Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters

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ABSTRACT

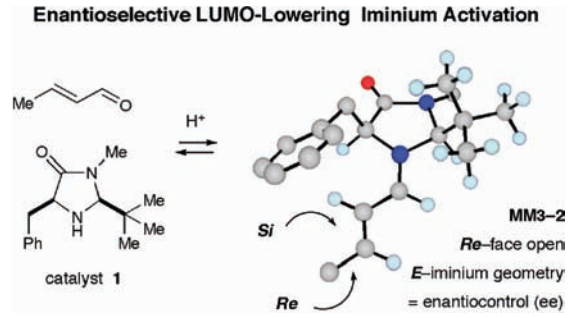
Within the realm of catalytic asymmetric hydrogenation, the focus continues to be on the use of chiral metal complexes in conjunction with a hydrogen source. Recently, the widespread development of organocatalysis, including the invention of iminium activation, has led to the discovery of many new enantioselective transformations. Based on this strategy, a number of bioinspired processes for the enantioselective organocatalytic transfer hydrogenation of α,β-unsaturated carbonyl compounds and imines have been discovered. These topics will be the focus of this Account.

Introduction

In the realm of enantioselective hydrogenation, the use of molecular hydrogen or a hydride donor in conjunction with a chiral metal catalyst system has emerged as the preeminent strategy for asymmetric catalysis within the chemical community.[1] It is intriguing to consider, however, that the vast majority of C−H stereogenic centers that currently exist globally were not created via organometallic catalysis. Indeed, this honor belongs to a series of biochemical processes that create hydrogen-bearing stereocenters in biological cascade sequences controlled by enzymes and hydride reduction cofactors.[2] With this in mind, our laboratory recently questioned whether the conceptual blueprints of biochemical transfer hydrogenation might be employed in a chemical reduction wherein enzymes and cofactors are replaced by small molecule organocatalysts and Hantzsch ester dihydropyridine systems. The present Account will discuss the advent and development of this new biomimetic organocatalytic strategy, which has subsequently been translated into operationally simple laboratory protocols for the development of chemo- and enantioselective hydride addition, transfer hydrogenation, and cascade catalysis reactions involving electron-deficient imines and olefin substrates.

Enantioselective LUMO-Lowering Iminium Activation

In 1999, our laboratory introduced the concept of iminium activation, which is based on the capacity of chiral amines to function as enantioselective LUMO-lowering catalysts for a broad range of synthetic transformations.[3] This



catalysis concept was founded on the mechanistic hypothesis that the reversible formation of iminium ions from α,β-unsaturated carbonyls and secondary amines could emulate the equilibrium dynamics and π-orbital electronics inherent to Lewis acid catalysis. For this purpose, we developed chiral secondary amine catalysts based on the imidazolidinone architecture **1**, incorporating the required elements for high levels of iminium geometry control and π-facial discrimination of the catalyst-activated iminium ion **MM3–2**. Currently, this organocatalytic LUMO-lowering iminium activation strategy has led to the development of over 30 different enantioselective transformations for asymmetric synthesis, including enantioselective cycloadditions,[4] Friedel–Crafts alkylations,[5] heteroconjugate additions,[6] epoxidations,[7] aziridination,[8] cyclopropanations,[9] and cascade reactions.[10]

Nature's Enantioselective Hydrogenation Strategies

Nature's biological systems create the element of C−H stereogenicity using transform-specific oxidoreductases.[2] These enzymes are comprised of cofactors that play the vital role of being "Nature's reducing agents". The dihydropyridine-based nucleotides NADH (reduced nicotinamide adenine dinucleotide) and the closely related NADPH (reduced nicotinamide adenine dinucleotide phosphate) are the most prevalent cofactors used for enantioselective biochemical hydrogenations. Based on this general transfer hydrogenation strategy, Nature's biosynthetic ma-

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David W. C. MacMillan was born in Bellshill, Scotland, in 1968. He received a B.S. at the University of Glasgow and earned a Ph.D. from the University of California, Berkeley, in 1996 under the guidance of Larry Overman. Following postdoctoral studies with David Evans at Harvard University, he began his independent career at University of California, Berkeley, in 1998 before moving to the California Institute of Technology in 2000. In 2006, he took a position at Princeton University as the A. Barton Hepburn Chair of Chemistry and Director of the Merck Center for Catalysis at Princeton University. His research interests are in asymmetric catalysis and natural product synthesis.

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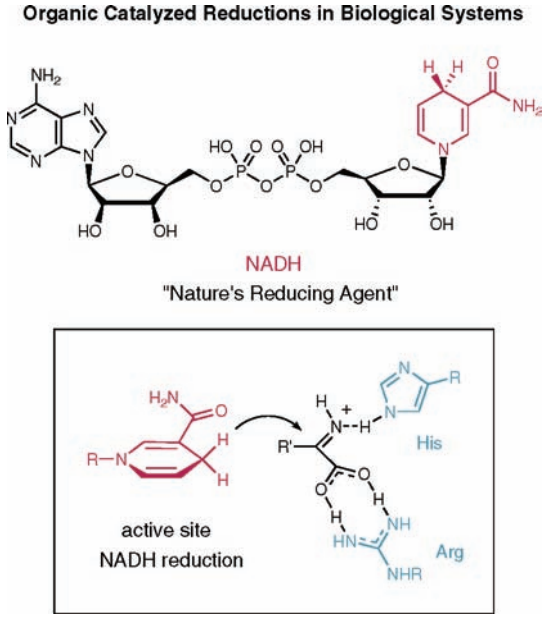
chines create important biomonomer building blocks, including chiral alcohols and amines, required for other essential metabolic processes.[2] From a chemical perspective, it is important to consider that molecules such as NADH incorporate two architectural components that function in concert to enable highly selective delivery of hydride to electrophilic biochemical species. First, the nucleosidic element is present to enable molecular recogition of a specific enzymatic environment wherein selective reduction might occur. Second, the dihydropyridine ring system (once positioned in the vicinity of a specific electrophile) has the capacity to deliver a hydride

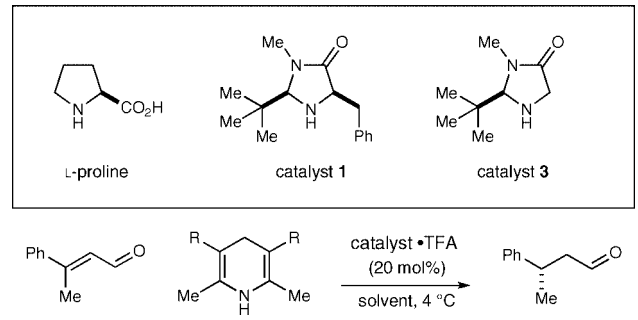


species to a carbonyl or imine to create an enantioenriched C−N or C−O stereogenic center.

Enantioselective Organocatalytic Transfer Hydrogenation (EOTH)

On the basis of the two catalysis concepts outlined above, we questioned whether the conceptual blueprints of biochemical reductions could be merged with iminium activation to enable a laboratory approach to olefin reduction wherein enzymes and cofactors are replaced by our imidazolidinone catalysts and an NADH analog. More specifically, we hypothesized that β,β'-disubstituted-α,β-unsaturated aldehydes might readily undergo enantioselective 1,4-hydrogenation upon subjection to our iminium catalysts in the presence of a Hantzsch ester.[11] In particular, we felt that Hantzsch esters might serve the role of a small-molecule NADH analog given that this dihydropyridine system has been demonstrated to participate in hydride delivery with electrophilic π-systems in a variety of noncatalytic processes (including enone hydrogenation). In this context, we designed a biochemically inspired protocol that formally allows the enantioselective transfer of hydrogen from Hantzsch esters[12] to enal/enone-olefins using simple amine catalysts. The implementation of this new strategy represented, to our knowledge, the first

