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Enantioselective Protonation of Enol Silanes**

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Citation	Beck, Elizabeth M., Alan M. Hyde, and Eric N. Jacobsen. 2011. Chiral sulfinamide/achiral sulfonic acid cocatalyzed enantioselective protonation of enol silanes. <i>Organic Letters</i> 13(16): 4260-4263.
Published Version	doi:10.1021/ol201608a
Accessed	February 19, 2015 9:58:01 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:8737993
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Chiral Sulfinamide/Achiral Sulfonic Acid Co-Catalyzed Enantioselective Protonation of Enol Silanes

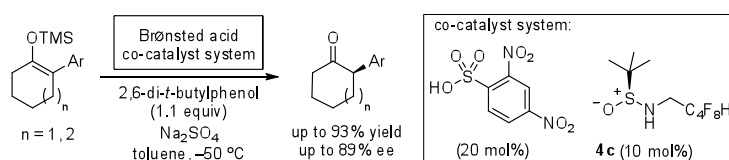
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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



The application of chiral sulfinamides and achiral sulfonic acids as a co-catalyst system for enantioselective protonation reactions is described. Structurally simple, easily accessible sulfinamides were found to induce moderate-to-high ee's in the formation of 2-aryl-substituted cycloalkanones from the corresponding trimethylsilyl enol ethers.

Weak-to-moderately strong chiral Brønsted acids, ranging from diols to phosphoric acids, have been applied in a variety of catalytic enantioselective transformations. Particular success has been achieved in catalysis of addition reactions to relatively basic electrophiles such as imines.¹ More recently, some effort has been directed towards accessing and utilizing stronger Brønsted acids, enabling expansion of the scope to the activation of carbonyl groups and certain olefins.²

We became interested in exploring the potential of the conjugate acids of chiral sulfinamides as a novel class of strong, chiral Brønsted acid catalysts. While sulfinamides find extensive use as chiral auxiliaries and ligands in

asymmetric synthesis,³ applications of these privileged chiral structures as organocatalysts are less common.^{4,5} Our design was inspired by recent studies with sulfinamide–urea catalyst **1a**, which revealed that the highly enantioselective addition of electron-rich alkenes to protoiminium ions can be achieved through a network of non-covalent interactions between the electrophile and the chiral urea-bound counteranion.⁵ In particular, spectroscopic and computational evidence was obtained for a hydrogen-bond interaction between the sulfinamide group of the catalyst and the N–H proton of the iminium

¹ For general reviews on chiral Brønsted acids as organocatalysts, see: (a) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (b) Terada, M. *Synthesis*, **2010**, *12*, 1929. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

² (a) Nakashima, D.; Yamamoto, H.; *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (c) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363. (d) Uragguachi, D.; Nakashima, D.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7242. (e) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature*, **2011**, *470*, 245.

³ For a recent, comprehensive review of the synthesis and applications of *tert*-butanesulfinamide, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. and for *p*-tolylsulfinamide, see: (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

⁴ For examples of sulfinamides as organocatalysts, see (a) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913. (b) Tan, K. L.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1315. (c) Wang, C.; Wu, X.; Zhou, L.; Sun, J. *Chem. Eur. J.* **2008**, *14*, 8789. (d) Pei, D.; Zhang, Y.; Wei, S.; Wang, M.; Sun, J. *Adv. Synth. Catal.* **2008**, *350*, 619. (e) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (f) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.

⁵ Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science*, **2010**, *327*, 986.

ion intermediate (Figure 1A). We hypothesized that in the absence of the Lewis-basic imine, the combination of a sulfonic acid and sulfinamide urea catalyst **1a** could produce a chiral acidic species capable of effecting enantioselective protonation reactions (Figure 1B). The proximity of the stereogenic sulfur to the proton would potentially enable high levels of stereochemical communication. Here we describe the development of this new approach for catalysis and its application to the enantioselective catalytic protonation of prochiral enol silanes as a method for the preparation of chiral, α -branched ketones.^{6,7}

