Asymmetric Synthesis of β-Amino Alcohols by Cross-Pinacol Coupling of Planar Chiral Ferrocenecarboxaldehydes with Imines

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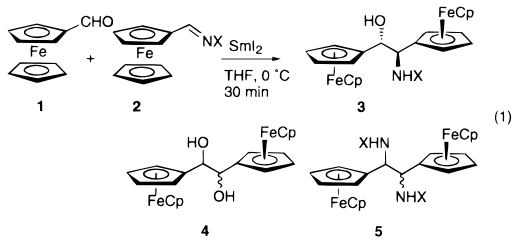
Although a pinacol coupling of carbonyl or imine compounds is the most direct way to synthesize 1,2-diols or diamines, a highly stereoselective formation of these compounds is problematic.[1] Furthermore, the preparation of optically enriched compounds is not so easy under pinacol coupling conditions.[2] In contrast to the *homo*-pinacol coupling, the cross-coupling reaction between two substrates is an even more complicated problem. Only few examples of an intermolecular cross-coupling of carbonyls with imines have been reported as a racemic form.[3] We now wish to report enantioselective synthesis of β-amino alcohols by samarium iodide-mediated cross-coupling of the planar chiral *N*-sulfonyl ferrocenylideneamine with carboxaldehydes.

To achieve an efficient cross-pinacol coupling between two substrates, it is apparently significant for either substrate to be more easily reduced to the corresponding ketyl radical or ionic species, and the generated reactive species to react with another substrate prior to the *homo*-coupling. We initially focused on the effect of the substituent on the nitrogen atom for the cross-coupling between ferrocenecarboxaldehyde and the corresponding aldimines (Table 1). Among various *N*-substituents studied, it was fortunately found that an electron-withdrawing *N*-phenylsulfonyl ferrocenylideneamine was critical for the effective cross-coupling with aldehyde **1**. Thus, reductive coupling of *N*-phenylsulfonyl ferrocenylideneamine **2** (X = SO_2Ar) with **1** gave *erythro* β-amino alcohol[4] as a single diastereomer (entries 6, 7). In any event, efficient achievement of cross-coupling between the aldehyde **1** and *N*-arylsulfonyl ferrocenylidenimines **2f**, **2g** would be attributed to the remarkable different reduction potentials between both substrates.[5]

We next turned our attention to the preparation of optically active β-amino alcohols utilizing planar chiral ferrocenyl compounds. (+)-(*R*)-2-Methylferrocenecarboxaldehyde **6a**[6] was coupled with (*R*)-*N*-tosyl 2-methylferrocenylideneamine **7a**[7] to give the *erythro* β-amino alcohol **8** ($R^1 = R^2 =$ Me) (Table 2, entry 1). The stereochemistry at α- and α′-positions was determined as ($R_α$,$S_{α'}$)-configuration by X-ray crystallography.[8] Similarly, the cross-coupling between other planar chiral ferrocenecarboxaldehydes **6b**,**c** and same planar chiral imines **7b**,**c** produced the corresponding ($R_α$,$S_{α'}$)-β-amino alcohols **8** (entries 2, 3). Interestingly, β-amino alcohols **8** obtained by the cross-coupling were *erythro* isomers, while the *homo*-pinacol coupling of the planar chiral ferrocenecarboxaldehydes gave exclusively the *threo*-diols.[9] Deiodination of the cross-coupling product **8** ($R^1 = R^2 =$ I) with *n*-BuLi gave ($R_α$,$S_{α'}$)-amino alcohol **8** ($R^1 = R^2 =$ H; $[α]^{26}_D$ +40.8, 95% ee)[8] in 96% yield.

