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Synthesis of New C_2-Symmetrical Bissulfonamide Ligands and Application in the Enantioselective Addition of Alkynylzinc to Aldehydes and Ketones

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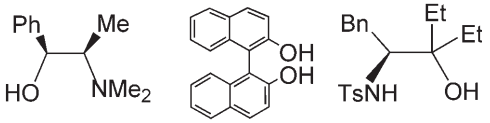
Abstract: Novel C_2-symmetrical bissulfonamide ligands were easily prepared in three simple steps and applied in the enantioselective addition of alkynylzinc reagents to aldehydes. Compound **7a** was found to be an outstanding ligand for this reaction. When the catalyst loading, 4 mol % of **7a**, was used, high enantioselectivity with an ee value up to 97% was achieved under very mild conditions. When the amount of ligand **7a** was lowered to 2 mol %, excellent levels of enantiocontrol up to 95% ee were still achieved. So far the most economic catalyst system was developed for the addition of terminal alkynes to aromatic aldehydes in terms of ligand loading and enantioselectivity. Moreover, ligand **7a** in combination with Ti(O-*i*-Pr)$_4$ was found to be effective in promoting the addition reaction of an alkynylzinc reagent to unactivated simple ketones under very mild conditions. The corresponding chiral tertiary propargylic alcohols were obtained with enantiomeric excesses of up to 81%.

Keywords: aldehydes; alkynylation; asymmetric catalysis; homogeneous catalysis; ketones

Introduction

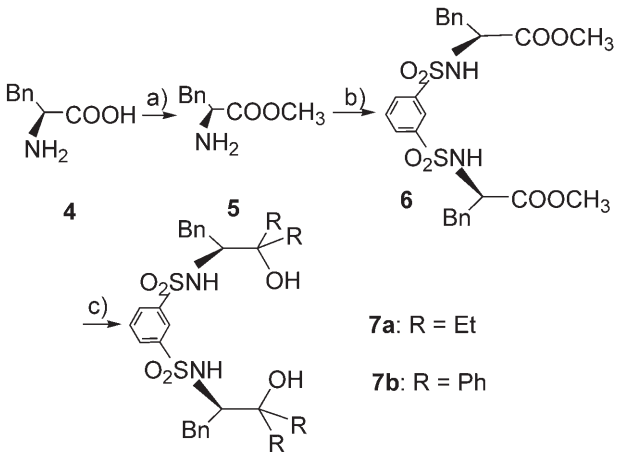
The enantioselective alkynylzinc addition to carbonyl compounds[1,2] is very useful for the synthesis of chiral propargyl alcohols, which are important and versatile building blocks for many biologically active compounds and natural products,[3] and has gained considerable significance in recent years. Among the catalytic methods developed for the asymmetric alkyne addition to aldehydes, the following three are currently considered the most practical. Carreira and co-workers discovered a catalyst based on the chiral amino alcohol *N*-methylephedrine (**1**) for the alkynylzinc addition to aldehydes.[4] High enantioselectivity and high product yields were achieved for the reaction of alkynylzincs with a variety of aliphatic aldehydes, and the method could even be run solvent-free with catalytic amounts of ligand and metal. Pu et al.[5] and Chan et al.[6] have found that binol (**2**) in combination with Ti(O-*i*-Pr)$_4$ can catalyze the alkynylzinc addition to aromatic aldehydes or aliphatic aldehydes with high enantioselectivity. We have described the highly enantioselective addition of phenylacetylene to aldehydes catalyzed by a β-sulfonamide alcohol **3** in combination with Ti(O-*i*-Pr)$_4$.[11a]



1 **2** **3**

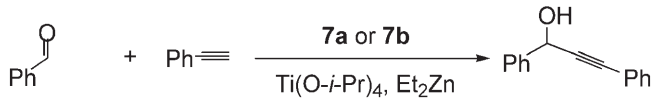
Although these advances have been achieved, the alkynylation of aldehydes has not yet reached the level of practicability that is required for a synthetically useful catalytic reaction. High loadings of ligands (usually 20 mol %) had to be employed in many examples cited above for achieving excellent stereoselectivity. And even in some cases, the gram amount of the employed ligand exceeded the amount of substrate. So the development of highly enantioselective processes with low chiral catalyst loading and readily available chiral ligands is still a challenging problem.