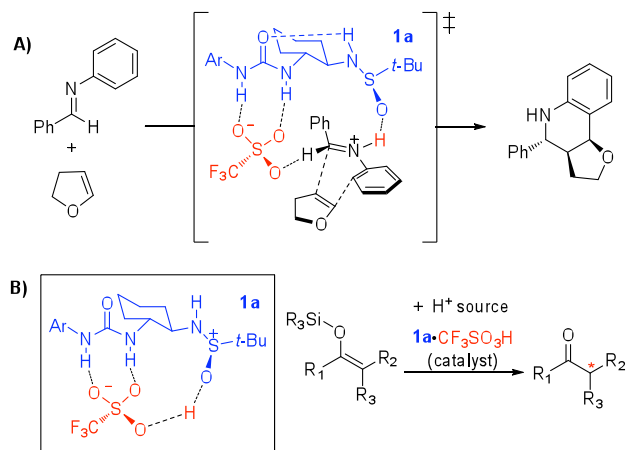


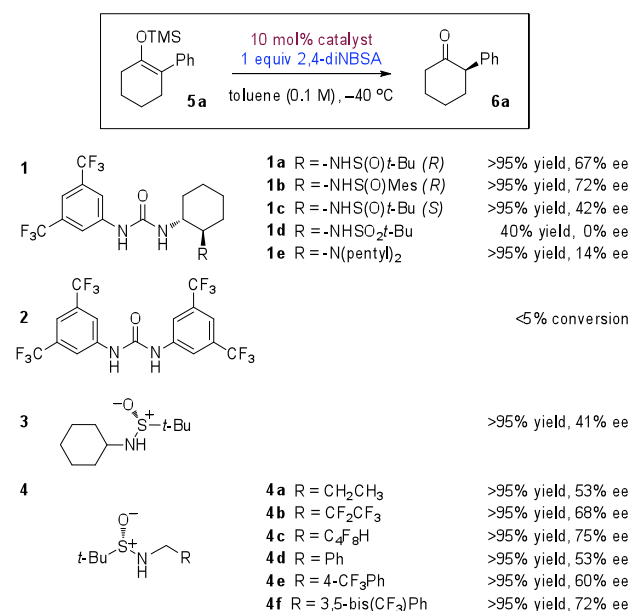
Figure 1. (A) Schematic representation of the geometry and energy-minimized lowest energy transition structure for sulfinamide-urea/TfOH co-catalyzed Povarov reaction (from ref 5). (B) Schematic representation of the energy-minimized lowest energy ground state structure for the sulfinamide-urea **1a**/TfOH 'chiral acid' complex. Structures calculated at the B3LYP/6-31G(d) level of density functional theory. Ar = 3,5-bis(CF₃)C₆H₃.

Silyl enol ether **5a**, derived from 2-phenylcyclohexanone, was selected as the model substrate (Scheme 1). A suitable achiral stoichiometric proton source was sought that would effect protonation of the sulfinamide catalyst scaffold without promoting a background racemic protonation pathway. It was found that 2,4-dinitrobenzene sulfonic acid (2,4-diNBSA) was well suited, as it is completely insoluble in toluene at -40 °C and, consequently, unreactive toward **5a** under these conditions. However, in the presence of catalytic levels

of sulfinamide-urea **1a**, substrate protonation occurred to generate the corresponding ketone **6a** in 67% ee. No reactivity toward **5a** was displayed by **1a** alone under these conditions. Ketone **6a** was found to be configurationally stable under the catalytic conditions.

Systematic variation of the catalyst structure revealed that replacement of the sulfinamide group with other basic functional groups such as sulfonamides (**1d**) or tertiary amines (**1e**) led to much less effective catalysts for the protonation of **5a** with 2,4-diNBSA, and that urea derivatives such as **2**, lacking a basic ancillary group, were completely unreactive (Scheme 1).

Scheme 1. Evaluation of catalyst structures^a



^aYield determined by ¹H NMR on a 0.05 mmol scale. Enantioselectivity determined by chiral HPLC.

Examination of simple sulfinamide **3**, which lacks a urea moiety, revealed that it was also catalytically active in the protonation of **5a**, affording ketone **6a** in >95% yield and 41% ee. The enantioselectivity observed with **3**, while moderate, revealed that enantioselective catalysis could be achieved with compounds bearing only the sulfinamide moiety. The synthetic accessibility of these simple structures allowed for the rapid preparation and screening of a large array of substituted sulfinamide derivatives.⁸ Testing analogues of **3** demonstrated that branching at the carbon center adjacent to the sulfinamide nitrogen was deleterious to both reactivity and enantioselectivity, so efforts were focused on simple primary sulfinamide derivatives (Scheme 1, **4a-f**). Interestingly, both simple alkyl- and benzyl-substituted

⁶ For previous examples of enantioselective protonation as a route to α -aryl cyclohexanones, see: (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (c) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (d) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem. Int. Ed.*, **2005**, *44*, 1546. (e) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246.

