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A Highly Enantioselective Indium-Mediated Allylation Reaction of Aldehydes

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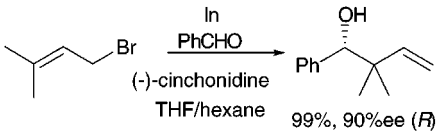
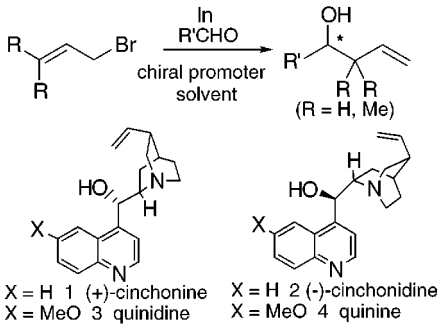
ABSTRACT



The first highly enantioselective indium-mediated allylation of aldehydes was reported. In most cases, good chemical yields and moderate to high enantioselectivies (up to 90% ee) were obtained in the presence of external chiral ligands, (+)-cinchonine and (–)-cinchonidine.

In recent years, indium-mediated allylation of carbonyl compounds has emerged as one of the most useful methods for the preparation of synthetically useful homoallylic alcohols.[1] Its mild reaction condition and wide applicability to a variety of allylic bromides and carbonyl compounds have made this reaction attractive for the construction of natural and unnatural complex molecules.[2] Although much attention has been focused on the stereochemical studies of this reaction, the development of a new method for the control of absolute stereochemistry in this indium-mediated allylation reaction continues to pose a challenge to organic chemists. Up to now, as far as we know, an enantioselective version of this reaction is still unavailable.[3] In this Letter, we showed that a highly enantioselective indium-mediated allylation reaction of aldehydes can be achieved using (+)-cinchonine **1** and (−)-cinchonidine **2**[4] as chiral ligands (Scheme 1).

Scheme 1



First, we investigated the indium-mediated allylation reaction of allyl bromide with benzaldehyde using various chiral promoters **1**−**5** (**5**, (−)-sparteine) under different conditions (eq i). The results are shown in Table 1. The following are the characteristic features of the reaction. In all cases except for entries 2, 4, and 7, the reactions

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(2) (a) Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747−748. (b) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937−7938. (c) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492−7507. (d) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333−5338. (e) Loh, T. P.; Cao, G. Q.; J. Pei, *Tetrahedron Lett.* **1998**, *39*, 1453−1457. (f) Yi, X. H.; Meng, Y.; Li, C. J. *Chem. Commun.* **1998**, *11*, 1237; (g) **1998**, *4*, 449−450.

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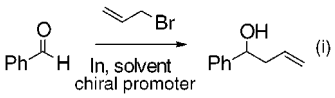
Table 1. Enantioselective Allylation of Benzaldehyde with Allyl Bromide



entry	chiral promoter	conditions[a]	yield (%)	ee[b] (%)
1	**1**	DMF/Hex 3:1	74	3(*R*)
2	**1**	THF	38	26(*S*)
3	**1**	THF/Hex 2:1	78	64(*S*)
4	**1**	THF/Hex 3:1	73	72(*S*)
5	**1**	THF/Hex 3:1[c]	86	38(*S*)
6	**1**	THF/Hex 3:1[d]	4	44(*S*)
7	**1**	THF/Hex 3:1[e]	0	
8	**1**	THF/Hex 3:1[f]	91	19(*S*)
9	**2**	THF/Hex 3:1	73	75(*R*)
10	**3**	THF/Hex 3:1	87	36(*S*)
11	**4**	THF/Hex 3:1	97	9(*R*)
12	**5**	THF/Hex 3:1	71	10(*S*)

[a] For experimental, refer to the Typical Experimental Procedure (ref 10) unless modification is indicated. [b] Determined by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assignment by comparison with literature value of optical rotation. [c] All the reactants were added together and stirred at 25 °C for 2 h. [d] Immediately before the addition of benzaldehyde, 0.5 mmol of water was added. [e] Immediately before the addition of benzaldehyde, 0.1 mL of water was added. [f] 1 mmol of indium was added.