Table 1. Effect of Catalyst and Dihydropyridine on EOTH

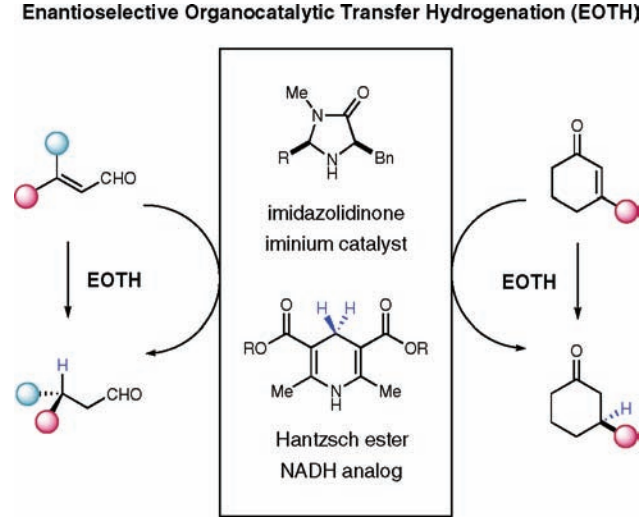


entry	catalyst	hydrogen source	solvent	% conversion[a]	% ee
1	L-proline	R = CO_2Et	toluene	47	15
2	**1**	R = CO_2Et	toluene	96	75
3	**3**	R = CO_2Et	toluene	95	88
4	**3**	R = CO_2Et	$CHCl_3$	99	85
5	**3**	NADH	$CHCl_3$	NR	NA
6	**3**	*N*-Bn-nicotinamide	$CHCl_3$	15	88
7	**3**	R = CO_2Bn	$CHCl_3$	94[b]	88
8	**3**	R = CO_2Et	$CHCl_3$	91[b]	93

[a] Conversion determined by GLC analysis. [b] Reaction conducted at –30 °C.

enantioselective organocatalytic transfer hydrogenation (EOTH).[13,14]

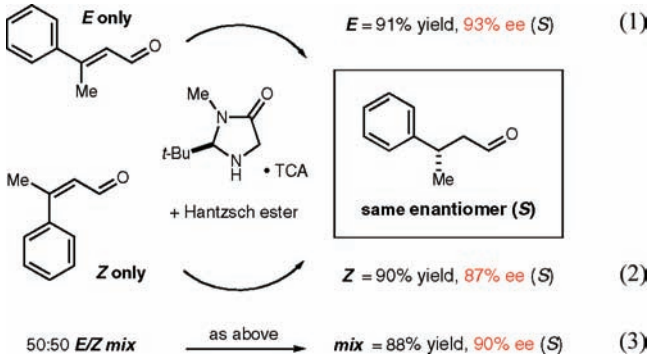
Enantioselective Organocatalytic Transfer Hydrogenation of Enals. We initiated studies to evaluate potential iminium catalysts and Hantzsch ester sources that would effectively participate in the enantioselective hydrogenation of α,β-unsaturated aldehydes (Table 1). Initial experiments were performed with 3-methyl-(*E*)-cinnamaldehyde in a variety of reaction media. Notably, attempts to employ



proline as an iminium catalyst in this context resulted in inefficient and nonselective reduction (entry 1). To our great delight, imidazolidinone-catalyzed hydride reductions (with both catalysts **1** and **3**) led to a dramatic increase in enantioselectivity and efficiency (entries 2–4). Interestingly, with respect to the evaluation of dihydropyridine analogs, we observed that NADH was not a viable reagent, whereas *N*-benzylnicotinamide was quite selec-

tive (entries 5 and 6). We presume that the lack of efficiency in both cases arises from the formation of a 1-alkyl-pyridinium ion byproduct in lieu of a protonated pyridine salt (a species that is required for catalyst turnover via proton-mediated hydrolysis of the initial enamine product). While a range of dihydropyridines that incorporate electron-withdrawing groups at the 3,5-position were useful, the ethyl substituted Hantzsch ester (HEH) proved to be superior (entry 8, 93% ee). Further optimization of the reaction parameters revealed that enhanced levels of asymmetric induction and efficiency were achieved by amine salt **3**•TFA in $CHCl_3$ at –30 °C to afford (*S*)-3-phenylbutanal in 91% yield and 93% ee.[15]

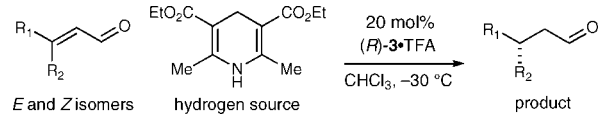
We next examined the influence of the geometrical purity of the aldehyde olefin on the sense of asymmetric induction, because it is well documented within the field of metal-mediated hydrogenations that olefin geometry generally dictates enantiospecific reduction.[16] In such cases, high levels of asymmetric induction can only be

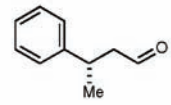
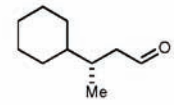
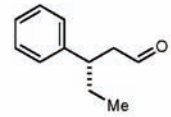
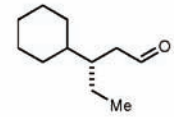
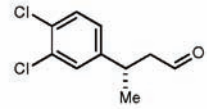
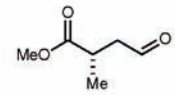
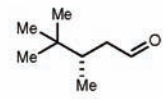
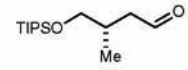


achieved if the substrate starting material is employed as a single olefin isomer. As shown in eqs 1 and 2, we were delighted to find that using our iminium activation protocol both olefin isomers *converged to provide the same enantiomer of the hydrogenated product*. Moreover, we showed that the levels of enantiomeric induction remained high and were effectively independent of the isomeric ratio present in the starting materials (eq 3, 90% ee). Preliminary mechanistic studies have shown that the origin of stereoconvergence arises from catalyst accelerated *E*−*Z* bond isomerization prior to selective reduction of the olefin isomer that positions the sterically more demanding substituent in the *trans*-orientation. We believe that the capacity to tolerate starting materials of low geometric purity enhances dramatically the general utility of this new hydrogenation protocol. More specifically, practitioners are free to employ nonselective technologies for the production of olefin starting materials prior to use of this enantioconvergent catalysis protocol.

Experiments that probe the scope of this new organocatalytic hydride reduction are summarized in Table 2. Significant latitude in the steric and electronic demands of the α,*β*-unsaturated aldehyde component is possible. High levels of enantiocontrol are obtained in transformations where the *β*,*β*-olefin substituents have similar steric constraints (entries 1−6, R_1 = Me, Et; R_2 = Ar, *c*-hexyl, *t*-butyl). Notably, the ethyl−cyclohexyl combination forms

Table 2. EOTH of α,*β*-Unsaturated Aldehydes: Substrate Scope



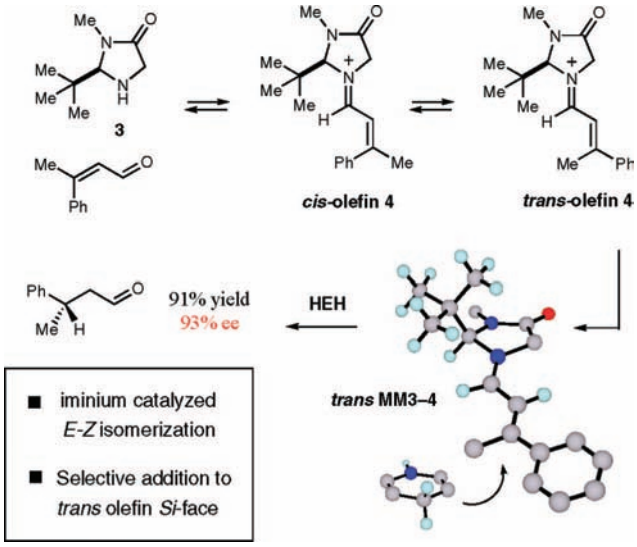
entry[a]	product	entry[a]	product
1	 91% yield, 93% ee[b]	5	 91% yield, 96% ee[b,e]
2	 74% yield, 94% ee	6	 95% yield, 91% ee[e,f]
3	 92% yield, 97% ee	7	 83% yield, 91% ee[e,g]
4	 95% yield, 97% ee[c,d]	8	 74% yield, 90% ee

[a] *E*/*Z* ratios for substrates were >20:1. [b] Performed at −45 °C. [c] Yield determined by NMR. [d] At 23 °C with 5 mol % catalyst. [e] *E*/*Z* ratios for substrates were between 3:1 and 5:1. [f] With 10 mol % catalyst. [g] At −50 °C.

