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Tetrahedron: *Asymmetry*

The use of bifunctional catalyst systems in the asymmetric addition of alkynylzinc to aldehydes

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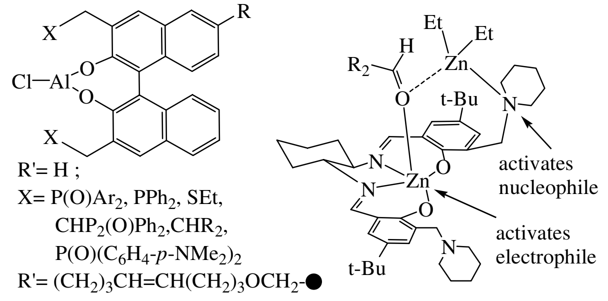
Abstract—The bifunctional ligand **2a** showed a more enhanced reactivity than that of the corresponding amino alcohol ligand in the asymmetric addition of alkynylzinc to benzaldehyde. The bifunctional ligand **2a** can catalyze the addition of phenylacetylene to various types of aldehydes including aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes with high enantioselectivity (81–98% ee). The conditions of this catalytic process are both mild and simple.

1. Introduction

The use of catalyst systems containing bifunctional ligands in the asymmetric construction of C–C bonds is an attractive method of emulating the reactivity of natural enzymes.[1] The most representative examples of this concept are a series of bifunctional Lewis acid–Lewis base (LALB) catalysts **1** (Fig. 1) derived from BINOL as the chiral scaffold, developed by Shibasaki and Kanai.[1f] Indeed, these catalyst systems containing chiral ligands with two or more reactive sites have proven successful in this class of reactions,[2] and separation of the Lewis acid and Lewis base sites in these ligands is proposed to account for this difference in reactivity. Recently, DiMauro and Kozlowski[3] have found that bifunctional Lewis acid–Lewis base catalyses **2** (Fig. 1) were much more reactive when compared to the Noyori DAIB or the Nugent MIB catalysts in the alkylation of aldehydes and α-ketoesters. Based on our recent report on the catalytic asymmetric addition of alkynylzinc to aldehydes,[4] we supposed that these catalyst systems containing bifunctional ligand would also enhance the reactivity in the asymmetric addition of alkynylzinc to aldehydes.



1 **2**

Figure 1.

The enantioselective alkynylzinc addition to carbonyl compounds[5,6] is very useful for the synthesis of chiral propargyl alcohols, which are important versatile building blocks of many biologically active compounds and natural products,[7] and has gained considerable significance in recent years. Among the catalytic methods developed for the asymmetric alkyne addition to aldehydes, the following two are currently considered the most practical. Carreira et al. discovered a catalyst based on the chiral amino alcohol *N*-methyl ephedrine for the alkynylzinc addition to aldehydes.[8] High enantioselectivity and high product yields were achieved for the reaction of alkynylzincs with a variety of aliphatic aldehydes. Pu et al.[9] and Chan et al.[10] have found that 1,1′-bi-2-naphthol (BINOL) in combination with Ti(O*i*-Pr)$_4$ can catalyze the alkynylzinc addition to aromatic aldehydes or aliphatic aldehydes with high

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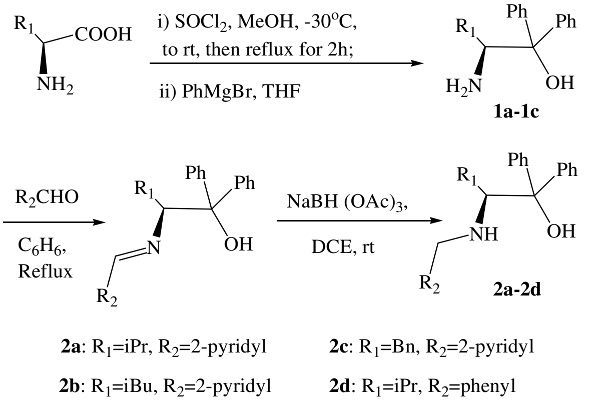
enantioselectivity. However the ligands and current methods for these reaction need to be further modified, Carreira's method is not catalytic for the addition to benzaldehyde and the BINOL method requires the use of both alkylzinc and Ti(O*i*-Pr)$_4$. In addition, the relationship between ligand structure enantioselectivity and the catalytic activity need to be studied, and there is a growing need to find a new catalyst, which can catalyze the asymmetric addition of terminal acetylenes to aldehydes with high ee values under mild and convenient conditions. Herein, we report a highly enantioselective alkyne addition to aldehydes catalyzed by catalyst systems containing a bifunctional ligand.

