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A Practical New Chiral Controller for Asymmetric Diels–Alder and Alkylation Reactions

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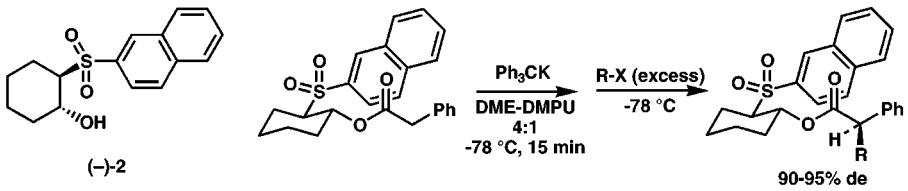
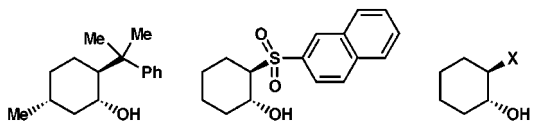
ABSTRACT



The enantiomerically pure hydroxy sulfones (+)- and (–)-2 have been prepared from 1,2-epoxycyclohexane by a simple and practical procedure. The acrylate esters of these alcohols undergo BCl_3-catalyzed Diels–Alder reactions with a variety of dienes at –78 to –55 °C in CH_2Cl_2 or C_7H_8 with high dienophile face selectivity (Table 1). The chiral esters so formed are readily cleaved with recovery of the controllers (+)- or (–)-2. Esters of (+)- and (–)-2 can be converted to *Z*-potassium enolates and alkylated with high face selectivity.

The introduction of the chiral 8-phenylmenthol controller group **1** demonstrated the effectiveness of a neighboring π-aromatic group on a chiral rigid cyclic structure for the realization of highly asymmetric Lewis acid-catalyzed Diels−Alder reactions.[1] This work also paved the way for the application of neighboring π-aromatic rings to many other enantioselective processes.[2] In addition, the 8-phenylmenthol controller group has been used as a chiral auxiliary for numerous other reactions including ene reactions,[3] organocopper-mediated conjugate addition,[4] carbonyl vinylation,[5] Michael addition,[6] imine addition,[7] photoaddition,[8] radical-induced cyclization,[9] and Pictet−Spengler cyclization.[10,11]

Although the 8-phenylmenthol reagent can usually be recovered efficiently for reuse, the multistep preparation which is required is time-consuming and thus presents an obstacle to its use. This fact and the great utility of the 8-phenylmenthol system in stereoselective synthesis provided the motivation to develop a more readily available replacement. In this Letter we present the results of this search which led to an outstanding new controller (−)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexanol (**2**) and its enantiomer which are readily accessible on a large scale and exceedingly promising for enantiocontrolled synthesis.



Recent research has demonstrated that a variety of racemic *trans*-2-cyclohexanol derivatives of general type **3** can be

(1) Corey, E. J.; Ensley, H. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(2) For a general discussion of neighboring π-aromatic groups in enantioselective syntheses, see: Corey, E. J. Roger Adams Award Lecture, *Abstracts of Papers of the 33rd National Organic Symposium*, p 3.
(3) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982,** 989.
(4) Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971.
(5) Mikami, K.; Wakabayashi, H.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 4337.
(6) Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025.
(7) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851.
(8) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392.
(9) Nishida, M.; Nobuta, M.; Nakaoka, K.; Nishida, A.; Kawahara, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2657.

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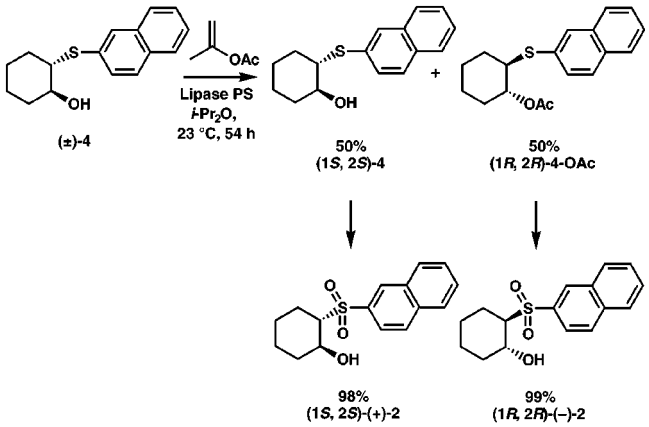
readily separated into enantiomerically pure forms by taking advantage of lipase-catalyzed enantioselective acetylation in organic solvents using 2-propenyl acetate as the stoichiometric reagent.[12] Stirring of a solution of (±)-**4**[13] and 2 equiv of 2-propenyl acetate in diisopropyl ether (ca. 10 mL per g of (±)-**4**) with finely divided Lipase PS (ca. 0.5 g per g of (±)-**4**, Amano Pharmaceutical Co., Inc.) at 23 °C for 54 h resulted in clean acetylation of one enantiomer as shown in Scheme 1. Separation by chromatography on silica gel

