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Pushing the Limits of Aminocatalysis: Enantioselective Transformations of α-Branched β-Ketocarbonyls and Vinyl Ketones by Chiral Primary Amines

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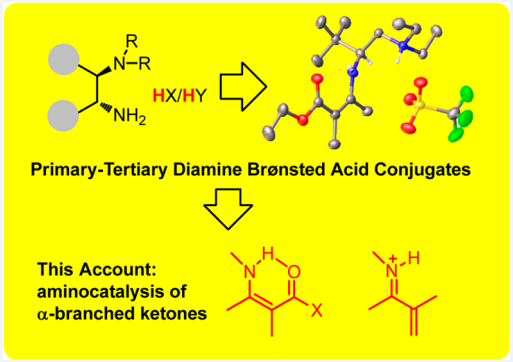
CONSPECTUS: Enantioselective α-functionalizations of carbonyl compounds are fundamental transformations for the asymmetric synthesis of organic compounds. One of the more recent developments along this line is in aminocatalysis, which leads to the direct α-functionalization of simple aldehydes and ketones. However, most of the advances have been achieved with linear aldehydes and ketones as substrates. Effective aminocatalysis with α-branched carbonyls, particularly α-branched ketones, has remained elusive. The primary difficulty arises from the space-demanding α-substituent, which impedes iminium/enamine formation. In 2005, synthetic organic chemists revived catalysis using primary amines, which brought new attention to these challenges, because of the conformational flexibility of primary amines. On the basis of early biomimetic studies by Hine, in 2007 we developed the bioinspired chiral primary amine catalysts featuring primary−tertiary diamines. This type of catalyst involves enamine/iminium catalysis, and we could apply this chemistry to all of the major types of ketones and aldehydes.



In this Account, we present research from our laboratory that significantly expands aminocatalysis to include α-branched ketones such as β-ketocarbonyls and α-substituted vinyl ketones. Our primary amine catalysis methodology, when used alone or in conjunction with metal catalysts, provides convenient access to both enantiopure α-tertiary and quaternary ketones, structures that are not available via other approaches. Our mechanistic studies showed that acidic additives play the critical role in facilitating catalytic turnover, most likely by shuttling protons during the enamine/iminium tautomerizations. These additives are also critical to induce the desired stereochemistry via ammonium N−H hydrogen bonding. Proton transfer by shuttling is also stereoselective, resulting in enantioselective enamine protonation as observed in the reactions of α-substituted vinyl ketones. In addition, we have carried out density functional theory studies that help to delineate the origins of the stereoselectivity in these reactions.

1. INTRODUCTION

The construction of chiral carbonyl compounds has been and continues to be a mainstay in organic synthesis because of their ubiquitous utilization in the synthesis of pharmaceuticals and natural products. Enantioselective methodology along this line undergoes constant rebirth echoing each of the advances in asymmetric catalysis. One of the most prominent advances is the advent of aminocatalysis,[1] an icon in organocatalysis that enables asymmetric direct α-functionalizations with ketones and aldehydes under rather mild conditions. Ever since its renaissance in 2000,[2] aminocatalysis, with enamine/iminium tautomerization at its core, has become a pillar-type approach for the direct functionalization of carbonyl compounds, particularly for linear aldehydes and ketones (Figure 1). Though extensively explored, aminocatalysis with α-branched aldehydes/ketones, an appealing process to access chiral carbonyls bearing α-quaternary stereogenic carbons, remains a challenging subject (Figure 1). Presumably, the challenges can be understood by considering the sterically hindered nature of α-branched carbonyls and the issues in controlling the geometry of the forming enamines/iminiums as well as in selectively steering the subsequent bond formations. The situation is even worse with α-branched ketones, as reflected by the scarcity of successful examples. In these cases, additional regioselectivity issues arise when the ketones are endowed with two differentiated α-positions.

Secondary amines, typically chiral pyrrolidines or imidazolines, are regarded as privileged structural motifs for aminocatalysts.[1] Tremendous advances in these catalysts in the past decade have eventually defined their utility and scope. As a result of the inherent structural constraints, secondary amine catalysts tend to be ineffective when space-demanding intermediates (e.g., Z-enamines or substrates such as α-branched aldehydes/ketones) are involved (Scheme 1). The revival of primary amines as effective aminocatalysts in 2005 has brought new light to the aforementioned challenging problems.[3] The developed

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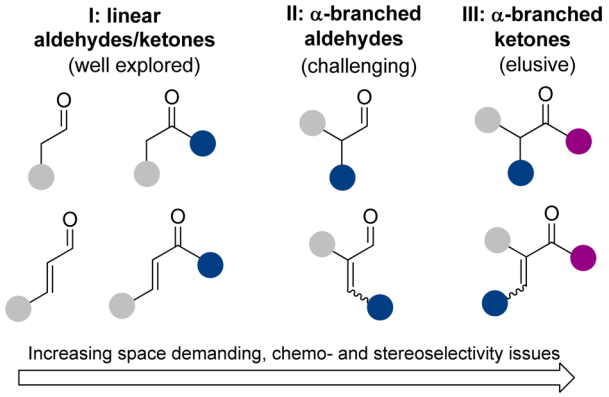
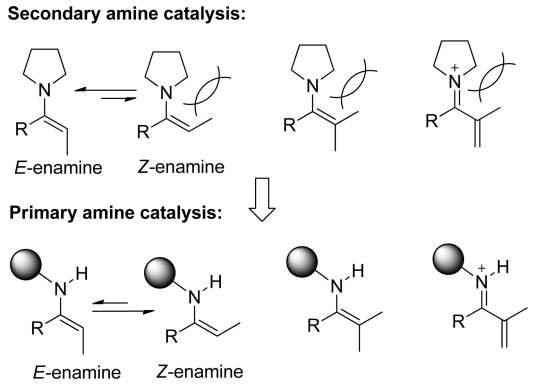


Figure 1. Current substrate status of aminocatalysis.

Scheme 1. Features of Primary Amine Catalysis versus Secondary Amine Catalysis



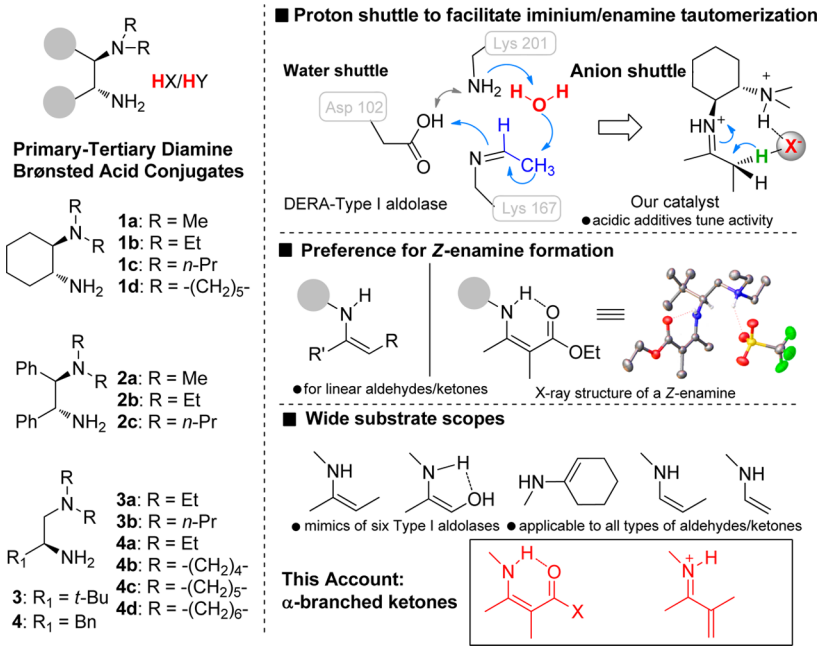
chiral primary amine catalysts, especially those based on vicinal diamine skeletons, have made effective asymmetric catalysis with sterically hindered ketones and α-branched aldehydes possible as a result of their structural and conformational flexibility[4] (Scheme 1).

