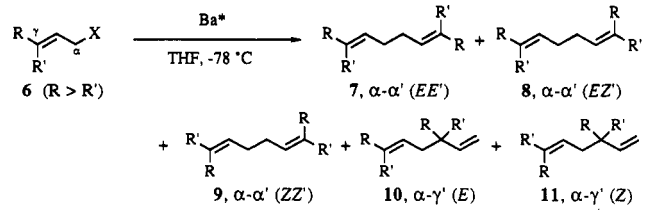
Table II. Regio- and Stereoselective Dimerization Reaction of Various Allylic Halides Using Barium Metal

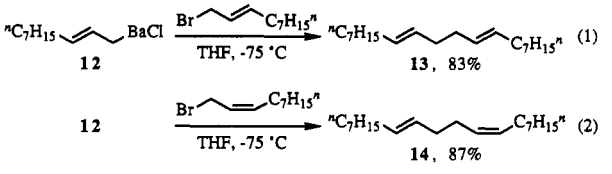


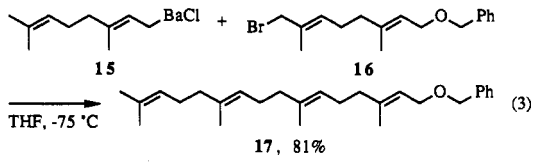
entry	allylic halide 6	yield,[a] %	ratio (α,α'/α,γ')	ratio of isomers 7–11[b] 7	8	9	10	11
1	$^nC_7H_{15}$ Cl	86	95:5	95	0	0	5	0
2	$^nC_7H_{15}$ Br	68	92:8	92	0	0	8	0
3	$^nC_7H_{15}$ Cl	88	51:49	0	0	51	0	49
4	$^nC_7H_{15}$ Br	50	77:23	0	0	77	0	23
5	Cl	70	91:9	89	2	0	9	0
6	Br	47	97:3	96	1	0	3	0
7	Cl	44	92:8	0	2	90	0	8
8	Cl	68	94:6	94	0	0	6	0
9	Cl	64	93:7	92	1	0	7	0

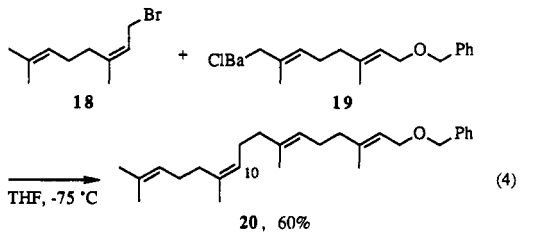
[a] Isolated yield. [b] Determined by GC analysis.

Table II summarizes the results obtained for the reaction of a variety of allylic halides **6** with reactive barium metal in THF at −78 °C.[8] Several characteristic features of the reaction have been noted: (1) Reaction of (*E*)-γ-mono- or disubstituted allyl halide resulted in >90% α,α' selectivities except (*Z*)-2-decenyl chloride and bromide (entries 3 and 4).[10] (2) Both allylic chloride and bromide can be used for the reaction with equal efficiency. (3) The double-bond geometry of the starting allylic halide was completely retained in each case. (4) (*E,E*)-Farnesyl chloride was stereospecifically converted to squalene in 64% yield (entry 8).

We have extended the scope of the reductive coupling method to include the synthesis of unsymmetrical dienes. Thus, α,α' cross-coupling products can be prepared stereospecifically and regioselectively by this method. For example, treatment of (*E*)-2-decenylbarium reagent (**12**) with (*E*)-2-decenyl bromide and (*Z*)-2-decenyl bromide afforded (*E,E*)-diene **13** and (*E,Z*)-diene **14** in high yield (eqs 1 and 2). Benzyl ether of geranylgeraniol **17** was







obtained almost exclusively in 81% yield by treatment of the primary allylic bromide **16**[11] with geranylbarium reagent **15** in THF at −75 °C (eq 3). Functionalized allylic barium reagent **19** was also readily prepared and allowed to react with neryl bromide (**18**) to provide a (10*Z*)-isomer of benzyl geranylgeranyl ether **20** (eq 4).

