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Asymmetric indium-mediated Barbier-type allylation reactions with ketones to form homoallylic alcohol products

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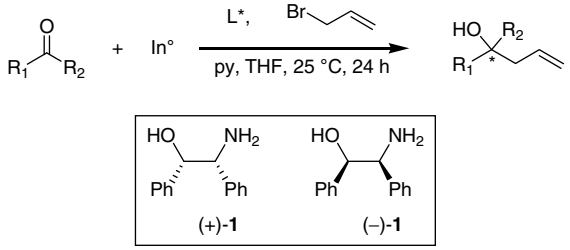
Abstract

We report a general method for the enantioselective allylation of both aromatic and aliphatic ketones under indium-mediated Barbier-type conditions. Using 2 equiv of a commercially available amino alcohol, either (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol ((+)-**1**) or (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol ((−)-**1**) as the chiral auxiliary, good yields and enantioselectivities were achieved. To our knowledge, the enantioselectivities reported herein are the highest obtained for the indium-mediated allylations of ketones, specifically the homoallylic alcohol product obtained from the addition to α,α,α-trifluoroacetophenone provided 80% enantiomeric excess.

The asymmetric allylation of carbonyls, such as aldehydes and ketones, remains one of the most useful methods for carbon–carbon bond-formation.[1a,2] In addition, the metal-mediated allylation of carbonyls continue to be a valuable method for the formation of chiral homoallylic alcohols,[3] as they are often used as building blocks in the synthesis of larger complex molecules.[1b,4] In particular, methods for the asymmetric allylation of ketones are desirable due to the formation of chiral tertiary alcohols.[5] Although numerous methods exist for the asymmetric allylation of aldehydes,[6] far fewer are known to employ ketones.[7] In recent years, indium-promoted reactions have gained appeal due to the lack of air- and moisture-sensitivity, toxicity, and ability to tolerate functionality.[8] Herein, we report a method for the synthesis of enantiomerically enriched tertiary homoallylic alcohols from ketones using indium.

Recently, our group has shown (+)-**1** to be an effective chiral promoter for asymmetric indium-mediated reactions. Various aldehydes were converted to the corresponding homoallylic alcohols in excellent enantiomeric excess (79–93%) using 2 equiv of allyl bromide, (+)-**1**, pyridine and indium powder.[9] Also, we have achieved the synthesis of homopropargylic alcohols in good yield (53–99%) and enantiomeric excess (75–95%) using propargyl bromide.[10] We envisioned that this methodology could be applied to the allylation of ketones (Scheme 1).

Using indium metal, allyl bromide and (+)-**1** in the presence of pyridine at −78 °C, acetophenone was not converted to the corresponding homoallylic alcohol (<5%) even after 2 h (Table 1, entry 1). Consequently, we focused our efforts on optimizing the reaction conditions to increase the product formation, as ketones are less reactive than aldehydes. We began by increasing the reaction time



Scheme 1. Asymmetric indium-mediated allylation of ketones.

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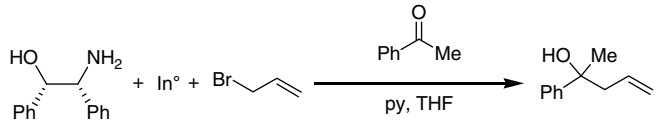
Table 1
Temperature and time optimization for the enantioselective allylation of acetophenone with allyl bromide[a]

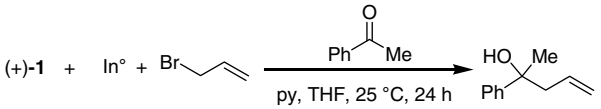


Entry	Temperature (°C)	Time (h)	% Conversion[b]	% ee[c]
1	−78	2	<5	—
2	−78 to 25	24	85	48
3	−40 to 25	24	97	50
4	−15 to 25	24	87	56
5	25	24	86	58
6	65	24	79	56

[a] Reactions run with In° (0.5 mmol), (+)-**1**(0.5 mmol), pyridine (0.5 mmol), allyl bromide (0.5 mmol) and ketone (0.25 mmol) in THF.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral GC analysis.

and temperature by allowing the reaction to warm slowly from −78 °C to room temperature overnight. This resulted in an 85% conversion of the acetophenone to the homoallylic alcohol in 48% enantiomeric excess (Table 1, entry 2).

