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Reversal of Stereoselectivity in [5 + 2] Pyrone−Alkene Cycloadditions Using a Sulfoxide-to-Sulfoximine Switch. Enantiodivergent Synthesis of 8-Oxabicyclo[3.2.1]octane Systems

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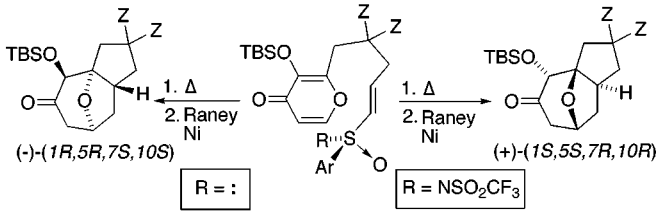
ABSTRACT



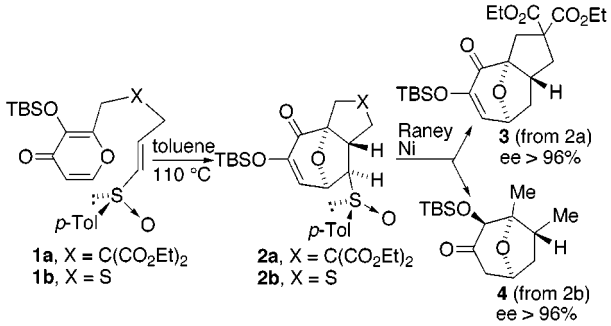
Switching from a sulfinyl to a sulfonimidoyl group allows the reversal of the sense of asymmetric induction in thermal [5C + 2C] intramolecular pyrone−alkene cycloadditions. Removal of the sulfoximine unit from the resulting cycloadducts yields optically active oxabicyclic systems that are enantiomeric to those obtained using the sulfinyl chiral auxiliary.

We have recently shown that the introduction of a homochiral *p*-tolylsulfinyl group at the *trans*-terminal position of an alkene accelerates its thermal [5C + 2C] intramolecular cycloaddition to β-silyloxy-γ-pyrones and leads to excellent levels of diastereodifferentiation.[1] Subsequent removal of the chiral auxiliary affords optically active, highly functionalized 8-oxabicyclo[3.2.1]octane derivatives (Scheme 1), synthetic intermediates that can be used to obtain a variety of valuable cyclic systems.[2]

The high diastereoselectivity of the cycloaddition was explained assuming that the alkenyl sulfoxide unit adopts an *S-trans* conformation with the alkene then approaching the pyrone from the face displaying the sulfur lone pair (Figure 1).[1]

One of the limitations of the above asymmetric cycload-

Scheme 1



(1) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 1005.
(2) For a recent review, see: Mascareñas, J. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; Jai Press: Stamford, 1999; Vol. 6, pp 1−54. (b) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 966. (d) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560. (e) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **2000**, *65*, 2528. (f) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Synthesis* **2000**, 980.

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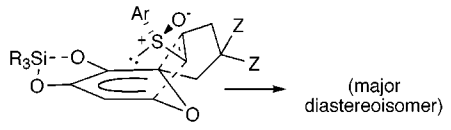
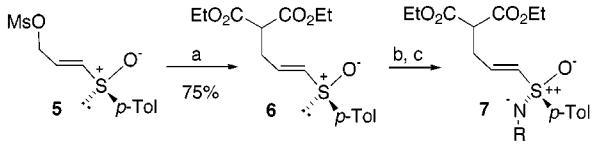


Figure 1.

dition, and of most other asymmetric reactions involving chiral auxiliaries, is that access to the enantiomeric series of products requires the assembly of precursors bearing the enantiomeric partner of the chiral auxiliary.[3] In our case this would need a seven-step synthesis starting from commercially available (−)-(S_s)-menthyl *p*-tolylsulfoxide. We envisaged that it might be possible to overcome this drawback by altering the priorities of the substituents at the sulfur in a way that reversed the diastereofacial selectivity of the cycloaddition. Although this tactic has few precedents, it has been reported that bulky aluminum-based Lewis acids are capable of changing the steric priority of the sulfinyl oxygen and thereby induce an inversion of topicity in sulfinyl-directed radical reactions.[4] This type of Lewis acid cannot be used in our system because of the basicity of the pyrone, but we reasoned that transforming the sulfoxide moiety of **1** into a sulfimide or a sulfoximine might be a practical strategy to alter the sterochemical outcome of the cycloaddition.

