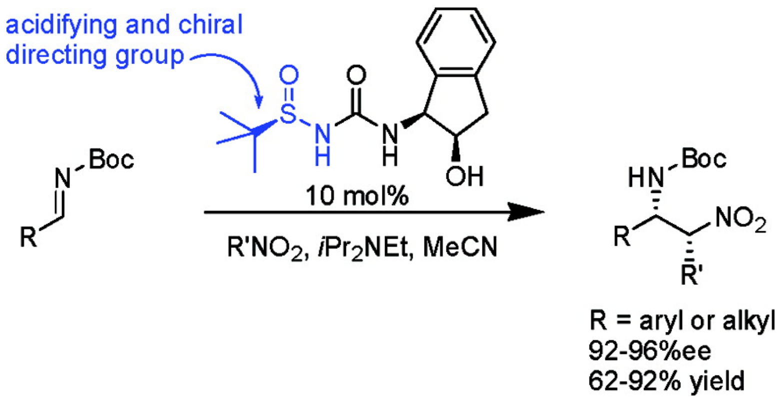
Communication

Enantioselective Aza-Henry Reaction with an *N*-Sulfinyl Urea Organocatalyst

MaryAnn T. Robak, Monica Trincado, and Jonathan A. Ellman

J. Am. Chem. Soc., **2007**, 129 (49), 15110-15111 • DOI: 10.1021/ja075653v



J|A|C|S
COMMUNICATIONS

Enantioselective Aza-Henry Reaction with an *N*-Sulfinyl Urea Organocatalyst

MaryAnn T. Robak, Monica Trincado, and Jonathan A. Ellman*

Department of Chemistry, University of California, Berkeley, California 94720

Received July 28, 2007; E-mail: jellman@berkeley.edu

Urea- and thiourea-based hydrogen-bonding (H-bonding) organocatalysts have been developed for a variety of nucleophilic additions to carbonyl, imine, and nitroolefin functionalities.[1] The two most popular classes of urea-based asymmetric catalysts either incorporate an acidifying group, as exemplified by structure **1** extensively developed by Takemoto, or incorporate a chiral directing group, as exemplified by structure **2** first developed by Jacobsen (Figure 1).[1] However, no urea organocatalyst has been reported to date with an acidifying *N*-substituent that also incorporates an adjacent chiral center. Herein, we report on the development of a new class of organocatalysts that incorporate the *N*-sulfinyl urea substituent, which is acidifying and serves as a chiral controlling element (**3**, Figure 1).[2] Furthermore, the utility of this new organocatalyst is demonstrated by the high selectivity provided in the aza-Henry reaction not only for aromatic *N*-Boc imine substrates[3] but also for aliphatic imine substrates for which H-bonding catalysis has not previously been demonstrated.

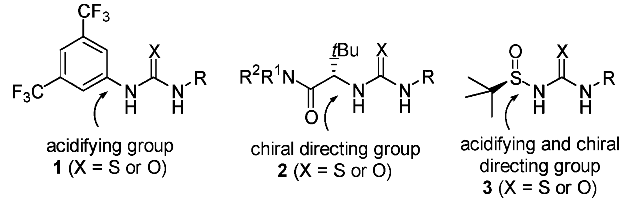
Sulfinyl ureas and thioureas may be synthesized in one step by condensing *tert*-butanesulfinamide with the appropriate isocyanate or isothiocyanate, respectively. The modular nature and straightforward synthesis of this scaffold therefore enables facile catalyst optimization. However, prior to evaluating catalysis, the acidifying nature of the sulfinyl substituent was first demonstrated by measuring the pK in DMSO of sulfinyl urea **4a** and thiourea **4b** (Figure 2).[4] For comparison, the pK's of electron-poor aryl urea **5a** and thiourea **5b** were also measured. These measurements clearly establish that the sulfinyl group is 2−3 pK units more acidifying than the frequently used 3,5-bis-CF$_3$-phenyl group.

In order to evaluate the potential of the sulfinyl urea scaffold as an asymmetric H-bonding organocatalyst, we decided to focus on the aza-Henry (or nitro-Mannich) reaction (Figure 3 and Table 1). A variety of sulfinyl ureas and thioureas were synthesized and screened as catalysts in the aza-Henry reaction of imine **9** with nitroethane to afford a mixture of diastereomers **10** and **11**. Promising initial results were obtained using sulfinyl urea **6a**, bearing a simple phenyl substituent. However, evaluation of a number of *N*-sulfinyl ureas and thioureas with different achiral aryl and aliphatic substituents such as **6b**−**e** did not result in improvements in selectivity.