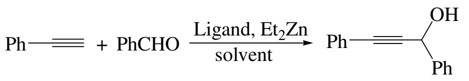
2. Results and discussion

Unlike Shibasaki's and Kozlowski's C_2-symmetric chiral bifunctional ligands (Fig. 1), we designed and synthesized a class of dissymmetric chiral bifunctional ligands. We used a natural amino acid as a starting material. After four simple steps, we got the bifunctional ligands **2a**–**c** and amino alcohol ligand **2d** in high yields (Scheme 1).[11]



Scheme 1. Preparation of ligands **2a**–**d**.

Bifunctional ligands **2a**–**c** and amino alcohol ligand **2d** were used to catalyze the reaction of phenylacetylene with benzaldehyde in the presence of Et$_2$Zn. The reactions were conducted at 0 °C in hexane–THF by the sequential treatment of chiral ligand, Et$_2$Zn, phenylacetylene, and then benzaldehyde (Scheme 2). The results are summarized in Table 1.



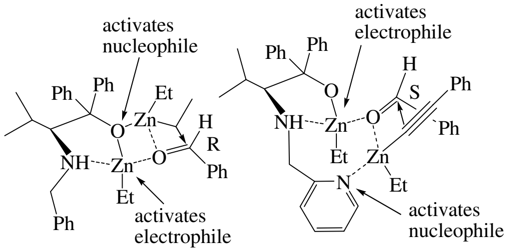
Scheme 2. Addition of phenylacetylene to benzaldehyde.

Table 1. Asymmetric addition phenylacetylene to benzaldehyde using **2** as ligands

Entry	Ligand	Time (h)	Yield (%)	Ee (%)	Confign[a]
1	**2a**	20	95	94	*S*
2	**2b**	24	80	46	*S*
3	**2c**	20	87	76	*S*
4	**2d**	24	88	57	*R*

[a] The absolute configuration is based on measurements of the specific rotation and comparison with the literature values.[6a,8b,13]

We found that bifunctional ligand **2a** showed an enhanced reactivity over that of amino alcohol ligand **2d** in the asymmetric addition of alkynylzinc to benzaldehyde (Table 1, entries 1 and 4). Based on our experimental findings and related mechanism suggested by literature,[11] a possible transition state is proposed in Figure 2. When β-aminoalkoxyl zinc catalyst **3** was employed, this reaction proceeded by dual activation of the aldehyde electrophile and dialkylzinc nucleophile (Fig. 2).[6j,12] When bifunctional catalyst **4** was used in this reaction, the β-aminoalkoxyl zinc atom could act as the Lewis acid center (LA) to activate the aldehyde, while the nitrogen atom of pyridyl group could act as the base center (LB) independently to activate the alkynylzinc nucleophile (Fig. 2).



3 4

Figure 2.

Among the bifunctional ligands **2a**, **2b** and **2c**, **2a** showed the best asymmetric induction, with 94% ee obtained (Table 1, entries 1–3). Obviously, the presence of an *i*-Pr group at the stereogenic carbon atom was crucial for the best asymmetric induction.

