Communication

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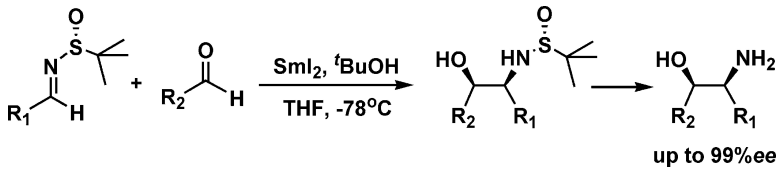

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A Highly Efficient and Direct Approach for Synthesis of Enantiopure β-Amino Alcohols by Reductive Cross-Coupling of Chiral *N*-*tert*-Butanesulfinyl Imines with Aldehydes

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Optically active β-amino alcohols are versatile building blocks for medicinal chemistry and natural product synthesis.[1] They have also been used as powerful chiral ligands or auxiliaries in asymmetric synthesis.[2] Due to their great importance, considerable efforts have been made to develop efficient methods for their preparation.[3] Among them, the pinacol-type cross-coupling between carbonyls and imines is one of the most direct ways to construct β-amino alcohols. However, a serious issue is that achievement of both good chemoselectivity and stereoselectivity is often difficult. Because of this, only a few examples of intermolecular cross-coupling to form racemic β-amino alcohols have been reported;[4] a highly diastereo- and enantioselective crossed pinacol coupling remains a significant synthetic challenge. To our knowledge, only recently has asymmetric synthesis of β-amino alcohols by cross pinacol coupling using planar chiral substrates been realized,[5] but the products are limited to ferrocenyl or $Cr(CO)_3$ aromatic derivatives; new approaches with broader substrate generality are still in high demand. In this communication, we wish to report a highly promising asymmetric pinacol-type coupling of chiral *N*-*tert*-butanesulfinyl imines with aldehydes, leading to enantiopure β-amino alcohols directly.

Our laboratory recently documented the first use of samarium diiodide-induced cross-coupling of nitrones with chiral *N*-*tert*-butanesulfinyl imines[6] for the asymmetric synthesis of unsymmetrical vicinal diamines.[7] Excellent enantioselectivities, as well as high diastereoselectivities, were observed in this reaction. On the basis of this success, we wondered whether this approach could be extended to asymmetric synthesis of vicinal amino alcohols. In our effort to develop such a process, we discovered that the cross-coupling between chiral *N*-*tert*-butanesulfinyl imines and aldehydes in the presence of samarium diiodide could lead to the formation of β-amino alcohols with excellent enantiomeric excesses and in good yields.

Cross-coupling of *N*-sulfinyl imine **1a** with benzaldehyde was initially examined using our previously reported conditions.[7] However, the result was disappointing. Considerable amount of the pinacol formation from benzaldehyde was found, and no desired cross-coupling product was isolated. With *p*-tolualdehyde, trace amounts of cross-coupling product were observed. Considering the relatively high reactivity of aromatic aldehydes under SmI_2,[8] we turned our attention to aliphatic aldehydes. To our delight, when isobutyraldehyde (1.2 equiv) was used as substrate, the reaction proceeded smoothly in the presence of 2 equiv of SmI_2. After 4 h, the expected β-amino alcohol derivative **2a** was obtained in 88% yield with extremely high diastereoselectivity (>99% de)[9] (Scheme 1), and no pinacol formation was detected in this reaction.

Scheme 1

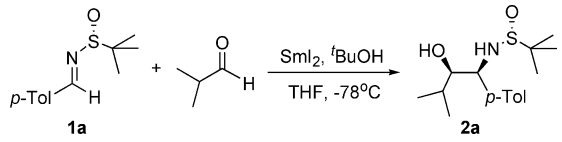
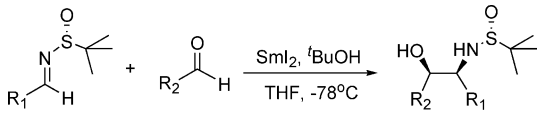


