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The asymmetric addition of phenylacetylene to aldehydes catalyzed by L-leucine derived chiral sulfonamide alcohol ligands

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Abstract

Several L-leucine derived chiral sulfonamide ligands were synthesized in simple three steps. When we used these ligands as the catalysts in the addition of phenylacetylene to aldehydes, the corresponding propargylic alcohols were obtained with enantiomeric excesses of up to 96%. The results showed that the R group of the α-carbon greatly influenced the enantioselectivity.

Keywords: Sulfonamide alcohol; Asymmetric addition reaction; Phenylacetylene; L-Leucine; Aldehyde

1. Introduction

The reaction of addition of terminal acetylenes to aldehydes is very useful and many methods have been developed over the past decade [1]. Niwa and Soai conducted the enantioselective alkynylation of aldehyde using alkynylethylzinc prepared from phenylacetylene and diethylzinc catalyzed by chiral amino alcohol [2]. Optically active propargylic alcohols constitute important building blocks for asymmetric synthesis, as they are used in diverse areas including the synthesis of natural products, pharmaceuticals, and macromolecules [3]. In recent years, some great progresses have been made in this reaction. Carreira et al. [4] and Jiang et al. [5] found that zinc acetylides, generated in situ from terminal alkynes and $Zn(OTf)_2$ in the presence of triethylamine, could enantioselectively add to aliphatic aldehydes promoted by chiral ligand *N*-methylephedrine; high ee up to 99% was achieved. Chan and coworkers have disclosed that a combination of chiral BINOL and sulfonamide with $Ti(O^iPr)_4$ could generate a highly enantioselective catalyst which could catalyze the addition of alkynylzinc, produced in situ from phenylacetylene and dimethylzinc, to aromatic aldehydes [6]. Moore and Pu developed a more convenient process, which was based on the BINOL-$Ti(O^iPr)_4$-Et_2Zn system, to produce highly optically active second propargylic alcohols, in which alkyl and aromatic aldehydes are both suitable substrates[7]. Other chiral ligands including amino alcohols [8] and oxazoline [9] have also been reported. Although these methods have been developed, more efforts are also needed to find cheap and highly enantioselective chiral ligands.

In our previous research, we have found that chiral sulfonamides from natural phenylalanine and camphor could be highly enantioselective ligands in the reaction of asymmetric addition of phenylacetylene to aldehydes [10]. These chiral sulfonamides could combine with $Ti(O^iPr)_4$ to catalyze this reaction. The ee value up to 98% was achieved. Although derivatives from L-phe were highly enantioselective catalysts, derivatives from other naturally occurring amino acids, especially from alkyl amino acids were rarely reported in this reaction to our knowledge up to today. In order to widen the scope of the chiral resources for the ligands applied to this reaction, we decided to examine the sulfonamides derived from the alkyl amino acids. Because of the special bulky feature of L-leucine, we chose it as the starting material to prepare ligands and observe the asymmetric catalytic activ-

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ity of its derivatives. Herein, we report the synthesis and application of chiral ligands **3a**–**3i**, which were derived from L-leucine.

2. Experimental

2.1. General remarks

All asymmetric reactions were carried out under an argon atmosphere. Solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were carried out using silica gel. All aldehydes, *p*-toluenesulfonyl chloride (TsCl) and L-leucine were purchased from Acros or Fluka. Diethylzinc was prepared from EtI and Zn and then was diluted with toluene to 1.0 M. $Ti(O^iPr)_4$ was freshly distilled prior to use. Melting points were uncorrected and recorded on an X-4 melting point apparatus. ^1H and ^{13}C NMR spectra were measured with a Bruker Am 400M spectrometer (NMR in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained with a Nicolet AVATAR 360 FT-IR. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. 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 a Waters® chromatograph with a 2996 UV-detector. Element analyses were recorded with a German Element Vario. EL apparatus.