At the onset of our work in 2005, we sought to develop effective primary amine catalysts by drawing inspiration from the primary aminocatalytic motif in nature. Capitalizing on Hine's seminal biomimetic studies on vicinal diamines,[5] in early 2007 we reported primary amine catalysts **1** based on a chiral cyclohexanediamine skeleton.[6] An unprecedented *syn*-aldol was realized via an otherwise inaccessible *Z*-enamine intermediate by the catalysis of **1c**, and the reaction expanded the previous amino acid catalysis to include linear aliphatic ketones (Scheme 2).[7] It is quite a coincidence that at almost the same time the groups of Chen, Melchiorre, and Connon independently reported primary amine catalysts based on a cinchona scaffold bearing also a primary−tertiary vicinal diamine motif.[8] Later on, the groups of Feng and Zhao also developed unique vicinal diamine catalysts.[9] Seeing the similarity and potential, we chose to focus only on the bioinspired primary amine catalysts with primary−tertiary vicinal diamine skeletons, and our continuous efforts along this line have revealed several distinctive features (Scheme 2):[10] (1) acidic additives are essential to facilitate enamine/iminium tautomerization via shuttled proton transfer in a manner closely resembling the water proton shuttle revealed in type-I aldolase (DERA), in many cases leading to enhanced catalytic turnovers; (2) *Z*-enamine formation is generally preferred for acyclic aldehydes and ketones; and (3) the catalysts functionally mimic six classes of type-I aldolases and are applicable to all of the major types of aldehydes and ketones in terms of enamine catalysis. With these features in mind, we have devoted much effort to exploring the unattained aminocatalysis with α-branched ketones in the past few years. In this Account, we will mainly focus on our recent achievements along this line.

2. ENANTIOSELECTIVE TRANSFORMATIONS OF α-SUBSTITUTED β-KETOCARBONYLS

Direct transformation of unfunctionalized α-branched ketones via aminocatalysis is regarded as a notorious challenge because of the steric hindrance in forming enamine/iminium intermediates. Previous successes have focused only on α-branched cyclic

Scheme 2. Bioinspired Primary Amine Catalysts Developed in This Group



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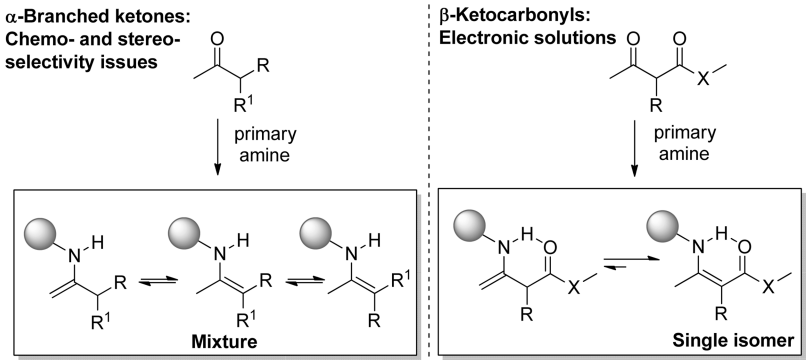
Scheme 3. Enamines Formed from Unfunctionalized Ketones and α-Substituted β-Ketocarbonyls



ketones. Toste and co-workers realized the enantioselective α-fluorination of α-branched cyclohexanones with the combination of a primary amine and a chiral lipophilic BINOL-derived phosphate.[11] Kang and Carter[12] found that a primary amine–thiourea catalyst could catalyze the asymmetric Michael addition of α-branched cyclohexanones and that several types of Michael acceptors could be involved. We also developed a series of retro-aldol and transfer-aldol processes of cyclohexanone-derived aldols using primary–tertiary diamine catalysts.[13] In moving from cyclic ketones to acyclic ones, the difficulties associated with aminocatalysis may increase considerably as a result of the increased conformational flexibility as well as issues with chemo- and stereoselectivity control (Scheme 3). In this regard, we have chosen to focus on α-substituted β-ketocarbonyls, wherein the endowed carbonyl moiety may form a hydrogen bond with the secondary enamine N–H, thus adding constraints on the possible geometries of the enamine intermediates. In addition, the electron-withdrawing carbonyl moiety may also thermodynamically balance the enamine formation to the substituted regioisomer (Scheme 3).

β-Ketocarbonyls are known to form stable enamine carbonyls, and thus, the catalytic turnover with β-ketocarbonyls is of serious concern and has remained elusive in aminocatalysis. In fact, preformed enamine carbonyls with chiral primary amines have been well-explored as chiral synthons in asymmetric synthesis.[14] We found that primary–tertiary diamine **3a** could stiochiometrically react with a series of α-substituted β-ketocarbonyls and that the so-formed enamines could be isolated via chromatography on basic alumina in moderate to high yields (Scheme 4). Notably, cyclic keto esters, existing mainly in their enol form, could also undergo smooth enamine formation (e.g., **6d**; Scheme 4). The obtained enamine intermediate was found to be in a *Z-s-trans* geometry by NMR analysis, which was unequivocally verified by an unprecedented X-ray crystal structure (Figure 2). Meanwhile, these enamine intermediates underwent facile hydrolysis when

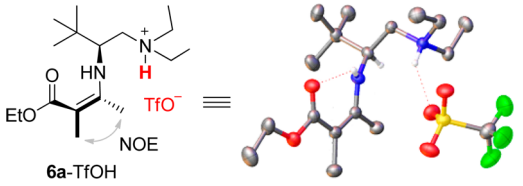


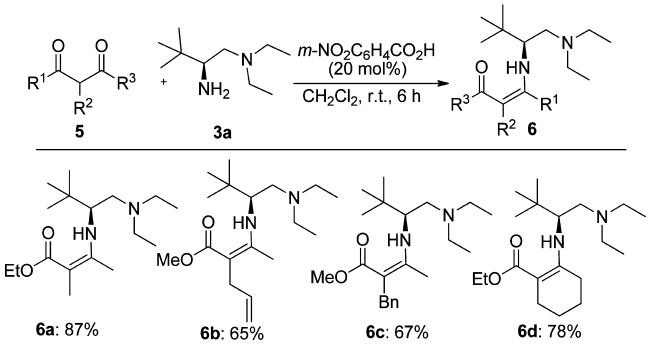
Figure 2. Solid and solution structures of enamine intermediate **6a**-TfOH.

treated with acidic additives such as TfOH/*m*-NO_2PhCOOH. Later on, these acidic additives were found to be critical in tuning the catalytic activity, a scenario consistent with our previously observed acidic additive effects with this type of primary amine catalyst.[10]

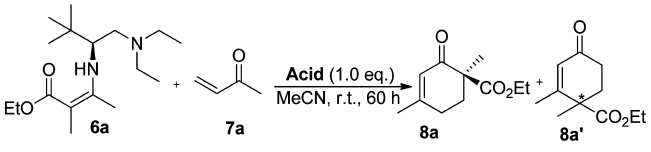
2.1. Asymmetric Robinson Annulation

We first examined a typical Robinson annulation between β-keto esters and methyl vinyl ketone (MVK). Though the reaction of cyclic 1,3-diketones with MVK, known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, has been well-explored for the synthesis of Wieland–Miescher and Hajos–Parrish ketones,[15] the acyclic version with β-keto esters has not been achieved. In examining the stoichiometric reaction between preformed enamine **6a** and MVK (**7a**), we found that the joint use of TfOH and *m*-nitrobenzoic acid could selectively facilitate the formation of adduct **8a** with 94% *ee* (Scheme 5). With the combined acidic additives, a catalytic version was realized following syringe pump addition of MVK, providing access to cyclohexenones bearing α-all-carbon quaternary stereocenters with high enantioselectivities (Scheme 6).[16] Our mechanistic

