m/z (M^+) calcd 466.0693, obsd 466.0682.

General Procedure for the Reduction of 8, 14, and 19 with Lithium Aluminum Hydride. To a suspension of lithium aluminum hydride (2 equiv) in 2% dry ether was added a 2.5% solution of substrate in dry THF at -78 °C under argon. The mixture was stirred for 45 min at the same temperature, treated with a 4% HCl, and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated in vacuo.

6a. Reduction of 8 with lithium aluminum hydride, following the procedure described above, gave one diastereomer (98% yield).

11c,d. Via the procedure described above, reduction of 14 gave a diastereomeric mixture (96:4) of alcohols (93% yield). **11c** (major): ^1H NMR δ 4.18 (d, 1 H, J = 2.0 Hz), 5.67 (d, 1 H, J = 2.0 Hz), 7.19-8.34 (m, 17 H, two diast.). **11d** (minor): ^1H NMR δ 4.27 (d, 1 H, J = 8.5 Hz), 5.47 (d, 1 H, J = 8.5 Hz), 7.19-8.34 (m, 17 H, two diast.).

18c. Reduction of 19 with lithium aluminum hydride, following the procedure described above, gave one diastereomer (98%) and traces of the other isomers: ^1H NMR δ 4.75 (d, 1 H, J = 9.2 Hz), 5.04 (d, 1 H, J = 9.2 Hz), 7.02-8.40 (m, 17 H); MS m/z (M^+) calcd for $C_{28}H_{20}O_3S_2 \cdot H_2O$ 450.0744, obsd 450.0751.

General Procedure for the Reaction of 8 and 14 with Methylmagnesium Iodide. A 3% solution of the substrate in dry THF/ether (1:2.5) under argon was cooled to -78 °C. Methylmagnesium iodide (5 equiv) was added dropwise via syringe. The reaction mixture was treated with water and saturated aqueous ammonium chloride. The combined organic extracts were dried over anhydrous sodium sulfate. The product was purified by flash chromatography, eluting with the specified solvent.

7a,b. Via the procedure described above, alkylation of 8 with methylmagnesium iodide gave a diastereomeric mixture (87:13) of alcohols (95% yield). The crude product was purified by flash chromatography, eluting with a gradient of petroleum ether-dichloromethane.

12a,b. As described above, a single diastereoisomer was obtained from the reaction of methylmagnesium iodide with 14 (64% yield) as a light yellow solid after flash chromatography (dichoromethane): ^1H NMR δ 2.25 (s, 3 H), 4.18 (s, 1 H), 6.75-8.31 (m, 17 H).

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Supplementary Material Available: X-ray crystallographic data including an ORTEP drawing (Figure 1) and tables of fractional coordinates, anisotropic thermal parameters, bond distances, and bond angles for compound 11a (Tables I-IV), ^1H NMR spectra for all title compounds in the Experimental Section, and HRMS data for selected compounds. (29 pages). Ordering information is given on any current masthead page.

Diastereoselective Cycloaddition of N-Lithiated Azomethine Ylides to (*E*)-α,β-Unsaturated Esters Bearing a C_2-Symmetric Imidazolidine Chiral Controller

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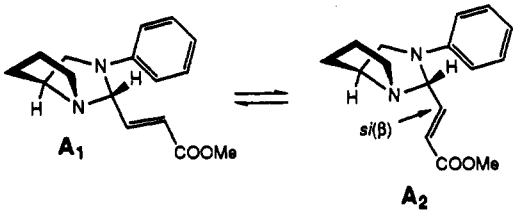
The 1,3-dipolar cycloaddition of N-metalated azomethine ylides to chiral (*E*)-3-(1,3-disubstituted 4,5-diphenylimidazolidin-2-yl)propenoates proceeded highly diastereoselectively. The previously unknown absolute configuration of optically pure 1,2-dianilino-1,2-diphenylethane was determined from the absolute configuration of the cycloadducts. What diastereotopic olefin face of the α,β-unsaturated ester was attacked by the ylide was found to depend dramatically upon the nature of N substituents of the chiral controller as well as upon the bulkiness of the ester moiety of the ylide.

Introduction

Despite its potentially great utility in the synthesis of heterocycles, asymmetric 1,3-dipolar cycloaddition has been the subject of few reports.[1] Nitrones and nitrile oxides are among the 1,3-dipoles that have been relatively widely applied synthetically.[2,3] Because few examples of efficient Lewis acid catalyzed stereocontrol of 1,3-dipolar cycloaddition are known,[1] the only way to achieve a high degree of asymmetric induction in 1,3-dipolar cycloaddition is by employing suitably designed chiral dipoles and dipolarophiles.

α,β-Unsaturated carbonyl compounds bearing a chiral controller are attractive intermediates for use in synthetic chemistry because they can not only be utilized as acceptor molecules in nucleophilic carbon-carbon bond-forming reactions but also serve as activated olefinic dipolarophiles

Scheme I



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[§] Faculty of Education.

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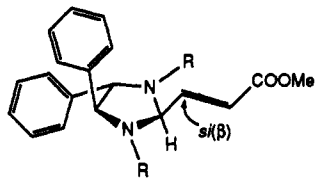
Scheme II[a]



[a] re(β) face is sterically hindered if the olefin assumes as an anti-periplanar conformation.

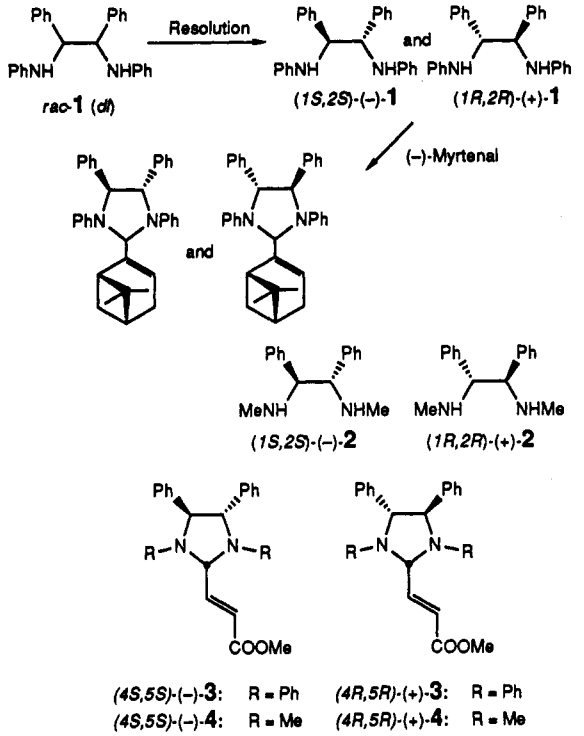
or dienophiles in cycloadditions that proceed under HOMO (dipole)–LUMO (dipolarophile) control.

We recently reported[4] the asymmetric cycloaddition of azomethine ylides[5] to α,β-unsaturated esters bearing an aminal chiral controller at the β position.[6,7] Among such esters, bicyclic aminal A was especially useful because the pure enantiomer could be synthesized from proline. The high diastereoselectivity of its cycloadditions was also noteworthy. The exclusive participation of the thermodynamically less stable syn-periplanar conformer A_2 rather than the more stable anti-periplanar conformer A_1 was observed. Only the *si*(β) face of the unsaturated ester was open to attack by ylides (Scheme I). The intermediacy of a chelation-stabilized transition state may have been responsible for the *si*(β) face selectivity.[4]

We have studied the behavior of α,β-unsaturated esters bearing an imidazolidine chiral auxiliary derived from a C_2-symmetric 1,2-diamine. Because both N substituents R of the 1,3-disubstituted *trans*-4,5-diphenylimidazolidine ring should arrange themselves trans to the adjacent *C*-phenyl groups, one side of the olefin face should be sterically shielded from attack by a 1,3-dipole (Scheme II).

The application of C_2-symmetric 1,2-diamine chiral controllers in asymmetric synthesis is of current interest.[8] To the best of our knowledge, however, no reports that deal with 1,3-dipolar cycloadditions to α,β-unsaturated carbonyl compounds bearing C_2-symmetric imidazolidine chiral controllers have appeared.

Scheme III



In the work described here, two α,β-unsaturated esters bearing a C_2-symmetric imidazolidine chiral controller at the β-position were prepared, and the cycloaddition of N-metalated azomethine ylides derived from *N*-benzylideneglycinates to the esters was examined. What diastereotopic face was attacked by the ylide was found to be dependent upon the nature of the N substituents of the chiral controller as well as upon the bulkiness of the ester moiety of the ylide.

Results and Discussion

Synthesis of the Chiral α,β-Unsaturated Esters 3 and 4. The synthesis and resolution of racemic 1,2-dianilino-1,2-diphenylethane (*rac*-1) have been reported. Of the reported syntheses of *rac*-1,[9] the reductive coupling of *N*-benzylideneaniline induced by sodium metal in tetrahydrofuran (THF) was the most practical and stereoselective. *rac*-1 was obtained as the major product in quantitative yield.[10] An undesired contaminant, *meso*-1, was removed by a single recrystallization of the crude product from methanol. The optically pure enantiomers (−)-1 and (+)-1 were separated by a modified (see Experimental Section) preferential crystallization procedure (Scheme III).[11,12] The optical rotations of (−)-1 and (+)-1 so obtained were lower than those reported: (+)-1 $[\alpha]^{25}_D$ +176.0° (*c* 1.00, benzene) [lit.[12] $[\alpha]^{18}_D$ +200° (*c* 1.53, benzene)]; (−)-1 $[\alpha]^{25}_D$ +180.0° (*c* 1.00, benzene) [lit.[12] $[\alpha]^{22}_D$

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−204° (*c* 1.60, benzene)]. However, because (1) repeated crystallization did not improve the optical purity, (2) condensation of either enantiomer with (−)-myrtenal provided a pure diastereomeric product in each case (see Experimental Section), and (3) similar condensation of *rac*-**1** with (−)-myrtenal gave a 1:1 mixture of the same two diastereomeric products, the purity of the enantiomers was established. The absolute configurations of (−)-**1** and (+)-**1** were previously unknown. Enantiomer (−)-**1** was found to be the 1*S*,2*S* enantiomer on the basis of the X-ray crystallographic analysis of a derivative, as described below.