Table 1. Cross-Coupling between Ferrocenecarboxaldehyde **1** and Ferrocenylideneamine **2**



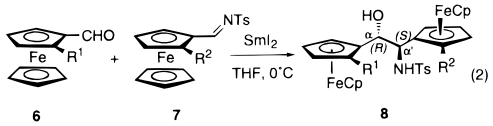
1 2 3 4 5 (1)

a: X = Me, **b:** X = Bn, **c:** X = Ph, **d:** X = NMe_2, **e:** X = $NHSO_2Ph$, **f:** X = $NHSO_2Ph$, **g:** X = $NHSO_2Ph$-(*p*-Me)

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

[a] Obtained **1** as hydrolysis product of **2** in >98% yield. [b] Recovered **2** in 90−98% yield.

Table 2. Samarium(II)-Mediated Cross-Coupling of Planar Chiral Ferrocenecarboxaldehydes **6** and Imines **7**



(2)

6
a: R^1 = Me
b: R^1 = I
c: R^1 = Br
d: R^1 = H

7
a: R^2 = Me
b: R^2 = I
c: R^2 = Br

8

entry	aldehydes % ee[a]	imines	**8** Yield (%)	$[α]_D$ ($CHCl_3$)	% ee **8**[b]
1	**6a** 95	**7a**	92	+99.7 (*c* 0.80)	95
2	**6b** 95	**7b**	90	−9.7 (*c* 0.40)	95
3	**6c** 97	**7c**	93	+1.8 (*c* 0.52)	97
4	**6d** −	**7a**	91	+90.3 (*c* 0.84)	92
5	**6d** −	**7b**	96	−16.8 (*c* 0.63)	94
6	**6d** −	**7c**	95	+3.8 (*c* 0.30)	97

[a] Enantiomeric excess was determined by HPLC with Chiralpack AS (eluted with hexane/2-propanol (9/1), 1.0 mL/min). [b] Enantiomeric excess was determined by HPLC with Chiralcel OD (eluted with hexane/2-propanol (9/1), 0.5 mL/min).

(1) Some representative reviews: Imamoto, T. *Lanthanoids in Organic Synthesis*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1994. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. Molander, G. A. *Org. React.* **1994**, *46*, 211.

(2) Matsubara, S., Hashimoto, Y., Okano, T.; Utimoto, K. *Synlett* **1999**, 1411−1412. Bandini, M.; Cozzi, G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997−2000.

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(4) The formation of *erythro* β-amino alcohols is sharp in contrast to the predominant formation of *threo*-diastereomers in $NbCl_3$-catalyzed cross-coupling between aldehydes and imines. see ref 3a.

(5) Reduction potential by cyclic voltammetric studies; −2.3 V for **1**; −2.4 V for **2a**; −2.0 V for **2c**, −1.8 V for **2g**.

(6) The planar chiral *ortho*-substituted ferrocenecarboxaldehydes **6** were prepared by diastereoselective lithiation of chiral ferrocenyl acetal according to the literature procedure. Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733−6745.

(7) Optically active ferrocenylimines **7** were prepared by treatment of the corresponding planar chiral ferrocenecarboxaldehydes **6** with *p*-$TsSO_2NH_2$ in the presence of molecular seives 4Å and catalytic amount of *p*-TsOH in refluxing toluene in good yields. The optical purities for imines **7** were identical with those of the corresponding aldehydes **6** by HPLC with Chiralcel OD.

(8) The authors have deposited atomic coordinates for the structures **8** ($R^1 = R^2 =$ I) and **9a** with the Cambridge Crystallographic Data Centre. The X-ray data can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(9) (a) Taniguchi, N.; Kaneta, N.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 6088−6089. (b) Taniguchi, N.; Uemura *Synlett* **1997**, 51−53. (c) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1998**, *39*, 5385−5388. (d) Taniguchi, N.; Uemura, M. *Tetrahedron* **1998**, *54*, 12775−12788.

(10) Enantiomeric excess for compounds **8**, **9**, and **10** was determined by HPLC with Chiralcel OD.

