Ligand accelerated indium(III)-catalyzed asymmetric alkynylation of aldehydes with 2-methyl-3-butyn-2-ol as an ethyne equivalent donor†

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Indium(III)-catalyzed asymmetric alkynylation of aryl, heteroaryl, alkyl and alkenyl aldehydes with 2-methyl-3-butyn-2-ol as an ethyne equivalent donor was realized, and products were obtained in moderate to good yields (up to 97%) and high enantioselectivities (up to 99% ee) using 2–10 mol% of catalyst.

Asymmetric alkynylation of carbonyl compounds is an efficient and attractive reaction for constructing chiral building blocks.[1] To achieve the reaction, metal acetylides are often utilized as nucleophiles, which are prepared using greater than stoichiometric amounts of a metal base, such as dialkyl zinc, prior to use in an asymmetric reaction.[1] From an atom-economical point of view, however, direct *in situ* generation of a metal acetylide species from alkynes using a *catalytic* amount of the metal source is highly desirable. To address this issue, Carreira and co-workers reported pioneering works on the asymmetric alkynylation of aldehydes utilizing catalytic amounts of $Zn(OTf)_2$, *N*-methylephedrine and Et_3N.[2,3] More recently, a few research groups,[4] including ours,[5] reported asymmetric alkynylation of aldehydes using catalytic amounts of a metal source and an amine base.

Among alkynylation reactions, the introduction of an ethyne unit is important because of the versatility of the products, terminal alkynes, for transformations such as Sonogashira coupling reactions and alkylations. Although there are several reports on the enantioselective addition of either ethyne itself or ethyne equivalents to aldehydes utilizing stoichiometric amounts of metal,[6–8] examples with a *truly catalytic* metal source are rare.[2,4a,9] Carreira and co-workers reported the utility of 2-methyl-3-butyn-2-ol (**1a**, Fig. 1) as an ethyne equivalent donor with stoichiometric amounts of $Zn(OTf)_2$.[7] The use of 2-methyl-3-butyn-2-ol (**1a**) is advantageous over the use of trialkylsilylacetylenes as ethyne equivalents because of the large cost difference.[10] **1a** itself gave good results with stoichiometric amounts of $Zn(OTf)_2$ and an amine base. In the catalytic variant, however, **1a** itself was not utilized and, instead, the hydroxyl group of **1a** was protected with TMS (**1b**, Fig. 1)[2a] or THP.[2b] Furthermore, asymmetric alkynylation of aromatic aldehydes with **1a** or **1b** using a *catalytic* metal source has not been realized.[11] Thus, there remains room for improvement. Herein, we report that an indium(III)–(*S*)-BINOL (**2a**)–amine base system is suitable for the catalytic asymmetric addition of unprotected **1a** to various aldehydes, giving products in up to 97% yield and 99% ee. During optimization of the reaction conditions, we also found that bidentate biaryldiol ligands accelerated the reaction.

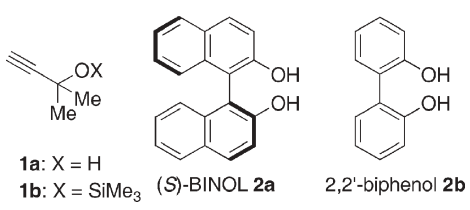

Fig. 1 Structures of 2-methyl-3-butyn-2-ol **1a**, TMS-protected alkyne **1b**, (*S*)-BINOL **2a**, and 2,2′-biphenol **2b**.

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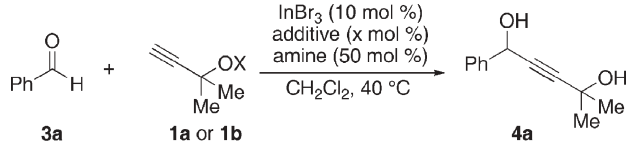
† Electronic supplementary information (ESI) available: General experimental information, spectral data of new compounds, and a copy of the ESI-MS spectrum. See DOI: 10.1039/b614958h

