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Highly enantioselective addition of linear alkyl alkynes to linear aldehydes

Yuhao Du [a,b], Mark Turlington [b], Xiang Zhou [a,*], Lin Pu [b,*]

[a] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China
[b] Department of Chemistry, University of Virginia, Charlottesville, VA 22904-4319, USA

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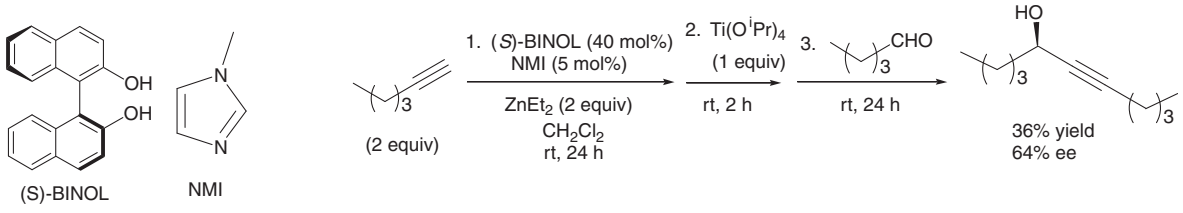
ABSTRACT

It is discovered that the use of biscyclohexylamine (Cy_2NH) as an additive can greatly enhance the enantioselectivity for the reaction of linear alkyl alkynes with linear aldehydes. The combination of (*S*)-BINOL (20 mol %), Cy_2NH (5 mol %), $ZnEt_2$ (2 equiv), and $Ti(O^iPr)_4$ (0.5 equiv) catalyzes the reaction at room temperature in diethyl ether solution with 81–89% ee and 57–77% yield.

In recent years, the catalytic asymmetric alkyne addition to aldehydes has been demonstrated as a very efficient method to generate the synthetically versatile chiral propargylic alcohols.[1–3] A number of highly enantioselective catalyst systems for a range of substrates have been developed. In spite of the significant progress in this area, however, almost no efficient catalyst was found to carry out the highly enantioselective reaction of linear aldehydes with terminal alkynes of linear alkyl substituents. This could be attributed to the less steric bias of linear alkyl groups on the substrates versus the branched alkyl and aryl groups as well as the susceptibility of linear aldehydes toward aldol addition in the presence of both acid and base catalysts. In an example reported by Carreira, the catalytic asymmetric reaction of 4-phenyl-1-butyne, a β-aryl substituted alkyne, with a linear aldehyde *n*-octanal was observed with high enantioselectivity, but the yield was low, and heating and slow addition of the aldehyde were needed.[2b] In two other examples of linear alkyne addition to linear aldehydes, the use of stoichiometric amount of chiral amino alcohols was required.[4]

Earlier, we reported the use of 1,1′-bi-2-naphthol (BINOL) in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ to catalyze the alkyne addition to aryl, alkyl, and vinyl aldehydes with high enantioselectivity.[3a,b] We further found that using HMPA as a Lewis base additive allows the reaction to be conducted entirely at room temperature and expands the substrates' scope to include various functional alkynes.[3c,d] Later, You and coworkers reported that *N*-methyl imidazole (NMI) can be used as a Lewis base additive in place of HMPA to increase the efficiency of the BINOL–$ZnEt_2$–$Ti(O^iPr)_4$ catalyst system.[5] We have tested the use of NMI in combination with (*S*)-BINOL, $Ti(O^iPr)_4$, and $ZnEt_2$ to catalyze the



Scheme 1. A linear alkyne addition to a linear aldehyde in the presence of (*S*)-BINOL and NMI.

* Corresponding authors. Tel.: +1 434 924 6953; fax: +1 434 924 3710.
E-mail address: lp6n@virginia.edu (L. Pu).

