Recoverable Chiral Sulfoxide: Asymmetric Diels–Alder Reaction Using Optically Active 1-(2-*p*-Tolylsulfinyl)pyrrolyl *α*,*β*-Unsaturated Ketones as a Dienophile

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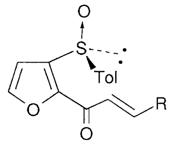
The Diels–Alder reaction of chiral cinnamoyl- and crotonyl (2-*p*-tolylsulfinyl)pyrrole with cyclopentadiene in the presence of $AlCl_3$ or $Yb(OTf)_3$ proceeded smoothly to give the corresponding *endo* adducts in excellent yield with high diastereoselectivity, ranging from 92 to 99% d.e. The chiral auxiliary, 2-pyrrolesulfoxide was efficiently recovered after alcoholysis of the adduct without loss of optical purity.

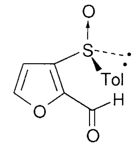
The asymmetric Diels–Alder reaction[1] using chiral sulfoxides as a chiral auxiliary is one of the useful reactions in organic synthesis. As a part of our studies on remote asymmetric induction by means of chiral sulfoxides, we recently reported highly diastereoselective Diels–Alder reaction and hetero-Diels–Alder reaction of the dienophiles **1**[2] and **2**[3] that possess the reaction site which may be remote from the sulfinyl group.

Although, to date, a high level of asymmetric induction in these reactions has been achieved, no much attention is focused on the development of chiral sulfoxides whose sulfinyl auxiliary can be recovered after the reactions.[4] Most reactions have made the recovery of the sulfinyl auxiliary from the product impossible since it was removed as sulfenic and sulfinic acids or by reductive cleavage of the sulfonyl derivative. To make the Diels–Alder reaction employing the chiral sulfoxides practically useful, we focused upon the use of (*S*)-2-pyrrolyl *p*-tolyl sulfoxide **3** for a *recoverable sulfoxide* after the diastereoselective reaction. Here we report the asymmetric Diels–Alder reaction of novel sulfoxides **4** and **5**, which were obtained from **3**, with cyclopentadiene in the presence of a Lewis acid.

The pyrrole sulfoxide **3** was prepared by lithiation of *N-tert*-butoxycarbonylpyrrole[5] with lithium diisopropylamide followed by addition of (*S*)-menthyl *p*-toluenesulfinate. The use of butyllithium[6] as a base in this reaction resulted in racemization of the product **3**. Treatment of **3** with sodium hydride followed by addition of cinnamoyl chloride and crotonyl chloride produced the enones **4** and **5**, respectively in good yield.



1a: R = Ph
1b: R = Me



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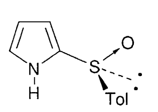

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All reactions of **4** and **5** were carried out with excess of cyclopentadiene in the presence of a Lewis acid in CH_2Cl_2 (Table 1). Although the reaction by the use of $BF_3{\bullet}Et_2O$ as a Lewis acid at 25 °C produced no adduct (entry 1), treatment of **4** and cyclopentadiene with 1.0 equiv. of $AlCl_3$ afforded the adducts **6a-d** in 99% yield (entry 3).[7] The use of a larger amount of $AlCl_3$ gave an unsatisfactory result. Attempts to employ other Lewis acids such as $ZnCl_2$ and Et_2AlCl in the reactions or to conduct without a Lewis acid were fruitless, and resulted in poor diastereoselectivities (*cf.* entry 2). On the other hand the ytterbium triflate-promoted Diels–Alder reactions[2,8] also proceeded smoothly to give the adducts with high diastereoselectivity, in good yields. The Diels–Alder reaction of **5** proceeded in a manner similar to that of **4** (entries 7 and 8).

