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Indium-mediated propargylation of aldehydes: regioselectivity and enantioselectivity studies

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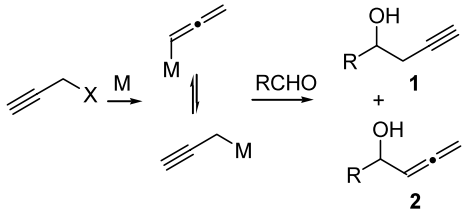
Abstract—An enantioselective propargylation reaction of aldehydes with enantioselectivity up to 85% has been achieved in organic solvents by using stoichiometric amounts of (–)-cinchonidine as the chiral source.

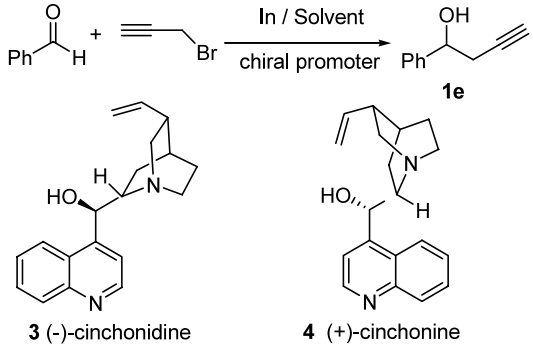
Chiral homopropargylic alcohols[1] **1** are versatile building blocks for the enantioselective synthesis of many biologically active compounds.[2] Therefore, many methods have been developed for the enantioselective syntheses of this class of compounds.[3] The most common methods involve the enantioselective addition of homopropargylic or allenylic metals to carbonyl compounds and afford both the propargylic and allenic alcohols at the same time (Scheme 1).[4] In this context, the synthesis of homopropargyl alcohols by the umpolung approach from propargylpalladium described by Tamaru et al. and the asymmetric synthesis of homopropargylic alcohols from aldehydes reported by Keck et al.[5] are extremely useful.

A recent method developed by Umani-Ronchi and co-workers using a chiral [Cr(Salen)] complex has afforded homopropargylic alcohols with moderate enantioselectivity.[6] Among the many metals employed, indium-mediated propargylation has attracted much attention due to its mild reaction conditions as well as wide functional group compatibility.[7] However, compared to the well-established allylic indium chemistry, the synthetic potential of propargylic indium reagents has not been fully exploited. This is because homopropargylic indiums can equilibrate in solution to give a mixture of homopropargylic and allenylic indium species.[8] This metallotropic rearrangement often results in poor regioselectivity since both organometallic species can react with the aldehydes. Although tuning to obtain either the homopropargylic alcohol or the allenic alcohol by varying the substrate or solvent has been achieved with some success[9] there is no report on the enantioselective indium-based homopropargylation using an external chiral ligand.

In view of our interest in the application of indium-mediated propargylation for the synthesis of complex molecules, efforts were directed towards exploring the regioselectivity and enantioselectivity of the indium-mediated propargylation reaction (Scheme 2).[10]



Scheme 1.



Scheme 2.

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We have previously succeeded in the asymmetric allylation of aldehydes with allylic bromides catalyzed by (−)-cinchonidine.[10] This present paper discloses the enantioselective indium-mediated propargylation of aldehydes using stoichiometric amounts of (−)-cinchonidine as the chiral ligand.

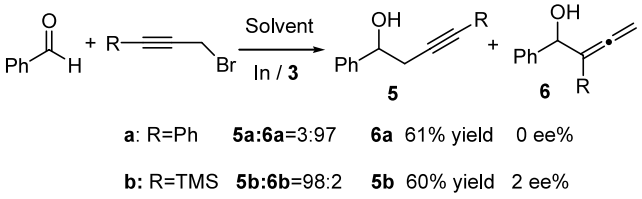
Initial investigations revealed that indium-mediated propargylation of benzaldehyde with propargylic bromide in dichloromethane/hexane in the presence of (−)-cinchonidine afforded *R*-**1e** with good enantioselectivity. The following are characteristic features of the reaction. In all cases, the reactions proceeded smoothly to afford the corresponding homopropargylic alcohols in good yields as the sole products. No detectable amount of allenic alcohol was observed. Contrary to the normal indium-mediated propargylation addition to carbonyl compounds, our reaction system is sensitive to water. The best result (72% ee, 71% yield) with (−)-cinchonidine **3** was obtained when a 3:1 THF/hexane mixed solvent was employed (Table 1, entry 5). The use of the pseudo-enantiomer, (+)-cinchonine, afforded the opposite enantiomer in 70% ee.

On the other hand, sterically demanding silicon and phenyl substituents completely diminished the enantioselectivity (Scheme 3). The allenic alcohol was obtained almost exclusively when the 1-phenylpropargylic bromide was used in the reaction. On the other hand, when the trimethylsilylpropargyl bromide was used, it afforded the propargylic alcohol exclusively. The origin of the differences in the regioselectivity of these reactions is still unknown. Further studies on the mechanism are in progress.

