Organocatalysis

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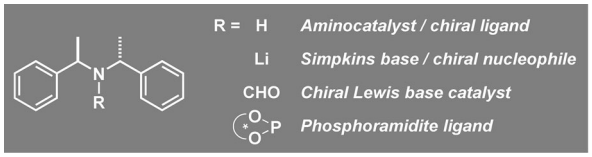
Catalytic Asymmetric Reductive Condensation of N–H Imines: Synthesis of C_2-Symmetric Secondary Amines

*Vijay N. Wakchaure and Benjamin List**

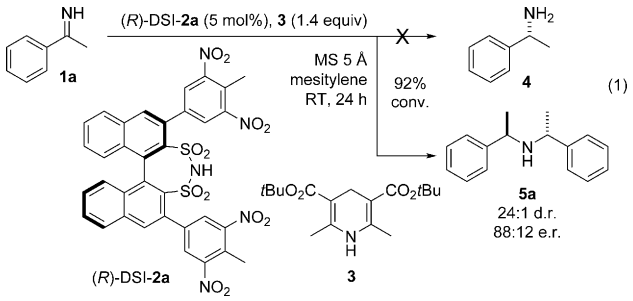
Abstract: *A highly diastereoselective and enantioselective Brønsted acid catalyzed reductive condensation of N–H imines was developed. This reaction is catalyzed by a chiral disulfonimide (DSI), uses Hantzsch esters as a hydrogen source, and delivers useful C_2-symmetric secondary amines.*

Enantiomerically pure C_2-symmetric secondary amines represent a privileged structural motif that is featured in organocatalysts,[1] chiral ligands,[2] and as a substructure of the phosphoramidite ligand class.[3] In addition, the corresponding chiral lithium amides[4] have been used in enantioselective deprotonations and as chiral ammonia equivalents in conjugate addition reactions.



Such C_2-symmetric secondary amines can be efficiently obtained through asymmetric imine reductions and reductive aminations of carbonyl compounds.[5] However, these methods require the stoichiometric use of a chiral amine auxiliary and are typically limited to commercially available chiral amines. We now report an alternative approach that involves a highly diastereoselective and enantioselective reductive condensation of N-H imines that is catalyzed by chiral disulfonimide (DSI) and uses Hantzsch esters as a hydrogen source.

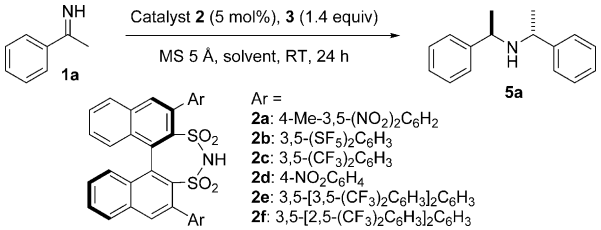
Recently, we developed a chiral-DSI-catalyzed highly enantioselective reduction of N-alkyl imines.[6–9] The reaction uses a Hantzsch ester as a hydrogen source in the presence of Boc_2O, and provides facile access to several enantioenriched N-Boc-protected N-alkyl amines. We became interested in advancing this concept to include the equally attractive but even more challenging unsubstituted N–H imines **1**. Initially, we hoped that this design would lead to direct entry to enantioenriched primary amines **4** [Eq. (1)]. Such reductions have rarely been studied and remain a major challenge.[10] Surprisingly, when investigating the reduction of imine **1a**



using Hantzsch ester **3** in the presence of DSI-**2a**, we found that instead of primary amine **4**, the corresponding C_2-symmetric secondary amine **5a** was obtained with promising diastereo- and enantioselectivity [Eq. (1)].[11]

This product has previously been reported as a byproduct in a chemoenzymatic dynamic kinetic resolution of racemic primary amine **4**.[12] However, to the best of our knowledge, such an asymmetric reductive condensation of N–H imines is so far unknown. Encouraged by our initial observation, and considering the various applications of C_2-symmetric secondary amines, a systematic exploration of different conditions was conducted to optimize the reaction (Table 1). The chiral DSI catalysts **2a–f**,[6a,13] which were recently developed in our laboratory, catalyzed the transformation more rapidly than alternative phosphoric acid type catalysts (see the Supporting

Table 1: Reaction development[a]



Entry	Cat.	Solvent	Conv.[%][b]	d.r.[b]	e.r.[c]
1	**2a**	mesitylene	92	24:1	88:12
2	**2b**	mesitylene	91	15.6:1	72:28
3	**2c**	mesitylene	93	24:1	84:16
4	**2d**	mesitylene	91	24:1	86:14
5	**2e**	mesitylene	96	65:1	89.5:10.5
6	**2f**	mesitylene	97	99:1	94:6
7	**2f**	MTBE	93	99:1	>99:1
8[d]	**2f**	MTBE	74	99:1	>99:1
9[e]	**2f**	MTBE	92	99:1	>99:1

[a] Reactions were run on a 0.05 mmol scale. [b] Determined by GC analysis.[11] [c] Determined by HPLC analysis. [d] Without 5 Å MS, reaction time 48 h. [e] Using 150 mg of Amberlite CG-50 resin instead of 5 Å MS. MTBE = methyl *tert*-butyl ether.

