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Enantioselective Organocatalytic Reductive Amination

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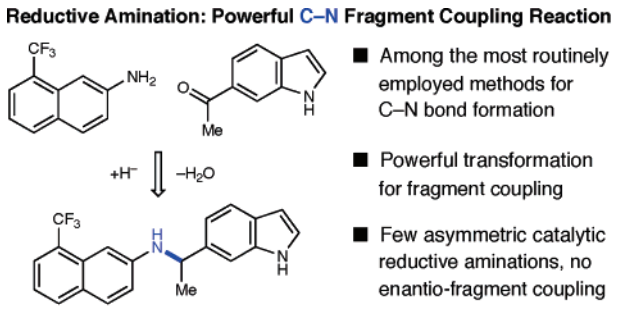
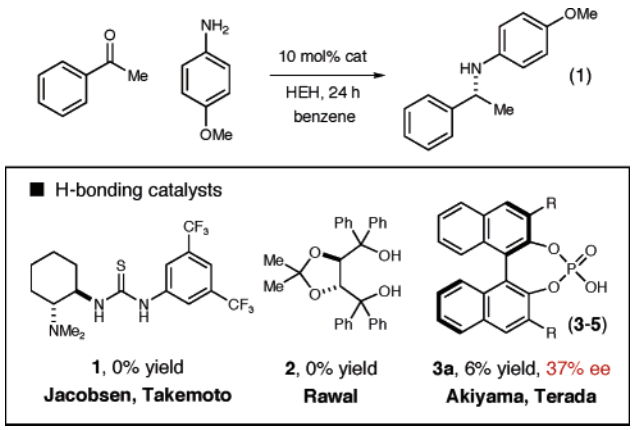
The reductive amination reaction remains one of the most powerful and widely utilized transformations available to practitioners of chemical synthesis in the modern era.[1] A versatile coupling reaction that enables the chemoselective union of diverse ketone and amine containing fragments, reductive amination can also provide rapid and general access to stereogenic C−N bonds, a mainstay 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),[2] it is surprising that few laboratory methods are known for enantioselective reductive amination.[1b,3] Moreover, the use of this ubiquitous reaction for the union of complex fragments remains unprecedented in the realm of asymmetric catalysis, a remarkable fact given the widespread application of both racemic and diastereoselective variants. In this communication, we report the first organocatalytic reductive amination, a biomimetic reaction that allows the asymmetric coupling of complex fragments using chiral hydrogen-bonding catalysts and Hantzsch esters.[4,5]



It has long been established that nature has perfected reductive amination as an in vivo chemical tool for the enantioselective synthesis of essential biomonomers. As a preeminent example, transferase enzymes utilize hydrogen bonding to selectively activate pyruvate-derived ketimines toward hydride delivery from NADH, thereby ensuring the enantiocontrolled formation of naturally occurring amino acids.[6] With this in mind, we recently questioned whether the conceptual blueprints of biochemical amination might be translated to an enantioselective reductive coupling wherein enzymes and cofactors are replaced by small organic catalysts and NADH analogues.[7] Specifically, we proposed that exposure of ketone and amine coupling partners to a chiral hydrogen-bonding catalyst[8] 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.[9] This proposal was further substantiated by the significant advances in hydrogen-bonding catalysis, arising from the pioneering studies of Jacobsen,[10] Corey,[11] Takemoto,[12] Rawal,[13] Johnston,[14] Akiyama,[15] and Terada.[16]



An initial evaluation of the proposed reductive amination was performed with acetophenone, *p*-anisidine, ethyl Hantzsch ester (HEH), and several classes of established hydrogen-bonding catalysts (eq 1, Table 1). While thiourea **1** and taddol **2** did not induce reductive amination, the binol phosphoric acid catalysts **3a**−**d** (introduced by Terada and Akiyama) did indeed provide the desired amine adduct, albeit with moderate conversion and stereoinduction (entries 1−5, 7−65% ee). To our great delight, we found that an unprecedented *ortho*-triphenylsilyl variant of the Terada−Akiyama catalyst **5** facilitates the desired coupling in high conversion and with excellent levels of enantiocontrol at 40 °C (entry 8, 94% ee).[17] Importantly, preliminary studies have revealed that water, generated in the initial condensation step, has a deleterious impact on both iminium formation and the hydride reduction step. As such, the introduction of 5 Å sieves was found to be critical to achieve useful reaction rates and selectivities.