proceeded smoothly to afford the corresponding homoallylic alcohols in good yields. It was noticed that in contrast to normal indium-mediated allylation reactions, our reaction was sensitive to water. The best result with (+)-cinchonidine **2** was obtained when a 3:1 THF/hexane mixed solvent was employed (entry 9). In contrast, the use of other solvent systems afforded the product in much lower enantioselectivities. The use of catalytic or substoichiometric amounts of the chiral promoter afforded the product in much lower enantioselectivity, demonstrating the importance of the formation of a 1:1 indium−chiral promoter complex (entry 8). Interestingly, replacement of the ligand from **1** to its "pseudo-enantiomer" **2** not only afforded higher enantioselectivity (from 72% to 75%) but also reversed the chirality of the homoallylic alcohol. It was also found that the ligands facilitated the "insertion" of indium into allyl bromide. In this aspect, **2** was much more effective than **1**, as indicated by the time required to form a clear solution from a suspension of insoluble ligands in THF (1 h with **2** and 3 h with **1**). Moreover, the chiral promoters could be easily recovered in high yield by routine acid−base workup (95% recovery for **1** and 97% recovery for **2**).

The optimized reaction condition was extended to various aldehydes with allyl bromide and prenyl bromide, and the results are summarized in Table 2 and Table 3, respectively.

Table 2. Enantioselective Indium-Mediated Addition of Allyl Bromide to Aldehydes

		1	**2**
entry	R	yield, ee[a]	yield, ee
1	Ph	73, 72(*S*)	73, 75(*R*)[5]
2	3-MeOC$_6$H$_4$	67, 59(*S*)[b]	90, 73(*R*)[6]
3	4-MeOC$_6$H$_4$	85, 38(*S*)	84, 73(*R*)[5]
4	1-naphthyl	78, 84(*S*)	89, 76(*R*)[7]
5	2-naphthyl	76, 56(*S*)	77, 62(*R*)[c]
6	(*E*)-PhCH=CH	87, 56(*S*)	92, 59(*R*)[5]
7	*n*-octyl	66, 30(*R*)[d]	69, 57(*S*)[8]

[a] Enantioselectivities determination by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assignment by comparison with literature value of optical rotations. [b] Enantioselectivities determination by HPLC analysis employing a Daicel Chiracel OJ column. [c] Absolute configuration assignment by analogy. [d] Enantioselectivitydetermination by optical rotation. $[\alpha]^{25}_{D}$ +3.2 (*c* 3.05 in CCl_4) for the product obtained with **1**; $[\alpha]^{25}_{D}$ −6.0 (*c* 2.46 in CCl_4) for the product obtained with **2**.

Consistent with the result obtained with benzaldehyde, **2** generally gave better selectivities than **1**. Another notable trend is that prenyl bromide afforded better chemical yields

Table 3. Enantioselective Indium-Mediated Addition of Prenyl Bromide to Aldehydes

		1	**2**
entry	R	yield, ee[a]	yield, ee
1	Ph	98, 76(*S*)	99, 90(*R*)[9]
2	3-MeOC$_6$H$_4$	96, 62(*S*)	95, 77(*R*)[c]
3	4-MeOC$_6$H$_4$	98, 29(*S*)[b]	97, 78 (*R*)[c]
4	1-naphthyl	91, 41(*S*)	83, 64(*R*)[c]
5	2-naphthyl	86, 29(*S*)	95, 81(*R*)[c]
6	(*E*)-PhCH=CH	88, 72(*S*)	98, 56(*R*)[c]
7	*n*-octyl	87, 27(*R*)[b]	89, 41(*S*)[c]

[a] Enantioselectivity determination by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assignment by comparison with literature value of optical rotation. [b] Enantioselectivity determination by HPLC analysis employing a Daicel Chiracel OD column of the corresponding 3,5-dinitrobenzoate derivatives. [c] Assigned by analogy.