Scheme 4. Synthesis of Enamine Intermediates



Scheme 5. Stoichiometric Reaction between Preformed Enamine 6a and MVK (7a)



Entry	Acid	8a	8a'
1	none	0	0
2	TfOH only	15%, 94% *ee*	53%, 18% *ee*
3	*m*-$NO_2C_6H_4CO_2H$ only	31%, 40% *ee*	35%, 13% *ee*
4	TfOH/*m*-$NO_2C_6H_4CO_2H$	67%, 94% *ee*	0

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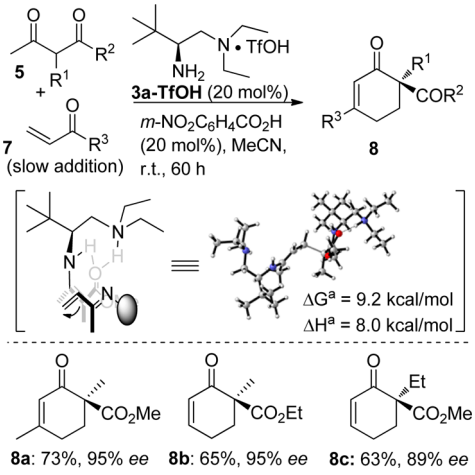
Scheme 6. Robinson Annulation Reactions of β-Ketocarbonyls

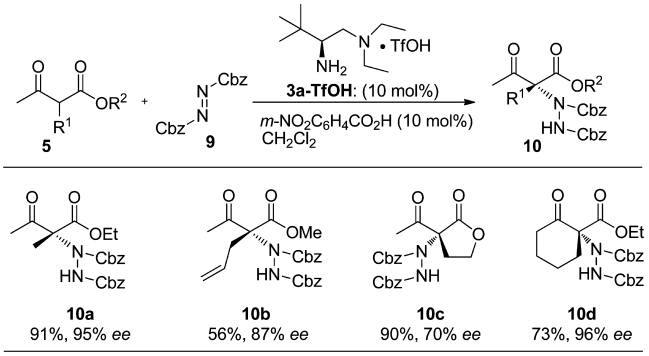


studies disclosed a dual activation mode wherein the enamine of the β-keto ester and the iminium of MVK couple to forge the critical C−C bond in a quaternary setting. The involvement of two catalyst molecules was supported by the observed positive nonlinear effect. As a consequence of this dual activation mode, the stereoinduction is mainly sterically guided rather than hydrogen-bonding-directed, as verified by density functional theory (DFT) calculations.[16,17]

2.2. Asymmetric α-Amination Reactions

Asymmetric α-aminations of carbonyl compounds are fundamental C−N bond-forming reactions in the construction of chiral materials and pharmaceuticals.[18] By employing our primary amine catalyst **3a**-TfOH, we found that the α-hydrazination of β-ketocarbonyls with diazodicarboxylates occurred smoothly to give the expected adducts with moderate to excellent enantioselectivities (Scheme 7).[16] Several α-substituents were tolerated, and the reactions also worked equally well with cyclic β-ketocarbonyls with moderate to high enantioselectivities.

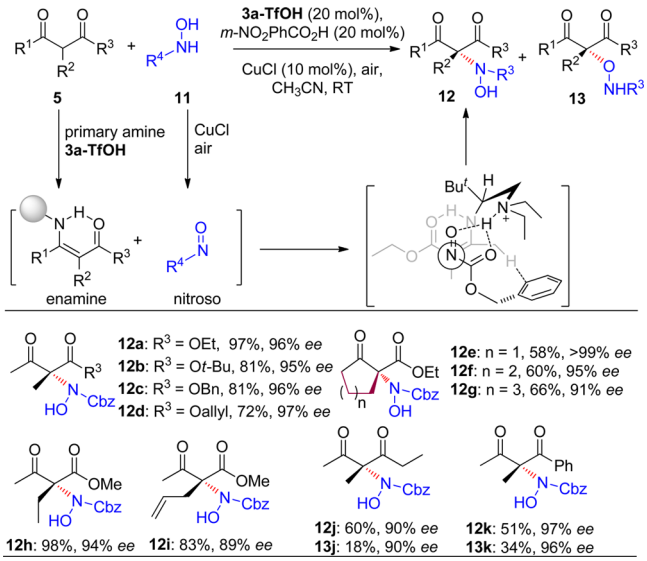
Scheme 7. α-Hydrazination of β-Ketocarbonyls



Parallel to the efforts on α-hydrazination, we also investigated the oxidative α-amination of β-ketocarbonyls with *N*-hydroxycarbamates under aerobic conditions. Recent studies by Yamamoto and Read de Alaniz demonstrated the significant synthetic potential of nitrosocarbonyls generated in situ via oxidation of *N*-hydroxycarbamates.[19] In pursuing the then-unachieved asymmetric oxidative α-amination of β-ketocarbonyls,[20] we were very pleased to find that primary amine catalyst **3a** could withstand the oxidative conditions and effectively promote the desired C−N bond formation between ethyl acetoacetate (**5a**) and *N*-hydroxycarbamate with the aid of CuCl.[21] The α-amination product **12a** was exclusively formed (**12a**/**13a** > 20:1) in 97% yield with 96% *ee*, and no degradation of the aminocatalyst was observed. In addition, the weak acid (*m*-nitrobenzoic acid) was essential to improve the yield and N/O ratio, a result consistent with the known acidic additive effect in promoting enamine turnover as we previously observed in similar catalysis.[10]

The reaction tolerated a wide range of α-substituted β-ketocarbonyls, including variations on the ester moieties (**12a**−**d**) and α-substituents (**12h** and **12i**) (Scheme 8). Cyclic β-keto

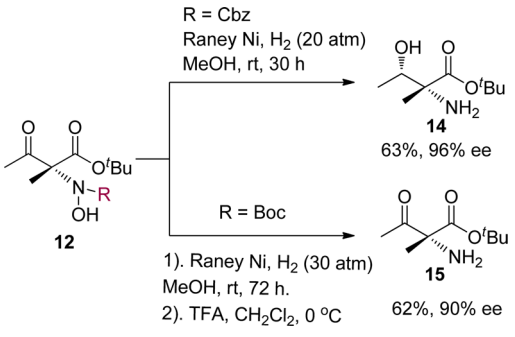
Scheme 8. Oxidative Amination of α-Substituted β-Ketocarbonyls



esters could also be incorporated into the oxidative amination protocol with equally good performance (**12e**−**g**). In particular, the reactions worked well with acyclic 1,3-diketones (**12j** and **12k**), an elusive type of substrate in asymmetric catalysis in general. The ability of our primary amine to discriminate the two keto moieties bypassed its own limitation to methyl ketones for effective enamine formation. The obtained α-amination adducts can be readily deprotected by Raney Ni hydrogenation to afford α-quaternary amino acids (Scheme 9).