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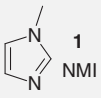
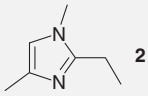
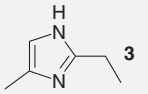
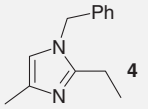
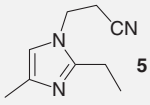
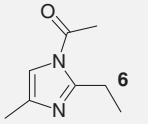
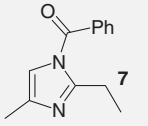
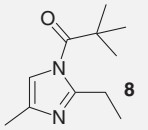
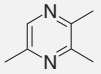
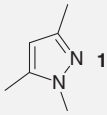
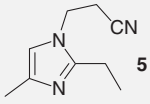
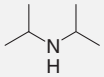
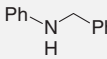
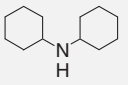
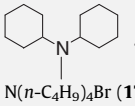
Table 1
1-Hexyne addition to valeraldehyde in the presence of various Lewis base additives

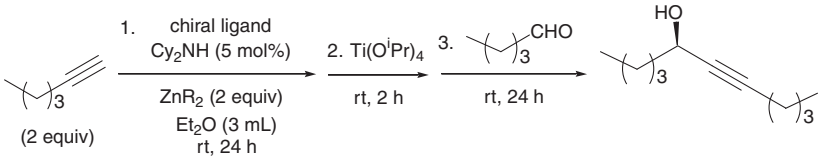
Entry	Base	Base (mol %)	Solvent	Isolated yield[a] (%)	ee[a] (%)
1	 **1** NMI	5	CH_2Cl_2	36	64
2	 **2**	5	CH_2Cl_2	92	62
3	 **3**	5	CH_2Cl_2	25	66
4	 **4**	5	CH_2Cl_2	44	70
5	 **5**	5	CH_2Cl_2	34	76
6		10	CH_2Cl_2	52	70
7		2.5	CH_2Cl_2	30	75
8	 **6**	5	CH_2Cl_2	49	71
9	 **7**	5	CH_2Cl_2	56	72
10	 **8**	5	CH_2Cl_2	49	61
11	 **9**	5	CH_2Cl_2	50	72
12	 **10**	5	CH_2Cl_2	75	60
13	 **5**	5	THF	95	55
14		5	Toluene	56	56
15		5	Et_2O	83	77
16	$CH_3NH(CH_2)_3NH_2$ (**11**)	5	Et_2O	91	64
17	 **12**	5	Et_2O	40	79
18	 **13**	5	Et_2O	76	77
19	 **14** Cy_2NH	5	Et_2O	59	84
20	Et_3N (**15**)	5	Et_2O	56	74
21	 **16**	5	Et_2O	51	78
22	$N(n\text{-}C_4H_9)_4Br$ (**17**)	5	Et_2O	44	77

[a] Determined by using the ^1H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)CO_2H.

reaction of a linear alkyne 1-hexyne with a linear aldehyde valeraldehyde at room temperature, but observed only 36% yield and 64% ee (Scheme 1). We have attempted to modify the structure of NMI and also examined various other nitrogen-based Lewis base additives for this reaction. Herein, we wish to report the discovery of greatly enhanced enantioselectivity for the asymmetric linear alkyne addition to linear aldehydes.

Table 1 lists the experiments we have conducted for the reaction of 1-hexyne with valeraldehyde in the presence of various Lewis base additives under the same conditions as those shown in

Table 2
Reaction conditions for 1-hexyne addition to valeraldehyde in the presence of Cy_2NH

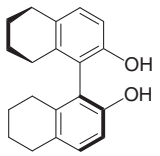


Entry	Ligand (mol %)	$Ti(O^iPr)_4$/BINOL	ZnR_2	Isolated yield (%)	ee[a] (%)
1	(*S*)-BINOL (40)	1.5	$ZnEt_2$	59	81
2	(*S*)-BINOL (40)	3.5	$ZnEt_2$	41	81
3[b]	(*S*)-BINOL (40)	2.5	$ZnEt_2$	88	82
4	(*S*)-BINOL (30)	2.5	$ZnEt_2$	49	81
5	(*S*)-BINOL (20)	2.5	$ZnEt_2$	73	81
6	(*S*)-BINOL (10)	2.5	$ZnEt_2$	63	55
7	(*S*)-BINOL (20)	2.5	$ZnMe_2$	44	83
8[c]	(*S*)-BINOL (20)	2.5	$ZnEt_2$	25	73
9[d]	(*S*)-BINOL (20)	2.5	$ZnEt_2$	32	52
10[e]	(*S*)-BINOL (20)	2.5	$ZnEt_2$	51	80
11	(*S*)-H_8BINOL (40)	2.5	$ZnEt_2$	68	78

