JOC Article

Asymmetric Synthesis of *anti*- and *syn*-β-Amino Alcohols by Reductive Cross-Coupling of Transition Metal-Coordinated Planar Chiral Arylaldehydes with Aldimines

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Samarium iodide-mediated *cross*-coupling of *N*-tosyl ferrocenylideneamine with planar chiral ferrocenecarboxaldehydes or benzaldehyde chromium complexes gave diastereoselectively the corresponding *anti*-β-amino alcohol derivatives in good yields, while *N*-tosyl benzylideneamine produced *syn*-β-amino alcohols by coupling with planar chiral arylaldehydes. Dynamic kinetic resolution of a configurationally equilibrated reactive species generated from achiral *N*-tosyl ferrocenilideneamine and benzylideneamine by reduction with samarium iodide was observed in the *cross*-coupling with planar chiral arylaldehydes giving both antipodes of β-amino alcohols depending on the planar chirality. The obtained *anti*-β-amino alcohol with the ferrocene ring was utilized as a chiral ligand for catalytic asymmetric reduction of acetophenone.

Introduction

Enantiomerically pure β-diols, diamines, and amino alcohols have found widespread use as chiral ligands or auxiliaries in asymmetric reactions,[1] and are also important as key synthetic intermediates for biologically active natural products.[2] While optically pure β-diols have been conveniently prepared by catalytic asymmetric dihydroxylation of the olefins with high optical purity,[3] the generally accepted method for the preparation of chiral diamines involves an optical resolution of racemic compounds with certain chiral carboxylic acids.[4] A reductive coupling of carbonyl or imine compounds, homo-pinacol coupling, is the most direct method for the preparation of β-diols or diamines. Although this reaction can be achieved in high yield by lanthanoid metals or low-valent transition metals,[5] highly diastereoselective formation of β-diols or diamines is problematic under conventional reductive coupling.[6] The utilization of some modified reducing agents in catalytic or stoichiometric reaction has been developed for the achievement of high diastereoselectivity for the pinacol coupling.[7] However, only moderate enantioselectivity of β-diols was achieved by pinacol coupling of aldehydes in the presence of a chiral source.[8] We have recently reported[9] that enantiomerically pure β-diols and diamines could be easily prepared by the reductive homo-coupling of planar chiral tricarbonylchromium complexes of benzaldehydes and

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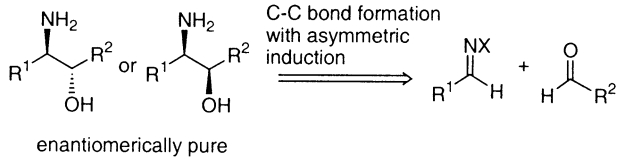
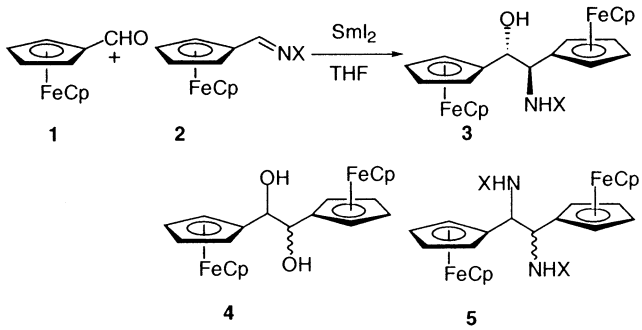


FIGURE 1. Carbon−carbon connection for β-amino alcohols.

benzaldimines, and the related planar chiral transition metal coordinated molecules with samarium iodide. On the other hand, β-amino alcohols are often prepared by direct reduction of amino acids. Indirect routes involving various permutations of stepwise bond construction with asymmetric induction also have been utilized for preparation of β-amino alcohols.[10] Usually, nucleophilic addition reactions to the chiral α-amino carbonyls, hydroxy imines, or hydroxyoximes are used for the stereoselective synthesis of optically active β-amino alcohols.[11] However, as the stereogenic α-carbon of α-amino carbonyl compounds is labile, the optical purity was sometimes decreased. Therefore, new synthetic strategy for the preparation of enantiopure β-amino alcohols is still highly demanded. Recently, *syn*-β-amino alcohols were prepared by catalytic asymmetric Mannich-type reaction from α-hydroxyacetone, aldehydes, and aniline in the presence of (*S*)-proline with high optical purity.[12] Reductive *cross*-coupling between aldehydes and aldimines seems to be the most direct route for the preparation of β-amino alcohols (Figure 1), but many problems preclude an efficient *cross*-coupling in this procedure. Thus, the homo-coupling of both substrates giving β-diols or diamines should be suppressed for the preparation of β-amino alcohols. Furthermore, construction of both stereogenic centers with asymmetric induction should be required in a single synthetic transformation involving addition to both C=N and C=O bonds. Only a few examples of an intermolecular *cross*-coupling of carbonyls with imines have been reported.[13] However, this *cross*-coupling afforded a diastereomeric mixture of *anti*- and *syn*-β-amino alcohols as *racemic* compounds. As part of our exploration of asymmetric synthesis utilizing the planar chiral transition metal-coordinated molecules, we have investigated the reductive *cross*-coupling of aldehydes with aldimines directed toward the synthesis of optically active β-amino alcohols.

TABLE 1. Cross-Coupling of Ferrocenecarboxaldehyde 1 with Ferrocenylideneamine 2



a: X = Me, **b:** X = Bn, **c:** X = Ph, **d:** X = NMe_2, **e:** X = $NHSO_2Ph$, **f:** X = SO_2Ph, **g:** X = Ts, **h:** X = Ms

entry	imine **2**	**3** yield (%)	**4**[a] yield (%)	**5** yield (%)
1[b]	**2a**	0	95	0
2[b]	**2b**	0	96	0
3	**2c**	0	96	95
4[c]	**2d**	0	98	0
5[c]	**2e**	0	92	0
6	**2f**	92	trace	0
7	**2g**	88	trace	0
8[d]	**2g**	28[a]	54	e
9	**2h**	94[f]	trace	0

[a] Obtained as a 1:1 diastereomeric mixture. [b] Obtained as the hydrolysis product of **2** in >98% yield. [c] Recovered **2** in 90−98% yield. [d] Carried out in 15% HMPA. [e] The C=N reduction product was obtained in 50% yield. [f] Ratio of anti and syn isomers: 9/1.

Results and Discussion

Samarium Iodide-Mediated *Cross*-Coupling of Ferrocenylideneamines with Aldehydes. To achieve an efficient *cross*-coupling between aldehydes and aldimines, it is apparently significant for either substrate to be more easily reduced to the corresponding reactive species which reacts with another substrate without homo-coupling. We initially studied the *cross*-coupling of ferrocenylideneamine with arylaldehydes directed toward the synthesis of optically enriched β-amino alcohols, and the reaction results are summarized in Table 1. Treatment of a mixture of ferrocenecarboxaldehyde (**1**) and *N*-alkyl ferrocenylideneamines **2a**, **2b** or hydrazone derivatives **2d**, **2e** with samarium iodide in THF gave homo-coupling β-diol **4** as a diastereomeric mixture along

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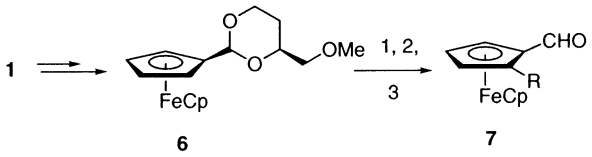
SCHEME 1[a]



[a] Reagent and conditions: (1) *t*-BuLi, ether; (2) electrophile (RX); (3) *p*-TsOH, CH_2Cl_2, H_2O.

with recovered ferrocenylideneamine or its hydrolyzed ferrocenecarboxaldehyde depending on the structure of ferrocenylimine (entries 1, 2, 4, and 5). With *N*-phenyl ferrocenylideneamine (**2c**), two corresponding homo-coupling products, 1,2-diol **4** and diamine **5**, were obtained as a diastereomeric mixture, respectively (entry 3). However, it was fortunately found that electron-withdrawing *N*-sulfonyl ferrocenylideneamine was critical for the effective *cross*-coupling with ferrocenecarboxaldehyde (**1**). Thus, the reductive *cross*-coupling of *N*-arylsulfonyl ferrocenylideneamines **2f**, **2g** with ferrocenecarboxaldehyde (**1**) gave *anti*-*β*-amino alcohol **3** as a single diastereomer (entries 6 and 7) without any formation of the corresponding homo-coupling products and the stereoisomer of the *β*-amino alcohol. With *N*-methanesulfonyl ferrocenylideneamine (**2h**), the corresponding *anti*-amino alcohol was obtained as the major diastereomer along with a small amount of *syn*-amino alcohol (entry 9). Interestingly, the *β*-amino alcohol derivatives obtained in this reductive *cross*-coupling were anti diastereomers, while the homo-pinacol coupling of the planar chiral ferrocenecarboxaldehydes gave exclusively *syn*-*β*-diols.[9] The formation of the *anti*-*β*-amino alcohols in the *cross*-coupling is also in contrast to the predominant formation of syn diastereomers in $NbCl_3$-mediated *cross*-coupling between aldehydes and aldimines.[13a] In the presence of HMPA, the *β*-amino alcohol was obtained as a 1:1 diastereomeric mixture in only 28% yield along with formation of homo-coupling *β*-diol and C=N double bond reduction product (entry 8).