Table 1. SmI_2-Induced Reductive Cross-Coupling of Aldehydes with *N*-*tert*-Butanesulfinyl Imines



entry[a]	R_1	R_2	**2**	*T* (h)	yield (%)[b]	dr[c]	ee[d]
1	4-$CH_3C_6H_4$	^{i}Pr	**2a**	4	92	>99:1	98
2	4-$CH_3C_6H_4$	C_6H_{11}	**2b**	7	90	99:1	>99
3	4-$CH_3C_6H_4$	$(Et)_2CH$	**2c**	7	73	>99:1	99
4	4-$CH_3C_6H_4$	n-C_5H_{11}	**2d**	7	90	91:9	95
5	4-$CH_3C_6H_4$	PhC_2H_4	**2e**	7	95	88:12	95
6	Ph	^{i}Pr	**2f**	7	86	99:1	97
7	4-FC_6H_4	^{i}Pr	**2g**	4	89	98:2	>99
8	4-ClC_6H_4	^{i}Pr	**2h**	4	71	99:1	98
9	4-BrC_6H_4	^{i}Pr	**2i**	4	70	>99:1	>99
10	4-$AcOC_6H_4$	^{i}Pr	**2j**	4	82	>99:1	>99
11	4-$CH_3OC_6H_4$	^{i}Pr	**2k**	4	84	>99:1	>99
12	3,4-$(MeO)_2C_6H_3$	^{i}Pr	**2l**	7	90	>99:1	>99
13	2,4-$(MeO)_2C_6H_3$	^{i}Pr	**2m**	7	73	>99:1	>99
14	^{i}Pr	^{i}Pr	**2n**	6	88	>99:1	98
15	$PhCH_2CH_2$	^{i}Pr	**2o**	6	87	96:4	>99
16	$CH_3(CH_2)_4$	^{i}Pr	**2p**	6	95	98:2	97
17	$BnOCH_2$	^{i}Pr	**2q**	8	82	>99:1	97

[a] See Supporting Information for reaction details. [b] Isolated yield. [c] According to HPLC-MS and ^{1}H NMR of the crude materials. [d] Enantiomeric excess for the free β-amino alcohols after acidic hydrolysis of **2**; see Supporting Information for details.

Subsequent optimization of the reaction condition indicated that a further improvement of the yield (92%) could be achieved by employing a little more excess (1.5 equiv) of aldehyde substrate. Also, *tert*-butyl alcohol was found to be essential in the reaction for the achievement of high yield.[10]

The success of the cross-coupling between *N*-sulfinyl imine **1a** and isobutyraldehyde prompted us to extend the general scope of the reaction. Under the optimized conditions, we were pleased to find that a series of *N*-sulfinyl imines reacted with various aldehydes smoothly to give the desired cross-coupling products in good to excellent yields and extremely high diastereomeric ratios (up to >99:1) (Table 1). Relatively lower yields (70−71%) were observed in the cases of aromatic imine substrates having *para*-Br and Cl substituents because of the formation of some homocoupling

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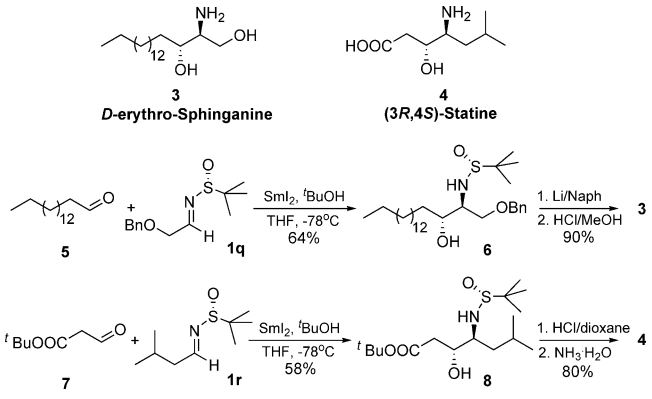
Scheme 2