Table 2
Optimization for the enantioselective allylation of acetophenone with allyl bromide[a]



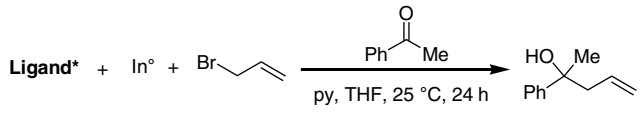
Entry	In°[b]	(+)-**1**[b]	Pyridine[b]	Allyl bromide[b]	% Conversion[c]	% ee[d]
1	2	2	2	2	87	58
2	2	2	2	3	50	53
3	2	2	2	4	43	54
4	2	2	2	6	55	56

[a] Reactions run with acetophenone (0.25 mmol) as the limiting reactant.
[b] Refers to number of equivalents.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral GC analysis of the acetylated homoallylic alcohol product.

Gratified by these initial results, we investigated various temperatures at longer reaction times. We found that by cooling the reaction flask to both −40 and −15 °C and allowing the mixture to warm to room temperature overnight increased the enantiomeric excess slightly to 50% and 56%, respectively (Table 1, entries 3 and 4). Apparently, the reaction is not taking place at −78 °C but occurs during the warm up. By conducting the reaction at room temperature overnight, 86% of the homoallylic alcohol was isolated in 58% ee (Table 1, entry 5). However, refluxing the reaction mixture did not increase conversion or ee, therefore the optimal conditions were identified as those shown in entry 5.

We then investigated the effect of excess allyl bromide on the allylation reaction. Initially, we used 2 equiv of allyl bromide in our reaction (Table 2, entry 1). We found that the use of 3 equiv of allyl bromide decreased the conversion of acetophenone to the corresponding homoallylic alcohol to 50% (Table 2, entry 2). In addition, we observed an overall reduction in the allylation of acetophenone with increasing equivalents of allyl bromide providing only 43%

Table 3
Screening of chiral auxiliaries for the enantioselective allylation of acetophenone with allyl bromide[a]



Entry	Ligand*	% Conversion[b]	% ee[c]
1	(+)-**1**	87	58
2	2	0	0
3	3	0	0
4	4	78	0
5	5	47	0
6	6	44	0
7	7	81	0

[a] Reactions run with In° (0.5 mmol), Ligand* (0.5 mmol), pyridine (0.5 mmol), allyl bromide (0.5 mmol) and ketone (0.25 mmol) in THF.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral GC analysis for the acetylated homoallylic alcohol product.

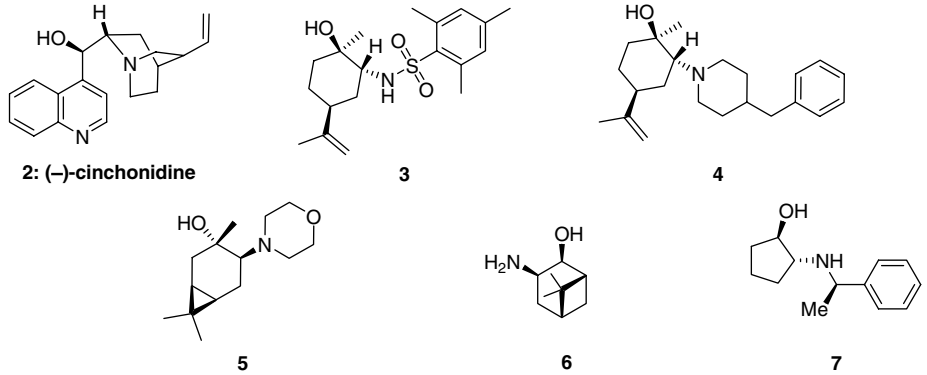
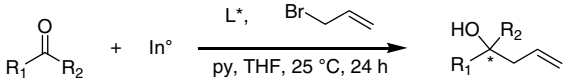


