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Asymmetric indium-mediated synthesis of homopropargylic alcohols

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Abstract—A method for the enantioselective synthesis of homopropargylic alcohols using indium under Barbier-like conditions is reported herein. Both aromatic and aliphatic aldehydes were successfully converted to the corresponding homopropargylic alcohols in good yield and high enantiomeric excesses using propargyl bromide, indium, and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as a chiral auxiliary.

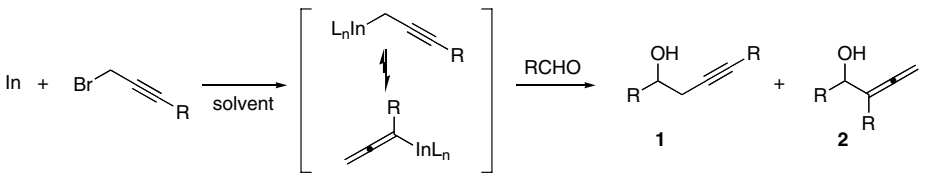
Enantiomerically pure homopropargylic alcohols are valuable synthetic intermediates used in the preparation of complex molecules.[1] Various asymmetric methodologies have been developed for the synthesis of homopropargylic alcohols from aldehydes and allenylmetal reagents.[2] For example, it has recently been shown that an air stable chiral allenylborane made from a Grignard reagent can produce homopropargylic alcohols with excellent enantioselectivity.[3]

Many researchers are now exploring the use of indium in organic reactions.[4] For instance, several examples of asymmetric indium-mediated allylations have been reported.[5] However, only one example has been reported for the asymmetric indium-mediated propargylation of aldehydes.[6]

It is known that many allenylmetals can undergo a metallotropic rearrangement resulting in either homopropargylic alcohol (**1**) or allenylic alcohol (**2**) upon reaction with an aldehyde (Scheme 1).[7] It has been found that with indium, the ratio of **1**:**2** can be varied by changing the solvent or substitution of the propargyl halide.[8] Chan and co-workers have studied the identity of the organoindium species under various conditions.[8c] Under the reaction conditions described herein (R = H), the homopropargylic alcohol (**1**) is observed to be the sole product.

Previously, we reported the highly enantioselective allylation of aldehydes using allyl bromide, indium, and commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as the chiral auxiliary. In this reaction, the addition of a stoichiometric amount of pyridine not only improved the yield of the reaction, but also increased the ee of the homoallylic alcohol.[9] Herein, we describe the use of indium and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**3**) to mediate the asymmetric addition of propargyl bromide to aldehydes under Barbier-like conditions to synthesize homopropargylic alcohols in high enantiomeric purity (Scheme 2).

Using 2 equiv of indium(0), **3**, propargyl bromide, and pyridine, the optimal temperature of the reaction was



Scheme 1.

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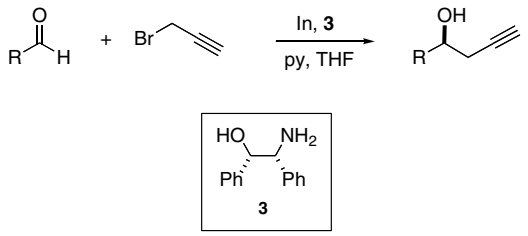


Scheme 2.

investigated (Table 1). Although the enantioselectivity of the reaction at −78 °C for 2 h was 76% (Table 1, entry 1), the conversion to the homopropargylic alcohol was only 58% based on unreacted aldehyde. By removing the dry ice/acetone bath after a period of 2 h and letting the flask warm to room temperature we were able to increase the yield of the alcohol, without compromising the enantioselectivity (Table 1, entry 2). Based on the results of a temperature study (Table 1), we observed the highest enantioselectivity (89% ee, entry 9) at −60 °C. However, cooling the flask to −78 °C for the addition of the aldehyde then allowing the flask to slowly warm to room temperature overnight gave comparable ee, but a much higher conversion to the alcohol product (Table 1, entry 3). In addition, it is noteworthy that we use only 2 equiv of propargyl bromide in our reaction.[6]