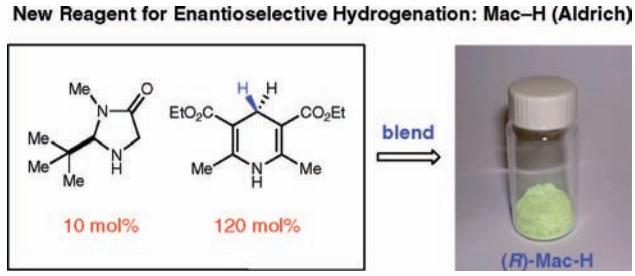
the corresponding product in 91% ee, a remarkable transformation that differentiates the geometrical location of methine and methylene substituents in an efficient dynamic kinetic resolution. It is important to note that a variety of chemical functionalities appear to be inert to these organocatalytic conditions that, in certain cases, can be susceptible to metal reduction (e.g., halogens, esters, and aldehydes). The sense of asymmetric induction observed in all cases is consistent with the selective engagement of the Hantzsch ester with the *Si*-face of the catalyst-activated *trans*-iminium ion as depicted as **MM3–4** (Scheme 1). Indeed, computational models provide supporting evidence that the *cis*-iminium ion will be energetically disfavored on the basis of nonbonding interactions between the carbon−carbon double bond and the *tert*-butyl group on the catalyst framework. In addition, the *tert*-butyl catalyst substituent also serves to effectively shield the *Re*-face of the activated olefin, exposing the *Si*-face for enantioselective hydride reduction.[14]

We have further enhanced the operational simplicity of the laboratory procedure by introducing a new bench-stable reagent for asymmetric hydrogenation. The reagent

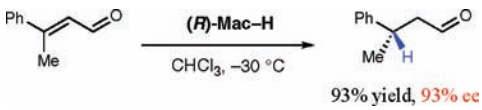
Scheme 1



is a blend of the imidazolidinone catalyst **3** (10 mol%) and the ethyl Hantzsch ester (120 mol%) and is marketed as (*R*)- or (*S*)-Mac-H (mixture for asymmetric catalytic hydrogenation).[17] Mac-H has been shown to remain catalytically active after 72 months shelf-time (0 °C storage)



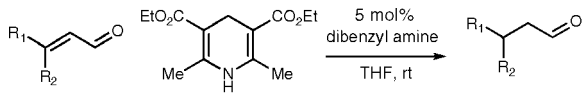
and performs the enantioselective hydrogenation of 3-methyl-cinnamaldehyde with identical results to those



(4)

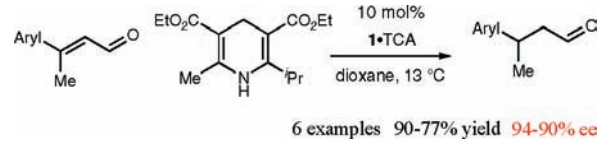
obtained with freshly prepared reagents (eq 4).

Based on our LUMO-lowering iminium activation strategy, List and co-workers also reported an almost identical variant of this organocatalytic hydride reduction involving α,β-unsaturated aldehydes.[18] Preliminary studies



(5)

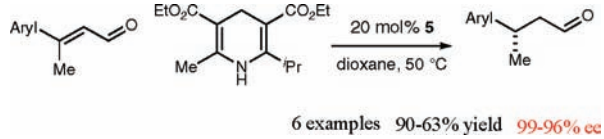
from their laboratory described a catalytic but nonasymmetric transformation wherein achiral secondary amines in conjunction with the ethyl Hantzsch ester, were found to effectively hydrogenate β-substituted and β,β-disubstituted-α,β-unsaturated aldehydes (eq 5). Subsequent to their initial studies, the List group also described an enantioselective variant of this hydrogenation protocol using our imidazolidinone catalyst **1**•TCA (eq 6). In comparing the catalysts that our laboratory has introduced for iminium activation, it has been our experience that imidazolidinone **3** far exceeds the reaction efficiency and enantiocontrol exhibited by imidazolidinone **1** in this conjugate reduction (using a broad range of β,β-disubstituted α,β-unsaturated aldehydes).



(6)

Recently, Mayer and List reported the development of a novel mode of iminium activation termed asymmetric counteranion-directed catalysis (ACDC), which can be readily employed for enantioselective transfer hydrogenation (eq 7).[19] In this case, a chiral Brønsted acid catalyzes the formation of an iminium ion via the reversible condensation of an α,β-unsaturated carbonyl system and an amine catalyst in analogy with our own LUMO-lowering activation studies. However, one ingenious difference is that the source of asymmetry in this catalyst system is located on the anionic counterion that resides in electrostatic contact with the activated iminium intermediate. The successful implementation of this strategy represents a powerful new mode of chirality transfer from a chiral counteranion to a LUMO-lowered pro-chiral iminium π-system that, in this first rendition, can enantioselectively intercept a hydride ion from the Hantzsch ester. We anticipate that a variety of the transformations that have been developed using our iminium ion activation strategy will be amenable to this new counterion variant.

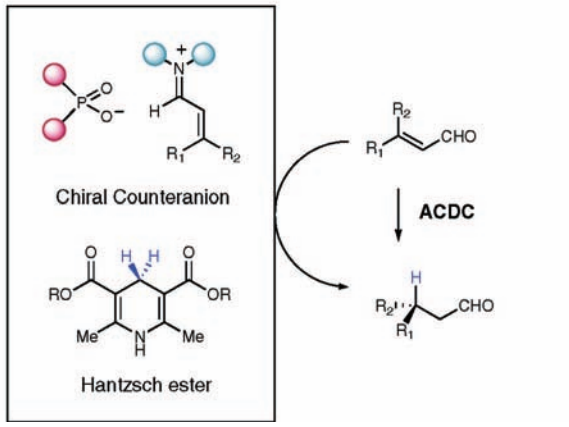
The most effective counteranion system for the reduction of α,β-unsaturated aldehydes was based on an *ortho*-2,4,6-triisopropyl-phenyl (TRIP catalyst) substituted variant of the Akiyama[20]–Terada[21] binaphthol phosphate and morpholine as the amine catalyst (catalyst **5**). The chiral iminium salt effectively undergoes enantioselective hydride reduction using the ethyl Hantzsch ester derivative as the hydrogen source. Evaluation of the substrate scope revealed that a broad range of β,β-aryl,methyl-disubstituted enals effectively participate as substrates in this transformation. Although this approach does not represent a general solution for the enantioselective reduction of β,β-alkyl-disubstituted α,β-unsaturated aldehydes, it was effective for the enantioselective synthesis of (*R*)-



(7)

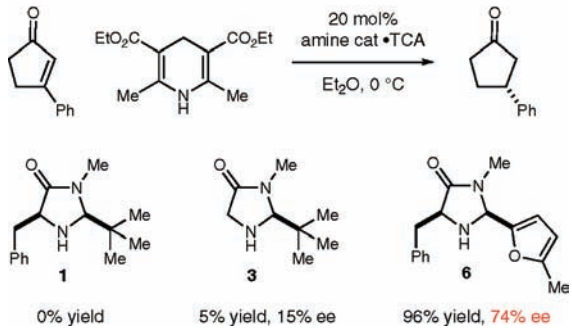
citronellal (71% yield, 90% ee) from the reduction of (*E*)-citral (Scheme 2).

List: Asymmetric Counteranion-Directed Transfer Hydrogenation



Enantioselective Organocatalytic Hydride Reduction of Enones. Inspired by our success on the enantioselective organocatalytic transfer hydrogenation of enals, we questioned whether we could further employ this biomimetic activation strategy to accomplish the enantio- and chemoselective reduction of cyclic enones. On this basis, we re-evaluated our design strategy considering that ketones are sterically and electronically deactivated toward iminium formation in comparison to aldehydic carbonyls. More specifically, we examined the furyl imidazolidinone catalyst **6** in our preliminary studies, an amine that we previously employed in enantioselective Diels–Alder reactions with cyclic α,β-unsaturated ketones.[4b] As expected, catalyst **6** was indeed successful, allowing the organocata-

Organocatalytic Enone Reduction: Preliminary Results



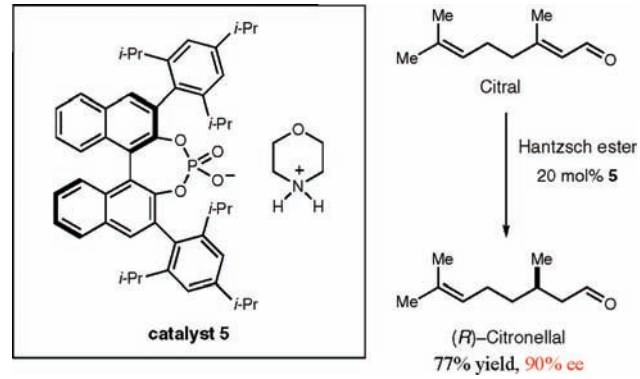
(8)

lytic hydrogenation of 3-phenyl-2-cyclopentenone with excellent reaction efficiency and suitable levels of enantiocontrol for subsequent optimization (eq 8, 96% yield, 74% ee).[22]

We next evaluated the structural influence of the dihydropyridine reagent on the enantioselectivity of this enone hydrogenation reaction. As noted for the hydride reduction of enals, the substitution pattern of the dihydropyridine reductant has a significant impact on both the efficiency and stereocontrol. Indeed, we observed a trend toward improved enantioselectivity as the size of the ester functionality at the 3,5-dihydropyridine site increased (R = Et, 96% conversion, 74% ee; R = *i*-Pr, 78% conversion, 78% ee; R = *t*-Bu, 86% conversion, 91% ee).