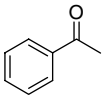
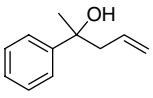
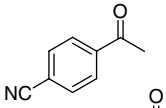
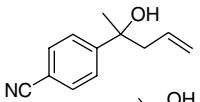
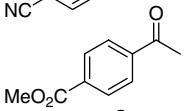
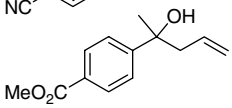
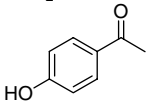
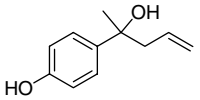
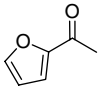
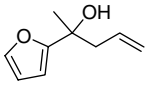
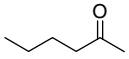
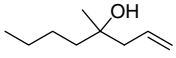
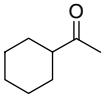
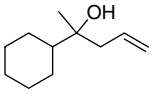
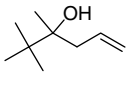
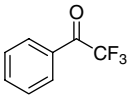
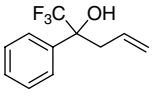
Figure 1. Ligands used in the indium-mediated allylation of acetophenone with allyl bromide.

conversion for 4 equiv and 55% conversion for 6 equiv (Table 2, entries 3 and 4). The enantiomeric excess for the corresponding homoallylic alcohol product remained essentially constant with increasing concentration of allyl bromide (Table 2, entries 2–4). Therefore, we used 2 equiv of allyl bromide in our subsequent reactions.

Although we had found that the chiral auxiliary (+)-**1** was the most effective for aldehydes, we screened other chiral amino alcohols for their efficiency in the allylation of ketones (Fig. 1). Under our reaction conditions, we did not observe the conversion of acetophenone to the corresponding homoallylic alcohol when using (−)-cinchonidine as the chiral director (Table 3, entry 2). We evaluated various β-amino alcohols derived from terpenes that were available in our lab[11] and found that one did not promote the conversion of acetophenone (Table 3, entry 3), while the other two provided the homoallylic alcohol product in 78% and 81%, respectively (Table 2, entries 4 and 7). However, **4** and **7** were inefficient chiral promoters and no enantiomeric excess was obtained (Table 3, entries 4 and 7). Ligands **5** and **6** provided moderate conversion of acetophenone, 47% and 44%, but the product was racemic (Table 3, entries 5 and 6). Since none of these other chiral amino alcohols gave better results, we used the commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol for further study (Table 3, entry 1).

Table 4
Enantioselective indium-mediated allylation of ketones[a]



Entry	Ketone	Product	L*	% Yield[b,c]	% ee[d,e]
1			(+)-**1**	87	58 (*S*)
2			(−)-**1**	72	57 (*R*)
3			(+)-**1**	92	48 (*S*)
4			(+)-**1**	74	48[f] (*S*)
5			(+)-**1**	77	41[f] (*S*)
6			(+)-**1**[g]	>99	44 (*S*)
7			(−)-**1**	77	45 (*S*)
8			(−)-**1**	46	42 (*S*)
9[13]			(−)-**1**	81	64 (*S*)
10[13]			(+)-**1**	94	80 (*S*)
11			(−)-**1**[g]	>99	78 (*R*)

[a] Reactions run with In° (1.0 mmol), 2-amino-1,2-diphenylethanol (1.0 mmol), pyridine (1.0 mmol), allyl bromide (1.0 mmol) and ketone (0.5 mmol) in THF at room temperature for 24 h.[13]
[b] Isolated yield of analytically pure product all products greater than 90% by ^{1}H NMR.
[c] Based on unreacted starting material.
[d] Determined by chiral GC analysis.
[e] Absolute configuration determined by comparison of the optical rotation with literature value,[14] all others were assigned by analogy.
[f] Determined by chiral RP-HPLC analysis.
[g] Reactions run with recovered and purified ligand.

