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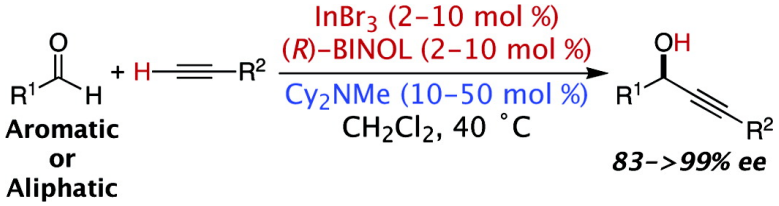
J. Am. Chem. Soc., **2005**, 127 (40), 13760-13761• DOI: 10.1021/ja053946n • Publication Date (Web): 20 September 2005



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Asymmetric Alkynylation of Aldehydes Catalyzed by an In(III)/BINOL Complex

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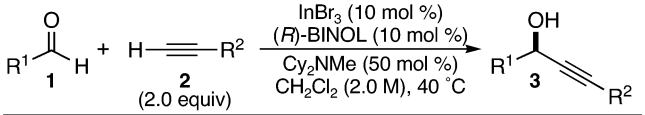
The alkynylation of aldehydes is one of the most useful carbon−carbon bond-forming reactions because of the versatility of the corresponding propargylic alcohols.[1a] There are highly enantioselective alkynylations of aldehydes that use stoichiometric amounts of corresponding metal reagents, such as organolithium and organozinc reagents, with catalytic amounts of chiral ligands or chiral Lewis acids.[1] Given the recent strong demand for an environmentally benign process with high total efficiency, the in situ catalytic generation of metal nucleophiles and their use in carbon−carbon bond-forming reactions is currently a major interest in organic synthesis.[2,3a] Thus, the use of only catalytic amounts of chiral metal salts to achieve *truly catalytic* asymmetric reactions using terminal alkynes directly as a substrate is eagerly anticipated. Carreira and co-workers reported the first sophisticated example of a catalytic system of $Zn(OTf)_2$, *N*-methylephedrine, and Et_3N, giving the corresponding products in a highly enantioselective manner.[3] Aromatic aldehydes, however, cannot be used in this catalytic system due to the Cannizzaro reaction.[3a] Herein, we describe a catalytic asymmetric alkynylation of both aromatic and aliphatic aldehydes promoted by a chiral In(III)/BINOL complex.

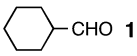
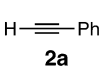
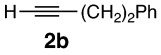
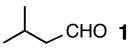
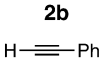
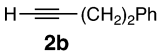
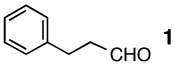
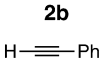
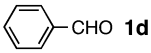
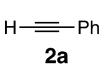
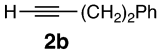
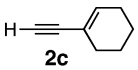
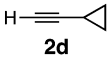
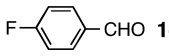
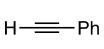
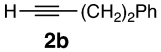
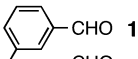
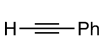
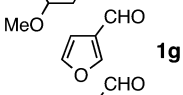
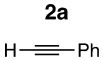
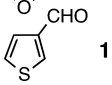
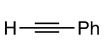
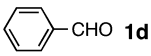
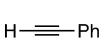
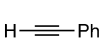
We previously reported a new catalytic system for the alkynylation of aldehydes and ketones with the combination of indium(III) salts and *i*-Pr_2NEt.[4,5] This catalytic system was developed based on our concept of bifunctional catalysis, such as heterobimetallic catalysis and Lewis acid−Lewis base catalysis.[6] As a new entry of bifunctional catalysts, we focused on the "bifunctional character" of indium(III), which acts as both a hard Lewis acid[7] and an effective activator of alkynyl groups.[8] That is, the success of this catalysis is attributed to the dual activation of soft nucleophiles (alkynes) and hard electrophiles (carbonyl compounds) by indium(III) salts. The dual activation was successfully confirmed by in situ IR and NMR spectroscopic studies.[4] The effective activation of both substrates enables the reaction to proceed under very mild conditions for a broad range of substrates, including ketones. These fascinating results prompted us to further develop asymmetric variants to produce versatile optically active propargylic alcohols.

Initial studies on the development of the asymmetric reaction conditions revealed that the use of BINOL as a chiral ligand had high enantioselectivity in the addition of phenylacetylene (**2a**) to cyclohexanecarboxaldehyde (**1a**); in the presence of 10 mol % of $InBr_3$,[9] 10 mol % of (*R*)-BINOL[10] (1:1 ratio), and 50 mol % of *i*-Pr_2NEt in CH_2Cl_2 at 40 °C, the propargylic alcohol **3aa** was obtained in 96% ee, although the chemical yield was moderate (46%, after 7 h). Further optimization of reaction conditions led to the finding that the use of Cy_2NMe instead of *i*-Pr_2NEt effectively accelerated the reaction,[11,12] giving the product in 84% yield and 98% ee (after 7 h).

