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Asymmetric alkyne addition to aldehydes catalyzed by Schiff bases made from 1,1′-bi-2-naphthol and chiral benzylic amines

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ABSTRACT

Several 1,1′-bi-2-naphthol (BINOL)-based Schiff bases were prepared from the condensation of (*R*)-3,3′-diformyl BINOL with chiral benzylic amine derivatives. These compounds were used to catalyze the reaction of phenylacetylene with aldehydes in the presence of $ZnEt_2$ with up to 85% ee and 83% yield.

1. Introduction

Catalytic asymmetric alkyne addition to aldehydes can generate chiral propargylic alcohols that are very useful in organic synthesis. In recent years, significant progress has been made in this area and a number of highly enantioselective catalysts have been developed.[1–3] In our laboratory, we have studied the use of 1,1′-bi-2-naphthol (BINOL) and its derivatives to catalyze the alkyne addition to aldehydes.[4] For example, we found that BINOL in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and Cy_2NH (Cy = cyclohexyl) can catalyze the reaction of a broad range of alkyne and aldehyde substrates with high enantioselectivity.[4c] We also found that when derivatives of BINOL, such as the salen compounds **1** and **2** (Fig. 1) were used in combination with ZnR_2 (R = Et or Me) in the absence of $Ti(O^iPr)_4$ and Cy_2NH, high enantioselectivity could still be achieved.[5] However, the analogous salen compounds **3**–**5** that contain chiral benzylic amine units rather than the cyclohexanediamine unit of **1** or **2** were found to give poor enantioselectivity.[5a] For the reaction of phenylacetylene with benzaldehyde in the presence of $ZnEt_2$, compounds **3**–**5** gave enantioselectivities of 13%, <10% and 17% ee respectively. In order to further explore BINOL-based catalysts for the asymmetric alkyne addition to aldehydes, we have synthesized several analogues of compounds **3**–**5** by preparing BINOL-based Schiff bases from chiral benzylic amines. When such compounds were used to catalyze the reaction of phenylacetylene with aldehydes, significantly improved enantioselectivity was achieved. Herein, these results are reported.

2. Results and discussion

As shown in Scheme 1, we obtained Schiff bases **6**–**9** via condensation of (*R*)-3,3′-diformyl-BINOL with several chiral benzylic amine derivatives.[6] (*R*)-3,3′-Diformyl-BINOL was prepared according to the previously reported procedure from (*R*)-BINOL.[7] Compound **6** was previously reported by Brunner and Goldbrunner for its use in the copper-catalyzed cyclopropanation of styrene with N_2CHCO_2Et, although low stereoselectivity was observed.[8] The acid catalyst used in the previous synthesis[8] of **6** was not necessary as described in our procedure.[6]

We first studied the use of compound **6** to catalyze the reaction of phenylacetylene with benzaldehyde and the results are summarized in Table 1. The reaction was carried out in two steps. In the first step, phenylacetylene, $ZnEt_2$ (1.0 M in hexane), and **6** were stirred in a solvent at room temperature for 1 h. Next, the mixture was cooled to 0 °C and benzaldehyde was added. The reaction was stopped after 24 h. In entries 1–4, various solvents were examined for this reaction. It can be seen that the use of nonpolar cyclohexane as the solvent gave the highest enantioselectivity (entry 4). Increasing the amount of phenylacetylene and $ZnEt_2$ (entry 5) enhanced both the yield and enantioselectivity to 83% and 85% ee respectively. The configuration of the propargylic alcohol product was determined to be (*R*) by comparing its specific rotation with that in the literature.[9] Increasing the concentration of the reaction mixture led to a reduced yield and enantioselectivity (entry 6), while decreasing the concentration reduced the ee slightly (entry 7). We also explored the effect of the reaction temperature of the second step on this catalytic process. It was found that both decreasing (entries 10–12) and increasing (entries 13 and 14) the reaction temperature reduced enantioselectivity. We also found that addition of a small amount of (*R*)-BINOL (entry 15) or (*S*)-BINOL (entry 16) could greatly influence the reaction, giving much lower or even opposite enantioselectivity. This indicates that BINOL could significantly alter the catalyst structure, probably by coordination to the Zn center.

Compound **7** is a diastereomer of **6** with the same chiral BINOL unit, but the opposite chiral amine configuration. When **7** was used for this reaction, the enantioselectivity was very low (entry 17).

