1,1′-Binaphthalene-2,2′-diol as a Chiral Auxiliary. Diastereoselective Alkylation of Binaphthyl Esters, Complex-Induced Proximity Effects in Enolate Formation, and One-Step Synthesis of an Optically Active β-Substituted Ketone

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Abstract: Diastereoselective alkylation of enolates derived from (*S*)-naphthyl phenylacetate **1** with LDA in THF gave the *S,S*-isomer as a major product. The diastereoselectivity increased as the bulkiness of the alkylating agent was increased. The low diastereomeric excess (~70%) of methylation was markedly raised to 92% by the use of *n*-BuLi as a base due to the complex-induced proximity effect (CIPE) in enolate formation. This highly diastereoselective methylation was used to synthesize the clinically important anti-inflammatory drugs (*S*)-naproxen (**60**) and (*S*)-suprofen (**68**). The stereochemistry of ketene trimethylsilyl acetals generated from several phenylacetates was investigated to understand the origin of the diastereoselectivity in this alkylation. Methyl phenylacetate (**46**) predominantly gave a (*Z*)-enolate by kinetic deprotonation, while the (*E*)-enolate was predominantly obtained from phenyl phenylacetate (**47**). An optically active ketone (**88**) was synthesized from binaphthyl ester **84** by a one-pot procedure involving the 1,4-addition, followed by the 1,2-addition, of organometallics. The CIPE again played a crucial role in the high enantiomeric excess in this case.

Introduction

Optically active 1,1′-binaphthyl derivatives have been used both catalytically and stoichiometrically in several asymmetric reactions.[1] In particular, derivatives of 1,1′-binaphthalene-2,2′-diol (BN-2,2′-OL) are important chiral modifiers in the reduction of carbonyl compounds,[2] the addition of organometallic reagents to carbonyl compounds,[3] carbonyl–ene reactions,[4] the Henry reaction,[5] imine condensations,[6] the Diels–Alder reaction,[7] and the oxidation of sulfides to sulfoxides.[8] On the other hand, the use of BN-2,2′-OL as a chiral auxiliary remains to be developed.[9] We describe here our work on the diastereoselective alkylation of the monoester of BN-2,2′-OL,[10] the marked complex-induced proximity effect (CIPE)[11] in enolate formation of binaphthyl esters,[12] its application to the syntheses of optically active nonsteroidal anti-inflammatory agents with the α-arylpropionic acid skeleton, extension of this alkylation to α,β-unsaturated esters,[13] and an enantioselective synthesis of ketones by the successive 1,4- and 1,2-additions of organometallic reagents to an α,β-unsaturated binaphthyl ester.[14]

Results and Discussion

I. Synthesis of Binaphthyl Esters and Their Alkylation. Novel binaphthyl esters **1–7** were easily prepared by either condensation with the corresponding acid in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC) or acylation of BN-2,2′-OL with the corresponding acid chloride. The latter gave the desired half-esters in a less satisfactory yield along with diesters. The yields and absolute configuration of the half-esters are given in Table 1.

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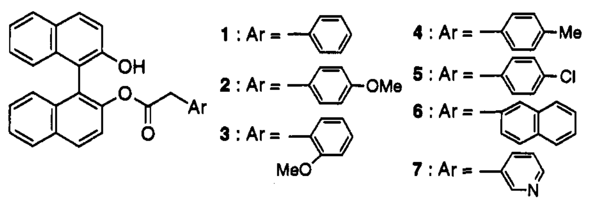
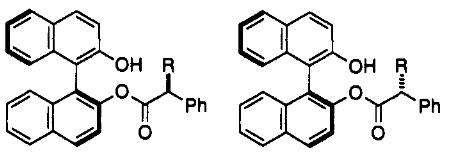
Table 1. Binaphthyl Esters of Arylacetic Acids Synthesized[a]

compound	yield, %	abs config	$[\alpha]^{20}_D$, deg (c, in $CHCl_3$)
1	79	*R*	+85.3 (0.3)
2	100	*S*	−82.7 (0.4)
3	97	*S*	−87.9 (1.0)
4	95	*S*	−93.1 (0.5)
5	96	*S*	−73.5 (1.0)
6	99	*R*	+92.8 (0.5)
7	39	*R*	+68.0 (0.1)

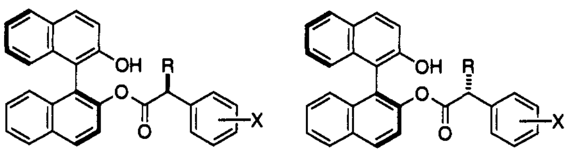
[a] All esters except **1** were synthesized by the WSC method.





8a : R = Me
9a : R = Et
10a : R = *n*-Pr
11a : R = *n*-Bu
12a : R = CH_2Ph
13a : R = $CH_2CH{=}CH_2$
14a : R = *i*-Pr
15a : R = *i*-Bu

8b : R = Me
9b : R = Et
10b : R = *n*-Pr
11b : R = *n*-Bu
12b : R = CH_2Ph
13b : R = $CH_2CH{=}CH_2$
14b : R = *i*-Pr
15b : R = *i*-Bu



16a : R = Me, X = *p*-OMe
17a : R = Et, X = *p*-OMe
18a : R = *n*-Pr, X = *p*-OMe
19a : R = *i*-Pr, X = *p*-OMe
20a : R = *i*-Bu, X = *p*-OMe
21a : R = *i*-Pr, X = *o*-OMe
22a : R = *i*-Bu, X = *o*-OMe
23a : R = *i*-Pr, X = *p*-Me
24a : R = *i*-Pr, X = *p*-Cl
25a : R = Me, X = *p*-Cl

16b : R = Me, X = *p*-OMe
17b : R = Et, X = *p*-OMe
18b : R = *n*-Pr, X = *p*-OMe
19b : R = *i*-Pr, X = *p*-OMe
20b : R = *i*-Bu, X = *p*-OMe
21b : R = *i*-Pr, X = *o*-OMe
22b : R = *i*-Bu, X = *o*-OMe
23b : R = *i*-Pr, X = *p*-Me
24b : R = *i*-Pr, X = *p*-Cl
25b : R = Me, X = *p*-Cl

An X-ray analysis of **2** revealed that the phenolic hydroxyl group oriented opposite the ester group in the crystalline state (supporting information). However, intramolecular hydrogen bonding of the hydroxyl group in solution was indicated by the sharp ^{1}H NMR signal of the hydroxyl group, whose chemical shift appeared at a constant value independent of the concentration. The absorption at 3534 cm^{-1} in the IR spectrum of **2** under high dilution (1 μmol/L in CCl_4) also indicated intramolecular hydrogen bonding in solution.

Optimization of the yield of diastereoselective methylation was attempted using binaphthyl ester **1** as a reference substrate with LDA as a base. The reaction proceeded slowly in THF or DME (entries 1−4, Table 2), but rapidly in THF/HMPA (entry 5, Table 2). Little effect was observed upon addition of another mole of *n*-BuLi after enolate formation, which is known to increase the yield by preventing the internal return process involving the reconversion of diisopropylamine into LDA.[15]

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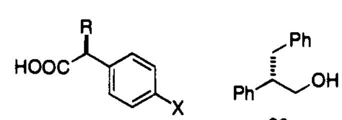
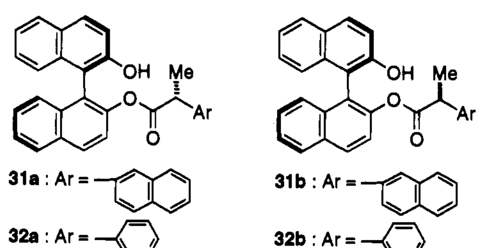
THF/HMPA was selected as a solvent system due to the shorter reaction time, although the diastereomeric excess (de) was slightly lower than for those without HMPA (entries 1−4). The results of the alkylations listed in Table 2 clearly demonstrate that bulkier alkylating agents give higher de's, up to 92% (entry 12). This tendency was also observed in the alkylation of (*S*)-binaphthyl ester **2** (entries 1−5, Table 3). No remarkable change in the de was observed with compounds containing either an electron-releasing group or an electron-withdrawing group on the aromatic ring.

The conditions for hydrolysis of the product were investigated to determine the absolute configuration of the newly created chiral carbon center. The pertinent results are listed in Table 4. Acid hydrolysis of the major isomer (*S,S*)-**14a** (>99% de) with concentrated sulfuric acid gave the corresponding acid (*S*)-**26** with negligible loss of optical purity and high yield, while **19a** (>99% de) afforded **27** in very low yield. Hydrolysis of esters **19a** and **24a** occurred smoothly under the basic conditions without any loss of optical purity to give the corresponding acids **27** and **28**.[19] The absolute configurations of acids **26**−**28** were determined to be *S* on the basis of their optical rotations. Acid hydrolysis of a 64:36 mixture of **8a** and **8b** obtained from (*S*)-**1** gave (*S*)-(+)-acid **29**. These chemical transformations show that alkylation of (*S*)-binaphthyl esters gives the *S,S*-isomer as the major product. Although there has been no direct comparison with other alkylation products, the relative stereochemistry of the major isomer was assigned to be the same in this alkylation. ^{1}H NMR signals were useful in determining the stereochemistry of the products. In the major isomer, the hydrogen on the chiral carbon always appeared at a lower field in $CDCl_3$ and the phenolic hydroxyl group resonates at a higher field, except in the benzylated products **12a** and **12b** (Table 5 in the supporting information). A 67:33 mixture of **12a** and **12b** derived from (*S*)-**1** was reduced to the (S)-(+)-alcohol **30**,[20] which confirmed that the relative stereochemistry of the major product **12a** is the same as those of other alkylation products.



26 : R = *i*-Pr, X = H
27 : R = *i*-Pr, X = OMe
28 : R = *i*-Pr, X = Cl
29 : R = Me, X = H

30



Although the alkylation described above gave satisfactory results when bulky alkylating agents were used, poor selectivity was observed with small alkylating agents. In particular, an increase in the de of methylation is important, since 2-arylpro-

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Table 2. Diastereoselective Alkylation of Binaphthyl Phenylacetate **1** Using LDA as a Base

run	1	alkylating agent	solvent	temp, °C	time, h	product (ratio)[a]	combined yield, %
1	*dl*	MeI	DME	−78 to ∼−40	2.5	**8a**:**8b** (86:14)	12[b]
2	*dl*	MeI	THF	−78	1.0	**8a**:**8b** (86:14)	35[c]
3	*S*	MeI	THF	−78	8.0	**8a**:**8b** (85:15)	86
4	*S*	MeI	THF[d]	−78	12.0	**8a**:**8b** (86:14)	93
5	*dl*	MeI	THF/HMPA[e]	−78	0.3	**8a**:**8b** (77:23)	85
6	*dl*	EtI	THF/HMPA[e]	−78	0.3	**9a**:**9b** (78:22)	70
7	*dl*	*n*-PrI	THF/HMPA[e]	−78	1.0	**10a**:**10b** (78:22)	83
8	*dl*	*n*-BuI	THF/HMPA[e]	−78	2.5	**11a**:**11b** (78:22)	90
9	*dl*	$PhCH_2Br$	THF/HMPA[e]	−78	0.3	**12a**:**12b** (78:22)	86
10	*dl*	$CH_2{=}CHCH_2Br$	THF/HMPA[e]	−78	0.3	**13a**:**13b** (82:18)	84
11	*dl*	*i*-PrI	THF/HMPA[e]	−78 to ∼−38	3.5	**14a**:**14b** (92:8)	95
12	*R*	*i*-BuI	THF/HMPA[e]	−78 to ∼−50	4.0	**15a**:**15b** (96:4)	76

[a] Determined by ^{1}H NMR. [b] A 12% yield of **1** was recovered, and a 49% yield of BN-2,2'-OL was obtained. [c] A 62% yield of **1** was recovered. [d] Another 1 M sample of ^{n}BuLi was added after the enolate formation. [e] 10 equiv to **1**.

Table 3. Alkylation of (*S*)-Binaphthyl Arylacetates Using LDA as a Base in THF/HMPA

entry	compound	alkylating agent	temp, °C	time, h	product (ratio)[a]	combined yield, %
1	**2**	MeI	−78	2.5	**16a**:**16b** (53:47)	85
2	**2**	EtI	−78	3.0	**17a**:**17b** (68:32)	85
3	**2**	*n*-PrI	−78	8.0	**18a**:**18b** (85:15)	81
4	**2**	*i*-PrI	−78 to ∼−65	8.0	**19a**:**19b** (98:2)	91
5	**2**	*i*-BuI	−78	10.5	**20a**:**20b** (100:0)	84
6	**3**	*i*-PrI	−78	8.0	**21a**:**21b** (99:1)	65[b]
7	**3**	*i*-BuI	78 to ∼−55	9.5	**22a**:**22b** (99:1)	62[c]
8	**4**	*i*-PrI	−78 to ∼−70	10.0	**23a**:**23b** (93:7)	84
9	**5**	*i*-PrI	−78 to ∼−48	9.3	**24a**:**24b** (91:9)	83

[a] Determined by ^{1}H NMR. [b] A 31% yield of **3** was recovered. [c] A 28% yield of **3** was recovered.

Table 4. Hydrolysis of Alkylated (*S*)-Binaphthyl Esters

ester			carboxylic acid				
structure	de, %	reaction conditions	structure	yield, %	$[\alpha]_D$,[a] deg	ee,[b] %	config
14a	>99	conc H_2SO_4	**26**	97[c]	+60.5[d]	97	*S*
19a	>99	conc H_2SO_4	**27**	3[c]			
19a	90	LiOH/THF/H_2O	**27**	90[e]	+41.2[f]	88	*S*
24a	96	LiOH/THF/H_2O	**28**	95[e]	+38.8[g]	91	*S*
8a	28	conc H_2SO_4	**29**	76[c]	+18.6[h]	24[i]	*S*

[a] Measured in $CDCl_3$. [b] Determined by HPLC analysis of its anilide with a chiral column (YMC-Pack KO3). [c] (*S*)-BN-2,2'-OL was not recovered. [d] At 28 °C (lit.[16] $[\alpha]^{25}_D$ +62.5° ($CHCl_3$)). [e] (*S*)-BN-2,2'-OL was recovered. [f] At 18 °C (lit.[17] $[\alpha]^{22}_D$ +52.8° ($CHCl_3$)). [g] At 27 °C (lit.[17] $[\alpha]^{21}_D$ +46.8° ($CHCl_3$)). [h] At 14 °C (lit.[18] $[\alpha]_D$ +76.2° ($CHCl_3$)). [i] Calculated from the $[\alpha]_D$ value.