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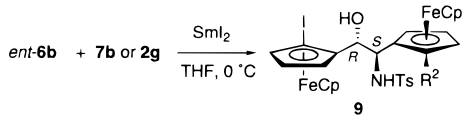
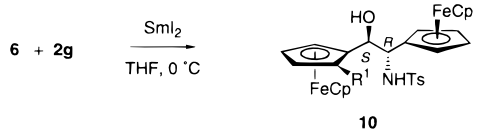
Scheme 1. Coupling of Antipode (−)-(*R*)-2-Iodoferrocenecarboxaldehyde *ent*-**6b**



a: R^2 = I (93%), **b:** R^2 = H (92%)

Scheme 2. Cross-Coupling of Planar Chiral Ferrocenecarboxaldehyde **6** with Non-Planar Chiral Imine **2g**



R^1 = Me (92%, 92%ee), I (94%, 94%ee), Br (91%, 93%ee), $SiMe_3$ (91%, 94%ee)

Our attention was next focused on the stereochemistry of the cross-coupling β-amino alcohols obtained by two combinations between the planar chiral ferrocenyl compounds and nonplanar chiral ferrocenes. The cross-coupling of nonplanar chiral ferrocenecarboxaldehyde **6d** with planar chiral *N*-tosyl 2-substituted ferrocenylideneamines **7a**∼**7c** gave amino alcohols **8** (R^1 = H, R^2 = Me, I, Br) as a single detectable cross-coupling product (Table 2, entries 4−6). Furthermore, the cross-coupling of antipode (−)-(*R*)-2-iodoferrocenecarboxaldehyde, *ent*-**6b**, (95% ee) with (*S*)-ferrocenyl imine **7b** gave an amino alcohol **9a** ($[\alpha]^{25}_D$ +5.0, 95% ee) (Scheme 1). The absolute stereochemistry of **9a** was confirmed by X-ray crystallography,[8] and the deiodination product was consistent with β-amino alcohol **8** ($R^1 = R^2$ = H) ($[\alpha]^{23}_D$ +40.8 ($CHCl_3$)) regarding all spectra data including optical rotation. These results indicate that the absolute stereochemistry at the α,α'-positions of β-amino alcohols was governed by the planar chirality of ferrocenylideneamines, regardless of the presence or absence of a substituent on the ferrocenecarboxaldehyde ring. In an alternative combination of the cross-coupling of nonplanar chiral *N*-tosyl ferrocenylideneamine **2g** with planar chiral 2-substituted ferrocenecarboxaldehydes, the absolute configuration of the cross-coupling β-amino alcohols was found to be controlled by the planar chirality of ferrocenecarboxaldehydes as follows (Scheme 2). Thus, the coupling of (+)-(*S*)-2-iodoferrocenecarboxaldehyde **6b** with **2g** gave an amino alcohol **10** (R^1 = I) which was converted to the deiodinated ($S_\alpha,R_{\alpha'}$)-compound **10** (R^1 = H) with *ent*-**8** ($R^1 = R^2$ = H). Similarly, the planar chiral ferrocenecarboxaldehydes **6** with other substituent gave the corresponding ($S_\alpha,R_{\alpha'}$)-amino alcohols **10** in good yields. On the other hand, (*R*)-2-iodoferrocenecarboxaldehyde *ent*-**6b** was coupled with nonplanar chiral imine **2g** to produce the enantiomeric ($R_\alpha,S_{\alpha'}$)-amino alcohol **9b** (95% ee) under the same conditions (Scheme 1).[11]

A reaction mechanism has been postulated to rationalize the observed stereoselectivities of the cross-coupling (Figure 1). Sulfonyl ferrocenylideneimine generates a dianion species by two electron reduction. Generation of the dianion intermediate was supported by reduction of *N*-tosyl imine **2g** with SmI_2 in the presence of CH_3OD in THF giving a deuterium-incorporated C═N reduction product. In the cross-coupling with planar chiral *N*-tosyl 2-substituted ferrocenylideneamines **7**, the dianion intermediate **11** generated by an *exo*-side attack of SmI_2 to an *anti*-oriented[12] C═N double bond to the *ortho*-substituent is configurationally stable against epimerization.[13] No epimerization between

