ORGANIC LETTERS

2002
Vol. 4, No. 5
835−838

Asymmetric Synthesis of β-Amino Alcohols by Reductive Cross-Coupling of Benzylideneamine with Planar Chiral Benzaldehydes

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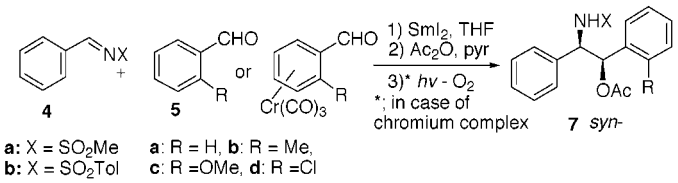
Received January 8, 2002

ABSTRACT



Samarium iodide mediated reductive cross-coupling of *N*-tosyl benzylideneamine with benzaldehydes or the corresponding chromium complexes gave *syn*-β-amino alcohol derivatives. A dynamic kinetic resolution of a configurationally equilibrated reactive species occurred in the cross-coupling with planar chiral benzaldehyde chromium complexes.

Enantiomerically pure β-amino alcohols have played significant roles as chiral ligands or auxiliaries in asymmetric reactions[1] and are important key synthetic intermediates for biologically active natural products.[2] When not available by direct reduction of amino acids, β-amino alcohols are often prepared by indirect routes involving various permutations of stepwise bond construction with asymmetric induction.[3] Usually, nucleophilic addition reactions to chiral α-amino carbonyls, hydroxy imines, or hydroxyoximes are employed for stereoselective synthesis of optically active β-amino alcohols.[4] New synthetic strategy for the preparation of enantiopure β-amino alcohols is still in high demand.

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10.1021/ol0255256 CCC: $22.00
Published on Web 02/14/2002

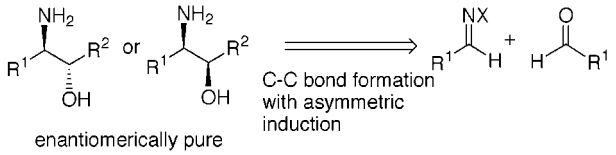
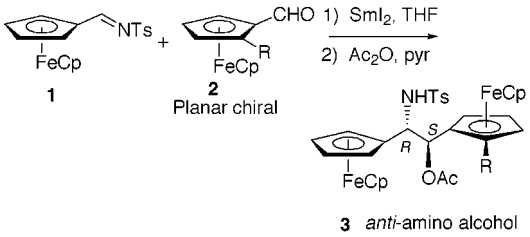


Figure 1. Carbon−carbon disconnection for β-amino alcohols.

Reductive cross-coupling between aldehydes and aldimines seems to be the most direct way for the preparation of β-amino alcohols (Figure 1), but many problems preclude an efficient cross-coupling in this procedure. 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. For an efficient cross-coupling between two substrates, it is apparently significant for either substrate to be more easily reduced to the corresponding radical or ionic species and the generated reactive species to couple with the other substrate prior to a *homo*-coupling. Only a few examples are reported of an intermolecular reductive cross-coupling between carbonyls and imines giving β-amino alcohols.[5] However, β-amino alcohols were obtained as a diastereomeric mixture of racemic *anti*- and *syn*-isomers in these methods. As part of our exploration of the asymmetric synthesis utilizing planar chiral transition metal-coordinated molecules, we have investigated the reductive cross-coupling giving optically active β-amino alcohols.

We recently reported that the reductive cross-coupling of *N*-tosyl ferrocenylideneamine (**1**) with planar chiral ferrocenecarboxaldehydes **2** in the presence of samarium iodide gave enantiomerically pure *anti* β-amino alcohol derivatives **3** in good yields (Scheme 1).[6] It was found that an electron-withdrawing sulfonyl group such as the *N*-substituent of the aldimine was essential for the achievement of efficient cross-coupling without *homo*-coupling.

Scheme 1. Cross-Coupling of *N*-Tosyl Ferrocenylideneamine with Planar Chiral Ferrocenecarboxaldehydes



(5) An intermolecular cross-coupling between carbonyls and imines for synthesis of β-amino alcohols: (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551. (b) Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, *32*, 525 (c) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191. (d) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *59*, 1730. (e) Machrouhi, H.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315. (f) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.***1991**, *32*, 3555.