Since propargyl bromide afforded the product with good enantioselectivity, the optimized reaction conditions using propargyl bromide were extended to other aldehydes. The results are summarized in Table 2.

In most cases, the reactions proceeded smoothly to afford the desired homopropargylic products in moderate to good yields. All these reactions proceeded with high regioselectivity affording the homopropargylic alcohols without any detectable amounts of the allenic alcohols. Interestingly, even the commercially available trifluoroacetaldehyde hemiacetal could be used directly without the need to use the unstable and volatile trifluoroacetaldehyde. Therefore, this method provides easy access to optically active secondary trifluoromethylated homopropargylic alcohols.

It can be noted from Table 2 that there is a correlation between the size of the aldehyde and the enantioselectivity. While the smaller aldehydes gave the products in low to moderate enantioselectivities, high enantioselectivities were observed with more bulky aldehydes such as chloral and trifluoroacetal aldehyde hemiacetal.



Scheme 3.

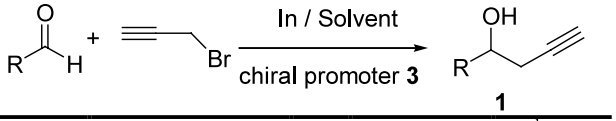
Table 1. Enantioselective propargylation of benzaldehyde with propargyl bromide

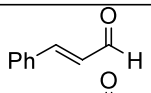
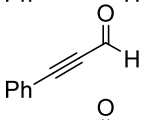
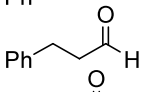
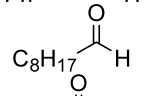
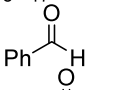
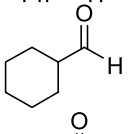
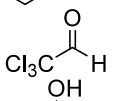
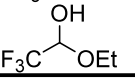
Entry	Chiral promoter	Solvent	Yield[a] (%)	ee[b] (%)
1	**3**	CH_2Cl_2	72	15 (*R*)
2	**3**	THF	78	22 (*R*)
3	**3**	CH_2Cl_2:hexane (3:1)	67	64 (*R*)
4	**4**	CH_2Cl_2:hexane (3:1)	60	63 (*S*)
5	**3**	THF:hexane (3:1)	71	72 (*R*)
6	**4**	THF:hexane (3:1)	69	70 (*S*)

[a] For experimental, refer to the typical experimental procedure (Ref. 11) unless modification is indicated.

[b] Determined by HPLC analysis employing a Daicel Chiral OD column. Absolute configuration assignment by comparison with literature values of the optical rotation.

Table 2. Enantioselective indium-mediated addition of propargyl bromide to various aldehydes



Entry	Aldehyde	1	Yield[a] (%)	ee[b] (%)
1		**a**	76	36(*S*)
2		**b**	74	55
3		**c**	63	56
4		**d**	70	68[c]
5		**e**	71	72(*R*)
6		**f**	72	76[c]
7		**g**	49	84[c]
8		**h**	52	85[c]

[a] Yields refer to isolated and purified products. [b] Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase (Chiral OD). Absolute configuration assignment by comparison with literature values of the optical rotation. [c] Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate (Chiral OD).

This method[11] has several advantages for the following reasons: (1) its experimental is simple and applicable to various aldehydes; (2) the chiral promoters, both (−)-cinchonidine and the corresponding pseudo-enantiomer (+)-cinchonine can be purchased as inexpensive commodities. In conclusion, we have discovered a simple and convenient method for the regioselective and enantioselective synthesis of homopropargylic alcohols. We believe this will make a useful and important addition to the existing methods and will find practical applications in organic synthesis. The identity of the propargyl indium-chiral promoter complexes and reaction mechanism still remains obscure, and further work in this area is underway in our laboratory.

Acknowledgements

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11. *Typical experimental procedure*: To a 50 mL round-bottom flask containing an egg-shaped stirring bar were added (−)-cinchonidine **3** (294 mg, 1.0 mmol) and indium powder (114 mg, 1.0 mmol). The solids were azeotropically dried twice with 3 mL of dry THF and then treated with 3 mL of dry THF and propargyl bromide (226 mL, 3.0 mmol). The mixture was stirred vigorously until it turned into a clear solution, to which was added dropwise 1 mL of dry hexane following by introduction of benzaldehyde (0.5 mL, 0.5 mmol) dropwise at rt. The reaction mixture was stirred at rt for 15 h, and finally quenched with 10 mL of dilute HCl solution. The aqueous layer was extracted with hexane (10 mL×3). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, concentrated under vacuum, and purified by flash silica gel column chromatography to afford 71% of the homopropargylic alcohol as a colorless oil (52 mg, 0.356 mmol).