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Indium-mediated Barbier-type allylation of aldehydes as a convenient method for the highly enantioselective synthesis of homoallylic alcohols

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This paper is dedicated to the memory of Professor Herbert C. Brown

Abstract—We report a general method for the indium-mediated Barbier-type enantioselective allylation of both aromatic and aliphatic aldehydes using commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as a chiral auxiliary. Using only two equivalents of allyl bromide, excellent yields and very good to excellent enantioselectivities are obtained. To our knowledge, the enantioselectivities reported herein are the highest obtained for indium-promoted allylations of carbonyl compounds.

The asymmetric allylation of aldehydes to form enantiomerically pure homoallylic alcohols remains a methodology of increasing interest,[1,2] as these products are important synthetic building blocks for making an array of chiral compounds.[3,4] Indium-promoted reactions are attractive because indium, as opposed to other metals, is less air- and moisture-sensitive, significantly less toxic, and able to tolerate numerous functionalities.[5,6] It has been reported that indium-mediated allylations of aldehydes using a sixfold excess of allyl halide can proceed with good enantioselectivity when cinchonidine is used as the chiral promoter.[7] Herein, we report a simple method for the enantioselective allylation of aldehydes using a twofold excess of allyl bromide, a commercially available chiral amino alcohol, and metallic indium.

We have previously shown that limonene-based amino alcohols can serve as effective ligands for enantioselective diethylzinc additions to aldehydes,[8] and we envisioned extending their use as chiral auxiliaries for the asymmetric allylation of aldehydes using indium. Our study began by screening the various limonene-based amino alcohols that have been developed in our laboratory.[9] During these studies we discovered that adding a stoichiometric amount of pyridine to the reaction increased both the yield and enantiomeric excess of the homoallylic alcohol product. Utilizing benzaldehyde, 2 equiv of the limonene amino alcohol ligands, 2 equiv of indium, and using a large excess of allylbromide as recommended in the literature,[7] the corresponding homoallylic alcohol was obtained in very good yields, but the maximum asymmetric induction achieved was only 40%. Consequently, we screened a wide variety of commercially available amino alcohols to assess their efficiency as chiral directors in this reaction.

These studies revealed (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**1a**) to be an effective chiral promoter in the allylation of benzaldehyde (Table 1, entry 1). Encouraged by these preliminary results, we then looked to optimize the reaction conditions. We began by reducing the amount of allyl bromide from 6 equiv to 2 equiv with respect to the aldehyde. To our delight, this change resulted in 99% conversion and a notable increase in enantioselectivity to 93% ee (Table 1, entry 2). Attempts to further decrease the amount of allyl bromide lowered both conversion and enantioselectivity (Table 1, entry 5). We also verified that the addition of pyridine was

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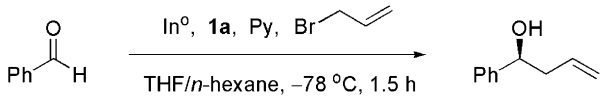
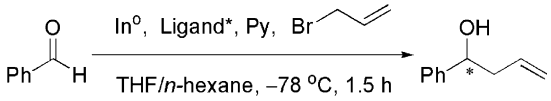
Table 1. Optimization of enantioselective allylation of benzaldehyde[a]



Entry	In^0	**1a**	Pyridine	Allylbromide	% Conv[b]	% Ee[b](*S*)[c]
1	2	2	2	6	99	76
2	2	2	2	2	99	93
3	2	2	0	2	65	60
4	1	2	2	2	50	66
5	2	2	2	1	55	70
6	1	1	1	1	50	79

[a] Table values refer to number of equivalents. Reactions run with benzaldehyde (0.5 mmol).
[b] Determined by chiral GC analysis.
[c] Absolute configuration determined by comparison of the optical rotation with literature value.[7]

Table 2. Screening of chiral auxiliaries for the enantioselective allylation of benzaldehyde with allyl bromide[a]



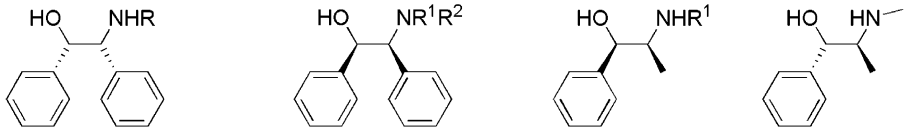
Entry	Ligand*	% Conversion[b] (*S*)	% Ee[b,c]
1	**1a**	99	93(*S*)
2	**1b**	13	62(*S*)
3	**2a**	10	46(*R*)
4	**1c**	50	8(*S*)
5	**1d**	33	0
6	**2b**	0	0
7	**3a**	98	30(*R*)
8	**3b**	50	34(*R*)
9	**4**	81	20(*R*)

[a] Reactions run with In^0 (1.0 mmol), chiral auxiliary (1.0 mmol), pyridine (1.0 mmol), allyl bromide (1.0 mmol), and benzaldehyde (0.5 mmol) in THF/*n*-hexane at −78 °C for 1.5 h.
[b] Determined by chiral GC analysis.
[c] Absolute configuration determined by comparison of the optical rotation with literature value.[7]

advantageous (Table 1, entry 3), but that raising the reaction temperature above −78 °C decreased the enantioselectivity in a linear fashion. Interestingly, reducing the amount of either the indium or allyl bromide in the reaction resulted in only 50% conversion to the homoallylic alcohol product (Table 1, entries 4 and 6). This result suggests the possibility of the formation of a reactive dimer.[5] Based on this optimization study, we identified the optimal reaction conditions and stoichiometry to be that shown in entry 2 (Table 1).