While it might be envisioned that such a trend in enantiocontrol arises on account of increased or decreased

Scheme 2

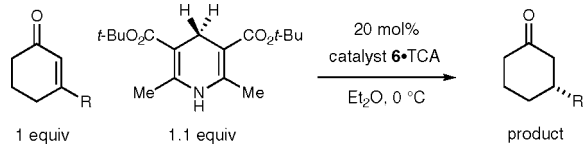


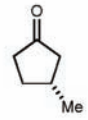
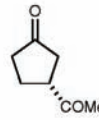
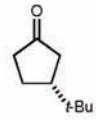
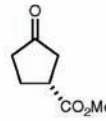
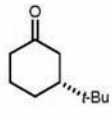
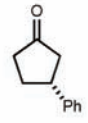
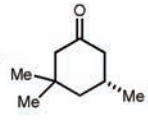
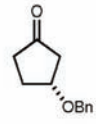
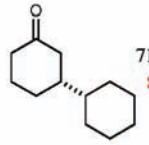
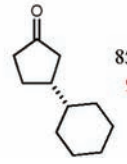
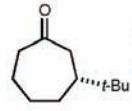
nonbonding interactions between the Hantzsch ester ring and the catalyst−iminium framework, we believe that electronic factors might also play a major role. Specifically, single-crystal X-ray analysis reveals that the *tert*-butyl Hantzsch ester ring exists in a boat conformation. Accordingly one of the hydrogen substituents at the 4-position of this dihydropyridine ring system is locked in an axial orientation thereby maintaining overlap between the nitrogen lone-pair and the hydridic C−H bond while in the ground state. In contrast the ethyl-substituted Hantzsch ester ring exists in a planarized form wherein poor π-orbital overlap between the analogous C−H bond and nitrogen renders a less reactive hydridic reagent. This analysis is consistent with not only an increase in enantiocontrol when using the more bulky *tert*-butyl Hantzsch ester but also improved reaction rate and efficiency. The superior levels of induction and efficiency exhibited by the bis(*tert*-butyl) Hantzsch ester, TCA salt of catalyst **6**, in Et_2O at 0 °C to afford (*R*)-3-phenylcyclopentanone prompted us to select these conditions for further exploration.[22]

The scope of the cyclic enone component was examined, and the results are highlighted in Table 3. A wide range of electronically and structurally diverse carbocycles and β-olefin substituents are tolerated in this enantioselective transfer hydrogenation. In particular, good levels of asymmetric induction were observed for substrates that do not readily participate in iminium ion formation (entry 7, R = COMe, 78% yield, 91% ee and entry 8, R = CO_2Me, 83% yield, 90% ee). Importantly, this strategy appears to be suitable for the enantioselective hydrogenation of a range of enone ring sizes, including cyclopentenyl (entry 1, 72% yield, 95% ee), cyclohexenyl (entry 9, 82% yield, 90% ee), and cycloheptenyl (entry 12, 70% yield, 92% ee), including enones that incorporate alkyl substituents at other positions, an important consideration with respect to natural product synthesis (entry 10, 66% yield, 98% ee).

It should be noted that the sense of asymmetric induction observed in all cases is consistent with the reduction of a *cis*-iminium ion **MM3–7** (Scheme 3) from the least sterically hindered *Si*-face. This result is in complete agreement with our previously reported Diels–Alder cycloaddition studies involving the imidazolidinone catalyst **6**.[4b]

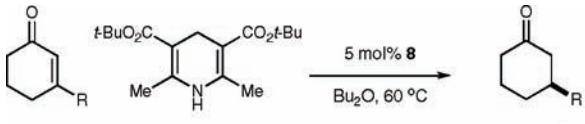
Table 3. Scope of the Organocatalytic Enone Reduction



entry	product		entry	product	
1		72% yield[a] 95% ee	7		78% yield 91% ee
2		81% yield[a] 96% ee	8		83% yield 90% ee
3		78% yield 90% ee	9		82% yield 90% ee
4		73% yield 91% ee	10		66% yield 98% ee
5[b]		89% yield 91% ee	11		71% yield 88% ee
6[c]		85% yield 96% ee	12		70% yield 92% ee

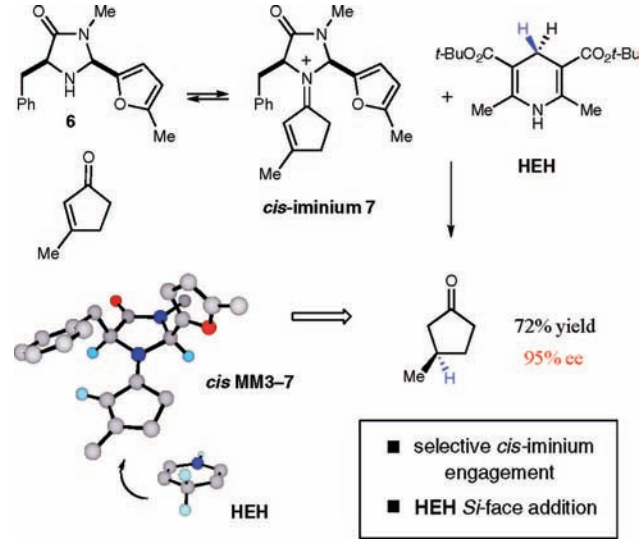
[a] Yield determined by NMR. [b] Performed with 1.3 equiv of Hantzsch ester. [c] Performed with 1.1 equiv of Hantzsch ester.

Subsequent to our studies, Martin and List reported a complimentary approach for the enantioselective transfer hydrogenation of enones using Hantzsch esters based on their previously developed asymmetric counteranion-directed catalysis (ACDC) strategy.[23] For this purpose, enantiopure α-amino acids were evaluated, where the L-valine salt of the TRIP catalyst (catalyst **8**, Scheme 4) provided the highest levels of enantioselectivity.

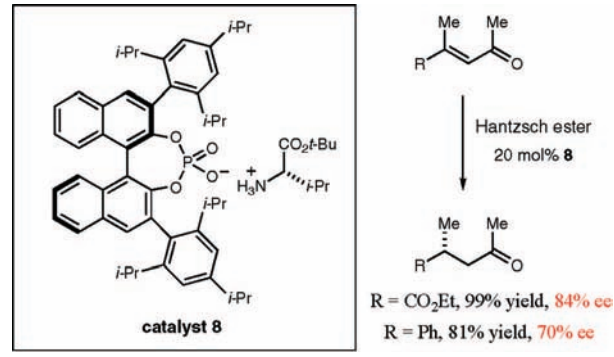


(9)

Scheme 3



Scheme 4

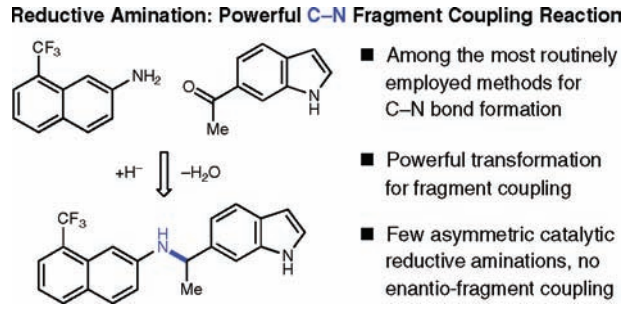


Investigation of the substrate scope revealed that a broad range of cyclic enones effectively participate as substrates in this transformation (eq 9). Interestingly, based on this catalysis platform, acyclic enones can also be reduced with moderate to good selectivities.