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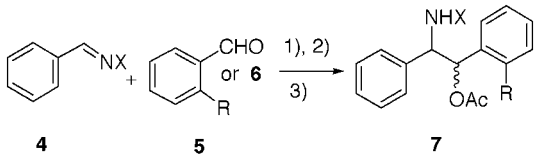
Scheme 2[a]



a: X = SO_2Me **a**: R = H, **b**: R = Me,
b: X = SO_2Tol **c**: R =OMe, **d**: R =Cl
6 : $Cr(CO)_3$ complex of **5**

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

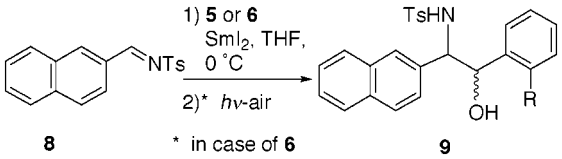
For further extension of the versatility of this type of reductive cross-coupling giving optically active β-amino alcohols, we studied other combinations between alidimines and aldehydes. Samarium iodide mediated cross-coupling of *N*-methanesulfonyl benzylideneamine (**4a**) with benzaldehydes **5** was initially studied, and the results are summarized in Table 1. Although the cross-coupling β-amino alcohol derivatives **7** were obtained in good yields without formation of *homo*-coupling products, the diastereoselectivity of *anti*- and *syn*-β-amino alcohols was extremely low (entries 1−3). The corresponding benzaldehyde tricarbonylchromium complexes **6** were also coupled with the imine **4a**, and the diastereoselectivity increased slightly (entries 4−6). The nitrogen substituent of electron-withdrawing benzylideneamine was next changed to an *N*-tosyl group directed toward high diastereoselectivity. Fortunately, the diastereoselectivities of the cross-coupling products in the combination between *N*-tosyl benzylideneamine (**4b**) and benzaldehydes increased appreciably (entries 7−10). Among the *ortho*-substituted benzaldehydes studied, *o*-chlorobenzaldehyde (**5d**) resulted with higher diastereoselectivity in 52% yield

Table 1. Cross-Coupling of Benzylideneamines **4** with Benzaldehydes **5** or Chromium Complexes **6**

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

[a] Isolated as *N*-mesyl amino alcohols without acetylation. [b] *Homo*-coupling 1,2-diols were obtained in 1−5% yields. [c] Yield of cross-coupling was 60% before photo-oxidation.

Scheme 3



(entry 10). Therefore, a coordination of more electron-withdrawing $Cr(CO)_3$ fragment to the arene ring would be expected to increase the diastereoselectivity. As expected, the cross-coupling of benzaldehyde chromium complex (**6a**) with *N*-tosyl benzylideneamine (**4b**) gave *β*-amino alcohol derivative **7** (X = *p*-Ts, R = H) with high diastereoselectivity in 73% overall yield after acetylation and subsequent demetalation (entry 11). The increase of diastereoselectivity by tricarbonylchromium complexation would be attributed to a stereoelectronic effect of the tricarbonylchromium fragment.[7]

Interestingly, the major *β*-amino alcohol **7** obtained in this combination was found to be a *syn*-isomer.[8] The formation of *syn*-amino alcohol in this combination is in sharp contrast to the samarium iodide mediated reductive cross-coupling between *N*-tosyl ferrocenylideneamine (**1**) and ferrocenecarboxaldehydes, in which the *anti*-amino alcohols were exclusively obtained as shown in Scheme 1.[9] Similarly, *ortho*-substituted benzaldehyde chromium complexes were coupled with *N*-tosyl benzylideneamine (**4b**) to produce the corresponding *syn*-amino alcohols along with formation of small amount (1−5%) of *homo*-coupling 1,2-diols derived from benzaldehyde chromium complexes under the same conditions (entries 12−14). Unfortunately, samarium iodide mediated cross-coupling of **4b** with ferrocenecarboxaldehyde instead of the benzaldehyde chromium complexes gave a *homo*-coupling 1,2-diol in 95% yield without formation of the expected *β*-amino alcohol. However, *N*-methanesulfonyl analogue **4a** was coupled with ferrocenecarboxaldehyde to give the corresponding *β*-amino alcohol as a diastereomeric mixture in only 15% yield.[10] Thus, the electronic factor of both substrates would be significant for the achievement of cross-coupling giving *β*-amino alcohols in high yield.