Having established the optimal conditions for hydrogen bond catalysis, we next examined the scope of the ketone component in this organocatalytic reduction. As revealed in Table 2, a variety of substituted acetophenone derivatives can be successfully coupled (eq 2), including electron-rich, electron-deficient, as well as ortho, meta, and para substituted aryl ketone systems (Table 2, entries 1−9, 60−87% yield, 83−95% ee). Moreover, 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 efficiencies or enantiocontrol.

Pleasingly, the pyruvic acid-derived cyclic imino ester (eq 3) also underwent facile reduction to yield the corresponding cyclic

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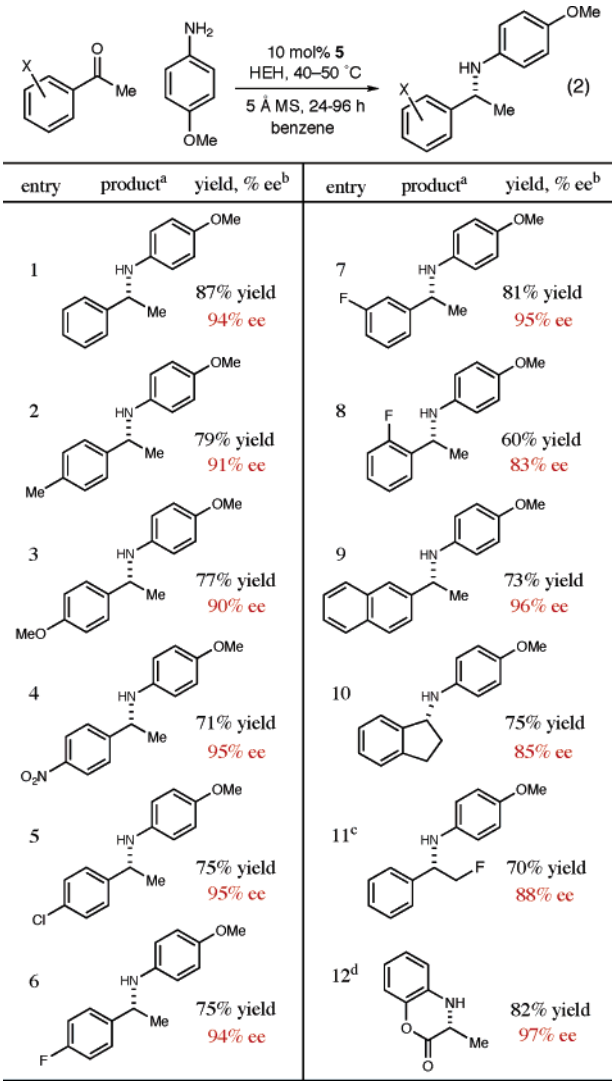
Table 1. Evaluation of Phosphoric Acid Catalyst Architecture

entry	cat.	cat. substitution (R)	additive	temp (°C)	% conv[a]	% ee[b]
1	**3a**	2-naphthyl	none	80	6	37
2	**3a**	2-naphthyl	5 Å MS	80	41	45
3	**3b**	H	5 Å MS	80	43	7
4	**3c**	3,5-NO_2-phenyl	5 Å MS	80	45	16
5	**3d**	3,5-CF_3-phenyl	5 Å MS	80	39	65
6	**4**	Si^{t}BuPh$_2$	5 Å MS	80	35	61
7	**5**	$SiPh_3$	5 Å MS	80	70	87
8	**5**	$SiPh_3$	5 Å MS	40	85	94