Acknowledgment. Financial support from the Ministry of Education, Science and Culture of the Japanese Government is gratefully acknowledged.

(8) A representative experimental procedure is given by the homocoupling of (*E,E*)-farnesyl chloride: To a suspension of anhydrous BaI_2[9] (458 mg, 1.2 mmol) in dry THF (3 mL) was added at room temperature a solution of preformed lithium biphenylide, prepared from freshly cut lithium (16 mg, 2.3 mmol) and biphenyl (365 mg, 2.4 mmol) in THF (5 mL) under argon atmosphere; the reaction mixture was stirred for 30 min at room temperature. To the resulting dark brown suspension of barium powder in THF was slowly added a solution of (*E,E*)-farnesyl chloride (378 mg, 1.6 mmol) in THF (1.5 mL) at −78 °C. The reaction mixture was stirred for 1 h at this temperature. 2 N HCl (10 mL) was added to the mixture at −78 °C, and the aqueous layer was extracted with ether. The combined organic extracts were washed with dilute sodium thiosulfate solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane) to afford a mixture of squalene and its regioisomer (220 mg, 68% combined yield): the α,α':α,γ' ratio was determined to be 94:6 by GC analysis. The large-scale reaction can be performed with equal efficiency. A procedure of the large-scale reaction using allylbarium will be submitted to *Org. Synth.*

(9) Anhydrous BaI_2 was prepared by drying commercially available $BaI_2 \cdot 2H_2O$ at 150 °C for 2 h under reduced pressure (<10 Torr).

(10) (*Z*)-γ-Monosubstituted allylbarium showed relatively low α-selectivities in the reaction with carbonyl compounds, see ref 6.

(11) Allylic bromide **16** was synthesized from geranyl benzyl ether by allylic oxidation with cat. SeO_2/TBHP/salicylic acid[12] and subsequent bromination with PBr_3.

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Asymmetric Synthesis of Sulfinimines: Applications to the Synthesis of Nonracemic β-Amino Acids and α-Hydroxyl-β-amino Acids

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Summary: Asymmetric oxidation of sulfenimines **1** affords sulfinimines **2** (88–90% ee) which are chiral ammonia imine synthons useful in the enantioselective synthesis of β-amino acids and α-hydroxy-β-amino acids such as the C-13 side chain of taxol (2*R*,3*S*)-**7**.

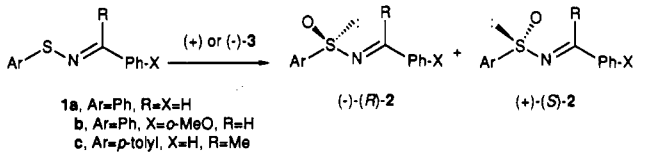
The oxidation of sulfenimines (*N*-alkylidenearenesulfenamides) **1** to racemic sulfinimines **2** with *m*-chloro-

Table I. Asymmetric Oxidation of Sulfenimines 1 to Sulfinimines 2 Using Oxaziridine 3 at 20 °C in CCl_4

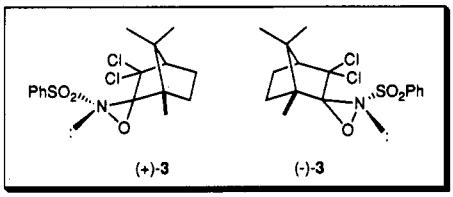
entry	sulfinimine	oxaziridine (h)	% yield[a]	% ee [c] (config)[b]	$[\alpha]^{20}_D$ ($CHCl_3$) [c]
1	2a	(-)-3 (5)	95	88 (R)	-112° (c 1.12)
2		(-)-3 (10)[e]	82	90 [>97][d] (R)	-118° (c 1.18) [-126° (c 1.1)]
3		(+)-3 (10)[e]	72	88 [>97] (S)	+112° (c 1.12) [+124° (c 1.18)]
4	2b	(-)-3 (4)	89	85 [>97][f] (R)	-300.5° (c 1.94) [-377.5° (c 1.07)]
5	2c	(-)-3 (48)	90	87 [>96][g] (R)	-85.9° (c 1.37) [-93.7° (c 1.0)]