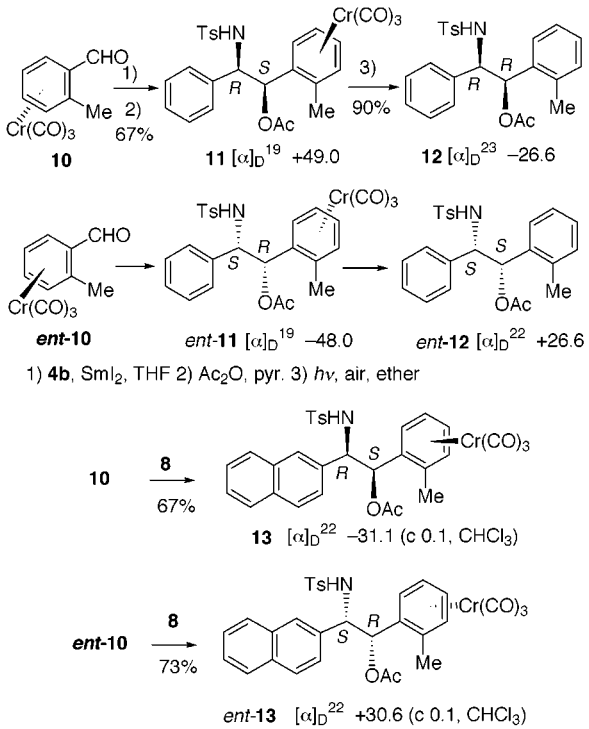
The cross-coupling of *N*-tosyl naphthylimines with benzaldehydes was also examined (Scheme 3, Table 2). *β*-Naphthylimine **8** was coupled with benzaldehydes **5** to give a diastereomeric mixture of *β*-amino alcohol derivatives **9** in good yield, while the corresponding α-naphthylimine gave no cross-coupling product under the same conditions. 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 cross-coupling with the imine **8**.

Table 2. Cross-Coupling of *β*-*N*-Tosyl Naphthylimines **8** with Benzaldehydes **5** or Chromium Complexes **6**

entry	aldehyde	yield **9** (%)	*syn*/*anti*
1	**5a**	83	65/35
2	**5b**	89	78/22
3	**5c**	76	74/26
4	**6a**	67	94/6
5	**6b**	74	83/17
6	**6c**	89	78/22

We next turned our attention to the preparation of optically active *β*-amino alcohol derivatives by using planar chiral benzaldehyde chromium complexes (Scheme 4). The planar chiral (+)-(1*S*)-*o*-methylbenzaldehyde chromium complex (**10**)[11] (>99% ee) was coupled with **4b** to give a chromium-complexed (1*S*,2*R*)-*β*-amino alcohol derivative **11** ($[\alpha]^{19}_D$ +49.0; >99% ee).[12] Exposure of **11** to sunlight gave a chromium-free (*R*,*R*)[13]-*syn*-*β*-amino alcohol derivative **12**

Scheme 4. Enantiopure *β*-Amiono Alcohol by Reductive Cross-Coupling



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

(8) Authentic stereodefined *anti*-*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.

(9) Similarly, the cross-coupling of *N*-tosyl ferrocenylideneamine (**1**) with benzaldehydes or the corresponding chromium complexes gave exclusively *anti*-*β*-amino alcohols under the same conditions: unpublished results.

(10) A *homo*-coupling 1,2-diol was in 80% yield as a major product.

(11) Enantiomerically pure chromium complexes were obtained by optical resolution of diastereomers derived from L-valinol: Bromley, L. A.; Davies, S. G.; Goodfellow, C. L. *Tetrahedron: Asymmetry* **1991**, *2*, 139.