Table 6. Diastereoselective Methylation of Binaphthyl Arylacetates Using *n*-BuLi as a Base

entry	compound	solvent	temp, °C	time, h	product (ratio)[a]	combined yield, %
1	*dl*-**1**	THF[b]	−78	4.0	**8a**:**8b** (96:4)	86
2	*dl*-**1**	THF[c]	−78 to ∼−48	3.2	**8a**:**8b** (87:13)	82
3	*dl*-**1**	THF/TMEDA[c]	-78 to ∼−40	2.3	**8a**:**8b** (85:15)	74
4	*dl*-**1**	THF[b,d]	−78	4.0	**8a**:**8b** (90:10)	65
5	*dl*-**1**	THF[b,e]	−78	1.0	**8a**:**8b** (93:7)	95
6	*dl*-**1**	THF/HMPA[b]	−78	1.0	**8a**:**8b** (69:31)	79
7	*S*-**2**	THF[b]	−78 to ∼−25	4.3	**16a**:**16b** (87:13)	72
8	*S*-**5**	THF[b]	−78 to ∼−30	2.0	**25a**:**25b** (92:8)	97
9	*R*-**6**	THF[b]	−78 to ∼−30	4.0	**31a**:**31b** (93:7)	76
10	*R*-**7**	THF[b]	−78 to ∼−30	3.5	**32a**:**32b** (95:5)	78

[a] Determined by ^{1}H NMR. [b] *n*-BuLi was added into the substrate. [c] *dl*-**1** was added into *n*-BuLi. [d] 2.4 equiv of diisopropylamine was added before methylation. [e] 10 equiv HMPA was added before methylation.

pionic acids constitute an important class of nonsteroidal anti-inflammatory agents.[21] To our surprise, the intermediate enolate was easily prepared from racemic **1** even with *n*-BuLi as a base, which is known to be inappropriate for generating enolates from esters due to its strong nucleophilicity. Exceptions include 2,6-di-*tert*-butyl-4-methylphenyl alkanoates[22] and methyl and *tert*-butyl phenylacetates,[23] all of which gave the corresponding enolate with *n*-BuLi in high yield. In addition to the easy formation of the enolate, methylation of **1** gave **8a** at a higher diastereomeric ratio (entry 1, Table 6) than that observed with LDA (entries 1−5, Table 2). The results in Table 6 reveal several important features: (1) reverse addition slightly decreased the de (entry 2), (2) addition of a dipolar aprotic compound before deprotonation decreased the de (entries 3 and 6), and (3) additives after enolate formation had a negligible effect on the de of the product (entries 4 and 5). The conclusion

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Table 7. ^{1}H NMR Chemical Shifts of the Methyl and the Phenolic Hydroxyl Groups of Methylated Binaphthyl Esters in DMSO-d_6

	chemical shift (δ, ppm)			
	methyl		phenolic OH	
ester	**a** (major)	**b** (minor)	**a** (major)	**b** (minor)
8[a]	0.84	0.96	9.53	9.47
16[b]	0.82	0.94	9.53	9.47
25[b]	0.88	0.99	9.52	9.46
31[b]	0.94	1.06	9.51	9.45
32[a]	0.89	1.00	9.53	9.45

[a] At 400 MHz. [b] At 200 MHz.

Table 8. Effects of the 2′-Substituent on the Enolate Formation and the Diastereoselectivity of the Methylation Using *n*-BuLi in THF

entry	compound	R	product (ratio)	yield, %	yield of **42**, %
1	*dl*-**1**	OH[a]	**8a**:**8b** (96:4)	86	0
2	*dl*-**34**	OMe	**37a**:**37b** (85:15)	60	*b*
3	*dl*-**35**	Me	**38a**:**38b** (75:25)[c]	25	24
4	*dl*-**35**[d]	Me	**38a**:**38b** (40:60)[c]	25	0

[a] Taken from Table 6 (run 1). [b] The ratio of **37** to **42** in the crude mixture was approximately 3:1 determined by ^{1}H NMR. [c] Stereochemistry was not determined. [d] In THF/HMPA.

drawn from these findings is that diastereoselectivity depends mainly on the conditions used to generate the enolate. α-Methylation of (*S*)-**2**, (*S*)-**5**, (*R*)-**6**, and (*R*)-**7** gave corresponding products at a high de under standard reaction conditions similar to those for entry 1 (entries 7–10). The ^{1}H NMR signals of the products (Table 7) indicated that the stereochemistry of the major product was *S,S* or *R,R*, as in the alkylation with LDA as a base. HMPA was indispensable for alkylation when a bulky alkylating agent such as isopropyl iodide was used. Thus, reaction of the enolate of **5** with isopropyl iodide gave **24a** and **24b** in 80% yield and as a 96:4 ratio upon addition of HMPA after enolate formation.

II. Complex-Induced Proximity Effects in Enolate Formation. An interesting question is why *n*-BuLi can be used as a base for deprotonation of binaphthyl esters. There are two possible explanations. First, we must consider the enhanced acidity of the proton to be removed. The attempted deprotonation of **33** or a mixture of **9a** and **9b** with *n*-BuLi failed due to the low acidity of the proton in question but gave a mixture of products arising from the nucleophilic attack of *n*-BuLi. Second, and more importantly, there may be a CIPE[11] process involving the phenolic hydroxyl moiety as a directing element. Table 8 shows the effects of a 2′-substituent on enolate formation. When the racemic ester **34**, which possesses a methoxy group instead of a hydroxy group, was used, it gave a mixture of **37a** and **37b** in lower yield than that of **8a** and **8b**, along with ca. 20% **42** arising from nucleophilic attack of *n*-BuLi at the ester carbonyl (entry 2). This tendency is very prominent with racemic **35** in which the Lewis basicity at the C-2′-substituent is totally eliminated. Thus, the combined yield of **38a** and **38b** was 25% with 24% **42** (entry 3). These findings clearly indicate that the phenolic hydroxy group plays a crucial role in the successful formation of the enolate. Demethylation of the major product **37a** with a combination reagent of $AlCl_3$/ethanethiol[24] gave **8a**, which confirmed that the relative stereochemistry of the major product **37a** was the same as that from **1**.

There is a question of whether the intramolecular phenolic hydroxyl group is indeed necessary, or if a phenolic hydroxyl

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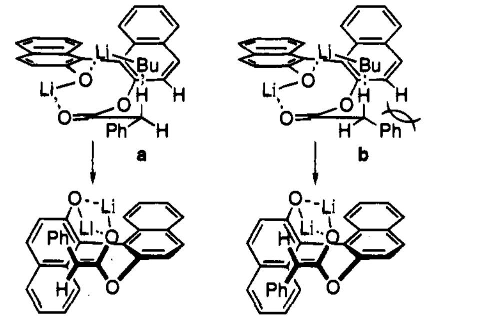

Figure 1. Plausible transition states **a** and **b** from **1** with *n*-BuLi leading to the (*E*)-enolate and the (*Z*)-enolate, respectively.

group can assist in the formation of the enolate intermolecularly. When naphthyl ester **39**, which lacks the upper part of the binaphthyl group, was alkylated under standard conditions (THF/1 equiv of *n*-BuLi), **42** was obtained in 22% yield along with a mixture of methylated products. Methylation of **39** in the presence of 1 mol equiv of 2-naphthol under similar conditions (THF/2 equiv of *n*-BuLi) gave similar results, with 23% **42**. Naphthyl ester **40** gave an approximately 3:2 mixture of **41** and **43**, regardless of the coexistence of 2-naphthol, confirming the necessity of an *intramolecular hydroxy group* for successful enolate formation from the binaphthyl ester. Figure 1 shows a plausible model for the CIPE in the formation of an enolate. The phenoxy anion formed by *n*-BuLi can coordinate with lithium of a second molecule of *n*-BuLi to give a suitable resident site for removing a hydrogen from the benzylic position to give the enolate. The importance of this spatial arrangement was demonstrated by the fact that a naphthyl ester (**44**) of vinylacetic acid gave the corresponding enolate with *n*-BuLi smoothly, while naphthyl crotonate **45** did not. The lower chemical yield of **37** (entry 2, Table 8) can be ascribed to the less effective coordination of the lithium to a methoxy group than that to an oxygen anion. A dramatic decrease in yield from racemic **35** (entry 3, Table 8) again supports the importance of the resident site of *n*-BuLi.

n-BuLi exists as an equilibrium mixture of the tetramer and the dimer in THF, which collapses into the mixed alkyllithium/lithium alkoxide complex to increase the polarization of the C–Li bond when alcohol is present in the medium.[25] Thus, the basicity of *n*-BuLi increases with coordination to an internal phenoxy group enough to suppress nucleophilicity. In conclusion, the enhanced acidity of the proton to be removed, the CIPE, including preformation of a phenoxy anion by a base, and the increased basicity of *n*-BuLi were shown to be responsible for the successful removal of a proton from 2′-hydroxybinaphthyl esters.

III. Origin of Diastereoselectivity Observed in Alkylation. The geometry of the intermediate enolate must be determined in order to discuss a reaction mechanism involving enolates. Except for a few examples,[26] the stereochemistry of ester enolates has been determined indirectly by trapping them as the corresponding ketene silyl acetals.[27–31] The validity of this

(25) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* *107*, **1985**, 1805.
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(27) Ireland, R. E.; Wipf. P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650 and references cited therein.
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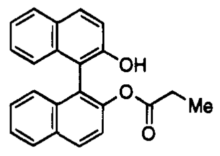
(31) Kamemasa, S.; Nomura, M.; Wada, E. *Chem. Lett.* **1991**, 1735.



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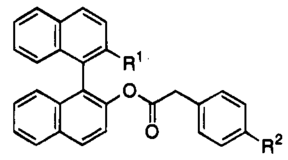
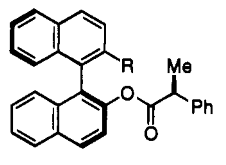
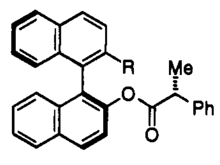


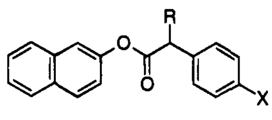
34 : R^1 = OMe, R^2 = H
35 : R^1 = Me, R^2 = H
36 : R^1 = OTMS, R^2 = Me



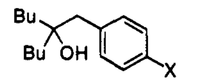
37a : R = OMe
38a : R = Me



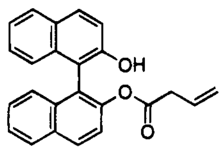
37b : R = OMe
38b : R = Me



39 : R = X = H
40 : R = H, X = Cl
41 : R = Me, X = Cl



42 : X = H
43 : X = Cl



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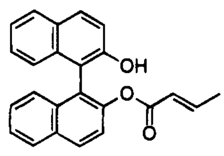
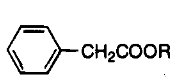


45

method has been confirmed using *tert*-butyl propionate by X-ray structural determination of the enolate and its transformation to the corresponding ketene *tert*-butyldimethylsilyl (TBDMS) acetal.[26] Extensive studies by Ireland *et al.*[27] demonstrated that the stereochemistry of ester enolates can be controlled by the solvent system. As shown in Scheme 1, an ester gives a ketene (*E*)-silyl acetal as a major product via a (*Z*)-enolate with LDA in THF, while a ketene (*Z*)-silyl acetal was the predominant product in THF/23% HMPA. These experimental observations were supported by a molecular mechanics based model.[32] The only inconsistency between the experimental results and the calculations involves methyl phenylacetate (**46**), which gave a 29:71 mixture of ketene (*E*)- and (*Z*)-TBDMS acetals in THF.[33] Calculations predicted that the kinetic deprotonation of **46** in THF would predominantly give (*Z*)-enolate, which leads to ketene (*E*)-silyl acetal as a major product. Since the cause of this ambiguity remains unclear, we investigated enolate formation from methyl phenylacetate (**46**) and the successive trapping of the enolate as a ketene silyl acetal.[34]



46 : R = Me
47 : R = Ph
48 : R = 2,6-diMe-C_6H_3

Stereochemistry of the Enolates Derived from Methyl Phenylacetate (46) in THF. Methyl phenylacetate (**46**) has been known to give the corresponding ketene trimethylsilyl (TMS) acetal[23,35] and ketene TBDMS acetal[33] with (TMS)Cl and (TBDMS)Cl, respectively. Addition of HMPA or *N,N′*-dimethyl-*N,N′*-propyleneurea before silylation is indispensable to obtain a good yield of ketene TBDMS acetal,[27] while (TMS)-Cl is reactive enough to provide the corresponding ketene acetal without HMPA.[23,35] To avoid the influence of HMPA, the *E*:*Z* ratio of the ketene TMS acetal was examined. The enolate, generated from methyl phenylacetate (**46**) with LDA in THF, was trapped with (TMS)Cl to give an 81:19 mixture of ketene (*E*)- and (*Z*)-TMS acetals **49**. The ratio observed here is completely opposite that with (TBDMS)Cl in the presence of HMPA.[27] The stereochemistries of TMS acetals **49** were established by means of ^{1}H NOE experiments (Figure 2). The olefinic signal was greatly enhanced for (*E*)-**49** and (*Z*)-**49** with irradiation at the $SiMe_3$ group and the OMe group, respectively.[36] The *E*:*Z* ratio was changed to 6:94 by the addition of HMPA just before the evaporation of compounds with a low boiling point in the reaction mixture under vacuum. Deprotonation with LDA in THF/HMPA afforded a 9:91 mixture of (*E*)-**49** and (*Z*)-**49**, which agrees with the results reported for ketene TBDMS acetals.[33] These findings indicate that disagreement between experimental results and calculations for the deprotonation of methyl phenylacetate (**46**) might stem from the equilibrium between ketene (*E*)- and (*Z*)-silyl acetals. ^{1}H NMR spectra of an isolated *E*/*Z* mixture of ketene TMS acetals **49** were measured in THF-d_8 under a variety of conditions to confirm the equilibrium between (*E*)-**49** and (*Z*)-**49**. The results are summarized in Table 9. Both ketene (*E*)- and (*Z*)-silyl acetals are stable in the presence of diisopropylamine, HMPA,

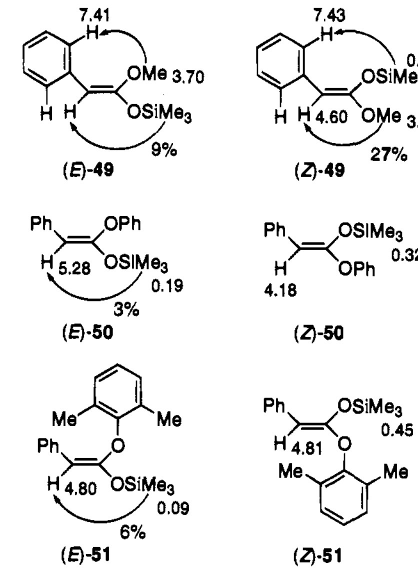
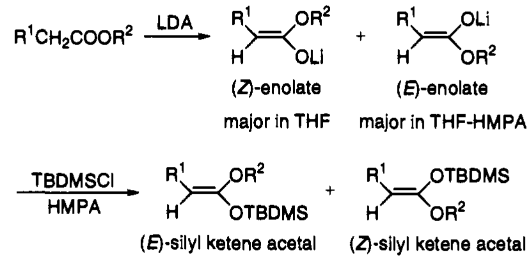


Figure 2. Chemical shifts and NOE correlation of ketene TMS acetals **49**–**51** in $CDCl_3$.