We recently reported catalytic alkynylation of aldehydes and ketones using an indium(III)–amine base system.[5] Based on the reports that indium reagents show relatively low heterophilicity in organic synthesis compared with other organometallic reagents,[12] we hypothesized that the interaction of indium(III) with a hydroxyl group may be weaker than that of zinc(II). Therefore, indium(III) would be more tolerant of nucleophiles possessing a hydroxyl group, such as **1a**. We first examined racemic reactions of aldehyde **3a** with alkyne **1a**. In contrast to our initial assumption, however, the reaction proceeded barely, if at all, using various indium(III) sources, such as, $InBr_3$ (2%), $InCl_3$ (1%), InF_3 (0%), InI_3 (1%), $In(OTf)_3$ (0%), $In(acac)_3$ (0%), and $In(OAc)_3$ (0%), with iPr$_2$NEt in DME.[13] The tendency was quite different from that in our previous studies using other alkynes such as phenylacetylene and terminal alkynes with a linear alkyl chain.[5a] After intensive optimization studies of the solvent, amine source, and other reaction conditions, product **4a** was obtained in 18% yield using 10 mol% of $InBr_3$ and 50 mol% of iPr$_2$NEt in CH_2Cl_2 at 40 °C (Table 1, entry 1). In contrast to $Zn(OTf)_2$ catalysis,[2a] the use of TMS-protected alkyne **1b** gave even worse results (entry 2, 0% yield). Thus, we tried to tune the indium(III) catalyst by adding ligands. Although various phenol derivatives, such as phenol, 4-MeO-phenol, 2,6-dimethylphenol, 2-phenylphenol, and catechol, were not effective (Table 1, entries 3–7), the reaction proceeded smoothly when 2,2′-biphenol (**2b**) was added, and product **4a** was obtained in 58% yield (entry 8). By changing the amine from iPr$_2$NEt to Cy$_2$NMe,[14] the reactivity was further improved (entry 9, 72% yield). With a chiral biaryldiol ligand, (*S*)-BINOL (**2a**), the reaction also proceeded smoothly, and **4a** was obtained in 88% yield by prolonging the reaction time (entry 10, 39 h). The enantioselectivity of **4a** was also satisfactory (97% ee).

The substrate scope of the present reaction is summarized in Table 2.‡ The reaction proceeded smoothly using an aryl aldehyde with an electron-withdrawing group (entry 2, 87% yield, 99% ee). With an electron-donating substituent, the reactivity decreased slightly, yet the product was obtained in high enantioselectivity

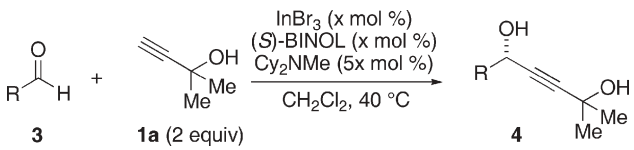
Table 1 Optimization of reaction conditions

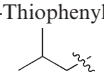


Entry	Additive (mol%)		Amine	1	Time/h	Yield (%)
1	None	—	*i*Pr$_2$NEt	**1a**	25	18
2	None	—	*i*Pr$_2$NEt	**1b**	45	0
3	Phenol	20	*i*Pr$_2$NEt	**1a**	26	Trace
4	4-MeO-phenol	20	*i*Pr$_2$NEt	**1a**	26	Trace
5	2,6-Me$_2$-phenol	20	*i*Pr$_2$NEt	**1a**	26	Trace
6	2-Ph-phenol	20	*i*Pr$_2$NEt	**1a**	26	Trace
7	Catechol	10	*i*Pr$_2$NEt	**1a**	24	0
8	2,2′-Biphenol **2b**	10	*i*Pr$_2$NEt	**1a**	24	58
9	2,2′-Biphenol **2b**	10	Cy$_2$NMe	**1a**	24	72
10[a]	(*S*)-BINOL **2a**	10	Cy$_2$NMe	**1a**	39	88

[a] **4a** was obtained in 97% ee.

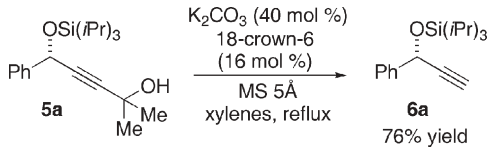
Table 2 Catalytic asymmetric addition of 2-methyl-3-butyn-2-ol **1a**[a]



Entry	Aldehyde: R		Catalyst (x mol%)	Time/h	Yield (%)	ee (%)
1	**3a**	Ph	10	39	88	97
2	**3b**	*p*-Cl–C$_6$H$_4$	10	48	87	99
3	**3c**	*p*-MeO–C$_6$H$_4$	10	48	62	99
4	**3d**	2-Furyl	10	40	89	93
5	**3e**	3-Thiophenyl	10	41	87	99
6	**3f**		10	19	81	99
7	**3g**		10	22	91	98
8	**3h**		10	19	97	99
9	**3i**		10	22	94	98
10	**3j**	(*E*)-Cinnamyl	10	39	40	99
11[b]	**3a**	Ph	5	24	88	99
12[c]	**3a**	Ph	2	48	82	98