Recent investigations in the field of metal catalysis have focused on the use of dinuclear metal complexes.[7] In these complexes, there are distinct synergistic effects occurring at the proximal metal centers (one metal center acts usually behaves as a Lewis acid to activate the carbonyl derivative, while the other metal center acts as an activating metal for the nucleophile[8]). As a result, the complexes display unique catalytic properties. On the other hand, it is almost universally observed that auxiliaries with C_2-symmetry elements perform in their capacity as stereochemical directors to provide higher levels of absolute stereochemical control as compared to those totally lacking in symmetry. The presence of a C_2-symmetry axis within a chiral ligand dramatically reduces the number of possible competing diastereomeric transition states.[9] Thus, Yus and co-workers reported the use of C_2-symmetrical bissulfonamide ligands in the addition of Et_2Zn to ketones, discovering the enhanced reactivity of these ligands.[10] Based on the above facts (the high enantioselectivities were obtained in the addition of phenylacetylene to aldehydes catalyzed by a C_1-symmetrical mononucleating β-sulfonamide alcohol **3** in combination with titanium tetraisopropoxide and the synergistic effects in dinuclear metal complexes) and our previous works,[11] we decided to prepare novel C_2-symmetrical bissulfonamide ligands and apply them in the addition of phenylacetylene to aldehydes and ketones, expecting that this kind of ligand with a C_2-symmetry axis can afford good results. Herein, we describe the preparation and use as chiral ligands of different bissulfonamide derivatives with C_2-symmetry.



Scheme 1. Preparation of **7a** and **7b** from benzene-1,3-disulfonyl chloride and natural L-phenylalanine. *Reagents and conditions*: a) $SOCl_2$, MeOH, −30 °C; b) Et_3N, DCM, benzene-1,3-disulfonyl chloride, room temperature, 5% HCl; b) RMgBr, THF, room temperature.

Table 1. Asymmetric addition of phenylacetylene to benzaldehyde using **7a** and **7b** as ligands.[a]



Entry	Ligand	Ligand [mol %]	Ligand/Ti(O-*i*-Pr)$_4$[b]	Et_2Zn [mol %]	Solvent	Temperature	ee[c] [%]/Config.[d]
1	**7a**	10	1/4	200	toluene	rt	80/*R*
2	**7a**	10	1/5	200	toluene	rt	87/*R*
3	**7a**	10	1/6	200	toluene	rt	90/*R*
4	**7a**	10	1/7	200	toluene	rt	82/*R*
5	**7a**	10	1/8	200	toluene	rt	79/*R*
6	**7a**	10	1/6	200	Et_2O	rt	83/*R*
7	**7a**	10	1/6	200	CH_2Cl_2	rt	86/*R*
8	**7a**	10	1/6	200	THF	rt	6/*R*
9	**7a**	10	1/6	300	toluene	rt	93/*R*
10	**7a**	10	1/6	400	toluene	rt	90/*R*
11	**7a**	15	1/6	300	toluene	rt	90/*R*
12	**7a**	5	1/6	300	toluene	rt	94/*R*
13	**7a**	4	1/6	300	toluene	rt	95/*R*
14	**7a**	3	1/6	300	toluene	rt	93/*R*
15	**7a**	2	1/6	300	toluene	rt	92/*R*
16	**7a**	1.5	1/6	300	toluene	rt	90/*R*
17	**7a**	1	1/6	300	toluene	rt	50/*R*
18	**7a**	4	1/6	300	toluene	0 °C	93/*R*
19	**7b**	4	1/6	300	toluene	rt	30/*R*

