whereas **15c** gives the minor enantiomer (*ent*)-**16b** with 97% ee. This provides a rationale for the decreased enantioselectivity of cycloaddition reactions with the methyl and ethyl derivatives **2a** and **2h** as compared to the *tert*-butyl-analogue **2g**. The dicationic nature and the low spin d^6 configuration of the above complexes are seen as the cause of their relatively high stability and inertness, which made possible the extensive studies of the Ru/PNNP catalyst system.[55] These properties, while beneficial for catalyst investigations, can bear the disadvantage of considerable product inhibition, which is also an often encountered problem in Nazarov cyclization reactions (see below).

The Ru/PNNP system based on complexes **15** also catalyzes the first example of an enantioselective Ficini reaction, which, in its original form, is the [2 + 2] cycloaddition between an ynamine and an enone (Scheme 16). Thus, ynamides **18** react with unsaturated β-ketoesters **2g** and **2h** to give the corresponding cyclobuteneamides **19** with excellent yield and

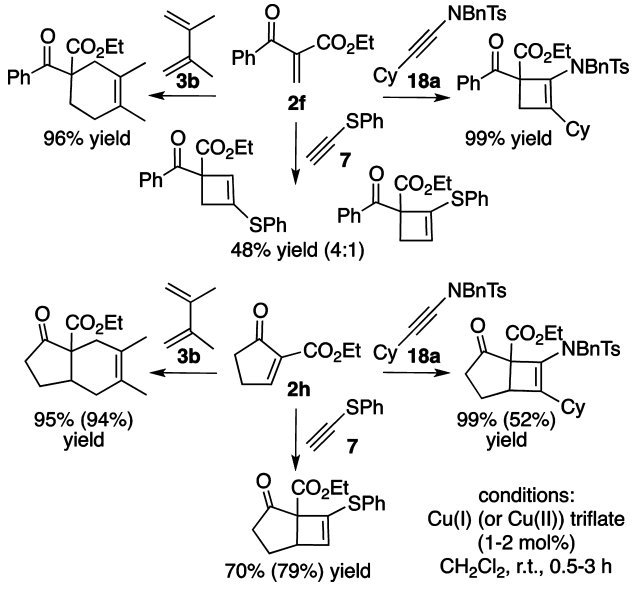
Scheme 16. First Example of an Enantioselective Ficini Reaction[56,57]



enantioselectivity (16 examples, up to 99.5% ee after recrystallization).[56,57] Cyclobuteneamides are versatile substrates, as shown by the functionalization of selected examples thereof to dienes (**20**), hybrid olefin/phosphite ligands (**21**), and to diphosphites (**22**) (Scheme 16).[57] Compounds **22** act as bidentate ligands and give moderate enantioselectivity in the rhodium-catalyzed hydrogenation of 2-acetamidoacrylate and in the palladium-catalyzed allylic alkylation of (*E*)-1,3-diphenyl-allyl acetate. Diene **20** does not coordinate to rhodium(I), and the alkene-phosphites **21** coordinate only in a monodentate fashion, though.

Complementary to the chiral Ru/PNNP catalyst, copper(I) or copper(II) triflate (1–2 mol %) provide a cheap and highly efficient entry to nonenantioselective cycloadditions onto ethyl 2-benzoylacrylate (**2f**) and 2-carboethoxy-cyclopentenone (**2h**) (Scheme 17, yields with copper(II) triflate in parentheses).[58] In

Scheme 17. Copper-Catalyzed Cycloaddition Reactions on Alkylidene β-Ketoesters[58]



the presence of these catalysts, **2f** and **2h** readily react with 2,3-dimethylbutadiene (**3b**) (Diels–Alder), *N*-benzyl-*N*-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**18a**) (Ficini reaction), and ethynyl(phenyl)sulfane (**7**) ([2 + 2] cycloaddition). Both cyclic **2h** and acyclic **2f** are converted to the corresponding cycloaddition products in good yields after reaction times of 0.5–3 h with this convenient protocol that does not require purified solvents or inert gas atmosphere.