The generality of this catalytic system (10 mol % of $InBr_3$ and (*R*)-BINOL, and 50 mol % of Cy_2NMe in CH_2Cl_2 at 40 °C) was examined, as summarized in Table 1. Even using the less reactive alkylacetylene **2b** instead of phenylacetylene (**2a**), good chemical yield was obtained with excellent enantioselectivity (entry 2), although a longer reaction time was required. The reaction with isovaleraldehyde (**1b**) also proceeded under the same conditions,

Table 1. $InBr_3$/BINOL Complex−Catalyzed Asymmetric Alkynylation of Various Aldehydes



entry	aldehyde		alkyne	time (h)	yield (%)	ee (%)
1		**1a**	 **2a**	9	95	98
2			 **2b**	36	77	>99
3		**1b**	 **2a**	25	85	96
4			 **2b**	48	46	98
5[a]		**1c**	 **2a**	24	85	98
6		**1d**	 **2a**	24	84	95
7			 **2b**	48	70	98
8			 **2c**	48	77	89
9			 **2d**	48	74	83
10		**1e**	 **2a**	24	75	95
11			 **2b**	45	61	99
12		**1f**	 **2a**	48	77	97
13		**1g**	 **2a**	20	84	98
14		**1h**	 **2a**	29	80	97
15[b]		**1d**	 **2a**	24	85	94
16[c]			 **2a**	48	85	96

[a] Aldehyde **1c** was slowly added over 22 h. [b] The reaction was performed under air atmosphere. [c] $InBr_3$ (2 mol %), (*R*)-BINOL (2 mol %), and Cy_2NMe (10 mol %) were used (10 M CH_2Cl_2).

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10.1021/ja053946n CCC: $30.25

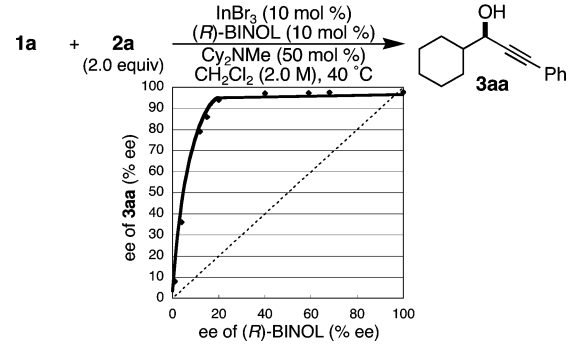

Figure 1. (+)-Nonlinear effects in asymmetric alkynylation catalyzed by an In(III)/BINOL complex.

and the corresponding products were obtained with high enantiomeric excess (entries 3 and 4). Even for the very easily enolizable aldehyde, hydrocinnamaldehyde (**1c**), slow addition of the aldehyde prevented side reactions, such as self-condensation, providing the desired product in good yield and excellent enantioselectivity (entry 5).

Furthermore, the optimized conditions were also applicable to aromatic aldehydes, which are quite challenging substrates for existing catalytic systems due to a competitive Cannizzaro reaction. The addition of phenylacetylene (**2a**) to benzaldehyde (**1d**) proceeded smoothly to give the corresponding product **3da** in 84% yield and 95% ee after 24 h. The use of the alkyl- and alkenylacetylenes also produced high enantioselectivity (entries 7−9). In addition, benzaldehyde derivatives with the electron-donating substituent or electron-withdrawing substituent gave satisfactory yields and high enantioselectivity (entries 10−12). Heteroaromatic aldehydes, such as 3-furaldehyde (**1g**) or 3-thiophenecarboxaldehyde (**1h**), can also be utilized as electrophiles (entries 13 and 14). The use of trimethylsilylacetylene or 3-trimethylsiloxy-1-propyne as an alkyne has been unsuccessful. It is noteworthy, however, that this catalytic system has broad generality for both aromatic and aliphatic aldehydes, as well as phenylacetylene, alkenylacetylenes, and alkylacetylenes.

The reaction proceeded under air atmosphere, giving the propargylic alcohol **3da** in comparable yield and enantioselectivity (entry 15). The catalyst loading could also be decreased, and 2 mol % of $InBr_3$, (*R*)-BINOL, and 10 mol % of Cy_2NMe provided **3da** in 85% yield and 96% ee after 48 h (entry 16).

On the basis of the previous mechanistic studies,[4] dual activation of both substrates is crucial, even in this asymmetric catalytic process. The precise mechanism, however, is not clear, especially whether one or two indium metals are involved in the reaction. When the reaction was performed using nonenantiopure BINOL, rather strong positive nonlinear effects[13] were observed between the enantiomeric excess of BINOL and the product (Figure 1), suggesting that the bimetallic mechanism is involved in the catalytic cycle.[14]

In conclusion, we developed a catalytic asymmetric alkynylation of aldehydes promoted by the In(III)/BINOL complex and Cy_2NMe. Dual activation of both substrates due to the "bifunctional character" of In(III) would make possible a broad range of substrate generality with high enantioselectivity. More precise mechanistic studies as well as further investigations, including catalytic alkynylation of ketones, are ongoing.

Acknowledgment. This work was supported by Grant-in-Aid for Encouragements for Young Scientists (A), and Grant-in-Aid for Specially Promoted Research from JSPS and MEXT. R.T. thanks the JSPS Research Fellowship for Young Scientists.

Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The monometallic mechanism cannot be completely excluded by only positive nonlinear effects. For the proposed bimetallic or monometallic mechanism, see Supporting Information.

JA053946N