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Highly Enantioselective Reduction of β-Amino Nitroolefins with a Simple *N*-Sulfinyl Urea as Bifunctional Catalyst

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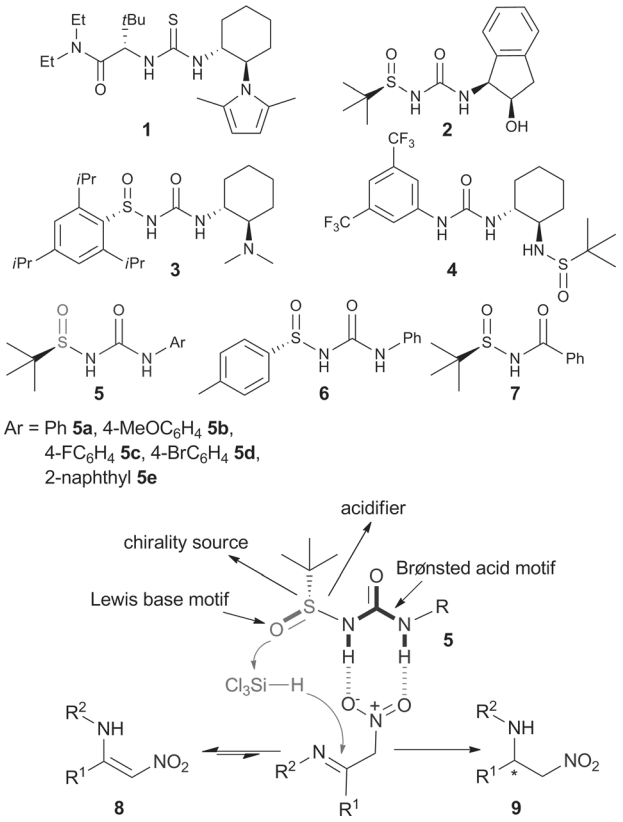
In recent years, bifunctional catalysis has proven to be a successful concept in asymmetric organocatalysis.[1] In particular, various highly efficient asymmetric catalytic protocols have been designed and implemented based on this concept by using (thio)urea-type bifunctional catalysts.[2,3] The combination of the double hydrogen-donating (thio)urea group with a Brønsted or Lewis basic group in these catalysts is the key for dual chemical activation. Normally, multiple stereogenic centers and electronically tuning groups plus certain spacer are installed with these two groups to ensure high reactivity and stereoselectivity. Thus, a relatively complex molecular structure constitutes a common feature of these catalysts. Herein, we document that *N*-sulfinyl ureas **5** (Scheme 1) with a particularly simple structure can also serve as highly efficient bifunctional catalysts. The unique feature of this catalyst system is that the simple *S*-chiral sulfinyl group plays three critical roles, that is, chirality source, Lewis base and acidifier, which enables the catalyst structure to be simplified to minimum. With the use of such catalysts, we developed an unprecedented catalytic pathway for the highly enantioselective reduction of β-arylamino nitroolefins.

Chiral β-amino nitroalkanes are important intermediates in organic synthesis, owing to their easy conversion into a variety of useful compounds, such as chiral α-amino acids[4] and 1,2-diamines.[5] The preparation of this type of compounds mainly relies on asymmetric aza-Henry reactions.[6] Recently, asymmetric aza-Michael additions have been successfully developed as highly effective approaches to chiral β-amino nitroalkanes.[7] In principle, the catalytic reduction of β-amino nitroolefins should provide an alternative straightforward pathway to construct chiral β-amino nitroalkanes, owing to the easy availability of starting materials. However, to the best of our knowledge, so far no efficient method for this transformation has been reported, despite the development of numerous efficient catalytic methods for the reduction of many other types of olefins.[8] This stimulated our strong interest to search for an efficient method to implement the high enantioselective reduction of β-amino nitroolefins.



Scheme 1. Catalyst structures and proposed activation pattern for the asymmetric hydrosilylation of β-amino nitroolefins **8**.