We then explored the conditions for the use of ligand **2a** in the reaction of phenylacetylene with benzaldehyde, with these experiments summarized in Table 2. We found that this reaction was strongly influenced by the solvent. In entries 1–5, various solvents including CH$_2$Cl$_2$, ether, THF, hexane, and toluene were tested, among which, THF–hexane was found to be the best. Decreasing the reaction temperature from 0 °C to −15 °C or increasing the reaction temperature from 0 °C to room temperature all led to a lower ee (entries 6 and 7). When we decreased the amount of ZnEt$_2$ from 4 to 3, 2, and 1.4 equiv on this reaction, we found the enantioselectivity was improved, and the appropriate amount of ZnEt$_2$ was 1.4 equiv (entries 8–10). Increasing the amount of **2a** from 10 to 20 mmol% in entry 11 gave enhanced ee. Reducing the amount of THF from 2 to 1 mL in entry 12 led to an increased ee.

Under the optimized reaction conditions of entry 12 in Table 2, ligand **2a** was employed to catalyze the enantio-

Table 2. Asymmetric addition phenylacetylene to benzaldehyde using **2a** as ligand[a]

Entry	**2a** (mmol%)	Solvent (mL)	Et_2Zn (equiv)	Temp. (°C)	Ee[b] (%)
1	10	CH_2Cl_2 (2)	2	0	11
2	10	Ether (2)	2	0	56
3	10	THF–Hex (2)	2	0	85
4	10	Hex[c] (2)	2	0	19
5	10	Toluene (2)	2	0	43
6	10	THF–Hex (2)	2	Rt[d]	79
7	10	THF–Hex (2)	2	−15	66
8	10	THF–Hex (2)	1.4	0	90
9	10	THF–Hex (2)	3	0	82
10	10	THF–Hex (2)	4	0	73
11	20	THF–Hex (2)	1.4	0	92
12	**20**	**THF–Hex (1)**	**1.4**	**0**	**94**

[a] Phenylacetylene/Et_2Zn = 1:1, benzaldehyde: 0.25 mmol.

[b] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

[c] Hex = hexane.

[d] Rt = room temperature.

selective addition of phenylacetylene to a variety of aldehydes (Table 3). High enantioselectivity was achieved for the addition of phenylacetylene to aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes with an ee value up to 98%.

Table 3. Asymmetric addition phenylacetylene to aldehydes promoted by ligand **2a**[a,b]

Entry	Aldehydes	Time (h)	Isolated yield (%)	Ee[c] (%)
1	Benzaldehyde	20	95	94
2	3-Tolualdehyde	24	85	93
3	4-Tolualdehyde	24	82	90
4	3-Anisaldehyde	24	90	92
5	4-Anisaldehyde	24	86	93
6	3-Bromobenzaldehyde	24	94	85
7	4-Bromobenzaldehyde	32	84	87
8	2-Chlorobenzaldehyde	24	95	85
9	4-Chlorobenzaldehyde	32	88	86
10	3-Nitrobenzaldehyde	24	80	98
11	4-Fluorobenzaldehyde	24	92	91
12	α-Naphthaldehyde	32	80	90
13	β-Naphthaldehyde	32	87	91
14	Isobutylaldehyde	32	91	91
15	Cyclohexanecarboxaldehyde	32	88	90
16	Cinnamicaldehyde	32	82	81

[a] In all of the entries: Et_2Zn/phenylacetylene/aldehyde/**2a** = 1.4:1.4:1.0:0.2.

[b] All the reactions were processed under argon and at 0 °C.