[a] Isolated yield. [b] Configuration based on sulfoxide model. [c] After crystallization from n-hexane. [d] Ee established by conversion to β-amino acid 5a. [e] At -20 to +20 °C. [f] Ee determined using $Eu(hfc)_3$. [g] Reference 5.

perbenzoic acid (m-CPBA) was first reported by us in 1974.[1,2] Our "silver-assisted" methodology, the reaction of aromatic disulfides, aldehydes, and ketones, silver nitrate, and ammonia was used to prepare 1.[3] Cinquini,[4]



1a, Ar=Ph, R=X=H
b, Ar=Ph, X=o-MeO, R=H
c, Ar=p-tolyl, X=H, R=Me



and more recently Hua,[5] prepared enantiopure examples of 2 by reaction of metaloketimines, synthesized by treatment of benzonitrile with Grignard and lithium reagents, with (-)-1-menthyl (S)-p-toluenesulfinate. However, this "Andersen-type" procedure is limited to the preparation of alkyl aryl sulfinimines 2 (R ≠ H). We describe here a general approach for the synthesis of nonracemic sulfinimines in both enantiomeric forms, which avoids this limitation. This methodology involves the asymmetric oxidation of sulfenimines 1 with (+)- or (-)-N-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (3, [3,3-dichloro-1,7,7-trimethyl-2'-(phenylsulfonyl)spiro]bicyclo[2.2.1]heptane-2,3'-oxaziridine]]).[6] The application of 2 in the stereoselective synthesis of β-amino acid derivatives, including the C-13 side chain of taxol, is also presented.

Oxidations were carried out by addition of 1.0 equiv of (+)- or (-)-3 to the appropriate sulfenimine 1 in CCl_4. After the oxidation was complete, as determined by TLC, the sulfinimines 2 were isolated by flash chromatography (30% ethyl acetate/n-pentane) in 85–95% yield and 88–90% ee. Crystallization from n-hexane improved the ee's to >97% (Table I). The ee and absolute configuration of 2a were established by conversion into the known β-amino acid 5a (vide infra) and for 2c by comparison with literature values.[4,5] These results are consistent with earlier studies using 3 for the asymmetric oxidation of sulfides[6] and selenides[7] to sulfoxides and selenoxides (up to >95% ee) where it was shown that the molecular recognition is predictable using an active-site model in which the nonbonded interactions between the R_L and R_S groups of the sulfide (R_L–S–R_S) and the active site surface are minimized. For sulfenimines 1 Ar acts as the R_L group.

Sulfenimines 1 are useful ammonia imine (RR'C=NH) synthons because addition of hydride, RM,[8] and enolates[9] affords sulfenamide derivatives (ArSNHCRR'R'') in which the S–N bond is cleaved under mild conditions to amines.[2] Reduction of nonracemic sulfinimines 2 (R = Me, n-Bu) with DIBAL affords secondary amines (92% ee), but addition of lithium and Grignard regents fails because deprotonation to form the sulfinimine enolate competes with addition.[5] However, high de's of tertiary sulfinamides were reported for addition of allylmagnesium bromide to 2 (Ar = p-tolyl, R = Me, n-Bu) which were subsequently transformed, in multistep sequences, to β- and γ-amino acids.[5]