Since *β*-amino alcohols could be obtained by the reductive *cross*-coupling between *N*-sulfonyl ferrocenylideneamines and ferrocenecarboxaldehyde in good yield, we next turned our attention to the preparation of optically active *β*-amino alcohols utilizing planar chiral ferrocenyl compounds.[14] Enantiomerically active α-substituted ferrocenecarboxaldehydes **7** as starting materials were prepared by the literature method.[15] Treatment of ferrocenecarboxaldehyde dimethyl acetal with (−)-(*S*)-1,2,4-butanetriol followed by methylation with MeI and NaH gave the chiral acetal of ferrocenecarboxaldehyde **6**. Diastereoselective lithiation of **6** with *t*-BuLi followed by trapping of electrophiles afforded optically active α-substituted ferrocenecarboxaldehydes **7** with high optical purity (Scheme 1). The corresponding planar chiral *N*-tosyl ferrocenylideneamines **8** were obtained by treatment of the chiral ferrocenecarboxaldehydes **7** with *p*-$TsNH_2$ in the presence of molecular sieves 4A and a catalytic amount of *p*-TsOH in good yields.

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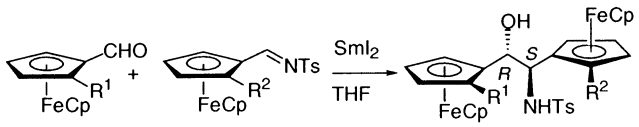
TABLE 2. Cross-Coupling of Planar Chiral *N*-Tosyl Ferrocenylideneamine and Ferrocenecarboxaldehydes



7
a: R^1 = Me
b: R^1 = I
c: R^1 = Br
d: R^1 = TMS
e: R^1 = H

8
a: R^2 = Me
b: R^2 = I
c: R^2 = Br
d: R^2 = TMS

9
a: $R^1 = R^2$ = Me
b: $R^1 = R^2$ = I
c: $R^1 = R^2$ = Br
d: R^1 = H, R^2 = Me
e: R^1 = H, R^2 = I
f: R^1 = H, R^2 = Br
g: $R^1 = R^2$ = H

entry	aldehyde **7** (% ee)[a]	imine **8**	**9** yield (%)	$[\alpha]_D$ ($CHCl_3$)	% ee[b] **9**
1	**7a** (95)	**8a**	92	+99.7 (*c* 0.83)	95
2[c]	**7a**	**8b**	93	+36.8 (*c* 0.44)	95
3	**7b** (95)	**8b**	90	−9.7 (*c* 0.40)	95
4	**7c** (97)	**8c**	93	+1.8 (*c* 0.52)	97
5	**7d** (96)	**8d**	0		
6	**7e**	**8a**	91	+90.3 (*c* 0.84)	92
7	**7e**	**8b**	96	−16.8 (*c* 0.63)	94
8	**7e**	**8c**	95	+3.8 (*c* 0.30)	97
9	**7e**	**8d**	0		

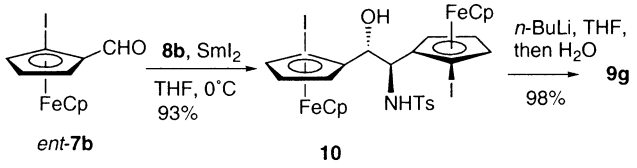
[a] Enantiomeric excess was determined by HPLC with Chiralpak AS (eluted with haxane/2-propanol (9/1), 1.0 mL/min). [b] Enantiomeric excess was determined by HPLC with Chiralcel OD-H (eluted with haxane/2-propanol (9/1), 0.5 mL/min). [c] Value of deiodination compound obtained from the cross-coupling product.

We initially studied the samarium iodide-mediated *cross*-coupling of a combination between the planar chiral *N*-tosyl α-substituted ferrocenylideneamines **8** and ferrocenecarboxaldehydes **7** (Table 2). (+)-(*R*)-α-Methylferrocenecarboxaldehyde (**7a**) was coupled with (*R*)-*N*-tosyl α-methylferrocenylideneamine (**8a**) to give *anti*-*β*-amino alcohol **9a** in 92% yield (entry 1). The stereochemistry of the *anti*-coupling product **9a** was determined as (1*R*,2*S*)-configuration by X-ray crystallography.[16] Similarly, the *cross*-coupling of α-halogenated ferrocenyl compounds produced the corresponding *anti*-*β*-amino alcohols without reduction of the halogen atom in good yields. However, *N*-tosyl 2-trimethylsilyferrocenylideneamine (**8d**) gave no *cross*-coupling product probably due to steric hindrance (entries 5 and 9). The *β*-amino alcohol derivatives **9b** and **9e** obtained by the *cross*-coupling with (+)-(*S*)-*N*-tosyl α-iodoferrocenylideneamine (**8b**) gave (+)-(1*R*,2*S*)-*β*-amino alcohol **9g** ($[\alpha]^{26}_D$ +40.8) by deiodination with *n*-BuLi in 96% yield. Furthermore, an antipode (−)-(*R*)-α-iodoferrocenecarboxaldehyde (*ent*-**7b**)[17] was coupled with **8b** to give *anti*-*β*-amino alcohol **10** as a single diastereomer (Scheme 2). The stereochemistry of **10** was

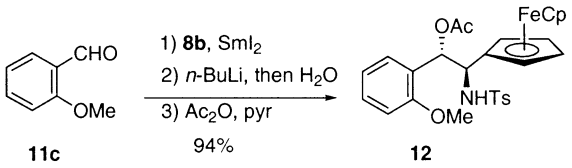
(16) Crystallographic data for the structures reported in this paper have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-189226 for **9a**. Crystal data for **9a**: empirical formula $C_{31}H_{33}NO_3SFe_2$, M = 611.36, orthorhombic, space group $P2_12_12_1$, a = 13.489 Å, b = 30.253 Å, c = 7.141 Å, V = 2914(2) Å^3, Z = 4, D_c = 1.393 g/cm^3, F_{000} = 1272.00, Mo Kα (λ = 0.71069 Å), no. of reflections measured 3812, least-square refinement using 1733 reflections with $I > 3.00\sigma(I)$, R = 0.050, R_w = 0.044.

(17) Antipode (*R*)-2-iodoferrocenecarboxaldehyde *ent*-**7b** was prepared from **6** by diastereoselective lithiation followed by quenching with Me_3SiCl, and then repeated lithiation and subsequent introduction of iodine and finally desilylation; (i) *t*-BuLi (ii) Me_3SiCl (iii) *t*-BuLi, (iv) $I(CH_2)_2I$, (v) *n*-Bu_4NF, (vi) aq HCl.

SCHEME 2



SCHEME 3



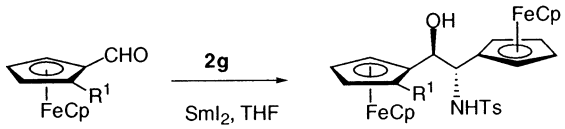
determined by X-ray crystallography,[18] and the generated stereogenic centers were also confirmed by comparison with authentic compound. Thus, spectra data including an optical rotation of the deiodinated *β*-amino alcohol derived from **10** were identical with that of **9g** obtained by deiodination of **9b**. In this way, the absolute configurations at the generated chiral centers of *anti*-*β*-amino alcohols in the *cross*-coupling with the planar chiral *N*-tosyl ferrocenylideneamines **8** were only governed by the planar chirality of ferrocenylimine **8**, regardless of the planar chirality of ferrocenecarboxaldehydes.

Similarly, the planar chiral (+)-(*S*)-*N*-tosyl α-iodoferrocenylideneamine (**8b**) was coupled with benzaldehyde. Thus, the *cross*-coupling of **8b** with *o*-methoxybenzaldehyde (**11c**) gave the corresponding *anti*-*β*-amino alcohol derivative **12** ($[\alpha]^{27}_D$ −47.8) as a single diastereomer after deiodination and subsequent acetylation (Scheme 3). The absolute configuration of **12** was determined as the (1*S*,2*S*)-configuration by comparison of the optical rotation with a stereochemically defined authentic compound (vide infra), and was also governed by the planar chirality of the ferrocenylimine **8**. However, the corresponding tricarbonylchromium complex of *o*-methoxybenzaldehyde **14c** gave homo-coupling *β*-diol in 80% yield without formation of the expected *cross*-coupling *β*-amino alcohol by the reaction with **8b** probably due to steric hindrance.

We next studied the *cross*-coupling with achiral *N*-tosyl ferrocenylideneamine. The samarium iodide-mediated *cross*-coupling of **2g** with planar chiral ferrocenecarboxaldehydes **7** gave similarly *anti*-*β*-amino alcohol derivatives in good yields without formation of diastereomers (Table 3). In this combination, α-trimethylsilylferrocenecarboxaldehyde (**7d**) fortunately gave the expected *anti*-*β*-amino alcohol by *cross*-coupling with **2g** (entry 4).