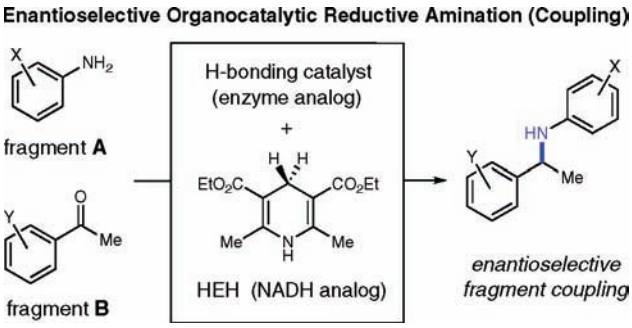
Enantioselective Organocatalytic Reductive Amination

The reductive amination reaction represents one of the most powerful and widely utilized transformations for the rapid introduction of stereogenic C−N bonds, a common synthon found in natural isolates and medicinal agents. While a variety of protocols have been described for the asymmetric reduction of ketimines (a strategy that requires access to preformed, bench stable imines), it is surprising that few laboratory methods are known for enantioselective reductive amination. Moreover, the use of this ubiquitous reaction for the union of complex ketone and amine- containing fragments remains unprecedented in the realm of asymmetric catalysis, a remarkable fact given the widespread application of both racemic and diastereoselective variants.

In contrast, Nature has perfected reductive amination as a powerful in vivo chemical tool for the enantioselective synthesis of essential amino acids via selective reduction of H-bond activated pyruvate-derived ketimines. With this



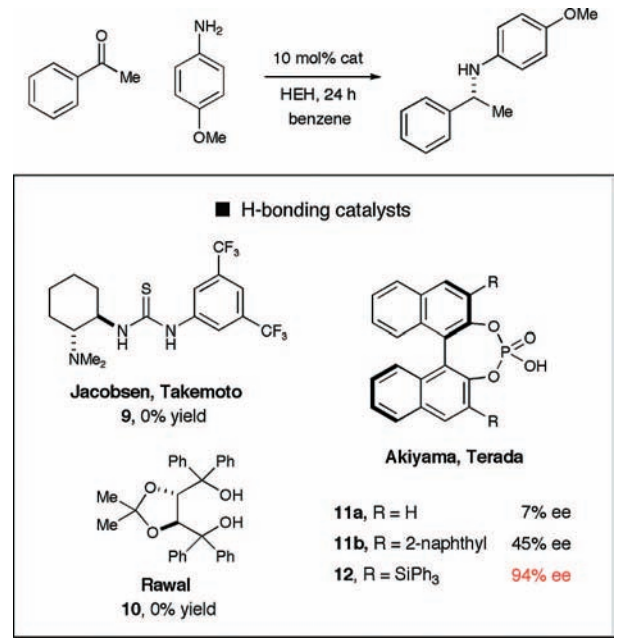
in mind, we proposed the design of an organocatalytic reductive amination strategy, based on the conceptual blueprints of biochemical amination wherein enzymes



and cofactors would again be replaced by small organic catalysts and NADH analogs such as Hantzsch ester. Specifically, we proposed that exposure of ketone and amine coupling partners to a chiral hydrogen-bonding catalyst would result in the intermediate formation of an iminium species that in the presence of a suitable Hantzsch ester would undergo enantioselective hydride reduction, thereby allowing asymmetric reductive amination in an in vitro setting. Given the tremendous advances in hydrogen-bonding catalysis over the last eight years (as pioneered by Jacobsen,[24] Corey,[25] Takemoto,[26] Rawal,[27] Johnston,[28] Akiyama,[19] and Terada[20]), we felt optimistic that a suitable catalyst class might be identified to bring this concept to fruition.

Our biomimetic reductive amination strategy was first investigated with acetophenone, *p*-anisidine, ethyl Hantzsch ester and several classes of well established hydrogen-bonding catalysts (eq 10). While thiourea **9** and taddol **10** failed to induce reductive amination, the binol phosphoric acid catalysts **11a,b** (introduced by Akiyama and Terada)[20,21] provided encouraging results (6–45% conversion, 7–65% ee). To our great delight, we found that an unprecedented *ortho*-triphenylsilyl variant of the Terada–Akiyama catalyst **12** facilitates the desired coupling in high conversion and excellent levels of enantiocontrol at 40 °C (85% conversion, 94% ee). The superior levels of asymmetric induction and reaction efficiency exhibited by the H-bonding catalyst **12** in benzene at 40 °C in the presence of 5 Å molecular sieves prompted us to select these conditions for further exploration.[29,30]

Experiments to probe the scope of the ketone component revealed that a wide range of electronically and structurally distinct substituted acetophenone derivatives could be successfully coupled with *p*-anisidine to yield



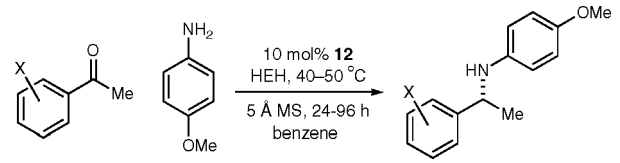
(10)

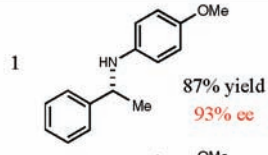
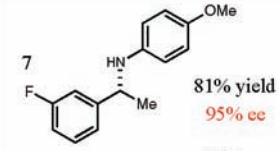
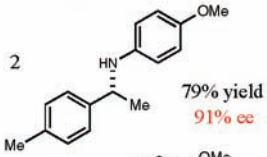
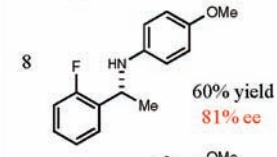
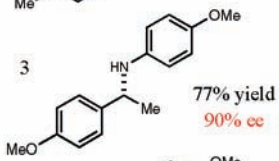
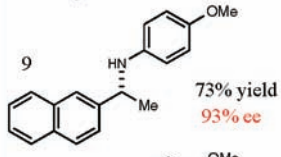
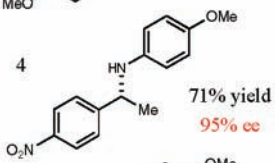
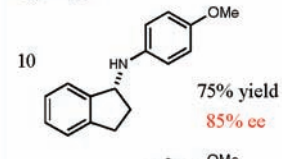
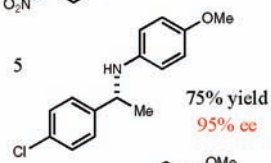
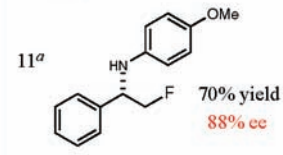
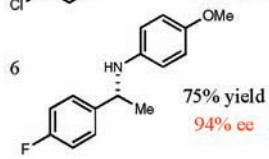
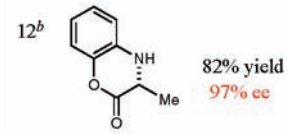
secondary amines with excellent enantiocontrol (Table 4). Notably, cyclic aryl ketones (entry 10, 75% yield, 85% ee) and α-fluoromethyl ketones (entry 11, 70% yield, 88% ee) are also tolerated in this process without loss in reaction efficiency or stereoselectivity.

During the course of our substrate scope studies, we also examined the pyruvic acid-derived cyclic imino ester and found that it effectively underwent reduction to yield the corresponding cyclic alanine amino ester **14** with valuable levels of enantiocontrol (eq 11). To our surprise, however, implementation of the corresponding ethyl-substituted imine **15** resulted in a dramatic decrease in efficiency (82% vs 27% yield, eq 11). Computational studies reveal that this remarkable change in reaction rate as a function of the alkyl ketone substituent likely arises from catalyst-imposed torsional constraints on substrate conformation (Figure 1). More specifically, iminium ions derived from methyl ketones are predicted to undergo selective catalyst association, wherein the C=N *Si*-face is exposed to hydride addition (**MM3–13**, green ball = H). In contrast, the corresponding ethyl-containing substrate (R = Et, **MM3–13**, green ball = Me) is conformationally required to position the terminal CH_3 of the ethyl group away from the catalyst framework, thereby ensuring that both enantiofacial sites of the iminium π-system are shielded.