Recently, List and co-workers discovered that Jacobsen-type thiourea **1** (Scheme 1) as catalyst can activate nitroolefins for asymmetric reduction with Hantzsch esters.[9] Meanwhile, Ellman developed a new type of chiral urea catalysts (**2** and **3**) for the activation of nitroolefins and nitroalkanes in asymmetric aza-Henry and Michael reactions.[3f,g] The *S*-chiral sulfinyl group in Ellman's catalysts was used as both acidifying and chiral-directing element. Such *S*-chiral sulfinyl group was also used by Jacobsen in a new design of urea catalyst **4**.[3h,i] In this case, the *S*-chiral sulfinyl group is not directly connected with the urea group and should have

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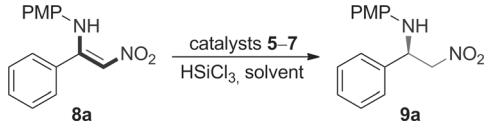
little acidifying effects on the urea function, but it plays both Lewis base activating and chiral-directing roles. Inspired by these works and based on our own work,[10] we envisioned that if all the chiral-directing, acidifying, and Lewis base activating functions of the *S*-chiral sulfinyl group could be fully utilized, *N*-sulfinyl ureas **5** with a relatively simple structure might serve as efficient catalyst to address the asymmetric reduction of β-amino nitroolefins through hydrosilylation in a new dual-functional activation pattern (Scheme 1).[11,12]

Thus, we prepared a small set of ureas **5** and tested their catalytic efficacies in the hydrosilylation of β-amino nitroolefin **8a.** Urea **6** and amide **7** were also prepared and tested for comparison. To our delight, all the ureas **5a–e**, regardless of the different electronic nature of the *N*′-aryl groups, could drive the hydrosilylation of **8a** to completion in 24 h and gave the desired β-amino nitroalkane product **9a** in high yield and excellent enantioselectivity (93–99% yield, 95–96% *ee*, entries 1–5, Table 1). In contrast, urea **6** showed

Table 1. Effects of catalysts and conditions on the hydrosilylation of **8a**.[a]



Entry	Catalyst	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**5a**	CH_3CN	H_2O	99	96
2	**5b**	CH_3CN	H_2O	97	95
3	**5c**	CH_3CN	H_2O	96	96
4	**5d**	CH_3CN	H_2O	99	96
5	**5e**	CH_3CN	H_2O	93	96
6	**6**	CH_3CN	H_2O	<10	–
7	**7**	CH_3CN	H_2O	63	15
8	**5a**	CH_3CN	–	<10	–
9	**5a**	CH_3CN	AcOH	89	95
10	**5a**	CH_3CN	*i*PrOH	98	92
11[d]	**5a**	CH_3CN	H_2O	95	94
12[e]	**5a**	CH_3CN	H_2O	98	92
13	**5a**	DCM	H_2O	76	80
14	**5a**	DCE	H_2O	68	53
15	**5a**	$CHCl_3$	H_2O	17	57
16	**5a**	toluene	H_2O	65	8

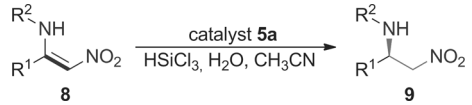
[a] Unless otherwise noted, all reactions were performed with **8a** (0.1 mmol), catalyst (10 mol%), $HSiCl_3$ (0.3 mmol), and additive (0.1 mmol) in solvent (1.0 mL) at −40 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC. The product **9a** was determined to be *R*-configured in all cases by comparison of the optical rotation with the literature data. [d] The reaction temperature was −30 °C. [e] The reaction temperature was −20 °C. PMP = *para*-methoxyphenyl, DCE = 1,2-dichloroethane.

almost no reactivity (entry 6), implying that the strong Lewis basicity of the sulfinyl group is critical for the chemical activation.[13] On the other hand, amide **7** retained moderate reactivity, but gave poor enantioselectivity (entry 7), suggesting that the urea motif is also important for both the reactivity and the stereoselectivity. Notably, one equivalent of water proved to be a crucial additive for the urea-catalyzed hydrosilylation, devoid of which a dramatic loss of reactivity was observed (entry 8). Other protic additives, such as acetic acid and isopropanol, were also found to be effective, affording high yields and slightly lower enantioselectivities (entries 9 and 10).

We further investigated other parameters of this transformation. We found that when the reaction temperature was increased from −40 to −20 °C, excellent yields remained (Table 1, entries 11 and 12), but a slight decrease in enantioselectivity occurred. Solvent effects were also examined. Other solvents, including dichloromethane and 1,2-dichloroethane, chloroform, and toluene, all proved to be inferior to acetonitrile (entries 13–16).