The origin of the N selectivity and stereoselectivity for this amination reaction was also investigated.[22] Both our experimental analysis and DFT computational studies confirmed that a

Scheme 9. Transformations of Hydroxyamination Adducts



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Z-s-trans-enamine, stabilized by an intramolecular N−H···O hydrogen bond, was the most stable geometric isomer. The N-selective transition state was 2.8 kcal/mol lower in free energy than the O-selective one, which could be ascribed to the bidentate hydrogen bonding as well as the weak C−H···π interaction between the two reaction counterparts (Figure 3). As

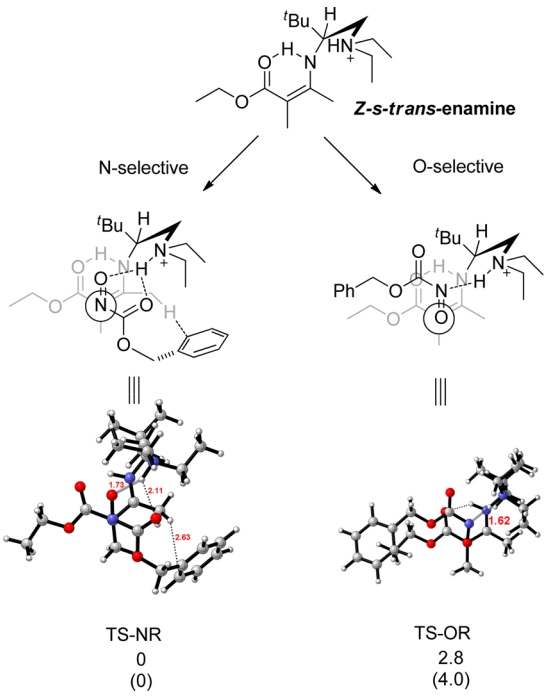


Figure 3. Origin of N/O chemoselectivity.

for the origin of the enantioselectivity, *R*-selective amination was found to proceed via *Re*-facial attack of the *Z-s-trans*-enamine and *S*-selective amination via *Si*-facial attack of the *E-s-trans*-enamine (Figure 4). The energy of the former pathway was 4.9 kcal/mol lower, in accordance with the experimental observation.

2.3. Asymmetric α-Benzoyloxylation

Asymmetric α-benzoyloxylation using readily available benzoyl peroxide (BPO) has recently been developed by List, Maruoka, and other groups.[23] This protocol provides straightforward access to chiral α-hydroxycarbonyls. However, the reactions are limited to simple aldehydes and cyclic ketones, while α-branched ketones remain challenging substrates. By using primary−tertiary diamine **3a**, we realized the asymmetric α-benzoyloxylation of β-ketocarbonyls (Scheme 10).[24] Under the optimized conditions, a series of β-ketocarbonyls such as acyclic β-keto esters, cyclic β-keto esters, 1,3-diketones, and β-keto amides were tested in this transformation, and enantioselectivities of >95% *ee* were obtained in most cases (Scheme 10). The reactions can be carried out on a gram scale with maintained performance.

2.4. Asymmetric α-Photoalkylation

Pioneered by MacMillan, the combination of photocatalysis with enamine catalysis has gained much attention because of its enormous potential in asymmetric catalysis.[25] In this regard, the α-photoalkylation of ketones, particularly α-substituted ketones, remains virtually undeveloped. We recently challenged the catalysis of chiral primary amines in the unprecedented α-alkylation of β-ketocarbonyls with phenacyl bromides. To our delight, the photoredox cycle with $Ru(bpy)_3Cl_2$ photocatalyst to generate phenacyl radical was successfully coupled with the

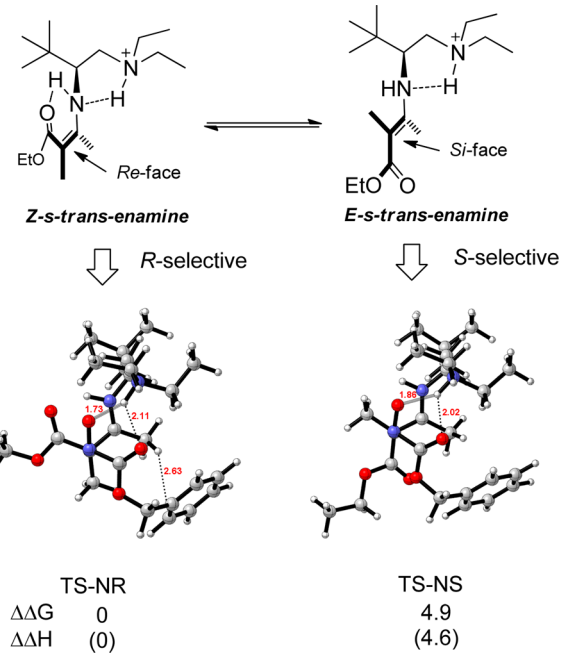
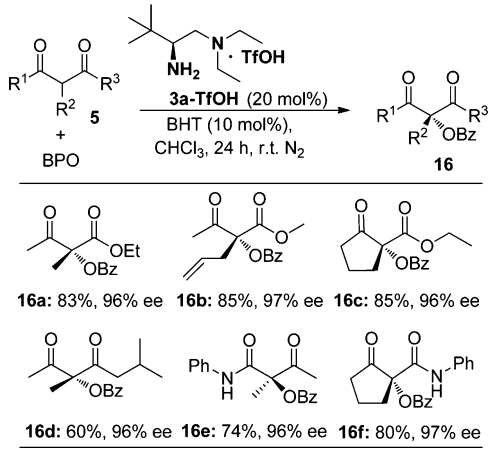


Figure 4. Origin of the enantioselectivity.

Scheme 10. α-Benzoyloxylation of β-Ketocarbonyls



enamine ester formed in situ from **3a**-TfOH to give alkylation adducts bearing acyclic all-carbon quaternary centers with excellent enantioselectivities.[26] Meanwhile, a photoresponsive electron donor−acceptor (EDA) mechanism, recently disclosed by Melchiorre,[27] may also coexist, as evidenced by the fact that the alkylation product could be obtained when no photocatalyst was loaded, albeit in low yield. Hydrogen bonding between the protonated tertiary amine and the keto moiety of the phenacyl radical would guide the approach of the radical species, accounting for the high enantioselectivity (Scheme 11).

Studies of the substrate scope showed that the reaction tolerated variations on the ester group, substitutions on phenacyl bromide, and different α-groups (**18a−c**; Scheme 12). Cyclic β-keto esters as well as cyclic β-keto nitriles were also workable substrates with excellent enantioselectivities (**18d−f**). Similar to the oxidative amination reactions, 1,3-diketone substrates also gave the desired photoalkylation products (**18g** and **18h**) with excellent enantioselectivity, albeit in decreased yields.

We further extended the scope of β-ketocarbonyls to the more challenging β-keto amides, with which N-alkylation would be a

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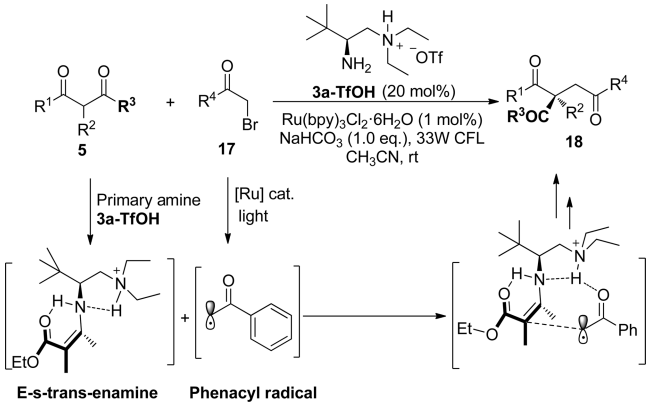
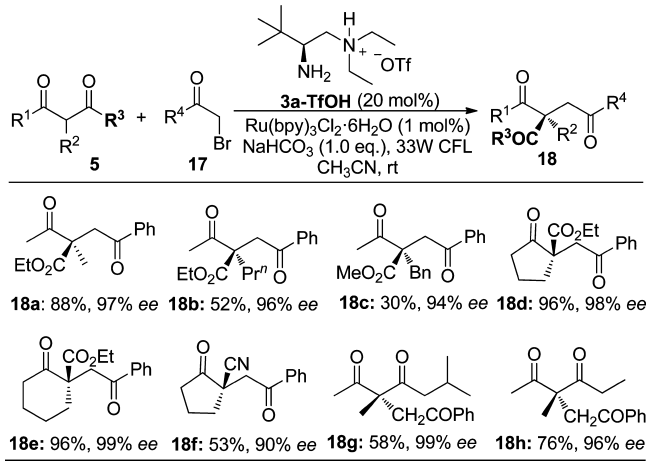
Scheme 11. Asymmetric α-Photoalkylation of β-Ketocarbonyls