Similarly, benzaldehydes and the corresponding tricarbonylchromium complexes were coupled with achiral ferrocenylideneamine **2g** to afford *anti*-*β*-amino alcohols **15** without formation of stereoisomers in good yields (Table 4). While the planar chiral α-substituted ferrocenylideneamine resulted in no *cross*-coupling products with a benzaldehyde chromium complex as mentioned above, achiral *N*-tosyl ferrocenylideneamine (**2g**) gave the

TABLE 3. Cross-Coupling of Achiral *N*-Tosyl Ferrocenylideneamine 2g with Planar Chiral Ferrocenecarboxaldehydes

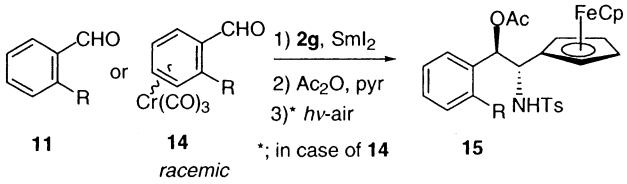


a: R^1 = Me, **b**: R^1 = I, **c**: R^1 = Br, **d**: R^1 = TMS

entry	aldehyde **7**	yield (%)	$[\alpha]_D$ ($CHCl_3$)	% ee[a] **13**
1	**7a**	92	−22.8 (*c* 0.88)	93
2	**7b**	94	−43.4 (*c* 0.94)	94
3	**7c**	91	−39.4 (*c* 0.50)	93
4	**7d**	91	−38.3 (*c* 0.27)	94

[a] Enantiomeric excess was determined by HPLC with Chiralcel OD-H (eluted with haxane/2-propanol (9/1), 0.5 mL/min).

TABLE 4. Cross-Coupling of 2g with Benzaldehydes or Corresponding Tricarbonylchromium Complexes



a: R = H, **b**: R = Me, **c**: R = OMe

	11a	**11b**	**11c**	**14a**	**14b**	**14c**
yield (%)	95	92	94	94	94	96

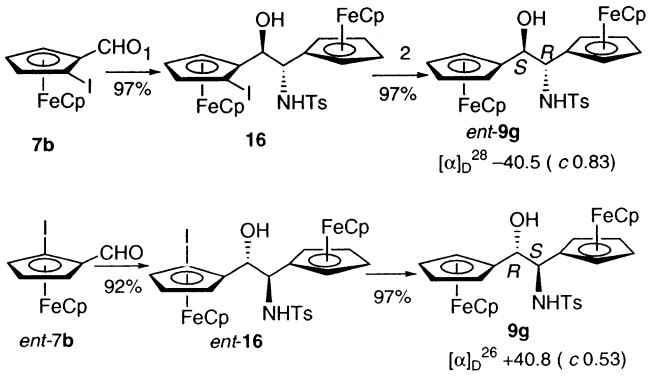
desired *β*-amino alcohols in good yields. These results would be attributed to the steric effect. However, the reaction of *o*-bromobenzaldehyde chromium complex with **2g** resulted in a complex mixture.

We next examined the absolute configuration at the stereogenic centers of the *β*-amino alcohols obtained by *cross*-coupling of achiral ferrocenylimine **2g** with planar chiral ferrocenecarboxaldehydes and benzaldehyde chromium complexes. The samarium iodide-mediated *cross*-coupling of **2g** with (+)-(*S*)-α-iodoferrocenecarboxaldehyde (**7b**) gave (−)-(1*S*,2*R*)-amino alcohol *ent*-**9g** ($[\alpha]^{26}_D$ −40.5) after deiodination by treatment with *n*-BuLi (Scheme 4). The obtained *β*-amino alcohol was an optical antipode with *anti*-*β*-amino alcohol **9g** obtained by the *cross*-coupling of the planar chiral (*S*)-*N*-tosyl α-iodoferrocenylideneamine (**8b**) with ferrocenecarboxaldehyde as discussed above. On the other hand, the corresponding *ent*-**7b** afforded the (+)-(1*R*,2*S*)-*β*-amino alcohol **9g** ($[\alpha]^{28}_D$ +40.8) by the same reaction sequence. Similarly, the planar chiral benzaldehyde chromium complexes afforded both enantiomers of *anti*-*β*-amino alcohols depending on the planar chirality (Scheme 5). Thus, (+)-(*S*)-*o*-methoxybenzaldehyde chromium complex (**17b**)[19] gave (+)-*anti*-*β*-amino alcohol derivative **18b** without formation

(18) Crystal data for *ent*-**10**: no. CCDC-189227, empirical formula $C_{29}H_{27}NO_3SFe_2I_2$, M = 835.10, monoclinic, space group $P2_1/a$, a = 11.903 Å, b = 21.818 Å, c = 12.204 Å, V = 3000.8 Å^3, Z = 4, D_c = 1.848 g/cm^3, F_{000} = 1624.00, Mo Kα (λ = 0.71069 Å), no. of reflections measured 7408, least-square refinement using 5741 reflections with $I > 0.00\sigma(I)$, R = 0.145, R_w = 0.190.

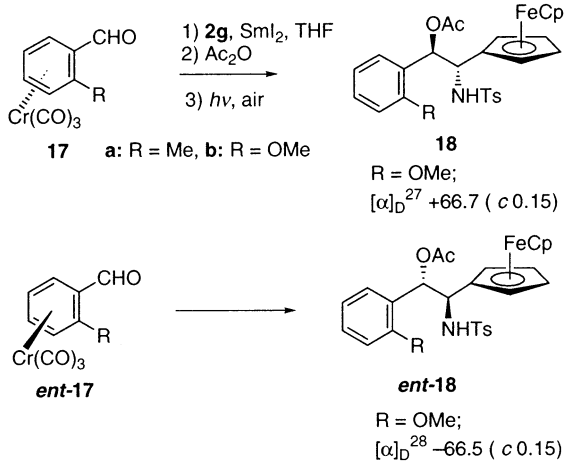
(19) Optically pure *o*-methoxy and methylbenzaldehyde chromium complexes were obtained by separation of diastereomers derived from L-valinol with column chromatography according to the literature method: (a) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 192. (b) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393. (c) Bromley, L. A.; Davies, S. G.; Goodfellow, C. L. *Tetrahedron: Asymmetry* **1991**, *2*, 139.

SCHEME 4[a]



[a] Reagent and conditions: (1) SmI_2, **2g**, THF; (2) *n*-BuLi, THF then H_2O.

SCHEME 5



of any stereoisomers in good yield. The absolute configuration of **18b** was determined by X-ray crystallography.[20] The corresponding (*R*)-(−)-*o*-methoxybenzaldehyde chromium complex (*ent*-**17b**) produced (−)-*anti*-*β*-amino alcohol derivative *ent*-**18b** under the same conditions. Also, optically pure *o*-methylbenzaldehyde chromium complexes, **17a** and *ent*-**17a** gave the corresponding *anti*-*β*-amino alcohols **18a** and *ent*-**18a**, respectively, under the same reaction sequence. Surprisingly, optical rotation of *o*-methyl-substituted *anti*-*β*-amino alcohol derivatives **18a** and *ent*-**18a** was almost zero in $CHCl_3$ solution, despite using the optically active arene chromium complexes as the starting material. However, CD spectra of the *β*-amino alcohol derivatives supported that both **18a** and *ent*-**18a** are optically active compounds (Figure 2). Thus, the *o*-methyl-substituted *anti*-*β*-amino alcohols, **18a** and *ent*-**18a**, have the same behavior with the optically active *β*-amino alcohols, **18b** and *ent*-**18b**, with *o*-methoxy substituent in the CD spectra. In conclusion, the absolute configuration at the α,α′-positions of *anti*-*β*-amino alcohols in the combination between achiral ferrocenylimine **2g** and planar chiral arylaldehyde was

(20) Crystal data for **18b**: no. CCDC-189228. empirical formula $C_{28}H_{29}NO_5SFe$, M = 547.45, monoclinic, space group $P2_1$, a = 12.781 Å, b = 10.519 Å, c = 20.434 Å, V = 2746(1) Å^3, Z = 4, D_c = 1.324 g/cm^3, F_{000} = 1144.00, Mo Kα (λ = 0.71069 Å), no. of reflections measured 13161, least-square refinement using 8292 reflections with $I > 0.00\sigma(I)$, R = 0.085, R_w = 0.077.

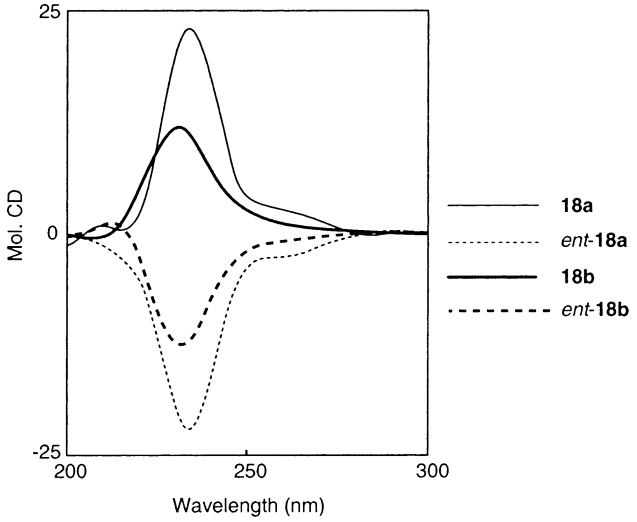


FIGURE 2. CD spectra.