[a] Determined by using the ^1H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)COOH.
[b] 4 equiv $ZnEt_2$ and 4 equiv hexyne were used.
[c] (*S*)-BINOL, Cy_2NH, hexyne, and Et_2Zn in Et_2O were stirred for 2 h, then $Ti(O^iPr)_4$ was added.
[d] After valeraldehyde was added, the reaction solution was stirred at 0 °C for 24 h.
[e] Cy_2NH, (*S*)-BINOL, and Et_2Zn in Et_2O were stirred for 6 h, and then hexyne was added. 18 h later, $Ti(O^iPr)_4$ was added.

Scheme 1 unless noted otherwise. We first modified the structure of NMI by introducing additional alkyl substituents to increase the basicity and steric bulkiness of NMI. As shown in entry 2, when compound **2** was used in place of NMI used in entry 1, the yield of the reaction was greatly increased but the enantioselectivity was reduced slightly. Removal of the *N*-methyl group of **2** diminished the yield (entry 3). The use of the *N*-benzyl group in **4** to replace the *N*-methyl group in **2** improved the enantioselectivity but decreased the yield (entry 4). Using compound **5** containing a polar *N*-alkyl group further improved the enantioselectivity (entry 5). Increasing the amount of **5** increased the yield but reduced the ee (entry 6). Decreasing the amount of **5** could not improve the reaction (entry 7). The use of *N*-acyl imidazole derivatives **6**, **7,** and **8** gave lower enantioselectivity than **5** (entries 8–10). Using other types of *N*-heterocycles such as **9** and **10** improved the yields but not the enantioselectivity (entries 11 and 12). We have studied the effect of solvent on the reaction carried out in the presence of **5**. When CH_2Cl_2 was replaced with THF in entry 13, the yield was greatly increased over entry 5 but the enantioselectivity was reduced. No improvement was observed by changing THF to toluene (entry 14). However, when Et_2O was used, the yield was improved without sacrificing the ee in comparison with entry 5 (entry 15). This demonstrates that Et_2O is a superior solvent over CH_2Cl_2 for this reaction. We also screened various alkyl amines for this reaction in Et_2O. The use of the primary amine **11** gave an excellent yield but the ee was low (entry 16). Using the secondary amine **12** gave a higher enantioselectivity but the yield was low (entry 17). *N*-Benzyl aniline (**13**) gave a better yield and a slightly reduced ee (entry 18). When the secondary amine Cy_2NH (**14**) was used, high enantioselectivity was observed also with much better yield than the initial NMI (entry 19). The tertiary amines **15** and **16** gave lower enantioselectivity than the secondary amine Cy_2NH (entries 20 and 21). Interestingly, the quaternary ammonium salt **17** gave a higher enantioselectivity than NMI (entry 22). This indicates that Br^- can also act as a Lewis base to promote this reaction.