Both enantiomers of 1,2-bis(methylamino)-1,2-diphenylethane ((1*S*,2*S*)-(−)-**2** and (1*R*,2*R*)-(+)-**2**)[7] were prepared in excellent yield by a modified two-step procedure that involved the N-ethoxycarbonylation of the known enantiomers of 1,2-diamino-1,2-diphenylethane[8c,13] and subsequent reduction with lithium aluminum hydride. The enantiomeric purity of (1*S*,2*S*)-(−)-**2** and (1*R*,2*R*)-(+)-**2** was determined by analysis of the derivatives (−)-**4** and (+)-**4** by HPLC with a chiral Chiralcel OD column (Daicel Chemical Co Ltd.).

Condensation of the 1,2-diamines (−)-**1** and (+)-**1** with methyl (*E*)-4-oxo-2-butenoate took place smoothly in refluxing toluene with continuous removal of water as the water–toluene azeotrope or in refluxing chloroform in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) to give methyl (*E*)-3-(1,3,4,5-tetraphenylimidazolidin-2-yl)propenoates ((−)-**3** and (+)-**3**), respectively, in 88% yield (Scheme III). Compound **3** is sufficiently stable to be purified by silica gel column chromatography. Such high chemical stability is presumably a result of the steric congestion in the vicinity of the aminal functional group.

Similar condensations of the *N*-methyl derivatives (1*S*,2*S*)-(−)-**2** and (1*R*,2*R*)-(+)-**2** in the presence of pyridinium *p*-toluenesulfonate (PPTS) were complete in 10 min at room temperature and gave quantitative yields of the methyl (*E*)-3-(1,3-dimethyl-4,5-diphenylimidazolidin-2-yl)propenoates ((1*S*,2*S*)-(−)-**4** and (1*R*,2*R*)-(+)-**4**), respectively, after silica gel column chromatography. Although the pure aminal **4** is sufficiently stable to be stored at room temperature, if not fully purified it undergoes slow decomposition to dark-colored products.

The optically inactive α,β-unsaturated esters *rac*-**3** and *rac*-**4** were similarly prepared. X-ray crystallographic analysis of the two esters gave useful information on the conformations of the imidazolidine rings. As shown in Figure 1, in the solid state the imidazolidine ring of the *N*-phenyl-substituted ester *rac*-**3** is relatively flat compared to that of the *N*-methyl-substituted ester *rac*-**4**. The rather flat geometry of the imidazolidine ring of *rac*-**3** is probably a result of the conjugation between the *N*-phenyl planes and the unshared electron pair of the nitrogen.

Such anilino type conjugation of *rac*-**3** in the solid state is also operating in solution. Thus, the ^{1}H NMR spectra of the esters show that H-2, H-4, and H-5 of *rac*-**3** are much more deshielded (for H-2, δ = 6.15; for H-4 and H-5, δ = 4.71, 4.76) than the corresponding protons of *rac*-**4** (for H-2, δ = 4.34; for H-4 and H-5, δ = 3.59, 3.71). Inspection of molecular models shows that these hydrogens lie in the middle of the deshielding zone of the *N*-phenyl substituents if the conformation of *rac*-**3** in solution is similar to that in the solid state (Figure 1).

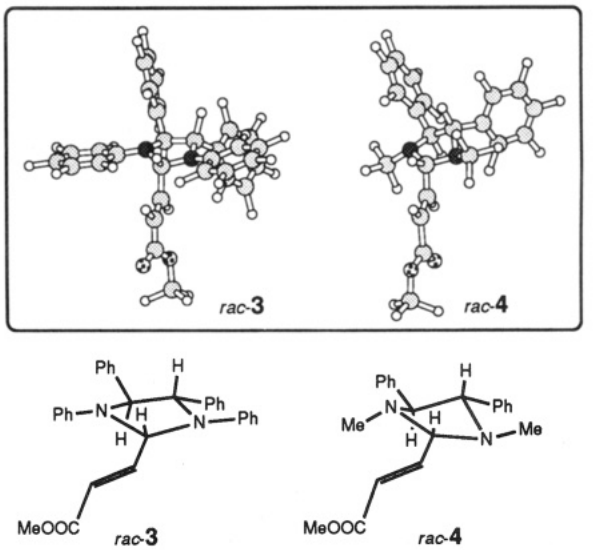

Figure 1. Stable conformations of the imidazolidine rings of *rac*-**3** and *rac*-**4** in the solid state (above, space-filling model; below, wire frame model).

The widely spaced *N*-phenyl substituents of *rac*-**3** seem to unable to efficiently hinder the approach of a dipole to either of the diastereotopic faces of the carbon–carbon double bond of the α,β-unsaturated ester moiety. On the other hand, the *N*-methyl derivative *rac*-**4** assumes a twisted envelope conformation in the solid state (Figure 1) in which both nitrogens are pyramidal. In this case, attack of a dipole at the β carbon of the α,β-unsaturated ester seems to be effectively restricted by one of the *N*-methyl groups. The significance of these points will be discussed later.

What role the conformation of the α,β-unsaturated ester moiety plays in the diastereoselectivity of the cycloaddition remains unclear. The α,β-unsaturated ester moiety of *rac*-**3** assumes an s-trans conformation in the solid state, whereas that of *rac*-**4** assumes an s-cis conformation. The s-cis conformation is that assumed in the transition state of cycloaddition, as described below.

Cycloadditions of N-Lithiated Azomethine Ylides to α,β-Unsaturated Esters *rac*-3 and *rac*-4. α,β-Unsaturated esters *rac*-**3** and *rac*-**4** served as dipolarophiles for the cycloaddition of N-metalated azomethine ylides. The N-lithiated azomethine ylide B (R′ = Me, M = Li) was generated from methyl (benzylideneamino)acetate (**5**, R′ = Me) by treatment with LiBr and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF.[14] The reaction of the ylide with the *N*-phenyl-substituted α,β-unsaturated ester *rac*-**3** at room temperature for 6 h gave an 85:15 mixture of two diastereomeric cycloadducts, *rac*-**6a** and *rac*-**6a′**, which were separated by silica gel column chromatography (Scheme IV). The relative configurations of the pyrrolidine rings of *rac*-**6a** and *rac*-**6a′** were established from spectroscopic data (see Experimental Section).

The yield of cycloadducts was found to be highly sensitive to methanol that had been entrapped in *rac*-**3** during its purification by recrystallization.[15] Therefore, before use, *rac*-**3** was freed of methanol by heating under reduced pressure.

A higher diastereomeric ratio, *rac*-**6a**/*rac*-**6a′** = 91:9, was observed when the reaction was performed at −78 °C

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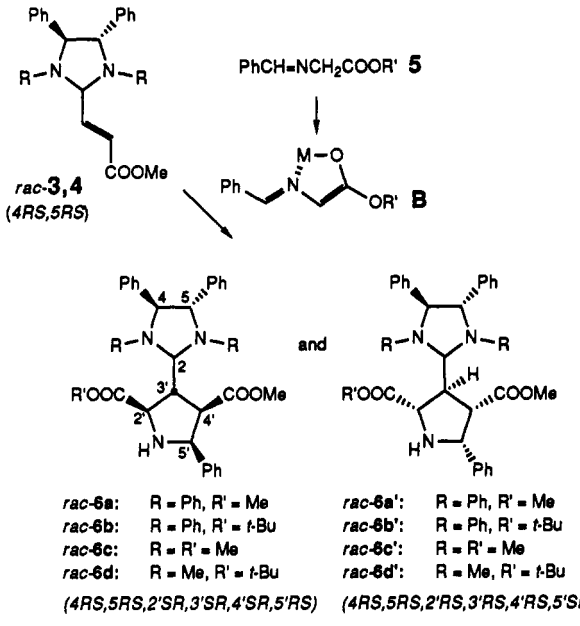
(15) The addition of 1 equiv of MeOH to the reaction mixture slowed the rate of reaction and led to the formation of many side products. At −78 °C, in the presence of MeOH, *rac*-**3** was quantitatively recovered.

Table I. Asymmetric 1,3-Dipolar Cycloaddition of N-Metalated Azomethine Ylides B to Chiral α,β-Unsaturated Esters 3 and 4[a]

entry	base (equiv)	imine 5 (equiv)	olefin	reaction conditions T (°C)	reaction conditions t (h)	product(s)	yield (%)[b]	isomer ratio[c]
1	LiBr/DBU (2.0/1.0)	R = Me (2.0)	3	rt	6	6a + 6a′	94	85:15
2	LiBr/DBU (1.5/1.0)	R = Me (1.5)	3	−78	24	6a + 6a′	79	91:9
3	LDA/MeOH (1.5/1.0)	R = Me (1.5)	3	0	1	6a + 6a′	97	87:13
4	LDA/MeOH (1.5/1.0)	R = Me (1.5)	3	−78	1.5	6a + 6a′	89	96:4
5	LDA/t-BuOH (1.5/1.0)	R = Me (1.5)	3	−78	1.5	6a + 6a′	80	96:4
6	n-BuLi (1.5)	R = t-Bu (1.5)	3	rt	21	6b + 6b′	61	45:55
7	n-BuLi (1.2)	R = t-Bu (1.5)	3	−78	2	6b + 6b′	20	20:80
8	LiBr/DBU (1.5/1.0)	R = Me (1.5)	4	rt	2	6c′	90	one product
9	LiBr/DBU (1.5/1.0)	R = Me (1.5)	4	−78	5.5	6c′	80	one product
10	LDA (1.5)	R = Me (1.5)	4	−78	5.5	d		
11	LDA/MeOH (1.5/1.0)	R = Me (1.5)	4	−78	1	6c′	98	one product
12	n-BuLi (1.3)	R = Me (1.2)	4	−78	2	d		
13	LiBr/DBU (2.0/1.0)	R = t-Bu (2.0)	4	rt	40 min	6d′	94	one product
14	n-BuLi/MeOH (1.5/1.5)	R = t-Bu (1.2)	4	−78	2	6d′	49	one product

[a] All reactions were performed in THF with 1 equiv of olefin 3 or 4. [b] Isolated yield. In all cases, the unreacted olefin 3 or 4 was recovered quantitatively. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Complex mixture of products.