Scheme 1



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(33) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(34) For a preliminary communication, see: Tanaka, F.; Fuji, K. *Tetrahedron Lett.* **1992**, *33*, 7885.

(35) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59.

(36) The similar NOE results in pyridine-d_5 were reported (ref 23) after our preliminary paper (ref 34) had appeared.

Table 9. Change of the Ratio of (*E*)-**49** to (*Z*)-**49** at 20 °C[a]

	original ratio				final ratio	
entry	**49**:**46**	(*E*)-**49**:(*Z*)-**49**	additive (mmol)	time	**49**:**46**	(*E*)-**49**:(*Z*)-**49**
1	>10:1	76:24	none	48 h	6:1	74:26
2	6:1	73:27	*i*-Pr_2NH (0.29)	13 h	5:1	72:28
3	>10:1	71:29	HMPA (0.23)	7.5 h	>10:1	70:30
4	5:1	69:31	*i*-Pr_2NH (0.29), HMPA (0.23)	17 h	4:1	67:33
5	>10:1	75:25	LiCl (0.12)	40 min	4:1	65:35
6				12 h	4:1	26:74
7				39 h	4:1	11:89
8	>10:1	72:28	LiCl (0.04),	5 min	7:1	69:31
9			HMPA (0.06)	15 min	7:1	64:36
10				65 min	7:1	48:52
11				4 h	7:1	30:70
12				8 h	7:1	15:85

[a] A mixture of ketene silyl acetals **49** (0.35 mmol) in THF-d_8 (0.5 mL).

or both additives in THF at 20 °C (entries 2−4). Lithium chloride promotes equilibrium between (*E*)- and (*Z*)-**49** (entries 5−7). A 75:25 mixture of (*E*)-**49** and (*Z*)-**49** was converted to an 11:89 mixture after 39 h at 20 °C,[37] which is practically the same ratio as that obtained from deprotonation with LDA in THF/HMPA. The rate of isomerization was dramatically facilitated in the presence of HMPA (entries 8−12), which gave a 15:85 mixture of (*E*)-**49** and (*Z*)-**49** from the 72:28 mixture after 8 h at 20 °C. These observations clearly indicate that the isomerization of (*E*)-**49** to (*Z*)-**49** occurs easily when lithium chloride and HMPA coexist in the medium. We conclude that the unusual results involving the predominant formation of the ketene (*Z*)-TBDMS acetal from **46** in THF[33] were not due to kinetic deprotonation but rather to thermodynamic equilibrium between the resulting ketene (*E*)- and (*Z*)-silyl acetals under these reaction conditions and/or during the workup procedure. *E*/*Z* isomerization in aliphatic ketene silyl acetals has been reported to be readily achieved with $HgBr_2$/(TMS)Br,[38] trialkylammonium perchlorate,[39] CF_3COCF_3 or CF_3COCH_3,[40] or CsF.[40] Recent studies of the methyl phenylacetate enolate by IR and ^{13}C NMR spectroscopy[23] have indicated that *E*/*Z* isomerization of the enolate itself was induced by HMPA.

Enolate Formation from Aryl Phenylacetates 47 and 48. Enolate formation from **47** and **48**, which are structurally more similar to the binaphthyl esters, was studied next. The stereochemistry of ketene TMS acetals **50** and **51** was again determined by NOE experiments. Treatment of the enolate generated from phenyl phenylacetate (**47**) with LDA in THF with (TMS)Cl gave a 31:69 mixture of ketene (*E*)- and (*Z*)-TMS acetals **50** with a 75% yield together with 25% starting ester **47** on the basis of the ^1H NMR spectrum of the crude reaction mixture obtained after the evaporation of volatile material under vacuum. This *E*:*Z* ratio is again opposite the normal case in which ketene (*E*)-silyl acetal is the major product. The addition of HMPA just before the evaporation gave decomposition products, but no (*E*)- or (*Z*)-**50**. The change in the *E*:*Z* ratio on standing was measured by ^1H NMR in THF-d_8, and the results are summarized in Table 10. Although the ratio of (*E*)-**50** to (*Z*)-**50** was biased in favor of the former, this change in the ratio was not due to equilibration but to the easier decomposition of (*Z*)-**50**, as indicated by the ratio of **50** to decomposition product. Thus, the predominant formation of ketene (*Z*)-TMS acetal **50** is the result of the kinetic formation of the (*E*)-enolate.

Table 10. Change of the Ratio of **50** to the Decomposition Product and (*E*)-**50** to (*Z*)-**50** at 20 °C

time, h	**50**:decomp prod	(*E*)-**50**:(*Z*)-**50**	time, h	**50**:decomp prod	(*E*)-**50**:(*Z*)-**50**
0	>10:1	47:53	1.0	2.2:1	76:24
0.3	6.5:1	62:38	1.5	1.5:1	83:17
0.7	3.4:1	69:31	2.0	1.2:1	85:15

Table 11. Summary on Enolate Formation from **46**−**48** under Kinetic Conditions in THF

		major ketene TMS acetal	
ester	major enolate	kinetic formation	after equilibrium
46	*Z*	(*E*)-**49**	(*Z*)-**49**
47	*E*	(*Z*)-**50**	(*E*)-**50**[a]
48	*Z*	(*E*)-**51**	(*Z*)-**51**

[a] This may not be a result of an equilibrium but of an easy decomposition of (*Z*)-**50**.

Table 12. Silylation of Lithium Enolates of Binaphthyl Esters in THF

entry	ester	base	product	ester:acetal[a]	*E*:*Z*[a]
1	*dl*-**1**	LDA	**52**	40:60	23:77
2	*dl*-**1**	*n*-BuLi	**52**	52:48	11:89
3	(*S*)-**2**	*n*-BuLi	**53**	17:83	15:85
4	(*S*)-**4**	LDA	**54**	26:74	19:81
5	(*S*)-**4**	*n*-BuLi	**54**	16:84	9:91
6	(*S*)-**5**	*n*-BuLi	**55**	29:71	13:87
7	*dl*-**34**	LDA	**56**	19:81	59:41
8	*dl*-**34**	*n*-BuLi	**56**	19:81	40:60
9	*dl*-**35**	LDA	**57**	48:52	63:37
10	*dl*-**35**	*n*-BuLi	**57**	*b*	49:51
11	(*S*)-**36**	LDA	**54**	38:62	55:45

[a] Determined by ^1H NMR integration of the crude reaction mixture. [b] Not determined.

2,6-Dimethylphenyl phenylacetate (**48**) afforded a 78:22 mixture of (*E*)-**51** and (*Z*)-**51** in THF, which is remarkably different from the ratio (4:96) observed with the addition of HMPA before workup. Time-dependent ^1H NMR studies on a mixture of (*E*)-**51** and (*Z*)-**51** indicated that they are stable enough to establish equilibrium. The important conclusion that can be drawn from trapping experiments involving enolates from **46**−**48** is that the *E*:*Z* ratio of ketene TMS acetal can reflect the stereochemistry of the corresponding enolate even in the phenylacetic acid esters of phenols, when HMPA is not present in the reaction mixture or during the workup procedure. Table 11 summarizes the results of the kinetic formation of the enolate from **46**−**48** in THF. It is worth noting that only phenyl phenylacetate (**47**) gave predominantly the (*E*)-enolate, which is opposite the results with the other esters, including **46** and **48**.

Proposed Model for Diastereoselective Alkylation. With these experimental results in hand, we carried out the trapping of enolates derived from binaphthyl esters in THF. The results are summarized in Table 12. A remarkable feature is the predominant formation of (*Z*)-ketene acetal, which corresponds to the (*E*)-enolate,[41] when an ester with a free hydroxyl group on another ring is used (entries 1−6). The amount of (*Z*)-acetal increases slightly when *n*-BuLi is used as a base instead of LDA (entries 1, 2 and 4, 5). On the other hand, no great difference

(37) Selective decomposition of (*E*)-**46** is not responsible for the change of the *E*:*Z* ratio (see the final ratio of **49** to **46** in entries 5−7).

(38) Burlachenko, G. S.; Manukina, T. A.; Baukov, Y. I. *J. Organomet. Chem.* **1971**, *33*, C59. Burlachenko, G. S.; Baukov, Y. I.; Dzherayan, T. G.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1975**, *45*, 81.

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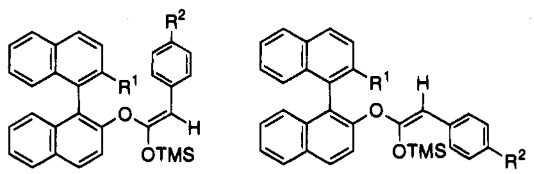
(40) Adam, W.; Wang, X. *J. Org. Chem.* **1991**, *56*, 7244.

(41) We postulated a (*Z*)-enolate from **1** on the analogy of the other esters without experimental evidence in a preliminary report.[10,12] The present investigation, however, clearly shows the predominant formation of the (*E*)-enolate.

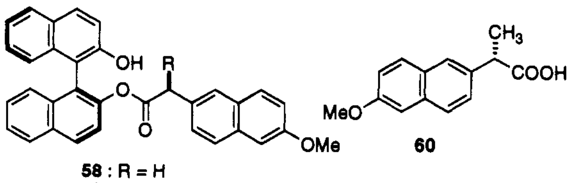
in the *E*:*Z* ratio was observed using esters with a substituent other than a hydroxyl group at the C-2′-position (entries 7−11). This observation indicates that the hydroxyl group plays a crucial role in the predominant formation of (*E*)-enolate in THF under kinetic control. Structural assignment of the ketene TMS acetals **52**−**57** was based on the ^{1}H NMR chemical shift of a vinylic hydrogen (Table 13 in the supporting information), which resonates at a lower magnetic field in the *E*-series than in the *Z*-series, and on the NOE observed between the vinylic hydrogen and the TMS group on the enol oxygen in the *E*-series.



(*E*)-**52** : R¹ = OTMS, R² = H (*Z*)-**52** : R¹ = OTMS, R² = H
(*E*)-**53** : R¹ = OTMS, R² = OMe (*Z*)-**53** : R¹ = OTMS, R² = OMe
(*E*)-**54** : R¹ = OTMS, R² = Me (*Z*)-**54** : R¹ = OTMS, R² = Me
(*E*)-**55** : R¹ = OTMS, R² = Cl (*Z*)-**55** : R¹ = OTMS, R² = Cl
(*E*)-**56** : R¹ = OMe, R² = H (*Z*)-**56** : R¹ = OMe, R² = H
(*E*)-**57** : R¹ = Me, R² = H (*Z*)-**57** : R¹ = Me, R² = H

Figure 1 illustrates plausible transition states leading to (*E*)- and (*Z*)-enolates from binaphthyl ester **1**. In transition state **a**, the CIPE of the phenolate provides a resident site for the second molecule of *n*-BuLi, which can abstract the *pro-S* hydrogen to give the (*E*)-enolate, whose phenoxy anions are captured by two lithium atoms, while an alternative transition state (**b**) leading to the (*Z*)-enolate suffers from considerable steric repulsion. The nucleophilic carbon of the resulting (*E*)-enolate is more open on the *si*-face than the *re*-face, which is highly hindered by the attached naphthyl ring. Thus, electrophilic attack preferentially takes place from the *si*-face of the (*E*)-enolate to give the observed *S**,*S**-isomer.

IV. Synthetic Applications. Synthesis of (*S*)-(+)-Naproxen (60) and (*S*)-(+)-Suprofen (68).[42] 2-Arylpropionic acids, including **60** and **68**, constitute an important class of clinically useful nonsteroidal anti-inflammatory agents.[21] Although they have been commercialized as a racemate, the *S*-enantiomers are known to possess higher pharmacological activity than the corresponding *R*-enantiomers. Thus, chiral synthesis of the *S*-enantiomer is highly desired. Although a plethora of papers have reported the synthesis of optically active 2-arylpropionic acids,[21] diastereoselective methylation of arylacetic acid derivatives[43] had received little attention before our communications.[10,12] We applied the diastereoselective methylation of binaphthyl esters to the synthesis of (*S*)-(+)-naproxen (**60**) and (*S*)-(+)-suprofen (**68**).