To probe the substrate scope, various β-arylamino nitroalkanes **8a–q** were subjected to the **5a**-catalyzed hydrosilylation. The results are summarized in Table 2. In general, in

Table 2. Scope of β-amino nitroolefins in the **5a**-catalyzed reduction.[a]



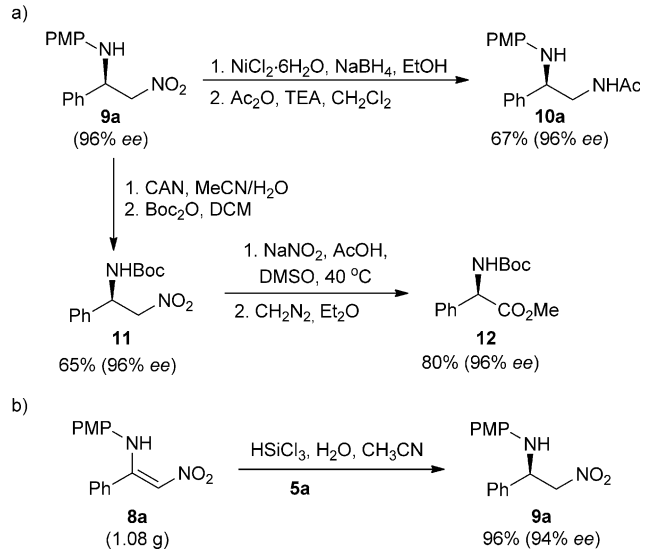
Entry	Substrate R^1	R^2		Yield [%][b]	*ee* [%][c]	Config.
1	Ph	PMP	**8a**	99	96	*R*(−)
2	4-$MeOC_6H_4$	PMP	**8b**	95	95	(−)
3	3-$MeOC_6H_4$	PMP	**8c**	94	94	(−)
4	4-MeC_6H_4	PMP	**8d**	98	97	(−)
5	3-MeC_6H_4	PMP	**8e**	93	96	(−)
6	2-naphthyl	PMP	**8f**	94	95	(−)
7	4-FC_6H_4	PMP	**8g**	92	95	(−)
8[d]	4-BrC_6H_4	PMP	**8h**	96	92	(−)
9[d]	4-ClC_6H_4	PMP	**8i**	94	93	(−)
10	3-ClC_6H_4	PMP	**8j**	96	91	(−)
11[e]	4-$CF_3C_6H_4$	PMP	**8k**	92	91	(−)
12[e]	3-$CF_3C_6H_4$	PMP	**8l**	95	88	(−)
13[e]	4-CNC_6H_4	PMP	**8m**	94	89	(−)
14	*c*-Hex	PMP	**8n**	97	90	(+)
15	*i*Pr	PMP	**8o**	96	82	(+)
16	Ph	Ph	**8p**	99	93	(−)
17	Ph	DMP	**8q**	84	93	(−)
18	2-thienyl	PMP	**8r**	82	92	(−)
19	2-furyl	PMP	**8s**	96	79	*R*(−)

[a] Unless otherwise noted, all reactions were performed with **8** (0.1 mmol), **5a** (10 mol%), $HSiCl_3$ (0.3 mmol), and water (1.0 equiv) in acetonitrile (1.0 mL) at −40 °C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Because the substrate solubility is not good, the reaction needed to be run at −30 °C for 48 h. [e] The catalyst loading was 20 mol%. DMP = 2,4-dimethoxyphenyl.

the presence of 10 mol% catalyst, the reactions with substrates bearing a β-aryl group went to completion in 24 h and the desired products were obtained in excellent yields (92–99%) and enantioselectivities (91–97% *ee*, entries 1–10). Substrates bearing a relatively electron-deficient β-aryl group **8k–m** tended to be less reactive and required a higher catalyst loading (20 mol%) to drive the reaction to completion in 24 h in satisfying yields (entries 11–13). In these cases, slightly lower enantioselectivities (88–91% *ee*) were observed. Notably, the β-alkyl-type substrates **8n** and

8o also smoothly underwent hydrosilylation under the optimal conditions and afforded the desired aliphatic β-amino nitroalkane product in high yield and good enantioselectivity (entries 14 and 15). Moreover, substrates **8p** and **8q**, derived from arylamines other than *para*-methoxyaniline, were also well tolerated in the present catalytic reaction system (entries 16 and 17). In addition, good results were obtained with heterocyclic substrates **8r** and **8s** (entries 18 and 19).