Michael Addition Reactions. Alkylidene β-ketoesters are intrinsically more reactive than standard enones in view of the additional conjugation involving the ester moiety. However, this advantage is partially lost in the cycloaddition reactions discussed above because they involve the formation of a hindered quaternary center. In contrast, Michael type additions, which do not necessarily form quaternary stereocenters, fully benefit from the activating effect of the ester group. Furthermore, alkylidene β-ketoesters can act as chelating ligands, thus improving stereocontrol. The saturated β-ketoester formed by the Michael attack can be exploited for further derivatization of the reaction products, which is frequently encountered in the examples described below and often gives access to polyfunctionalized building blocks or key

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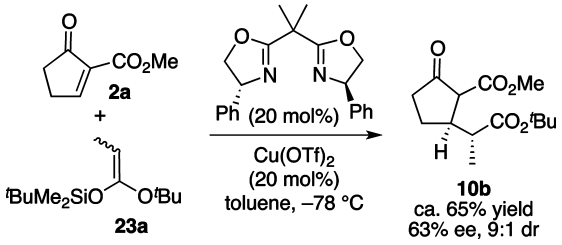
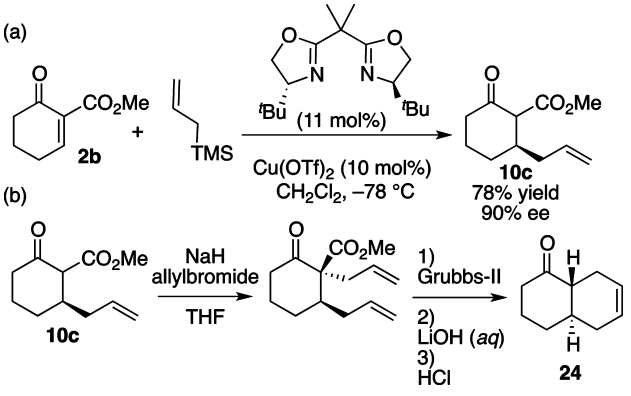
intermediates of natural product synthesis. One of the first enantioselective Michael additions of alkylidene β-ketoesters is found in the Mukaiyama−Michael addition of silyl ketene acetal **23a** onto **2a** catalyzed by copper(II)-BOX ligand systems (BOX = bisoxazoline).[59] Although different copper(II) sources, BOX ligands, and solvents were screened, only moderate yields of **10b** (up to 63%) and enantioselectivities (up to 66% ee) were obtained (Scheme 18).

Scheme 18. Enantioselective Mukaiyama−Aldol Reaction on Alkylidene β-Ketoesters[59]



Recently, Shizuka and Snapper used a similar system in the first enantioselective Hosomi−Sakurai conjugate allylation reaction to give **10c** with high enantioselectivity. Cyclic unsaturated β-ketoesters with different ring sizes were used as substrates.[60] Although a large array of mono- and bisoxazolines was screened, high enantioselectivity was only achieved using the *tert*-butyl substituted ligand depicted below (Scheme 19, a).

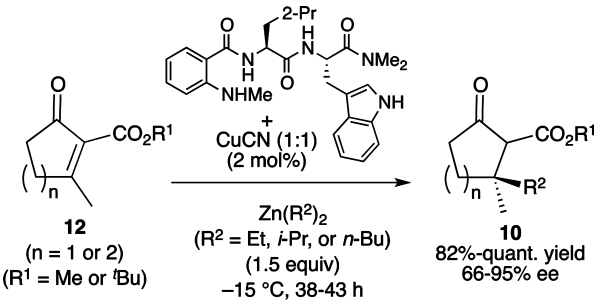
Scheme 19. First Enantioselective Hosomi−Sakurai Conjugate Allylation Reaction[60]



The presence of the ester group is mandatory, as standard cyclic enones did not react at all. The versatile β-ketoester moiety was exploited for further functionalization and transformation of the addition products by ring-closing and cross metathesis reactions. For instance, the functionalization of **10c** gave **24**, a useful synthetic building block (Scheme 19, b).