Scheme 1



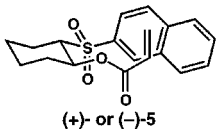
afforded the unreacted alcohol (1*S*,2*S*)-**4** and the acetate of the enantiomer (1*R*,2*R*)-**4**-OAc, which was methanolyzed ($NaOCH_3$, CH_3OH) to the corresponding alcohol (1*R*,2*R*)-**4**. Analysis of (+)- and (−)-**4** by HPLC revealed the enantiomeric purity (>99% ee) for each enantiomer of **4**. Oxidation of each enantiomer of **4** with 2.2 equiv of peroxyacetic acid at 0 to 23 °C produced the dextro and levo chiral sulfones **2** as colorless crystals in excellent yields. The absolute configuration of the dextro sulfone was determined by conversion to the crystalline 4-bromobenzoate and analysis by X-ray crystallography.[14]

The chiral phenyl sulfone analogues of the β-naphthyl sulfones (+)- and (−)-**2** were also readily prepared by the same general approach. However, these chiral controllers were not crystalline and their derivatives were also less conveniently purified than those of the β-naphthyl controllers (+)- and (−)-**2**.

The chiral controllers (+)- and (−)-**2** were converted to the corresponding acrylate esters, (+)- and (−)-**5**, respectively, by reaction with acrylic acid, triethylamine, and 2-chloro-1-methylpyridinium iodide (Avocado-US) in CH_2Cl_2. The acrylate esters **5** were obtained in >90% yields as crystalline solids, mp 86 °C. X-ray crystallographic analysis of (+)-**5** clearly reveals π-stacking between the β-naphthyl ring and the acrylate subunit which is in the *s-trans* (antiperiplanar C=O and α,β-C=C subunits) arrangement.[15]

Diels−Alder Reactions of 5. The acrylate dienophiles (+)- and (−)-**5** underwent highly diastereoselective Diels−Alder reactions with a wide variety of dienes under catalysis by boron trichloride (BCl_3)[16] in toluene or CH_2Cl_2 solution at temperatures in the range of −55 to −78 °C. The results for (+)- or (−)-**5** and five dienes are summarized in Table 1.

Table 1. BCl_3-Catalyzed Diels−Alder Reactions of (+)- or (−)-**5** with Dienes



Diene → (BCl3, 1 equiv) → Cycloadducts

Substrate	Diene	Diene equiv	Solvent	Temp. (°C)	Time (h)	Yield (%)	Major product	de[c] (%)
(+)-5		4	$PhCH_3$	-78	0.5	99	(−)-6a[a]	97
(+)-5		4	CH_2Cl_2	-78	-	polymer	-	-
(+)-5		5	$PhCH_3$	-67	22	93	(+)-7a[b]	92
(+)-5		7	CH_2Cl_2	-78	5.5	94	(+)-7a[b]	97
(−)-5		8	$PhCH_3$	-78	6.5	98	(−)-8a	93.5
(−)-5		8	CH_2Cl_2	-78	3.5	98	(−)-8a	93.5
(−)-5		10	$PhCH_3$	-55	23	92	(−)-9a	94
(−)-5		12	CH_2Cl_2	-60	38	97	(−)-9a	94
(−)-5		12	$PhCH_3$	-55	65	96	(−)-10a	93
(−)-5		10	CH_2Cl_2	-65	45	60	(−)-10a	92

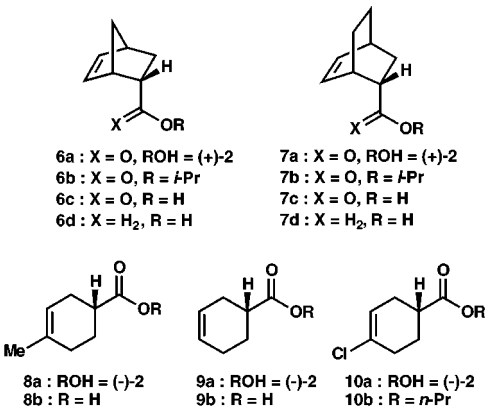
[a] 0.15 Equiv of BCl_3 was used; *endo-exo* ratio 98.5:1.5 (HPLC). [b] *Endo-exo* ratio >99:1. [c] Determined by HPLC analysis.