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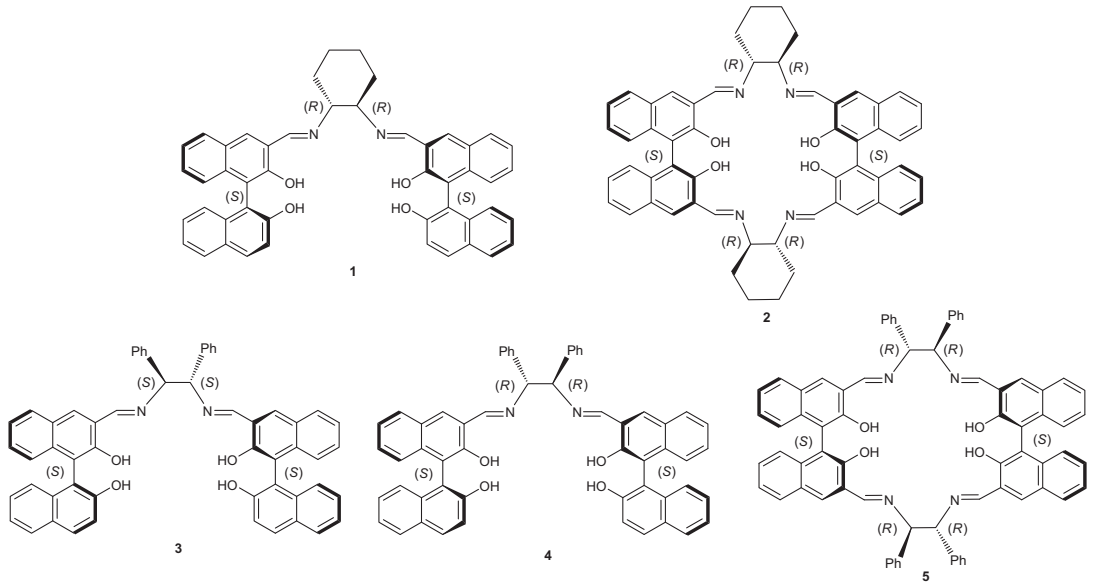
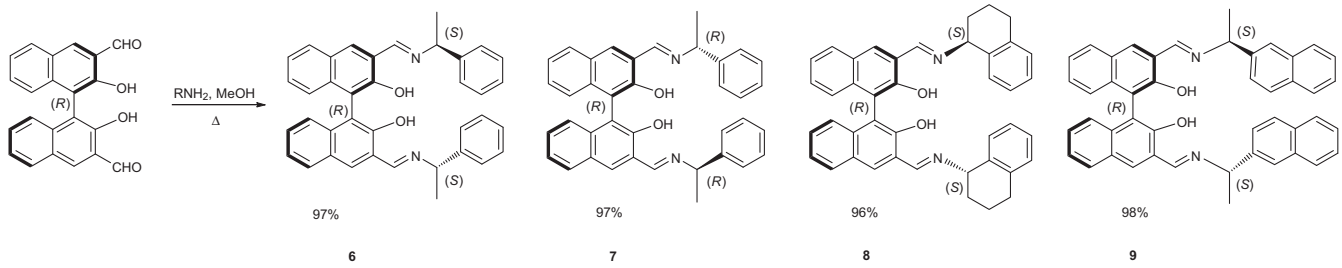
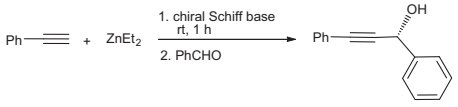


Figure 1. BINOL-based chiral salens used for the asymmetric alkyne addition to aldehydes.



Scheme 1. Preparation of the BINOL-based Schiff bases **6**–**9**.

Table 1
Results of the use of Schiff bases **6**–**9** in combination with $ZnEt_2$ for the reaction of phenylacetylene with benzaldehyde[a]