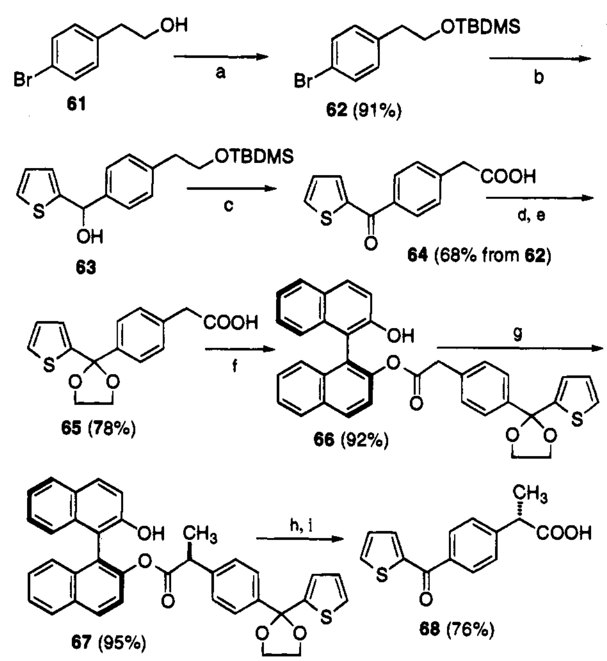


58 : R = H
59 : R = Me

Condensation of 6-methoxy-2-naphthylacetic acid[44] with (*S*)-BN-2,2′-OL afforded the half-ester **58** in 88% yield. Methylation of **58** under the standard conditions using *n*-BuLi gave (*S*,*S*)-**59** (94%) with 84% de. (*S*)-(+)-Naproxen (**60**) of 82% enantiomeric excess (ee) was obtained in 73% yield by the basic hydrolysis of (*S*,*S*)-**59**.

(42) For racemic suprofen, see: van Rompay, J. F. H.; Pattyn, W. J.; Demoen, P. J. A. W. *Arzneim.-Forsch.* **1975**, *25*, 1501.
(43) González, A. *Synth. Commun.* **1991**, *21*, 1353.
(44) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203.

Scheme 2[a]



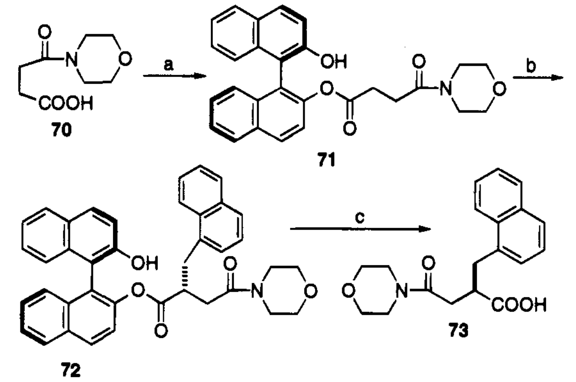
[a] Reagents: (a) (TBDMS)Cl; (b) (i) *n*-BuLi/THF, (ii) 2-thiophenecarboxaldehyde; (c) Jones oxidation; (d) ethylene glycol/TsOH; (e) NaOH; (f) BN-2,2′-OL/WSC/DMAP; (g) (i) *n*-BuLi/THF, (ii) MeI; (h) LiOH/aqueous THF; (i) 10% HCl.

An outline of the synthesis of (*S*)-(+)-suprofen (**68**) is shown in Scheme 2. Protection of the hydroxyl group in 4-bromophenethyl alcohol (**61**) with (TBDMS)Cl gave **62**. Nucleophilic attack of the aryllithium, prepared by halogen−metal exchange of **62** with *n*-BuLi, to 2-thiophenecarboxaldehyde afforded the alcohol **63**, which gave **64** after Jones oxidation. Ketalization of **64** yielded **65**. Esterification of **65** with BN-2,2′-OL gave **66**, which was converted to **67** with 96% de and 95% yield by the standard methylation procedure using *n*-BuLi as a base. Basic hydrolysis followed by treatment with acid provided (*S*)-(+)-suprofen (**68**) of 93% ee,[45] which was characterized as its anilide.

Synthesis of the *N*-Terminal Component 73 of Renin Inhibitors. Renin inhibitors designed from angiotensinogen transition state analogs have attracted considerable attention as effective antihypertensive agents. In particular, compounds of general structure **69** possessing 3-(morpholinocarbonyl)-2-(*R*)-(1-naphthylmethyl)propionic acid (**73**) as an *N*-terminal moiety have been extensively investigated.[46,47] Diastereoselective alkylation of a binaphthyl ester of an aliphatic acid was used to synthesize **73**, as shown in Scheme 3. Esterification of **70**, prepared from succinic anhydride and morpholine, with (*R*)-BN-2,2′-OL gave the half-ester **71**. Treatment of the anion generated from **71** with LDA (2 equiv) in THF/HMPA with 1-(bromomethyl)naphthalene provided an 85:15 mixture of

(45) Although it is reported that kinetic resolution of a racemic methyl ester of suprofen with *Candida* lipase gave (*S*)-(+)-suprofen, no physical data were presented; see: Wu, S. -H. ; Guo, Z.-W.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 1990.
(46) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707 and references cited therein.
(47) Nishi, T.; Saito, F.; Nagahori, H.; Kataoka, M.; Morisawa,Y.; Yabe, Y.; Sakurai, M.; Higashida, S.; Shoji, M.; Matsushita, Y.; Iizima, Y.; Okizumi, K.; Koike, H. *Chem. Pharm. Bull.* **1990**, *38*, 103.

Scheme 3[a]



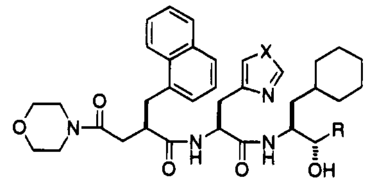
[a] Reagents: (a) (R)-BN-2,2′-OL/WSC/DMAP; (b) LDA/THF/HMPA/1-(bromomethyl)naphthalene; (c) LiOH/aqueous THF.

Table 14. Diastereoselective Alkylation of Binaphthyl Crotonate **45**[a] in THF/HMPA

entry	alkylating agent	temp, °C	time, h	product	combined yield, %	ratio[b] a:b
1	MeI	−78	0.3	**74**	72[c]	85:15[d]
2[e]	EtI	−78	19	**75**	0[f]	
3	EtI	−78	0.5	**75**	53[g]	93:7
4	$PhCH_2Br$	−78	0.7	**76**	83	90:10
5	*i*-PrI	−78 to ∼−45	2.3	**77**	64	90:10
6	*i*-BuI	−78 to ∼−45	1.5	**78**	32	92:8

[a] *dl*-**45** was used. [b] Determined by ^{1}H NMR. [c] A 13% yield of **79** was obtained. [d] Exact ratio was not determined due to overlap of signals. [e] Without HMPA. [f] A 67% yield of **44** was obtained. [g] A 21% yield of **80** was obtained.

(*R*,*R*)-**72** and the *R*,*S*-isomer in a yield of 81%. The *R*,*R*-configuration of the major isomer **72** was unambiguously determined by X-ray analysis (supporting information). Pure **72** obtained by recrystallization was converted into optically pure **73**[48] in a yield of 85%.

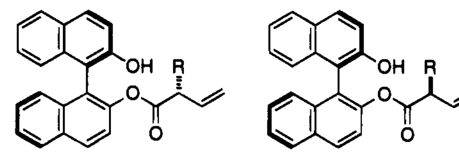


69

V. Extension of Diastereoselective Alkylations to Other Systems. Alkylation of the Binaphthyl Ester of an α,β- and β,γ-Unsaturated Acid. In section II, we reported that binaphthyl crotonate **45** did not give the corresponding enolate with *n*-BuLi as a base, since the arrangement between the hydroxyl group and the hydrogen to be removed did not meet the requirements necessary for CIPE. However, LDA can abstract the hydrogen in THF/HMPA to generate the enolate, which gives the α-alkylated products along with migration of the double bond. The results are listed in Table 14. It is well accepted that lithium dienoates predominantly undergo α-alkylation,[49] although a few exceptions have been reported.[50] In our work, exclusive α-alkylation was observed in all cases. No alkylated product was obtained without HMPA (entry 2), probably due to internal proton return[51,52] because the rearranged product **44** was obtained in a yield of 67%. High diastereoselectivity (9:1) was observed regardless of the bulkiness of the alkylating agent. Recrystallization of a 9:1 mixture of the optically active **77a** and **77b** obtained from (*R*)-binaphthyl crotonate afforded **77a** of 94% de which, on catalytic hydrogenation followed by reduction with $LiAlH_4$, gave (*S*)-2-ethyl-3-methylbutan-1-ol. This species was characterized as its naphthylcarbamate **81**.[53] This transformation confirmed the *R*,*R*-configuration of the major isomer **77a**. It is likely that the stereochemistry of the major isomer of the other alkylated products is the same as that of **77a**, although there is no direct evidence to support this supposition.

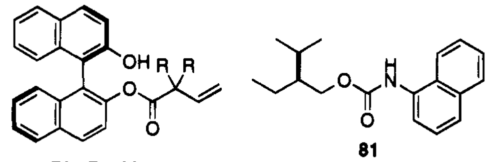
Table 15. Diastereoselective Alkylation of (*R*)-**44** under the CIPE Conditions

entry	alkylating agent	temp, °C	time, h	product	combined yield, %	ratio a:b
1	MeI	−78	1	**74**	75	91:9
2	EtI	−78	20	**75**	43	91:9
3	*i*-PrI	−78 to ∼−35	2.5	**77**	62	95:5



74a : R = Me
75a : R = Et
76a : R = CH_2Ph
77a : R = *i*-Pr
78a : R = *i*-Bu

74b : R = Me
75b : R = Et
76b : R = CH_2Ph
77b : R = *i*-Pr
78b : R = *i*-Bu



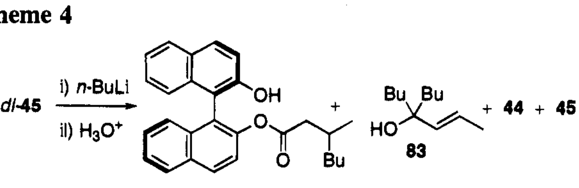
79 : R = Me
80 : R = Et

81

The CIPE is expected to affect binaphthyl allylacetate **44**, since the disposition of the methylene group of **44** is likely to be similar to that in binaphthyl phenylacetate **1**. Moreover, the acidity of **44** should be higher than that of **45**. These considerations led us to examine the deprotonation of **44** with *n*-BuLi. As expected, successful deprotonation was observed. The enolate was alkylated to give **74**,**75**, and **77** with de's (Table 15) comparable to those obtained from **45**.

VI. Successive 1,4- and 1,2-Additions of Organometallic Reagents. Product analysis of the reaction of naphthyl crotonate **45** with *n*-BuLi revealed that the major products were **82** (28%) and **83** (24%), from 1,4- and 1,2-additions, respectively (Scheme 4). Formation of **82** encouraged us to investigate a new transformation from an α,β-unsaturated carboxylic acid to an optically active β-substituted carboxylic acid *via* **d**, which could

Scheme 4



(48) Nishi, T.; Sakurai, M.; Sato, S.; Kataoka, M.; Morisawa, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2200.
(49) Kende, A. S. ; Toder, B. H. *J. Org.Chem.* **1982**, *47*, 167 and references cited therein.
(50) Smith, A. B., III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 4193.
(51) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(52) Seebach, D.; Boes. M.; Naef, R.; Schweizer. W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.
(53) Tsuda, K.; Kishida, Y.; Hayatsu, R. *J. Am. Chem. Soc.* **1960**, *82*, 3396.

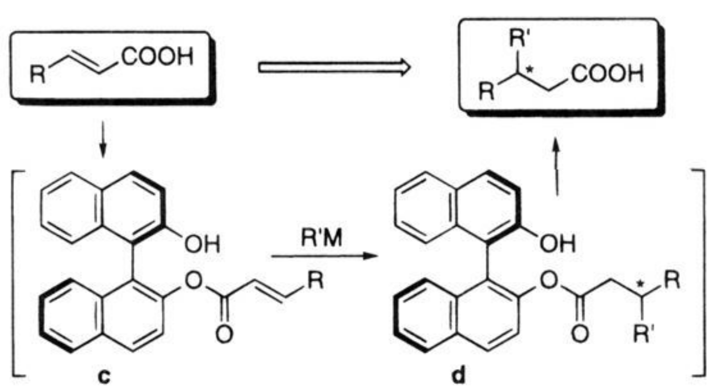
Table 16. One-Step Synthesis of **88**

			reaction conditions			product		
entry	ester	alkylating agent (equiv)	solvent	temp, °C	time, h	yield,[a] %	% ee	config
1	(*S*)-**84**	Me_2CuLi (10)	Et_2O/toluene	0	1	84 (92)[b]	87	*R*
2	(*S*)-**84**	Me_2CuLi (10)	Et_2O	0	2	73 (86)[b]	82	*R*
3	(*S*)-**84**	Me_2CuLi (10)	toluene	0	2	77 (87)[b]	74	*R*
4	(*S*)-**84**	Me_2CuLi (10)	Et_2O/THF/hexane	0	0.3	72	63	*R*
5	(*S*)-**84**	Me_2CuLi (10)	Et_2O/DME	0	7	26	11	*R*
6	(*R*)-**84**	Me_2CuLi (10)	THF	0	1	21	36	*S*
7	(*S*)-**84**	Me_2CuLi (10)	Et_2O/THF	0	0.3	62	63	*R*
8	(*R*)-**84**	Me_2CuLi (5)	Et_2O/THF	0	0.3	51	60	*S*
9	(*R*)-**84**	Me_2CuLi (3)	Et_2O/THF	0	0.4	36	36	*S*
10	(*S*)-**84**	Me_2CuLi (10)	Et_2O/THF	20	0.5	65	65	*R*
11	(*S*)-**84**	Me_2CuLi (10)	Et_2O/THF	−20 to ∼−10	2	62	65	*R*
12	(*S*)-**84**	Me_2CuLi (10)	Et_2O/THF	−50 to ∼−40	2	*c*		
13	(*S*)-**84**	MeMgBr-CuI(10)	Et_2O/THF	0	0.3	73	48	*S*
14	(*S*)-**84**	MeMgBr-CuI(10)	Et_2O/DME	0	5	31	49	*S*
15	(*R*)-**85**	MeMgBr-CuI(10)	Et_2O/THF	0	30	88	7	*S*
16	(*S*)-**86**	Me_2CuLi (10)	Et_2O/THF	0	18	65	15	*R*
17	(*R*)-**87**	Me_2CuLi (10)	Et_2O/toluene	0	15	84	19	*S*

[a] Isolated yield. [b] Determined by GLC. [c] A mixture of products probably arising from the 1,4-addition was obtained.

be obtained by the diastereoselective Michael addition of alkylmetals to **c** (Scheme 5).