2.2. General procedure for synthesis of (*S*)-*N*-*p*-toluene-sulfonylleucine methyl ester (*2*)

1.8 g L-leucine methyl ester hydrochloride (10 mmol) was suspended in CH_2Cl_2 (20 mL). Et_3N (22 mmol) was added dropwise to the solution and then cooled to 0 °C. A CH_2Cl_2 solution of *p*-toluenesulfonyl chloride (11 mmol) was added dropwise while stirring over 4 h. The resulting mixture was washed with 1N HCl (2 × 10 mL), 2N NaOH (2 × 10 mL) and saturated brine (2 × 20 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give the product as a pale yellow solid, which was recrystallized from CH_2Cl_2/hexane to afford (**S**)-**2** as white needles 2.8 g (93.6% yield), mp 52–53 °C. $[\alpha]_D^{28}$ −14 °C (*c* 2.14, EtOAc), ^1H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.71–7.73 (d, 2H, Ph–H, *J* = 8.0 Hz), 7.28–7.30 (d, 2H, Ph–H, *J* = 8.4 Hz), 5.16–5.19 (d, 1H, NH), 3.90–3.96 (m, 1H, CH), 3.44 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 1.75–1.81 (m, 1H, CH), 1.46–1.50 (m, 2H, CH_2), 0.86–0.88 (d, 3H, CH_3, *J* = 6.8 Hz), 0.89–0.91 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.399, 21.430, 22.628, 24.266, 42.306, 52.153, 54.359, 76.685, 77.000, 77.315, 127.308, 129.498, 136.800, 143.536, 172.660. IR (KBr): 3285, 2959, 2872, 1746, 1599, 1460, 1433, 1320, 1266, 1225, 1207, 1161, 1099, 1015, 934, 899, 845, 813, 667, 584, 548 cm^{-1}. ESI-MS for $(C_{14}H_{21}NO_4S–H)^-$: 298. Anal. Calcd. for $C_{14}H_{21}NO_4S$: C, 56.19%; H, 7.02%; N, 4.68%; O, 21.40%. Found: C, 56.29%; H, 6.91%; N, 4.62%; O, 21.32%.

2.3. General procedure for synthesis of ligand *3a*–*3i*

Ligands **3a**–**3i** were prepared according to literature [11].

2.3.1. (*S*)-3-(*p*-toluenesulfonylamino)-2,5-dimethyl-hexan-2-ol, (*S*)-*3a*

Yellow needles (77% yield), mp 102–103 °C. $[\alpha]_D^{26}$ −32 °C (*c* 2.0, EtOAc), ^1H NMR (400 M, $CDCl_3$, ppm) δ: 7.78–7.80 (d, 2H, Ph–H, *J* = 8.4 Hz), 7.29–7.31 (d, 2H, Ph–H, *J* = 8.4 Hz), 4.86–4.88 (d, 1H, NH), 3.18–3.23 (m, 1H, CH), 2.42 (s, 3H, CH_3), 2.38 (s, 1H, OH), 1.26–1.33 (m, 1H, CH), 1.19–1.24 (m, 2H, CH_2), 1.16 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.76–0.77 (d, 3H, CH_3, *J* = 6.4 Hz), 0.58–0.60 (d, 3H, CH_3, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 20.989, 21.454, 23.801, 24.321, 25.014, 27.370, 41.156, 61.583, 72.573, 76.677, 77.000, 77.315, 127.111, 129.537, 138.210, 143.347. IR (KBr): 3502, 3284, 2958, 2869, 1598, 1463, 1429, 1322, 1155, 1093, 1071, 1019, 924, 814, 666, 580, 547 cm^{-1}. ESI-MS for $(C_{15}H_{25}NO_3S–H)^-$: 298. Anal. Calcd. for $C_{15}H_{25}NO_3S$: C, 60.20%; H, 8.36%; N, 4.68%; O, 16.05%. Found: C, 59.97%; H, 8.125%; N, 4.417%; O, 16.13%.

2.3.2. (*S*)-4-(*p*-toluenesulfonylamino)-6-methyl-3-ethylheptan-3-ol, (*S*)-*3b*