Scheme IV



(Table I, entries 1, 2). Because ylide B (R′ = Me, M = Li) showed reduced reactivity toward *rac*-3 when generated from 5 by treatment with LiBr and NEt_3,[14] that method of azomethine ylide generation was abandoned.

Previously, it was reported[16] that the reactions of α,β-unsaturated esters like acrylates and crotonates with the ylide B (M = Li) generated from methyl (benzylideneamino)acetate (5, R′ = Me) by the action of lithium diisopropylamide (LDA) in THF provided irreproducible yields of cycloadducts. In the reaction of *rac*-3, similar difficulties, i.e., (1) formation of complex mixtures of products, (2) recovery of 3 even after prolonged reaction, (3) unsatisfactory yields of *rac*-6a and *rac*-6a′, (4) a low *rac*-6a/*rac*-6a′ ratio (60:40 to 80:20), and (5) lack of reproducible results, were encountered.

However, constantly high yields (>80%) and a satisfactory diastereomeric excess (92% de) were obtained when the ylide B (R′ = Me, M = Li) generated by the reaction of 5 with LDA in THF at −78 °C was pretreated with an equimolar amount of an alcohol and the cycloaddition to *rac*-3 was performed at that temperature (entries 3–5). The results are in striking contrast to those obtained by the use of DBU, mentioned above. The bulkiness of the alcohol used was not important because methanol and *tert*-butyl alcohol afforded comparable results. That the diastereoselectivity could be improved by the use of an additive was observed previously in the Michael addition of lithiated camphor imines of aminoacetates.[17]

The reaction of the azomethine ylide B (R′ = *t*-Bu, M = Li) with *rac*-3 gave quite different results. The reversible generation of ylide B (R′ = *t*-Bu, M = Li) by the use of LiBr and DBU was totally ineffective. When generated from the *tert*-butyl ester 5 (R′ = *t*-Bu) by treatment with butyllithium in THF, the ylide B (R′ = *t*-Bu, M = Li) was less reactive than the ylide B (R′ = Me, M = Li), and the *rac*-6b/*rac*-6b′ product ratio was much lower (entry 6). No significant differences in reactivity and diastereoselectivity were observed in the reactions shown in entries 6 and 7 when they were performed in the presence of an alcohol additive. Reaction at −78 °C gave an 80:20 mixture of diastereomers, albeit in 20% overall yield. However, surprisingly, the major product was not *rac*-6b but *rac*-6b′ (entry 7). The reasons for this reversed diastereoselectivity will be discussed below. The relative configurations of the pyrrolidine rings of *rac*-6b and *rac*-6b′ were assigned on the basis of the spectroscopic data (see Experimental Section). The determination of their absolute configurations will be discussed later.

The *N*-magnesioazomethine ylide B (R′ = Me, M = MgCl),[18] generated by the reaction of 5 with *tert*-butylmagnesium chloride in THF, also was only slightly reactive toward *rac*-3 (room temperature, 17 h, 22% overall yield, *rac*-6a/*rac*-6a′ = 61:39).

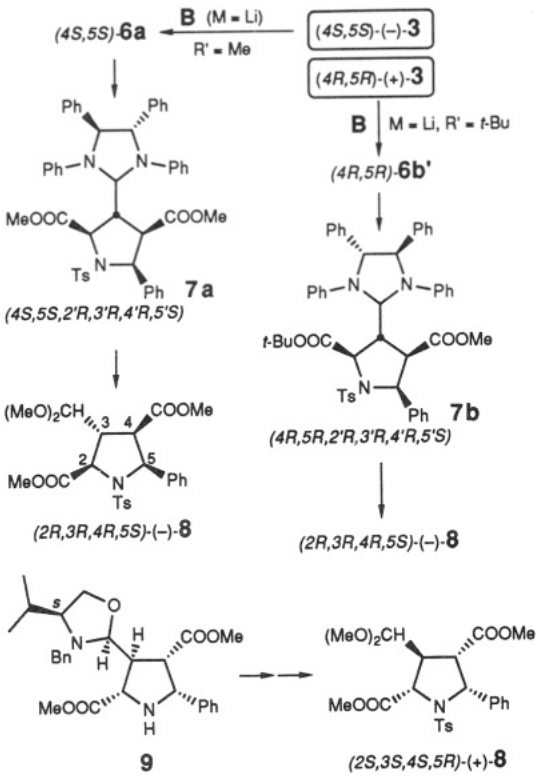
The reaction of the *N*-methyl-substituted α,β-unsaturated ester *rac*-4 with the ylide B (R′ = Me, M = Li) generated from 5 by treatment with LiBr and DBU gave excellent yields (>80%) of the corresponding cycloadduct, *rac*-6c, as single diastereomer (Scheme IV and Tables I, entries 8, 9). That the product was assigned *rac*-6c′, not *rac*-6c, indicated that the *N*-phenyl α,β-unsaturated ester *rac*-3 and the *N*-methyl α,β-unsaturated ester *rac*-4 were

(16) The reaction produced a complex mixture of products. Addition of a few equivalents of water to the reaction mixture reduced the number of products (see ref. 14).

(17) Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301–1304. Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875–2883.

(18) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411–4417.

Scheme V



attacked by ylide B from opposite diastereotopic faces.

The ylide generated by the use of LDA or butyllithium alone reacted with *rac*-**4** to yield a complex mixture of products (entries 10, 12). However, pretreatment with methanol again improved the chemical yield and diastereoselectivity of the cycloaddition (entry 11). In contrast with the extremely low reactivity displayed by *rac*-**3** toward the *tert*-butyl ester ylide B (R′ = *t*-Bu, M = Li), *rac*-**4** was sufficiently reactive to give *rac*-**6d′** in high yield as the sole diastereomer (entries 13, 14), even at room temperature (entry 13).

Enantioselective Synthesis of Pyrrolidines and Determination of Their Absolute Configurations. A mixture of two optically active cycloadducts, **6a** and **6a′**, was obtained from the reaction of the ylide B (R′ = Me, M = Li) and the optically pure α,β-unsaturated ester (−)-**3**. Diastereomer **6a**, the major product, was separated from **6a′** by column chromatography (Scheme V). The absolute configurations of both the starting α,β-unsaturated ester (−)-**3** and the pyrrolidine ring of cycloadduct **6a** were unknown at this stage. Therefore, the pyrrolidine ring was detached from **6a** and its absolute configuration was determined. Compound **6a** was quantitatively tosylated to give **7a**, which was further transformed to acetal **8** by a literature procedure.[4] Earlier, it was reported[4b] that the absolute configuration of the cycloadduct **9** was determined by X-ray crystallography, and **9** was then converted to (2*S*,3*S*,4*S*,5*R*)-(+)-**8**.[4b] From the sign of its optical rotation and the result of HPLC analysis with a Chiral Pack OD column, the enantiomer **8** derived from **7a** was shown to be (2*R*,3*R*,4*R*,5*S*)-(−)-**8**.

Now that the pyrrolidine ring of **7a** was known to possess the 2*R*,3*R*,4*R*,5*S* configuration, an X-ray structure analysis of **7a** was performed. In Figure 2, the X-ray determined 4*S*,5*S*,2′*R*,3′*R*,4′*R*,5′*S* configuration of **7a** is depicted with a space-filling molecular model. Thus, (−)-1,2-dianilino-1,2-diphenylethane [(−)-**1**] was the 1*S*,2*S* stereoisomer, and, therefore, (−)-**3** was the 4*S*,5*S* stereoisomer.

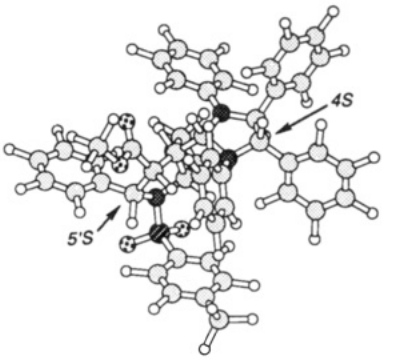
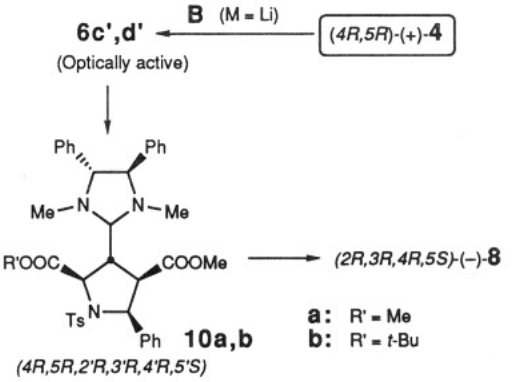


Figure 2. X-ray-determined stereostructure of **7a** (space-filling molecular model).