Scheme 5



The reaction of (*S*)-**84** with lithium dimethylcuprate (10 equiv) unexpectedly gave (*R*)-4-phenyl-2-pentanone (**88**)[54] via the 1,4-addition of the cuprate followed by a formal 1,2-addition of methyl anion to the carbonyl. This transformation constitutes a new one-pot synthesis of optically active β-substituted ketone. We investigated the reaction of **84** with lithium dimethylcuprate, and the results are compiled in Table 16. The best results (84%, 87% ee) were obtained in Et_2O/toluene at 0 °C (entry 1). Less polar solvents such as toluene and Et_2O were more suitable for achieving effective transformation than solvents with higher ligating ability, such as THF and DME. Decreasing the amount of the reagent decreased both the chemical yield and the ee (entries 8 and 9). Lowering the reaction temperature below −40 °C gave no ketonic product (entry 12), since elimination of the binaphthyl moiety does not occur to create the intermediate ketene which gives **88** by the addition of a second molecule of the Gilman reagent. The hydroxyl group on the naphthyl ring was proven to be indispensable for the high ee. Thus, a decrease in the ee was observed when silyl ether **86** or diester **87** was used as a starting material.

Mixed copper/magnesium reagents have been used for conjugate additions.[55] However, neither the chemical yield nor the ee was impressive in this case (entries 13 and 14). It is worth noting that (*S*)-**84** gives (*S*)-**88** as opposed to the results observed with the Gilman reagent (compare entry 1 with entry 13), which gives an interesting example of the formation of both enantiomers from the same starting material by controlling the reagent. A decrease in ee was also observed when the phenolic hydroxyl group was masked (entry 15). These findings suggest that intramolecular delivery of a methyl group occurred from the reagent captured by the phenolic hydroxyl group to give **88**. The conformation of the cinnamate moiety is important for understanding the sense of chiral induction. X-ray analysis revealed that (*R*)-**84** exists in the *s-cis-syn*-conformation[56] in the crystalline state (Figure 3). Although it is premature to present a detailed mechanistic rationale, the model proposed in Figure 4 can explain the reagent-dependent stereochemistry of

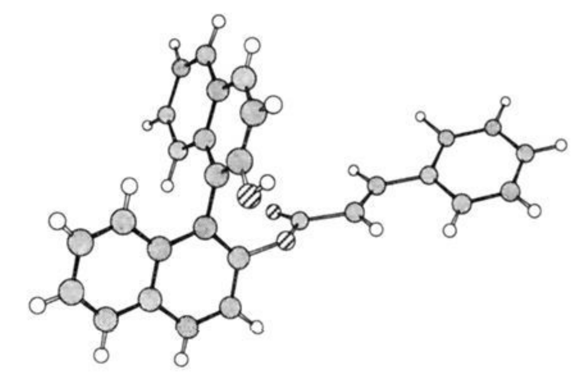


Figure 3. Crystalline structure of (*R*)-**84**.

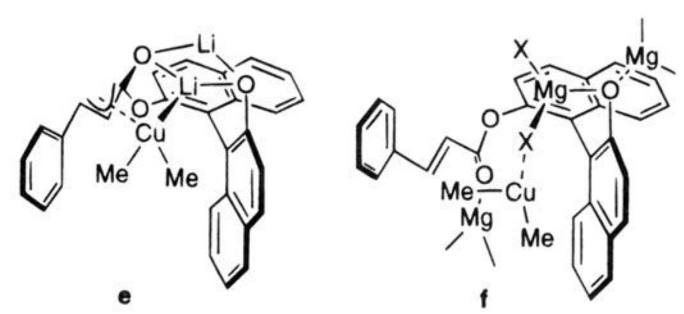
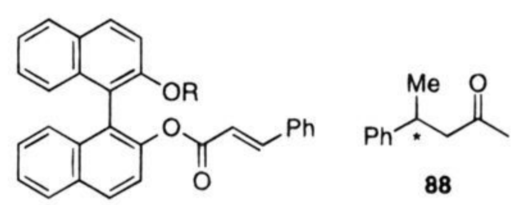


Figure 4. Transition model for the addition of Gilman reagent (**e**) and the mixed copper−magnesium reagent (**f**) leading to (*S*)-**88** and (*R*)-**88**, respectively, from (*R*)-**84**.



84 : R = H
85 : R = Me
86 : R = TBDMS
87 : R = COCH=CHPh

(54) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1975**, 3.

(55) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Lipschutz, B. H. *Synthesis* **1987**, 325.

(56) For a detailed discussion on the conformation of enoates, see: Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Ymamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068 and references cited therein.

the product and the reversal of enantioselectivity by assuming that the *s-cis*-conformation of the enoate is maintained throughout the reaction process. The lithium of the cuprate coordinates with the ester carbonyl in the first event followed by complexation with the oxyanion of the naphthyl ring to give a cyclic intermediate (**e**). This tethering effect might direct the enoate moiety to achieve the best overlap with the HOMO of the cuprate from the *si* face to yield (*S*)-**88** from (*R*)-**84**. Polar solvents would interfere with this chelation and presumably decrease the ee. In the case of the MeMgBr/CuI system, the bulkiness of the (solvated) ligands in the reagents prevents the formation of a cyclic intermediate, and instead leads to alternative intermediate **f** by the rotation of the oxygen−naphthyl bond by 180°. Intramolecular transfer of a methyl group in this intermediate gives (*R*)-**88**. This one-pot procedure could be extended to the synthesis of a wide variety of optically active β-substituted ketones. Further studies along these lines are underway.

Conclusion

We examined the usefulness of BN-2,2′-OL as a chiral auxiliary in the stoichiometric transformations of several types of half-esters. We have shown that the remaining hydroxyl group of BN-2,2′-OL plays a crucial role in achieving higher stereoselectivity.[57] These findings raise the interesting suggestion that nonprotected hydroxyl groups should generally be taken into account to realize high selectivity. Although, in reactions involving anionic species, the hydroxyl group can waste the reagent, the advantage of the high ee may outweigh this loss.

Another important conclusion is related to the geometry of the enolate kinetically generated from phenylacetates **46**−**48** in THF with LDA. We have shown that kinetic deprotonation of methyl phenylacetate (**46**) gives predominantly the (*Z*)-enolate, in contrast to other reported results.[33] Thus, all of the esters reported so far seem to give (*Z*)-enolate as a major enolate. However, we found an exception in the formation of the enolate of **47**, which gave the (*E*)-enolate as a major product under kinetic conditions. All of these findings show that special precaution is required when discussing the stereochemistry of the enolates of arylacetates.

Experimental Section

Materials. Ether and THF used for the reaction involving anions were distilled from sodium/benzophenone ketyl under nitrogen atmosphere. 2′-Methoxy-1,1′-binaphthalen-2-ol (registry no. 35193-70-5), 2′-methyl-1,1′-binaphthalen-2-ol (registry no. 142088-91-3), compound **70** (registry no. 67900-19-0) are known.[61] Compound **61** is commercially available. Silica gel plates were used for preparative TLC (PTLC). ^{1}H NMR spectra were measured in $CDCl_3$.

Binaphthyl Ester 1. General Procedure for Binaphthyl Esters 33 and 34 Using Acid Chloride. To a mixture of (*R*)-BN-2,2′-OL (910 mg, 3.2 mmol), DMAP (41 mg, 0.33 mmol), and Et_3N (575 μL, 4.1 mmol) in THF (7 mL) was added phenylacetyl chloride (462 μL, 3.5 mmol) in THF (7 mL) at −5 °C. After stirring for 12 min at the same temperature the reaction mixture was worked up to give a mixture of **1** and the corresponding diester. Purification by column chromatography over silica gel (AcOEt:hexane = 1:5) yielded (*R*)-**1** (1.0g, 79%): mp 104.5−105.5 °C (from Et_2O/hexane); ^{1}H NMR δ 3.41 (s, 2H), 5.15 (s, 1H), 6.68−8.08 (17H). Anal. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.31; H, 5.38.

Data for *dl*-33: 68%; mp 147−148.5 °C (from Et_2O/hexane); ^{1}H NMR δ 0.70 (t, 3H, J = 7.7 Hz), 1.97−2.28 (m, 2H), 5.21 (s, 1H), 7.03−8.11 (12H). Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.87; H, 5.25.

Data for *dl*-34: 91%; mp 116−117.5 °C (from Et_2O); ^{1}H NMR δ 3.37 (s, 2H), 3.63 (s, 3H), 6.67−8.04 (17H). Anal. Calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.30. Found: C, 83.23; H, 5.29.

General Procedure for Binaphthyl Esters 2−7, 35, 44, and 45. To a mixture of BN-2,2′-OL (1.2 g, 4.2 mmol), arylacetic acid (1.1 equiv), and DMAP (0.1 equiv) in CH_2Cl_2 (100 mL) was added WSC (1.5 equiv) at room temperature, and the mixture was stirred for 3−4 h under N_2. The reaction mixture was poured into dilute HCl and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried, and evaporated to give a residue which was purified by flash column chromatography.

Data for (*S*)-2: mp 122.0−122.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 3.39 (s, 2H), 3.79 (s, 3H), 5.16 (s, 1H), 6.53−6.70 (m, 4H), 6.99−8.10 (12H); IR ($CHCl_3$) 3540, 3010, 1745, 1620, 1600, 1515, 1250, 1125, 815 cm^{-1}; FT-IR (CCl_4, 0.0011 mol/L) 3534, 1753 cm^{-1}; FT-IR (CCl_4, 0.0033 mol/L) 3534, 1753 cm^{-1}. Anal. Calcd for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 80.24; H, 4.89.

Data for (*S*)-3: mp 159.0−159.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 3.45 (s, 2H), 3.62 (s, 3H), 5.22 (s, 1H), 6.63−8.07 (16H). Anal. Calcd for $C_{29}H_{22}O_4$: C, 80.17; H, 5.10. Found: C, 79.96; H, 5.03.

Data for (*S*)-4: mp 95.5−96.0 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 2.27 (s, 3H), 3.38 (s, 2H), 5.14 (s, 1H), 6,61−8.08 (16H). Anal. Calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.30. Found: C, 83.25; H, 5.22.

Data for (*S*)-5: mp 112.0−115.0 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 3.39 (s, 2H), 5.06 (s, 1H), 6.56−8.08 (16H). Anal. Calcd for $C_{28}H_{19}O_3Cl$: C, 76.62; H, 4.36. Found: C, 76.38; H, 4.21.

Data for (*R*)-6: mp 138.0−138.8 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 3.59 (s, 2H), 5.08 (s, 1H), 6.79−8.08 (19H). Anal. Calcd for $C_{32}H_{22}O_3$: C, 84.56; H, 4.88. Found: C, 84.23; H, 4.92.

Data for (*R*)-7: mp 163.5−165.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 3.40 (s, 2H), 5.6 (br s, 1H), 6.85−8.32 (16H). Anal. Calcd for $C_{27}H_{19}O_3N$: C, 79.98; H, 4.72; N, 3.45. Found: C, 80.00; H, 4.79; N, 3.52.

Data for *dl*-35: 100%; mp 93.5−94.0 °C (from AcOEt/hexane); ^{1}H NMR δ 1.99 (s, 3H), 3.31 (s, 2H), 6.62−8.01 (17H). Anal. Calcd for $C_{29}H_{22}O_2$: C, 86.54; H, 5.51. Found: C, 87.01; H, 5.58.

Data for (*R*)-44: 97%; amorphous solid; ^{1}H NMR δ 2.85 (m, 2H), 4.77−4.88 (m, 2H), 5.15 (s, 1H), 5.21−5.42 (m, 1H), 7.02−8.10 (12H); HRMS for $C_{24}H_{18}O_3$ (M^+), calcd 354.1257, found 354.1300.

Data for *dl*-45: 72%; mp 178−181 °C (from Et_2O/CH_2Cl_2); ^{1}H NMR δ 1.72 (dd, 3H, J = 1.7, 7 Hz), 5.37 (s, 1H), 5.67 (dq, 1H, J = 15.5, 1.7 Hz), 6.78 (dq, 1H, J = 15.5, 7 Hz), 7.04−8.10 (12H); HRMS for $C_{24}H_{18}O_3$ (M^+), calcd 354.1257, found 354.1273.

General Procedure for Diastereoselective Alkylation of 1 Using LDA as a Base (Entry 5 in Table 2). A solution of racemic **1** (200 mg, 0.5 mmol) and HMPA (826 μL, 5 mmol) in THF (4 mL) was added dropwise to a THF (2 mL) solution of LDA (1 mmol) under N_2 at −78 °C. After 15 min, CH_3I (1.1 mL, 18 mmol) was added, and the solutionwas stirred for 15 min and then poured into cold dilute HCl followed by extractive workup using Et_2O. The crude product was purified by column chromatography on silica gel (AcOEt:hexane = 1:3.5) followed by PTLC with the same solvent system to give an inseparable mixture of **8a** and **8b** (77:2, 176 mg, 85%): ^{1}H NMR δ 1.08 (d, 3 × 23/100H, J = 7.3 Hz), 1.10 (d, 3 × 77/100H, J = 7.3 Hz), 3.55 (q, 1 × 23/100H, J = 7.3 Hz), 3.59 (q, 1 × 77/100H, J = 7.3 Hz), 5.18 (s, 1 × 77/100H), 5.20 (s, 1 × 23/100H); IR ($CHCl_3$) 3540, 3010, 1745, 1620, 1600, 1380, 1150 cm^{-1}. Anal.[58] Calcd for $C_{29}H_{22}O_3$: C, 83.23; H, 5.03. Found: C, 83.03; H. 5.29.