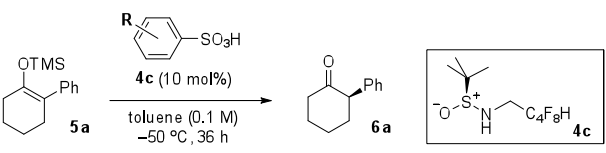
⁷ For enantioselective protonation of other silyl enol ether substrate classes, see: (a) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090. (b) Poisson, T.; Oudeyer, S.; Dalla, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, 2447. (c) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2366. (d) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858. (e) Uraguchi, D.; Kinoshita, N.; Ooi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12240.

⁸ For additional details of other sulfinamide structures and associated selectivities in the enantioselective protonation reaction, see supporting information.

catalysts performed comparably (**4a** vs. **4d**). For both, however, a significant increase in enantioselectivity was observed with analogues bearing additional electron-withdrawing groups. This effect was especially pronounced with fluorinated analogues (**4a** vs. **4b** and **4c**; **4d** vs. **4e** and **4f**).

The enantioselectivity was also found to be responsive to the identity of the sulfonic acid, even though none of the sulfonic acid derivatives examined displayed any background reactivity in the absence of catalyst **4c** (Table 1, entries 2–5). Reactions with 2,4-dinitrobenzene sulfonic acid as the strong acid source afforded highest ee's. Further, it was observed that it is possible to use a catalytic quantity of the sulfonic acid as long a stoichiometric proton source such as water or a phenol is introduced (entries 6–8). In particular, reactions with hindered phenols such as 2,6-di-*tert*-butylphenol afforded product **6a** in highest enantioselectivity (entry 8). Addition of a desiccant such as sodium sulfate to remove residual water associated with the hygroscopic sulfonic acids had a beneficial effect on both yield and ee (entries 1 vs. 2, and 8 vs. 9). Under optimal conditions, product **6a** was obtained in 86% ee using **4c** as the catalyst with 0.2 equiv 2,4-diNBSA, 1.1 equiv 2,6-di-*tert*-butylphenol and 2.0 equiv Na₂SO₄ in toluene at –50 °C (Table 2, entry 9).

Table 1. Effect of the proton source on enantioselectivity^a

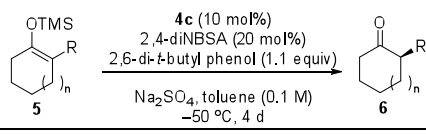


entry	R	equiv ArSO ₃ H	H ⁺ source	conversion ^c (%)	ee ^d (%)
1	2,4-(NO ₂) ₂	1.0	-	>95	76
2 ^b	2,4-(NO ₂) ₂	1.2	-	>95	85
3 ^b	2-NO ₂	1.2	-	>95	69
4 ^b	3-NO ₂	1.2	-	>95	55
5 ^b	2,4,5-Cl ₃	1.2	-	>95	58
6	2,4-(NO ₂) ₂	0.1	H ₂ O	43	69
7	2,4-(NO ₂) ₂	0.1	PhOH	>95	76
8	2,4-(NO ₂) ₂	0.1	2,6-(<i>t</i> -Bu) ₂ C ₆ H ₃ OH	70	83
9 ^b	2,4-(NO ₂) ₂	0.2	2,6-(<i>t</i> -Bu) ₂ C ₆ H ₃ OH	78	86

^a Reactions were carried out on 0.05 mmol scale. ^b 2 equiv Na₂SO₄ included. ^c Determined by ¹H NMR. ^d Determined by HPLC using commercial chiral columns.

A variety of silyl enol ethers were examined under these conditions in the enantioselective protonation reaction (Table 2). Several 2-aryl-substituted cyclic ketones bearing electron-donating or withdrawing para substituents could be obtained in high yield and with ee's between 78 and 89% (entries 1–6). Substituents in the ortho and meta positions were also tolerated (entries 7–9). The cycloheptanone derivative **5j**, however, underwent protonation with measurably lower enantioselectivity (entry 10).