SCHEME 6

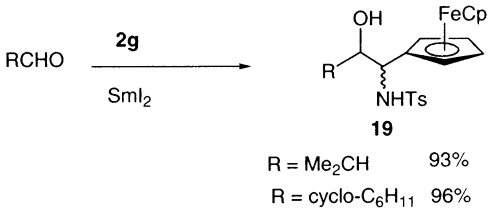


TABLE 5. Reduction Potentials[a]

1	11a	14a	2a	2c
−2.34	−2.04	−1.70	−2.42	−2.02
2g	**2h**	**29a**	**29b**	**31**
−1.80	−1.74	−1.56	−1.50	−1.44

[a] Potential in volts vs Ag/Ag^+ with a glassy carbon working electrode, a platinum flag counter electrode in MeCN using tetrabutylammonium perchlorate (0.05 M) as a supporting electrolyte, and a sweep rate of 50 mV s^{-1}.

dependent on using the planar chirality of ferrocenecarboxaldehydes and benzaldehyde chromium complexes in the coupling reaction.

Also, aliphatic aldehydes in analogy with arylaldehydes gave the expected *β*-amino alcohols by samarium idodide-mediated cross-coupling with *N*-tosyl ferrocenylideneamine (**2g**) under the same conditions in good yields without formation of homo-coupling products (Scheme 6). However, the obtained *cross*-coupling products **19** were a 1:1 diastereomeric mixture of *anti*- and *syn*-amino alcohols.

Reaction Mechanism of Cross-Coupling with *N*-Tosyl Ferrocenylideneamines

A reaction mechanism has been postulated to rationalize the observed stereoselectivity of the *cross*-coupling of *N*-tosyl ferrocenylideneamines with arylaldehydes. An efficient achievement of the *cross*-coupling between ferrocenecarboxaldehyde **1** and *N*-arylsulfonyl ferrocenylidenimines **2f**, **2g** would be attributed to different reduction potentials between both substrates (Table 5). The redox properties of these compounds were examined by cyclic

voltammetry. The voltammograms of all compounds exhibited clear reduction waves but no apparent oxidation waves. Therefore, the differences between these compounds were compared by the potentials at which they began to be reduced. Electron-withdrawing *N*-sulfonyl ferrocenylideneamines **2g** and **2h** were found to be more easily reduced than the corresponding ferrocenecarboxaldehyde **1**. We next studied whether the reactive intermediated species generated from *N*-sulfonyl imine is a radical or ionic species. Reduction of *N*-tosyl imine **2g** with SmI_2 in the presence of CH_3OD in THF gave a deuterium-incorporated C=N reduction product in good yield. The incorporation of deuterium in the reduction product shows that the reactive intermediate species would be the ionic species. Thus, single-electron reduction of the sulfonyl ferrocenylideneimine generates a ketyl radical intermediate, which would be further reduced to a dianion species.

In the *cross*-coupling with the planar chiral *N*-tosyl α-substituted ferrocenylideneamines, samarium iodide attacks the anti-oriented C=N double bond to the α substituent[21] from the *exo*-side to generate dianion intermediate **21**, which is configurationally stable against epimerization (Figure 3).[22] No epimerization between **21** and **22** would be attributed to an interaction of the p-orbital of α-carbon with the d-orbital of the iron metal, resulting in the formation of an *exo*-cyclic double bond character **23**. Taking into account the following transition states **24a** and **24b**, the *N*-tosyl group is oriented anti[23] to the carbonyl oxygen of arylaldehydes due to dipole−dipole repulsion. The carbonyl oxygen of the planar chiral ferrocenecarboxaldehydes is also known to exist preferentially in the anti conformation[21] to the ortho substituent. When the planar chiral arylaldehydes **7** were coupled with a dianion intermediate, the transition state **24a** caused a severe steric interaction between the FeCp ring of ferrocenecarboxaldehyde and ferrocenylimine because of the same planar chirality of both substrates. Therefore, the anti-oriented carbonyl oxygen in transition state **24a** would be isomerized to the alternative syn-oriented transition state **24b**, giving the *anti*-*β*-amino alcohols **9**. In the case of cross-coupling with optical antipode *ent*-**7**, the sterically stable anti-oriented transition state **25** is preferred for *anti*-*β*-amino alcohol formation.

On the other hand, the reactive species generated from achiral ferrocenylideneamine **2g** rapidly equilibrates at the stereogenic center due to a lack of the α-substituent on the Cp ring (Figure 4). The planar chiral α-substituted ferrocenecarboxaldehyde could intercept either configurated species among the equilibrated carbanions depending on the planar chirality of arylaldehydes. Thus, the anti-oriented carbonyl of the planar chiral ferrocenecarboxaldehydes **7** is attacked via transition state **27** giving a single *anti*-amino alcohol **16**. On the other hand, *ent*-**7** gave the antipode *anti*-*β*-amino alcohol, *ent*-**16**, via the transition state **28**. In the *cross*-coupling of the achiral ferrocenylideneamine with planar chiral arylaldehydes, dynamic kinetic resolution takes place among the equilibrating α-ferrocenyl carbanion configuration.

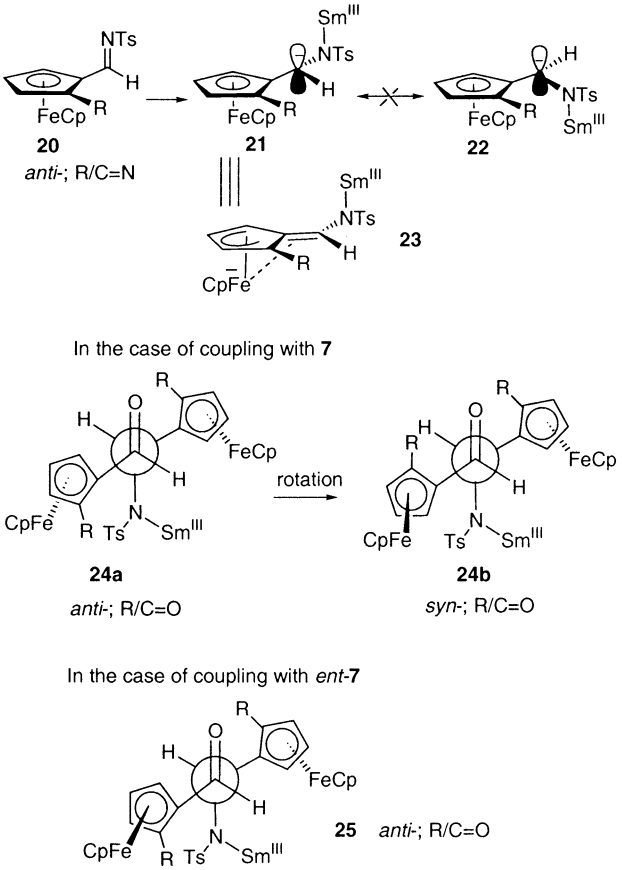


FIGURE 3. Proposed reaction mechanism of cross-coupling with planar chiral *N*-tosyl ferrocenylideneamine.

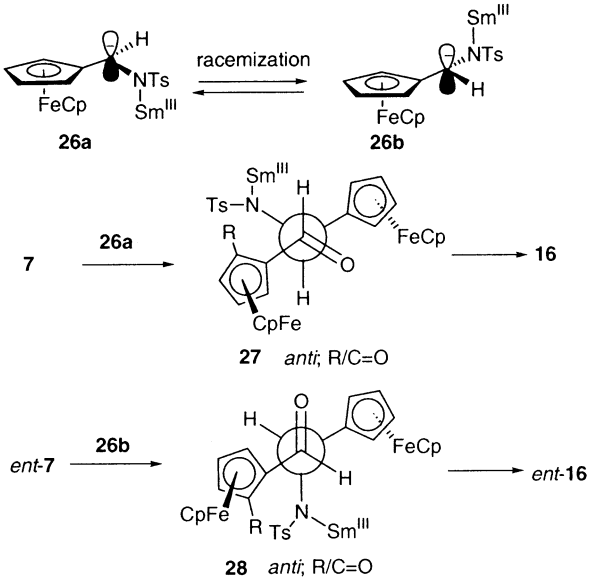


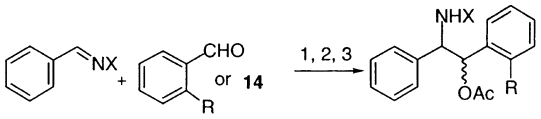
FIGURE 4. Proposed reaction mechanism of cross-coupling with achiral *N*-tosyl ferrocenylideneamine.

(21) Predominant anti conformation of the C=O or C=N double bond to the ortho substituents of ferrocenyl compounds was proposed by diastereoselective nucleophilic addition to the double bond. For a review see: *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995.