[a] Phenylacetylene/Et_2Zn = 1 : 1.
[b] Ti(O-*i*-Pr)$_4$ Was freshly distilled.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OJ-H column.
[d] The absolute configuration was based on determination of the specific rotation and in comparison with the literature, see ref.[12]

Results and Discussion

Preparation of Chiral Bissulfonamide Ligands

Three simple steps were required to prepare **7a** and **7b** from commercially available benzene-1,3-disulfonyl chloride and natural L-phenylalanine (Scheme 1). Compound **6** was prepared from benzene-1,3-disulfonyl chloride by reaction with (S)-phenylalanine methyl ester **5** in the presence of triethylamine at 0 °C. Then the successive reaction of the Grignard reagents with **6** gave ligands **7a** and **7b**.

Asymmetric Addition of Alkynylzinc to Aldehydes

Once ligands **7a** and **7b** were prepared, they were applied in the enantioselective addition of alkynylzinc to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$ (Table 1). We varied the amount of Ti(O-*i*-Pr)$_4$ and found that the best ee values are obtained when the **7a**/Ti(O-*i*-Pr)$_4$ ratio is 1:6 (Table 1, entries 1–5). We found that the reaction was strongly influenced by the solvent.

Table 2. Asymmetric addition of phenylacetylene to aldehydes using 4 mol % of ligand **7a**.[a-d]

Entry	Aldehyde	Yield [%]	ee[e] [%]/Config.[g]
1	benzaldehyde	92	95/*R*
2	3-tolualdehyde	86	94
3	4-tolualdehyde	90	97
4	2-anisaldehyde	85	84[f]
5	3-anisaldehyde	89	91
6	4-anisaldehyde	87	81
7	4-fluorohenzaldehyde	86	90
8	3-bromobenzaldehyde	83	84
9	4-bromobenzaldehyde	86	93
10	4-chlorobenzaldehyde	89	91
11	2-naphthaldehyde	68	91
12	1-naphthaldehyde	65	83
13	cinnamic aldehyde	63	71[f]
14	isobutyl aldehyde	89	57[f]

[a] In all of the entries, the Et_2Zn/phenylacetylene/aldehyde/Ti(O-*i*-Pr)$_4$/**7a** ratio was 3:3:1:0.24:0.04.
[b] All reactions were performed under argon and at room temperature.
[c] Ti(O-*i*-Pr)$_4$ was freshly distilled before use.
[d] The reactions were carried out for 32 h.
[e] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OJ-H column.
[f] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OD-H column.
[g] The absolute configuration was based on determination of the specific rotation and in comparison with the literature, see ref.[12]

Table 3. Asymmetric addition of phenylacetylene to aldehydes using 2 mol % of ligand **7a**.[a-d]

Entry	Aldehyde	Yield [%]	ee [%][e]
1	benzaldehyde	84	92
2	4-chlorobenzaldehyde	82	90
3	4-tolualdehyde	83	95
4	3-tolualdehyde	81	87
5	4-bromobenzaldehyde	82	90
6	4-fluorohenzaldehyde	78	86

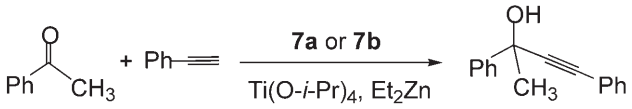
[a] In all of the entries, the Et_2Zn/phenylacetylene/aldehyde/Ti(O-*i*-Pr)$_4$/**7a** ratio was 3:3:1:0.12:0.02.
[b] All reactions were performed under argon and at room temperature.
[c] Ti(O-*i*-Pr)$_4$ was freshly distilled before use.
[d] The reactions were carried out for 37 h.
[e] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OJ-H column.