[a] Reactions were performed using aldehyde **3** (0.40 mmol), **1a** (0.80 mmol), $InBr_3$ (0.04 mmol), (*S*)-BINOL (0.04 mmol), and Cy_2NMe (0.20 mmol) in CH_2Cl_2 (2.0 M) at 40 °C unless otherwise noted. [b] Reaction was performed using aldehyde **3a** (40 mmol), **1a** (80 mmol), $InBr_3$ (2.0 mmol), (*S*)-BINOL (2.0 mmol), Cy_2NMe (10 mmol) in CH_2Cl_2 (4.0 M) at 40 °C. [c] Reaction was performed using **3a** (1.0 mmol), **1a** (2.0 mmol), $InBr_3$ (0.02 mmol), (*S*)-BINOL (0.02 mmol), and Cy_2NMe (0.10 mmol) in dichloroethane (10 M) at 80 °C.

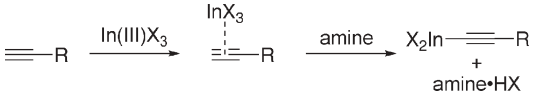
(entry 3, 62% yield, 99% ee). Heteroaromatic aldehydes also afforded products in good yield and ee (entries 4 and 5). Various aliphatic aldehydes were also applicable to the present system; α-non-substituted (entry 6), α-substituted (entries 7 and 8), and α,α-disubstituted (entry 9) aldehydes gave the products in good yields and high enantioselectivities (entries 6–9: 81–97% yield and 98–99% ee). α,β-Unsaturated aldehyde **3j** gave only a modest yield under standard reaction conditions, albeit in high ee (entry 10, 40% yield, 99% ee). Trials to reduce the catalyst loading are summarized in entries 11 and 12. The reaction proceeded without difficulty with 5 mol% catalyst (entry 11). In entry 11, 10 mL of solvent was used in a 40 mmol scale reaction (4.0 M), affording 6.7 g of **4a** (88% yield) in 99% ee. The high volumetric productivity is noteworthy. With 2 mol% catalyst, and by performing the reaction at 80 °C in dichloroethane under highly concentrated conditions (10 M), **4a** was obtained in 82% yield, while maintaining high ee (entry 12, 98% ee). Removal of the acetone moiety was demonstrated under the reported conditions,[7a,15] with slight modification (Scheme 1). Treatment of TIPS-protected product **5a** with 40 mol% of K_2CO_3 and 16 mol% of 18-crown-6 in the presence of MS 5 Å in refluxing xylenes afforded product **6a** in 76% yield. The use of MS 5 Å had beneficial effects, improving the isolated yield of **6a** when using substoichiometric amounts of K_2CO_3.



Scheme 1 Removal of the protecting group to give terminal alkyne **6a**.

In the present reaction using alkyne **1a**, drastic ligand acceleration was observed (Table 1). This observation was quite different from those of our previous studies using the same indium catalysis and other alkynes.[16] We speculate that the unexpected low reactivity encountered using alkynes **1a** and **1b** in the racemic system (Table 1, entries 1 and 2) is due to the steric bulkiness of alkynes **1a** and **1b**, rather than to adverse effects of the hydroxyl group of **1a**. For efficient *in situ* deprotonation of alkynes with amine bases, activation of the alkyne with π-acidic indium(III) is important (Scheme 2).[17] The bulky substituent (R = –C(OH)Me$_2$) in **1a** would prevent efficient coordination of **1a** to the In(III) metal center. The results shown in Table 1 suggested that the complexation of indium(III) with a bidentate biaryldiol ligand was important (entries 3–7 *vs.* entry 8). An $InBr_3$–BINOL complex was observed when analyzing the mixture of $InBr_3$, (*S*)-BINOL, and aldehyde **3a** with ESI-MS.[18]† Although it is difficult to discuss precisely the structures and differences in steric factors of indium(III) complexes with or without ligands at the current stage of studies,[19] we speculate that the bidentate complexation with biaryldiol ligands, such as 2,2′-biphenol (**2b**) and BINOL **2a**, would change the steric factor around the indium metal center, thereby enabling efficient coordination of sterically-hindered **1a** to π-acidic indium. Further mechanistic studies to elucidate the structure of the $InBr_3$–BINOL complex are ongoing.