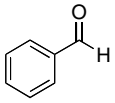
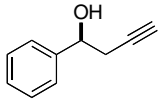
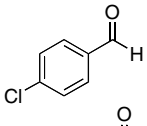
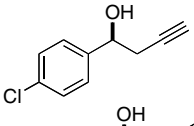
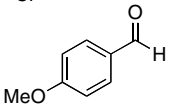
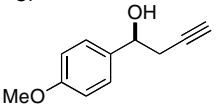
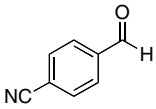
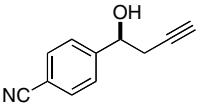
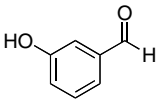
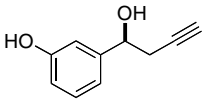
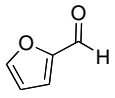
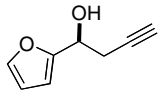
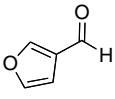
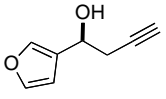
Table 1. Temperature effects on the asymmetric indium-mediated propargylation of benzaldehyde[a]

Entry	Time (h)	Temperature (°C)	% Conversion[b] (isolated yield)	% ee[c] (*S*)[d]
1	2	−78	58	76
2	2.5	−78 → 25 (fast)	87	74
3	16	−78 → 25 (slow)	91 (90)	88
4[e]	16	−78 → 25 (slow)	>97	89
5	16	25	>97	77
6	2.5	0	87	84
7	2.5	−20	89	83
8	2.5	−40	88	84
9	2.5	−60	48	89

[a] Reactions run with In^0 (1.0 mmol), **3** (1.0 mmol), pyridine (1.0 mmol), propargyl bromide (1.0 mmol), and aldehyde (0.5 mmol) in THF.
[b] Percent conversion determined by ^1H NMR.
[c] Determined by chiral GC analysis.
[d] Absolute configuration determined by comparison of the optical rotation with literature value.[3]
[e] THF/hexanes 7:1.

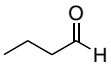
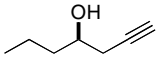
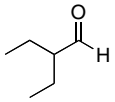
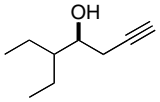
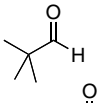
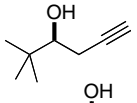
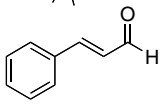
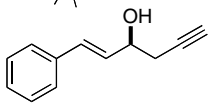
In order to explore the generality of this reaction, we screened a variety of structurally diverse aldehydes

Table 2. Enantioselective indium-mediated propargylation of aromatic aldehydes[a]

Entry	Aldehyde	Product	% Yield[b]	% ee[c]
1			90	88 (*S*)[d]
2			89	84 (*S*)
3			82	88 (*S*)
4			75	83 (*S*)
5			90	85[e] (*S*)
6			78	78 (*S*)
7			69	78 (*S*)

[a] Reactions run with In^0 (1.0 mmol), **3** (1.0 mmol), pyridine (1.0 mmol), propargyl bromide (1.0 mmol), and aldehyde (0.5 mmol) in THF (see Table 1, entry 3).
[b] Isolated yield.
[c] Determined by chiral GC analysis.
[d] Absolute configuration determined by comparison of the optical rotation with literature value.[3] All others were assigned by analogy.
[e] Enantiomeric excess determined by chiral GC analysis of the diacetylated homopropargylic alcohol.