Reactions with cyclopentadiene and 1,3-cyclohexadiene gave the *endo* products in 97% de with excellent *endo:exo* selectivity. Isoprene, 1,3-butadiene, and 2-chloro-1,3-buta-

(10) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, *26*, 2995.
(11) For a review of applications of the 8-phenylmenthol controller to enantioselective syntheses, see: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.
(12) (a) Fujisawa, T.; Yamanaka, K.; Mobele, B. I.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 399. (b) Fukazawa, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2323. (c) Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130. (d) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959. (e) Lemke, K.; Lemke, M.; Theil, F. *J. Org. Chem.* **1997**, *62*, 6268.
(13) Prepared in 94% yield by $NaOCH_3$-catalyzed reaction of 2-naphthalenethiol with cyclohexene oxide in CH_3OH at reflux for 30 min.
(14) X-ray data for 4-bromobenzoate ester of (1*S*,2*S*)-(+)-**2**: $C_{23}H_{21}BrO_4S$; monoclinic; $P2_1$; a = 11.372(2) Å, b = 7.5370(10) Å, c = 13.227(2) Å; α = 90°, β = 108.210(10)°, γ = 90°; Z = 2; $R_1(I > 2\sigma(I))$ = 0.1039.
(15) X-ray data for acrylate ester of (1*S*,2*S*)-(+)-**5**: $C_{19}H_{20}O_4S$; monoclinic; $P2_1$; a = 10.719(2) Å, b = 7.557(2) Å, c = 11.016(2) Å; α = 90°, β = 100.75(3)°, γ = 90°; Z = 2; $R_1(I > 2\sigma(I))$ = 0.0425.
(16) 1.0 M solution in heptane (Aldrich Chemical Co.).

diene reacted with high selectivity as well, giving the cycloadducts with de values in the range of 93−94%. Under optimum conditions, the Diels−Alder cycloadditions proceeded in >94% yield to give solid products that were purified by recrystallization or chromatography to 100% de. The structures of the major cycloadducts **6a**, **7a**, **8a**, and **9a** are shown in Scheme 2 and were determined unequivocally

Scheme 2



Structures of major Diels-Alder products and derivatives.

after removal of the controller group. Assignment of the stereochemistry of major product **10a** was done by correlation to the structurally related products **8a** and **9a**.

BF_3 and $BF_3{\cdot}OEt_2$ were also effective catalysts for the reaction of (+)-**5** and cyclopentadiene. Acrylate esters of the (+)- and (−)-β-hydroxy sulfides **4** were inferior to the corresponding sulfones with regard to stereoselectivity in Lewis acid-catalyzed Diels−Alder reactions. It is possible that Lewis acid complexation with the basic sulfur of **4** is a complicating factor.

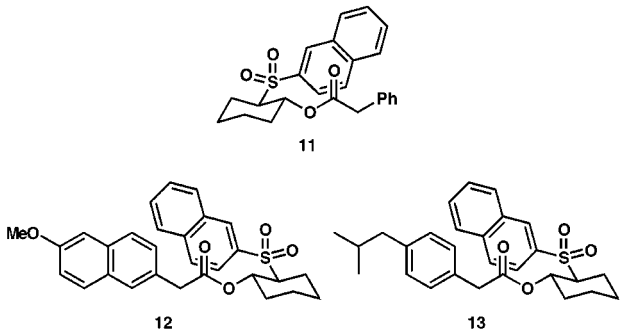
Removal and recovery of the chiral auxiliary from the Diels−Alder products was achieved by titanium(IV) isopropoxide-catalyzed transesterification to isopropyl esters. For example, cycloadduct (−)-**6a** was cleaved by being heated at 85 °C in 2-propanol containing 3.3 equiv of Ti(*i*-PrO)$_4$ for 52 h, according to Seebach's protocol.[17] After silica gel chromatography, isopropyl ester (−)-**6b** was obtained in 91% yield and controller (+)-**2** was recovered in 88% yield. The isopropyl ester (−)-**6b** was hydrolyzed in aqueous LiOH in CH_3OH at 23 °C in 36 h to give the pure *endo* carboxylic acid (−)-**6c** in 90% yield.