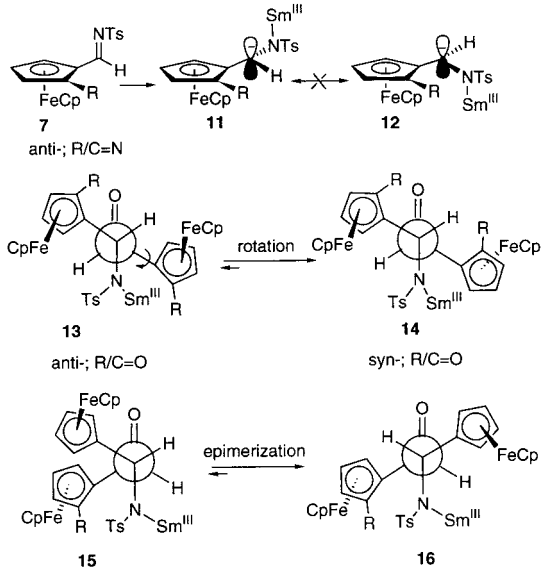


Figure 1. Proposed reaction mechanism.

11 and **12** would be attributed to an interaction of p-orbital of α-carbon with d-orbital of iron metal, resulting in the formation of an *exo*-cyclic double bond character. Taking into account the following transition states **13** and **14**, the *N*-tosyl group is oriented in *anti*-orientation[14] to the carbonyl oxygen of ferrocenecarboxaldehydes due to dipole repulsion. Although the carbonyl oxygen of ferrocenecarboxaldehydes exists preferentially in *anti*-conformation[12] to the *o*-substituent, the transition state **13** causes severe steric interaction between the FeCp ring of aldehyde and the ferrocenyl imine because of the same planar chirality of both substrates. Therefore, an alternative *syn*-oriented transition state **14** is favorable for the cross-coupling, giving the ($R_\alpha,S_{\alpha'}$)-amino alcohols **8**. Thus, the proposed model of the cross-coupling for *erytho*-selectivity is different with *homo*-pinacol coupling of ferrocenecarboxaldehydes giving *threo* 1,2-diols via coordination model of the samarium with two oxygens.[9] On the other hand, the generated dianion species from nonplanar chiral ferrocenylideneamine **2g** is rapidly equilibrating at the generated stereogenic center. However, the planar chiral ferrocenecarboxaldehyde could intercept either dianion species among the equilibrated carbanions depending on the planar chirality of carboxaldehyde. Thus, the *anti*-oriented carbonyl of ferrocenecarboxaldehyde is attacked via sterically less hindered transition state **16** giving single *erytho* amino alcohol. In this way, the cross-coupling of the nonplanar chiral ferrocenylideneimine with *o*-substituted ferrocenecarboxaldehydes occurs through a dynamic kinetic resolution of an enantiotopic face of the equilibrating α-ferrocenyl carbanion configuration.

In summary, we have developed the synthesis of enantiomerically pure β-amino alcohols by cross-coupling of the planar chiral ferrocenylideneimines with aldehydes.

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Supporting Information Available: Experimantal details for the cross-pinacol coupling as well as spectra data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The same stereochemical behavior was observed in samarium iodide-mediated cross-coupling between **2g** and planar chiral benzaldehyde tricarbonylchromium complexes. *N*-Phenylsulfonyl benzylideneamine was also coupled with aldehydes giving β-amino alcohols.

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

(13) α-Ferrocenyllithium 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*, 1457−1460.

(14) A mechanism of acyclic selection in intermolecular radical reactions and intramolecular radical cyclization between carbonyls and imines. (a) Smadja, W. *Synlett* **1994**, 1−26. (b) Bobo, S.; Storch de Gracia, I.; Chiara, J. S. *Synlett* **1999**, 1551−1554. (c) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877−5882.