To evaluate the generality of this reaction, we screened several ketones under the optimized reaction conditions. In addition to using (+)-**1** as the chiral director for the allylation of ketones, the enantiomer, (−)-**1**, was employed for several ketone substrates providing the opposite enantiomer of the homoallylic alcohol products. We investigated (−)-**1** with acetophenone and were pleased to see that (*R*) homoallylic alcohol was obtained in good yield and in 57% ee (Table 4, entry 2).[12] Although the enantioselectivity was only moderate for 4-acetylbenzonitrile, methyl-4-acetylbenzoate, 4-hydroxyacetophenone (41–48% ee), these substrates demonstrated that various functionalities were tolerated under our reaction conditions and provided good to excellent yield (74–92%) of the corresponding homoallylic alcohols (Table 4, entries 3–5). In addition, 2-acetylfuran afforded the corresponding homoallylic alcohol in quantitative yield and moderate enantiomeric excess, 44% (Table 4, entry 6). Aliphatic ketones provided the corresponding homoallylic alcohols in good yields and enantiomeric excesses. The homoallylic alcohols from 2-hexanone and cyclohexylmethyl ketone were obtained in moderate to high yields and enantiomeric excesses of 45% and 42%, respectively (Table 4, entries 7 and 8). We found that the reaction with the more sterically demanding pinacolone afforded the product in a higher enantiomeric excess of 64% (Table 4, entry 9). Similarly, α,α,α-trifluoroacetophenone produced the corresponding homoallylic alcohol in 80% ee, the highest observed for this ketone under indium-mediated Barbier reaction (Table 4, entry 11).[15] Using (−)-**1** we obtained the enantiomeric (*R*) homoallylic alcohol in 78% ee in excellent yield (Table 4, entry 10). As ketone substrates are more sterically hindered and less electrophilic than aldehydes, diminished yields were not surprising. Nevertheless, this demonstrates an effective method for the enantioselective indium-mediated allylation of ketones, both aromatic and aliphatic, using a chiral amino alcohol (see Table 4).

In summary, we have demonstrated a general method for the indium-promoted enantioselective allylation of both aromatic and aliphatic ketones using both enantiomers of a commercially available chiral auxiliary, (+) or (−)-2-amino-1,2-diphenylethanol. The chiral ligand is recoverable in high yield and purity from the reaction mixture. Although the enantioselectivities reported herein are moderate, they are the highest for the indium-mediated allylations of trifluoroketone.

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12. *Representative procedure*: An oven-dried 25-mL round bottom flask with stirbar was cooled under argon and charged with (1*S*,2*R*)-(−)-2-amino-1,2-diphenylethanol (0.213 g, 1 mmol), indium powder (0.115 g, 1 mmol) and anhydrous THF (14 mL). The flask was vacuum purged with argon (5X), at which time anhydrous pyridine (0.08 mL, 1 mmol) and allyl bromide (0.09 mL, 1 mmol) were added and the mixture was stirred vigorously at 25 °C. After 30 min at 25 °C, acetophenone (0.06 mL, 0.5 mmol) was added dropwise. After 24 h the reaction was quenched with saturated ammonium chloride (6 mL), and the mixture was transferred to a separatory funnel with hexanes (5 mL). The aqueous layer was removed and the organic layer was washed with dilute hydrochloric acid (HCl, 2 × 8 mL), brine (1 × 8 mL), dried with magnesium sulfate ($MgSO_4$), filtered through a silica plug, and evaporated to give 2-phenylpent-4-en-2-ol as a clear, yellow oil (0.058 g, 72% yield). Enantiomeric excess was determined to be 57% by chiral GC analysis. GC conditions: 121 °C isothermal, t_R for the (*R*)-alcohol = 29.14 min, and t_R for the (*S*)-alcohol = 29.41 min.
13. For entries 9 and 10, the reaction conditions were as follows: In° (4.0 mmol), 2-amino-1,2-diphenylethanol (4.0 mmol), pyridine (1.0 mmol), allyl bromide (4.0 mmol) and ketone (2.0 mmol) in THF (24 mL) at room temperature for 24 h.
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