White needles (98% yield), mp 102 °C. $[\alpha]_D^{26}$ −35 °C (*c* 2.0, EtOAc), ^1H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.77–7.79 (d, 2H, Ph–H, *J* = 8.4 Hz), 7.28–7.30 (d, 2H, Ph–H, *J* = 8.0 Hz), 4.71 (s, 1H, NH), 3.39–3.44 (m, 1H, CH), 2.41 (s, 3H, CH_3), 1.98 (s, 1H, OH), 1.41–1.60 (m, 2H, CH_2), 1.29–1.38 (m, 3H, CH_2CH), 1.12–1.27 (m, 2H, CH_2), 0.76–0.89 (m, 9H, CH_3), 0.63–0.64 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.091, 21.414, 23.990, 24.242, 38.233, 38.730, 40.479, 58.897, 75.842, 76.677, 77.000, 77.315, 127.032, 129.482, 138.541, 143.181. IR (KBr): 3458, 3185, 2960, 2872, 1599, 1463, 1439, 1321 1169, 1152, 1094 1072, 1017, 952, 921, 812, 733, 666, 592, 567, 548, 522 cm^{-1}. ESI-MS for $(C_{17}H_{29}NO_3S–H)^-$: 326. Anal. Calcd. for $C_{17}H_{29}NO_3S$: C, 62.39%; H, 8.87%; N, 4.28%; O, 14.68%. Found: C, 62.65%; H, 8.638%; N, 4.347%; O, 14.83%.

2.3.3. (*S*)-5-(*p*-toluenesulfonylamino)-7-methyl-4-propyl-octan-4-ol, (*S*)-*3c*

White needles (67% yield), mp 95–96 °C. $[\alpha]_D^{26}$ −27 °C (*c* 2.0, EtOAc), ^1H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.76–7.78 (d, 2H, Ph–H, *J* = 8.4 Hz), 7.28–7.30 (d, 2H, Ph–H, *J* = 7.6 Hz), 4.68–4.70 (d, 1H, NH), 3.34–3.39 (m, 1H, CH), 2.41 (s, 3H, CH_3), 2.04 (s, 1H, OH), 1.12–1.34 (m, 11H, CH_2), 0.78–0.90 (m, 9H, CH_3), 0.65–0.67 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 21.052, 21.477, 23.975, 24.274, 27.780, 28.040, 40.368, 58.322, 75.913, 76.677, 77.000, 77.315, 127.016, 129.490, 143.244. IR (KBr): 3476, 3278,

2958, 2871, 1598, 1460, 1431, 1323 1154, 1093 1065, 1016, 959, 929, 813, 736, 706, 669, 587, 548, 524 cm^{-1}. ESI-MS for $(C_{19}H_{33}NO_3S–H)^-$: 354. Anal. Calcd. for $C_{19}H_{33}NO_3S$: C, 64.23%; H, 9.296%; N, 3.94%; O, 13.52%. Found: C, 64.49%; H, 9.165%; N, 3.785%; O, 13.44%.

*2.3.4. **(S)**-6-(p-toluenesulfonylamino)-8-methyl-5-butylnonan-5-ol, **(S)-3d***

White needles (51% yield), mp 88–89 °C. $[\alpha]_D^{26}$ −24 °C (*c* 2.0, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.76–7.78 (d, 2H, Ph–H, *J* = 8.4 Hz), 7.28–7.30 (d, 2H, Ph–H, *J* = 8.4 Hz), 4.58–4.63 (d, 1H, NH), 3.35–3.41 (m, 1H, CH), 2.42 (s, 3H, CH_3), 1.95 (s, 1H, OH), 1.08–1.39 (m, 15H, CH_2), 0.80–0.91 (m, 9H, CH_3), 0.68–0.69 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.139, 21.438, 23.092, 23.321, 24.038, 24.242, 24.920, 25.393, 35.594, 36.075, 40.471, 58.920, 75.810, 76.685, 77.008, 77.323, 127.008, 129.490, 138.565, 143.181. IR (KBr): 3465, 3186, 2953, 2868, 1598, 1464, 1435, 1326 1156, 1093 1072, 1020, 960, 934, 911, 814, 794, 777, 705, 667, 586, 548, 530 cm^{-1}. ESI-MS for $(C_{21}H_{37}NO_3S–H)^-$: 382. Anal. Calcd. for $C_{21}H_{37}NO_3S$: C, 65.796%; H, 9.66%; N, 3.66%; O, 12.53%. Found: C, 65.93%; H, 9.433%; N, 3.584%; O, 12.40%.