Entry	Schiff base (equiv)	Phenylacetylene (equiv)	$ZnEt_2$ (equiv)	Solvent (mL)	Temperature of 2nd step (°C)	Isolated yield (%)	ee[e] (%)
1	**6** (0.1)	2	2	THF (3)	0	23	47
2	**6** (0.1)	2	2	CH_2Cl_2 (3)	0	60	50
3	**6** (0.1)	2	2	Toluene (3)	0	71	55
4	**6** (0.1)	2	2	Cyclohexane (3)	0	63	75
5	**6 (0.1)**	**4**	**4**	**Cyclohexane (3)**	**0**	**83**	**85**
6	**6** (0.1)	4	4	Cyclohexane (2)	0	39	78
7	**6** (0.1)	4	4	Cyclohexane (4)	0	85	82
8	**6** (0.2)	4	4	Cyclohexane (3)	0	72	74
9	**6** (0.05)	4	4	Cyclohexane (3)	0	62	17
10	**6** (0.1)	4	4	Cyclohexane (3)	−10	85	81
11	**6** (0.1)	4	4	Cyclohexane (3)	−20	60	67
12	**6** (0.1)	4	4	Cyclohexane (3)	−40	52	63
13	**6** (0.1)	4	4	Cyclohexane (3)	10	79	73
14	**6** (0.1)	4	4	Cyclohexane (3)	30	89	68
15[b]	**6** (0.1)	4	4	Cyclohexane (3)	0	62	27
16[c]	**6** (0.1)	4	4	Cyclohexane (3)	0	60	−19
17	**7** (0.1)	4	4	Cyclohexane (3)	0	58	27
18	**8** (0.1)	4	4	Cyclohexane (3)	0	74	75
19[c]	**8** (0.1)	4	4	Cyclohexane (3)	0	89	75
20[c,d]	**8** (0.1)	4	4	Cyclohexane (3)	0	90	75
21[d]	**9** (0.1)	4	4	Cyclohexane (3)	0	77	55

[a] Phenylacetylene (0.5 or 1.0 mmol), $ZnEt_2$ (0.5 or 1.0 mmol, 1.0 M in hexane), and a chiral Schiff base were mixed in a solvent at rt for 1 h. Benzaldehyde (0.25 mmol, distilled and stored cold) was then added and stirred for 24 h.
[b] Add 0.1 equiv (*R*)-BINOL.
[c] Add 0.1 equiv (*S*)-BINOL.
[d] Benzaldehyde was freshly distilled and used immediately.
[e] Determined by HPLC equipped with a chiral column.

This demonstrates that there is mismatched chirality between the BINOL unit and the amino carbon centers in **7**. In compound **8**, its conformation around the amino carbon centers is restricted with the introduction of a cyclic structure. This reduced the enantioselectivity with or without the use of the (*S*)-BINOL additive or the freshly distilled benzaldehyde (entries 18–20). In compound **9**, a larger naphthyl substituent at each of the chiral amino carbons was used to replace the phenyl substituent in **6**. This compound gave a lower enantioselectivity than **6** (entry 21).

Compound **6** contains only half of the structural units of the BINOL-based macrocycle **5**, but with the same relative chirality between the BINOL unit and the amino carbon centers. As shown in entry 5 of Table 1, compound **6** gave good enantioselectivity for the reaction of phenylacetylene with benzaldehyde in the presence of $ZnEt_2$. The greatly enhanced enantioselectivity of **6** over **5** and the other BINOL-chiral benzylic amine-based Schiff bases **3** and **4** for this reaction prompted us to explore the reaction of other aldehydes catalyzed by **6**. Figure 2 summarizes the results for the reaction of phenylacetylene with various aromatic aldehydes using the conditions in entry 5 of Table 1.[10] All of these products were isolated and their characterization data matched those previously reported.[4a,11] The configurations of the products were assigned by analogous with the product of entry 5 of Table 1. The results in Figure 2 show that various propargylic alcohols could be prepared with encouraging results by using the easily prepared compound **6** as a catalyst. Thus, the BINOL-based Schiff base represents a promising class of catalyst for asymmetric alkyne addition to aldehydes.

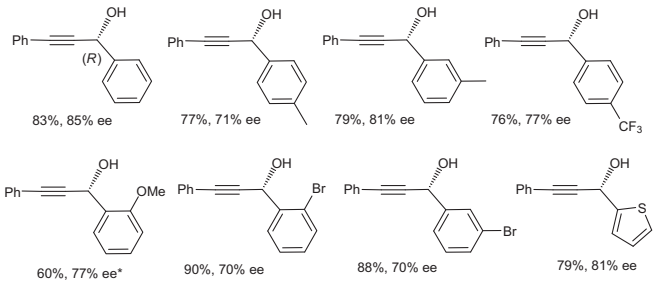


Figure 2. Propargylic alcohols prepared from the reaction of phenylacetylene with various aldehydes in the presence of **6** and $ZnEt_2$. *A mixed solvent of cyclohexane/Et_2O (11:1) was used.