(22) α-Ferrocenyl lithium derivatives have similar stereochemical character for the electrophilic quenching depending on the α-position in the presence or absence of an ortho substituent on the Cp ring. Ireland, T.; Perea, J. J. A.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1457.

(23) A mechanism of acyclic selection in intermolecular radical reactions and intramolecular radical cyclization. (a) Smadja, W. *Synlett* **1994**, 1. (b) Bobo, S.; Storch de Gracia, I.; Chiara, J. S. *Synlett* **1999**, 1551. (c) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem*. **1998**, *63*, 5877.

TABLE 6. Cross-Coupling of Benzylideneamine 29 with Benzaldehyde or the Corresponding Chromium Complexes[a]



29 **11** **30**

a: X = Ms
b: X = Ts

a: R = H, **b**: R = Me, **c**: R =OMe, **d**: R =Cl

14: $Cr(CO)_3$ complex of **11**

a: X = Ms, Y = H, R = H
b: X = Ms, Y = H, R = Me
c: X = Ms, Y = H, R =OMe
d: X = Ts, Y = Ac, R = H
e: X = Ts, Y = Ac, R = Me
f: X = Ts, Y = Ac, R = OMe
g: X = Ts, Y = Ac, R = Cl

Reagent and conditions: (1) SmI_2, THF, 0° C, rt; (2) Ac_2O, pyr; (in case of **29b**); (3) In case of chromium complex: *hν*-air.

entry	imine	aldehyde	**30** (yield, %)	syn/anti
1[a]	**29a**	**11a**	**30a** (77)	54/46
2[a]	**29a**	**11b**	**30b** (70)	50/50
3[a]	**29a**	**11c**	**30c** (93)	50/50
4[a]	**29a**	**14a**	**30a** (78)	67/33
5[a]	**29a**	**14b**	**30b** (63)	60/40
6[a]	**29a**	**14c**	**30c** (89)	67/33
7	**29b**	**11a**	**30d** (81)	70/30
8	**29b**	**11b**	**30e** (74)	80/20
9	**29b**	**11c**	**30f** (76)	70/30
10	**29b**	**11d**	**30g** (52)	87/13
11[b]	**29b**	**14a**	**30d** (73)	97/3
12[b]	**29b**	**14b**	**30e** (60)	95/5
13[b]	**29b**	**14c**	**30f** (33)	97/3
14[b]	**29b**	**14d**	**30g** (38)[c]	97/3

[a] Isolated as amino alcohols without acetylation. [b] Homocoupling 1,2-diols were obtained in 1−5% yields. [c] Yield of cross-coupling was 60% before photooxidation.

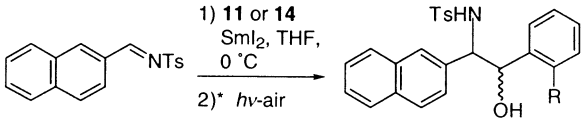
Cross-Coupling of Benzylideneamines with Aldehydes

For further extension of the reductive cross-coupling giving optically active β-amino alcohols, we next studied the cross-coupling with benzylideneamines.[24] *N*-Sulfonyl benzylideneamines **29a** and **29b** would be expected to give β-amino alcohols in the cross-coupling with arylaldehydes by judging of the reduction potentials (Table 5). Indeed, the cross-coupling of *N*-methanesulfonyl benzylideneamine (**29a**) with benzaldehyde **11** gave the corresponding β-amino alcohol derivatives **30** in good yields without formation of homo-coupling products (Table 6). However, the diastereoselectivity of *anti*- and *syn*-β-amino alcohols was extremely low (entries 1−3). The corresponding benzaldehyde tricarbonylchromium complexes **14** were also coupled with the imine **29a** with a slight increase of the diastereoselectivity (entries 4−6). With *N*-tosyl benzylideneamine (**29b**), the diastereoselectivity of the cross-coupling products increased appreciably (entries 7−10). Among the ortho-substituted benzaldehydes studied, *o*-chlorobenzaldehyde (**10d**) resulted with higher diastereoselectivity in 52% yield (entry 10). The cross-coupling of benzaldehyde chromium complex (**14a**) with *N*-tosyl benzylideneamine (**29b**) gave β-amino alcohol derivative **30d** with high diastereoselectivity in 73% overall yield after acetylation and subsequent demetalation (entry 11). The increase of diastereoselectivity by the tricarbonylchromium complexation would be attributed to a stereoelectronic effect of the tricarbonylchromium fragment.[25]

Interestingly, the major β-amino alcohol **30** obtained in this combination was found to be a syn isomer.[26] The predominant formation of the *syn*-β-amino alcohol in this combination is in sharp contrast to the reductive cross-coupling of *N*-tosyl ferrocenylideneamine with arylaldehydes giving the *anti*-β-amino alcohols as mentioned above. Similarly, ortho-substituted benzaldehyde chromium complexes were coupled with *N*-tosyl benzylideneamine (**29b**) to produce the corresponding *syn*-amino alcohols along with formation of a small amount (1−5%) of homo-coupling β-diols derived from benzaldehyde chromium complexes under the same conditions (entries 12−14). However, the cross-coupling of ferrocenecarboxaldehyde with **29b** gave a homo-coupling β-diol in 95% yield without formation of the expected β-amino alcohol, while the cross-coupling of *N*-tosyl ferrocenylideneamines with ferrocenecarboxaldehydes proceeded in good yields as mentioned above. The electronic factor of aldehydes and imines seems to be also significant for an efficient achievement of the cross-coupling giving β-amino alcohols. Therefore, an electron-donating methoxy group was introduced on the arene ring of *N*-tosyl benzylideneamine (**29b**) for the reductive cross-coupling. As expected, *N*-tosyl 3,4,5-trimethoxybenzylideneamine was coupled with ferrocenecarboxaldehyde to give a 1:1 diastereomeric mixture of the corresponding β-amino alcohols, albeit in 30% yield.

Furthermore, the cross-coupling of *N*-tosyl naphthylimines with benzaldehydes was examined (Table 7). β-Naphthylimine **31** was coupled with benzaldehydes **11** to give a diastereomeric mixture of β-amino alcohol derivatives **32** in good yields. The major isomers of the obtained β-amino alcohols were also syn isomers. Similarly, the corresponding tricarbonylchromium complexes of benzaldehyde increased syn diastereoselectivity in the

TABLE 7. Cross-Coupling of β-Naphthylimine 31



31 * in case of **14** **32**

a: R = H, **b**: R = Me, **c**: R = OMe

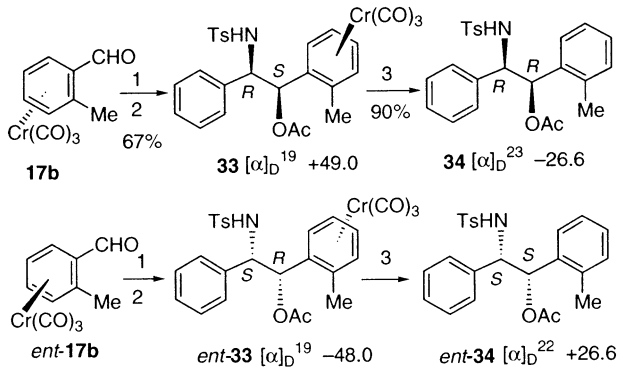
entry	aldehyde	yield **32** (%)	syn/anti
1	**11a**	83	65/35
2	**11b**	89	78/22
3	**11c**	76	74/26
4	**14a**	67	94/6
5	**14b**	74	83/17
6	**14c**	89	78/22

(24) A preliminary report: Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835.

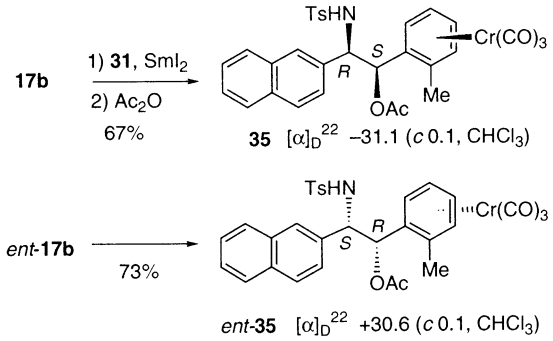
(25) The coordination of a tricarbonylchromium fragment to the arene ring was found to also increase the diastereoselectivity in the asymmetric allyboration of aromatic aldehydes: Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143.

(26) Authentic *N*-tosyl-2-amino-1,2-diphenylethyl alcohol derivative was prepared by the following literature procedure: (a) Davis, F. A.; Hague, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021. (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. The corresponding *syn*-β-amino alcohol: (c) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375.

SCHEME 7[a]



[a] Reagent: (1) **29b**, SmI_2, THF; (2) Ac_2O, pyr; (3) *hv*, air, ether.



cross-coupling with *β*-naphthylimine **31**. However, the corresponding α-naphthylimine gave no cross-coupling *β*-amino alcohol product under the same conditions.