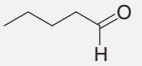
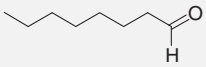
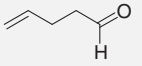
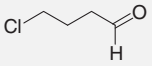
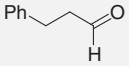
The result in entry 19 of Table 1 demonstrates that Cy_2NH is a much better base additive than NMI, giving a high enantioselectivity for the reaction of 1-hexyne with valeraldehyde. We have further explored the reaction conditions for the use of Cy_2NH and the experiments are listed in Table 2. When the amount of $Ti(O^iPr)_4$ was decreased, a slight reduction of the ee was observed (entry 1). Increasing the amount of $Ti(O^iPr)_4$ decreased the yield (entry 2). When the amounts of $ZnEt_2$ and 1-hexyne were doubled (4 equiv), a high yield was obtained but there was no gain in ee (entry 3). Varying the amount of (*S*)-BINOL in entries 4–6 showed that 20 mol % of (*S*)-BINOL gave good yield and good ee (entry 5). Using $ZnMe_2$ in place of $ZnEt_2$ significantly decreased the yield (entry 7). Decreasing the reaction time in the first step from 24 h to 2 h gave a diminished yield, indicating insufficient formation of the nucleophilic alkynylzinc reagent (entry 8). Conducting the reaction at 0 °C in the third step decreased both the yield and ee (entry 9). Mixing (*S*)-BINOL, Cy_2NH, and $ZnEt_2$ in Et_2O for 6 h followed by the addition of 1-hexyne in the first step (entry 11) gave a lower yield than that in entry 5. When (*S*)-BINOL was replaced with the partially hydrogenated (*S*)-H_8BINOL (40 mol %), lower enantioselectivity was observed (entry 11).



(*S*)-H_8BINOL

Because entry 5 in Table 2 gives the reduced usage of the chiral ligand and the higher reaction yield and ee, its conditions are applied to catalyze the reactions of other linear alkynes and aldehydes, and the results are summarized in Table 3. As shown in the table, high enantioselectivity and moderate to good yields have been achieved for the reactions of linear alkynes with a variety of linear aldehydes. The absolute configurations of the products are assigned to be *R* in analogous to the previously reported reac-

Table 3
Reactions of various linear alkynes with linear aldehydes in the presence of (*S*)-BINOL, Cy_2NH, $ZnEt_2$, and $Ti(O^iPr)_4$[a]

Entry	Alkyne	Aldehyde	Isolated yield (%)	ee[b] (%)
1	n-C_4H_9—		73	81
2	n-C_6H_{13}—		61	87
3	Cl		77	88
4	n-C_4H_9—		76	85
5	n-C_6H_{13}—		67	85
6	Cl		70	89
7	n-C_4H_9—		63	87
8	n-C_6H_{13}—		59	83
9	Cl		60	88
10	n-C_6H_{13}—		57	77
11	Cl		61	83
12	n-C_4H_9—		71	83
13	n-C_6H_{13}—		74	84
14	Cl		65	89

[a] Reagents used: (*S*)-BINOL/$ZnEt_2$/alkyne/Cy_2NH/$Ti(O^iPr)_4$/aldehyde = 0.2:2:2:0.05:0.5:1.
[b] Determined by using the ^1H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)CO_2H.

tions.[3,5] It is interesting to notice that 5-chloro-1-pentyne consistently gave better enantioselectivity than the other linear alkynes when reacted with various aldehydes. The results in Table 3 demonstrate that the readily available BINOL–Cy_2NH–$ZnEt_2$–$Ti(O^iPr)_4$ catalyst system is useful for the synthesis of chiral propargylic alcohols from linear alkynes and aldehydes.

A general procedure for the reactions in Table 3 is given below. Under nitrogen, (*S*)-BINOL (14.3 mg, 0.05 mmol) was dissolved in Et_2O (3 mL) in a flame-dried flask. $ZnEt_2$ (53 μL, 0.5 mmol), an alkyne (0.5 mmol), and Cy_2NH (2.4 μL, 0.0125 mmol) were added sequentially and the resulting mixture was stirred at room temperature for 24 h. $Ti(O^iPr)_4$ (37 μL, 0.125 mmol) was then added and the reaction mixture was stirred for 2 h. To the resulting solution was added an aldehyde (0.25 mmol). After 24 h, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted three times with CH_2Cl_2 and the organic phase was dried with sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel eluted with hexanes/Et_2O (10:1) to give the product as an oil. The ee was determined by using the ^1H NMR spectra of their esters prepared with (*R*)-PhCH(OAc)CO_2H.

Acknowledgments

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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.2010.07.082.

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