Importantly, these computational studies have been substantiated in part by a single crystal X-ray analysis of a related aryl imine bound to our phosphoric acid catalyst (Figure 2). As revealed in Figures 1 and 2, there exists a remarkable correlation between this X-ray structure and **MM3–13** in terms of both hydrogen bond orientation and the specific architectural elements that dictate iminium enantiofacial discrimination. It should be noted that the *p*-NO_2 acetophenone-derived imine used in this structural analysis readily undergoes reduction in the presence of

Table 4. Organocatalytic Reductive Amination of Aromatic Ketones



entry	product	yield, % ee	entry	product	yield, % ee
1		87% yield 93% ee	7		81% yield 95% ee
2		79% yield 91% ee	8		60% yield 81% ee
3		77% yield 90% ee	9		73% yield 93% ee
4		71% yield 95% ee	10		75% yield 85% ee
5		75% yield 95% ee	11[a]		70% yield 88% ee
6		75% yield 94% ee	12[b]		82% yield 97% ee

[a] Performed at 5 °C. [b] Reduction of preformed cyclic imine.

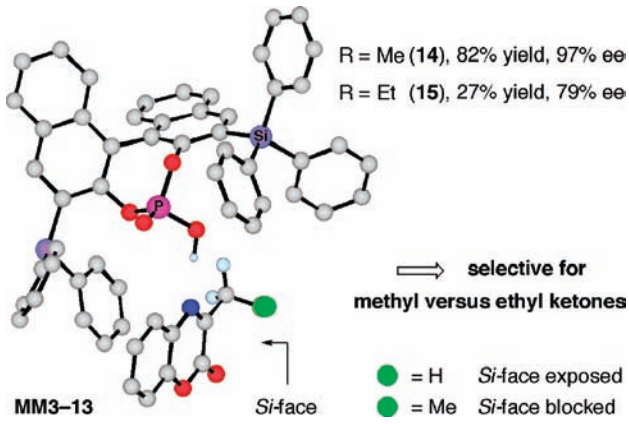


FIGURE 1. Computational analysis of catalyst-bound imine structure (a phenyl substituent on silicon has been removed for clarity).

catalyst **12** with enantioselectivities and efficiencies that are in accord with the studies outlined herein.

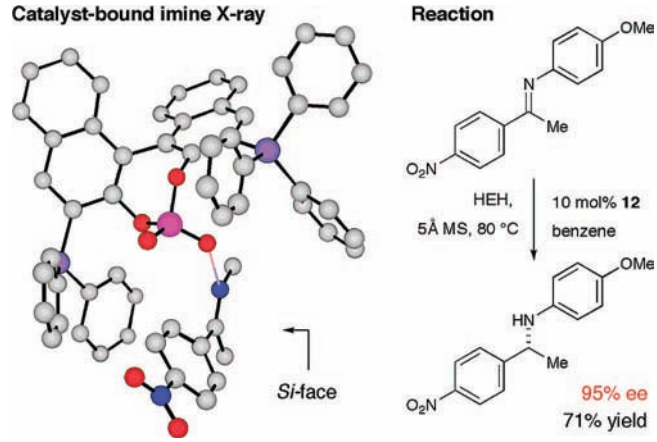
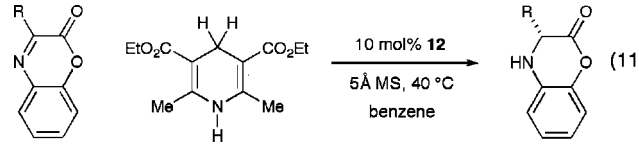
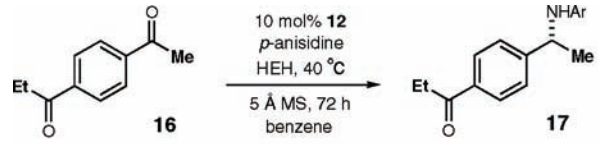


FIGURE 2. X-ray structural analysis of catalyst-bound imine structure (a phenyl substituent on silicon has been removed for clarity).

Inspection of both the X-ray and calculated structures revealed the possibility that catalyst **12** might be generically selective for the reduction of iminium ions derived from methyl ketones. Indeed control experiments to further probe this methyl versus ethyl chemoselectivity were conducted in acyclic systems and have verified that the catalyst system exhibits high levels of torsional control leading to such remarkable chemoselection.

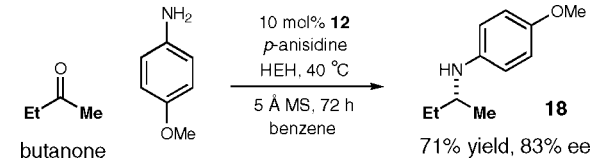


(11)



18:1 Methyl vs Ethyl ketone selectivity 85% yield, 96% ee

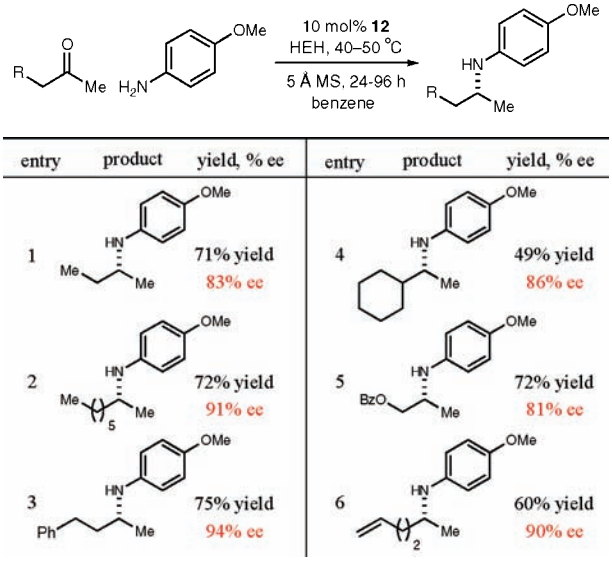
(12)



(13)

For example, we examined the amination of *para*-substituted aryldiketone **16**, a system that has the option to undergo reductive amination at either a methyl or ethyl aryl ketone position. In accord with our torsional-control hypothesis, diketone **16** underwent chemoselective reduction to yield monoaminated **17** with an 18:1 preference for coupling at the methyl ketone site (eq 12, 85% yield, 96% ee). Perhaps most importantly, we tested this chemoselectivity feature in the amination of butanone, a prochiral ketone that contains both the methyl and ethyl alkyl substituents on the same carbonyl (eq 13). To our great delight, the corresponding 2-amino-butane product **18** was furnished with notable levels of enantiocontrol

Table 5. Organocatalytic Reductive Amination of Alkyl−Alkyl Ketones



(83% ee), thereby revealing that ketones containing dialkyl substituents of similar steric and electronic character are viable substrates for this process (e.g., *A* values Me = 1.7 vs Et = 1.75). Indeed, the capacity of catalyst **12** to selectively function with a broad range of methyl-alkyl-substituted ketones has been established (Table 5, entries 1–4, 49–75% yield, 83–94% ee).

In this context, it is important to underscore a key benefit of reductive amination versus imine reduction. Specifically, imines derived from alkyl–alkyl ketones are unstable to isolation, a fundamental limitation that is comprehensively bypassed using direct reductive amination.

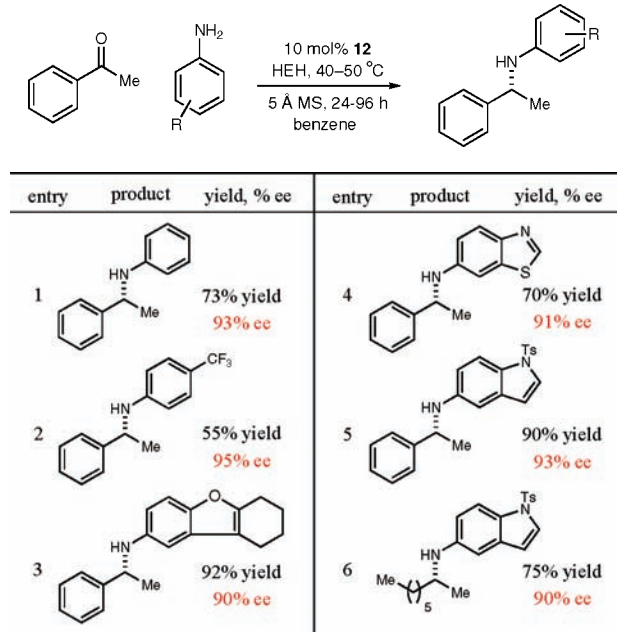
A central tenet of these studies was to develop an enantioselective reductive amination that can be employed in complex fragment couplings (Table 6). This goal has also been accomplished as a variety of electronically diverse aryl and heteroaromatic amines effectively participate in combination with aryl ketones (entries 1–5, 90–95% ee) and alkyl–alkyl carbonyls (entry 6, 90% ee).