We next turned our attention to the preparation of optically active *β*-amino alcohol derivatives by using planar chiral benzaldehyde chromium complexes (Scheme 7). Enantiomerically pure (+)-(1*S*)-*o*-methylbenzaldehyde chromium complex (**17b**) was coupled with **29b** to give a chromium-complexed (+)-(1*S*,2*R*)-*β*-amino alcohol derivative **33** (>99% ee). Exposure of **33** to sunlight gave a chromium-free (−)-(*R*,*R*)[27]-*β*-amino alcohol derivative **34**. On the other hand, an antipode (−)-*o*-methylbenzaldehyde chromium complex (*ent*-**17b**) produced (+)-(*S*,*S*)-*β*-amino alcohol *ent*-**34** under the same reaction sequence. In this way, both enantiomers of *syn*-*β*-amino alcohol could be prepared by the coupling of *N*-tosyl benzylideneamine with the planar chiral benzaldehyde chromium complexes. Similarly, the cross-coupling of *N*-tosyl *β*-naphthylimine **31** with the planar chiral benzaldehyde chromium complexes **17b** and *ent*-**17b** gave both enantiomers of the corresponding *syn*-*β*-amino alcohol derivatives **35** and *ent*-**35**, respectively, depending on the planar chirality. Thus, configurationally equilibrated reactive species generated from *N*-tosyl imines **29b** or **31** obviously underwent a dynamic kinetic resolution in the cross-coupling with the planar chiral benzaldehyde chromium complexes, in analogy with the cross-coupling of achiral *N*-tosyl ferrocenylideneamine **2g** with planar chiral arylaldehydes as shown in Schemes 4 and 5.

(27) The absolute configuration of the syn-coupling product **34** was determined as the (*R*,*R*)-configuration by comparison of the optical rotation sign of authentic *syn*-*β*-amino alcohol derived from (*R*)-2-phenylglycine according to ref 26c.

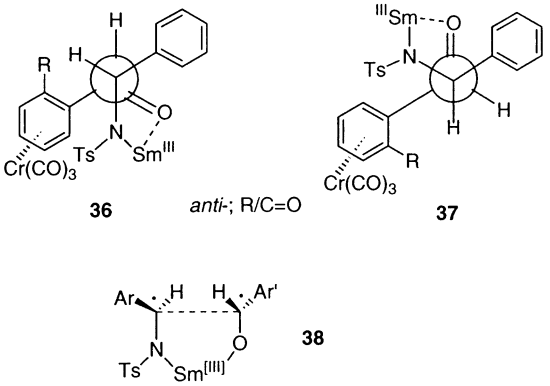
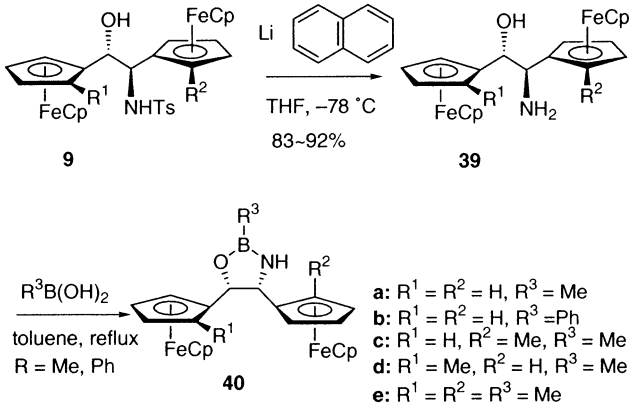


FIGURE 5.

A reaction mechanism of the cross-coupling of *N*-tosyl aldimines **29b** or **31** with planar chiral benzaldehyde chromium complexes has been postulated to rationalize the observed syn stereoselectivity (Figure 5). The reactive species generated from the imines would be rapidly equilibrated at the newly created stereogenic center as well as achiral *N*-tosyl ferrocenylideneamine **2g**. The planar chiral ortho-substituted benzaldehyde chromium complex is oriented anti of the carbonyl oxygen to the ortho substituents.[28] The transition state giving the *syn*-amino alcohols is proposed as the coordination structure of the samarium with both nitrogen and carbonyl oxygen atoms **36** or **37** via dynamic kinetic resolution of the generated reactive species depending on the planar chirality of benzaldehyde chromium complexes. As shown in Figures 3 and 4, the transition states of the cross-coupling with *N*-tosyl ferrocenylideneamines were proposed as the dipole−dipole repulsion intermediate between *N*-Sm^{III} and carbonyl oxygen groups. An alternative transition state might be proposed in the cross-coupling with *N*-tosyl benzylideneamine from the following results. The reaction of benzylideneamine **29b** with aliphatic aldehydes was different from the cross-coupling of *N*-tosyl ferrocenylideneamine with aliphatic aldehydes. Thus, *N*-tosyl benzylideneamine (**29b**) gave a complex mixture by reaction with aliphatic aldehydes, while the ferrocenylideneamine afforded the expected *β*-amino alcohols by coupling with both aromatic and aliphatic aldehydes in good yields as shown above. These results indicate that in the cross-coupling of **29b** with arylaldehydes, both ketyl radical species generated from the imine and arylaldehydes might be coupled via a coordination structure **38** with the samarium metal without stepwise reaction. On the other hand, in the combination between *N*-tosyl ferrocenylideneamine and aldehydes, the dianion species would be initially generated from the imine and the generated reactive species reacts with aldehydes to give the *β*-amino alcohols. Further elucidation of the reaction mechanism is necessary for an explanation of the stereochemically distinguished cross-coupling between *N*-tosyl ferrocenylideneamine and benzylideneamine.

(28) (a) Solladié-Cavallo, A. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, p 99. (b) Davies, S. G.; McCarthy, T. D. *Comprehensive Oragnometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, p 1039.

SCHEME 8



Application to Asymmetric Reaction

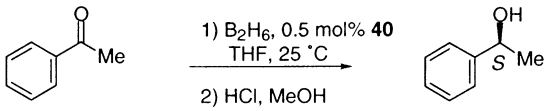
Having established a general method for the preparation of optically active β-amino alcohol derivatives, we explored the possibility of asymmetric reaction as a chiral ligand. At first, the catalytic efficiency of these new chiral ferrocenyl ligands was studied for CBS reduction[29] of ketones. The chiral β-amino alcohols **39** were prepared by reductive elimination of the *N*-tosyl group of **9** with lithium naphthalide in good yields (Scheme 8). These chiral *anti*-β-amino alcohols **39** were converted to *B*-methyl or phenyl oxazaborolidines **40** by treatment with methylboronic acid or phenylboronic acid under dehydrating conditions.

The effect of the substituent R on the borane of **40** was initially studied in catalytic asymmetric reduction of acetophenone. The reduction was carried out in the presence of 5 mol % of *B*-substituted oxazaborolidine **40** and equivalent borane in THF at room temperature. *B*-Phenyl-substituted oxazaborolidine **40b** resulted in lower yield and enantioselectivity than the corresponding *B*-methyl-substituted ligand **40a** due to the steric effect. We next examined the steric effect of the substituent on the Cp ring. It is obvious from Table 8 that the methyl substituent on the ferrocene ring has no significant effect for the asymmetric induction of reduction of acetophenone. The oxazaborolidine **40a** without a methyl substituent has enough steric effect for direction of the substrate approach based on the cis conformation of both ferrocene rings. Thus, asymmetric reduction of acetophenone was achieved by using chiral oxazaborolidine **40a** with high optical purity.

In conclusion, we have demonstrated asymmetric synthesis of β-amino alcohols by samarium iodide-mediated cross-coupling of the planar chiral arylaldehydes with arylaldimines. The diastereoselectivity of *anti*- and *syn*-β-amino alcohols was governed by the nature of arylaldimines used. *N*-Tosyl ferrocenylidenamines gave *anti*-β-amino alcohols by coupling with arylaldehydes, while benzylideneamines afforded *syn*-β-amino alcohols. Also, dynamic kinetic resolution of the generated reactive species from achiral *N*-tosyl ferrocenylidenamine and benzylideneamine was observed by the coupling with planar chiral arylaldehydes. High catalytic asymmetric reduction of acetophenone was achieved by using chiral oxazaborolidine derived from *anti*-β-amino alcohols with ferrocene rings as a chiral ligand.

(29) Some representative references; (a) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (d) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (e) Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley and Sons: New York, 2001; p 367.

TABLE 8. Asymmetric CBS Reduction of Acetophenone[a]



entry	ligand **40**	yield (%)	% ee[b] (configuration)
1	**40a**	83	91 (*S*)
2	**40b**	62	66 (*S*)
3	**40c**	77	90 (*S*)
4	**40d**	78	90 (*S*)
5	**40e**	73	90 (*S*)

[a] Enanriomeric purity of chiral β-amino alcohols used in this study was ~95% ee. [b] Enantiomeric excess was determined by HPLC with Chiralcel OD-H (eluted with hexane/2-propanol (9/1), 0.5 mL/min).

Experimental Section

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon with inert gas/vacuum double-manifold techniques. All melting points were determined on a Yanagimoto MPJ-2 micro melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. Optical rotations were measured on a JASCO DIP-370 automatic polarimeter at 589 nm (sodium D line) using a 0.5-dm cell. Reductive potentials were measured with a Potentiostat/Galvanostat (Hokuto Denko HA-501G) and a Function Generater (Hokuto Denko HB-105). Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use. Methylene chloride was distilled over P_2O_5 before use.