Scheme 12. Substrate Scope of the α-Photoalkylation Reaction



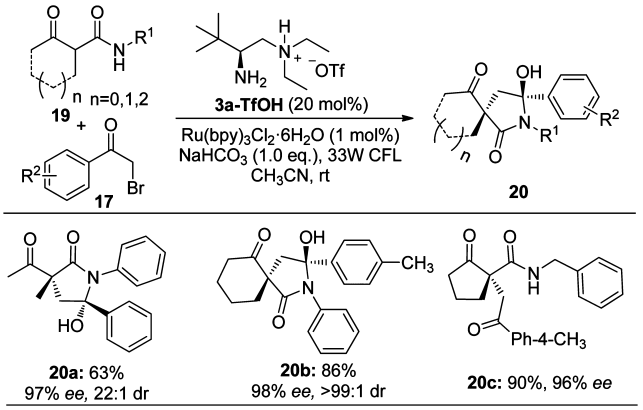
competitive byproduct pathway. Fortunately, the alkylation reaction worked well with these substrates, giving exclusively the C-alkylation products. Moreover, an intriguing intramolecular ketalization occurred spontaneously when *N*-phenylamides were used, and spiro-γ-lactams containing two nonadjacent quaternary stereocenters, known as bioactive agents,[28] were obtained as single diastereoisomers with high enantioselectivities (**20a** and **20b**; Scheme 13). Interestingly, the same reaction with *N*-benzylamide produced the alkylation product (**20c**), but no ketalization occurred.

The photoalkylation products could be easily transferred to useful compounds via simple manipulations (Scheme 14). The reaction of alkylation product **18e** with phenylhydrazine under acidic conditions could form the indole derivative **21** or dihydropyridazine **22** with maintained enantiomeric excess, and the Norrish type-II photoreaction of **18e** furnished chiral cyclobutane **23**. All of these compounds are known to have promising biological profiles.

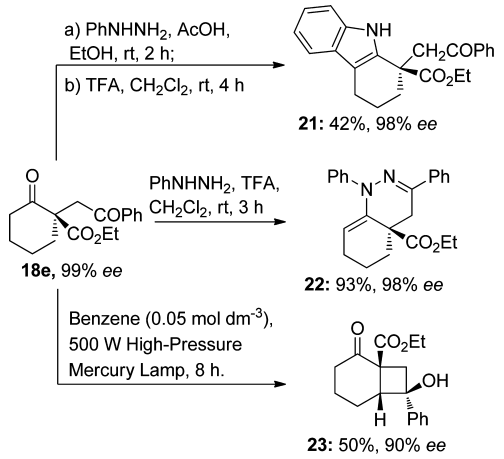
3. ENANTIOSELECTIVE TRANSFORMATIONS OF α-BRANCHED VINYL KETONES

Like enamine catalysis with α-branched ketones, iminium catalysis with α-branched enones also remains unexplored, and successful examples along this line are sparse.[29] Liu and co-workers reported that a cinchona alkaloid-derived primary amine catalyzed the enantioselective transformation of Morita−Baylis−

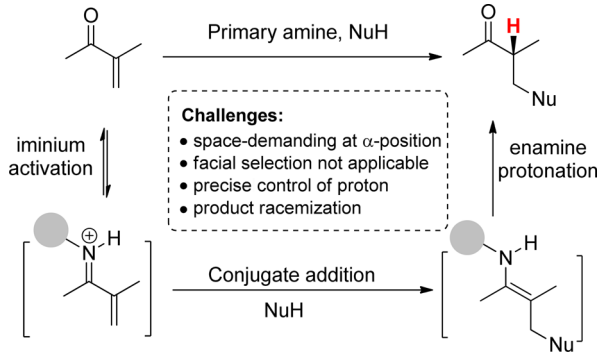
Scheme 13. α-Photoalkylation of β-Keto Amide Substrates



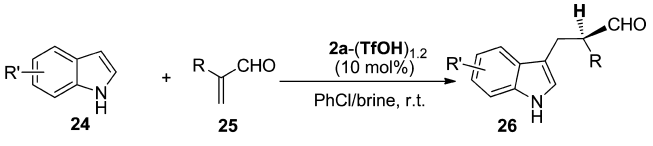
Scheme 14. Transformations of Photoalkylation Product 18e



Scheme 15. Challenges in the Aminocatalyzed Enantioselective α-Protonation of α-Branched Vinyl Ketones



Scheme 16. Enantioselective Enamine Protonation of α-Branched Acroleins



Hillman alcohols, and an intriguing δ-regioselective functionalization was observed.[30] Melchiorre and co-workers realized the enantioselective sulfa-Michael reaction of α,β-disubstituted

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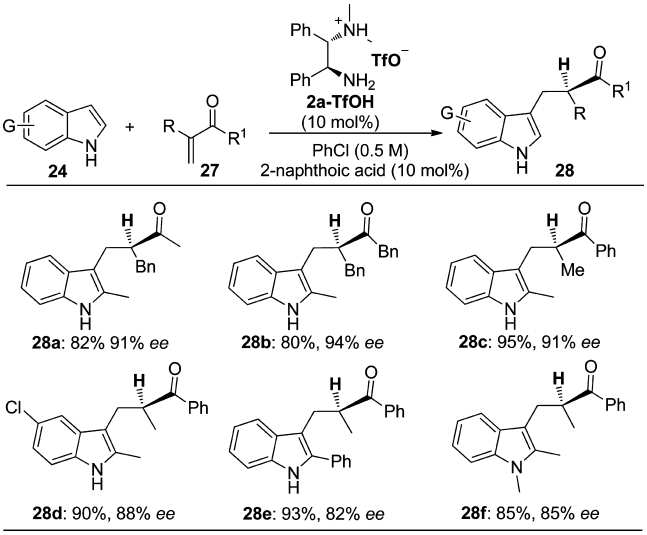
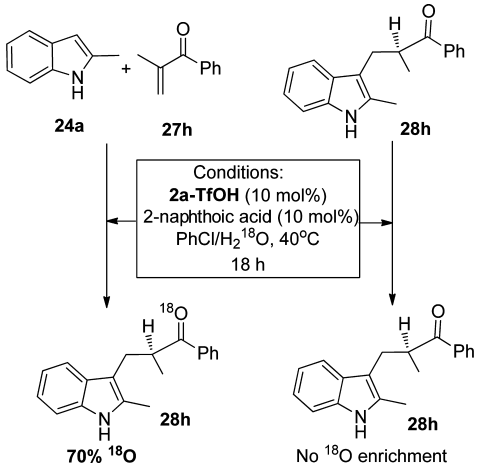
Scheme 17. Enantioselective Enamine Protonation of α-Branched Vinyl Ketones



Scheme 18. ^{18}O-Labeling Studies



enones by a combining cinchona alkaloid-derived primary amine with phosphoric acids.[31] In our studies, we mainly focused on iminium catalysis of α-branched vinyl ketones. This reaction represents a challenging yet fundamental method for generating chiral α-tertiary ketones that features an intriguing enamine protonation as the stereogenic step. As the most straightforward method for constructing chiral α-tertiary carbonyls, enantioselective protonation is widely utilized in nature, and the corresponding enol/enolate protonation has also been extensively explored in asymmetric catalysis.[32] Despite the notable advances with enol/enolate protonation,[33] enantioselective protonation via enamine intermediates has been an elusive goal until very recently.[34] The difficulties include the frequently encountered problems in enantioselective protonation, such as precise delivery of the proton and racemization of the products, as well as the difficulty of facilitating aminocatalysis with α-congested ketones. The usefully applied steric mode in iminium catalysis may not be applicable in this case since no stereocenter is generated in the addition step (Scheme 15), thus posing an intriguing stereocontrol issue. With the aim to develop a modular approach to the synthesis of chiral α-tertiary carbonyls, the reaction of α-branched vinyl ketones was pursued using our primary amine catalysts.