Table 2. Substrate scope^a



entry	enol silane	n	R	ketone	yield ^b (%)	ee ^c (%)
1	5a	1	C ₆ H ₅	6a	91	86
2	5b	1	4-MeC ₆ H ₄	6b	92	88
3	5c	1	4-OMeC ₆ H ₄	6c	90	84
4	5d	1	4-ClC ₆ H ₄	6d	89	89
5	5e	1	4-FC ₆ H ₄	6e	88	81
6	5f	1	4-CO ₂ MeC ₆ H ₄	6f	84	78
7	5g	1	3-MeC ₆ H ₄	6g	92	84
8	5h	1	2-MeC ₆ H ₄	6h	91	85
9	5i	1	2-Naphthyl	6i	93	82
10	5j	2	C ₆ H ₅	6j	88	73

^a Reactions were carried out on 0.15 mmol scale. Silyl enol ether and **4c** were added as a solution in toluene to 2,4-diNBSA, 2,6-di-*tert*-butylphenol and Na₂SO₄ in toluene at –78 °C. ^b Isolated yield based on silyl enol ether. ^c Determined by HPLC using commercial chiral columns.

While the sulfonamide appears to promote the protonation reaction by functioning as a solid-to-solution phase transfer catalyst for the insoluble 2,4-diNBSA,⁹ the basis for stereoselection in these reactions is intriguing and not at all apparent. As outlined below, our preliminary mechanistic investigation suggests several interesting possibilities for how a catalyst as simple as **4c** might participate in cooperative stabilizing interactions in the selectivity-determining transition structure.

A linear dependence of reaction enantioselectivity on the enantiopurity of **4c** was observed, indicating the sulfonamide catalyst maintains a monomeric structure in the ground state and in the ee-determining transition state. Accordingly, our analyses considered only pathways involving one chiral catalyst molecule.

In principle, either proton transfer or silyl transfer may be rate- and enantiodetermining in the protonation of silyl enol ethers catalyzed by **4c**.¹⁰ Both scenarios were evaluated computationally in the reaction of silyl enol ether **5a** with protonated sulfonamide catalyst CF₃CH₂NHS(O)*t*-Bu (**4g**) (Figure 2). Given the structural and functional group simplicity of the chiral catalyst, we were especially interested in whether attractive noncovalent interactions might play a role in organizing

⁹ The complexation behavior of the sulfonamide catalysts with 2,4-diNBSA was investigated by ¹H NMR. Peak integration of mixtures in C₆D₆ revealed that bifunctional catalysts **1a–e** form a 1:1 complex with 2,4-diNBSA. In contrast, no dissolution of 2,4-diNBSA was observed with the simple urea **2**. Simple sulfonamides **4c** and **4f**, lacking a urea component, also induced solubilization of the sulfonic acid. These data point to a role of the sulfonamides as solid-to-solution phase transfer catalysts.

¹⁰ For an example in which rate-limiting desilylation is proposed, see ref. 6c.

the transition structures into energetically well-defined geometries.¹¹

Preliminary calculations indicated that proton transfer should occur from the oxygen atom of the sulfinamide, as NH-to-C proton transfer was significantly higher in energy. We examined a series of transition structures incorporating NH- π , CH- π or hydrogen bonding interactions, as well as others lacking secondary non-covalent interactions. Of these, the lowest energy structures were those that included CH- π interactions from the electron-deficient CH₂ side chain of the catalyst to the substrate aryl ring (one representative structure is shown in Figure 2A). In this structure the distance from the closest hydrogen of catalyst to the centroid of the arene is 2.47 Å. Since the existence of a weak noncovalent interaction cannot be inferred from atomic distance only, analysis of the electron density and its derivatives was carried out using the NCIPLOT program recently developed by Yang and co-workers.¹² This approach allows for the generation of gradient isosurfaces that indicate the location and strength of noncovalent interactions of all types.

