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Catalytic Asymmetric Addition of Thiols to Nitrosoalkenes Leading to Chiral Non-Racemic α-Sulfenyl Ketones

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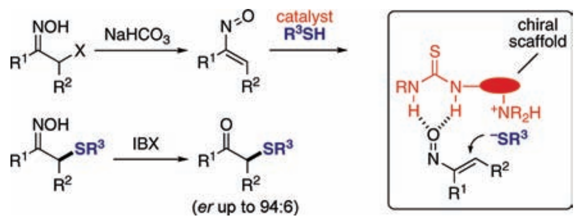
ABSTRACT



The first asymmetric organocatalytic sulfenylation of in situ derived nitrosoalkenes leading to chiral nonracemic α-sulfenylated ketones is described. The transformation proceeds in an umpolung fashion, relative to enolate/azaenolate methods, and uses simple thiols, thereby obviating the need for electrophilic sulfur reagents.

The α-functionalization of ketones in an umpolung sense, wherein a nucleophilic species adds to an electrophilic α-carbon, provides an attractive alternative to enolate/azaenolate-based methods and is well suited to catalysis. We are currently exploring ways to achieve this through the use of activated alkenes (e.g., azo- and nitrosoalkenes) obtained by the oxidation of hydrazones and related compounds.[1] Recent reports by Jørgensen,[2] Deng,[3] and Fu[4] highlight the general importance of asymmetric sulfenylation reactions. Chiral nonracemic sulfur-containing compounds are important both biologically[5] and in a synthetic context[6] through their use as chiral auxiliaries,[7] ligands for metal catalysis,[8] and organocatalysts.[9] We reasoned that the umpolung strategy we are investigating could provide the basis for the development of a novel approach to the asymmetric synthesis of α-sulfenylated ketones. Such compounds are normally obtained from the addition of an electrophilic sulfur species to a preformed enolate/azaenolate.[10,11] Unfortunately, no general and effective method is available to

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(11) For asymmetric methods employing chiral auxiliaries, see: (a) Enders, D.; Schäfer, T.; Mies, W. *Tetrahedron* **1998**, *54*, 10239–10252. (b) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159–161. For an asymmetric method employing a stoichiometric chiral ligand, see:(c) Yura, T.; Iwasawa, N.; Clark, R.; Mukaiyama, T. *Chem. Lett.* **1986**, 1809–1812. For an asymmetric method employing a chiral sulfenylating reagent, see: (d) Hiroi, K.; Nishida, M.; Nakayama, A.; Nakazawa, K.; Fujii, E.; Sato, S. *Chem. Lett.* **1979**, 969–972.

(12) Use of the Enders SAMP/RAMP auxiliaries has proven effective in delivering α-sulfenylated SAMP/RAMP hydrazones (48–87% yield; dr = 95.5:4.5 to 98:2). However, complications during auxiliary removal result in low yields of the corresponding α-sulfenylated ketones or in compromised enantiomer ratios. See ref 11a.

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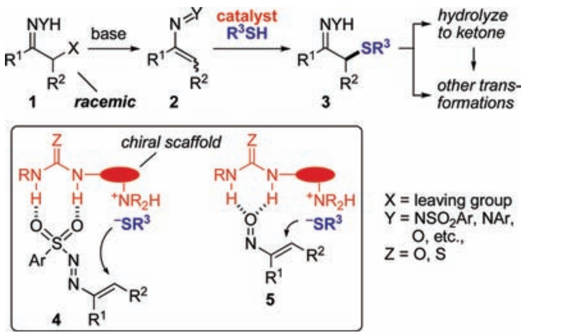
conduct this transformation asymmetrically,[11,12] and a catalytic asymmetric process has never been reported. In what follows, we describe the first catalytic asymmetric sulfenylation of in situ derived nitrosoalkenes, leading to chiral nonracemic α-sulfenylated ketones. This method reliably delivers high levels of asymmetric induction and occurs under mild and operationally simple conditions. Moreover, the transformation proceeds in an umpolung fashion, relative to conventional enolate/azaenolate methods, using simple thiols.