By screening about 90 ligand candidates, Hoveyda and Hird developed a highly enantioselective system for the copper-catalyzed Michael addition of simple dialkyl zinc reagents to tetrasubstituted enones **12** (Scheme 20).[61] Running the reactions in nondistilled toluene proved to be crucial for high enantioselectivity, which was assumed to be due to the presence of adventitious water. As opposed to an earlier method by Alexakis et al.[62] based on trialkyl aluminum reagents and β-substituted unsaturated ketones, the more electrophilic alkylidene β-ketoesters can be used with the less Lewis acidic and more atom economical dialkyl zinc reagents. The highly

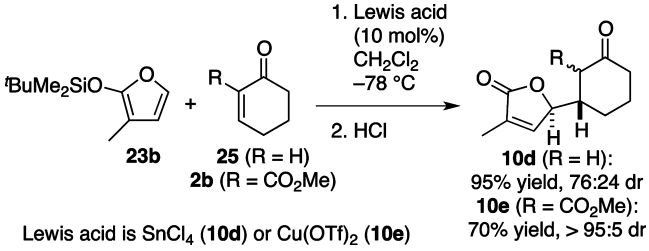
Scheme 20. Enantioselective Michael Addition of Alkyl-Zinc Reagents to β′-Methyl Substituted Alkylidene β-Ketoesters 12[61]



efficient, enantioselective formation of a quaternary stereocenter in the β′-position and the low catalyst loading are impressive. The addition products (**10**) were converted to versatile building blocks by exploiting the saturated β-ketoester moiety formed during the reaction.

Chabaud and Gillou used the additional conjugation to the ester moiety to improve the reactivity and stereoselectivity of their vinylogous Mukaiyama−Michael reactions of 2-silyloxyfurans like **23b** with cyclic enones (Scheme 21).[44] By changing

Scheme 21. Diastereoselective Michael Addition Reactions with 2-Silyloxyfurans[44]

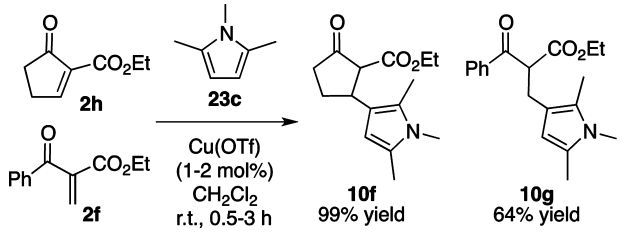


the Michael acceptor from cyclohexenone **25** to a cyclic alkylidene β-ketoester, for instance **2b**, they were able to use milder Lewis acids, such as $Cu(OTf)_2$ instead of $SnCl_4$, and to achieve higher diastereoselectivity in the formation of **10e** as compared to **10d**. The latter effect was attributed to the formation of a well-defined chelate catalyst-substrate adduct, as opposed to the unselective coordination of the Lewis acid to either side of standard cyclic enones.

Besides cycloaddition reactions (see Scheme 17), copper(I) triflate efficiently catalyzes the nonenantioselective Michael addition reaction of 1,2,5-trimethyl-1*H*-pyrrole (**23c**) with alkylidene β-ketoesters **2f** and **2h** (Scheme 22).[58]

Alkylidene β-ketoesters have also been employed in organocatalytic reactions. However, the mechanism of these

Scheme 22. Copper Catalyzed Michael Addition Reaction of 1,2,5-Trimethyl-1*H*-pyrrole (23c)[58]



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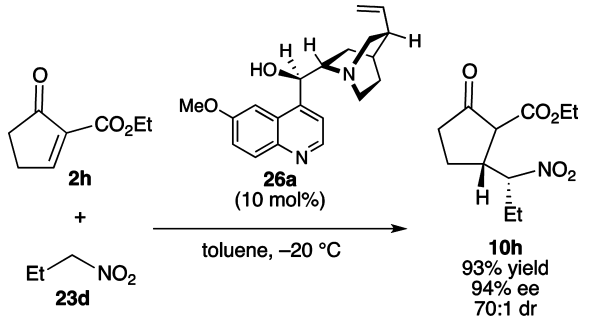
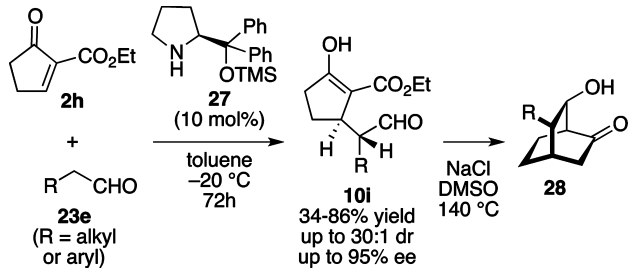
reactions does not always involve activation of the unsaturated β-ketoester itself. In 2010, Bella et al. reported highly enantioselective Michael-type addition reactions with nitroalkanes such as **23d**, activated as nucleophiles by chiral tertiary amines like the *cinchona* alkaloid derivative **26a** (Scheme 23).[63]