In summary, we realized a catalytic asymmetric addition of ethyne equivalent **1a** in a free-OH form. The chiral propargyl alcohols were obtained from various aryl, heteroaryl, alkyl, and



Scheme 2 Postulated mechanism for *in situ* generation of indium acetylide from alkynes.

alkenyl aldehydes in moderate to good yields (40–97%) and high enantioselectivities (93–99% ee) using catalytic amounts of $InBr_3$, BINOL, and Cy_2NMe. Catalyst loading was successfully reduced to 2–10 mol%. Biaryldiol ligands **2a** and **2b** accelerated the present reaction.

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Notes and references

‡ **Representative procedure**: To a flame-dried test tube, under an argon atmosphere, were added (*S*)-BINOL (0.04 mmol), $InBr_3$ (0.04 mmol), dry CH_2Cl_2 (0.2 mL) and then benzaldehyde (**3a**) (40.7 μL, 0.4 mmol) at room temperature. The resulting solution was stirred for 10 min, and Cy_2NMe (42.8 μL, 0.2 mmol) was added. After stirring again for 10 min, 2-methyl-3-butyn-2-ol (**1a**) (77.5 μL, 0.8 mmol) was added. The mixture was warmed up to 40 °C (oil bath temperature) and stirred for 39 h. After work-up and purification by flash column chromatography (silica gel, hexane : AcOEt = 6 : 1 to 3 : 1), **4a** (67.2 mg, 0.353 mmol, 88% yield, 97% ee) was obtained as a colorless solid.

1 For recent reviews, see: (*a*) G. Lu, Y. M. Li, X. S. Li and A. S. C. Chan, *Coord. Chem. Rev.*, 2005, **249**, 1736; (*b*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2004, 4095; (*c*) L. Pu, *Tetrahedron*, 2003, **59**, 9873.

2 (*a*) N. K. Anand and E. M. Carreira, *J. Am. Chem. Soc.*, 2001, **123**, 9687; (*b*) R. Fässler, C. S. Tomooka, D. E. Frantz and E. M. Carreira, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5843.

3 For related works using stoichiometric amounts of $Zn(OTf)_2$, amine, and a chiral ligand, see the review: (*a*) D. E. Frantz, R. Fässler, C. S. Tomooka and E. M. Carreira, *Acc. Chem. Res.*, 2000, **33**, 373 and references therein. See also: (*b*) D. E. Frantz, R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806. For other examples of asymmetric alkynylation of aldehydes using stoichiometric amounts of preformed metalated alkynes, see reviews in ref. 1. See also ref. 8, and references therein.

4 (*a*) M. Yamashita, K.-I. Yamada and K. Tomioka, *Adv. Synth. Catal.*, 2005, **347**, 1649; (*b*) B. Jiang, Z. Chen and W. Xiong, *Chem. Commun.*, 2002, 1524; (*c*) Z. Chen, W. Xiong and B. Jiang, *Chem. Commun.*, 2002, 2098; (*d*) D. P. G. Emmerson, W. P. Hems and B. G. Davis, *Org. Lett.*, 2006, **8**, 207. In ref. 4*b*–4*d*, only phenylacetylene was applicable under catalytic conditions.

5 Racemic reaction: (*a*) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima and M. Shibasaki, *Org. Lett.*, 2005, **7**, 1363. Asymmetric reaction: (*b*) R. Takita, K. Yakura, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13760. For related works using stoichiometric amounts of $InBr_3$ and amine base, see: (*c*) N. Sakai, M. Hirasawa and T. Konakahara, *Tetrahedron Lett.*, 2003, **44**, 4171.

6 For the use of acetylene gas in asymmetric addition to aldehydes, see: H. Sasaki, D. Boyall and E. M. Carreira, *Helv. Chim. Acta*, 2001, **84**, 964.

7 (*a*) D. Boyall, F. López, H. Sasaki, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2000, **2**, 4233; (*b*) J. W. Bode and E. M. Carreira, *J. Am. Chem. Soc.*, 2001, **123**, 3611; (*c*) D. Boyall, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2002, **4**, 2605. Both 2-methyl-3-butyn-2-ol and trialkylsilylacetylenes were applicable in their system. See, also ref. 3*b*.