Data for *dl*-9a and *dl*-9b: inseparable mixture (78:22); ^{1}H NMR δ 0.54 (t, 3H, J = 7.3 Hz), 1.18−1.94 (m, 2H), 3.27 (t, 1 × 22/100H, J = 7.7 Hz), 3.32 (t, 1 × 78/100H, J = 7.7 Hz), 5.17 (s, 1 × 78/100H), 5.28 (s, 1 × 22/100H); IR ($CHCl_3$) 3540, 3010, 1745, 1620, 1150 cm^{-1}. Anal.[58] Calcd for $C_{30}H_{24}O_3$: C, 83.31; H, 5.59. Found: C, 83.03; H, 5.63.

Data for *dl*-10a and *dl*-10b: inseparable mixture (78:22); ^{1}H NMR δ 0.61 (t, 3H, J = 7.3 Hz), 0.72−0.92 (2H), 1.26−1.41 (1H), 1.53−1.64 (1H), 3.37 (t, 1 × 22/100H, J = 7.8 Hz), 3.41 (t, 1 × 78/100H, J = 7.8 Hz), 5.16 (s, 1 × 78/100H), 5.27 (s, 1 × 22/100H); IR ($CHCl_3$)

(57) For another instance, see: Fuji, K.; Tanaka, K.; Ahn, M.; Mizuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 957.

(58) Elemental analysis was carried out on the mixture of diastereomers to prove that other contaminants did not exist in the mixture.

3540, 3010, 1740, 1620, 1600, 1150, 1130 cm^{-1}. Anal.[58] Calcd for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.32; H, 6.08.

Data for *dl*-11a and *dl*-11b: inseparable mixture (78:22); ^{1}H NMR δ 0.70 (t, 3H, *J* = 7.3 Hz), 0.73−1.66 (6H), 3.34 (t, 1 × 22/100H, *J* = 7.6 Hz), 3.39 (t, 1 × 78/100H, *J* = 7.6 Hz), 5.18 (s, 1 × 22/100H), 5.28 (s, 1 × 78/100H); IR ($CHCl_3$) 3540, 2960, 1740, 1620, 1600, 1150 cm^{-1}. HRMS for $C_{32}H_{28}O_3$ (M^+), calcd 460.2037, found 460.2017.

Data for *dl*-12a and *dl*-12b: inseparable mixture (78:22); ^{1}H NMR δ 2.76 (dd, 1 × 78/100H, *J* = 7, 14 Hz), 2.77 (dd, 1 × 22/100H, *J* = 7, 14 Hz), 2.92 (dd, 1 × 22/100H, *J* = 8, 14 Hz), 3.09 (dd, 1 × 78/100H, *J* = 9, 14 Hz), 3.68 (dd, 1 × 22/100H, *J* = 7, 8 Hz), 3.72 (dd, 1 × 78/100H, *J* = 7, 9 Hz), 5.10 (s, 1 × 22/100H), 5.13 (s, 1 × 78/100H); IR ($CHCl_3$) 3540, 3060, 3030, 1745, 1620, 1600, 1150, 1135 cm^{-1}. HRMS for $C_{35}H_{26}O_3$ (M^+), calcd 494.1882, found 494.1891.

Data for *dl*-13a and *dl*-13b: inseparable mixture (82:18); ^{1}H NMR δ 2.15−2.24 (1H), 2.40−2.50 (1H), 3.46 (dd, 1 × 18/100H, *J* = 6.8, 8.8 Hz), 3.50 (dd, 1 × 82/100H, *J* = 6.8, 8.8 Hz), 4.78−4.86 (2H), 5.16 (s, 1 × 82/100H), 5.25 (s, 1 × 18/100H), 5.29−5.41 (1H); IR ($CHCl_3$) 3550, 3070, 1750, 1620, 1600, 1520, 1380, 1150 cm^{-1}. Anal.[58] Calcd for $C_{31}H_{24}O_3$; C, 83.76; H, 5.44. Found: C, 83.53; H, 5.45.

Data for *dl*-14a and *dl*-14b: inseparable mixture (92:8); ^{1}H NMR δ 0.49 (d, 3 × 92/100H, *J* = 6.8 Hz), 0.50 (d, 3 × 8/100H, *J* = 6.8 Hz), 0.59 (d, 3 × 92/100H, *J* = 6.4 Hz), 0.62 (d, 3 × 8/100H, *J* = 6.4 Hz), 1.19−2.12 (1 × 92/100H), 2.07−2.18 (1 × 8/100H), 3.01 (d, 1 × 8/100H, *J* = 10.3 Hz), 3.02 (d, 1 × 92/100H, *J* = 10.3 Hz), 5.13 (s, 1 × 92/100H), 5.33 (s, 1 × 8/100H); IR ($CHCl_3$) 3550, 3070, 1750, 1115 cm^{-1}. Anal.[58] Calcd for $C_{31}H_{26}O_3$: C, 83.38; H, 5.87. Found: C, 83.52; H, 5.96.

In another experiment, (*S*,*S*)-**14a** was obtained by recrystallization from Et_2O/hexane: mp 127−129 °C; $[\alpha]^{19}_D$ +18.7 (*c* 1.2, $CHCl_3$).

Data for *dl*-15a: mp 136−138 °C (from CH_2Cl_2/hexane); ^{1}H NMR δ 0.56 (d, 3H, *J* = 6.3 Hz), 0.61 (d, 3H, *J* = 6.8 Hz), 0.80−0.92 (1H), 1.17−1.26 (1H), 1.45−1.52 (1H), 3.51 (t, 1H, *J* = 7.8 Hz), 5.17 (s, 1H), 6.90−8.00 (17H). Anal. Calcd for $C_{32}H_{28}O_3$: C,83.45; H, 6.12. Found: C, 83.42; H, 6.20.

Data for (*S*,*S*)-16a and (*S*,*R*)-16b: inseparable mixture (87:13); ^{1}H NMR (DMSO-d_6) δ 0.82 (d, 3 × 87/100H, *J* = 7 Hz), 0.94 (d, 3 × 13/100H, *J* = 7 Hz), 3.70 (s, 3 × 87/100H), 3.71 (s, 3 × 13/100H), 9.47 (s, 1 × 13/100H), 9.53 (s, 1 × 87/100H); IR ($CHCl_3$) 3540, 3060, 3010, 1745, 1625, 1600, 1515, 1250, 1180, 1150 cm^{-1}. Anal.[58] Calcd for $C_{30}H_{24}O_4$: C, 80.33; H, 5.39. Found: C, 80.27; H, 5.40.

Data for (*S*,*S*)-17a and (*S*,*R*)-17b: inseparable mixture (68:32); ^{1}H NMR δ 0.56 (t, 3H, *J* = 7.3 Hz), 1.10−1.92 (2H), 3.23 (t, 1 × 32/100H, *J* = 7.3 Hz), 3.27 (t, 3 × 68/100H, *J* = 7.3 Hz), 3.77 (s, 3H), 5.16 (s, 1 × 68/100H), 5.25 (s, 1 × 32/100H); IR ($CHCl_3$) 3540, 3060, 3010, 2970, 2940, 1745, 1625, 1615, 1600, 1515, 1250, 1180, 1150 cm^{-1}; HRMS for $C_{31}H_{26}O_4$ (M^+), calcd 462.1831, found 462.1854.

Data for (*S*,*S*)-18a and (*S*,*R*)-18b: inseparable mixture (85:15); ^{1}H NMR δ 0.63 (t, 3H, *J* = 7.3 Hz), 0.75−0.95 (2H), 1.26−1.40 (m, 1H), 1.55−1.65 (m, 1H), 3.33 (t, 1 × 15/100H, *J* = 7.8 Hz), 3.37 (t, 1 × 85/100H, *J* = 7.8 Hz), 3.77 (s, 3H), 5.16 (s, 1 × 85/100H), 5.24 (s, 1 × 15/100H); IR ($CHCl_3$) 3540, 3060, 3010, 2960, 2940, 1740, 1620, 1610, 1600, 1515, 1465, 1380, 1250, 1180, 1150 cm^{-1}; HRMS for $C_{32}H_{28}O_4$ (M^+), calcd 476.1988, found 476.1989.

Data for (*S*,*S*)-19a: mp 133−134 °C (from CH_2Cl_2/hexane); $[\alpha]^{16}_D$ −29.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.50 (d, 3H, *J* = 6.8 Hz), 0.62 (d, 3H, *J* = 6.3 Hz), 2.03 (m, 1H), 2.98 (d, 1H, *J* = 10.8 Hz), 3.81 (s, 3H), 5.14 (s, 1H), 6.57−8.03 (16H). Anal. Calcd for $C_{32}H_{28}O_4$: C, 80.64; H, 5.92. Found: C, 80.91; H, 6.04.

Data for (*S*,*S*)-20a: amorphous solid; ^{1}H NMR δ 0.59 (d, 3H, *J* = 6.8 Hz), 0.64 (d, 3H, *J* = 6.4 Hz), 0.93 (m, 1H), 1.18−1.25 (m, 1H), 1.45−1.53 (m, 1H), 3.47 (t, 1H, *J* = 7.8 Hz), 3.77 (s, 3H), 5.14 (s, 1H), 6.54−8.02 (16H); HRMS for $C_{33}H_{30}O_4$ (M^+), calcd 490.2143, found 490.2135.

Data for (*S*,*S*)-21a: mp 124.5−125.2 °C (from CH_2Cl_2/hexane); $[\alpha]^{16}_D$ +19.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.51 (d, 3H, *J* = 6.8 Hz), 0.71 (d, 3H, *J* = 6.3 Hz), 2.07 (m, 1H), 3.41 (s, 3H), 3.80 (d, 1H, *J* = 10.3 Hz), 5.17 (s, 1H), 6.56−8.03 (16H). Anal. Calcd for $C_{32}H_{28}O_4$: C, 80.64; H, 5.92. Found: C, 80.87; H, 5.96.

Data for (*S*,*S*)-22a: mp 105.5−106.0 °C (from hexane/CH_2Cl_2/AcOEt); ^{1}H NMR δ 0.60 (d, 3H, *J* = 6.8 Hz), 0.65 (d, 3H, *J* = 6.8 Hz), 0.96 (m, 1H), 1.17−1.25 (m, 1H), 1.43−1.50 (m, 1H), 3.55 (s, 3H), 4.09 (t, 1H, *J* = 7.8 Hz), 5.17 (s, 1H), 6.61−8.03 (16H). Anal. Calcd for $C_{33}H_{30}O_4$: C, 80.79; H, 6.16. Found: C, 80.41; H, 6.08.

Data for (*S*,*S*)-23a: mp 130.8−133.0 °C (from AcOEt/hexane); $[\alpha]^{16}_D$ −28.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.49 (d, 3H, *J* = 6.8 Hz), 0.59 (d, 3H, *J* = 6.8 Hz), 1.98−2.07 (m, 1H), 2.31 (s, 3H), 2.99 (d, 1H, *J* = 10.7 Hz), 5.13 (s, 1H), 6.77−8.02 (16H). Anal. Calcd for $C_{32}H_{28}O_3$: C, 83.45; H, 6.13. Found: C, 83.32; H, 6.19.

Data for (*S*,*S*)-24a: >96% de; mp 133.0−134.2 °C (from AcOEt/hexane); $[\alpha]^{16}_D$ −50.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.45 (d, 3H, *J* = 6 Hz), 0.63 (d, 3H, *J* = 6 Hz), 1.19−1.23 (m, 1H), 3.03 (d, 1H, *J* = 10 Hz), 6.46 (s, 1H), 6.80−8.06 (16H). Anal. Calcd for $C_{31}H_{24}O_3Cl$: C, 77.41; H, 5.24. Found; C, 77.50; H, 5.23.

(*S*)-3-Methyl-2-phenylbutyric Acid (26). To a concentrated sulfuric acid was added (*S*,*S*)-**14a** (>98% de, 41 mg, 0.9 mmol). Immediately after resolving, the reaction mixture was poured into ice−water followed by usual workup to give **26**[16] (15 mg, 97%).

(*S*)-2-(4′-Methoxyphenyl)-3-methylbutyric Acid (27). A mixture of (*S*,*S*)-**19a** (90% de, 27 mg, 0.056 mmol) and LiOH·H_2O (17 mg, 0.4 mmol) in THF (1 mL)/H_2O (0.5 mL) was stirred for 12 h at room temperature. Usual workup gave **27**[17] (10.5 mg, 90%). The acid **28**[17] (95%) was obtained from **24** by a similar procedure.

(*S*)-2,3-Diphenylpropanol (30). $LiAlH_4$ (27 mg, 0.71 mmol) was added to a THF solution of **12** (**12a**:**12b** = 67:33, 69 mg, 0.14 mmol). After being stirred for 10 min, the reaction mixture was worked up to give **30**:[20] 27 mg, 92%; $[\alpha]^{18}_D$ +30.5 (*c* 1.4, $CHCl_3$)}.

General Procedure for Methylation Using *n*-BuLi as a Base (Table 6). To a solution of binaphthyl ester (0.2 mmol, 1.0 equiv) in THF (3.0 mL) was added a hexane solution of *n*-BuLi (2.1 equiv) at −78 °C. After 5 min, CH_3I (20 equiv) was added and stirred under the conditions in Table 6.