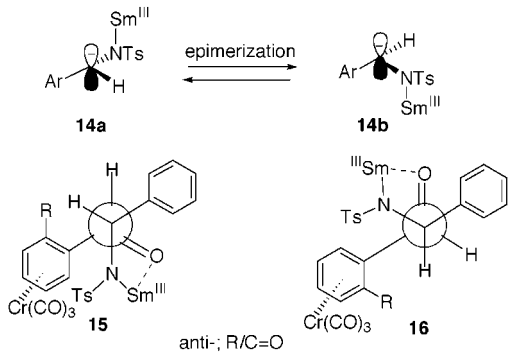


Figure 2. Proposed reaction mechanism.

([α]$^{23}_{D}$ −26.6).[12] On the other hand, an antipode (−)-*o*-methylbenzaldehyde chromium complex *ent*-**10** produced (+)-(*S*,*S*)-*syn*-*β*-amino alcohol *ent*-**12** ([α]$^{23}_{D}$ +26.6) under the same reaction sequence. In this way, both enantiomers of *syn*-*β*-amino alcohol were stereoselectively prepared by the coupling of benzylideneamine with the planar chiral benzaldehyde chromium complex. Similarly, the cross-coupling of *N*-tosyl *β*-naphthylimine **8** with planar chiral benzaldehyde chromium complexes **10** and *ent*-**10** gave both enantiomers of the corresponding *syn*-*β*-amino alcohol derivatives **13** and *ent*-**13**, respectively, depending on the planar chirality. Thus, a configurationally equilibrated reactive species generated from the imines **4b** or **8** by the reduction with samarium iodide underwent a dynamic kinetic resolution in the cross-coupling with the planar chiral benzaldehyde chromium complexes in analogy with the cross-coupling[6] of *N*-tosyl ferrocenylideneamine with the planar chiral ferrocenecarboxaldehydes.

In this way, the cross-coupling of *N*-tosyl benzylideneamine (**4b**) with benzaldehydes or their chromium complexes gave predominantly *syn*-*β*-amino alcohols in the presence of samarium iodide. A reaction mechanism has been postulated to rationalize the observed *syn*-stereoselectivity (Figure 2). The generated reactive species from the imine **4b** would be rapidly equilibrated at the newly created stereogenic center between **14a** and **14b**. The planar chiral *ortho*-substituted benzaldehyde chromium complex could exclusively intercept either configurational species depending on the planar chirality. Taking into account the following transition states **15** and **16**, the samarium metal could coordinate with both nitrogen and carbonyl oxygen atoms. Furthermore, it is well-known that the carbonyl oxygen of *ortho*-substituted benzaldehyde chromium complexes exists preferentially in an *anti*-conformation with the *ortho*-substituent as the result of a stereoelectronic effect in both solid and solution state.[14] Therefore, (+)-planar chiral benzaldehyde chromium complex **10** reacts with the intermediate **14a** to give the *syn*-*β*-amino alcohol derivative **11** through the transition state **15** with minimal steric hindrance. The corresponding antipode (−)-*ent*-**10** reacted with **14b** giving the antipode amino alcohol derivative via the transition state **16**. However, the *anti*-*β*-amino alcohols were obtained in the cross-coupling between *N*-tosyl ferrocenylideneamine (**1**) and aldehydes through the transition state with a dipole−dipole repulsion between the nitrogen and carbonyl oxygen atoms. The formation of the stereochemically different *β*-amino alcohols in both combinations might be attributed to an electronic character between two the aldimines **1** and **4b**, although the precise reaction mechanism is not clear at the present time. We are now investigating asymmetric reaction utilizing the optically pure *β*-amino alcohols as a chiral ligand or auxiliary and elucidation of plausible reaction mechanism.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research from a Ministry of Education, Science, Sports and Culture.

Supporting Information Available: Experimental procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Optical purities of **11** and chromium-free **12** were determined by chiral HPLC. For racemic **11**: chiralcel OD-H, hexane/2-propanol (9/1), flow rate 0.5 mL/min, 40 °C, retention time 33.1 and 36.0 min. For racemic **12**: chiralcel OJ-H, hexane/2-propanol (9/1), flow rate 0.5 mL/min, 40 °C, retention time 20.4 and 25.0 min.

(13) The absolute configuration of the *syn*-coupling product **12** was determined as (*R*,*R*)-configuration by comparison of the optical rotation sign of authentic *syn*-*β*-amino alcohol derived from (*R*)-2-phenylglycine according to ref 8c.

(14) (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, 1995; Vol. 12, p 1039.