Scheme VI

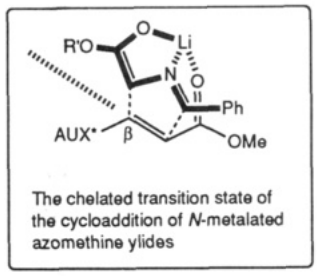


The major diastereomer **6b′** obtained from the reaction of (4*R*,5*R*)-(+)-**3**, the antipode of (4*S*,5*S*)-(−)-**3**, and the *tert*-butyl ester ylide B (R′ = *t*-Bu, M = Li) was found to be the 4*R*,5*R*,2′*R*,3′*R*,4′*R*,5′*S* stereoisomer on the basis of the results of the following experiments. Optically pure **6b′** was converted to the *N*-tosyl derivative **7b**. This was refluxed in methanol in the presence of a catalytic amount of concentrated sulfuric acid. Both conversion of the aminal to a dimethyl acetal and transesterification took place to give **8** in quantitative yield (Scheme V). The retention time of the enantiomer **8** on the chiral HPLC column indicated that it was (2*R*,3*R*,4*R*,5*S*)-(−)-**8**.

It was now clear that the methyl ester ylide B (R′ = Me) and the *tert*-butyl ester ylide B (R′ = *t*-Bu) attacked opposite diastereotopic faces, the *si*(β) and *re*(β) faces respectively, of the *N*-phenyl-substituted α,β-unsaturated ester (4*S*,5*S*)-(−)-**3**.

It was found that the methyl ester ylide B (R′ = Me, M = Li) showed opposite diastereofacial selectivities in its reaction with the *N*-phenyl-substituted ester **3** and the *N*-methyl-substituted ester **4**. Reaction of B (R′ = Me, M = Li) with (4*R*,5*R*)-(+)-**4** provided the optically pure cycloadduct **6c′** after purification by column chromatography. This was then tosylated in the aforementioned manner to give **10a** (Scheme VI). Treatment of **10a** with methanol containing a catalytic amount of sulfuric acid gave the acetal (2*R*,3*R*,4*R*,5*S*)-(−)-**8**.

The optically pure cycloadduct **6d′** obtained from the reaction of the *tert*-butyl ester ylide B (R′ = *t*-Bu, M = Li) with (4*R*,5*R*)-(+)-**4** was identified as the 4*R*,5*R*,2′*R*,3′*R*,4′*R*,5′*S* stereoisomer because it could be similarly transformed to the *N*-tosyl derivative **10b** and eventually to (2*R*,3*R*,4*R*,5*S*)-(−)-**8** (Scheme VI). Thus, the methyl ester ylide B (R′ = Me) and the *tert*-butyl ester ylide B (R′ = *t*-Bu) both attacked the same diastereotopic face of the *N*-methyl-substituted ester **4**. In contrast, when allowed to react with the *N*-phenyl-substituted ester **3**,



The chelated transition state of the cycloaddition of *N*-metalated azomethine ylides

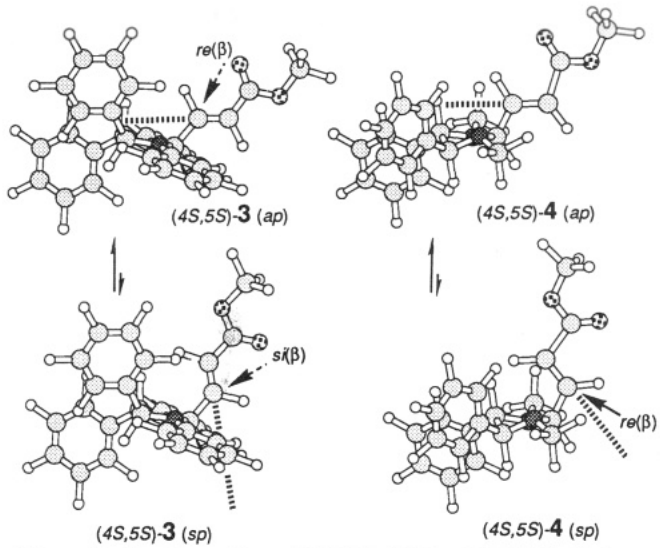


Figure 3. Conformations of (4*S*,5*S*)-(−)-**3** and (4*S*,5*S*)-(−)-**4**, *ap* and *sp* conformers, assumed in the transition state of cycloaddition.

each ylide preferentially attacked a different diastereotopic face.

Nature of the Transition State. It has been proposed that the cycloaddition of N-metalated azomethine ylides to α,β-unsaturated ester proceeds through a rigid chelation-stabilized transition state, as shown in the inset in Figure 3.[17-19] In the transition state, the α,β-unsaturated ester assumes an *s-cis* conformation when the alkoxy group (R′O) of the ylide B and the β substituent of the α,β-unsaturated ester, a chiral auxiliary (AUX*) in this case, are sufficiently bulky.

In Figure 3, the **X**-ray crystallographically determined structures of the anti-periplanar conformers, (4*S*,5*S*)-**3** (*ap*) and (4*S*,5*S*)-**4** (*ap*), are depicted again by space-filling molecular models (top). Therein the original s-trans conformer of **3** has been converted to the s-cis conformer by rotating the methoxycarbonyl group 180° about the C(α)–C(carbonyl) bond. The bottom two structures represent the syn-periplanar conformers (4*S*,5*S*)-**3** (*sp*) and (4*S*,5*S*)-**4** (*sp*), which were produced from (4*S*,5*S*)-**3** (*sp*) and (4*S*,5*S*)-**4** (*sp*), respectively, by rotating the methoxycarbonyl group 180° about the C(2)–C(β) bond.

Although the four molecular models shown in Figure 3 represent relatively stable ground-state conformations, it is still important to recognize differences in their respective topologies in a consideration of the transition state. The imidazolidine ring of the *N*-phenyl-substituted α,β-unsaturated ester **3** is somewhat flat. Consequently, the two *C*-phenyl groups protrude out of the plane of the imidazolidine ring, while the planes of the two *N*-phenyl groups are nearly coplanar with that of the imidazolidine ring. Therefore, it can not be expected that the *N*-phenyl groups will effectively differentiate attack by the N-metalated azomethine ylide B on the *si*(β) and *re*(β) faces.

The imidazolidine ring of the *N*-methyl-substituted α,β-unsaturated ester **4** assumes a zigzag shape so that the *C*-phenyl groups are accommodated in the imidazolidine plane and the *N*-methyls protrude. Therefore, one side of each of the olefin faces is sterically hindered by the adjacent cis *N*-methyl substituent.

Attack of the methyl ester ylide B (R′ = Me, Li) on (4*S*,5*S*)-**3** at the *si*(β) face of the thermodynamically more stable conformers **3** (*ap*) appears to be difficult as a result of the pronounced mutual steric repulsion of the R′O and 4-Ph moieties. Attack at the *re*(β) face of **3** (*ap*) is also sterically hindered. Thus, an opportunity exists for the thermodynamically less stable conformer **3** (*sp*) to participate in the cycloaddition. Because approach to the *re*(β) face of **3** (*sp*) is sterically hindered by the 4-Ph moiety, attack at the *si*(β) face of **3** (*sp*) occurs preferentially to give (4*S*,5*S*,2′*R*,3′*R*,4′*R*,5′*S*)-**6a**.

When ylide B bears a bulky *tert*-butyl group (R′ = *t*-Bu, M = Li), the steric effects of the *N*-phenyl substituents inhibit the involvement of **3** (*sp*) in the cycloaddition. The rate and the diastereoselectivity of the cycloaddition decrease. The *re*(β) face of **3** (*ap*) is relatively more open to the attack by N-lithiated ylide B (R′O = *t*-BuO).

In the case of the *N*-methyl-substituted α,β-unsaturated ester (4*S*,5*S*)-**4**, the approach of the ylide B (R′ = Me or *t*-Bu) to either the *si*(β) or *re*(β) face of the *ap* conformer is seriously hindered, by the 4-Ph group in the former instance and by the *N*-Me substituents in the latter instance. Approach to the *re*(β) face of **4** (*sp*) is much more favorable. Products of attack at the *re*(β) face are, in fact, those that are obtained.

In conclusion, the presence of a chiral C_2-symmetric imidazolidine controller at the β position of the α,β-unsaturated esters **3** and **4** insured that a satisfactory degree of asymmetric induction was observed in the cycloaddition of N-metalated azomethine ylides B to the esters. The dramatic differences in the observed diastereoselectivity, which depend upon the nature of the N substituents of the olefins and the bulkiness of the ester moiety of ylides B, indicate that some degree of stereocontrol can be imposed. Other asymmetric reactions utilizing the chiral olefins **3** and **4** are under study. The results of these studies will be reported in due time.

Experimental Section

General. Melting points are uncorrected. The X-ray diffraction data were collected with graphite-monochromatized Mo Kα radiation (λ = 0.710 69). Structure analyses were performed with a TEXSAN system.[20] The structure was solved by the MITHRIL[21] direct method and defined by full-matrix least squares. Wako C-200, Wako C-300, and Merck silica gel 60 were used for preparative column chromatography. High performance liquid chromatography (HPLC) was performed with a Chiralcel OD column (Daicel Chemical Co Ltd.).

Optical Resolution of (1*RS*,2*RS*)-1,2-Dianilino-1,2-diphenylethane (*rac*-1). A modified procedure for the isolation of optically pure (1*S*,2*S*)-1 and (1*R*,2*R*)-1 by preferential crystallization was used.[11] Thus, seed crystals of (+)-1 were prepared.[12] To a hot solution of *rac*-1 (3.6 g) in MeOH (300 mL) was added a piece of seed crystal. The mixture was kept at 45 °C for 24 h. The prismatic crystals formed were collected and washed with a small amount of cold MeOH to give 0.35–0.5 g of (+)-1. A new portion of *rac*-1 (equal weight) was added to the filtrate and dissolved by heating under reflux. The mixture was kept at 45

(19) (a) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 869–874. (b) Kanemasa, S.; Yoshioka, M.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2196–2200. (c) Kanemasa, S.; Uchida, O.; Wada, E.; Yamamoto, H. *Chem. Lett.* **1990**, 105–108.