Scheme 1. Proposed Catalytic Asymmetric Umpolung Sulfenylation



N-Sulfonyl azo- and nitrosoalkenes undergo conjugate addition by certain nucleophiles.[1,13] Addition of benzene thiol to α-chloro *N*-sulfonyl hydrazones can be achieved using Et_3N.[13a] However, greater than 2 equiv of base are needed to ensure in situ formation of both the azoalkene intermediate and the corresponding ammonium thiolate. We theorized that if the activated olefin were generated (**1** → **2**, Scheme 1) irreversibly[14] prior to the thiolate addition step, then a catalytic amount of a chiral amine could be used, leading to an asymmetric sulfenylation reaction (**2** → **3**). Moreover, a racemic halogen species (**1**) would be adequate as the olefin precursor. As potential catalysts for this transformation, we were particularly interested in chiral amino (thio)ureas (cf. Figure 1). Such compounds should provide greater structural organization than simple chiral amines during the key bond-forming step as a result of hydrogen bonding (cf. **4** and **5**, Scheme 1) and facilitate intracomplex attack of the nucleophile.

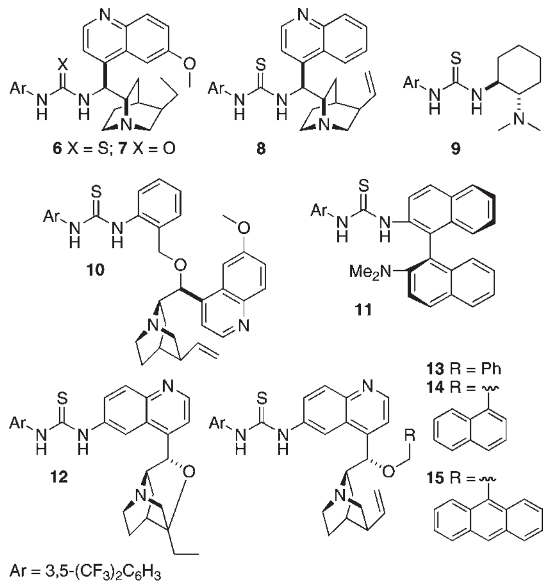


Figure 1. Amino (thio)urea catalysts **6**–**15**.

The general structure of the catalysts we required for our work is well-known in the context of certain bifunctional catalysts, which have been used to facilitate a variety of transformations.[15] Although our mechanistic proposal deviates from the mechanism that appears operative in those reports, the catalysts they employed provided us with an excellent starting point from which to launch our studies. Thus, we began by investigating the sulfenylation of α-chloro oxime **16** and α-chloro *N*-sulfonyl hydrazone **17** using the readily accessible compound **6**[15a] as a potential asymmetric catalyst (Table 1). The intermediate nitroso- and azoalkenes, respectively, were generated by treatment with $NaHCO_3$. Gratifyingly, compound **6** indeed catalyzed the formation of the desired product enantioselectively beginning from substrate **16**. However, no asymmetric induction resulted under the same conditions in the case of substrate **17**. The structurally related urea catalyst **7** was also tried with α-chloro oxime **16** but gave poorer asymmetric induction than its thiourea counterpart (**6**). Several other amino thioureas were tested as catalysts for the transformation (see Table 1), but only **14** and **15**[3] showed a clear improvement in enantioselectivity over **6**. Notably, catalysts **14** and **15** were complementary to **6** with regard to the absolute sense of asymmetric induction, offering a convenient way of accessing either enantiomer of **18**.

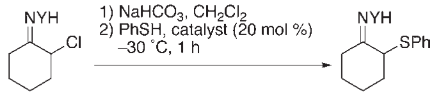
To further investigate the effect of temperature and solvent, the transformation between **16** and benzene thiol was studied using catalyst **6** (Table 2). Interestingly, no

(13) For example, see: (a) Reese, C. B.; Sanders, H. P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2719–2724. (b) Cacchi, S.; Misiti, D.; Felici, M. *Synthesis* **1980**, 147–149. (c) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372–7374. (d) Korboukh, I.; Kumar, P.; Weinreb, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 10342–10343. (e) Ohno, M.; Torimitsu, S.; Naruse, N.; Okamoto, M.; Saki, I. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1129–1134.

(14) Cf. Rosini, G.; Baccolini, G. *J. Org. Chem.* **1974**, *39*, 826–828 and references therein.

(15) For example, see: (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (c) Zhang, Z.; Schreimer, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. (d) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2008**, *7*, 1967–1969. (e) Andres, J. M.; Manzano, R.; Pedrosa, R. *Chemistry* **2008**, *14*, 5116–5119. (f) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315–1317. (g) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841–6844. (h) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049. (i) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419. (j) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125. (k) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293–4296. (l) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713–4716. (m) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370. (n) Song, J.; Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. (o) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