[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

3. Conclusion

We have conveniently synthesized a series of bifunctional ligands **2a**–**c** and amino alcohol ligand **2d** with high yields. We have discovered that the bifunctional ligand **2a** showed an enhanced reactivity over that of amino alcohol ligand **2d** in the asymmetric addition of alkynylzinc to benzaldehyde, and that the bifunctional ligand **2a** can catalyze the addition of phenylacetylene to both aromatic and aliphatic aldehydes with ee values up to 98%. The conditions of this catalytic process are both mild and simple.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere and solvents dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were carried out using silica gel. All aldehydes and amino acid were purchased from Acros or Fluka. Diethylzinc was prepared from EtI with Zn and then diluted with toluene or hexane to 1.0 M. Melting points are uncorrected and were recorded on an X-4 melting point apparatus. ^1H NMR spectra were measured on DRX-200 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained on Nicolet NEXUS 670 FT-IR. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. HR-MS were measured with an APEX II 47e mass spectrometer and the ESI-MS was recorded on a Mariner® biospectrometer. The ee value determination was carried out using chiral HPLC with a Daicel Chiracel® OD column on Waters® with a 996 UV-detector.

4.2. Preparation of 1a–c and 2a–d

Amino alcohols **1a**–**c** were synthesized according to literatures: Refs. 11 and 14. The bifunctional ligand **2a**–**c** and amino alcohol ligand **2d** were synthesized according to literature procedures: Ref. 11.

4.2.1. (*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol 1a. Colorless needle crystals, yield 65%; mp: 95–97 °C; $[\alpha]_D^{18} = -124.0$ (c 1.27, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 7.60$ (d, $J = 8$ Hz, 2H, Ph–H), 7.48 (dd, $J = 8.6$ Hz, $J = 1.4$ Hz, 2H, Ph–H), 7.33–7.10 (m, 6H, Ph–H), 4.436 (s, 1H, OH), 3.83 (d, $J = 2.2$ Hz, 1H, CHN), 1.73 (m, 1H, $CH(CH_3)_2$), 1.157 (br, 2H, NH_2), 0.91 (d, $J = 8.2$ Hz, 3H, CH_3), 0.87 (d, $J =$ 7 Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 16.39$, 23.27, 28.13, 60.46, 79.97, 125.78, 126.20, 126.55, 126.87, 128.30, 128.68, 145.20, 148.34; IR(KBr): 3341, 3059, 3082, 3023, 2959, 2926, 2873, 1591, 1490, 1446, 1382, 1367, 1174, 1049, 965, 940, 896, 748, 700, 668 cm^{-1}; MS (ESI): m/z: 256 $[M + H]^+$.

4.2.2. (*S*)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol 1b. Colorless needle crystals, yield 55%; mp: 132–134 °C; $[\alpha]_D^{18} = -105.0$ (c 1.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.61$ (d, $J = 7.5$ Hz, 2H, Ph–H), 7.47 (d, $J = 8.1$ Hz, 2H, Ph–H), 7.33–7.13 (m, 6H, Ph–H), 3.98 (d, $J = 10.2$ Hz, 1H, CHN), 1.58 (m, 1H, $CH(CH_3)_2$), 1.25 (m, 1H, $CH_ACH(CH_3)_2$), 1.11 (m, 1H, $CH_BCH(CH_3)_2$), 0.89 (d, $J = 7.8$Hz, 3H, CH_3), 0.86 (d, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.25$, 24.00, 25.28, 39.41, 54.45, 79.03, 125.53, 125.82, 126.29, 126.57, 127.97, 128.37, 144.50, 147.16; IR(KBr): 3332, 3262, 2950, 2864, 1589, 1490, 1468, 1445, 1387, 1179, 1054, 1006, 972, 948, 899, 837, 744, 699 cm^{-1}; MS (ESI): *m*/*z*: 270 $[M + H]^+$.