(20) TEXSAN; TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).

(21) Gilmore, C. J. *J. Appl. Crystallogr.* **1984**, *17*, 42.

°C for 24 h. The crystals formed (0.35–0.5 g) were collected and washed with a small amount of cold MeOH to give (−)-1. Each enantiomer (+)-1 and (−)-1 was prepared by repeating this procedure. Each enantiomer was purified by crystallization from MeOH. (1*R*,2*R*)-(+)-1: $[\alpha]^{20}_D$ +127.9° (*c* 0.50, $CHCl_3$); $[\alpha]^{25}_D$ +179.0° (*c* 1.00, benzene) [lit.[12] $[\alpha]^{18}_D$ +200° (*c* 1.53, benzene)]. (1*S*,2*S*)-(−)-1: $[\alpha]^{21}_D$ −125.8° (*c* 1.03, $CHCl_3$); $[\alpha]^{25}_D$ −180.0° (*c* 1.00, benzene) [lit.[12] $[\alpha]^{22}_D$ −204° (*c* 1.60, benzene)].

Condensation of (1*R*,2*R*)-(+)-1 or (1*S*,2*S*)-(−)-1 with (−)-Myrtenal. A mixture of (+)-1 (0.364 g, 1 mmol), (−)-myrtenal (0.46 mL, 3 mmol), and a catalytic amount of *p*-toluenesulfonic acid was refluxed in toluene (10 mL) for 12 h. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 20:1) to give a pure diastereomer of the condensation product (0.333 g, 67%): colorless prisms (MeOH); mp 93–95 °C; ^{1}H NMR (C_6D_6) δ 0.19, 1.12 (each s, each 3 H, Me), 1.32 (d, J_{gem} = 8.4 Hz, 1 H, one of H-7′), 1.87 (m, 1 H, H-5′), 2.22 (m, 2 H, H-4′), 2.45 (dt, J_{gem} = 8.4 and $J_{7'-1'}$ = $J_{7'-5'}$ = 5.5 Hz, 1 H, the other of H-7′), 2.64 (dt, $J_{1'-7'}$ = $J_{1'-5'}$ = 5.5 and $J_{1'-3'}$ = 1.5 Hz, 1 H, H-1′), 4.86, 4.99 (each d, J_{4-5} = 7.7 Hz, each 1 H, H-4 and H-5), 5.79 (br s, 1 H, H-3′), 6.11 (s, 1 H, H-2), 6.6–7.3 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.77, 26.52 (each Me), 31.36, 31.72, 37.97, 40.06, 43.20 (CH_2, CH, and C), 70.44, 73.03 (C-4 and C-5), 83.42 (C-2), 114.58, 118.17, 118.74, 119.20, 125.34, 126.46, 127.45, 127.64, 127.73, 128.00, 128.53, 128.58, 128.65, 140.25, 140.34, 143.19, 147.57, 148.13 (Ph and olefinic); MS *m*/*z* (rel intensity) 496 (M^+, 12), 376 (31), 375 (base peak), 315 (48), 274 (29), 272 (16), 247 (17), 246 (80), 180 (21), 104 (15), 77 (23). Anal. Calcd for $C_{36}H_{36}N_2$: C, 87.05; H, 7.31; N, 5.64. Found: C, 87.28; H, 7.26; N, 5.70.

Similarly, (−)-1 and (−)-myrtenal gave another diastereomer of the condensation product (62%): colorless prisms (MeOH); mp 96–98 °C; ^{1}H NMR (C_6D_6) δ 0.15, (d, J_{gem} = 8.8 Hz, 1 H, one of H-7′), 0.97, 1.25 (each s, each 3 H, Me), 1.81 (m, 1 H, H-5′), 1.97 (dt, J_{gem} = 8.8 and $J_{7'-1'}$ = $J_{7'-5'}$ = 5.5 Hz, 1 H, the other of H-7′), 2.13, 2.22 (each dt, J_{gem} = 18.0 and $J_{4'-3'}$ = $J_{4'-5'}$ = 2.9 Hz, each 1 H, H-4′), 2.57 (dt, $J_{1'-7'}$ = $J_{1'-5'}$ = 5.5 and $J_{1'-3'}$ = 1.5 Hz, 1 H, H-1′), 4.81, 4.92 (each d, J_{4-5} = 7.3 Hz, each 1 H, H-4 and H-5), 5.68 (br s, 1 H, H-3′), 6.05 (s, 1 H, H-2), 6.6–7.3 (m, 20 H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.67, 26.29 (each Me), 30.18, 31.36, 38.10, 40.64, 42.27 (CH_2, CH, and q-C), 70.74, 73.04 (C-4 and C-5), 84.84 (C-2), 114.68, 118.12, 118.89, 119.31, 125.71, 126.40, 127.54, 127.67, 128.51, 128.53, 128.58, 140.24, 140.67, 143.61, 146.98, 147.76 (Ph and olefinic); MS *m*/*z* (rel intensity) 496 (M^+, 17), 376 (30), 375 (base peak), 315 (52), 274 (30), 272 (13), 247 (17), 246 (86), 180 (15), 104 (14), 77 (23). Anal. Calcd for $C_{36}H_{36}N_2$: C, 87.05; H, 7.31; N, 5.64. Found: C, 87.07; H, 7.39; N, 5.62.

(1*RS*,2*RS*)-1,2-Bis(methylamino)-1,2-diphenylethane (*rac*-2). To a solution of *rac*-1,2-diphenyl-1,2-ethanediamine[13] (0.106 g, 0.5 mmol) in EtOH (2 mL) was added ethyl chloroformate (0.48 mL, 5 mmol). The mixture was stirred at room temperature for 10 min, then was poured into ice water (20 mL), and was extracted with CH_2Cl_2 (20 mL × 2). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (0.172 g, 97%) was almost pure diethyl *N*,*N*′-(1,2-diphenylethylene)-biscarbamate [^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J* = 6.7 Hz, 3 H × 2, COOEt), 4.19 (q, *J* = 6.7 Hz, 2 H × 2, COOEt), 5.02 (m, 2 H, CH), 6.28 (br, 2 H, NH), 7.0–7.3 (m, 10 H, Ph)]. It was used in the following reaction without further purification.

To a suspension of $LiAlH_4$ (0.086 g, 2.26 mmol) in dry THF (1.5 mL) was added drop-by-drop at 0 °C, a solution of the carbamate (0.134 g, 0.38 mmol) in THF (1.5 mL). The mixture was refluxed for 9.5 h and then was cooled to 0 °C. EtOH (2 mL) and aqueous Na_2CO_3 were added. The mixture was extracted with Et_2O (20 mL × 4). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give *rac*-2 (0.088 g, 98%). From optically pure (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine,[13] optically pure (1*R*,2*R*)-(+)-2 was obtained: $[\alpha]^{23}_D$ +16.4° (*c* 1.34, $CHCl_3$) [lit.[7] $[\alpha]^{25}_D$ +20° (*c* 0.15, $CHCl_3$)].

Methyl (4*RS*,5*RS*)-(*E*)-3-(1,3,4,5-Tetraphenylimidazolidin-2-yl)propenoate (*rac*-3). A solution of *rac*-1 (3.67 g, 10 mmol), methyl (*E*)-4-oxo-2-butenoate[22] (1.37 g, 12 mmol), a catalytic amount of PTSA, and $CHCl_3$ (30 mL) was refluxed for 5 h. The mixture was cooled to room temperature, and saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/CH_2Cl_2, 1:3) to give *rac*-3 (4.4 g, 96%): colorless prisms (MeOH); mp 202.5–203.5 °C; IR (KBr) 1720, 1590, 1490, 1265, 745, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H, COOMe), 4.71, 4.76 (each d, J_{4-5} = 7.3 Hz, each 1 H, H-4 and H-5), 6.15 (d, J_{2-CH} = 7.7 Hz, 1 H, H-2), 6.33 (d, J_{trans} = 15.8 Hz, 1 H, =CH(α)), 6.6–6.8 (m, 6 H, *o*- and *p*-H of NPh), 6.98 (dd, J_{trans} = 15.8 and J_{CH-2} = 7.7 Hz, 1 H, =CH(β)), 7.0–7.3 (m, 14 H, Ph); ^{13}C NMR ($CDCl_3$) δ 51.72 (COOMe), 69.99, 73.12 (each C-4 and C-5), 78.90 (C-2), 113.57, 118.50, 119.31, 120.28, 124.42, 126.72, 127.38, 127.87, 128.71, 128.75, 129.07, 138.63, 139.59, 143.09, 144.76, 145.87 (Ph and =CH), 166.20 (COOMe); MS *m*/*z* (rel intensity) 460 (M^+, 11), 375 (20), 280 (12), 279 (61), 221 (18), 220 (base peak), 181 (14), 180 (13), 104 (16), 77 (31). Anal. Calcd for $C_{31}H_{28}N_2O_2$: C, 80.84; H, 6.13; N, 6.08. Found: C, 80.70; H, 6.26; N, 6.10. Optically active samples, (4*S*,5*S*)-3 and (4*R*,5*R*)-3, were obtained starting from optically pure 1. (4*S*,5*S*)-(−)-3: $[\alpha]^{23}_D$ −218.4° (*c* 1.04, $CHCl_3$). (4*R*,5*R*)-(+)-3: $[\alpha]^{23}_D$ +223.9° (*c* 1.06, $CHCl_3$).