Cycloadducts **8a** and **9a** were conveniently cleaved by methanolysis followed by hydrolysis in a one-pot sequence. Substrate **8a** (93.5% de) was treated with an excess of $LiOCH_3$ in CH_3OH−THF at −10 °C for 24 h, followed by 1.0 equiv of 0.5 M aqueous LiOH at 23 °C for 2 h. After standard workup, carboxylic acid (+)-**8b** was obtained in 98% yield and 92.5% ee along with auxiliary (−)-**2** (92% yield).

The acid-stable cycloadduct **10a** (93.5% de) was transesterified by *n*-PrOH at 85 °C in 20 h, in the presence of excess methanesulfonic acid ($MeSO_3H$). Workup and silica gel chromatography afforded *n*-propyl ester (+)-**10b** in 90% yield and 93% ee.

Alternatively, **6a** and **7a** were cleaved reductively with diisobutylaluminum hydride (DIBAL-H). For example, reduction of (−)-**6a** by 2.0 equiv of DIBAL-H in CH_2Cl_2 at −78 °C for 1 h afforded *endo* alcohol (−)-**6d** in 88% yield and controller (+)-**2** in 93% yield after silica gel chromatography.

α-Alkylation of Esters of (+)- and (−)-2. Aryl acetate esters **11**, **12**, and **13** derived from controllers (+)- and (−)-**2** underwent highly stereoselective enolization−alkylation reactions with a variety of electrophiles. Ester (−)-**11** was



prepared in 89% yield from (−)-**2** and phenylacetic acid in CH_2Cl_2 in the presence of 1,3-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), and activated 4 Å molecular sieves at 23 °C for 4.5 h. Similarly, esters (+)-**12** and (+)-**13** were synthesized from (+)-**2** and 6-methoxynaphthylacetic acid[18] or 4-isobutylphenylacetic acid by DCC coupling in 85% and 90% yields, respectively.

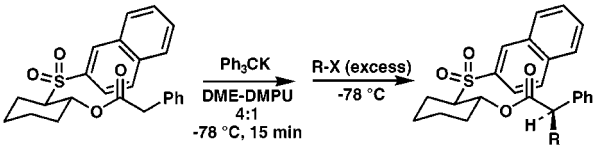
The best alkylation results were obtained via the potassium enolate which was formed with triphenylmethylpotassium as the base. Tritylpotassium was readily prepared in quantity in dimethoxyethane (DME) solution by the procedure of House[19] or more conveniently by reaction of potassium hydride, triphenylmethane, and a catalytic amount of dimethyl sulfoxide (DMSO).[20]

The results of the alkylation reaction of ester (−)-**11** with five different electrophiles are shown in Table 2. In a typical experiment, 1.0 equiv of a solution of Ph_3CK in DME (ca. 0.6 M) was diluted to ca. 0.1 M with DME and *N*,*N*′-dimethylpropyleneurea (DMPU) to a final solvent ratio of 4:1, cooled to −78 °C, and treated with a solution of (−)-**11** in 4:1 DME−DMPU. The enolate of **11**, which was rapidly formed as evidenced by the change in color from blood-red to deep orange, was then treated with the alkylating agent. The alkylation reactions were complete within a few minutes, as judged by the decolorization of the reaction mixture. Diastereomerically pure alkylation products were obtained by recrystallization. The stereochemical assignment

(17) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(18) González, A. *Synth. Commun.* **1991**, *21*, 1353.
(19) House, H. O.; Kramar, V. *J. Org. Chem.* **1962**, *27*, 4146.
(20) (a) Huffman, J. W.; Harris, P. G. *Synth. Commun.* **1977**, *7*, 137. (b) Matthews, F. J. *J. Chem. Educ.* **1997**, *74*, 996.

Table 2. Alkylation Reactions of Phenylacetate Ester (−)-**11**



(−)-11 14 - 18

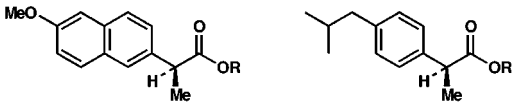
Entry	R-X	Time (min)[a]	Product	R	% Yield	% de[b]
1	MeI	0.5	14	Me	90	92
2	EtI	5	15	Et	92	95
3	*n*-PrI	10	16	*n*-Pr	95	95
4	BnBr	2	17	Bn	93	90
5	AllylBr	0.5	18	Allyl	87	95[c]

[a] After addition of R-X.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.

of major products **14**−**17** was made after excision of the auxiliary (vide infra), measurement of optical rotation, and comparison with known values. The *R* configuration of the new stereocenter is in accord with attack of the electrophile on the front face of the *Z*-enolate (Table 2). The configuration of **18** was assigned by analogy with products **14**−**17**.