Scheme 23. Enantioselective Michael Addition Reaction with 1-Nitropropane 23d[63]



The high diastereoselectivity of the formation of **10h** (and of related products) is noteworthy, as it requires additional control over the labile stereocenter on the highly acidic nitroalkane moiety. The saturated β-ketoester moiety was utilized as a nucleophile in a second Michael addition on methyl vinyl ketone in a tandem reaction with excellent enantioselectivity. Recently, the same group extended the method to use aldehydes **23e** as nucleophiles.[64] However, the same *cinchona* derivative **26a** (in combination with proline) exerted only poor stereocontrol. In contrast, the proline-derived organocatalyst **27** gave the desired products in moderate to high yields and up to >95% ee in the absence of the *cinchona* derivative **26a** (Scheme 24). This time, the nucleophile is activated by formation of the

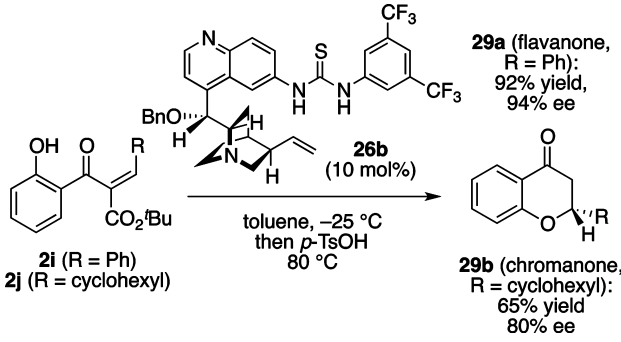
Scheme 24. Enantioselective Michael Addition Reactions with Aldehydes 23e as Nucleophiles[64]



enamine with **27**, and the β-ketoester moiety of **10i** was subsequently used for an aldol reaction on the attached aldehyde under Krapcho conditions, forming the tricyclic compounds **28**.

Cinchona alkaloids were also used as chiral backbone for the thiourea-based catalyst **26b** in the first example of an asymmetric oxo-conjugate addition to unsaturated β-ketoesters developed by Scheidt et al.[65] This enantioselective ring closing reaction yields the naturally abundant flavanone (**29a**) and chromanone (**29b**) structures with high enantioselectivity after acid-catalyzed decarboxylation (Scheme 25). The additional ester functionality in substrates **2i** and **2j** was introduced to provide a second basic site for additional interaction with the catalyst, favor cyclization, and increase the reactivity. Indeed, the reaction does not occur with simple enones, that is, in the

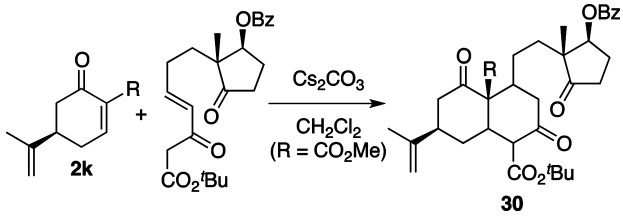
Scheme 25. Asymmetric Oxo-conjugate Addition to Unsaturated β-Ketoesters[65]



absence of the ester moiety. After the reaction, the *tert*-butyl ester group is easily cleaved under acidic conditions.

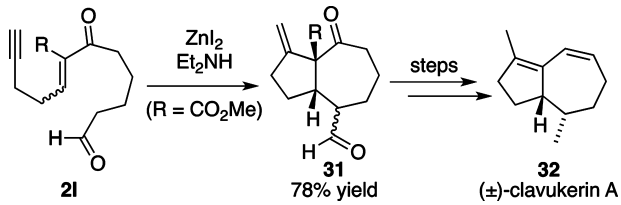
For the sake of completeness, we also mention that noncatalytic reactions of alkylidene β-ketoesters have also been exploited in natural product synthesis. An interesting example is the diastereoselective double Michael addition reaction of the unsaturated β-ketoester **2k** in the synthesis of the biologically valuable, highly oxygenated cardenolide backbone **30** reported by Deslongchamps et al. (Scheme 26).[66]