More recently, we have undertaken detailed studies to gain further insight into the mechanistic features that govern this biomimetic reductive amination strategy. During the initial evaluation of optimal reaction conditions, we noted that excess ketone was required to achieve >85% conversion and a rather unproductive (<5% conversion) reaction was observed with excess *p*-anisidine.

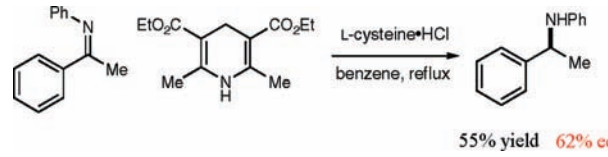
Enantioselective Organocatalytic Imine Reduction

While the studies outlined above represent the first examples of enantioselective catalytic reductive amination using Hantzsch esters, it is important to note that these NADH analogs have previously been used for the asymmetric hydrogenation of imines. As a transformation, the reduction of preformed imines has some limitations relative to reductive amination (e.g., most alkyl imines are not stable to isolation and as such the imine scope is

Table 6. Organocatalytic Reductive Amination of Aromatic and Heterocyclic Amines

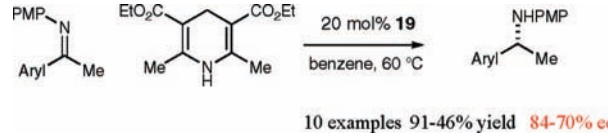


typically restricted to aryl imines), however, when imine reduction is possible, the chiral C−N bond forming event is effectively identical for the two processes. It is clear, therefore, that for certain imine classes, enantioselective reduction of preformed imines represents a complimentary strategy to enantioselective reductive amination for the construction of the benzylic amine stereocenters. Historically, the first enantioselective imine reduction using Hantzsch esters was reported in 1989 by Singh and Batra.[31] Employing the isolable *N*-phenyl ketimine from

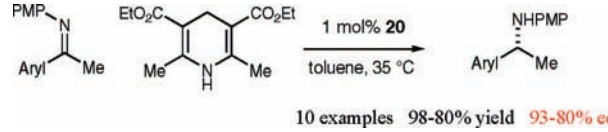


(14)

acetophenone as the substrate, a variety of chiral acids were evaluated for the reduction process. Notably α-amino acids such as cysteine effectively catalyzed imine reduction to provide the corresponding amine (eq 14).

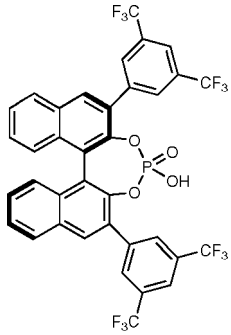


(15)

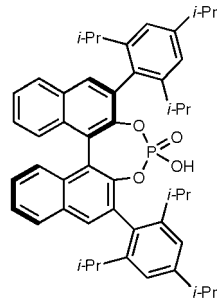


(16)

In the modern era, this transformation did not reach prominence until the report of Rueping and co-workers[32]



catalyst 19

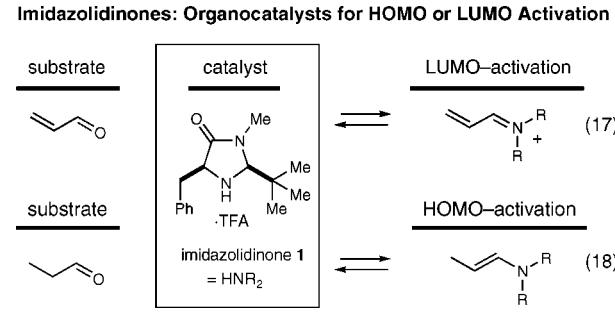


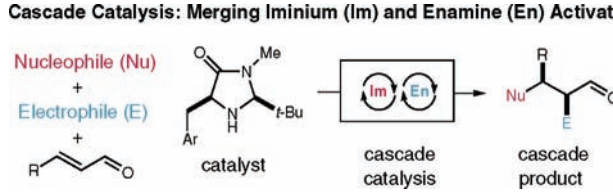
catalyst 20

demonstrated that selectivities in moderate to good levels could be accomplished using a phosphoric acid derived from the Akiyama−Terada family of binol-derived catalysts. Rueping initially reported conditions for the organocatalytic reduction of preformed ketimines using catalytic amounts of diphenylphosphoric acid. This was further extended to an enantioselective strategy for aryl-methyl-substituted imines using the 3,5-(CF_3)-phenyl-substituted binaphthol phosphate catalyst (**19**, eq 15). Shortly following Rueping's first disclosure in this area, List and co-workers[33] reported a similar protocol also using a variant of the Akiyama−Terada catalyst. The List group was able to achieve higher levels of enantioselectivity for similar aryl-methyl-substituted imines, using the *ortho*-2,4,6-triisopropyl-phenyl-based binaphthol phosphoric acid (TRIP) catalyst (**20**, eq 16). In the same manuscript, the List group also reported one example of a ketone that could be used directly to generate imines in situ in the presence of the phosphoric acid catalyst prior to addition of the Hantzsch ester substrate. While this does not constitute a reductive amination per se (reductive amination requiring that the intermediate imine undergo chemoselective reduction in the presence of the carbonyl reagent), it was, however, the first example of using a ketone substrate in a one-pot process for this type of imine reduction.[33]

Enantioselective Organo-Cascade Catalysis

The identification of new chemical strategies that allow increasingly rapid access to structural complexity remains a preeminent goal for the chemical sciences. While the medicinal agent target or total synthesis approach to molecular complexity has traditionally focused upon a "stop and go" sequence of individual reactions, it has long been known that biological systems produce elaborate molecules in a continuous process, wherein enzymatic transformations are combined in highly regulated catalytic cascades. Fundamental to the success of these biological "assembly lines" is the capacity of discrete transform-specific enzymes to coexist in the same reaction medium without the unfavorable consequences that might arise when synthetic catalysts are combined (e.g., catalyst−catalyst interactions, ligand exchange, redox processes). As part of our studies in organic catalysis, we made the intriguing finding that imidazolidinones can not only provide LUMO-lowering activation in the form of iminium catalysis (eq 17 and vide supra) but that the same catalyst family is broadly useful for asymmetric enamine catalysis (HOMO-raising activation) (eq 18). On the basis of the expectation



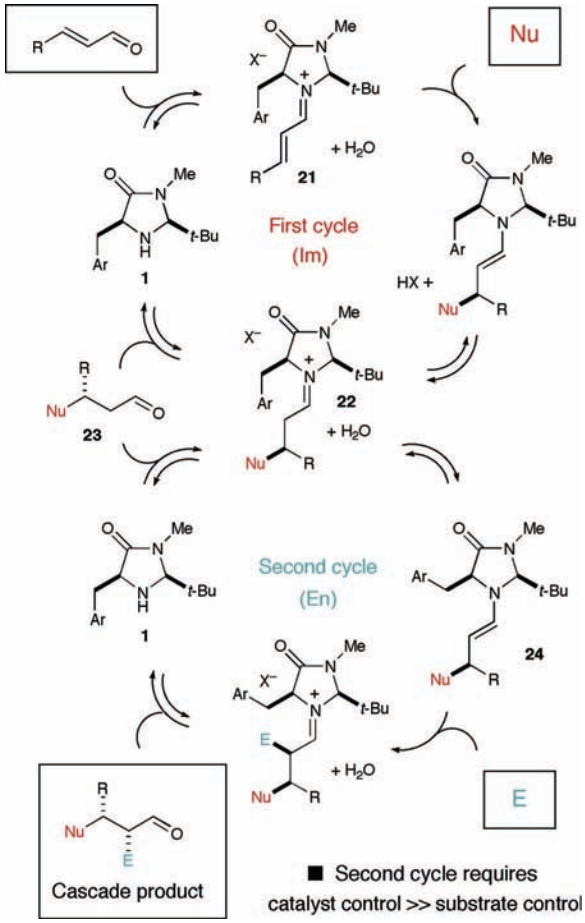


that amine catalysts should coexist without deleterious interactions, we recently questioned whether the conceptual blueprints of biosynthesis might be translated to a laboratory "cascade catalysis" sequence. Specifically, we hoped to build structural and stereochemical complexity in a highly expeditious fashion via the use of multiple catalytic cycles that are chemically connected to become one overall transformation.