4.2.3. (*S*)-2-Amino-1,1,3-triphenylpropan-1-ol 1c. Colorless crystals, yield 70%; mp: 134–136 °C; $[\alpha]_D^{18} = -85.0$ (*c* 1.10, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 7.65–7.57$ (m, 4H, Ph–H), 7.35–7.15 (m, 11H, Ph–H), 4.514 (s, 1H, OH), 4.16 (dd, 1H, $J = 2.6$ Hz, $J = 10.6$ Hz, CHN), 2.63 (d, 1H, $J = 11.6$ Hz, $PhCH_A$), 2.43 (dd, 1H, $J = 10.8$ Hz, $J = 13.8$ Hz, $PhCH_B$), 1.161 (s, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 37.10$, 58.55, 78.86, 125.73, 126.12, 126.78, 127.10, 128.56, 128.82, 128.99, 129.42, 139.98, 144.67, 147.14; IR(KBr): 3511, 3335, 3243, 3083, 3058, 3025, 2920, 2850, 1596, 1490, 1445, 1362, 1324, 1272, 1169, 1103, 1056, 1030, 960, 900, 857, 749, 699 cm^{-1}; MS (ESI): *m*/*z*: 304 $[M + H]^+$.

4.2.4. (*S*)-3-Methyl-2-[(2-pyridylmethyl)amino]-1,1-diphenylbutan-1-ol 2a. Colorless crystals, yield 82.4%; mp: 119–121 °C; $[\alpha]_D^{21} = -63.0$ (*c* 1.01, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.49$ (d, $J = 4.8$ Hz, 1H, Py-α-H), 7.72–7.12 (m, 12H, Ph–H, Py–H), 6.85 (d, $J = 7.6$ Hz, 1H, Ph–H), 5.193 (s, 1H, OH), 3.58 (d, $J = 2$ Hz, 1H, CHN), 3.49 (d, $J = 14$ Hz, 1H, $PyC–H_A$), 3.34 (d, $J = 14$ Hz, 1H, $PyC–H_B$), 2.186 (s, 1H, NH), 1.98 (m, 1H, $CH(CH_3)_2$), 0.92 (d, $J = 6.6$ Hz, 3H, CH_3), 0.76 (d, $J = 6.6$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.95$, 22.48, 28.92, 55.50, 68.74, 78.59, 121.95, 122.33, 125.74, 126.06, 126.34, 127.83, 127.98, 136.20, 145.44, 149.15, 159.23; IR(KBr): 3332, 3058, 3026, 2956, 2871, 1593, 1570, 1490, 1473, 1449, 1430, 1390, 1371, 1177, 1151, 1088, 1056, 1029, 994, 750, 703, 668, 630 cm^{-1}; MS (ESI): *m*/*z*: 347 $[M + H]^+$. Anal. Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.96; H, 7.260; N, 8.185.

4.2.5. (*S*)-4-Methyl-2-[(2-pyridylmethyl)amino]-1,1-diphenylpentan-1-ol 2b. Colorless crystals, yield 87%; mp: 100–101 °C; $[\alpha]_D^{25} = -45$ (*c* 0.97, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.48$ (d, $J = 4.8$ Hz,1H, Py-α-H), 7.67–7.06 (m, 12H, Ph–H, Py–H), 6.85 (d, $J = 7.6$ Hz, 1H, Ph–H), 4.899 (s, 1H, OH), 3.66 (dd, $J = 4.2$ Hz, $J = 8.6$ Hz, 1H, CHN), 3.44 (d, $J = 14$ Hz, 1H, $PyC–H_A$), 3.25 (d, $J = 14$ Hz, 1H, $PyC–H_B$), 1.889 (s, 1H, NH), 1.59 (m, 1H, $CH(CH_3)_2$), 1.27 (m, 2H, CH_2), 0.79 (d, $J = 6.6$ Hz, 3H, CH_3), 0.75 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.57$, 23.93, 25.20, 40.58, 54.52, 62.95, 78.57, 121.91, 122.32, 125.88, 126.12, 126.20, 126.42, 127.91, 128.02, 136.22, 145.20, 148.07, 149.15, 159.41; IR(KBr): 3340, 3085, 3059, 3027, 2955, 2868, 1592, 1571, 1490, 1468, 1449, 1383, 1365, 1314, 1176, 1153, 1096, 1052, 1032, 998, 907, 751, 703, 662, 638 cm^{-1}; MS (ESI): *m*/*z*: 361 $[M + H]^+$. Anal. Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found: C, 80.10; H, 7.284; N, 7.950.