3.1. Asymmetric Friedel–Crafts Reactions of Indoles

In 2011, we reported the first catalytic asymmetric enamine protonation process in the Friedel–Crafts reaction of α-branched acroleins with indoles.[34] The reaction was enabled by primary–tertiary diamine **2a**, and various α-branched acroleins could participate in this reaction in moderate to good yields with 72–93% *ee* (Scheme 16).

The same catalyst **2a**-TfOH could also be applied to the reactions with α-branched vinyl ketones with not unexpectedly low activity but high enantioselectivity.[35] Subsequent screening and optimization indicated that the use of an acid additive such as 2-naphthoic acid could significantly improve the reaction rate. Under the optimized conditions, an array of α-substituted vinyl ketones, including both aliphatic and aromatic vinyl ketones, afforded the products in good yields with high enantioselectivities (Scheme 17).

The mechanism of this Michael addition/protonation reaction, particularly in regard to the stereocontrol, was next investigated.[35] ^{18}O-labeling studies ruled out a possible noncovalent acid catalytic pathway and were supportive of an iminium–enamine catalytic sequence (Scheme 18). Kinetic studies showed that the reaction is zeroth order with respect to the indole substrate (Figure 5A), indicating that iminium formation, prior to C–C bond formation and enamine protonation, is the rate-limiting step. Kinetic profiles also revealed a marked effect of the acidic additive on the activity but a marginal impact on the enantioselectivity (Figure 5B).

In our previous studies, we disclosed the origin of the enantioselectivity of the primary-amine-catalyzed enamine protonation of α-branched acroleins by DFT calculations. It was found that only the *E*-enamine was formed from the most stable *E-s-trans*-iminium ion after the Michael addition step. The enantioselectivity was controlled by face-selective protonation of the in situ-formed *E*-enamine via H_2O-bridged protonation wherein an O–H···π interaction with the reacting indole ring was involved (Scheme 19).[34,35]

Unlike the reaction of α-branched acroleins, both *E-s-trans*- and *E-s-cis*-iminium ions are accessible from the condensation between α-branched vinyl ketones and **2a.** The two iminium ion isomers can interconvert rapidly via single-bond rotation with a barrier of only 8.9 kcal/mol (Figure 6). The subsequent irreversible C–C bond formations of the *E-s-trans*- and *E-s-cis*-iminium ions with indole give the *E*- and *Z*-enamines, respectively. This constitutes a classical kinetic scenario that fits the Curtin–Hammett principle, and thus, the ratio of *E*- and *Z*-enamines could be determined according to the difference between the activation energies of the two reaction pathways.

DFT studies of the subsequent enamine protonation showed that it proceeds via a weak-acid-bridged proton transfer pathway. Moreover, the protonation was found to be enantiospecific, with the *E*-enamine giving the *S* product and the *Z*-enamine forming the *R* product exclusively (Scheme 20). Taken together, these results disclose an unprecedented Curtin–Hammett stereocontrol process in this reaction, with the enantioselectivity ultimately being governed by the ratio of the *Z*- and *E*-enamines, which is determined by the activation energy difference in the irreversible C–C bond formation step. The computed enantioselectivities according to this stereocontrol mode showed good consistency with the experimental outcomes.

According to this mechanistic scenario, the notoriously challenging task of manipulating selective proton transfer is transferred into regular selectivity tuning associated with the C–C bond formation. Hence, successful extensions to other

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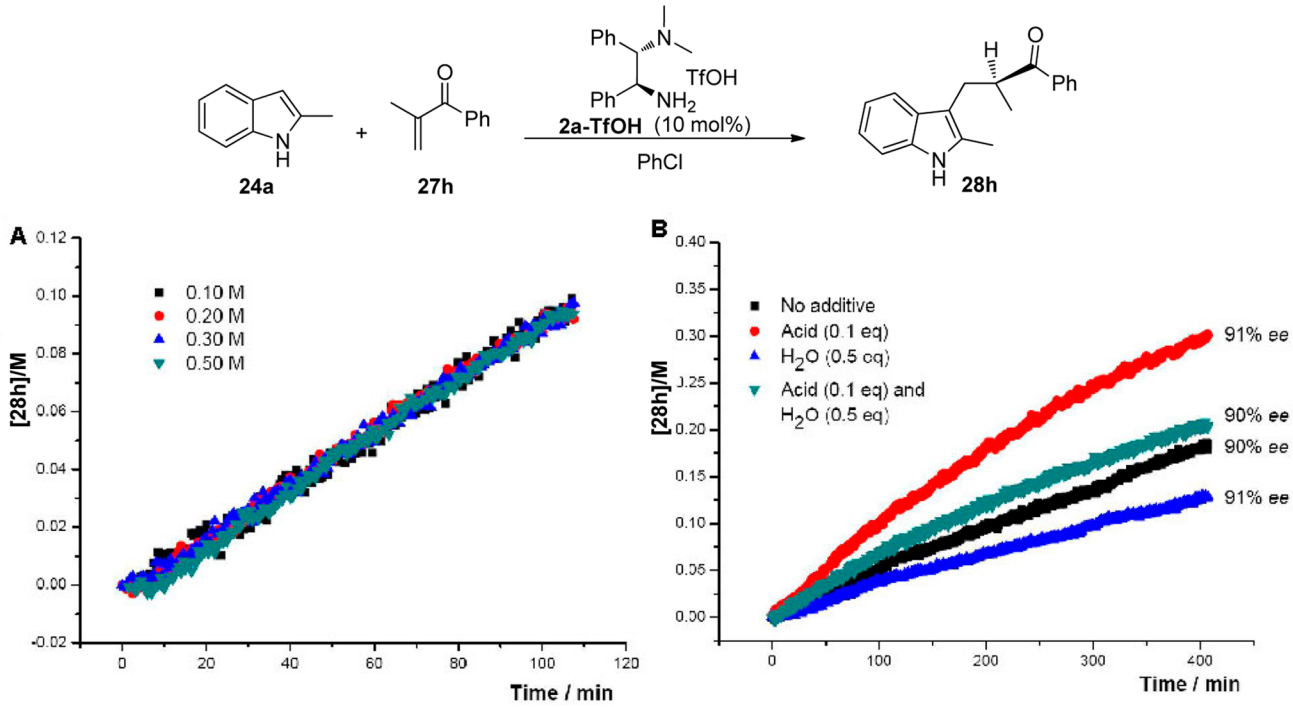
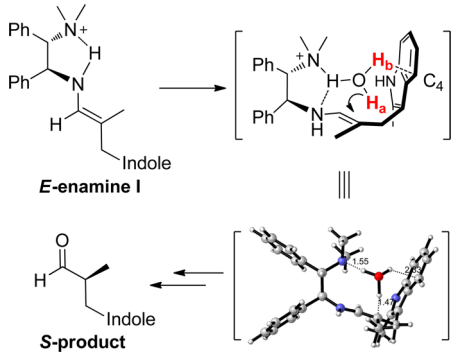


Figure 5. Reaction profiles of 2-methylindole (**24a**) and phenyl vinyl ketone (**27h**) with (A) varied initial concentrations of indole and (B) different additives ("Acid" denotes 2-naphthoic acid).