X-ray Structure Analysis of *rac*-3. A single crystal grown from MeOH had space group $P2_12_12_1$, *a* = 14.524 (7), *b* = 17.644 (6), and *c* = 9.9978 (4) Å, *V* = 2562 (2) Å^3, *Z* = 4. The final *R* factor was 0.043 for 1533 observed reflections.[23]

Methyl (4*RS*,5*RS*)-(*E*)-3-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)propenoate (*rac*-4). To a solution of *rac*-2 (2.58 g, 10.7 mmol) in CH_2Cl_2 (30 mL) was added methyl (*E*)-4-oxo-2-butenoate[22] (1.35 g, 11.8 mmol) at room temperature. After a few minutes, saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1). The solid so obtained was recrystallized (MeOH) to give *rac*-4 (2.13 g, 59%): colorless needles; mp 109–110 °C; IR (KBr) 1725, 1440, 1280, 765, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.26, 2.19 (each s, each 3 H, NMe), 3.59, 3.71 (each d, J_{4-5} = 8.4 Hz, each 1 H, H-4 and H-5), 3.79 (s, 3 H, COOMe), 4.34 (d, J_{2-CH} = 8.8 Hz, 1 H, H-2), 6.15 (d, J_{trans} = 15.4 Hz, 1 H, =CH(α)) 6.9–7.3 (m, 11 H, Ph and =CH(β)); ^{13}C NMR ($CDCl_3$) δ 34.50, 37.91 (each NMe), 51.67 (COOMe), 76.59, 77.94 (each C-4 and C-5), 84.81 (C-2), 123.26 (=CH(α)), 127.53, 127.63, 127.83, 128.09, 128.13, 128.16, 138.53, 138.93 (each Ph), 147.76 (=CH(β)), 166.53 (COOMe); MS *m*/*z* (rel intensity) 336 (M^+, 6), 335 (16), 251 (37), 218 (12), 217 (82), 159 (13), 158 (base peak), 98 (11). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.10, H, 7.05; N, 8.24.

Optically pure (4*R*,5*R*)-(+)-4 was obtained from optically pure (1*R*,2*R*)-(+)-2. (4*R*,5*R*)-(+)-4: $[\alpha]^{23}_D$ +45.0° (*c* 0.60, $CHCl_3$).

X-ray Structure Analysis of *rac*-4. A single crystal grown from MeOH had space group $P2_1/n$, *a* = 9.78 (2), *b* = 5.751 (6), and *c* = 33.33 (5) Å, β = 96.4 (1)°, *V* = 1902 (5) Å^3, *Z* = 4. The final *R* factor was 0.076 for 559 observed reflections.[23]

General Procedure for the Cycloadditions of N-Metalated Azomethine Ylides B to *rac*-3 and *rac*-4. Method 1. To a solution of *rac*-3 (0.231 g, 0.5 mmol), LiBr (0.065 g, 0.75 mmol), and dry THF (3 mL) were slowly added, by syringe, at −78 °C under N_2, a solution of methyl (benzylideneamino)acetate (0.133 g, 0.75 mmol) in THF (1 mL) and DBU (0.076 g, 0.5 mmol), in that order. The mixture was stirred at −78 °C for 24 h, then treated with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (20 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. A solution of the residue in hexane/EtOAc (2:1) was passed through a short column of silica gel. The eluate was concentrated in vacuo. ^{1}H NMR analysis of the residue (0.252 g, 79%) showed it to be a 91:9 mixture of diastereomers. The major diastereomer, *rac*-6a, was isolated by chromatography on silica gel (hexane/EtOAc, 4:1).

Method 2. To a solution of *i*-Pr_2NH (0.11 mL, 0.75 mmol) in

(22) Bohlmann, F.; Inhoffen, E. *Chem. Ber.* **1956**, *89*, 1276–1281.

(23) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

dry THF (3 mL) were added, drop-by-drop by syringe, at −78 °C under N_2, BuLi (1.55 M in hexane, 0.48 mL, 0.75 mmol), a solution of methyl (benzylideneamino)acetate (0.138 g, 0.75 mmol) in THF (1 mL), MeOH (0.013 mL, 0.5 mmol), and a solution of *rac*-3 (0.23 g, 0.5 mmol) in THF (1 mL), in that order. The mixture was stirred at −78 °C for 1.5 h, treated with saturated aqueous NH_4Cl, and extracted with Et_2O (20 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel column chromatography of the crude product gave ***rac*-6a** (0.285 g, 89%, 96:4). Results are listed in Table I.

***rac*-6a**: colorless prisms (MeOH); mp 167–168 °C; IR (KBr) 1740, 1600, 1500, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3 H, 4′-COOMe), 3.28 (dd, $J_{4'-5'}$ = 8.1 and $J_{4'-3'}$ = 4.4 Hz, 1 H, H-4′), 3.73 (s, 3 H, 2′-COOMe), 3.79 (dt, $J_{3'-2'}$ = 6.6 and $J_{3'-4'}$ = $J_{3'-2}$ = 4.4 Hz, 1 H, H-3′), 4.34 (d, $J_{2'-3'}$ = 6.6 Hz, 1 H, H-2′), 4.42 (d, $J_{5'-4'}$ = 8.1 Hz, 1 H, H-5′), 4.65, 4.99 (each d, J_{4-5} = 7.7 Hz, each 1 H, H-4 and H-5), 6.18 (d, $J_{2-3'}$ = 4.4 Hz, 1 H, H-2), 6.7–7.3 (m, 25 H, Ph); ^{13}C NMR ($CDCl_3$) δ 51.17, 52.25 (each COOMe), 53.00, 53.39 (C-3′ and C-4′), 62.83 (C-2′), 65.74 (C-5′), 71.26, 75.61 (C-4 and C-5), 79.81 (C-2), 116.21, 120.05, 120.89, 121.31, 126.72, 126.91, 127.56, 127.63, 127.74, 128.15, 128.43, 128.46, 128.79, 129.23, 138.44, 138.73, 139.91, 143.83, 148.30 (each Ph), 173.21, 173.60 (each COOMe); MS *m/z* (15 eV, rel intensity) 638 (M^+ + 1, 13), 456 (5), 377 (32), 376 (base peak), 279 (4). Anal. Calcd for $C_{41}H_{39}N_3O_4$: C, 77.21; H, 6.16; N, 6.59. Found: C, 77.33; H, 6.27; N, 6.83.

rac-**6a′**: colorless prisms (MeOH); mp 199–200 °C; IR (KBr) 1720, 1580, 1480, 730, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (s, 3 H, 4′-COOMe), 3.57 (dd, $J_{4'-5'}$ = 8.4 and $J_{4'-3'}$ = 5.1 Hz, 1 H, H-4′), 3.73 (ddd, $J_{3'-2'}$ = 8.8, $J_{3'-4'}$ = 5.1, and $J_{3'-2'}$ = 2.9 Hz, 1 H, H-3′), 3.91 (s, 3 H, 2′-COOMe), 4.09 (d, $J_{2'-3'}$ = 8.8 Hz, 1 H, H-2′), 4.60 (d, $J_{5'-4'}$ = 8.4 Hz, 1 H, H-5′), 4.82, 5.07 (each d, J_{4-5} = 7.6 Hz, each 1 H, H-4 and H-5), 6.52 (d, $J_{2-3'}$ = 2.9 Hz, 1 H, H-2), 6.6–7.4 (m, 25 H, Ph); ^{13}C NMR ($CDCl_3$) δ 50.97, 51.00, 51.79, 52.45 (COOMe × 2, C-3′ and C-4′), 62.06 (C-2′), 65.27 (C-5′), 69.69, 77.26 (C-4 and C-5), 78.17 (C-2), 116.91, 118.89, 119.35, 120.54, 126.48, 126.63, 127.34, 127.77, 127.87, 127.97, 128.04, 128.42, 128.66, 128.69, 129.33, 140.43, 142.95, 149.60 (each Ph), 172.39, 172.74 (each COOMe); MS *m/z* (rel intensity) 637 (M^+, 3), 376 (30), 375 (base peak), 272 (14), 180 (17), 104 (15), 77 (19). Anal. Calcd for $C_{31}H_{39}N_3O_4$: C, 77.21; H, 6.16; N, 6.59. Found: C, 77.49; H, 6.13; N, 6.59.

***rac*-6b′**: colorless prisms (MeOH); mp 180–182 °C; IR (KBr) 1730, 1600, 1590, 1155, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (s, 9 H, COOBu-*t*), 2.78 (s, 3 H, COOMe), 3.55 (dd, $J_{4'-5'}$ = 8.1 and $J_{4'-3'}$ = 5.1 Hz, 1 H, H-4′), 3.60 (ddd, $J_{3'-2'}$ = 9.2, $J_{3'-4'}$ = 5.1, and $J_{3'-2}$ = 2.6 Hz, 1 H, H-3′), 4.02 (d, $J_{2'-3'}$ = 9.2 Hz, 1 H, H-2′), 4.58 (d, $J_{5'-4'}$ = 8.1 Hz, 1 H, H-5′), 4.85, 5.09 (each d, J_{4-5} = 7.7 Hz, each 1 H, H-4 and H-5), 6.52 (d, $J_{2-3'}$ = 2.6 Hz, 1 H, H-2), 6.6–7.4 (m, 25 H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.31 (COOBu-*t*), 50.90 (C-3′), 51.24 (C-4′), 52.17 (COOMe), 62.69 (C-2′), 65.21 (C-5′), 69.39, 77.39 (C-4 and C-5), 78.21 (C-2), 82.30 (COOBu-*t*), 116.87, 118.61, 119.19, 120.40, 126.42, 126.52, 127.22, 127.79, 127.89, 127.93, 128.04, 128.36, 128.68, 128.74, 129.18, 137.84, 140.43, 140.76, 142.86, 149.80 (each Ph), 171.34, 172.48 (COOMe and COOBu-*t*); MS *m/z* (rel intensity) 680 (M^+ + 1, 5), 679 (M^+, 10), 498 (2), 497 (4), 377 (5), 376 (31), 375 (base peak), 321 (2). Anal. Calcd for $C_{44}H_{45}N_3O_4$: C, 77.73; H, 6.67; N, 6.18. Found: C, 77.46; H, 6.79; N, 6.18.