The sequence of enantioselectivities in solvents was toluene > CH_2Cl_2 > Et_2O > THF (Table 1, entries 3, 6, 7 and 8). The reaction was also affected by the amount of Et_2Zn. When we increased the amount of Et_2Zn, the ees increased from 90% to 93% (Table 1, entries 3, 9 and 10). When the amount of the ligand was increased from 10% to 15%, the ees decreased from 93% to 90% (Table 1, entries 9, 11). To our astonishment, the ees increased when we decreased the amount of ligand (Table 1, entries 11–17). With 4 mol % of **7a**, the reaction gave the best ee (95%). We were pleased to find that working at a catalyst loading of 1.5 mol % still afforded excellent levels of enantiocontrol (90% ee). No significant changes in ee values were observed when the temperature of the reaction was deceased from room temperature to 0 °C (Table 1, entry 18). Ligand **7b** was tested in this reaction and resulted in a low enantioselectivity (Table 1, entry 19).

Under the above optimized reaction conditions, ligand **7a** was employed to promote the enantioselective addition of phenylacetylene to a number of aldehydes. In most cases, enantioselectivities $\geqslant$90% could be obtained using 4 mol % ligand for aromatic aldehydes (Table 2, entries 1–12). Moreover, 4-tolualdehyde gave the best ee (97% ee). Only 2-anisaldehyde, 4-anisaldehyde, 3-bromobenzaldehyde and 1-naphthaldehyde gave lower ee values (Table 2, entries 4, 6, 8 and 12). When aliphatic aldehydes were used as substrates, moderate to good enantioselectivity was achieved. For example, cinnamic aldehyde and isobutyl aldehyde gave respectively 71 and 57% ee (Table 2, entries 13 and 14). This also supports the literature evidence that the $Zn(OTf)_2/Et_3N$ protocol seems to be superior for aliphatic substrates.[2p]

In order to exemplify the effectiveness of the present catalytic system even at lower catalyst loadings, a series of substrates was submitted to the enantioselective addition of phenylacetylene using a 2 mol % loading (Ta-

Table 4. Asymmetric addition of phenylacetylene to acetophenone with **7a** and **7b** as ligands.[a]



Entry	Ligand	Ligand [mol%]	Solvent	Ligand\Ti(O-*i*-Pr)$_4$[b]	Et_2Zn	ee[c] [%]
1	**7a**	10	Toluene	1:2	200	61
2	**7b**	10	Toluene	1:2	200	25
3	**7a**	10	Et_2O	1:2	200	10
4	**7a**	10	CH_2Cl_2	1:2	200	3
5	**7a**	10	Toluene	1:4	200	50
6	**7a**	10	Toluene	1:6	200	35
7	**7a**	15	Toluene	1:2	200	65
8	**7a**	15	Toluene	1:2	300	67
9	**7a**	20	Toluene	1:2	300	69
10	**7a**	25	Toluene	1:2	300	71

[a] Phenylacetylene/Et_2Zn = 1:1.
[b] Ti(O-*i*-Pr)$_4$ was freshly distilled.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OD-H column.

ble 3). Although the ee values exhibited slight drops, high to excellent enantioselectivities were still obtained (up to 95% ee).

Asymmetric Addition of Alkynylzincs to Ketones

Ligands **7a** and **7b** were initially tested in the asymmetric addition of phenylacetylene to acetophenone (Table 4). We found that ligand **7a** afforded a higher ee value than ligand **7b** (Table 4, entries 1 and 2). Also, the solvents strongly influenced the results of the reaction. Highest enantioselectivities were obtained in toluene while lower enantioselectivities were afforded respectively in ether (Table 4, entry 3), CH_2Cl_2 (Table 4, entry 4). Ligand **7a** and Ti(O-*i*-Pr)$_4$ were mixed in different proportions and tested. When the **7a**/Ti(O-*i*-Pr)$_4$ ratio is 1:2, the reaction gave the highest ee value (Table 4, entries 1, 5 and 6). When we increased the amount of ligand **7a** from 10 mol % to 15 mol %, the ee increased (Table 4, entries 1, 7). When we increased the amount of Et_2Zn from 200 to 300 mol %, the enantioselectivity increased slightly (Table 4, entry 8). When the amount of the ligand was increased from 15 mol % to 25 mol %, the ees increased from 67% to 71% (Table 4, entries 8, 9 and 10).