Since our initial attempts to prepare the *N*-tosylsulfimide from the sulfoxide **1a** gave low yields and seemed to be flawed by partial racemization, we turned our attention to the configurationally more robust sulfoximine derivatives. Sulfoximines have received rather little attention as chiral auxiliaries in asymmetric synthesis even though the presence of a nitrogen substituent on the sulfur would seem to offer interesting possibilities for modulating the steric and electronic characteristics of the chiral unit.[5] Among the various possible routes to prepare the required optically active sulfoximines, reaction of the alkenylsulfoxide **1a** with MSH (*O*-mesitylsulfonylhydroxylamine)[6] appeared to be the best choice since the resulting "free" aminated product is amenable to divergent *N*-substitution. Unfortunately, all attempts to carry out this transformation failed, most of them giving the desilylated pyrone as the only product. Nonetheless, the sulfoximine **7a**, an immediate precursor of the desired cycloaddition substrate, was efficiently prepared from optically active **5**[1] by sequential alkylation with diethylmalonate and subsequent amination with MSH in CH_3CN (Table 1).[7] That the amination reaction proceeded with complete stereoselectivity was confirmed by analysis and comparison of the ^{1}H NMR spectra of the Mosher [(+)-MPA and (±)-MPA] amide derivatives.[6b] This analysis revealed an optical purity of at least 96%, similar to that of the sulfoxide precursor **5**. To our best knowledge this is the first reported case of the formation of an optically active *N*-unsubstituted alkenylsulfoximine from an α,β-unsaturated sulfoxide.[5,6] After a brief, small-scale test of the viability of the coupling between the *N*-acetyl derivative **7b** and the bromopyrone **8** and of the cycloaddition of the resulting product, sulfoximine **7a** was transformed into a variety of *N*-substituted derivatives (Table 1).

Table 1. Preparation of *N*-Substituted Sulfoximines



(a) *i*) KI, acetone, rt, *ii*) $CH_2(CO_2Et)_2$, NaH, THF. (b) MSH, CH_3CN, rt. (c) See table below

entry	conditions (c)[a]	R	**7** (yield[b])
1		H	**7** (79%)
2	CH_3COCl, Et_3N, 0 °C	$COCH_3$	**7b** (82%)
3	$(CF_3CO)_2O$, Et_3N, rt	$COCF_3$	**7c** (72%)
4	PhCOCl, Et_3N, DMAP, rt	COPh	**7d** (60%)
5	*p*-$NO_2C_6H_5COOH$, EDC, DMAP, rt	CO*p*NO_2Ph	**7e** (81%)
6	CH_3SO_2Cl, Et_3N, 0 °C	SO_2CH_3	**7f** (75%)
7	$(CF_3SO_2)_2O$, Py, 0 °C	SO_2CF_3	**7g** (65%)
8	*p*-$TolSO_2Cl$, Py, 0 °C	SO_2pTol	**7h** (71%)
9	MPA, EDC, DMAP, rt	MPA	**7i** (74%)

[a] All of these reactions were carried out in CH_2Cl_2, except entry 8. [b] Overall yield for steps b and c.

The couplings between the alkenylsulfoximines **7** and the bromopyrone **8** all proceeded cleanly to give the expected cycloaddition precursors **9** in yields of between 77% for the *N*-acetyl derivative **9b** and 93% for **9c**.

Remarkably, the [5C + 2C] cycloaddition reactions of alkenylsulfoximines **9a**−**h** took place over three times faster than those of their sulfinyl analogues, an acceleration that must be related to the stronger electron-withdrawing character of the sulfonimidoyl group.[5] As illustrated in Table 2, except for the *N*-unsubstituted derivative **9a**, the cycloadditions of the acyl or sulfonylsulfoximines **9b**−**h** gave a reasonable degree of facial diastereoselectivity, which ranged from a modest 58:42 for the *p*-nitrobenzoyl derivative **9e** to a notable 90:10 for the *N*-tosyl compound **9h**. In all cases, except those of the *N*-tosyl, *N*-mesyl, and *N*-acetyl derivatives, it was possible to separate the two diastereoisomeric cycloadducts by flash chromatography.

The structures of the major diastereoisomers were unequivocally established as the oxabicycles **10b**−**h** by the

(3) *Stereochemistry of Organic Compounds*; Eliel, E., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1995.

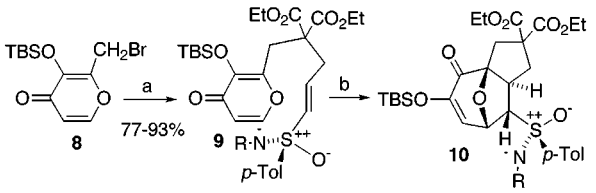
(4) (a) Renaud, P.; Bourquard, T.; Gerster, M.; Moufid, N. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 1601. (b) Lacôte, E.; Delouvrié, B.; Fensterbank, E.; Malacria, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2116. (c) Delouvrié, B.; Fensterbank, E.; Lacôte, E.; Malacria, M. *J. Am. Chem. Soc.* **1999**, *121*, 11395.

(5) A recent comprehensive review on sulfoximines: Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.

(6) It has been shown that amination of sulfoxides with MSH proceeds with complete retention of chirality at the sulfur atom: (a) Johnson, C. R.; Kirchhof, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. See also: (b) Yabuuci, T.; Kusumi, T. *J. Am. Chem. Soc.* **1999**, *121*, 10646.