Preparation of (*S*)-*N*-Tosyl α-Iodoferrocenylideneamine (8b). A mixture of (*S*)-α-iodoferrocenecarboxaldehyde (**7b**) (100 mg, 0.3 mmol), *p*-tosyl sulfonamide (55 mg, 0.3 mmol), a catalytic amount of *p*-TsOH (5 mg), and MS 4A (1 g) in ether (5 mL) was stirred for 14 h at room temperature. After filtration, the mixture was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ether, 1/1) to give *N*-tosyl benzylideneamine **8b** (105 mg, 71%) as a red oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.43 (3H, s), 4.20 (5H, s), 4.80−4.82 (1H, m), 4.92−4.94 (1H, m), 5.04−5.05 (1H, m), 7.34 (2H, d, J = 8.2 Hz), 7.88 (2H, d, J = 8.2 Hz), 9.13 (s, 1H); $[\alpha]_D^{26}$ +1400 (*c* 0.09, $CHCl_3$).

Cross-Coupling of Planar Chiral Arylaldehydes with *N*-Tosyl Arylaldimines. A typical procedure for the preparation of **9a** is as follows: To a solution of **7a** (107.0 mg, 0.47 mmol) and **8a** (167.0 mg, 0.43 mmol) in dry THF (1.0 mL) was added a solution of SmI_2 (0.10 M, 21.5 mL, 2.15 mmol) in THF at 0 °C, and the solution was stirred at the same temperature for 30 min under argon atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was filtered through a Celite pad. The filtrate was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with Et_2O/hexane) to give 245.7 mg (92%) of **9a**. Yellow crystals; mp 159−160 °C dec; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.30 (3H, s), 2.05 (1H, d, J = 4.6 Hz), 2.49 (3H,

s), 3.73 (1H, s), 3.79 (1H, s), 3.86 (1H, t, J = 5.0 Hz), 3.95 (5H, s), 3.98−3.99 (2H, m), 4.00 (5H, s), 4.07−4.14 (2H, m), 4.43 (1H, t, J = 5.9 Hz), 5.49 (1H, d, J = 5.0 Hz), 7.45 (2H, d, J = 8.2 Hz), 7.97 (2H, d, J = 8.2 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 13.2, 13.7, 21.6, 57.5, 65.9, 66.1, 66.3, 68.0, 68.8, 69.0, 69.1, 69.3, 70.8, 72.6, 82.8, 84.2, 84.8, 127.3, 129.9, 137.9, 143.9. Anal. Calcd for $C_{31}H_{33}NO_3SFe_2$: C, 60.90; H, 5.44; N, 2.29. Found: C, 60.70; H, 5.18; N, 2.40; $[\alpha]_D^{22}$ +99.7 (*c* 0.80, $CHCl_3$); enantiomeric purity was determined by HPLC with Chiralcel OD-H (eluted with hexane/2-propanol (9/1), 0.5 mL/min); 95% ee.

10: 93%; yellow crystals; mp 177−178 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.35 (1H, d, J = 3.0 Hz), 2.48 (3H, s), 3.38−3.39 (1H, m), 4.03 (5H, s), 4.05 (5H, s), 4.07−4.29 (6H, m), 4.64 (1H, br), 5.53 (1H, d, J = 5.9 Hz), 7.42 (2H, d, J = 8.2 Hz), 8.08 (2H, d, J = 8.2 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 21.7, 44.9, 45.8, 56.8, 65.3, 68.0, 69.1, 70.8, 71.3, 71.6, 73.5, 74.3, 75.9, 81.0, 87.5, 127.6, 129.8, 137.2, 143.7. Anal. Calcd for $C_{29}H_{27}NO_3SFe_2I_2$: C, 41.71; H, 3.26; N, 1.68. Found: C, 41.68; H, 3.30; N, 1.61. $[\alpha]_D^{25}$ +5.0 (*c* 0.76, $CHCl_3$).

13a: yellow crystals; mp 145−146 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.69 (3H, s), 2.00 (1H, br), 2.46 (3H, s), 3.60 (2H, d, J = 7.5 Hz), 3.83 (1H, br), 3.93 (5H, s), 3.95−3.98 (3H, br), 4.05−4.06 (1H, br), 4.07 (5H, s), 4.12−4.22 (1H, m), 4.45 (1H, br), 5.27 (1H, d, J = 7.5 Hz), 7.38 (2H, d, J = 8.2 Hz), 7.91 (2H, d, J = 8.2 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 13.5, 21.6, 58.0, 65.3, 65.5, 66.0, 67.0, 67.7, 68.7, 68.8, 69.0, 69.8, 70.8, 82.7, 85.1, 86.6, 127.1, 129.5, 138.3, 143.3. Anal. Calcd for $C_{30}H_{31}NO_3SFe_2$: C, 60.32; H, 5.23; N, 2.34. Found: C, 60.19; H, 5.21; N, 2.30. $[\alpha]_D^{22}$ −22.8 (*c* 0.88, $CHCl_3$).

Cross-Coupling of Achiral Ferrocenylideneamine 2g with Benzaldehyde and the Corresponding Chromium Complexes. A typical procedure for the preparation of **18b** is as follows: To a solution of (*S*)-(+)-tricarbonyl(*o*-methoxybenzaldehyde)chromium (**17b**) (>99% ee) (100.0 mg, 0.27 mmol) and **2g** (100 mg, 0.27 mmol) in THF (1.0 mL) was added a solution of SmI_2 (0.10 M, 13.5 mL, 1.35 mmol) at 0 °C, and the mixture was stirred for 30 min. Usual workup gave the coupling product which was used for acetylation without purification. A solution of the obtained crude product in pyridine (2 mL), acetic anhydride (1 mL), and 4-dimethylaminopyridine (10.0 mg) was stirred at room temperature for 1 h under argon. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with ether. The reaction mixture was extracted with ether, and the extract was washed with aqueous 6 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with Et_2O/hexane; 1/1) to give 140.5 mg (94%) of **18b**: mp 154−155 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.43 (3H, s), 3.60 (1H, br), 3.79 (3H, s), 3.96 (1H, br), 4.04 (1H, br), 4.09 (1H, br), 4.15 (5H, s), 4.61 (1H, dd, J = 4.0, 7.6 Hz), 5.21 (1H, d, J = 7.6 Hz), 6.07 (1H, d, J = 4.0 Hz), 6.66 (1H, t, J = 7.9 Hz), 6.68 (1H, d, J = 7.2 Hz), 6.74 (1H, J = 7.9 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.30 (2H, d, J = 8.2 Hz), 7.80 (2H, d, J = 8.2 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 21.1, 21.6, 55.4, 55.5, 65.9, 66.9, 67.7, 68.7, 69.1, 71.7, 86.2, 110.0, 120.1, 125.2, 126.8, 126.9, 128.7, 129.5, 138.2, 143.1, 155.6, 169.2; IR (Nujol) 3250, 1740, 1600, 1320, 1230, 1160 cm^{-1}. Anal. Calcd for $C_{28}H_{29}NO_5SFe$: C, 61.43; H, 5.34; N, 2.56. Found: C, 61.25; H, 5.35; N, 2.45. $[\alpha]_D^{27}$ +66.7 (*c* 0.15, $CHCl_3$).

The cross-coupling products **30** derived from *N*-mesyl benzylideneamine (**29a**) with benzaldehydes or the corresponding chromium complexes were isolated as alcohol derivatives. **30a**: ^{1}H NMR (300 MHz, $CDCl_3$) for the syn isomer, δ 2.32 (1H, d, J = 3.3 Hz), 2.39 (3H, s), 4.65 (1H, t, J = 5.6 Hz), 4.94 (1H, dd, J = 5.6, 3.3 Hz), 5.32 (1H, d, J = 5.6 Hz), 7.03−7.11 (4H, m), 7.27−7.34 (6H, m); ^{1}H NMR (300 MHz, $CDCl_3$)for the anti isomer, δ 2.28 (1H, d, J = 4.4 Hz), 2.56 (3H, s), 4.73 (1H, dd, J = 8.1, 4.4 Hz), 5.13 (1H, t, J = 4.4 Hz), 5.15 (1H, d, J = 8.1 Hz), 7.05−7.11 (4H, m), 7.22−7.29 (6H, m); IR (Nujol) 3460, 3270, 1600, 1310, 1140 cm^{-1}. HRMS (FAB$^-$) calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0855.

The coupling products **30** derived from *N*-tosyl benzylideneamine (**29b**) with benzaldehydes or the corresponding chromium complexes were isolated as acetate derivatives. **30d**: colorless amorphous; ^{1}H NMR (300 MHz, $CDCl_3$) for the syn isomer, δ 2.03 (3H, s), 2.31 (3H, s), 4.68 (1H, t, J = 7.3 Hz), 5.57 (1H, br), 5.89 (1H, d, J = 7.3 Hz), 6.88−7.53 (14H, m); ^{1}H NMR (300 MHz, $CDCl_3$) for the anti isomer, δ 1.97 (3H, s), 2.32 (3H, s), 4.81 (1H, dd, J = 9.0, 4.5 Hz), 5.35 (1H, br), 5.91 (1H, d, J = 4.5 Hz), 6.88−7.53 (14H, m); IR (Nujol) 3300, 1730, 1600, 1320, 1240, 1160 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{23}H_{24}NO_4S$ 410.1427, found 410.1427.