Data for (*S*,*S*)-25a: mp 119−120.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR (DMSO-d_6) δ 0.88 (d, 3H, *J* = 7 Hz), 3.63 (q, 1H, *J* = 7 Hz), 6.72−8.09 (16H), 9.52 (s, 1H). Anal. Calcd for $C_{29}H_{21}O_3Cl$: C, 76.90; H, 4.67. Found: C, 76.59; H, 4.63.

Data for (*R*,*R*)-31a: mp 183.5−186 °C (from CH_2Cl_2/hexane); ^{1}H NMR (DMSO-d_6) δ 0.94 (d, 3H, *J* = 7 Hz), 3.73 (q, 1H, *J* = 7), 6.83−8.08 (19H), 9.51 (s, 1H). Anal. Calcd for $C_{33}H_{24}O_3$: C, 84.59; H, 5.16. Found: C, 84.31; H, 5.19.

Data for (*R*,*R*)-32a: mp 169−170.5 °C (from CH_2Cl_2/hexane); ^{1}H NMR (DMSO-d_6) δ 0.89 (d, 3H, *J* = 7.3 Hz), 3.67 (q, 1H, *J* = 7.3 Hz), 6.84−8.35 (16H), 9.53 (s, 1H); HRMS for $C_{28}H_{21}O_3N$ (M^+), calcd 419.1520, found 419.1505.

(*S*)-36. (TMS)Cl (36 μL, 0.29 mmol) was added to a mixture of (*S*)-**4** (109 mg, 0.26 mmol), Et_3N (55 μL, 0.39 mmol), and DMAP (4.0 mg, 0.03 mmol) in THF (2.0 mL) at 0 °C, and the mixture was stirred for 20 min at the same temperature. Usual workup gave (*S*)-**36**: oil; ^{1}H NMR δ −0.18 (s, 9H), 2.28 (s, 3H), 3.31 (d, 1H, *J* = 15.4 Hz), 3.33 (d, 1H, *J* = 15.4 Hz), 6.65 (m, 2H), 6.88 (m, 2H), 7.13−7.95 (12H); HRMS for $C_{29}H_{22}O_3Si$ (M^+), calcd 490.1964, found 490.1996.

***dl*-38a, *dl*-38b, and 42**: A solution of *n*-BuLi (0.35 mmol) in hexane was added to a solution of **35** (127 mg, 0.32 mmol) in THF (4.5 mL) at −78 °C. After 5 min, CH_3I (394 μL, 20 equiv) was added, and the mixture was stirred for 4 h at −78 °C. Usual workup followed by PTLC (AcOEt/hexane) gave a mixture of racemic **38a** and **38b** (32 mg, 25%) and **42** (18 mg, 24%).

Data for *dl*-38a and *dl*-38b: inseparable mixture (75:25); ^{1}H NMR δ 0.98 (d, 3 × 25/100H, *J* = 7 Hz), 1.00 (d, 3 × 75/100H, *J* = 7 Hz), 2.01 (s, 3 × 25/100H), 2.03 (s, 3 × 75/100H), 3.45 (q, 1H, *J* = 7 Hz). Anal.[59] Calcd for $C_{30}H_{24}O_2$: C, 86.51; H, 5.81. Found: C, 86.08; H, 5.84.

Data for 42: oil; ^{1}H NMR δ 0.88−1.05 (6H), 1.20−1.55 (12H), 2.74 (s, 2H), 7.18−7.35 (5H); IR ($CHCl_3$) 3010, 1750, 1510, 1450, 1370, 1140 cm^{-1}; HRMS for $C_{16}H_{26}O$ (M^+), calcd 234.1983, found 234.1982.

***dl*-37a and *dl*-37b**: inseparable mixture (85:15); ^{1}H NMR δ 1.01 (d, 3 × 85/100H, *J* = 7 Hz), 1.08 (d, 3 × 15/100H, *J* = 7 Hz), 3.45 (q, 1 × 85/100H, *J* = 7 Hz), 3.50 (q, 1 × 15/100H, *J* = 7 Hz), 3.60

(59) Giordano, C.; Castaldi, G.; Cavicchioli, S.; Villa, M. *Tetrahedron* **1989**, *45*, 4243.

(s, 3 × 85/100H), 3.63 (s, 3 × 15/100H); IR ($CHCl_3$) 3060, 1750, 1630, 1600, 1510, 1460, 1265, 1150 cm^{-1}. Anal.[58] Calcd for $C_{30}H_{24}O_3$: C, 83.31; H, 5.59. Found: C, 83.13; H, 5.56.

2-Naphthyl Phenylacetate (39) and 2-Naphthyl 4-Chlorophenylacetate (40). The general procedure using WSC was applied.

Data for 39: mp 76.0−77.0 °C (from Et_2O); ^1H NMR δ 3.92 (s, 2H), 7.17−7.86 (12H). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.03; H, 5.41.

Data for 40: mp 91−93 °C (from Et_2O); ^1H NMR δ 3.89 (s, 2H), 7.16−7.86 (11H); HRMS for $C_{18}H_{13}O_2Cl$ (M^+), calcd 296.0604, found 296.0629.

41 and 43. Attempted Methylation of 40. The general procedure using *n*-BuLi (1.1 equiv instead of 2.1 equiv) gave a 3:2 mixture of 2-naphthyl 2-(4-chlorophenyl)propionate (**41**) and 2-butyl-1-(4-chlorophenyl)hexan-2-ol (**43**), which was purified by PTLC.

Data for 41: oil, ^1H NMR δ 1.64 (d, 3H, J = 7 Hz), 4.01 (q, 1H, J = 7 Hz), 7.09−7.85 (m, 1H). Anal. Calcd for $C_{19}H_{15}O_2Cl$: C, 73.43; H, 4.86. Found: C, 73.40; H, 4.81.

Data for 43: oil, ^1H NMR δ 0.86−1.00 (6H), 1.15 (br s, 1H), 1.20−1.50 (8H), 2.71 (s, 2H), 7.10−7.32 (m, 4H). Anal. Calcd for $C_{16}H_{25}OCl$: C, 71.49; H, 9.37. Found: C, 71.68; H, 9.59.

2,6-Dimethylphenyl Phenylacetate (48). The general procedure using phenylacetyl chloride was applied: oil; ^1H NMR δ 2.01 (s, 6H), 3.89 (s, 2H), 7.02 (s, 3H), 7.25−7.46 (5H). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.25; H, 6.85.

Trapping of Enolates Generated from 47 with (TMS)Cl. A solution of **47** (45 mg, 0.21 mmol) in THF (2 mL) was added to LDA (0.25 mmol) in THF (1 mL) at −78 °C. After 30 min at the same temperature, (TMS)Cl (107 μL, 0.84 mmol) was added, and the temperature was raised to room temperature over a period of 1 h. The volatile compounds were removed at room temperature under reduced pressure to give a residue consisting of **47**, (*E*)-**50**, and (*Z*)-**50**, the ^1H NMR spectrum of which was measured immediately.

Ketene TMS Acetals 51−57. Essentially the same procedure described above was applied, and the ^1H NMR spectra were taken on the crude mixture to determine the *E*:*Z* ratio.

(*S*)-**58**. Esterification of (*S*)-BN-2,2′-OL with 6-methoxy-2-naphthylacetic acid[45] by the general procedure using WSC gave (*S*)-**58** (88%): mp 136−136.5 °C (from CH_2Cl_2/hexane); $[\alpha]^{20}_D$ −98.1 (c 1.0, $CHCl_3$); ^1H NMR δ 3.55 (s, 2H), 3.95 (s, 3H), 5.10 (s, 1H), 6.78−8.08 (18H). Anal. Calcd for $C_{33}H_{24}O_4$: C, 81.80; H, 4.99. Found: C, 81.89; H, 4.91.

(*S*,*S*)-59 was prepared by the general procedure for methylation using *n*-BuLi as a base in 94% yield: oil (84% de); ^1H NMR δ 1.19 (d, 3 × 8/100H, J = 7 Hz), 1.24 (d, 3 × 92/100H, J = 7 Hz), 3.64 (q, 1 × 8/100H, J = 7 Hz), 3.70 (q, 1 × 92/100H, J = 7 Hz), 3.78 (s, 3 × 8/100H), 3.96 (s, 3 × 92/100H), 5.08 (s, 1 × 92/100H), 5.15 (s, 1 × 8/100H); IR ($CHCl_3$) 3540, 3060, 3010, 1745, 1610, 1510, 1485, 1380, 1265, 1175, 1150 cm^{-1}; HRMS for $C_{34}H_{26}O_4$ (M^+), calcd 498.1830, found 498.1825.

(*S*)-Naproxen (60). A procedure similar to that used for the hydrolysis of **19** was applied for (*S*,*S*)-**59** (84% de) and gave **60** in 73% yield: $[\alpha]^{28}_D$ +52.6 (c 1.0, $CHCl_3$) (lit.[59] $[\alpha]^{20}_D$ +68.5 (c 1.0, $CHCl_3$). The ee of **60** was determined to be 82% by HPLC on a chiral column (YMC-Pack KO3, hexane:CH_2Cl_2:MeOH = 90:9:1) after conversion into its anilide.

TBDMS Ether 62. A mixture of 4-bromophenethyl alcohol (**61**; 10.4 g, 51.5 mmol), (TBDMS)Cl (8.5 g, 56.7 mmol), Et_3N (9.3 mL, 67.0 mmol), and DMAP (622 mg, 5.1 mmol) in CH_2Cl_2 was stirred at room temperature for 1 h. Usual workup followed by distillation under reduced pressure gave **62** as an oil (bp 106−108 °C, 0.32 Torr), which was used without further purification: ^1H NMR δ −0.02 (s, 6H), 0.88 (s, 9H), 2.76 (t, 2H, J = 7 Hz), 3.78 (t, 2H, J = 7 Hz), 7.08 (m, 2H), 7.40 (m, 2H).

Alcohol 63. To a solution of **62** (4.8 g, 16.0 mmol) in THF (30 mL) was added a hexane solution of *n*-BuLi (16.8 mmol) followed by the addition of 2-thiophenecarboxaldehyde (1.6 mL, 16.8 mmol) at −78 °C, and the mixture was stirred for 10 min at the same temperature. Usual workup gave **63** as an oil, which was used without purification: ^1H NMR δ −0.02 (s, 6H), 0.82 (s, 9H), 2.39 (d, 1H, J = 4 Hz), 2.80 (t, 2H, J = 7 Hz), 3.78 (t, 2H, J = 7 Hz), 6.01 (d, 1H, J = 4 Hz), 6.83−7.37 (7H).

4-(2-Thenoyl)phenylacetic Acid (64).[60] The Jones reagent (29.5 mmol) was added dropwise to a solution of **63** (3.5 g) in 70 mL of acetone (distilled from $KMnO_4$) at 0 °C, and the mixture was stirred for 6 h at 0−15 °C. Extractive workup with AcOEt under acidic conditions gave **64** (1.5 g, 68% from **62**): mp 82.0−83.0 °C (from AcOEt/hexane); ^1H NMR δ 3.77 (s, 2H), 7.15−7.88 (7H). Anal. Calcd for $C_{13}H_{10}O_3S$: C, 63.40; H, 4.09. Found: C, 63.13; H,4.15.

Ketal 65. A mixture of **64** (500 mg, 2.0 mmol), ethylene glycol (5.6 mL, 100 mmol), and TsOH (3 mg, 0.02 mmol) in benzene (15 mL) was refluxed in a flask attached to a total reflux phase-separating head packed with 3A molecular sieves for 24 h. Usual workup followed by flash cholumn chromatography afforded the ethylene glycol ester of **65** (560 mg, 83%) as an oil, a portion (177 mg, 0.53 mmol) of which was stirred with 10% NaOH/MeOH to give **65** (145 mg, 94%): mp 115.0−116.0 °C (from CH_2Cl_2/hexane); ^1H NMR δ 3.66 (s, 2H), 3.98−4.22 (m, 4H), 6.83−7.58 (7H); HRMS for $C_{15}H_{14}O_4S$ (M^+), calcd 290.0612, found 290.0603.

(*S*)-Binaphthyl Ester 66. The general procedure using WSC afforded (*S*)-**66** (92%) as an oil: $[\alpha]^{20}_D$ −64.7° (c 0.54, $CHCl_3$); ^1H NMR δ 3.42 (s, 2H), 3.99 (m, 2H), 4.17 (m, 2H), 5.10 (s, 1H), 6.48−8.06 (19H); HRMS for $C_{35}H_{26}O_5S$ (M^+), calcd 558.1500, found 558.1497.

Methylation of (*S*)-66 To Give (*S*,*S*)-67. The general procedure using *n*-BuLi as a base gave (*S*,*S*)-**67** (95%, 96% de): oil; ^1H NMR δ 1.09 (d, 3H, J = 7.2 Hz), 3.59 (q, 1H, J = 7.2 Hz), 3.86−4.22 (m, 4H), 5.16 (s, 1H), 6.70−8.07 (19H); HRMS for $C_{36}H_{28}O_5S$ (M^+), calcd 572.1657, found 572.1667.

(*S*)-Suprofen (68). To a solution of **67** (96% de, 79 mg, 0.14 mmol) in THF (3 mL) and H_2O (1.5 mL) was added LiOH·H_2O (25 mg, 0.6 mmol) at 0 °C, and the mixture was stirred for 1.5 h at the same temperature. Usual workup followed by PTLC over silica gel (hexane:AcOEt:*i*-PrOH = 10:1:1) gave (*S*)-**68** (24 mg, 66%), $[\alpha]^{28}_D$ +39.5 (c 1.2, $CHCl_3$), which was converted into the anilide by the standard method with aniline, WSC, and DMAP: oil; 93% ee determined by HPLC with YMC-Pack KO3 (hexane:CH_2Cl_2:MeOH = 90:10:2); ^1H NMR δ 1.63 (d, 3H, J = 7 Hz), 3.79 (q, 1H, J = 7 Hz), 7.05−7.89 (13H); HRMS for $C_{20}H_{17}O_2NS$ (M^+), calcd 335.0979, found 335.0970.