Scheme 19. Enamine Protonation with α-Branched Acroleins



nucleophiles in the reactions with vinyl ketones would be readily achieved.

3.2. Asymmetric Azole Addition

Though heavily studied, the 1,4-conjugate addition of azoles to α-branched vinyl carbonyls has not been reported to date. On the basis of the mechanistic scenario mentioned above, we examined the reaction between vinyl ketones and a series of azole compounds.[36] Notable enantioselectivity could be easily achieved simply by screening different primary amine catalysts. As shown by the results (Scheme 21), when benzotriazole was used as the nucleophile, aromatic and aliphatic vinyl ketones were well-accommodated with good activity and enantioselectivity. Other azoles, such as 1,2,4-triazole, 6-chloropurine, and

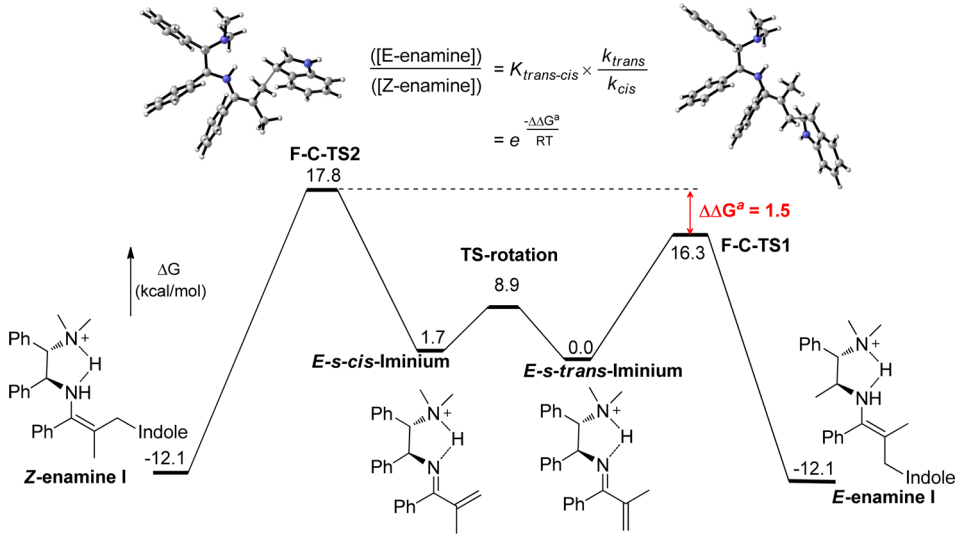


Figure 6. Curtin–Hammett control in the Friedel–Crafts step.

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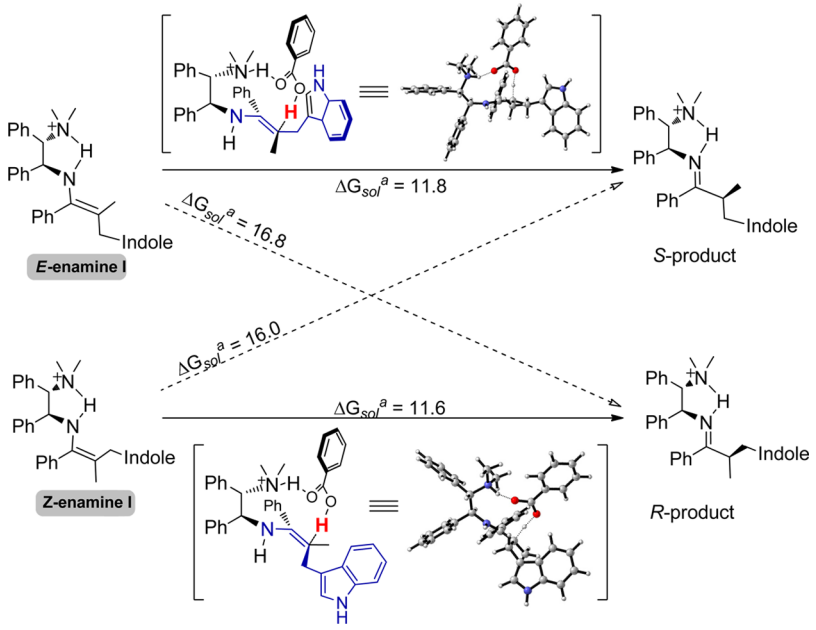
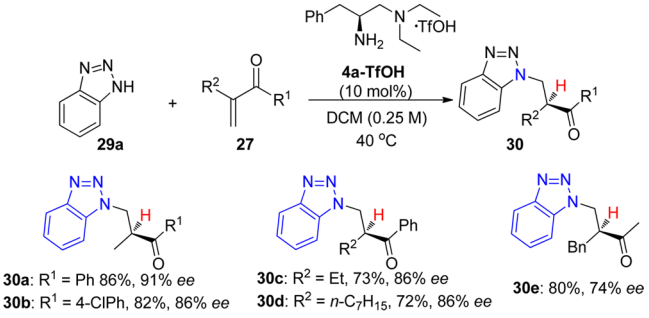
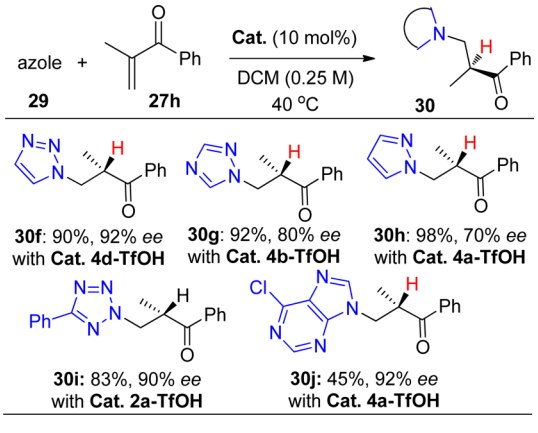
Scheme 20. Enantiospecific Enamine Protonation Step



Scheme 21. Reactions of Benzotriazole with α-Substituted Vinyl Ketones

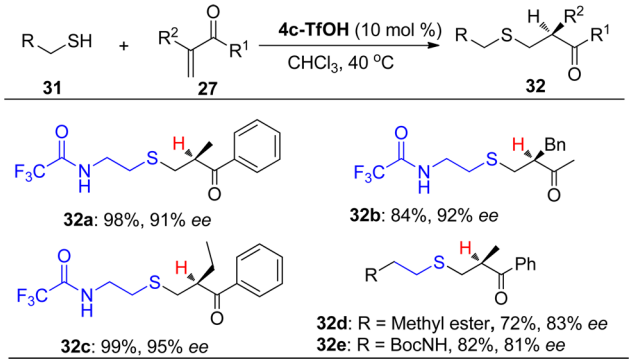


Scheme 22. Reactions of Azoles with α-Substituted Vinyl Ketones

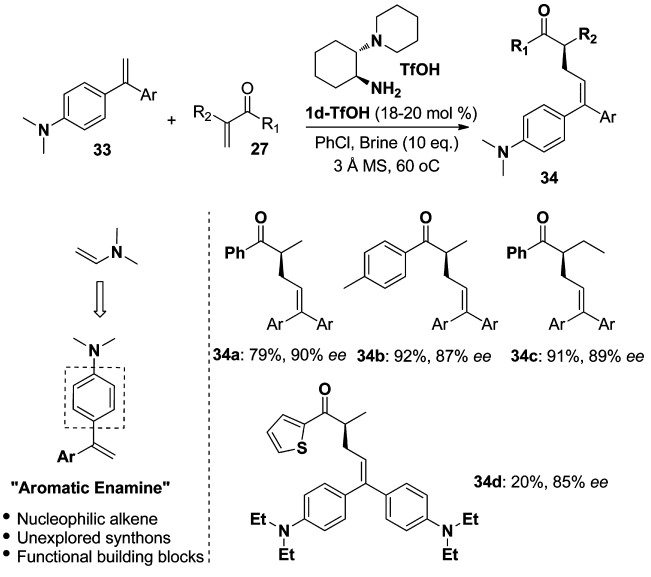


pyrazole, could also be applied in this aza-Michael addition/protonation reaction (Scheme 22) with good reactivity and enantioselectivity. Further DFT studies confirmed the Curtin–Hammett stereocontrol in this case.