Central to this new laboratory strategy were three key objectives: (i) each cycle would selectively install stereogenicity via catalyst control (as opposed to substrate control), (ii) each catalytic cycle would reveal or produce functionality that would allow access to a subsequent cycle, thereby orchestrating a highly specific sequence of stereoselective cascade catalytic cycles and (iii) each cycle in a sequence could be selectively activated by a specific catalyst that chemoselectively functions in the presence of the other amine catalysts (in theory there should be one catalyst present for each cycle in any given cascade sequence). We recognized that this latter objective (a process we call cycle-specific catalysis) would be the most difficult to achieve yet at the same time felt it would be essential to the realization of enantioselective organo-cascade catalysis as a strategy that would generically impact complex target synthesis.

Cascade Catalysis Design Plan. In accord with our previous studies, we presumed that exposure of α,β-unsaturated aldehydes to imidazolidinone catalysts (of type **1**) would generate activated iminium species **21** (Scheme 5) that can enantioselectively intercept a wide variety of generic π- or hydrido-nucleophiles (Nu). Upon rapid hydrolysis of the resulting iminium **22**, we assumed that the conjugate addition adduct **23** would then enter a second catalytic cycle wherein enamine activation **24** would enable highly diastereoselective additions to a wide array of electrophiles (E). Central to the utility of this new cascade-catalysis process is the mechanistic requirement that induction in the enamine addition step should arise

Scheme 5

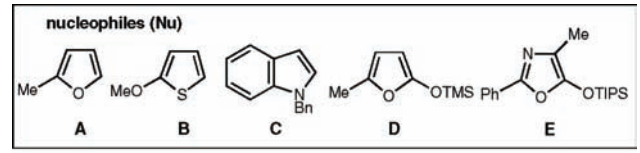


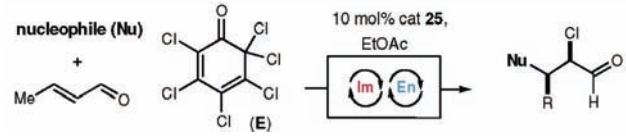
from catalyst control (as opposed to substrate control). Specifically, this would ensure high levels of diastereoselectivity for the overall process regardless of the stereogenicity forged in the first catalytic step. Within this mechanistic scenario, modular control of the enforced sense of enantio- and diastereoinduction (e.g., *R* vs *S*, *syn* vs *anti*), could be achieved via judicious selection of the amine enantiomer involved in each catalytic cycle.

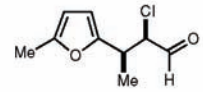
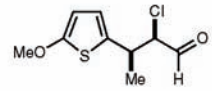
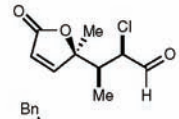
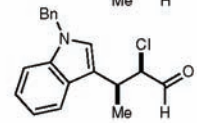
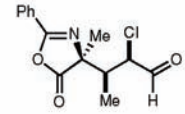
We have indeed achieved these ideals and demonstrated that a wide range of electronically and sterically diverse α,β-unsaturated aldehydes and aromatic π-nucleophiles in conjunction with our α-chlorination chemistry, effectively participate in enantioselective organo-cascade sequences.[10a,34] As revealed in Table 7, a large variety of nucleophilic reaction partners can be employed without any apparent chlorination of these π-rich sytems. Indeed, a prominent feature of this new type of cascade synthesis is the chemoselective partitioning of nucelophiles to undergo addition only to the highly reactive α,β-unsaturated iminium species and for the electrophilic component to selectively combine only with the enamine generated in the second catalytic cycle.

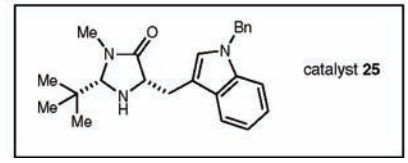
We further hypothesized that implementation of our enantioselective transfer hydrogenation conditions using Hantzsch esters, in combination with our α-chlorination and α-fluorination technologies, would allow the asymmetric addition of the elements of HCl and HF across trisubstituted olefins. Most importantly, based on this

Table 7. Enantioselective Organo-Cascade Catalysis





entry	nucleophile	product	temp (°C)	% yield	dr	% ee
1	A		–50	86	14:1	99
2	B		–50	77	11:1	99
3	D		–55	71	>25:1	>99
4	C		–60	75	12:1	>99
5	E		–40	97	9:1	>99



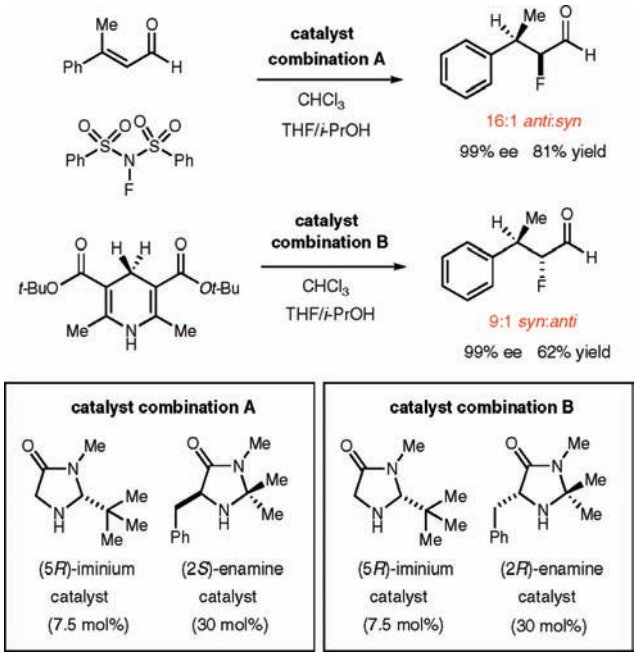
organo-cascade sequence, we have devised cascade sequences with *cycle-specific amine catalysts*, which can be modulated to provide a required diastereo- and enantioselective outcome via the judicious choice of the enantiomeric series of the amine catalysts.

As revealed in Scheme 6, implementation of catalyst combination **A**, incorporating the (2*S*)-enamine catalyst allows the formal addition of HF with 16:1 *anti* selectivity (99% ee). Remarkably, the *syn* HF addition product can be accessed with 9:1 selectivity and in 99% ee by simply changing the enantiomeric series of either amine employed in this catalyst combination (catalyst combination **B**).[10a] At the present time, our laboratory is exercising great efforts to employ this new enantioselective cascade catalysis strategy for the construction of a number of natural products.

Conclusion

Over the past ten years, the field of enantioselective organocatalysis has grown at an extraordinary pace from

Scheme 6



a small collection of unique chemical reactions to a fundamental branch of asymmetric catalysis. The discovery of new activation modes within the realm of organocatalysis has led to the development of unprecedented and complimentary transformations to those previously established within metal and enzyme catalysis. As seen in this Account, recently developed organocatalytic enantioselective transfer hydrogenation strategies represent powerful transformations for the enantioselective introduction of the C−H stereogenic structural motif. Within this catalysis platform, the successful design of small molecule organic catalysts and the use of NADH analogs to replace enzymes and cofactors has led to the development of the first enantioselective organocatalytic reduction of α,β-unsaturated aldehydes, α,β-unsaturated ketones, and imines and reductive amination reactions. The remarkable levels of selectivity obtained in these processes will certainly prove to be a valuable asset for practitioners of chemical synthesis. Moreover, these transfer hydrogenation technologies are highly amenable for the incorporation into enantioselective organo-cascade sequences for the rapid construction of molecular complexity.

For the studies described in this Account, I am deeply indebted to a highly talented group of co-workers. Support for this program is currently provided by the National Institutes of Health (National Institute of General Medical Sciences, Grant RO1-GM078201-01-01) and by kind gifts from Merck, Amgen, and Roche.

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