Binaphthyl Ester 71. The general procedure from **70** (1.6 g, 8.5 mmol) and (*R*)-binaphthol (2.0 g, 7.0 mmol) using WSC (2.0 g, 10.6 mmol) and DMAP (91 mg, 0.75 mmol) gave **71** (2.4 g, 76%): amorphous solid; $[\alpha]^{24}_D$ +77.5 (c 1.0, $CHCl_3$); ^1H NMR δ 2.10 (t, 2H, J = 7.2 Hz), 2.34−2.61 (m, 2H), 3.11−3.16 (m, 2H), 3.50−3.64, (6H), 5.44 (s, 1H), 7.04−8.10 (12H); HRMS for $C_{28}H_{25}O_5N$ (M^+), calcd 455.1732, found 455.1725.

(*R*,*R*)-72. After addition of a solution of **71** (453 mg, 1.0 mmol) in THF (8 mL) to LDA (2.1 mmol) in THF (5 mL) and HMPA (1.6 mL, 1.0 mmol) at −78 °C, the mixture was stirred for 1 h at the same temperature, and 1-(bromomethyl)naphthalene (485 mg, 2.2 mmol) in THF (3 mL) was added. Usual workup after stirring for 2 h at −45 °C gave 482 mg (81%) of an 85:15 mixture of (*R*,*R*)-**72** and (*R*, *S*)-**72**, which was recrystallized from CH_2Cl_2/Et_2O to give pure (*R*,*R*)-**72**: mp 131.0−134.5 °C; $[\alpha]^{24}_D$ +53.9 (c 1.0, $CHCl_3$); ^1H NMR δ 2.01 (dd, 1H, J = 6.0, 16.3 Hz), 2.10 (dd, 1H, J = 7.9, 16.3 Hz), 2.56 (dd, 1H, J = 9.2, 13.9 Hz), 2.86 (dd, 1H, J = 5.9, 13.9 Hz), 3.04 (m, 2H), 3.19 (m, 1H), 3.39−3.51 (6H), 5.46 (s, 1H), 7.07−8.06 (19H); HRMS for $C_{39}H_{33}O_5N$ (M^+), calcd 595.2358, found 595.2348.

2-(*R*)-[(1-Naphthyl)methyl]-3-(morpholinocarbonyl)propionic Acid (73). A mixture of (*R*,*R*)-**72** (48 mg, 0.08 mmol) and LiOH·H_2O (17 mg, 0.39 mmol) in THF (1 mL) and H_2O (0.5 mL) was stirred for 8 h at 0 °C. Usual workup followed by PTLC gave (*R*)-**78** (22 mg, 85%): $[\alpha]^{27}_D$ −38.2 (c 0.6, $CHCl_3$) (lit.[49] $[\alpha]^{20}_D$ −37.9 ($CHCl_3$). The ee was determined to be 99% by HPLC analysis of the corresponding anilide with YMC-Pack KO3 (hexane:CH_2Cl_2:MeOH = 90:10:1).

Diastereoselective Alkylation of 45 Using LDA as a Base. General Procedure for Runs in Table 14. To a solution of LDA

(60) Although this compound was reported elsewhere, the melting points (126−129 °C) is different from ours (82.0−83.0 °C). The values calculated for $C_{13}H_{10}O_3S$ in the other paper were wrong, and the elemental analysis coincides with the wrong values; see: van Daele, P. G. H.; Boey, J. M.; Sipido, V. K.; de Bruyn, M. F. L.; Janssen, P. A. J. *Arzneim.-Forsch.* **1975**, *25*, 1495.

(61) The registry numbers given in this paper were supplied by the author.

(2.1 equiv) in THF (1 mL) and HMPA (10 equiv) was added dropwise *dl*-**66** (80 mg, 1.0 equiv) in THF (2.5 mL) at −78 °C. After 30 min, alkyl halide (10 equiv) was added, and the mixture was stirred under the conditions in Table 14. Usual workup followed by purification by PTLC over silica gel (AcOEt/hexane) gave a mixture of diastereomers which was used for the determination of the de by ^{1}H NMR.

Data for *dl*-74a and *dl*-74b: inseparable mixture (85:15); ^{1}H NMR δ 0.74 (d, 3 × 15/100H, *J* = 7 Hz), 0.81 (d, 3 × 85/100H, *J* = 7 Hz), 2.97 (q, 1H, *J* = 7 Hz), 4.64−5.32 (4H), 7.03−8.10 (12H); IR ($CHCl_3$) 3450, 1750, 1620, 1600, 1150 cm^{-1}; HRMS for $C_{25}H_{20}O_3$ (M^+), calcd 368.1413, found 368.1415.

Data for *dl*-79: amorphous solid; ^{1}H NMR δ 0.78 (s, 3H), 0.91 (s, 3H), 4.74 (dd, 1H, *J* = 1, 10 Hz), 4.79 (dd, 1H, *J* = 1, 18 Hz), 5.12 (s, 1H), 5.54 (dd, 1H, *J* = 10, 18 Hz), 6.96−8.11 (12H); HRMS for $C_{26}H_{22}O_3$ (M^+), calcd 382.1568, found 382.1529.

***dl*-75a**: crystalline solid (from CH_2Cl_2/hexane); ^{1}H NMR δ 0.55 (t, 3H, *J* = 7 Hz), 1.08−1.19 (m, 1H), 1.28−1.39 (m, 1H), 2.75 (q, 1H, *J* = 7 Hz), 4.72−4.77 (m, 2H), 5.15 (s, 1H), 5.20−5.28 (m, 1H), 7.03−8.07 (12H). Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.31; H, 5.80.

Data for *dl*-80: oil; ^{1}H NMR δ 0.48 (t, 6H, *J* = 7 Hz), 1.20−1.64 (m, 4H), 4.71−5.62 (m, 4H), 6.97−8.06 (m); HRMS for $C_{28}H_{26}O_3$ (M^+), calcd 410.1881, found 410.1871.

Data for *dl*-76a and *dl*-76b: inseparable crystalline mixture (9:1); ^{1}H NMR δ 2.41 (dd, 1H, *J* = 8, 14 Hz), 2.71 (dd, 1H, *J* = 8, 14 Hz), 3.11 (q, 1 × 1/10H, *J* = 8 Hz), 3.15 (q, 1 × 9/10H, *J* = 8 Hz), 4.52−5.47 (m, 3H), 5.06 (s, 1 × 1/10H), 5.14 (s, 1 × 9/10H); IR ($CHCl_3$) 3540, 3070, 1745, 1620, 1600, 1520, 1510, 1500, 1470, 1460, 1380, 1360, 1275, 1170, 1150 cm^{-1}. Anal.[58] Calcd for $C_{31}H_{24}O_3$: C, 83.76; H, 5.44. Found: C, 83.73; H, 5.61.

Data for *dl*-77a: mp 131.0−132.0 °C (from AcOEt/hexane); ^{1}H NMR δ 0.57 (d, 3H, *J* = 6 Hz), 0.58 (d, 3H, *J* = 6 Hz), 1.58−1.70 (m, 1H), 2.55 (t, 1H, *J* = 9 Hz), 4.71 (dd, 1H, *J* = 1.17 Hz), 4.79 (dd, 1H, *J* = 1, 10 Hz), 5.18 (s, 1H), 5.34 (ddd, 1H, *J* = 9, 10, 17 Hz), 7.03−8.06 (12H). Anal. Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.85; H, 6.03.

Data for *dl*-78a and *dl*-78b: inseparable crystalline mixture (92:8); ^{1}H NMR δ 0.54 (d, 3H, *J* = 5.4 Hz), 0.63 (d, 3H, *J* = 6.8 Hz), 0.88−1.10 (m, 3H), 2.94 (q, 1H, *J* = 7.8 Hz), 4.76−4.82 (m, 2 × 92/100H), 4.88−4.96 (m, 2 × 8/100H), 5.14 (s, 1 × 92/100H), 5.18 (s, 1 × 8/100H), 5.26−5.35 (m, 1 × 92/100H), 5.36−5.45 (m, 1 × 8/100H), 7.03−8.08 (12H); HRMS for $C_{28}H_{26}O_3$ (M^+), calcd 410.1881, found 410.1863.

(*S*)-Naphthylcarbamate 81. A solution of (*R*)-**77a** (94% de, 52 mg, 0.13 mmol) in THF (3 mL) was stirred with 10% Pd/C (40 mg) for 24 h under atmospheric hydrogen. Removal of the solvent after filtration gave a residue (52 mg) which was redissolved in THF (2 mL) followed by addition of $LiAlH_4$ (74 mg). Usual workup after stirring for 20 min at 0 °C gave crude 2-ethyl-3-methylbutyl alcohol (9 mg), which was dissolved in benzene (2 mL). 1-Naphthyl isocyanate (19 μL, 0.13 mmol) and pyridine (1 drop) were added, and the mixture was stirred at room temperature for 14 h. Usual workup followed by PTLC (AcOEt:hexane = 1:4) afforded (*S*)-**81** (19 mg, 50%): $[\alpha]^{24}_D$ −3.5 (*c* 1.47, $CHCl_3$) (lit.[53] $[\alpha]^{25}_D$ −3.8 (*c* 2.1, $CHCl_3$)).

Reaction of *dl*-45 with *n*-BuLi. 82 and 83. To a solution of *dl*-**45** (68 mg, 0.19 mmol) in THF (2.5 mL) was added *n*-BuLi (1.6 M hexane solution, 250 μL, 0.40 mmol) at −78 °C, and the mixture was stirred for 5 min. Usual workup followed by PTLC (AcOEt:hexane = 1:3) gave an inseparable diastereomeric mixture (3:1) of **82** (22 mg, 28%) and **83** (9 mg, 24%) and a mixture (11 mg, 16%) of *dl*-**44** and *dl*-**45**.

Data for *dl*-82: oil; ^{1}H NMR δ 0.51 (d, 3 × 1/4H, *J* = 6.6 Hz), 0.52 (d, 3 × 3/4H, *J* = 6.6 Hz), 0.81 (d, 3H, *J* = 7 Hz), 0.84−1.52 (7H), 1.92 (dd, 3 × 1/4H, *J* = 7.7, 14.7 Hz), 1.94 (dd, 1 × 3/4H, *J* = 8.4, 14.7 Hz), 2.14 (dd, 1 × 3/4H, *J* = 5.5, 14.7 Hz), 2.19 (dd, 1 × 1/4H, *J* = 5.5, 14.7 Hz), 5.25 (s, 1 × 3/4H), 5.28 (s, 1 × 1/4H), 7.02−8.07 (12H); HRMS for $C_{28}H_{28}O_3$ (M^+), calcd 412.2038, found 412.2021.

Data for 83: oil; ^{1}H NMR δ 0.87−1.53 (18H), 1.71 (dd, 3H, *J* = 1, 6 Hz), 5.45 (dq, 1H, *J* = 16, 1 Hz), 5.59 (dq, 1H, *J* = 16, 6 Hz); HRMS for $C_{12}H_{24}O$ (M^+), calcd 184.1826, found 184.1811.

Binaphthyl Esters 84 and 87. The same procedure as that described for **1** was used to give **84** (86%) and **87** (14%).

Data for 84: mp 134−135 °C (from Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ −235 (*c* 0.35, $CHCl_3$); ^{1}H NMR δ 5.40 (s, 1H), 6.23 (d, 1H, *J* = 8 Hz), 7.08−8.13 (19H). Anal. Calcd for $C_{29}H_{20}O_3$: C, 83.63; H, 4.84. Found: C, 84.00; H, 4.84.

Data for 87: mp 139.5−141 °C (from *i*-Pr_2O); ^{1}H NMR δ 6.22 (d, 2H, *J* = 16 Hz), 7.27−8.04 (24H). Anal. Calcd for $C_{38}H_{26}O_4$: C, 83.50; H, 4.79. Found: C, 83.13; H, 4.74.

Methyl Ether 85. To a solution of (*S*)-**84** (150 mg, 0.35 mmol) in MeOH was added diazomethane in ether, and the mixture was left for 1.5 h. Usual workup followed by PTLC (hexane:AcOEt = 4:1) gave **85** (51 mg, 33%): ^{1}H NMR δ 3.75 (s, 3H), 6.18 (d, 1H, *J* = 16.0 Hz), 7.16−8.05 (18H). Anal. Calcd for $C_{30}H_{22}O_3$: C, 83.70; H, 5.15. Found: C, 83.97; H, 5.12.

TBDMS Ether 86. A mixture of (*S*)-**84** (512 mg, 1.23 mmol), (TBDMS)Cl (560 mg, 3.7 mmol), and imidazole (136 mg, 2.0 mmol) in DMF was stirred at room temperature for 60 h. Extractive workup with AcOEt followed by flash column chromatography (hexane:AcOEt = 6:1) gave (*S*)-**86** (326 mg, 50%): ^{1}H NMR δ −0.18 (s, 3H), −0.03 (s, 3H), 0.48 (s, 9H), 6.14 (d, 1H, *J* = 16 Hz), 7.14−8.02 (18H); HRMS for $C_{35}H_{34}O_3Si$(M^+), calcd 530.2276, found 530.2265.

General Procedure for the Preparation of 88 in Table 16. Use of Me_2CuLi. A solution of **84** (70 mg, 0.17 mmol) in the appropriate solvent (2.5 mL) was added at 0 °C to Me_2CuLi (10 equiv), prepared by the addition of MeLi (20 equiv) in hexane to CuI (10 equiv) in ether (1 mL). The mixture was treated under the conditions in Table 16 followed by purification with PTLC (hexane:AcOEt = 3:1) to give **88**.

Use of MeMgBr/CuI. The reagent was prepared by the addition of MeMgBr (10 equiv in ether) to CuI (0.5 equiv), and a procedure similar to that for Me_2CuLi was employed.

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Supporting Information Available: Figures showing the crystalline structures of (*S*)-**2** and (*R,R*)-**72**, tables giving the X-ray crystallographic data for (*S*)-**2**, (*R,R*)-**72**, and (R)-**84**, and Tables 5 and 13 listing ^{1}H NMR chemical shifts of methine, phenolic OH, and **52**−**57** (16 pages). This material is contained in many libraries on microfiche, immediately follows thes article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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