A more general approach to β-amino acids, essential intermediates in organic synthesis,[10,11] is addition of enolates to chiral sulfinimines. Thus, addition of the 1.5 equiv of the lithium enolate of methyl acetate (LDA, methyl acetate) to enantiopure (R_S)-2a and (R_S)-2c gave sulfinamides 4a and 4c. Sulfinamide 4a was obtained as a 90:10 mixture of diastereoisomers by flash chromatography and on crystallization from n-hexane afforded (R_S,3S)-4a [$[\alpha]^{20}_D$ -115.0° (c 1.29 $CHCl_3$)] diastereometrically pure in 74% isolated yield. Sulfinamide (R_S,3S)-4c [$[\alpha]^{20}_D$ -37.6° (c 1.76 $CHCl_3$)] was obtained diastereomerically pure in 90% yield. *Significantly, enolization of sulfinimine 2c does not compete with enolate addition to the C–N double bond.* The absolute configurations of the new amino stereocenters in 4a and 4c were determined by hydrolysis, without epimerization, to β-amino acids (3S)-5a and (3S)-5c with 4 equiv of CF_3CO_2H/MeOH (0 °C, 2 h). Isolation was accomplished by evaporation of the solvent to dryness, extraction with 15% HCl, addition of CH_2Cl_2 to the aqueous layer, followed by careful neutralization

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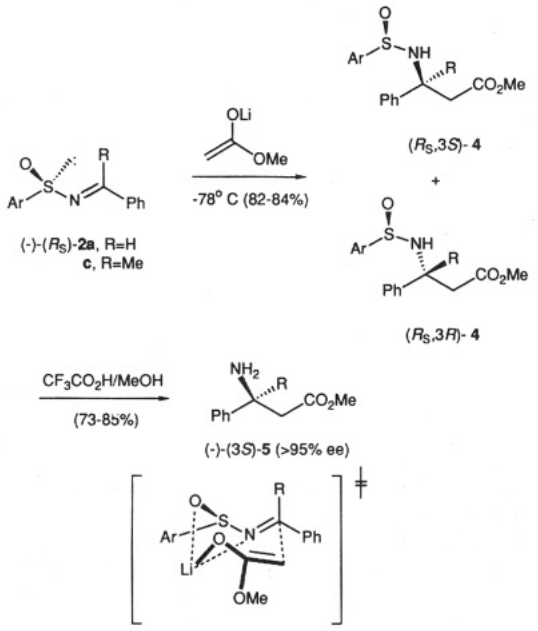
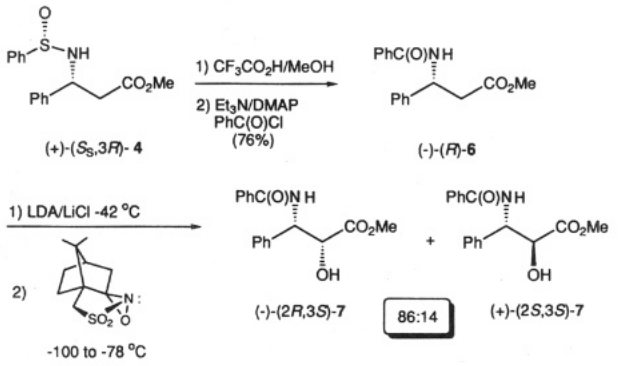
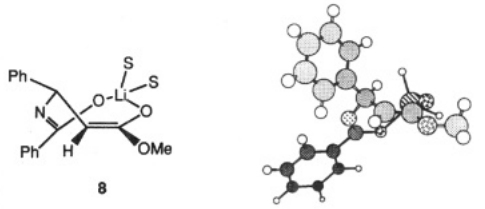
with Na_2CO_3 to pH 7.5, affording (−)-(*S*)-methyl 3-amino-3-phenylpropanoate (**5a**)[12,13] and (−)-(*S*)-methyl 3-amino-3-phenylbutanoate (**5c**)[5,14] in 73 and 85% yields, respectively. A Zimmerman–Traxler-type six-membered transition state **TS-1** favoring approach of the enolate from the *Si*-face of **2** is consistent with these results.