Table 1. Survey of Conditions for Asymmetric α-Sulfenylation

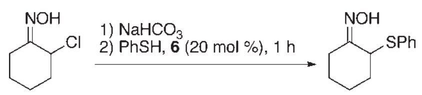


entry	substrate (Y)	catalyst	product	er[a]	yield (%)
1	**16** (O)	**6**	**18**	10:90	86
2	**17** (NSO_2Tol)	**6**	**19**	49:51	74
3	**16**	**7**	**18**	32:68	82
4	**16**	**8**	**18**	14:86	84
5	**16**	**9**	**18**	77:23	78
6	**16**	**10**	**18**	56:44	70
7	**16**	**11**	**18**	53:47	72
8	**16**	**12**	**18**	91:9	84
9	**16**	**13**	**18**	90:10	82
10	**16**	**14**	**18**	94:6	86
11	**16**	**15**	**18**	94:6	84

[a] Determined by chiral HPLC analysis.

improvement in asymmetric induction resulted at temperatures above or below −30 °C (entries 1−4).[16] This was also true of the various solvents tried for the reaction at −30 °C (entries 5−9), each of which gave inferior results in comparison to CH_2Cl_2 with regard to both asymmetric induction and yield.

Table 2. Effect of Solvent and Temperature on the Asymmetric α-Sulfenylation of **16** Catalyzed by **6**



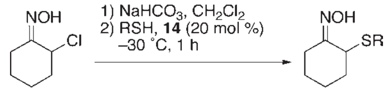
16 **18**

entry	solvent	temp (°C)	er[a]	yield (%)
1	CH_2Cl_2	23	20:80	76
2	CH_2Cl_2	4	12:88	80
3	CH_2Cl_2	−30	10:90	86
4	CH_2Cl_2	−78	10:90	81
5	$CHCl_3$	−30	20:80	68
6	Et_2O	−30	26:74	24
7	MeCN	−30	25:75	23
8	toluene	−30	12:88	82
9	THF	−30	20:80	70

[a] Determined by chiral HPLC analysis.

Since the best result of our study to this point was obtained using catalyst **14** in CH_2Cl_2 at −30 °C, these conditions were used to investigate the scope of the reaction with various thiols (Table 3). Both electron-rich and -deficient systems reacted effectively. No trend could be ascertained in these initial studies with regard to asymmetric induction, and the electronic properties of the thiols used. Interestingly, however, the two most sterically hindered thiols underwent the addition reaction with relatively low enantioselectivity (entries 7 and 8). Of the thiols examined, the best enantioselectivity resulted with the use of benzene thiol and 2-mercaptothiophene (entries 1 and 2).

Table 3. Scope of the Asymmetric α-Sulfenylation Reaction with Various Thiols



16

entry	thiol (R =)	product	er[a]	yield (%)
1	Ph	**18**	94:6	86
2	2-Thienyl	**20**	93:7	84
3	4-F-C_6H_4	**21**	90:10	85
4	2-Thiazole	**22**	91:9	88
5	4-MeO-C_6H_4	**23**	89:11	82
6	4-CF_3-C_6H_4	**24**	87:13	86
7	2,6-$(Me)_2$-C_6H_4	**25**	80:20	76
8	CPh_3	**26**	70:30	78
9	4-NO_2-C_6H_4	**27**	69:31	79
10	3,4-$(CF_3)_2$-C_6H_4	**28**	65:35	86

[a] Determined by chiral HPLC analysis.

We next turned our attention to investigating the scope of the reaction with different α-chloro oximes and benzene thiol (Table 4). The transformation extended to the use of other cyclic α-chloro oximes (entries 2 and 3), although the asymmetric induction was compromised somewhat for the five-membered system (**33**). We were pleased to find that the reaction could also be conducted in an asymmetric fashion with acyclic α-chloro oximes. In this case, the best results were obtained when there was a clear steric distinction between the α and α′ substituents (cf. **42**). Presumably this is due to a bias for the formation of the most sterically favored olefin configuration of the nitrosoalkenes, during deprotonation of the α-chloro oximes.

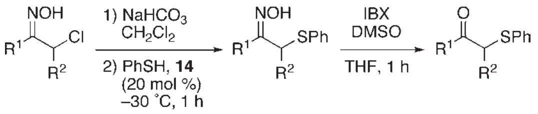
Having established an effective catalytic asymmetric sulfenylation reaction, we investigated the hydrolysis of the product oximes to ensure that they could be converted to the corresponding α-sulfenyl ketones without compromising the integrity of the new stereogenic center. After some experimentation, we were led to the use of IBX,[17] which allowed us to generate the α-sulfenyl ketones from the oximes without epimerization and in high yield (Table 4).