Under the above optimized reaction conditions, ligand **7a** was employed to induce the enantioselective addition of phenylacetylene to a number of ketones. The ee values were up to 81% while yields up to 74% were obtained (Table 5).

Table 5. Asymmetric addition of phenylacetylene to aromatic ketones promoted by ligand **7a**.[a-d]

Entry	Ketone	Yield [%]	ee [%][e]
1	Acetophenone	64	71
2	2′-Fluoroacetophenone	62	62
3	4′-Fluoroacetophenone	46	67
4	3′-Bromoacetophenone	74	77
5	4′-Chloroacetophenone	51	70
6	1′-Naphthacetophenone	36	81
7	3′-Methylacetophenone	60	74
8	4′-Methylacetophenone	42	68
9	3′-Methoxyacetophenone	58	74
10	Benzalacetone	70	55

[a] In all of the entries, the Et_2Zn/phenylacetylene/ketone/Ti(O-*i*-Pr)$_4$/**7a** ratio was 3:3:1:0.5:0.25.
[b] All reactions were performed under argon and at room temperature.
[c] Ti(O-*i*-Pr)$_4$ was freshly distilled before use.
[d] The reactions were carried out for 120 h.
[e] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OD-H column.

Conclusion

We have readily synthesized new C_2-symmetrical bissulfonamide ligands in three simple steps and applied them in the enantioselective addition of alkynylzincs to aldehydes under very mild conditions. Ligand **7a** exhibits excellent catalytic activity in this reaction with a low catalyst loading(4 mol %). Lowering the amount of ligand **7a** to 2 mol % still provided excellent levels of enantiocontrol (up to 95% ee). As a result, the developed protocol reflects the most economic catalyst system so far for the

addition of a terminal alkyne to aromatic aldehydes in terms of ligand loading and enantioselectivity. Also, we have successfully demonstrated that ligand **7a** in combination with Ti(O-*i*-Pr)$_4$ is an effective chiral catalyst for the asymmetric addition of alkynylzinc to unactivated simple ketones under very mild conditions.

Experimental Section

General Remarks

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 chromatographic purifications were carried out using silica gel. All aldehydes, ketones and amino acids were purchased from Acros or Fluka. Diethylzinc was prepared from EtI with Zn and then diluted with toluene to 1.0 M. Melting points are uncorrected and were recorded on an X-4 melting point apparatus. ^{1}H NMR spectra were measured on a Mercury Plus-300 BB (in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained on a Nicolet NEXUS 670 FT-IR. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. Mass spectra were recorded on VG-FAB mass spectrometer. The ee value determination was carried out using chiral HPLC with a Chiralcel OJ-H column on a Waters apparatus with a 996 UV-detector.

Preparation of (S)-Phenylalanine Methyl Ester (5)

(*S*)-Phenyalanine methyl ester was easily prepared according to literature procedures from natural L-phenylalanine.[11i] $[\alpha]_D^{23}$: +25.0 (*c* 4.04, C_2H_5OH); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 1.44$ (s, 2H, NH_2), 2.74–2.85 (dd, 1H, PhCH), 2.99–3.08 (dd, J =13.4 Hz, 1H, PhCH), 3.65–3.71 (m, J= 5.2 Hz, J=8.0 Hz, 4H, CHN, CH_3), 7.11–7.30 (m, 5H, Ph-H); IR (KBr): $\nu = 3380$, 3314, 3061, 3028, 2950, 2852, 1738, 1602, 1495, 1438, 1276, 1198, 1174, 112, 1076, 1010, 839, 747, 701 cm^{-1}; ESI-MS: $m/z = 180$ $(M+H)^+$.