32a: colorless amorphous; ^{1}H NMR (300 MHz, $CDCl_3$) for the syn isomer, δ 2.14 (3H, s), 2.71 (1H, br), 4.60 (1H, t, J = 6.2 Hz), 4.88 (1H, d, J = 6.2 Hz), 5.77 (1H, t, J = 6.2 Hz), 6.81−7.82 (16H, m); ^{1}H NMR (300 MHz, $CDCl_3$) for the anti isomer, δ 2.10 (3H, s), 2.55 (1H, br), 4.70 (1H, dd, J = 7.5, 3.9 Hz), 5.08 (1H, d, J = 3.9 Hz), 5.94 (1H, d, J = 7.5 Hz), 6.81−7.82 (16H, m); IR (Nujol) 3450, 3240, 1590, 1320, 1150 cm^{-1}. HRMS (FAB$^-$) calcd for $C_{25}H_{22}NO_3S$ 416.1321, found 416.1329.

Compound 33 (67%): yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (3H, s), 2.12 (3H, s), 2.29 (3H, s), 4.60 (1H, dd, J = 9.4, 6.5 Hz), 4.76 (1H, d, J = 6.2 Hz), 5.09 (1H, t, J = 6.2 Hz), 5.40 (1H, t, J = 6.2 Hz), 5.72 (1H, d, J = 6.2 Hz), 5.92 (1H, t, J = 6.5 Hz), 6.04 (1H, d, J = 9.4 Hz), 6.76−7.65 (9H, m); IR (Nujol) 3250, 1960, 1870, 1740, 1600, 1330, 1230, 1160 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{25}NO_7SCr$ 559.0757, found 559.0762; $[\alpha]^{19}_D$ +49.0 (*c* 0.10, $CHCl_3$). A solution of the chromium-complexed β-amino alcohol derivative **33** (56 mg, 0.10 mmol) in ether (5 mL) was exposed to sunlight at 0 °C for 30 min, and the mixture was filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with ether/hexane) to give (*R*,*R*)-*syn*-amino alcohol **34** (39 mg, 90%) as a colorless solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.96 (3H, s), 2.02 (3H, s), 2.33 (3H, s), 4.70 (1H, t, J = 7.1 Hz), 5.31 (1H, d, J = 7.1 Hz), 6.05 (1H, dt, J = 7.1 Hz), 6.89−7.39 (13H, m); IR (Nujol) 3180, 1720, 1600, 1340, 1240, 1160 cm^{-1}; HRMS (FAB−OAc) calcd for $C_{22}H_{22}NO_2S$ 364.1372, found 364.1372; $[\alpha]^{23}_D$ −26.6 (*c* 0.12, $CHCl_3$). The diastereomeric ratio of the syn and anti isomers was determined by ^{1}H NMR of the crude product without purification at each step. The protons of C*H*(NTs)-CH(OAc)- for the syn isomer appeared usually at higher field than those of the corresponding protons of the anti isomer. **34**: for the anti isomer 4.72 (1H, dd, J = 8.4, 4.6 Hz, −C*H*(NTs)−CH(OAc)−), 6.11 (1H, d, J = 4.6 Hz, −CH(NTs)−C*H*(OAc)−). The enantiomeric purity of **33** was determined by chiral HPLC with Chiralcel OD-H (eluted with hexane/2-propanol (9/1), 0.5 mL/min) and the ee of **34** was determined with Chiralcel OJ-H (eluted with hexane/2-propanol (9/1), 0.5 mL/min).

35: yellow amorphous; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (3H, s), 2.11 (3H, s), 2.14 (3H, s), 4.73 (1H, d, J = 6.2 Hz), 4.77 (1H, t, J = 7.7 Hz), 5.14 (1H, t, J = 6.2 Hz), 5.40 (1H, t, J = 6.2 Hz), 5.55 (1H, d, J = 7.7 Hz), 5.76 (1H, t, J = 6.2 Hz), 6.04 (1H, d, J = 7.7 Hz), 6.88 (2H, d, J = 7.3 Hz), 7.05 (1H, d, J = 8.8 Hz), 7.37−7.72 (8H, m); IR (Nujol) 3230, 1950, 1870, 1730, 1600, 1330, 1220, 1160 cm^{-1}; HRMS calcd for $C_{31}H_{27}NO_7SCr$ 609.0914, found 609.0915; $[\alpha]^{22}_D$ −31.1 (*c* 0.1, $CHCl_3$); 99% ee. HPLC conditions: Chiralcel OD, hexane/2-propanol (9/1), flow rate 0.5 mL/min, 40 °C, retention time 50.6 min.

Deiodonation of the Cross-Coupling Products 9b, 10, and *ent*-16 with *n*-BuLi. A typical procedure is as follows: To a solution of β-amino alcohol **9b** (100.0 mg, 0.12 mmol) in THF (5.0 mL) was added *n*-BuLi (1.6 M, 0.3 mL, 0.48 mmol) in hexane at 0 °C, and the solution was stirred at the same temperature for 1 h under argon atmosphere. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with Et_2O/hexane) to give 70.6 mg (95%) of **9g**: yellow

crystals; mp 146−147 °C dec; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.14 (1H, br), 3.69 (1H, s), 2.47 (3H, s), 3.66 (1H, s), 3.81 (2H, s), 3.97−4.01 (3H, m), 4.03 (5H, s), 4.06 (5H, s), 4.27−4.33 (3H, m), 5.08 (1H, d, J = 7.9 Hz), 7.41 (2H, d, J = 8.2 Hz), 7.92 (2H, d, J = 8.2 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 21.6, 59.1, 65.9, 66.4, 67.4, 67.5, 67.6, 67.7, 67.8, 67.9, 68.5, 68.8, 72.6, 84.9, 87.6, 127.2, 129.8, 138.1, 143.7. Anal. Calcd for $C_{29}H_{29}NO_3SFe_2$: C, 59.71; H, 5.01; N, 2.40. Found: C, 59.67; H, 5.04; N, 2.34. $[\alpha]_D^{26}$ +40.8 (c 0.61, $CHCl_3$).

Desulfonylation of 9. A typical procedure is as follows: A mixture of Li metal (29.0 mg, 4.25 mmol) and naphthalene (4.0 mg, 0.03 mmol) in dry THF (5.0 mL) was stirred for 2 h at −78 °C under argon atmosphere. A solution of amino alcohol **9g** (100.0 mg, 0.17 mmol) in dry THF (3.0 mL) was added to a lithium naphthalenide solution at −78 °C with stirring for 2 h. The reaction mixture was quenched with MeOH and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with ethyl acetate/hexane) to give 67.5 mg (92%) of desulfonylated amino alcohol **39** ($R^1 = R^2 = H$): yellow crystals; mp 157−158 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.87 (1H, br), 3.69 (1H, d, J = 5.0 Hz), 3.96 (1H, s), 4.04 (1H, s), 4.08−4.10 (8H, m), 4.11 (5H, s), 4.15 (5H, s), 4.23 (1H, d, J = 5.0 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 56.6, 65.1, 65.4, 67.3, 67.5, 67.6, 67.7, 68.2, 68.3, 68.4, 68.6, 74.5, 89.6, 90.5. Anal. Calcd for $C_{22}H_{23}NOFe_2$: C, 61.58; H, 5.40; N, 3.26. Found: C, 61.51; H, 5.42; N, 3.23. $[\alpha]^{23}_D$ −24.0 (c 0.20, $CHCl_3$).

Catalytic Asymmetric Reduction of Acetophenone. After a solution of methylboronic acid (0.05 mmol) and chiral β-amino alcohol **39** ($R^1 = R^2 = H$) (0.042 mmol) in toluene (20 mL) was refluxed for 2 h, the reaction mixture was reduced by vacuum pump. The residue was dissolved in dry toluene (2 mL) and evaporated under reduced pressure. After carrying out this operation three times, the residue was dissolved in THF (4 mL). To the above solution was added a borane (1.0 M in THF, 0.83 mL, 0.83 mmol), and the reaction mixture was stirred for 15 min at room temperature. A solution of acetophenone (100 mg, 0.83 mmol) in THF (1 mL) was added to the above solution at room temperature with a syringe over 10 min, and stirring was continued for 1 h. After being quenched with MeOH (4 mL) and 1 M aqueous HCl (4 mL), the reaction mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography to give α-phenyl ethyl alcohol. The enantiomeric purity and absolute configuration were determined by chiral HPLC with chiralcel OD-H with comparison of authentic optically active and racemic compounds. HPLC conditions: hexane/2-propanol 9/1, column temperature 40 °C, flow rate 0.5 mL/min, (*S*)-(+)-isomer 12.3 min, (*R*)-(−)-isomer 13.1 min.

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Supporting Information Available: Experimental details for the reductive cross-coupling, as well as spectral data for new compounds and X-ray analysis of **9a**, *ent*-**10**, and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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