Scheme 26. Diastereoselective Double Michael Addition Reaction[66]



In 2010, Lee et al. reported an amine-induced Michael/Conia-ene cascade reaction with alkylidene β-ketoesters like **2l**, leading to polyfunctionalized 5/7 (or 6/6) bicyclic systems such as **31** (Scheme 27).[67] During the reaction, the nucleophilic

Scheme 27. Amine-Induced Michael/Conia-ene Cascade Reaction[67]



β-ketoester functionality formed by the initial Michael addition attacks the terminal alkyne moiety. This irreversible reaction is believed to deliver the driving force for the challenging 7-endo-trig Michael cyclization, pushing the equilibrium to the product side. The reaction cascade was applied in a formal synthesis of (±)-clavukerin A (**32**), a trinorguaiane sesquiterpene isolated from soft coral.[68]

Martin and co-workers recently reported the diastereoselective Michael addition of a pyridylmethyl cuprate (**23f**) (formed in situ) to alkylidene β-ketoester **2m** to give **10j** (Scheme 28).[69] After ring closing and transesterification with

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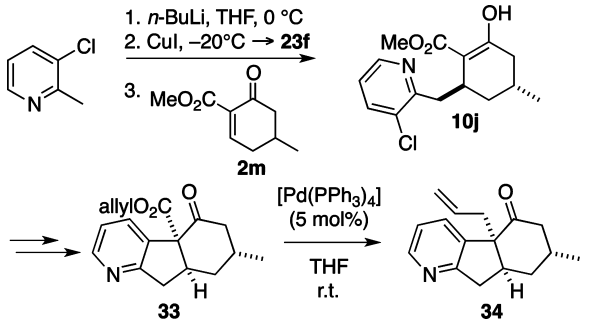
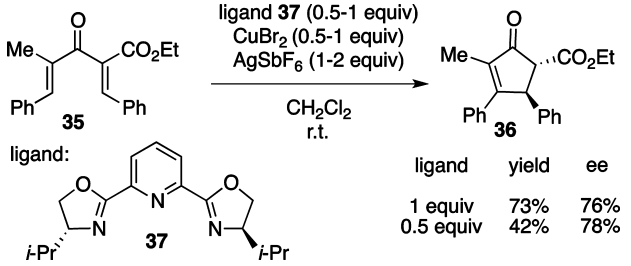
Scheme 28. Diastereoselective Michael Addition of a Pyridylmethyl Cuprate (23f)[69]



allylic alcohol, they used the remaining β-ketoester moiety in **33** for a palladium catalyzed, decarboxylative allylation to give **34**, a key intermediate in their synthesis of (±)-lycopladine A.

Nazarov Reaction. For the sake of completeness, we mention here the Nazarov cyclization, which is the 4π electrocyclization of cross-conjugated dienones (for instance **35**) to substituted cyclopentenones such as **36** catalyzed either by Brønsted or by Lewis acids (Scheme 29). The connection to

Scheme 29. Enantioselective Nazarov Cyclization by Aggarwal and Belfield[78]



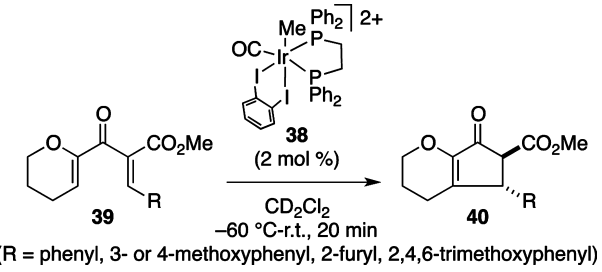
the topic of this perspective article is that α-alkoxycarbonyl-substituted divinyl ketones like **35**, a particular class of unsaturated β-ketoesters, are common Nazarov substrates. In fact, the ester moiety (or another electron-withdrawing or -donating group) is required to polarize the dienone, which directs the regio- and stereoselectivity (torquoselectivity) and lowers the energy barrier for the cyclization reaction.[70,71] As the topic has been exhaustively covered in recent, excellent reviews,[72−76] only relevant selected aspects will be discussed below.