Scheme 23. Sulfa-Michael Addition/Enamine Protonation of α-Branched Vinyl Ketones



Scheme 24. α-Protonation Reaction Triggered by Alkenes



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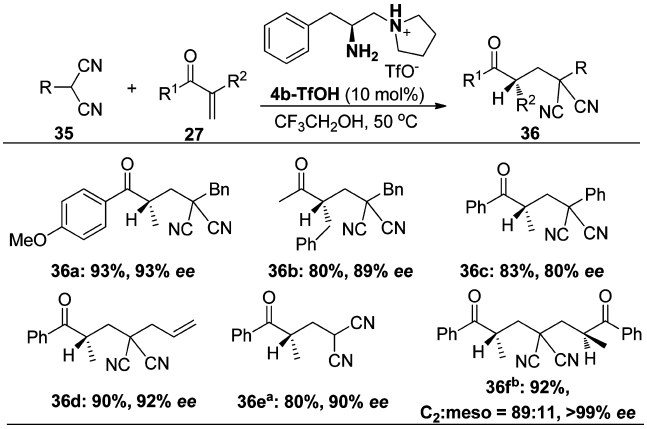
Scheme 25. α-Protonation Reaction Triggered by Malononitriles



[a]Malononitrile:α-methyl vinyl ketone = 3:1. [a]Malononitrile:α-methyl vinyl ketone = 1:3.

3.3. Asymmetric Sulfa-Michael Addition

The asymmetric sulfa-Michael addition to electron-deficient alkenes has significant potential in pharmaceutical synthesis. Despite tremendous achievement on this reaction in the past decades, sulfa-Michael addition to α-branched vinyl ketones has not been achieved. This type of reaction was also pursued with our developed primary amine catalysts.[37] As expected, high enantioselectivity could be readily reached after simple screening of the primary amine catalysts. Both aromatic and aliphatic vinyl ketones gave excellent enantioselectivities with the odorless thiol **31a** (**32a**–**c**; Scheme 23). Furthermore, thioglycolate and its analogues were also applicable sulfur sources for this catalytic system, affording the desired adducts in good yields and enantioselectivities (**32d** and **32e**).

3.4. Asymmetric Alkene Addition

Alkenes are seldom utilized in conjugate addition reactions because of their low nucleophilicity as well as the uncontrolled side reactions accompanying such processes. We recently found that *p*-vinylanilines **33**, endowed with an intervening aromatic ring between the amine and vinyl group, demonstrated nucleophilic reactivity closely resembling that of typical enamines.[38] These alkene nucleophiles were also tested in the enantioselective α-protonation reaction.[39] With the aid of primary–tertiary diamine **1d**, the reactions with aromatic vinyl ketones proceeded smoothly, and the desired products **34** were obtained with good to high enantioselectivities (Scheme 24).

3.5. Asymmetric Addition with Malononitriles

Very recently, we further expanded this asymmetric α-protonation protocol to the reactions with malononitrile nucleophiles.[40] Under the catalysis of **4b**, the addition of 2-substituted malononitriles to α-branched vinyl ketones produced the α-protonation products in high to excellent yields and enantioselectivities (Scheme 25). The substitutions on the nucleophiles could be phenyl, benzyl, allyl, and others (**36a**–**d**). When unsubstituted malononitrile was used as a nucleophile, mono- or disubstituted products could be obtained selectively depending on the substrate loading (**36e** and **36f**). The reaction could also be performed under cascade conditions, where the nucleophiles were generated in situ by the reduction of 2-benzylidenemalononitriles with Hantzsch ester (Scheme 26).

4. CONCLUSION

In this Account, we have summarized our recent advances in asymmetric aminocatalysis with sterically congested α-branched ketones, an elusive goal in aminocatalysis. These enantioselective transformations have been enabled by the identification of a uniform type of chiral primary amine catalyst that features a primary–tertiary vicinal diamine skeleton. Because of their intrinsic conformational flexibility as well as the tuning ability of acidic additives, the chiral primary amine catalysts are able to facilitate the enamine-based transformations with α-substituted ketones, particularly β-ketocarbonyls, in generating chiral α-quaternary ketones. Similarly, the primary–tertiary diamine–Brønsted acid conjugates allow for exquisite stereocontrol of the elusive enamine protonation, thus making possible the tandem conjugate addition/stereogenic enamine protonation reactions with α-substituted vinyl ketones, leading to a plethora of chiral α-tertiary ketones. Another salient feature of the current catalytic system is the compatibility with transition-metal catalysis, as verified in its synergy with copper-catalyzed aerobic oxidation and Ru-mediated photoredox catalysis. On the basis of the versatility of our primary amine catalysts, enormous potential in pursuing synergistic catalysis in concert with transition metals is anticipated. Last but not least, the development of a new generation of primary amine catalysts with improved catalytic turnover is also warranted in order to enhance their practicality.

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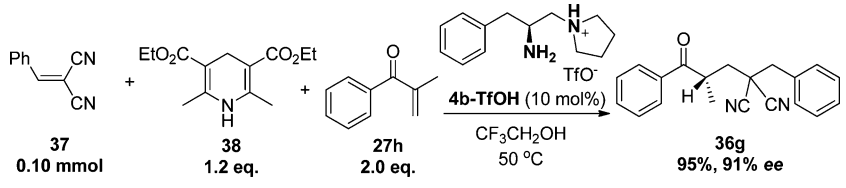
Notes

The authors declare no competing financial interest.

Biographies

Long Zhang was born in 1980 in Hebei, China. He graduated from Nankai University in 2005 with a major in chemistry. He then spent 5 years pursuing a Ph.D. degree in a joint project between Nankai University and the Institute of Chemistry of the Chinese Academy of Sciences (ICCAS) under the supervision of Prof. Jin-Pei Cheng and Prof. Sanzhong Luo. After gaining his Ph.D., he joined Prof. Luo's group as an assistant professor in July 2010 and was promoted to associate professor in 2013. His work focuses on the development of new asymmetric aminocatalysts as well as on DFT studies of mechanisms.

Scheme 26. Tandem Reduction and Michael Addition/Protonation Reaction



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Niankai Fu was born in 1987 in Hubei, China. He graduated from Hubei University in 2009 and gained his Ph.D. from the ICCAS in 2014 under the supervision of Prof. Jin-Pei Cheng and Prof. Sanzhong Luo. Immediately afterward, he joined Prof. Luo's group as an assistant professor. He is currently working on enantioselective enamine protonation reactions.

Sanzhong Luo was born in 1977 in Henan, China. He graduated from Zhengzhou University in 1999 and then spent his graduate studies successively at Nankai University, the Chinese Academy of Sciences (CAS), and The Ohio State University (USA), gaining his Ph.D. from CAS in 2005 under the supervision of Prof. Jin-Pei Cheng. He was a visiting scholar at Stanford University in 2009 (with B. M. Trost). He started his independent career in July 2005 at ICCAS and became a full professor there in 2011. His laboratory focuses on asymmetric catalysis and synthesis, emphasizing the development of new catalysts and catalytic modes by drawing inspirations from nature.

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