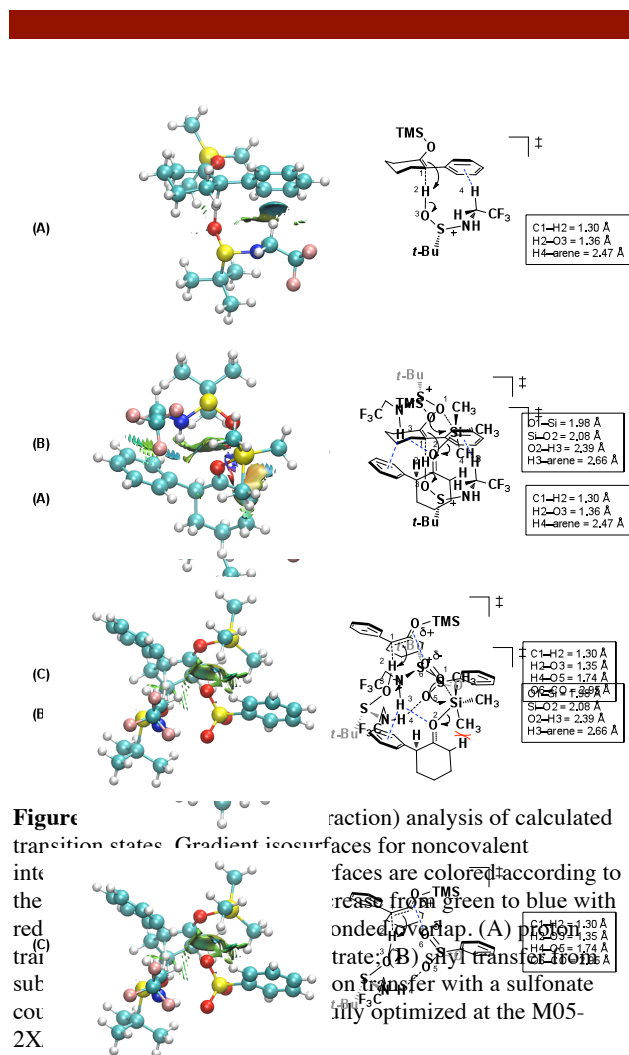
Transition structures for silyl transfer from a C-protonated silyl enol ether intermediate to the sulfinamide oxygen were also modeled. In one such structure, hydrogen bonding from the NH of **4g** to the incipient carbonyl and also to the arene is observed to provide a rigidifying framework (Figure 2B).

The identity of the sulfonate counterion has a measurable influence on enantioselectivity (Table 1). Modeling the proton transfer step with a benzene sulfonate counterion included (Figure 2C) also revealed a network of potential attractive interactions. In the most energetically accessible structures, the sulfonate appears to be held in place by hydrogen bonding to the sulfinamide NH. However, NCI analysis points to electrostatic attraction with the CO bond developing positive charge as the dominant force that positions the sulfonate.

At this stage, development of a rigorous stereochemical model is beyond the scope of this analysis, and would likely require a dynamic approach that considers an ensemble of structures. Nevertheless, intriguing possibilities have been identified for how the structurally simple sulfinamide catalysts might engage in noncovalent, attractive interactions that can play a critical role in transition state organization.

In summary, simple chiral sulfinamide derivatives used in conjunction with a strong achiral sulfonic acid are effective catalysts for enantioselective protonation of prochiral silyl enol ethers. The use of these sulfinamide catalysts as acid shuttles introduces a new role for these

readily accessible compounds, and we anticipate extension of this reactivity principle to other types of synthetically interesting enantioselective protonation reactions.



¹¹ Accurately reproducing noncovalent interactions is a challenge for many density functional theory methods. We utilized Truhlar's M05-2X functional, which has been shown to be suitable in this respect: Zhou, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

¹² (a) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. *J. Am. Chem. Soc.* **2010**, *132*, 6498. (b) Contreras-García, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. *J. Chem. Theory Comput.* **2011**, *7*, 625.

Acknowledgment This work was supported by the NIGMS (PO1 GM-69721 and RO1 GM-43214) and by a Mary Fieser Postdoctoral Fellowship to E.M.B. from Harvard University and an NIH postdoctoral fellowship to A.M.H. We thank Amanda Turek for catalyst synthesis and Stephan Zeund for providing the calculated structure in Figure 1B.

Supporting Information Available Full experimental procedures, syntheses of substrates and catalysts, characterization data for all new compounds, NMR spectra and HPLC traces for protonation products, additional optimization with details of additional sulfinamide scaffolds, methods for computational analysis, cartesian coordinates for calculated structures, and NCIPLOT structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