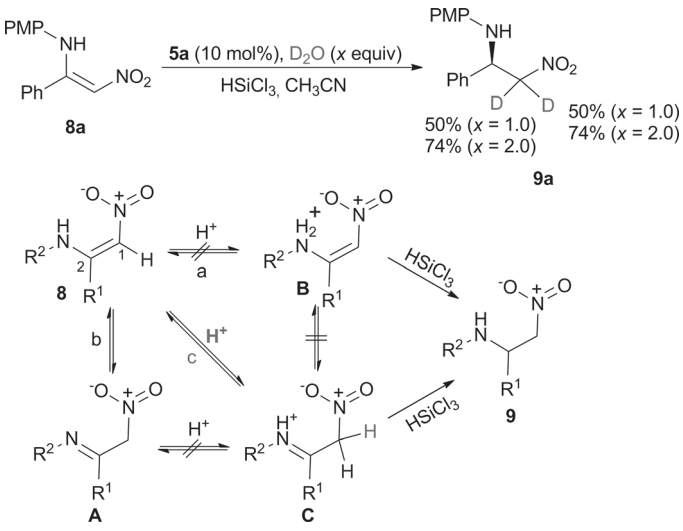
To illustrate the synthetic utility of the present method, the conversion of the resulting product **9a** into 1,2-diamine and amino acid derivatives were conducted by known nitro-reduction[14] and Nef oxidation[15] methods, respectively (Scheme 2a). The corresponding products **10a** and **12** were



Scheme 2. a) Conversion of the β-amino nitroalkane product **9a** into diamine and amino acid derivatives and b) gram-scale reduction of **8a**.

obtained in good yields with complete preservation of the enantiopurity. Moreover, a gram-scale reaction for the reduction of **8a** was performed, which retained the excellent yield and enantioselectivity (Scheme 2b).

To obtain insights into the reaction mechanism of the present catalytic system, we conducted deuterium-labeling experiments in the **5a**-catalyzed reduction of **8a** by using deuterated water as additive (Scheme 3). Interestingly, both α-hydrogen atoms in product **9a** were partially labeled, and no labeling of the amino group occurred at all. Moreover, the labeling percentage of both hydrogen atoms rose by over 20% when the amount of deuterated water was increased from 1.0 to 2.0 equivalents. These results clearly suggest that the reaction should prefer path c to other possible paths, such as a and b (Scheme 3). The acid, generated from the reaction of water with trichlorosilane, first protonates C1 of **8** to form iminium intermediate **C**, which is then subjected to the reduction by trichlorosilane in the presence of the catalyst. The deuterium labeling of the second hydrogen on C1 is due to the fast equilibrium between intermediate **C** and **8**.



Scheme 3. Deuterium-labeling experiments and proposed reaction pathway.

In conclusion, we have developed a novel method for the asymmetric reduction of β-amino nitroolefins by using structurally simple *S*-chiral *N*-sulfinyl ureas as bifunctional catalyst and trichlorosilane as reducing agent. A broad range of substrates was reduced in high yield and excellent enantioselectivity. The product can easily be transformed into practically useful diamine and amino acid derivatives. Not only does this method provide a new approach to chiral β-amino nitroalkanes, but it also offers a new strategy for the design and implementation of efficient bifunctional catalysts, particularly for the asymmetric reduction through hydrosilylation.

Experimental Section

General procedure: Trichlorosilane (30 μL, 0.3 mmol) was added dropwise to a stirred solution of **8** (0.1 mmol), catalyst **5a** (0.01 mmol), and water (1.8 μL, 0.1 mmol) in anhydrous acetonitrile (1.0 M) at −40 °C under an argon atmosphere. The mixture was stirred at the same temperature for 24 h. Then, the reaction was quenched by addition of water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The crude product was further purified by column chromatography (silica gel, hexane/EtOAc) to afford the desired pure β-amino nitroalkanes **9**.

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Keywords: amino nitroolefins · asymmetric catalysis · bifunctional catalyst · hydrosilylation · reduction · sulfinyl ureas

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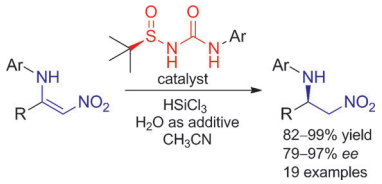
Simple but effective: A structurally simple *N*-sulfinyl urea was found to be a highly efficient bifunctional catalyst, which allows for the development of a novel pathway for the construction of chiral β-amino nitroalkanes through enantioselective reduction of β-amino nitroolefins by trichlorosilane. High yields and excellent enantioselectivities were obtained for a broad range of β-arylamino nitroolefin substrates (see scheme).



Organocatalysis

*X.-W. Liu, Y. Yan, Y.-Q. Wang, C. Wang, J. Sun** ..... ▮▮▮▮–▮▮▮▮

Highly Enantioselective Reduction of β-Amino Nitroolefins with a Simple *N*-Sulfinyl Urea as Bifunctional Catalyst