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6. *Preparation and characterization of* ***6–9****:* In a round bottom flask equipped with a reflux condenser, (*R*)-3,3′-Diformyl-1,1′-bi-2-naphthol (100 mg, 0.3 mmol) was dissolved in MeOH (25 mL), and a chiral primary amine (0.6 mmol) was then added. The mixture was heated and refluxed for 1–4 h. After the reaction was completed, the solution was concentrated under vacuum and then filtered. The solid product was washed with MeOH without further purification. Compound **6**: 97% yield. Mp 132–135 °C. ^{1}H NMR (300 MHz, DMSO) δ 13.33 (s, 2H), 8.97 (s, 2H), 8.26 (s, 2H), 7.97–8.00 (d, 2H, J = 8.0 Hz), 7.39–7.42 (m, 4H), 7.23–7.35 (m, 10H), 6.90 (d, 2H, J = 8.1 Hz), 4.74–4.78 (m, 2H), 1.57 (d, 6H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.8, 154.3, 143.8, 134.7, 133.5, 129.0, 128.6, 128.3, 127.1, 127.0, 126.4, 124.1, 123.2, 120.7, 116.0, 67.4, 24.4. $[\alpha]_D^{20} = +168.3$ (c 1.0, $CHCl_3$). HRMS(ESI) calcd for $C_{38}H_{32}N_2O_2$+H: 549.2537. Found for MH$^+$: 549.2522. Compound **7**: 97% yield. Mp 134–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.18 (s, 2H), 8.67 (s, 2H), 7.09–7.94 (m, 20H), 4.60 (d, J = 6.7 Hz, 2H), d1.62 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 154.6, 143.3, 135.3, 133.5, 128.8, 128.6, 128.3, 127.5, 127.3, 126.7, 124.8, 123.3, 121.1, 116.6, 68.9, 24.7. $[\alpha]_D^{20} = -20$ (c 1.0, $CHCl_3$). HRMS(ESI) calcd for $C_{38}H_{32}N_2O_2$+H: 549.2537. Found for MH$^+$: 549.2522. Compound **8**: 96% yield. Mp170–172 °C. ^{1}H NMR (300 MHz, DMSO) δ 13.20 (s, 2H), 8.98 (s, 2H), 8.25 (s, 2H), 7.97–8.00 (m, 2H), 7.28–7.31 (m, 4H), 7.10–7.15 (m, 8H), 6.91–6.94 (m, 2H), 4.64–4.65 (m, 2H), 1.98–2.03 (m, 2H), 1.87–1.91 (m, 4H), 1.74–1.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 156.0, 137.8, 137.1, 136.3, 134.4, 130.0, 129.8, 128.8, 128.5, 128.0, 126.8, 125.5, 124.0, 123.9, 122.2, 117.6, 67.6, 32.0, 29.8, 20.3. $[\alpha]_D^{20} = +36.6$ (c 1.0, $CHCl_3$). HRMS(ESI) calcd for $C_{42}H_{36}N_2O_2$+H: 601.2852. Found for MH$^+$: 601.2852. Compound **9**: 98% yield. Mp >184.1 °C. ^{1}H NMR (300 MHz, DMSO) δ 13.32 (s, 2H), 10.36 (s, 2H), 8.26-8.29 (m, 4H), 7.95–7.98 (m, 4H), 7.83–7.86 (d, 2H, J = 8.2 Hz), 7.46–7.61 (m, 8H), 7.32–7.35 (m, 4H), 7.02 (s, 2H), 5.60–5.66 (m, 2H), 1.67–1.69 (d, 6H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 154.7, 138.9, 135.3, 133.9, 133.7, 130.5, 130.0, 129.1, 128.8, 128.4, 127.8, 127.6, 126.2, 125.7, 125.5, 124.8, 124.3, 123.3, 123.0, 121.1, 116.6, 63.8, 24.2. HRMS(ESI) calcd for $C_{46}H_{36}N_2O_2$+H: 649.2850. Found for MH$^+$649.2856. $[\alpha]_D^{20} = +328.4$ (c 1.0, $CHCl_3$).
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10. General procedure for the addition of phenylacetylene to aldehydes catalyzed by **6**. Under nitrogen, phenylacetylene (1.0 mmol, 110 μL) and **6** (0.025 mmol) were mixed in dry cyclohexane (3 mL) in a 25 mL flask at room temperature. Next, a solution of diethylzinc (1.0 M in hexane, 1 mL) was added. After the mixture was stirred at room temperature for 1 h, the yellow solution was cooled to 0 °C to which was added an aldehyde (0.25 mmol) and stirred for 24 h. The reaction was then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluted with EtOAc/petroleum ether (1:15) to give the product. The enantiomeric excess (ee) was determined by HPLC analysis using a chiral stationary phase (Daicel Chiralcel OD-H, Daicel Chiralcel AD-H), eluting with *i*-PrOH–hexanes or EtOH–hexanes, and using UV detection at 254 nm.
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