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Information) and also afforded amine **5a** with higher diastereo- and enantioselectivity (entries 1–6). Gratifyingly, catalyst **2f**, which contains the unusual 2,5-ditrifluoromethylbenzene substitution in the 3,3′-position of the backbone,[14] afforded an excellent d.r. of 99:1 and an e.r. of 94:6 (entry 6). Furthermore, solvent screening revealed MTBE to be optimal, affording the amine product with an almost perfect e.r. of > 99:1 (entry 7). In the absence of molecular sieves (MS), the reaction becomes slower and partial hydrolysis of the imine is observed, while the diastereo- and enantioselectivity remain identical (entry 8). Compared to 5 Å MS, Amberlite CG-50 resin under the standard reaction condition gave similar results (entry 9), thus suggesting that 5 Å MS may trap the ammonia byproduct, thereby enhancing catalyst turnover.

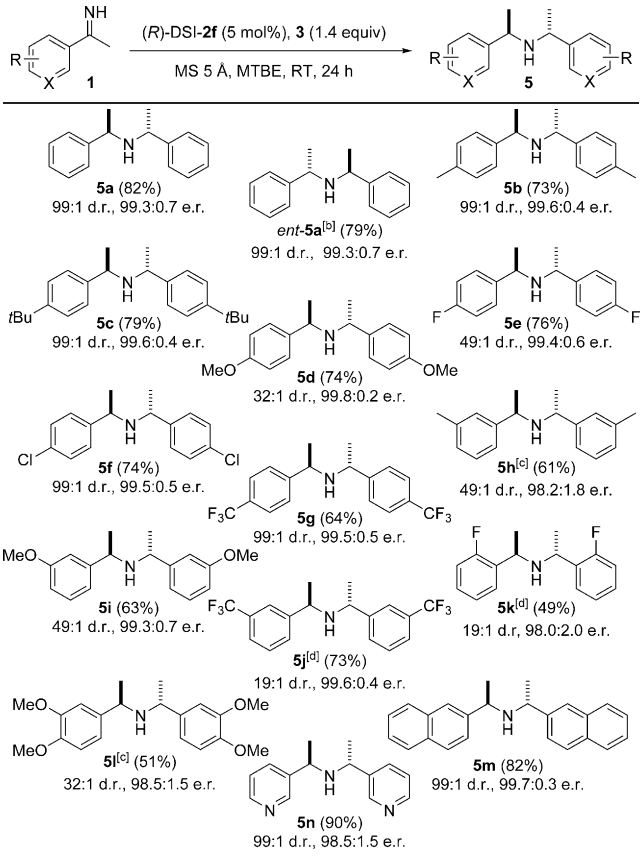
With the optimal conditions in hand, we next began investigating the substrate scope of the enantioselective reductive condensation of N–H imines (Table 2).

A variety of N–H imines efficiently underwent the reductive condensation in the presence of disulfonimide **2f** (5.0 mol%) to afford the corresponding C_2-symmetric secondary amines in good yields and with outstanding diastereo- and enantioselectivity. Electron-donating *para* substituents are well tolerated (products **5b–5d**). For example, *p-tert*-butyl-substituted imine **1c** provided secondary amine **5c** in 79% yield and with a d.r. of 99:1 and an e.r. of 99.6:0.4. Substrates with electron-withdrawing *para* substituents, such as fluorine, chlorine, or trifluoromethyl groups, could also be used, furnishing products **5e–5g** with uniformly superb diastereoselectivity and enantioselectivity. Substitutions at the *meta* position are equally well tolerated and both electron-donating and electron-withdrawing groups provided the corresponding secondary amines in good yields and with remarkably high diastereoselectivity and enantioselectivity (products **5h–5j**). Substrates with *m*-methyl and *m*-trifluoromethyl groups (**1h**, **1j**) were less reactive and required longer reaction time. *o*-Fluoro-substituted imine **1k** also reacted more slowly and provided secondary amine **5k** in 49% yield and with a d.r. of 19:1 and an e.r. of 98:2. *m*,*p*-Disubstitution led to similar results (product **5l**). Interestingly, the 2-naphthyl N–H imine afforded amine product **5m** in good yield and with a d.r. of 99:1 and an e.r. of 99.7:0.3. A heterocyclic substrate, pyridine derivative **1n**, efficiently underwent the reductive condensation to afford the corresponding secondary amine **5n** in 90% yield and with a d.r. of 99:1 and an e.r. of 98.5:1.5. This result further underscores the remarkable base tolerance of our reaction. Unfortunately, the corresponding phenyl,ethyl-substituted N–H imine and an aliphatic cyclohexyl,methyl-substituted N–H imine did not react to the desired product.