***rac*-6b**: colorless prisms (MeOH); mp 103–104 °C; IR (KBr) 1700, 1580, 1475, 1430, 1140, 730, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9 H, COOBu-*t*), 3.09 (s, 3 H, COOMe), 3.40 (dd, $J_{4'-5'}$ = 7.7 and $J_{4'-3'}$ = 3.7 Hz, 1 H, H-4′), 3.70 (ddd, $J_{3'-2'}$ = 7.0 and $J_{3'-2}$ = $J_{3'-4'}$ = 3.7 Hz, 1 H, H-3′), 4.22 (d, $J_{2'-3'}$ = 7.0 Hz, 1 H, H-2′), 4.28 (d, $J_{5'-4'}$ = 7.7 Hz, 1 H, H-5′), 4.67, 4.97 (each d, J_{4-5} = 8.1 Hz, each 1 H, H-4 and H-5), 6.16 (d, $J_{2-3'}$ = 3.7 Hz, 1 H, H-2), 6.7–7.3 (m, 25 H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.16 (COOBu-*t*), 51.11 (COOMe), 53.32 (C-3′), 54.84 (C-4′), 63.86 (C-2′), 65.80 (C-5′), 71.99, 74.66 (C-4 and C-5), 80.76 (C-2), 82.26 (COOBu-*t*), 115.84, 119.59, 121.49, 122.46, 126.68, 126.82, 127.54, 127.81, 128.13, 128.33, 128.49, 128.75, 128.82, 129.15, 137.91, 144.13, 147.80 (each Ph), 171.96, 173.27 (COOMe and COOBu-*t*); MS *m/z* (rel intensity) 679 (M^+, 16), 376 (32), 375 (base peak). Anal. Calcd for $C_{44}H_{45}N_3O_4$: C, 77.73; H, 6.67; N, 6.18. Found: C, 77.71; H, 6.56; N, 6.14.

***rac*-6c′**: colorless prisms (MeOH); mp 134–135 °C; IR (KBr) 1725, 1430, 1155, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10, 2.57 (each s, each 3 H, NMe), 3.10 (br, 1 H, NH), 3.20 (s, 3 H, 4′-COOMe), 3.26 (m, 1 H, H-3′), 3.69 (dd, $J_{4'-5'}$ = 7.7 and $J_{4'-3'}$ = 4.4 Hz, 1 H, H-4′), 3.75 (d, J_{4-5} = 9.0 Hz, 1 H, H-4), 3.87 (s, 3 H, 2′-COOMe), 3.98 (d, J_{5-4} = 9.0 Hz, 1 H, H-5), 4.17 (d, $J_{2'-3'}$ = 7.3 Hz, 1 H, H-2′), 4.25 (d, $J_{2-3'}$ = 2.2 Hz, 1 H, H-2), 4.85 (d, $J_{5'-4'}$ = 7.7 Hz, 1 H, H-5′), 7.2–7.4 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 35.29, 42.53 (each NMe), 51.24 (C-3′), 52.08 (C-4′), 52.35, 52.73 (each COOMe), 63.15 (C-2′), 66.72 (C-5′), 74.74, 77.62 (C-4 and C-5), 85.76 (C-2), 127.48, 127.77, 128.10, 128.25, 128.51, 128.64, 128.85, 138.51, 138.54, 139.49 (each Ph), 173.51, 173.77 (each COOMe); MS *m/z* (rel intensity) 514 (M^+ + 1, 5), 513 (M^+, 12), 252 (19), 251 (base peak), 178 (3). Anal. Calcd for $C_{31}H_{35}N_3O_4$: C, 72.49; H, 6.87; N, 8.14. Found: C, 72.28; H, 6.87; N, 8.04.

***rac*-6d′**: colorless prisms (MeOH); mp 127–128 °C; IR (KBr) 1705, 1430, 1140, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 9 H, COOBu-*t*), 2.02, 2.60 (each s, each 3 H, NMe), 3.05 (br, 1 H, NH), 3.15 (m, 1 H, H-3′), 3.20 (s, 3 H, COOMe), 3.72 (dd, $J_{4'-5'}$ = 7.3 and $J_{4'-3'}$ = 3.7 Hz, 1 H, H-4′), 3.76, 3.96 (each d, J_{4-5} = 8.8 Hz, each 1 H, H-4 and H-5), 4.04 (d, $J_{2'-3'}$ = 7.7 Hz, 1 H, H-2′), 4.30 (d, $J_{2-3'}$ = 1.8 Hz, 1 H, H-2), 4.84 (d, $J_{5'-4'}$ = 7.3 Hz, 1 H, H-5′), 7.2–7.4 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.19 (COOBu-*t*), 34.74, 42.86 (each NMe), 51.14 (C-3′), 52.67, 52.91 (C-4′ and COOMe), 64.03 (C-2′), 66.87 (C-5′), 74.73, 78.14 (C-4 and C-5), 81.64 (COOBu-*t*), 85.64 (C-2), 126.46, 127.34, 127.43, 127.76, 128.19, 128.23, 128.78, 138.41, 138.79, 139.56 (each Ph), 172.16, 173.86 (COOMe and COOBu-*t*); MS *m/z* (rel intensity) 555 (M^+, 5), 252 (19), 251 (base peak), 210 (5). Anal. Calcd for $C_{34}H_{41}N_3O_4$: C, 73.48; H, 7.44; N, 7.56. Found: C, 73.51, H, 7.24; N, 7.62.

Tosylation of (4*S*,5*S*)-6a To Yield 7a. To a solution of (4*S*,5*S*)-**6a** (0.36 g, 0.564 mmol), TsCl (0.161 g, 0.85 mmol), and $CHCl_3$ (10 mL) was added NEt_3 (0.12 mL, 0.85 mmol) at room temperature. The mixture was refluxed for 12 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **7a** (0.334 g, 75%): colorless prisms (MeOH); mp 247–250 °C; IR (KBr) 1740, 1600, 1490, 1355, 1170, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H, *p*-Me), 2.78 (dd, $J_{4'-3'}$ = 12.5 and $J_{4'-5'}$ = 9.5 Hz, 1 H, H-4′), 3.24 (s, 3 H, 4′-COOMe), 3.37 (s, 3 H, 2′-COOMe), 4.10 (d, J_{4-5} = 8.1 Hz, 1 H, H-4 or H-5), 4.28 (ddd, $J_{3'-4'}$ = 12.5, $J_{3'-2'}$ = 9.5, and $J_{3'-2}$ = 1.5 Hz, 1 H, H-3′), 4.92 (d, $J_{2'-3'}$ = 9.5 Hz, 1 H, H-2′), 4.96 (d, $J_{5'-4'}$ = 9.5 Hz, 1 H, H-5′), 5.12 (d, J_{5-4} = 8.1 Hz, 1 H, H-5 or H-4), 5.99 (d, $J_{2-3'}$ = 1.5 Hz, 1 H, H-2), 6.5–7.4 (m, 27 H, Ph), 7.72 (d, J = 8.4 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.53 (*p*-Me), 44.88 (C-4′), 50.14 (C-3′), 51.50, 52.28 (each COOMe), 61.28 (C-2′), 64.62 (C-5′), 70.43, 75.88 (C-4 and C-5), 81.06 (C-2), 117.45, 118.15, 124.19, 125.01, 127.20, 127.43, 128.03, 128.06, 128.28, 128.35, 128.79, 129.18, 129.73, 134.08, 138.44, 138.73, 139.66, 142.23, 143.78, 148.92 (Ph and Ar), 169.30, 170.29 (each COOMe); MS *m/z* (rel intensity) 791 (M^+, 1), 377 (5), 376 (31), 375 (base peak). Anal. Calcd for $C_{48}H_{45}N_3O_6S$: C, 72.80; H, 5.73; N, 5.31. Found: C, 72.59; H, 5.74; N, 5.09.

X-ray Structure Analysis of 7a. A single crystal grown from EtOAc had space group $P2_12_12_1$, a = 10.810 (2), b = 23.581 (2), and c = 16.916 (2) Å, β = 107.66 Å, V = 4190 (1) Å^3, Z = 4. The final R factor was 0.05 for 2676 observed reflections.[22]

Tosylation of (4*S*,5*S*)-6b′ Leading to 7b. A procedure similar to that described above was used. A mixture of (4*S*,5*S*)-**6b′** (0.16 g, 0.235 mmol), TsCl (0.067 g, 0.353 mmol), NEt_3 (0.05 mL, 0.353 mmol), and $CHCl_3$ (5 mL) was refluxed for 5 h. Silica gel column chromatography (hexane/EtOAc, 3:1) gave **7b** (0.156 g, 80%): colorless prisms (MeOH); mp 197.5–198.5 °C; IR (KBr) 1700, 1590, 1270, 1150, 750, 700, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 9 H, COOBu-*t*), 2.28 (s, 3 H, *p*-Me), 2.67 (s, 3 H, COOMe), 3.65 (dd, $J_{4'-5'}$ = 9.9 and $J_{4'-3'}$ = 8.8 Hz, 1 H, H-4′), 3.79 (ddd, $J_{3'-4'}$ = $J_{3'-2'}$ = 8.8 and $J_{3'-2}$ = 2.9 Hz, 1 H, H-3′), 4.44 (d, $J_{2'-3'}$ = 8.8 Hz, 1 H, H-2′), 4.68, 4.70 (each d, J_{4-5} = 7.3 Hz, each 1 H, H-4 and H-5), 4.93 (d, $J_{5'-4'}$ = 9.9 Hz, 1 H, H-5′), 6.35 (d, $J_{2-3'}$ = 2.9 Hz, H-2), 6.4–7.5 (m, 29 H, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ 21.48 (*p*-Me), 28.15 (COOBu-*t*), 47.20 (C-4′), 51.19 (C-3′ and COOMe), 63.96 (C-2′), 66.02 (C-5′), 69.75, 76.37 (C-4 and C-5), 77.20 (C-2), 82.81 (COOBu-*t*), 117.07, 118.27, 119.16, 120.92, 126.49, 127.50, 127.58, 127.66, 127.90, 128.00, 128.40, 128.43, 128.65, 129.41, 133.36, 138.58, 140.11, 140.30, 142.85, 143.65, 149.31 (Ph and Ar), 168.91, 170.62 (COOMe and COOBu-*t*); MS *m/z* (rel intensity) 833 (M^+, 1), 390 (12), 376 (31), 375 (base peak), 246 (12), 203 (13), 182 (36), 181 (12), 180 (15), 144 (20), 143 (17), 117 (14), 56 (12). Anal. Calcd

for $C_{51}H_{51}N_3O_6S$: C, 73.44; H, 6.16; H, 5.04. Found: C, 73.51; H, 6.23; N, 5.08.