This alkylation methodology was tested by application to the synthesis of the nonsteroidal antiinflammatory agents (*S*)-naproxen and (*S*)-ibuprofen which are the active enantiomers.[21]

The naproxen precursor (+)-**12**, derived from controller (+)-**2**, was deprotonated by Ph_3CK in DME−DMPU as described above and methylated with MeI (reaction complete within 1 min) to form **19** in 88% yield and 95% de.



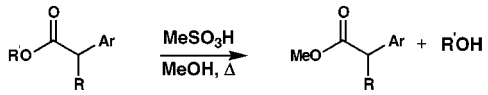
19 : ROH = (+)-2
(*S*)-Naproxen : R = H

20 : ROH = (+)-2
(*S*)-Ibuprofen : R = H

Recrystallization from EtOAc−MeOH provided pure (+)-**19**. Similarly, the ibuprofen precursor (+)-**13** was converted to **20** (95% yield, 92% de), which was purified by recrystallization from MeOH. The *S* configuration of the products **19** and **20** was confirmed by transformation to the methyl esters of (*S*)-naproxen and (*S*)-ibuprofen which were formed by transesterification using $MeSO_3H$ in CH_3OH at reflux. The methyl esters were obtained in excellent yields without racemization, as judged by chiral HPLC analysis. The chiral auxiliary was recovered in high yield. Acidic hydrolysis of the methyl esters **19** and **20** afforded pure naproxen and ibuprofen of 100% ee.

Results on the conversion of various alkylation products to the corresponding methyl esters by acid-catalyzed methanolysis are summarized in Table 3. Transesterification of substrates **14**−**20** with Ti(*i*-PrO)$_4$ in *i*-PrOH at reflux afforded the isopropyl esters in ca. 95% yield with no epimerization.

Table 3. Methanesulfonic Acid-Catalyzed Methanolysis of Alkylation Products

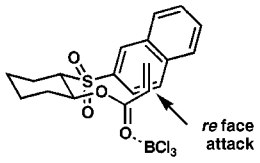


14 - 20

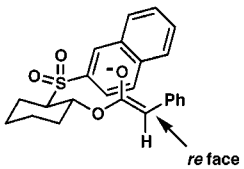
Substrate[a]	R'OH	R	% de	Time (h)	% Yield (% ee)[b]	$[\alpha]_D$[c]	Config.	ROH % Yield
14	(−)-2	Me	92	21	90 (92)	-81.6	*R*	100
15	(−)-2	Et	95	24	90 (96)	-78.3	*R*	96
16	(−)-2	*n*-Pr	95	28	93 (95)	-65.0	*R*	94
17	(−)-2	Bn	90	33	97 (90)	-101.5	*R*	91
18	(−)-2	Allyl	95	24	86 (95)	-89.0	*R*	97
19	(+)-2	Me	95	19	93 (94)	+72.5	*S*	100
20	(+)-2	Me	92	15	93 (93)	+59.4	*S*	93

[a] Ar = Ph for 14 to 18; Ar = 6-methoxynaphthalen-2-yl for 19; Ar = 4-isobutylphenyl for 20.
[b] Determined by chiral HPLC.
[c] Measured in $CHCl_3$.

The stereochemical course which has been observed for these Diels−Alder reactions is consistent with the expected *re* π-face selectivity shown in **21** for (+)-**5**−BCl_3 complex. It seems likely that the neighboring 2-naphthyl group serves as a π-electron-providing neighboring group which interacts strongly with the electron deficient carbonyl carbon both in the BCl_3 complex **21** and in the transition state for Diels−Alder addition.



21



22

Highly diastereoselective alkylation reactions of various esters of (+)- and (−)-**2** have also been demonstrated in this work. The stereochemistry of these alkylation reactions can be rationalized by a pathway involving for esters of (−)-**2** the alkylation of the *Z*-enolate **22** at the sterically accessible *re* face, as shown.

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

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(21) For a recent review of Profen drugs, see: Stahly, G. P.; Starrett, R. M. In *Chirality in Industry II.;* Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: Chichester, 1997; pp 19−40.