*2.3.5. **(S)**-8-(p-toluenesulfonylamino)-10-methyl-7-hexylundecan-7-ol, **(S)-3e***

White needles (69% yield), mp 72–73 °C. $[\alpha]_D^{26}$ −16 °C (*c* 1.09, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.76–7.78 (d, 2H, Ph–H, *J* = 8.0 Hz), 7.27–7.29 (d, 2H, Ph–H, *J* = 8.4 Hz), 4.61–4.63 (d, 1H, NH), 3.35–3.40 (m, 1H, CH), 2.42 (s, 3H, CH_3), 1.88 (s, 1H, OH), 1.12–1.48 (m, 23H, CH_2), 0.81–0.91 (m, 9H, CH_3), 0.68–0.70 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.154, 21.430, 22.565, 22.612, 22.722, 23.171, 24.046, 24.235, 29.749, 29.930, 31.711, 31.766, 35.917, 36.406, 40.502, 58.952, 75.881, 76.677, 77.000, 77.315, 127.016, 127.347, 129.482, 138.644, 143.126. IR (KBr): 3478, 3278, 2954, 2928, 2864, 1598, 1462, 1427, 1325 1157, 1092 1073, 1016, 958, 927, 842, 813, 730, 706, 668, 585, 547 cm^{-1}. ESI-MS for $(C_{25}H_{45}NO_3S–H)^-$: 438. Anal. Calcd. for $C_{25}H_{45}NO_3S$: C, 68.34%; H, 10.25%; N, 3.19%; O, 10.93%. Found: C, 68.41%; H, 10.123%; N, 3.172%; O, 10.86%.

*2.3.6. **(S)**-1-(3′-methyl-1′-p-toluenesulfonylamino-butyi)-cyclopentanol, **(S)-3f***

White needles (59% yield), mp 90–91 °C. $[\alpha]_D^{28}$ −41 °C (*c* 2.09, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.75–7.77 (d, 2H, Ph–H, *J* = 8.0 Hz), 7.26–7.28 (d, 2H, Ph–H, *J* = 8.4 Hz), 4.93 (s, 1H, NH), 3.30–3.35 (m, 1H, CH), 2.41 (s, 3H, CH_3), 1.18–1.68 (m, 11H, CH_2), 0.75–0.77 (d, 3H, CH_3, *J* = 6.4 Hz), 0.70–0.71 (d, 3H, CH_3, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.304, 21.454, 23.431, 23.793, 24.109, 37.643, 38.856, 41.463, 60.110, 76.685, 77.000, 77.323, 85.406, 126.882, 129.411, 139.108, 143.000. IR (KBr): 3420, 3233, 2955, 2868, 1597, 1440, 1419, 1302 1159, 1092 1064, 1007, 954, 915, 850, 813, 707, 661, 572, 530 cm^{-1}. ESI-MS for $(C_{17}H_{27}NO_3S–H)^-$: 324. Anal. Calcd. for $C_{17}H_{27}NO_3S$: C, 62.77%; H, 8.31%; N, 4.31%; O, 14.77%. Found: C, 62.92%; H, 8.290%; N, 4.344%; O, 14.74%.

*2.3.7. **(S)**-1-(3′-methyl-1′-p-toluenesulfonylamino-butyi)-cyclohexanol, **(S)-3g***

Pale yellow oil (50% yield), $[\alpha]_D^{23}$ −99 °C (*c* 1.80, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.75–7.77 (d, 2H, Ph–H, *J* = 8.0 Hz), 7.27–7.29 (d, 2H, Ph–H, *J* = 8.0 Hz), 4.69–4.71 (d, 1H, NH), 3.25–3.30 (m, 1H, CH), 2.41 (s, 3H, CH_3), 1.81(s, 1H, OH), 1.16–1.31 (m, 13H, CH_2), 0.75–0.76 (d, 3H, CH_3, *J* = 6.0 Hz), 0.66–0.67 (d, 3H, CH_3, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.280, 21.446, 21.603, 21.745, 23, 833, 24.321, 25, 574, 33.735, 38.257, 40.053, 60.748, 73.408, 76.685, 77.000, 77.323, 114.790, 126.953, 129.419, 138.943, 143.039. IR (KBr): 3505, 3284, 2948, 2865, 1598, 1450, 1429, 1323, 1156, 1092, 1056, 1012, 961, 921, 844, 813, 733, 706, 668, 547 cm^{-1}. ESI-MS for $(C_{18}H_{29}NO_3S–H)^-$: 338. Anal. Calcd. for $C_{18}H_{29}NO_3S$: C, 63.71%; H, 8.55%; N, 4.13%; O, 14.19%. Found: C, 63.86%; H, 8.490%; N, 4.166%; O, 14.22%.