Taking advantage of the flexibility of the sulfinyl urea scaffold, we evaluated several derivatives that incorporate additional chirality and functionality. Both diaminocyclohexane derivative **7a** and *cis*-amino indanol derivative **8a** were found to be excellent catalysts for this reaction, giving both high conversion and selectivity under the screening conditions.

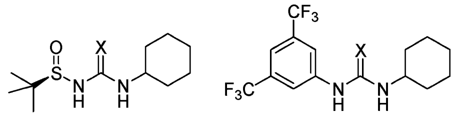
Optimization of reaction conditions, including solvent and stoichiometry, revealed higher selectivity in acetonitrile with 0.5 equiv of amine base (see Supporting Information for details).

Under the optimized reaction conditions, several variants of catalyst **8a** were tested to determine the relationship between the structure of the catalyst and its activity (Table 2). The more acidic thiourea derivative **8b** and the even more acidic sulfonyl derivative **8f** were both found to be considerably less efficient catalysts than **8a**. Clearly, urea acidity is not the sole factor responsible for reaction rate. It is possible that these catalysts are deactivated by proton transfer to the amine base additive, *i*-Pr$_2$NEt.



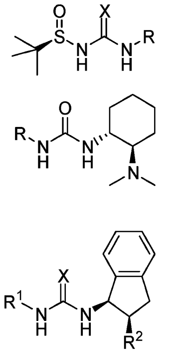
1 (X = S or O) **2** (X = S or O) **3** (X = S or O)

Figure 1. Urea-based asymmetric organocatalysts.



4a X = O, pK = 15.5
4b X = S, pK = 11.2
5a X = O, pK = 18.1
5b X = S, pK = 13-14

Figure 2. The pK's of ureas and thioureas.



6a X = O, R = C$_6$H$_5$
6b X = S, R = C$_6$H$_5$
6c X = O, R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
6d X = O, R = *n*Bu
6e X = O, R = *t*Bu

7a R = (*R*)-S(O)*t*Bu
7b R = (*S*)-S(O)*t*Bu

8a X = O, R^1 = (*R*)-S(O)*t*Bu, R^2 = OH
8b X = S, R^1 = (*R*)-S(O)*t*Bu, R^2 = OH
8c X = O, R^1 = (*S*)-S(O)*t*Bu, R^2 = OH
8d X = O, R^1 = (*R*)-S(O)*t*Bu, R^2 = OTBS
8e X = O, R^1 = (*R*)-S(O)*t*Bu, R^2 = H
8f X = O, R^1 = SO$_2$*t*Bu, R^2 = OH
8g X = O, R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$, R^2 = OH
8h X = S, R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$, R^2 = OH

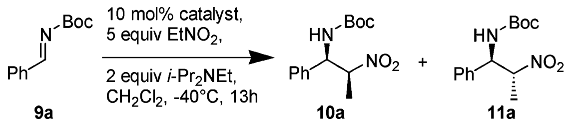
Figure 3. Sulfinyl ureas tested in the aza-Henry reaction.

Structure activity relationships were also determined to assess the impact of different substituents on reaction selectivity. The hydroxyl group of **8a** is essential for the high enantioselectivity observed, as demonstrated by derivatives **8d**, which has a silyl protecting group, and **8e**, which lacks the alcohol functionality. The influence of the chirality of the sulfinyl group is also clearly demonstrated by the significant drop in enantioselectivity when the sulfinyl group is replaced by the benchmark acidifying group, the 3,5-(bis)trifluoromethylphenyl substituent, for both urea (entry 7) and thiourea (entry 8) organocatalysts. Changing the stereochemistry of the sulfinyl group also results in a drop in enantioselectivity (entry 3).