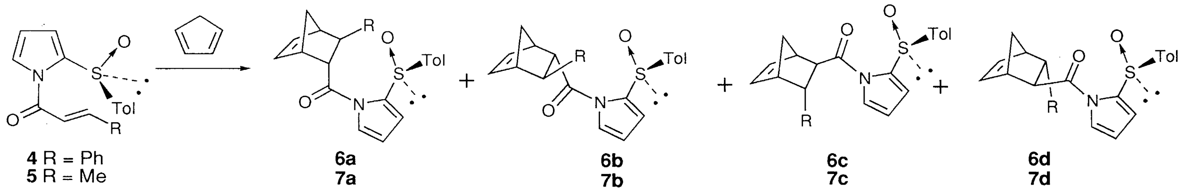


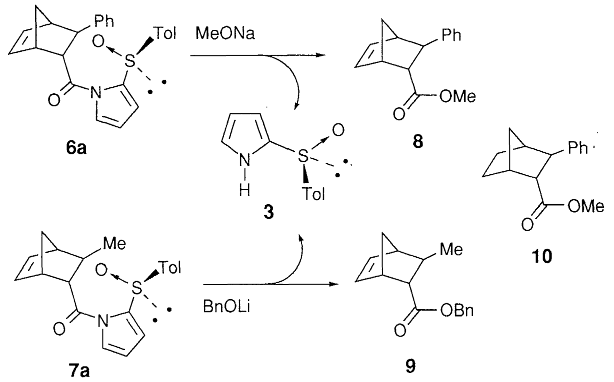
Table 1. Asymmetric Diels–Alder reaction of sulfinyl dienophiles **4** and **5** with cyclopentadiene in CH_2Cl_2 at 25 °C.[a]

Entry	Dienophile	Lewis acid (equiv.)		Reaction conditions Time / h	Yield / %[b]	Ratio of *endo*/*exo* (**a**+**b**) / (**c**+**d**)	D.e. / %[c] (*endo*)
1	4	$BF_3{\bullet}Et_2O$	1.0	17	0	—	—
2	4	$ZnCl_2$	1.0	29	60	77 / 23	38
3	4	$AlCl_3$	1.0	13	99	95 / 5	>99
4	4	$AlCl_3$	2.0	6	84	59 / 41	11
5	4	$Yb(OTf)_3$	0.2	16	33	80 / 20	80
6	4	$Yb(OTf)_3$	1.0	45	61	69 / 31	89
7	5	$Yb(OTf)_3$	1.0	9	93	92 / 8	93
8	5	$AlCl_3$	1.0	13	100	91 / 9	92

[a]The reactions conducted without a Lewis acid in refluxing dichloromethane or benzene resulted in poor diastereoselectivities and/or poor yields. [b]Isolated yield. [c]The ratio was determined by the pertinent olefinic signals of the adducts in ^1H-NMR spectrum.

These adducts obtained were inseparable each other by column chromatography, but the major adducts obtained from highly diastereoselective reactions were isolated by crystallization or preparative HPLC. The absolute stereochemistry of **6a** was determined by transformation into the known ester **10**,[2] derived from alcoholysis followed by hydrogenation of the resulting **8** (Scheme 1).[9] The absolute stereochemistry of **7a** was also established by converting into **9** with the known configuration.[10] The diastereoisomeric relationship between **6a** and **6b** was confirmed by deoxygenation of the sulfinyl group of **6a** with Zn/$TiCl_4$[11] followed by oxidation of the resulting sulfide with 3-chloroperoxybenzoic acid to afford nearly an equal amount of **6a** and the enantiomer of **6b**. The relationship between **7a** and **7b** was also confirmed in a similar manner. The stereochemistry of minor *exo* adducts **6c**, **6d**, **7c** and **7d** was tentatively assigned based upon the reaction mechanism previously proposed.[2,12]

From the result, it is emphasized that removal of chiral auxiliary from the adducts can be easily accomplished in quantitative yield without loss of optical purity (>99% e.e.).



Scheme 1.

Although the reaction mechanism of the Diels–Alder reaction still remains unclear, it may be probable that the cyclic transition state would be favorable under the chelation-controlled conditions in *endo* mode, and that the addition of cyclopentadiene might take place not from the sterically hindered *p*-tolyl group, but from the less hindered lone-paired electrons site, giving the major *endo* adduct **6a** or **7a** (Figure 1).

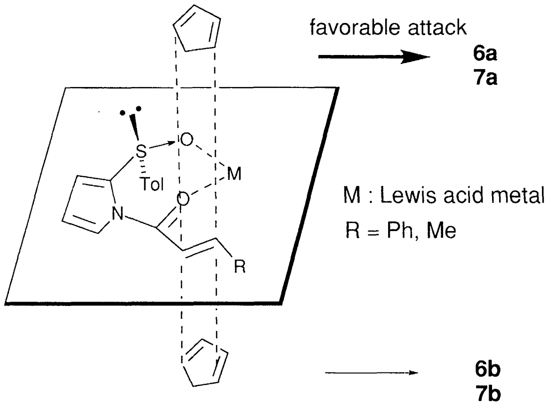


Figure 1. Stereochemical outcome of *endo* addition of **4** and **5**.