*2.3.8. **(S)**-2-(p-toluenesulfonylamino)-1,1-diphenyl-3-methyl-1-pentanol, **(S)-3h***

White needles (74% yield), mp 198–199°C. $[\alpha]_D^{26}$ −14 °C (*c* 2.0, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) δ: 7.21–7.45 (m, 10H, Ph–H), 7.09–7.17 (m, 4H, Ph–H), 4.49–4.57 (m, 2H, NHCH), 2.96 (s, 1H, OH), 2.36 (s, 3H, CH_3), 1.56–1.60 (m, 1H, CH), 1.26–1.36 (m, 2H, CH_2), 0.87–0.89 (d, 3H, CH_3, *J* = 6.4 Hz), 0.73–0.74 (d, 3H, CH_3, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) *δ*: 21.077, 21.394, 23.838, 24.306, 41.773, 59.719, 76.683, 77.000, 77.317, 81.030, 126.323, 126.459, 126.696, 127.034, 127.235, 128.152, 129.240, 142.637, 143.528, 144.385. IR (KBr): 3519, 3260, 2956, 2923, 2866, 1599, 1495, 1448, 1318, 1299, 1233, 1150, 1094, 1063, 1019, 975, 947, 909, 879, 822, 807, 744, 699, 673, 603, 553, 479 cm^{-1}. ESI-MS for $(C_{25}H_{29}NO_3S–H)^-$: 422. Anal. Calcd. for $C_{25}H_{29}NO_3S$: C, 70.92%; H, 6.86%; N, 3.31%; O, 11.35%. Found: C, 71.09%; H, 6.847%; N, 3.220%; O, 11.39%.

*2.3.9. **(S)**-2-(p-toluenesulfonylamino)-1,1-dibenzyl-3-methyl-1-pentanol, **(S)-3i***

White needles (47% yield), mp 149–150°C. $[\alpha]_D^{28}$ −29 °C (*c* 1.54, EtOAc), ^{1}H NMR (400 M, $CDCl_3$, ppm) *δ*: 7.45–7.47 (d, 2H, Ph–H, *J* = 8.4 Hz), 7.23–7.35 (m, 10H, Ph–H), 7.17–7.19 (d, 2H, Ph–H, *J* = 8.0 Hz), 4.11–4.13 (d, 1H, NH), 3.17–3.23 (m, 1H, CH), 2.85–2.88 (d, 2H, CH_2, *J* = 13.6 Hz), 2.67–2.70 (d, 2H, CH_2, *J* = 13.6 Hz), 2.39 (s, 3H, CH_3), 1.37–1.40 (m, 2H, CH_2), 1.24–1.29 (m, 1H, CH), 0.82–0.83 (d, 3H, CH_3, *J* = 6.4 Hz), 0.23–0.25 (d, 3H, CH_3, *J* = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$,, ppm) *δ*: 20.422, 21.455, 24.236, 24.412, 41.058, 42.393, 43.960, 58.777, 75.609, 76.683, 77.000, 77.317, 126.590, 126.686, 127.215, 128.041,

128.328, 129.442, 130.721, 130.772, 136.430, 136.984, 143.387. IR (KBr): 3423, 3228, 2954, 2928, 2868, 1598, 1493, 1458, 1392, 1316, 1251, 1200, 1153, 1090, 1035, 1007, 957, 926, 876, 833, 811, 779, 749, 701, 662, 637, 590, 549, 506 cm^{-1}. ESI-MS for $(C_{27}H_{33}NO_3S–H)^-$: 450. Anal. Calcd. for $C_{27}H_{33}NO_3S$: C, 71.84%; H, 7.32%; N, 3.104%; O, 10.64%. Found: C, 71.66%; H, 7.286%; N, 3.338%; O, 10.65%.