As the fine-tuning of the Lewis acidity is required to suppress undesired competing reactions,[76] much of the progress on the field is associated with metal catalysis. Also, the Nazarov reaction can be performed in a stereoselective way either by preintroducing a chiral center to the dienone[77] or by using a chiral Lewis acid as catalyst. Asymmetric Nazarov cyclization has been pioneered by Aggarwal and Belfield with a chiral Cu(II) complex of the PYBOX ligand **37** (Scheme 29).[78] However, the metal complex had to be used in a nearly stoichiometric ratio.

Recently, much progress has been achieved in the field of asymmetric, metal-catalyzed Nazarov reactions with β-keto-esters. Oxazoline-based ligands played a major role in the development of this chemistry. For example, Itoh and co-workers have shown that Fe(II) and Co(I) BOX complexes catalyze enantioselective Nazarov cyclization, albeit with moderate yields and still very high catalyst loading (50 mol %).[79] The tris(oxazoline) Cu(II) system employed by Tang et al.[80] gave high yields with much lower catalyst loadings (10 mol %), possibly because the tridentate ligand assists product displacement. Very high enantioselectivity (up to 98% ee) was achieved, and the β-ketoester moiety was utilized for a number of transformations on the enantiomerically enriched products, such as Michael addition and electrophilic fluorination reactions. Ma and co-workers reported a related example, a tandem Nazarov cyclization/electrophilic fluorination reaction that uses a standard Ph-BOX ligand and NFSI.[81] The products were obtained in high yields, excellent diastereoselectivity and up to 95.5% ee.

Besides oxazoline complexes, square-planar dicationic Ni(II) complexes containing a chiral tridentate phosphine were reported to catalyze Nazarov reactions with high degrees of enantioselectivity by Togni and Walz.[82] The chiral environment provided by the Ni(II) catalyst exerts a high degree of torquoselectivity during the electrocyclization step. However, like in many Nazarov cyclization reactions, the catalyst activity is very low because of strong product inhibition. In fact, kinetic issues, and in particular product inhibition, are often encountered problems in catalytic Nazarov reactions. An interesting exception are the iridium(III) complexes **38** reported by Frontier and Eisenberg, which are very active catalysts for nonenantioselective Nazarov reactions of **39** to give the corresponding cyclopentenones **40** in quantitative yield with a catalyst loading as low as 2 mol % (Scheme 30).[83−85]

Scheme 30. Nazarov Cyclization Chemistry by Frontier and Eisenberg[83−85]



This feature defies the inertness of octahedral d^6 complexes toward ligand substitution[86] and is explained by the weak bonding of the 1,2-diiodobenzene ligand in the catalysts precursor, which is replaced by the substrate even at low temperature.[83]

Although the Nazarov cyclization exploits a particular subclass of unsaturated β-ketoesters, the above discussion gives a further example of how recently developed catalytic approaches have opened new perspectives to the use of these substrates in (enantioselective) organic synthesis.

CONCLUSION

Alkylidene β-ketoesters are more reactive than standard enones because of the conjugation with the ester group. This is an advantage in terms of reactivity, but the challenge associated with their synthesis and reactivity has hindered their application in asymmetric catalysis for a long time. Recently, unsaturated β-ketoesters have attracted increasing interest in asymmetric catalysis, though. For cycloaddition reactions, catalytic systems have been developed that are mild and, at the same time, powerful enough to achieve the challenging task of forming the quaternary stereocenter in the α-position effectively and

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without triggering polymerization. In 1,4-conjugate additions, which do not necessarily involve the difficult formation of a quaternary stereocenter, the activation caused by the ester moiety goes to the full advantage of the reactivity of the system. The nucleophilic saturated β-ketoesters formed in the reactions are frequently used in situ for cascade reactions or for subsequent functionalization and, after having served its purpose, the β-ketoester can be decarboxylated under mild conditions.

The advantages described above should attract even broader interest in asymmetric catalysis in the near future and motivate the synthetic community to find efficient, high yielding, and nontoxic preparation methods for alkylidene β-ketoesters as versatile substrates that give access to multifunctionalized molecules, including many natural products.

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Notes

The authors declare no competing financial interest.

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