Preparation of Bissulfonamide (6)

To a solution of (*S*)-phenylalanine methyl ester (2.58 g, 14.4 mmol) and triethylamine (3.9 mL, 28 mmol) in CH_2Cl_2 (10 mL) at 0 °C was slowly introduced a solution of benzene-1,3-disulfonyl chloride (1.93 g, 7 mmol) in CH_2Cl_2 (10 mL). The temperature was allowed to rise to room temperature and the reaction mixture stirred overnight. Then the mixture was extracted with HCl (5%) and the organic layer was dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, the product recrystallized as a white solid; yield: 3.18 g (81.1%); mp 133.5–134.5 °C; $[\alpha]_D^{18}$: −20 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 2.98$–3.03 (dd, $^3J_{H,H} = 6.4$ Hz, $^2J_{H,H} = 14.2$ Hz, 2H, PhH_AH_B), 3.04–3.09 (dd, $^3J_{H,H} = 5.6$ Hz, $^2J_{H,H} = 14.2$ Hz, 2H, PhH_AH_B), 3.52 (s, 6H, CH_3), 4.22–4.27 (m, 2H, CHN), 5.24–5.26 (d, $^3J_{H,H} = 9.2$ Hz, 2H, NH), 7.04–8.14 (m, 14H; 3 × Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 39.226$, 52.579, 56.880, 76.685, 77.000, 77.315, 125.700, 127.410, 128.670, 129.293, 130.010, 130.726, 134.689, 141.283, 170.974; IR (KBr): $\nu = 3455$, 3428, 3326, 3248, 3093, 3029, 3003, 2953, 2861, 2761, 1813, 1721, 1603, 1584, 1495, 1450, 1431, 1339, 1311, 1274, 1253, 1207, 1178, 1156, 1099, 1079, 1041, 1010, 936, 910, 837, 802, 773, 747, 702, 683, 615, 605, 580, 559, 534, 502, 421 cm^{-1}; FAB-MS: $m/z =$ 561.4 [calcd. for $(M+H)^+$: 561].

General Procedure for Preparation of 7 *via* the Reaction of 6 with Grignard Reagents

A solution of **6** (1.53 g, 2.72 mmol) in 8 mL THF was added dropwise under an argon atmosphere at 0 °C to a solution of RMgBr (32.6 mmol) in 15 mL THF, which was freshly prepared in the usual way. The reaction mixture was then stirred at room temperature over 38 h. When the reaction was complete (checked by TLC), a cold saturated aqueous NH_4Cl solution was dropped into the mixture under vigorous stirring. The mixture was extracted three times, then the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography with ethyl acetate and petroleum ether as mobile phase.

Bissulfonamide (7a): White solid; yield: 1.11 g (66%); mp 72–73 °C; $[\alpha]_D^{18}$: −124 (*c* 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 0.98$–1.04 (m, 12H, CH_3), 1.51–1.85 (m, 8H, CH_2Me), 2.41–2.49 (dd, $^3J_{H,H} = 10.8$ Hz, $^2J_{H,H} = 14.1$ Hz, 2H, PhH_AH_B), 2.65 (s, 2H, OH), 2.84–2.90 (dd, $^3J_{H,H} =$ 2.7 Hz, $^2J_{H,H} = 14.1$ Hz, 2H, PhH_AH_B), 3.61–3.67 (m, 2H, CHN), 6.00–6.03 (d, ^3JH,H = 8.7 Hz, 2H, NH), 6.82–7.65 (m, 14H, 3 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.460$, 7.765, 27.638, 28.035, 36.475, 62.484, 76.161, 76.573, 77.000, 77.427, 124.759, 126.637, 128.499, 128.835, 129.201, 129.506, 137.382; IR (KBr): $\nu = 3524$, 3284, 3064, 3027, 2970, 2941, 2883, 2251, 1721, 1602, 1495, 1458, 1427, 1324, 1260, 1201, 1147, 1081, 1053, 965, 909, 837, 794, 734, 699, 679, 589 cm^{-1}; FAB-MS: $m/z = 623$ [calcd. for $(M+Li)^+$: 623], 639 [calcd. for $(M+Na)^+$]: 639.