2.4. Typical procedure for catalytic asymmetric addition of phenylacetylene to aldehydes

Under argon atmosphere, in a 10 mL round bottom flask, ligand **3b** (16.4 mg, 0.05 mmol) was dissolved in dry toluene (2 mL). $Ti(O^iPr)_4$ (20.0 μL, 0.065 mmol) was added at room temperature and the reaction was allowed to continue for 1 h. Then a solution of diethylzinc (0.5 mL, 0.5 mmol, 1.0 mmol/mL in dry toluene) was introduced, and after the mixture was stirred for another 1 h, phenylacetylene (54 μL, 0.5 mmol) was added into the flask and the reaction continued for another 1 h at room temperature. Then the flask was put into an ice-water bath, the mixture was cooled to 0 °C, then benzaldehyde (25 μL, 0.25 mmol) was introduced. The reaction temperature was allowed to return to room temperature. The reaction mixture was stirred to complete as checked by TLC. The flask was cooled to 0 °C, and then the reaction was quenched with a 5% aqueous HCl. The product was extracted by ether three times. The organic layers were combined and washed with a small amount of brine, dried over anhydrous Na_2SO_4, and then concentrated to dryness. The resulting oil was purified by preparative TLC, and thus the expected alcohol was obtained as pale yellow oil.

3. Results and discussion

Series of novel ligands **3a**–**3i** were conveniently prepared in three steps [11] (Scheme 1).

According to Walsh and his coworkers [12], the N–H of the sulfonamide is weakly acidic due to the highly electron withdrawing nature of the sulfonyl group. Thus, the sulfonamide nitrogen is a poor electron donor and the resulting complexes of sulfonamide with $Ti(O^iPr)_4$ behaved as a Lewis acid which catalyze the asymmetric addition of zinc acetylene to the aldehydes. Ligands prepared by us could form a similar intermediate (Fig. 1). Herein we attempted to confirm that the R group of the ligand could also affect the enantioselectivity of this reaction.

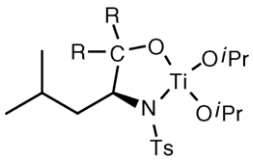
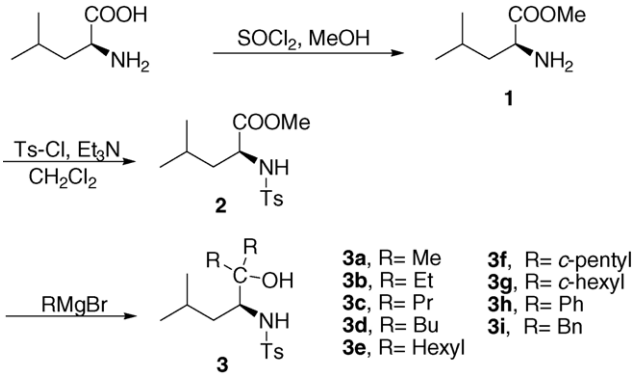


Fig. 1. Compound **3** combined with $Ti(O^iPr)_4$.

We initially performed a catalyst screening. Ligands **3b** and **3h** were firstly used for catalyzing the addition of phenylacetylene to benzaldehyde with Et_2Zn and $Ti(O^iPr)_4$. The reactions were conducted at room temperature in toluene by the sequential treatment of the chiral ligand, $Ti(O^iPr)_4$, Et_2Zn, phenylacetylene and benzaldehyde. Fortunately, we obtained the desired propargylic alcohol with high ee values and chemical yield by using ligand **3b**. But the use of ligand **3h** led to the low ee values and moderate chemical yield. This result prompted us to figure out the reason for the large difference. Ligands **3a**, **3c**–**3g** and **3i** were prepared and used in the same catalytic reaction under the same conditions. As shown in Fig. 2, we found that ligands **3b**–**3e** which have a flexible R group of the α-carbon provided almost the same high enantioselectivities. But the chemical activity dropped dramatically as the R group became bulky. Ligand **3a** which has the smallest *R* group showed good enantioselectivity and chemical yield. Ligands **3f** and **3g** which have a rigid *R* group of the α-carbon provided good enantioselectivity but the chemical activity was low. Ligands **3h** and **3i** showed low enantioselectivity and low chemical activity. The aryl group of the α-carbon probably affected the complexation of the ligand with $Ti(O^iPr)_4$.

We next studied the application of the ligand **3b** in the reaction of phenylacetylene with benzaldehyde under various conditions. The results are summarized in Table 1.



Scheme 1. Synthesis of ligands **3a**–**3i**.