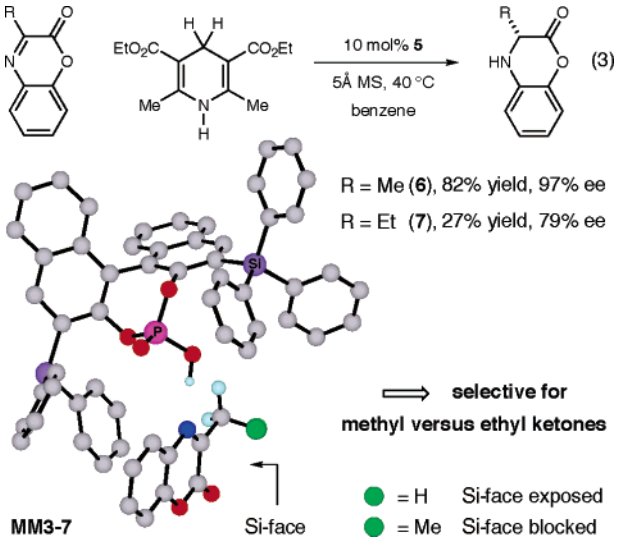
[a] Conversion determined by GLC analysis. [b] Enantiomeric excess determined by chiral GLC analysis (Varian CP-chirasil-dex-CB).

Table 2. Organocatalytic Reductive Amination of Aromatic Ketones

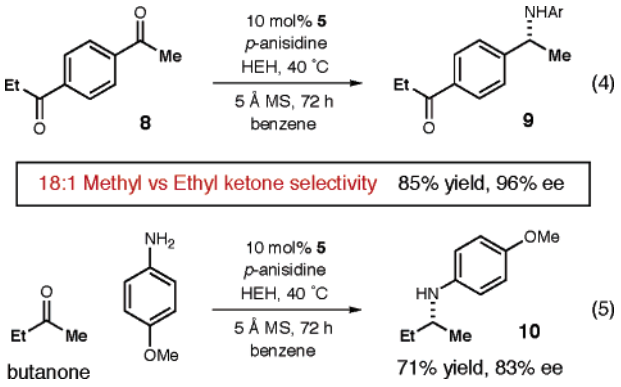


[a] Absolute stereochemistry determined by chemical correlation. [b] Enantiomeric excess determined by chiral GLC or SFC-HPLC analysis. [c] Performed at 5 °C. [d] Reduction of preformed cyclic imine.

alanine amino ester with excellent enantioselectivity (Table 2, entry 12, 82% yield, 97% ee). However, implementation of the corresponding ethyl substituted imine **7** resulted in a dramatic decrease in efficiency (82 vs 27% yield). Computational studies reveal that this remarkable change in reaction rate as a function of alkyl substituent likely arises from catalyst imposed torsional constraints on substrate conformation. More specifically, imines that incorporate a methyl group are predicted to undergo selective catalyst association wherein the C=N *Si*-face is exposed to hydride addition (**MM3**−**7**, green dot = H). In contrast, the ethyl-containing substrate (R_2 = Et, **MM3**−**7**, green dot = 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 (**MM3**−**7**, green dot = Me). As shown in Figure 1 (Supporting Information), we have recently obtained a single-crystal X-ray structure of a catalyst-bound aryl imine that exhibits a remarkable correlation to **MM3**−**7** in terms of both hydrogen bond orientation and the specific architectural elements that dictate iminium enantiofacial discrimination.[18]

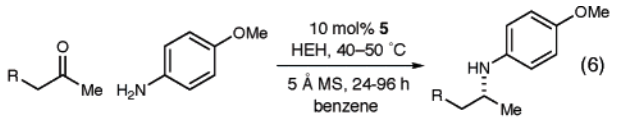


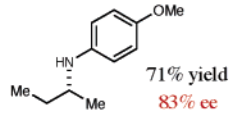
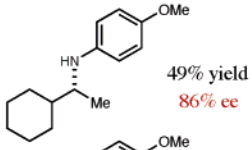
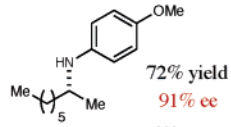
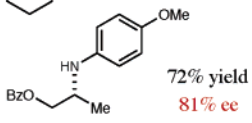
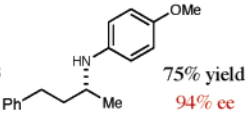
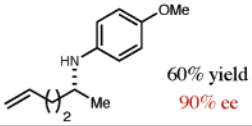
Both these X-ray and calculated structures suggest that catalyst **5** should be generically selective for the reduction of iminium ions derived from methyl ketones. To test this hypothesis, we next examined the amination of para substituted aryldiketone **8**. In accord with our torsional-control hypothesis, diketone **8** underwent chemoselective reduction to yield monoaminated **9** with a 18:1 preference for coupling at the methyl ketone site (eq 4, 85% yield, 96% ee).