8 For selected recent examples of asymmetric addition of trialkylsilylacetylenes to aldehydes using more than a stoichiometric amount of dialkyl zinc reagents: (*a*) D. Moore and L. Pu, *Org. Lett.*, 2002, **4**, 1855; (*b*) B. M. Trost, A. H. Weiss and A. J. von Wangelin, *J. Am. Chem. Soc.*, 2006, **128**, 8; (*c*) C. Wolf and S. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 10996 and references therein. For other examples, see reviews in ref. 1.

9 In contrast to the asymmetric alkynylation of carbonyl compounds, there are many successful asymmetric alkynylations of C=N bonds using *catalytic* metal sources. See the review: (*a*) C. Wei, Z. Li and C.-J. Li, *Synlett*, 2004, 1472 and references therein. For recent selected examples using ethyne equivalent donors, and also diastereoselective reactions with **1a** and trialkylsilylacetylenes, see: (*b*) R. Fässler, D. E. Frantz, J. Oetiker and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2002, **41**, 3054. Catalytic enantioselective reactions with trialkylsilylacetylenes: (*c*) N. Gommermann and P. Knochel, *Chem.–Eur. J.*, 2006, **12**, 4380 and references therein; (*d*) N. Gommermann, C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5763; (*e*) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2004, **43**, 5971.

10 2-Methyl-3-butyn-2-ol **1a** is an inexpensive and readily available bulk chemical. In contrast, trialkylsilylacetylenes are expensive. For more discussion concerning the utility of **1a** as an ethyne equivalent donor, see ref. 7*a*.

11 Tomioka and co-workers realized asymmetric alkynylation of benzaldehyde with triethylsilylacetylene using a catalytic amount of $Zn(OTf)_2$ at 100 °C. Although an excellent ee was achieved (90%), the yield was unsatisfactory (30%). See ref. 4*a*.

12 Reviews on indium-mediated organic reactions: (*a*) V. Nair, S. Ros, C. N. Jayan and B. S. Pillai, *Tetrahedron*, 2004, **60**, 1959; (*b*) P. Cintas, *Synlett*, 1995, 1087.

13 The use of an In(III) salt and iPr$_2$NEt in DME or neat conditions were the optimized conditions in the previous studies using other terminal alkynes. See ref. 5*a*.

14 For recent representative examples of the beneficial effects of Cy_2NMe in metal-catalyzed enantioselective reactions, see: (*a*) R. Imbos, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2002, **124**, 184; (*b*) M. M.-C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 4572; (*c*) R. Shintani and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4082; (*d*) R. Shintani and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 10778 and references therein. See also: (*e*) P. Zhao and D. B. Collum, *J. Am. Chem. Soc.*, 2003, **125**, 14411. See also ref. 5.

15 In the original report (ref. 7*a*, Carreira and co-workers), **6a** was obtained in good yield using 1 equiv. of K_2CO_3 under a stream of nitrogen in toluene at reflux, without using MS 5 Å. In our hands, a higher reaction temperature (xylenes, reflux, under Ar) and MS 5 Å were required to obtain the product in good yield.

16 With other alkynes, such as phenylacetylene and terminal alkynes with a linear alkyl chain, both the racemic system and the chiral In(III)–BINOL system worked nicely. See ref. 5*a* and 5*b*. In contrast, with **1a**, a large difference in reactivity was observed.

17 For mechanistic studies on *in situ* generation of metal acetylides, see ref. 2*b* and 5*a*.

18 Although an In : BINOL 1 : 1 complex was observed under ESI-MS analysis conditions, the possibility that a dimeric complex (In : BINOL 2 : 2 complex) or other oligomeric complexes are active species cannot be ruled out at the present stage of the studies because a strong positive non-linear effect was observed (see ref. 5*b*). In ESI-MS analysis, a peak containing two BINOL units for one indium(III) was also observed. Further mechanistic studies to elucidate the structure of the active species are ongoing.

19 Indium(III) bromide itself is known to have a similar aggregate structure to YCl_3 and $AlCl_3$, where a metal(III) center is surrounded with six halogen atoms. We speculate that the complexation with a bidentate ligand would have beneficial effects and change the aggregation state, making more space around the indium(III) center. At the moment, however, other explanations to rationalize the beneficial effects of bidentate ligands cannot be ruled out. For the crystal structure of indium(III) bromide, see: (*a*) T. Staffel and G. Meyer, *Z. Anorg. Allg. Chem.*, 1988, **563**, 27. See also: (*b*) D. H. Templeton and G. F. Carter, *J. Phys. Chem.*, 1954, **58**, 940.