(7) Use of CH_3CN was critical for the success of these aminations; see: Johnson, C. R.; Corkins, H. G. *J. Org. Chem.* **1978**, *43*, 4136.

Table 2. Intramolecular [5 + 2] Thermal Cycloaddition



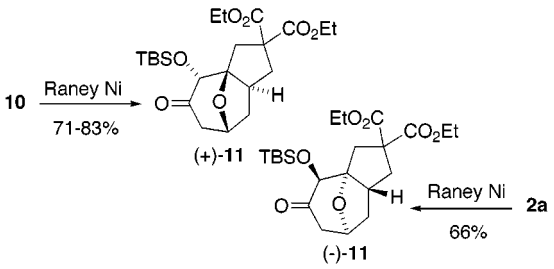
(a) **7**, NaH, THF, rt. (b) toluene, 110 °C, 60-90 min.

entry	pyrone	R	dr[a]	yield[b]
1	**9a**	H	50:50	75%
2	**9b**	$COCH_3$	65:35[c]	86%
3	**9c**	$COCF_3$	86:14	85%
4	**9d**	COPh	76:24	95%
5	**9e**	$CO\textit{p}NO_2Ph$	58:42	91%
6	**9f**	SO_2CH_3	77:23[c]	88%
7	**9g**	SO_2CF_3	87:13	80%
8	**9h**	SO_2pTol	90:10[c]	88%

[a] Diastereoisomeric ratio determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yield of the cycloaddition after chromatography. [c] The two diastereoisomers could not be separated by simple flash chromatography techniques.

optical rotation of their desulfonimidoylated derivative **11** ($[\alpha]_D = +19$, *c* 1, $CHCl_3$) being similar but of opposite sign to that of the same compound when obtained from the stereochemically fully characterized sulfoxide **2a**[1] (Scheme 2). The

Scheme 2



desulfurization reaction was efficiently achieved with Raney nickel in refluxing THF (71−83% yields),[8] but the need to use an excess of reagent caused concomitant reduction of the enone system. The sign of the optical rotation was the same in all cases (**b**−**h**), showing that the *N*-substituent affects the degree but not the sense of the induction.

The data of Table 2 suggest that the stereoselectivity of the cycloaddition is particularly affected by the polarity of the substituent on the nitrogen (compare entries 2 and 3, and 6 and 7). Therefore a tentative explanation for the stereochemical outcome of the cycloaddition could invoke a reactive conformation of the alkenylsulfoximine being as sketched in the Figure 2, with the amide substituent in *S-trans* arrangement with respect to the alkene in order to avoid repulsive dipole−dipole interactions with the pyrone. The

(8) Johnson, C. R.; Stark, C. J., Jr. *J. Org. Chem.* **1982**, *47*, 1193.

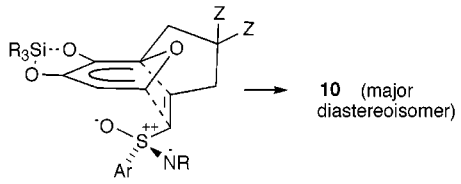
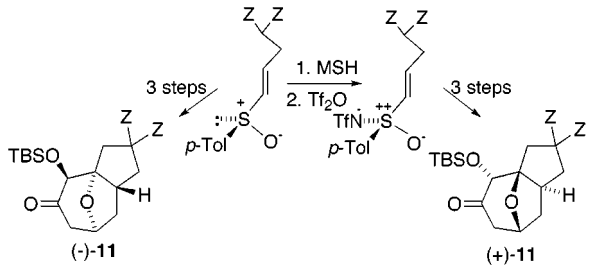


Figure 2.

alkene then approaches to the pyrone from its less hindered face, i.e., the face *anti* to the bulky *p*-tolyl group.

In summary, optically active alkenylsulfoxides, previously used as efficient chiral auxiliaries in [5 + 2] pyrone−alkene cycloadditions, can be readily transformed into sulfoximines with complete conservation of the stereochemistry at the sulfur atom. These alkenyl sulfoximines are excellent two-carbon partners for the cycloaddition, which takes place with diastereofacial selectivity opposite to that of their precursor sulfoxides. Therefore by simply choosing between a sulfoxide or its *N*-acyl or *N*-sulfonylsulfoximine derivatives both enantiomeric partners of the oxabicyclic adducts can be readily synthesized (Scheme 3). This removes the need to as-

Scheme 3



semble precursors with sulfoxide units of both configurations.

It seems reasonable to surmise that the success of this stereochemical tactic may not be limited to the above type of cycloaddition but might also find applicability in others among the many sufinyl-directed reactions described to date.[9]

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Supporting Information Available: Characterization data and experimental procedures for the preparation of **6**, **7a**−**i**, **9b**−**h**, **10a**−**h** and **11** and copies of ^{1}H NMR spectra relevant for deducing diastereo- and enantioselectivities. This material is available free of charge via the Internet at http://pubs.acs.org.

OL007061M

(9) For a review on sulfinyl-directed asymmetric reactions, see: Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.