Table 3. Enantioselective indium-mediated propargylation of aliphatic aldehydes[a]

Entry	Aldehyde	Product	% Yield[b]	% ee[c]
1			63	74[e] (*R*)[d]
2			60	83 (*S*)
3			53	95[e] (*S*)
4			71	75 (*S*)

[a] Reactions run with In^0 (1.0 mmol), **3** (1.0 mmol), pyridine (1.0 mmol), propargyl bromide (1.0 mmol), and aldehyde (0.5 mmol) in THF (see Table 1, entry 3).
[b] Isolated yield.
[c] Determined by chiral GC analysis.
[d] Absolute configuration were assigned by analogy.
[e] Enantiomeric excess determined by chiral GC analysis of the acetylated homopropargylic alcohol.

under the optimized reaction conditions (Table 1, entry 3).[10] The results of this study are shown in Tables 2 and 3. Both aromatic and aliphatic aldehydes are converted to the corresponding homopropargylic alcohols in very good yield and high enantioselectivities.

Various aromatic aldehydes have been propargylated in high enantiomeric excesses and these results are shown in Table 2. Benzaldehyde was converted to 4-phenyl-1-butyn-4-ol in 90% isolated yield and 88% ee (entry 1). Functionalized aldehydes were used in order to investigate the chemoselectivity of this asymmetric propargylation reaction. Gratifyingly, comparable results were obtained with the functionalized benzaldehyde derivatives. 4-Chlorobenzaldehyde, *p*-anisaldehdye, and 4-cyanobenzaldehdye gave the corresponding homopropargylic alcohols in 84%, 88%, and 83% ee, respectively (entries 2–4, respectively). Most notably, 3-hydroxybenzaldehdye also gave 85% ee, showing that this reaction tolerates an unprotected phenol (entry 5). Additionally, 2- and 3-furaldehdye both furnished the homopropargylic alcohol in 78% ee (entries 6 and 7, respectively).

We were pleased to find that the propargylation of aliphatic aldehydes under our reaction conditions resulted in very high enantioselectivities (Table 3). The least substituted aliphatic aldehyde, *n*-butyraldehdye, gave the homopropargylic alcohol in 74% ee (entry 1). As expected, the enantioselectivity of the reaction increased with increasing substitution at the alpha-carbon of the aldehyde.

In summary, we have demonstrated a general method for the indium-promoted enantioselective propargylation 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 2 equiv of propargyl bromide. The homopropargylic alcohol products are obtained in high yield, and with enantiomeric excesses up to 95%. To our knowledge, the enantioselectivities reported herein are the highest obtained for indium-promoted propargylations. Furthermore, the amino alcohol ligand, which is commercially available in either enantiomer, can be recovered via a simple acid–base extraction.[11]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.049.

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6. The first and only example was by Loh and co-workers where the cinchona alkaloids were utilized with a six-fold excess of propargyl bromide to synthesize homopropargylic alcohols. Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507–509.
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9. Hirayama, L. C.; Gamsey, S.; Knueppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315–2318.
10. Representative procedure: An oven-dried 25 mL round bottom flask with egg shaped 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 (7 mL). The flask was vacuum purged with argon (5X), at which time anhydrous pyridine (0.08 mL, 1 mmol) and propargyl bromide (0.11 mL, 1 mmol) were added and the mixture was stirred vigorously at 25 °C. After 25 min at room temperature, the solution was cooled to −78 °C (dry ice/acetone bath), and freshly distilled benzaldehyde (0.05 mL, 0.5 mmol) added dropwise. After 16 h the reaction was quenched with 1 M HCl (3 mL), the layers separated and the aqueous layer extracted with diethyl ether/*n*-hexanes 1:1 (2×3 mL). The combined organic layers were washed with 1 M HCl (3 mL), DI H_2O (3 mL) and brine (3 mL), dried with anhydrous magnesium sulfate, filtered through a silica plug and evaporated to give 1-phenyl-3-butyn-1-ol as a clear, colorless oil (0.058 g, 90% yield). Enantiomeric excess was determined to be 88% by chiral GC analysis. GC conditions: 141 °C isothermal, t_R for the (*R*)-alcohol = 24.87 min, and t_R for the (*S*)-alcohol = 25.94 min.
11. (1*S*,2*R*)-(+)-2-Amino-1,2-diphenylethanol was recovered in 99% yield and purity by NMR via acid–base extraction from the aqueous layer of two combined runs.