(3) For selected enantioselective allylation of aldehydes with allylzinc reagents, see: (a) Hong, B.-C.; Hong, J.-H.; Tsai, Y.-C. *Angew. Chem. Int. Ed.* **1998**, *37*, 468−470; *Angew. Chem.* **1998**, *110*, 482−484. For enantioselective reaction with allylsilanes, see: (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (c) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495. For enantioselective reaction with allylstannanes, see: (d) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723−4724. (e) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. For enantioselective reaction with allyltitanium reagents, see: (f) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336. For enantioselective ene reaction, see: (g) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949−3954. (h) For enantioselective reaction with allylboranes, see: Corey, E. J.; Yu, C. M.; S. S. Kim, *J. A. Chem. Soc.* **1989**, *111*, 5495−5496.

(4) The cinchona alkaloids have been applied to other enantioselective organic transformations. (a) Reformatsky reactions: Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711−713. (b) Michael additions: Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173−176. (c) Dihydroxylation: Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science*, **1993**, *259*, 64−66 and references therein. (d) [1,3]-Proton shift reaction: Soloshonok, V. A.; Kirilenko, A. G.; Galushko, S. V.; Kukhar, V. P. *Tetrahedron Lett.* **1994**, *35*, 5063−5064. (e) Acetylide addition to ketimines: Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590−1594. (f) Enolate alkylation: Corey, E. J.; Xu, F.; Noe, M. N. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415 and references therein. (g) Hydrogenation: Kunkle, N.; Szabo, A.; Schurch, M.; Wang, G.; Mallat, T.; Baiker, A. *Chem. Commun.* **1999**, 1377−1378 and referances cited therein.

and better enantioselectivities than allyl bromide. The best result (99% yield, 90%(*R*) ee) was obtained when benzaldehyde was treated with prenyl bromide in the presence of **2** (Table 3, entry 1). The allylation reaction of most aromatic aldehydes gave good results, except for 4-methoxybenzaldehyde in the presence of **1** (entry 3). However, application of the protocol to an α,*β*-unsaturated aldehyde such as (*E*)-cinnamaldehyde (entry 6) and an aliphatic aldehyde such as nanyl aldehyde (entry 7) only led to moderate selectivities. In the case of cinnamaldehyde, only the 1,2-addition product was obtained without any detectable 1,4-addition byproduct.

This new method[10] has several advantages due to the following reasons: (1) its experimentation is practically simple and applicable to various allyl bromides and aldehydes; (2) the chiral promoters can be easily obtainable commercially at low cost and recoverable by simple manipulations; (3) in general, good yields and moderate to high selectivities were obtained and both enantiomers of the homoallylic alcohols can be easily obtained by changing the chiral source. The identity of the allyl indium−chiral promoter complexes and reaction mechanism still remains obscure, and further work in this area is underway in our laboratory.

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Supporting Information Available: General procedure of the indium-mediated addition of the allylic bromides to aldehydes and ^{1}H and ^{13}C NMR and HPLC data of all of the homoallylic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Wang, Z.; Wang, D.; Sui, X. *Chem. Commun.* **1996**, 2261−2262.

(9) Manabe, S. *Chem. Commun.* **1997**, 737−738.

(10) **Typical Experimental Procedure:** To a 50 mL round-bottom flask containing an egg-shaped stirring bar were added (−)-chinchonidine **2** (0.5 mmol) and indium powder (0.5 mmol, 57 mg). The solids were azeotropically dried with 3 mL of dry THF twice and then treated with 3 mL of dry THF and allyl bromide (1.5 mmol, 126 mL). The mixture was stirred vigorously till it turned into a clear solution, to which was added dropwise 1 mL of dry hexane. The resulting clear solution was cooled to −78 °C, followed by introduction of benzaldehyde (0.25 mmol, 25 mL) dropwise. The reaction mixture was stirred at −78 °C for 2 h, then allowed to warm to room temperature, and finally quenched with 10 mL of a dilute HCl solution. The aqueous layer was extracted with hexane (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under vacuum, and purified by flash silica gel column chromatography to afford 73% of the homoallylic alcohol as a colorless oil (27 mg, 0.183 mmol); $[\alpha]^{25}_{D}$ +49.5 (*c* 1.05, benzene).[9] The aqueous phase was neutralized with 1 M sodium bicarbonate solution and extracted with ethyl acetate (10 mL × 5). The combined organic extracts were dried with sodium sulfate and concentrated under vacuum to give 97% of **2** as a white solid (143 mg, 0.243 mmol).