product (entries 8 and 9). As previously reported,[11] these two substrates are subject to easy homocoupling under the similar reaction conditions. Fortunately, the absolute structure of the obtained cross pinacol product was unambiguously established by X-ray crystallography, and the stereochemistry of the two newly formed carbon centers was revealed to possess *R,S*-configuration.[12] When the R_1 or R_2 substituent became more bulky, the coupling reaction still proceeded well (entries 2, 3, 12, and 13). In the reaction with isobutyraldehyde, different substituted aromatic imines gave similar selectivities (entries 1 and 6−13), suggesting that the diastereoselectivity was primarily controlled by the stereochemistry of the *N*-sulfinyl group rather than by the electronic effect. However, the diastereoselectivity was found to be influenced by the steric hindrance of the aldehyde substrate (entries 1−5). Less hindered aldehydes, such as hexanal and 3-phenylpropanal, resulted in a decrease in diastereoselectivity (91:9 and 88:12) (entries 4 and 5). Besides the aromatic *N*-sulfinyl imines, we also evaluated the cross-coupling of aliphatic imines with isobutyraldehyde and found that the reactions could equally be accomplished in high yields and high diastereomeric ratios (entries 14−17). Thus, the reaction substrate scope is largely expanded, indicating the great compatibility and efficiency of the method. Notably, for those β-amino alcohol products **2h**−**2k**, the *para*-halogen, acetoxy, or methoxy substituent on the benzene ring would be a useful functionality for further modification, such as adjustment of the solubility or attachment onto support materials via O-alkylation or coupling reactions.[13] For product **2q**, it is also worth noting that removal of the *N*-sulfinyl and benzyl groups will afford the chiral 2-amino-1,3-propanediol derivative, which is a synthetically very useful building block.

Cleavage of the sulfinyl group under acidic conditions (HCl/MeOH) was subsequently accomplished to afford β-amino alcohols in high yields. Very gratifyingly, excellent enantiomeric excesses (>95%) were observed in all cases (Table 1). These results clearly indicate that the *N*-sulfinyl serves as a powerful chiral directing group and predominates the stereoselectivity of the reaction.

As described above, this highly diastereo- and enantioselective crossed pinacol coupling method offers a significantly more efficient and direct construction of β-amino alcohol scaffolds. To further demonstrate the synthetic value, the rapid preparation of two biologically active compounds D-*erythro*-sphinganine (**3**) and (3*R*,4*S*)-statine (**4**) was then carried out (Scheme 2).

The cross-coupling of palmitaldehyde **5** (4 equiv)[14] with imine **1q** was performed at −78 °C under standard conditions to provide **6** as a single diastereomer in 64% yield.[15] Removal of the benzyl and sulfinyl groups gave D-*erythro*-sphinganine (**3**) in 90% overall yield with 97% ee. When aldehyde **7**[16] (2 equiv) was treated with *N*-sulfinyl imine **1r** under similar reaction conditions, **8** was isolated in 58% yield with 99% de. The *tert*-butyl ester and *N*-sulfinyl were then easily cleaved by acidic hydrolysis in one step to afford optically pure (3*R*,4*S*)-statine (**4**) in high yield. To our knowledge, this approach represents one of the most convenient and direct syntheses of **3** and **4** reported to date.[17]

In summary, we have developed a highly efficient and practical approach for the synthesis of enantiomerically pure β-amino alcohols by the SmI_2-mediated reductive cross-coupling of chiral *N*-*tert*-butanesulfinyl imines with aldehydes. This method is found to be very effective for the preparation of a broad range of chiral β-amino alcohols, including functionalized ones under mild conditions. Diastereoselectivities and enantioselectivities in these reactions are excellent in most cases. Moreover, it provides a solution to a long-standing difficulty in direct construction of enantiopure β-amino alcohols via the pinacol-type cross-coupling between carbonyls and imines. We believe that both this methodology and the obtained β-amino alcohols will find wide use in asymmetric synthesis. The application in natural product synthesis is currently in progress.

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Supporting Information Available: Experimental procedures and characterization data, including X-ray data of **2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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