Initial investigations into the mechanism of the transformation were conducted as follows. First, to confirm that the nitrosoalkene was indeed formed and the putative electrophile in the reaction, a solution of **16** in $CDCl_3$ (distilled over CaH_2) was treated with saturated aqueous $NaHCO_3$ and then dried ($MgSO_4$). The product of this

(16) Studies are underway to determine if this temperature effect translates to other catalysts.

(17) Bose, D. S.; Srinivas, P. *Synlett* **1998**, 977–978.
(18) Francotte, E.; Merenyi, R.; Viehe, H. *Helv. Chim. Acta* **1981**, *64*, 1208–1218.

Table 4. Scope of the Asymmetric α-Sulfenylation Reaction with Various Thiols



entry	α-chloro oxime	α-sulfenyl oxime	er[a]	yield (%)	α-sulfenyl ketone	er[a]	yield (%)
1	16	18	94:6	86	29	94:6	95
2	30	31	92:8	87	32	91:9	94
3	33	34	84:16	81	35	83:17	92
4	36	37	84:16	85	38	84:16	93
5	39	40	88:12	85	41	88:12	91
6	42	43	93:7	89	44	92:8	96

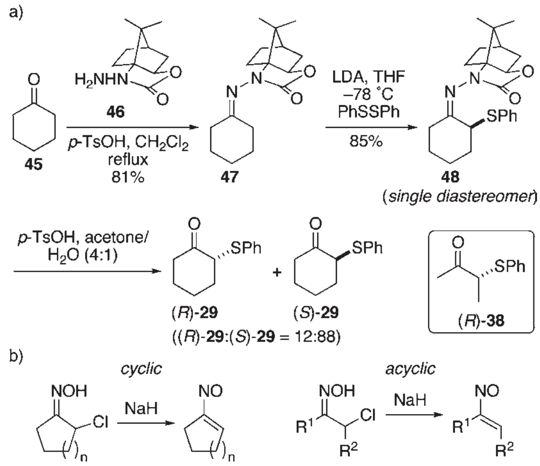
[a] Determined by chiral HPLC analysis.

reaction exhibited ^{1}H NMR data consistent with the corresponding nitrosoalkene.[18] In a second set of experiments, racemic **18** was prepared and combined with catalyst **14** in CH_2Cl_2. The product composition was analyzed after 1 h and showed a 50:50 mixture of enantiomers, indicating that no enantiomeric enrichment had occurred. This supports the notion that, for the enantioselective transformation, asymmetric induction results during addition of the ammonium thiolate to the nitrosoalkene.

The absolute stereochemistry of the addition reaction was determined using our recently developed method for asymmetric ketone α-functionalization,[19] as outlined in Scheme 2a. To do so, cyclohexanone was converted to *N*-amino cyclic carbamate (ACC) hydrazone **47** by condensation with ACC auxiliary **46**. Sulfenylation of this compound via the derived azaenolate gave **48** as a single diastereomer, and the crystal structure of this compound was obtained.[20] Hydrolysis of **48** then gave (*S*)-**29** as the major enantiomer,[21] which was the opposite of that formed from the present

(19) (a) Lim, D.; Coltart, D. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5207–5210. (b) Krenske, E. H.; Houk, K. N.; Lim, D.; Wengryniuk, S. E.; Coltart, D. M. *J. Org. Chem.* **2010**, *75*, 8578–8584.
(20) See the Supporting Information for details.
(21) Some epimerization occurred during hydrolysis.

Scheme 2. (a) Determination of Absolute Stereochemistry; (b) Proposed Nitrosoalkenes Intermediates



umpolung sulfenylation method. Using a related approach, we were able to establish that the major enantiomer of the ketone (**38**) produced from α-chloro oxime **36** (Table 3, entry 4) also had the *R*-configuration at the new stereogenic center (see (*R*)-**38**, Scheme 2a).[19] Since sulfenylation of both acyclic compound **36** and cyclic compound **16** gave the same sense of chirality at the newly formed stereogenic center, we assume that, like the cyclic α-chloro oximes, the acyclic systems also react via the nitrosoalkene in which the nitrogen and the α-alkyl substituent have the *E*-configuration about the carbon−carbon bond (cf. Scheme 2b).

In conclusion, we have developed the first catalytic asymmetric approach to the sulfenylation of in situ derived nitrosoalkenes, leading to chiral nonracemic α-sulfenylated ketones. The transformation proceeds in an umploung fashion, relative to conventional enolate/azaenolate methods, using simple thiols and known derivatives of readily accessible cinchona alkaloids as catalysts. Further mechanistic studies of this transformation are underway, as are studies on the use of different electrophiles and nucleophiles, and the exploration and development of improved catalysts.

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