Recent interest in the synthesis of (−)-*N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**7**, R = H), the C-13 side chain of the remarkable antitumor agent taxol, has been stimulated not only by the fact that this moiety is essential for its bioactivity[15] but also that 10-deacetyl baccatin III, which lacks this structural unit, is available from a renewable source.[16] (+)-(*R*)-Methyl 3-amino-3-phenylpropanoate (**5a**) is an advanced precursor of **7** requiring only benzoylation of the amino group and stereospecific introduction of the hydroxyl group. One-pot hydrolysis–benzoylation of (S_S,3*R*)-**4**, prepared by addition of the lithium enolate of methyl acetate to (+)-**2a** (Table I, entry 3) followed by flash chromatography, gave (*R*)-**6** in 76% yield. (+)-(Camphorylsulfonyl)oxaziridine[17,18]-mediated hydroxylation of the enolate dianion of (*R*)-**6** at −100 to −78 °C in the presence of 1.6 equiv of LiCl gave an 86:14 syn–anti mixture of (2*R*,3*S*)-**7**:(2*S*,3*S*)-**7** in 58% yield.[19] Higher temperatures result in diminished de's, and yields were markedly lower in the absence of LiCl (<15%). Chromatographic separation of the diastereoisomers afforded (−)-(2*R*,3*S*)-**7**, the methyl ester of the taxol C-13 side chain, in 49% yield and >93% enantiomeric purity: $[\alpha]^{20}_D$ −46.2° (*c* 0.97, MeOH) [lit[20] $[\alpha]^{20}_D$ −49.6° (*c* 0.97, MeOH)].[21] The minor, anti isomer, (+)-(2*S*,3*S*)-**7**, apparently not previously reported was isolated in 9% yield: mp 158–9 °C; $[\alpha]^{20}_D$ +8.7° (*c* 1.03, MeOH)]. Based on the 20% recovery of starting material the yield of (−)-(2*R*,3*S*)-**7** is 62%.



The facial selectivity for enolate hydroxylations using *N*-sulfonyloxaziridines nearly always occurs at the least hindered face of the enolate.[17] Thus, the fact that (−)-(2*R*,3*S*)-**7** seems to involve approach of the oxaziridine from the more hindered face of the enolate of **6** was unexpected. However, if the enolate dianion of (*R*)-**6** forms an intramolecular eight-membered chelate **8**, approach of the oxaziridine can be rationalized as occurring from the least hindered direction.[22] The calculated lowest energy conformer (MMX) of the chelated dianion **8** supports this hypothesis indicating that the *Si*-face is the most accessible to electrophilic attack.[23]



Nonracemic sulfinimines **2** are useful chiral synthons for imines of ammonia as demonstrated by their utility in the asymmetric synthesis of β-amino acids and their derivatives.

Acknowledgment. This work was supported by the National Science Foundation through grant CHE-8800471.

Supplementary Material Available: Experimental procedures and compound characterization data (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) Isolated as the hydrochloride: $[\alpha]^{20}_D$ +6.8° (*c* 2.05, MeOH); (*S*)-**5a** [lit.[12] $[\alpha]^{20}_D$ +7.8° (*c* 2, MeOH)]. The ee was determined to be >95% ee using the chiral shift reagent Eu(hfc)$_3$ on the acetamide of **5a**, mp 121–122 °C; $[\alpha]^{20}_D$ +19.4° (*c* 1.0, $CHCl_3$).

(14) Isolated as *N*-acetyl-(*S*)-3-amino-3-phenylbutanoic acid; $[\alpha]^{20}_D$ −23.1° (*c* 1.15, MeOH) [lit.[5] $[\alpha]^{20}_D$ +24.3° (*c* 1.55, MeOH) for the *R* isomer].

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(21) Chiral HPLC analysis on a Pirkle covalent L-leucine column (55:45 2-propanol/*n*-hexane, at a flow rate of 0.5 mL/min) indicated that (−)-(2*R*,3*S*)-**7** was better than 97% ee.

(22) For a related study on the alkylation and hydroxylation of the dienolates of δ-hydroxyl carboxylic acids see: Narasaka, K.; Ukaji, Y.; Watnabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1457.

(23) PCMODEL, Serena Softward, Bloomington, IN. MMX version by K. E. Gilbert and J. J. Gajewski based on MM@ (Allinger, QCPE 395) and MMP1 Pi (Allinger, QPEC 318) modified by K. Steliou.