It should be anticipated that the α,β-unsaturated *N*-acyloxazolidinones as a Diels–Alder dienophile would be less reactive than the corresponding β-alkoxycarbonyl-substituted derivatives.[13] Our synthetic sulfinyl pyrroles **4** and **5** showed similar reactivities toward relatively unreactive dienes. That is, the Diels–Alder reaction of **4** and **5** with such dienes as isoprene and cyclohexa-1,3-diene gave no satisfactory result; however, it was found that $AlCl_3$-promoted Diels–Alder reaction of **4** with 2,3-dimethylbuta-1,3-diene proceeds to afford the adduct with 87% d.e. in 58% yield.

In summary, we succeeded in the highly asymmetric Diels–Alder reaction of the chiral sulfinylpyrrolyl α,β-unsaturated enones and efficient recovery of the chiral auxiliary, sulfoxide **3** without any loss of optical purity. Other applications using pyrrolyl sulfoxides to asymmetric reactions are now in progress.

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References and Notes

1 H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992); M. Carmen Carreño, *Chem. Rev.*, **95**, 1717 (1995).

2 Y. Arai, T. Masuda, Y. Masaki, and M. Shiro, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 759.

3 Y. Arai, T. Masuda, Y. Masaki, and M. Shiro, *Tetrahedron:Asymmetry*, **7**, 1199 (1996).

4 For a review of successful efforts of the recovery of auxiliary in isoborneol-derived sulfoxides chemistry, see: Y. Arai and T. Koizumi, *Sulfur reports*, **15**, 41 (1993);

5 I. Hasan, E. R. Marinelli, L.-C. Chang Lin, F. W. Fowler, and A. B. Levy, *J. Org. Chem.*, **46**, 157 (1981).

6 W. Chen, E. K. Stephenson, M. P. Cava, and Y. A. Jackson, *Org. Synth.*, **70**, 151 (1992).

7 All new compounds gave satisfactory spectroscopic and analytical data. **3**: mp 111-113 °C; $[\alpha]_D^{27}$ +31.9° (*c* 2.0, $CHCl_3$) for >99% e.e. The enantiomeric excess of **3** was confirmed by the corresponding Mosher's amide derivative according to the reported procedure (D. E. Ward and C. K. Rhee, *Tetrahedron Lett.*, **32**, 7165 (1991)); **4**: mp 131-133 °C; $[\alpha]_D^{26}$ −295° (*c* 1.1, $CHCl_3$); **5**: mp 130-132 °C; $[\alpha]_D^{25}$ −254° (*c* 1.3, $CHCl_3$).

8 S. Kobayashi, H. Ishitani, and S. Nagayama, *Chem. Lett.*, **1995**, 423.

9 **6a**: $[\alpha]_D^{23}$ −360° (*c* 1.0, $CHCl_3$); **7a**: $[\alpha]_D^{24}$ −350° (*c* 1.1, $CHCl_3$). Judging from the high optical purity (97% e.e.) of **10** by chiral HPLC (chiral column, Chiralcel OD®), the enantiomeric excess of **8** was estimated as ≥97%. A racemic sample (±)-**10** was obtained by hydrogenation of the *endo* Diels–Alder adduct of methyl *trans*-cinnamate and cyclopentadiene (L. Nicolas, M. Beugelmans-Verrier, and J. Guilhem, *Tetrahedron*, **37**, 3847 (1981)). The e.e. of **9** {$[\alpha]_D^{25}$ −122.5° (*c* 2.2, $CHCl_3$)} was estimated as 94% by comparison with the reported value[10] of the optical rotation {$[\alpha]_D^{25}$ −132° (*c* 3.13, $CHCl_3$)}.

10 D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

11 J. Drabowicz and M. Mikolajczyk, *Synthesis*, **1978**, 138.

12 Y. Arai, M. Matsui, T. Koizumi, and M. Shiro, *J. Org. Chem.*, **56**, 1983 (1991); B. Ronan and H. B. Kagan, *Tetrahedron: Asymmetry*, **2**, 75 (1991); I. Alonso, J. C. Carretero, and J. L. García Ruano, *J. Org. Chem.*, **59**, 1499 (1994).

13 K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989).