The scope of the reaction with respect to both the imine and the nitroalkane was explored under the optimized reaction conditions

10.1021/ja075653v CCC: $37.00

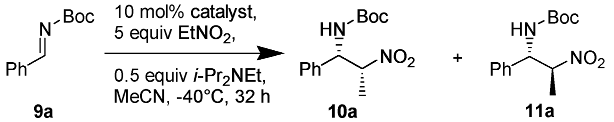
Table 1. Sulfinyl Urea Catalyzed Aza-Henry Reaction



entry	catalyst	conv[a] (%)	dr[b] (**10**:**11**)	**10** ee[b] (%)
1	none	23	25:75	0
2	**4a**	75	18:82	10
3	**6a**	59	57:43	30
4	**6b**	17	30:70	0
5	**6c**	36	50:50	28
6	**6d**	73	38:62	5
7	**6e**	71	16:84	8
8	**7a**	85	75:25	89
9	**7b**	56	45:55	60
10	**8a**	82	80:20	−90[c]

[a] Conversion to product was determined by ^{1}H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. [b] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC. [c] Opposite enantiomer obtained as the major product.

Table 2. Sulfinyl Urea Catalyzed Aza-Henry Reaction

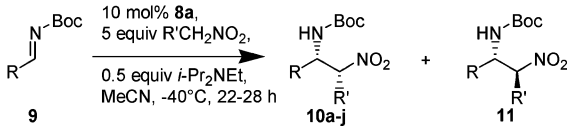


entry	catalyst	conv[a] (%)	dr[b] (**10**:**11**)	**10** ee[b] (%)
1	**8a**	99	83:17	94
2	**8b**	42	43:57	58
3	**8c**	90	71:29	80
4	**8d**	73	19:81	−7
5	**8e**	99	21:79	0
6	**8f**	35	26:74	16
7	**8g**	82	83:17	80
8	**8h**	65	76:24	79

[a] Conversion to product was determined by ^{1}H NMR analysis of crude product relative to hexamethylbenzene as an internal standard. [b] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC.

(Table 3). Excellent enantioselectivity was observed with imines bearing both electron-rich and electron-poor aromatic substituents (entries 1−6). More significantly, aliphatic *N*-Boc imines were found to be effective substrates, yielding adducts **10g**−**j**, which were previously unreported, with very high selectivity. High diastereoselectivities and enantioselectivities were achieved with additions to unbranched and β-branched imine substrates (entries 7−10). The addition of β-phenylnitroethane to give **10i** with high selectivity demonstrates that larger nitroalkanes can be used (entry 9), and the addition of nitromethane to give **10j** demonstrates that high enantioselectivity can be achieved even when a product that lacks α-branching is obtained (entry 10).

Table 3. Catalytic Enantioselective Aza-Henry Reaction with Representative *N*-Boc Imines



entry	R	R′	major product	yield[a] (%)	dr[b] (**10**:**11**)	**10** ee[b] (%)
1	C_6H_5	Me	**10a**	84	85:15	95
2	*p*-$MeOC_6H_4$	Me	**10b**	64	90:10	95
3	*p*-MeC_6H_4	Me	**10c**	68	79:21	95
4	*p*-$CF_3C_6H_4$	Me	**10d**	92	77:23	92
5	*o*-ClC_6H_4	Me	**10e**	88	80:10	94
6	2-naphthyl	Me	**10f**	80	84:16	93
7	*n*-Bu	Me	**10g**	80	92:8	96
8	*i*-Bu	Me	**10h**	76	93:7[c]	96
9	*i*-Bu	Bn	**10i**	62	88:12	96
10	*i*-Bu	H	**10j**	64		95

[a] Isolated yield after chromatography. [b] Diastereomeric ratio and enantiomeric excess were determined by chiral HPLC. [c] Absolute configuration rigorously determined by chemical correlation (see Supporting Information).

In conclusion, *N*-sulfinyl ureas are a new class of organocatalysts with the sulfinyl group serving both as an acidifying agent and as a chiral controlling element. The effectiveness of this class of organocatalysts was demonstrated by catalysis of the aza-Henry reaction with high selectivity, including the first examples of enantioselective H-bonding-catalyzed additions to aliphatic *N*-Boc imines.

Acknowledgment. The support of NSF (CHE-0446173) and Merck is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews of H-bonding organocatalysis, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

(2) Other sulfinamide-based catalysts: (a) Owens, T. D.; Hollander, F. J.; Oliver, A. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 1539−1540. (b) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3−10. (c) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545−548. (d) Pei, D.; Wang, Z. Y.; Wei, S. Y.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5912−5915. (e) Sola, J.; Reves, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020−5023. (f) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315−1317.

(3) Other organocatalytic aza-Henry reactions: (a) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (c) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466. (d) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2005**, *62*, 375. (e) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 341. (f) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643.

(4) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

JA075653V