4.2.6. (*S*)-2-[(2-Pyridylmethyl)amino]-1,1,3-triphenylpropan-1-ol (2c). Colorless needle crystals, yield 83%; mp: 80–82 °C; $[\alpha]_D^{25} = -40$ (*c* 1.1, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.30$ (d, $J = 4.2$ Hz,1H, Py-α-H), 7.74–6.98 (m, 17H, Ph–H, Py–H), 6.64 (d, $J = 7.6$ Hz, 1H, Ph–H), 4.00 (dd, $J = 2.2$ Hz, $J = 10.2$ Hz, 1H, CHN), 3.26 (s, 2H, $PyC–H_2$), 2.95 (d, $J = 14.6$, 1H, PhCH), 2.45 (dd, $J = 10.4$, $J = 14.6$, 1H, PhCH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 37.90$, 54.23, 66.02, 78.64, 121.66, 121.87, 125.86, 126.20, 126.48, 126.71, 128.20, 129.00, 136.06, 139.61, 145.19, 147.52, 149.05, 159.10; IR(KBr): 3370, 3159, 3083, 3057, 3024, 2918, 2848, 1597, 1566, 1491, 1446, 1388, 1350, 1181, 1150, 1120, 1105, 1056, 1030, 1002, 969, 891, 763, 745, 699, 660, 627, 565 cm^{-1}; MS (ESI): *m*/*z*: 395 $[M + H]^+$. Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 82.24; H, 6.724; N, 7.156.

4.2.7. (*S*)-3-Methyl-2-benzylamino-1,1-diphenylbutan-1-ol 2d. Colorless crystals, yield 76%; mp: 132–134 °C; $[\alpha]_D^{25} = -34$ (*c* 1.24, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 7.5$ Hz, 2H, Ph–H), 7.61 (d, $J = 8.7$ Hz, 2H, Ph–H), 7.36–7.12 (m, 11H, Ph–H), 3.67 (s, 1H, CNH), 3.47 (d, $J = 12$ Hz, 1H, $PhC–H_A$), 3.28 (d, $J = 12$ Hz, 1H, $PhC–H_B$), 2.08 (m, 1H, $CH(CH_3)_2$), 1.00 (d, $J = 6.6$ Hz, 3H, CH_3), 0.73 (d, $J = 6.6$ Hz, 3H, CH_3); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta = 15.90$, 22.63, 28.72, 55.00, 68.48, 78.57, 125.81, 126.07, 126.45, 127.19, 127.87, 128.04, 128.28, 128.38, 140.11, 145.29, 148.86; IR(KBr): 3340, 3085, 3060, 3026, 2955, 2870, 2834, 1656, 1598, 1491, 1472, 1449, 1373, 1177, 1077, 1058, 1028, 986, 943, 903, 750, 725, 701, 669, 636 cm^{-1}; MS (ESI): *m*/*z*: 346 $[M + H]^+$. Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.06. Found: C, 83.27; H, 7.767; N, 4.256.

4.3. General procedures for the addition of phenylacetylene to aldehydes

To a solution of ligand **2a** (0.05 mmol, 17.4 mg) in THF (1 mL), was added a solution of Et_2Zn (0.35 mmol, 1.0 M in hexane, 0.35 mL) at room temperature. After the mixture was stirred at the room temperature for 1 h, phenylacetylene (0.35 mmol, 38 μL) was added, and stirring continued for another 1 h. The solution was cooled to 0 °C and treated with aldehyde (0.25 mmol, 25 μL) and then the resultant mixture stirred for 20–32 h at 0 °C. After the reaction was complete (checked by TLC), it was quenched by 5% aqueous HCl at 0 °C. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 12.5% EtOAc in hexane) to give the product.

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