We next proposed to test this methyl versus ethyl chemoselectivity in a productive fashion via the amination of butanone, a prochiral ketone that contains both such alkyl substituents on the same carbonyl (eq 5). In the event, the corresponding 2-amino butane product **10** was furnished with notable levels of enantiocontrol (83% ee), thereby revealing that ketones that contain 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 **5** to selectively function with a broad range of methyl alkyl substituted ketones has now been established (Table 3, entries 1−4, 49−75% yield, 83−94% ee). In

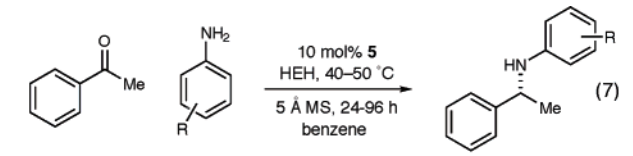
Table 3. Organocatalytic Reductive Amination of Alkyl−Alkyl Ketones

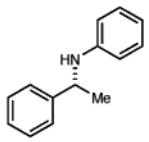
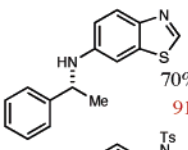
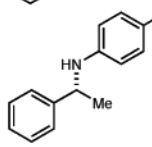
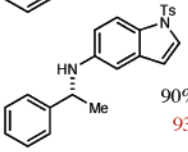
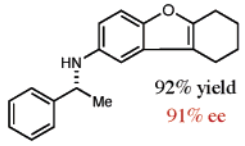
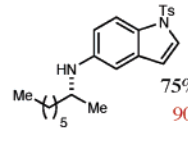


entry	product[a]	yield, % ee[b]	entry	product[a]	yield, % ee[b]
1		71% yield 83% ee	4		49% yield 86% ee
2		72% yield 91% ee	5		72% yield 81% ee
3		75% yield 94% ee	6		60% yield 90% ee

[a] Absolute stereochemistry determined by chemical correlation. [b] Enantiomeric excess determined by chiral GLC or SFC-HPLC analysis.

Table 4. Organocatalytic Coupling of Aromatic and Heterocyclic Amines



entry	product	yield, % ee[a]	entry	product	yield, % ee[a]
1		73% yield 93% ee	4		70% yield 91% ee
2		55% yield 95% ee	5		90% yield 93% ee
3		92% yield 91% ee	6		75% yield 90% ee

[a] Enantiomeric excess determined by chiral SFC-HPLC.

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.

Last, a central tenet of this investigation was to develop an enantioselective reductive amination that can be employed in complex fragment couplings (eq 7). As revealed in Table 4, this goal has now been accomplished using a variety of electronically diverse aryl and heteroaromatic amines in combination with aryl ketones (entries 1−5, 91−95% ee) as well as alkyl−alkyl carbonyls (entry 6, 90% ee).

In summary, we have developed the first enantioselective organocatalytic reductive amination. This mild and operationally simple fragment coupling has been accomplished with a wide range of ketones in combination with aryl and heterocyclic amines. Further mechanistic studies of this amination reaction will be reported shortly.

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Supporting Information Available: Experimental procedures, structural proofs, and X-ray and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Catalysts **1** and **3** were prepared using procedures outlined in refs 8 and 12. Catalyst **5** was first prepared and applied to this catalytic protocol on October 13, 2004, to furnish the amine in Table 2, entry 1, in 94% ee.
(18) The crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, and copies can be obtain on request, free of charge, by quoting the publication citation and the deposition number 287655.

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