Bissulfonamide (7b): White solid; yield: 1.27 g (58%); mp 119–120 °C; $[\alpha]_D^{18}$: +79 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.50$ (s, 2H, OH), 2.74–2.81 (dd, $^3J_{H,H} =$ 7.05 Hz, $^2J_{H,H} = 14.1$ Hz, 2H, PhH_AH_B), 3.12–3.17 (dd, $^3J_{H,H} =$ 2.55 Hz, $^2J_{H,H} = 14.1$ Hz, 2H, PhH_AH_B), 4.64–4.70 (m, 2H, CHN), 5.09–5.12 (d, $^3J_{H,H} = 8.1$ Hz, 2H, NH), 6.80–7.82 (m, 34H; 7 × Ph-H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.880$, 62.103, 76.573, 77.000, 77.427, 80.877, 124.851, 125.187, 125.874, 127.003, 127.125, 127.492, 128.163, 128.575, 128.728, 128.942, 129.629, 136.970, 141.442, 143.534; IR (KBr): 3525, 3303, 3060, 3027, 2974, 2930, 2866, 1954, 1889, 1809, 1709, 1600, 1494, 1449, 1418, 1375, 1332, 1257, 1171, 1148, 1083, 1058, 1035, 1000, 974, 909, 828, 795, 770, 744, 701, 679, 577, 553, 509 cm^{-1}; FAB-MS: $m/z = 815$ [calcd. for $(M+Li)^+$: 815], 831 [calcd. for $(M+Na)^+$: 831].

Typical Procedure for Catalytic Asymmetric Addition of Phenylacetylene to Aldehydes

Under an argon atmosphere, in a 10-mL round-bottom flask, 6.2 mg (0.01 mmol) of ligand **7a** was dissolved in 2 mL of dry toluene and 17.8 μL (0.06 mmol) of Ti(O-*i*-Pr)$_4$ were added

at room temperature followed by a solution of diethylzinc (0.75 mL; 0.75 mmol, 1.0 M in dry toluene). After the mixture was stirred for 12 h, 82.4 μL (0.75 mmol) of phenylacetylene were added into the flask and the reaction continued for 1 h at the same temperature. The flask was put into an ice-water bath and the mixture was cooled to 0 °C, and 25 μL (0.25 mmol) of benzaldehyde were introduced. The reaction temperature returned to room temperature naturally. The reaction mixture was stirred to completion (checked by TLC). After the reaction was complete, it was cooled to 0 °C and quenched with cold aqueous HCl (5%). The mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The resulting oil was purified by flash column chromatography to give the product. The ee values were measured by HPLC using a chiral column.

General Procedures for the Addition of Phenylacetylene to Ketones

Under argon, the ligand **7a** (23.1 mg, 0.0375 mmol) and Ti(O-*i*-Pr)$_4$ (22.2 μL, 0.075 mmol) were mixed in dry toluene(0.50 mL) at room temperature. A solution of Et_2Zn (1.0 M in toluene, 0.45 mL) was then added. After the mixture was stirred at room temperature for 24 h, phenylacetylene (49.4 μL, 0.45 mmol) was added and the stirring continued for 1 h. The solution was cooled to 0 °C and treated with ketone (0.15 mmol). The resulting mixture was allowed to warm to room temperature and stirred to completion (checked by TLC). After the reaction was complete, it was cooled to 0 °C and quenched with cold aqueous HCl (5%). The mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The resulting oil was purified by flash column chromatography to give the product. The ee values were measured by HPLC using a chiral column.

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