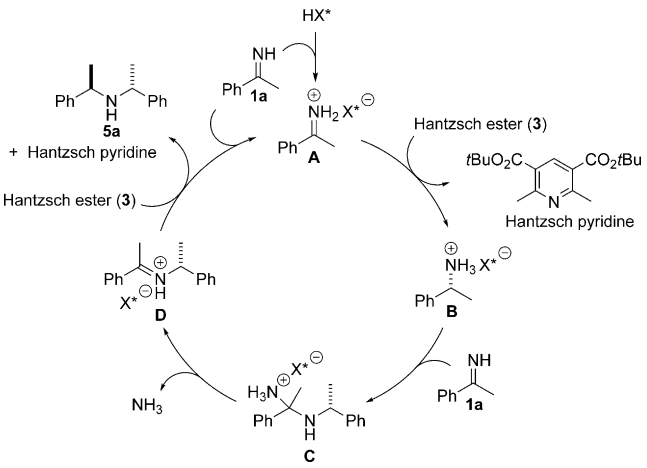
Preliminary studies towards applying the newly available C_2-symmetric secondary amines in asymmetric synthesis, in which they were used as a lithium amide base in a benchmark enol silane synthesis, and as part of a new phosphoramidite ligand for use in the asymmetric addition of arylboron reagents to acyclic enones,[15] confirmed their promise. Both reactions investigated gave results comparable to analogous known transformations.[16]

We currently envision a catalytic cycle that is initiated by the protonation of imine **1a** by chiral DSI-**2f** (Scheme 1). The resulting iminium ion pair **A** undergoes reaction with Hantzsch dihydropyridine **3** to give enantiomerically enriched primary amine salt **B** and the corresponding Hantzsch pyridine. Subsequently, amine **B** undergoes a transimination with substrate **1a**, first to produce aminal **C**, which then

Table 2: Substrate scope.[a]



[a] Reactions run on 0.25 mmol scale. The e.r. was determined by HPLC. The d.r. was determined by GC, NMR, or LC analysis. The absolute configurations of **5a**, ent-**5a**, and **5d** were determined by comparing known optical rotation values (see the Supporting Information). [b] Using (*S*)-DSI-**2f**. [c] 48 h. [d] 72 h.



Scheme 1. Proposed catalytic cycle.

liberates ammonia to form the secondary iminium ion pair **D**.[17] Finally, a second reduction of intermediate **D** provides diastereo- and enantioenriched secondary amine product **5a**. It should be noted that we observed some degree of kinetic resolution in the reduction of iminium ion pair **D**, which further enhances the enantiomeric ratio of our C_2-symmetric secondary amine products (see the Supporting Information). This perhaps explains the superb enantioselectivity observed.

In summary, we have developed an asymmetric Brønsted acid catalyzed reductive condensation of N–H imines. The reaction is catalyzed by a disulfonimide catalyst, uses a Hantzsch ester as hydrogen source, and provides facile access to several C_2-symmetric secondary amines in good yields and with remarkably high diastereo- and enantioselectivity. Remarkably, with amine **5**, ammonia, and the Hantzsch pyridine, our reaction delivers three fairly basic products and yet turnover with our DSI Brønsted acid catalyst is maintained. Selected secondary amine products have already shown promise as chiral lithium amide bases in an enantioselective enol silane synthesis and as a subunit of a phosphoramidite ligand in an asymmetric addition of arylboron reagents to acyclic enones.

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Keywords: Brønsted acids · C_2-symmetric secondary amines · disulfonimide · organocatalysis · reduction

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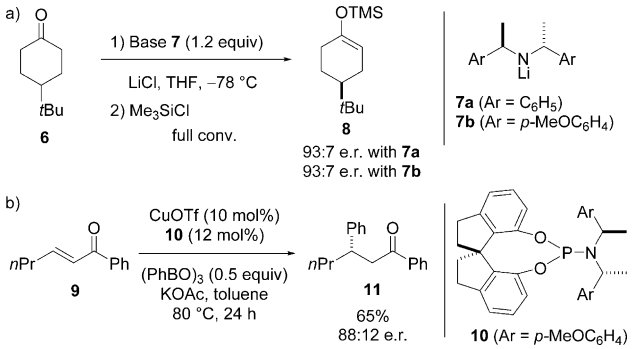

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[17] One referee suggested the possible involvement of a 1,3-hydride shift in intermediate **D**, which we can neither exclude nor confirm at this point.

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Communications

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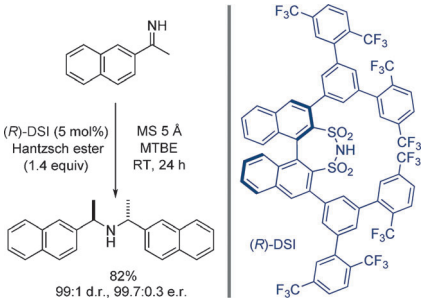
Catalytic Asymmetric Reductive Condensation of N–H Imines: Synthesis of C_2-Symmetric Secondary Amines



Acids for base building: A highly diastereoselective and enantioselective Brønsted acid catalyzed reductive condensation of N–H imines was developed. This dimerizing reduction is catalyzed by a chiral disulfonimide (DSI), uses Hantzsch esters as a hydrogen source, and delivers useful C_2-symmetric secondary amines.