In an attempt to improve our system further, we screened other structurally similar ligands under the optimized reaction conditions. Norephedrine, ephedrine, and pseudoephedrine were found to be significantly less effective as chiral promoters (Table 2, entries 7, 8, and 9, respectively). In addition, a series of secondary *N*-substituted derivatives of 2-amino-1,2-diphenylethanol were synthesized and evaluated (Fig. 1). Use of the *N*-methyl, *N*-isopropyl, *N*-α-methylbenzyl, and *N*-tosyl derivatives resulted in decreased conversion and ee (Table 2, entries 2, 3, 4, and 5, respectively). Interestingly, when a tertiary amine (*N*-pyrrolidino) was used as the chiral promoter, no product formation was observed after 1.5 h (Table 2, entry 6).[10] The results of this study clearly show unmodified **1a** to be the most effective ligand for our system.

To evaluate the generality of this reaction, we performed the allylation on several different aldehydes (Table 3). As can be seen from the summarized results, this method is effective for a range of substituted aromatic aldehydes. Additionally, excellent enantioselectivity is attained with cyclohexylcarboxaldehyde (Table 3, entry 11), allowing this system to be extended to aliphatic aldehydes as well. These data also show that functionality on the aromatic aldehyde is tolerated during the reaction (Table 3, entries 2, 9, and 10). Upon close inspection of the data in Table 3, we noticed that aldehydes with a strong electron-donating group in the *para*-position (Table 3,



1a: R = H
1b: R = Me
1c: R = α-methyl benzyl
1d: R = Tosyl

2a: R^1 = H, R^2 = *i*-Pr
2b: R^1 = R^2 = pyrrolidine

3a: R = H
3b: R = Me

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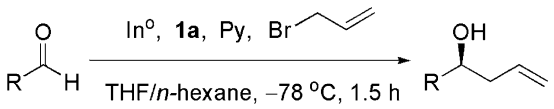
Figure 1. Ligands used in the indium-mediated allylation of benzaldehyde with allyl bromide.

Table 3. Enantioselective allylation using **1a** as a chiral promoter[a]



Entry	R	% Yield[b]	% Ee[c] (*S*)[d]
1	Ph	90	93
2	4-CH_3O–C_6H_4	92	89
3	*o*-CH_3–C_6H_4	94	88
4	*m*-CH_3–C_6H_4	97	79
5	*p*-CH_3–C_6H_4	92	87
6	2-Cl–C_6H_4	97	78
7	3-Cl–C_6H_4	90	80
8	4-Cl–C_6H_4	92	93
9	4-CH_3O_2C–C_6H_4	94	76
10	4-CN–C_6H_4	99	80
11	Cyclohexyl	93	93[e]

[a] Reactions run with In^0 (2.0 mmol), **1a** (2.0 mmol), pyridine (2.0 mmol), allyl bromide (2.0 mmol), and aldehyde (1.0 mmol) in THF/*n*-hexane at −78 °C for 1.5 h.
[b] Isolated yield of analytically pure product.
[c] Determined by chiral GC analysis.
[d] Absolute configuration determined by comparison of the optical rotation with literature value,[7] all others were assigned by analogy.
[e] Enantiomeric excess determined by chiral GC analysis of the acetylated homoallylic alcohol.

entries 2 and 5) give a higher enantiomeric excess than those with an electron-withdrawing group in the *para*-position (Table 3, entries 9 and 10).[11] Apparently, electron-withdrawing groups increase the reactivity of the aldehyde functionality, therefore decreasing the enantioselectivity of the reaction.

In summary, we have demonstrated a general method for the indium-promoted enantioselective allylation of both aromatic and aliphatic aldehydes using commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as a chiral auxiliary and using only two equivalents of allyl bromide. The homoallylic alcohol products are obtained in high enantiomeric excesses and in excellent yields and purity. Furthermore, the amino alcohol ligand can be recovered via a simple acid–base extraction.[12] We are presently extending this method to functionalized allylic halides, and studies to elucidate mechanistic details are also currently underway.

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Supplementary data

Experimental procedures and characterization data for homoallylic alcohol products and synthesized ligands. This material is available free of charge via the WWW. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.01.169.

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12. When the reaction was run on a 2.5 mmol scale, the amino alcohol ligand was recovered from the aqueous layer via an acid–base extraction in 70% yield and in high analytical purity.