Conversion of 7a to (2*R*,3*R*,4*R*,5*S*)-(−)-8. Dry HCl was bubbled through a solution of **7a** (0.158 g, 0.2 mmol) in CH_2Cl_2 (6 mL) and MeOH (10 mL) at 0 °C for 20 min. The solution was then stirred at room temperature for 30 min, then neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give (2*R*,3*R*,4*R*,5*S*)-(−)-8 (0.79 g, 80%): $[\alpha]^{20}_D$ −40.90° (*c* 1.00, $CHCl_3$), [lit.[4a] $[\alpha]^{20}_D$ −40.36° (*c* 0.99, $CHCl_3$)].

Conversion of 7b to (2*R*,3*R*,4*R*,5*S*)-(−)-8. To a solution of **7b** (0.115 g, 0.14 mmol), $CHCl_3$ (5 mL), and MeOH (5 mL) at room temperature was added concentrated H_2SO_4 (0.3 mL). The mixture was refluxed for 12 h, then neutralized with aqueous $NaHCO_3$, and extracted with Et_2O (30 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1) to give (2*R*,3*R*,4*R*,5*S*)-(−)-8 (0.055 g, 81%). Its absolute configuration and enantiomeric purity were determined by HPLC analysis. The retention time (t_R) was 21.21 min under the conditions employed. Column: Chiralcel OD; eluent: hexane/*i*-PrOH, 9/1; flow rate: 0.5 mL/min). The antipode, (+)-8, had t_R = 18.48 min.

Tosylation of (4*R*,5*R*)-6c′ To Yield 10a. To a solution of (4*R*,5*R*)-**6c′** (0.2 g, 0.39 mmol), TsCl (0.082 g, 0.42 mmol), and $CHCl_3$ (10 mL) at room temperature was added NEt_3 (0.06 mL, 0.42 mmol). The mixture was refluxed for 1.5 h, then treated with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized (MeOH) to give **10a** (0.242 g, 93%): colorless prisms (MeOH); mp 214–215 °C dec; IR (KBr) 1720, 1160, 1020, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86, 2.20 (each s, each 3 H, NMe), 2.39 (s, 3 H, *p*-Me), 3.28 (s, 3 H, 4′-COOMe), 3.36 (dd, $J_{4'-3'}$ = 11.7 and $J_{4'-5'}$ = 9.5 Hz, 1 H, H-4′), 3.39 (d, $J_{2-3'}$ = 2.9 Hz, 1 H, H-2), 3.68 (ddd, $J_{3'-4'}$ = 11.7, $J_{3'-2'}$ = 9.2, and $J_{3'-2}$ = 2.9 Hz, 1 H, H-3′), 3.71 (d, J_{4-5} = 10.2 Hz, 1 H, H-4), 3.80 (s, 3 H, 2′-COOMe), 4.21 (d, J_{5-4} = 10.2 Hz, 1 H, H-5), 4.53 (d, $J_{2'-3'}$ = 9.2 Hz, 1 H, H-2′), 5.36 (d, $J_{5'-4'}$ = 9.5 Hz, 1 H, H-5′), 7.1–7.6 (m, 17 H, Ph and Ar), 7.71 (d, *J* = 8.1 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.54 (*p*-Me), 38.66, 39.88 (each NMe), 47.17 (C-3′), 50.86 (C-4′), 51.68, 52.53 (each COOMe), 62.72 (C-2′), 65.87 (C-5′), 72.40, 73.14 (C-4 and C-5), 87.14 (C-2), 127.60, 127.66, 127.77, 127.89, 127.94, 128.07, 128.16, 129.43, 129.99, 134.83, 135.46, 138.34, 138.66, 143.80 (Ph and Ar), 169.51, 172.29 (each COOMe); MS *m*/*z* (rel intensity) 667 (M^+, 1), 393 (5), 252 (41), 251 (base peak), 170 (8), 138 (19), 133 (21), 124 (10), 92 (10). Anal. Calcd for $C_{38}H_{41}N_3O_6S$: C, 68.27; H, 6.18; N, 6.29. Found: C, 68.16; H, 6.17; N, 6.26.

Tosylation of (4*R*,5*R*)-6d′ To Yield 10b. In a similar manner, a mixture of (4*R*,5*R*)-**6d′** (0.261 g, 0.47 mmol), TsCl (0.178 g, 0.93 mmol), NEt_3 (0.13 mL, 0.93 mmol), and $CHCl_3$ (10 mL) was refluxed for 12 h. The usual hydrolytic workup and silica gel column chromatography (hexane/EtOAc, 3:1) gave **10b** (0.291 g, 93%): colorless prisms (MeOH); mp 174.5–175.5 °C; IR (KBr) 1720, 1140, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (s, 9 H, COOBu-*t*), 1.85, 2.25 (each s, each 3 H, NMe), 2.41 (s, 3 H, *p*-Me), 3.23 (s, 3 H, COOMe), 3.28 (overlapping, 1 H, H-4′), 3.47 (d, $J_{2-3'}$ = 2.2 Hz, 1 H, H-2), 3.59 (ddd, $J_{3'-4'}$ = 10.7, $J_{3'-2'}$ = 9.5, and $J_{3'-2}$ = 2.2 Hz, 1 H, H-3′), 3.66, 4.08 (each d, J_{4-5} = 9.5 Hz, each 1 H, H-4 and H-5), 4.26 ($J_{2'-3'}$ = 9.5 Hz, 1 H, H-2′), 5.27 (d, $J_{5'-4'}$ = 9.5 Hz, 1 H, H-5′), 7.1–7.6 (m, 17 H, Ph and Ar), 7.82 (d, *J* = 8.0 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.55 (*p*-Me), 28.06 (COOBu-*t*), 38.93, 39.58 (each NMe), 46.28 (C-3′), 50.83 (C-4′), 51.58 (COOMe), 64.84 (C-2′), 65.93 (C-5′), 72.99, 73.19 (C-4 and C-5), 82.20 (COOBu-*t*), 86.62 (C-2), 127.51, 127.57, 127.63, 127.79, 127.93, 128.06, 128.12, 128.36, 128.56, 129.56, 129.56, 129.73, 134.29, 136.09, 138.43, 139.22, 143.78 (Ph and Ar), 169.56, 170.00 (each COOMe and COOBu-*t*); MS *m*/*z* (rel intensity) 709 (M^+, 1), 289 (5), 252 (19), 251 (base peak). Anal. Calcd for $C_{41}H_{47}N_3O_6S$: C, 69.67; H, 6.67; N, 5.92. Found: C, 69.27; H, 6.48; N, 5.89.

Conversion of 10a to (2*R*,3*R*,4*R*,5*S*)-(−)-8. A procedure similar to that applied to **7a** was used. Thus, a mixture of **10a** (0.134 g, 0.2 mmol), concentrated H_2SO_4 (0.3 mL), MeOH (5 mL), and $CHCl_3$ (3 mL) was refluxed for 10 h. Workup and silica gel column chromatography ($CHCl_3$) gave (2*R*,3*R*,4*R*,5*S*)-(−)-8 (0.094 g, 95%). Its absolute configuration and enantiomeric purity were determined by HPLC analysis.

Conversion of 10b to (2*R*,3*R*,4*R*,5*S*)-(−)-8. A procedure similar to that applied to **7a** was used. Thus, a mixture of **10b** (0.1 g, 0.14 mmol), concentrated H_2SO_4 (0.3 mL), MeOH (5 mL), and $CHCl_3$ (3 mL) was refluxed for 15 h. Workup and silica gel column chromatography ($CHCl_3$) gave (2*R*,3*R*,4*R*,5*S*)-(−)-8 (0.066 g, 95%). Its absolute configuration and enantiomeric purity were determined as described above.

Studies on the Mechanism of Transfer Hydrogenation of Nitroarenes by Formate Salts Catalyzed by Pd/C

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The hydrogenation of nitroarenes to aminoarenes using formate salts as hydrogen donors and Pd/C as catalyst in a liquid/liquid/solid system was found to be a true hydrogen-transfer process. The mechanism of the reaction comprises successive adsorption of all three substrates to a single catalytic active site in the following order: nitroareane, formate anion, and water. Optimal concentrations of the substrates should be maintained to attain maximum reaction rate and overall yield. A general reaction mechanism is proposed.

Introduction

Numerous hydrogen donors were reported for the liquid-phase catalytic transfer hydrogenation of nitroarenes to the corresponding aminoarenes both under homogeneous and heterogeneous conditions.[1-3] Typical examples are alcohols,[4] formic acid and its derivatives,[5-9] cyclic amines,[10] and hydroaromatic derivatives.[11] Of particular interest are the alkali metal formate salts, which are very

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