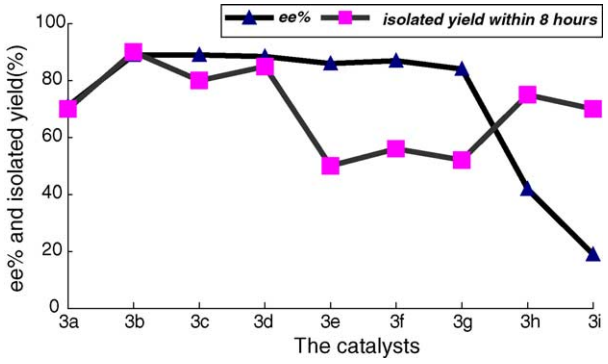


Fig. 2. Comparison of the catalytic activity and enantioselectivity of the catalysts **3a**–**3i** in the asymmetric addition of phenylacetylene to benzaldehyde.

Table 1
The enantioselective addition of phenylacetylene to benzaldehyde in the presence of ligand **3b**

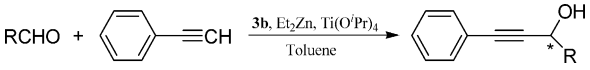
Entry	Ligand[a] (%)	$Ti(O^iPr)_4$[b]	Et_2Zn[a]	Solvent	Temperature (°C)	ee[c] (%)/configuration[d]
1	20	1.0	2.0	Toluene	rt	24 (*R*)
2	20	1.3	2.0	Toluene	rt	93 (*R*)
3	20	2.0	2.0	Toluene	rt	89 (*R*)
4	20	3.0	2.0	Toluene	rt	80 (*R*)
5	20	4.0	2.0	Toluene	rt	78 (*R*)
6	20	1.3	1.0	Toluene	rt	82 (*R*)
7	20	1.3	3.0	Toluene	rt	89 (*R*)
8	20	1.3	4.0	Toluene	rt	83 (*R*)
9	5	1.3	2.0	Toluene	rt	82 (*R*)
10	10	1.3	2.0	Toluene	rt	85 (*R*)
11	30	1.3	2.0	Toluene	rt	86 (*R*)
12	20	1.3	2.0	THF	rt	11 (*S*)
13	20	1.3	2.0	DCM	rt	16 (*S*)
14	20	1.3	2.0	Hexane	rt	18 (*S*)
15	20	1.3	2.0	Benzene	rt	85 (*R*)
16	20	1.3	2.0	Toluene	0	90 (*R*)

[a] The amount equivalent to the substrate.
[b] The equivalent to the ligand **3b**.
[c] The ee was determined by chiral HPLC on a Daicel Chiracel OD column.
[d] The absolute configurations were based on determination of the specific rotation and in comparison with literature [13].

The amount of $Ti(O^iPr)_4$ used in this reaction greatly influenced the enantioselectivity (Table 1, entries 1–5). When the amount was 1.3 equivalent to the ligand, the highest ee was obtained. When the amount of diethylzinc was increased, the ee value was decreased; 2.0 equiv diethylzinc to the substrate was optimal (entries 2 and 6–8). As for the amount of the ligands (entries 2 and 9–11), 20% equivalent to the substrate was appropriate. When the amount of the ligand increased from 20% to 30%, the ee value was decreased. Solvents produced a marked effect on the asymmetric reaction; benzene and toluene were effective, and toluene was the best (entries 2 and 12–15). When the reaction temperature was lowered to 0 °C, the ee value was increased but the reaction speed was greatly decreased.

Under these optimized reaction conditions of entry 2 (Table 1), ligand **3b** was employed to catalyze the addition of phenylacetylene to both aromatic and alkyl aldehydes (Table 2). All aromatic aldehydes gave good to high enantioselectivity (entries 1–14). 3-Nitrobenzaldehyde achieved the highest ee up to 96% (entry 10). 3-Bromobenzaldehyde and β-naphthaldehyde also led to high ee (entries 7 and 12). For alkyl aldehydes (entry 15), α,β-unsaturated

Table 2
Phenylacetylene asymmetric addition to aldehydes catalyzed by $Ti(O^iPr)_4$ combined with ligand **3b**



Entry	Aldehyde	Time (h)	Yield[a] (%)	ee[b] (%)/configuration[c]
1	Benzaldehyde	8	95	93 (*R*)
2	4-Chlorobenzaldehyde	8	92	85
3	4-Bromobenzaldehyde	8	90	84
4	4-Fluorobenzaldehyde	8	92	86
5	4-Anisaldehyde	8	92	90
6	4-Tolualdehyde	8	90	89
7	3-Bromobenzaldehyde	7	91	92
8	3-Anisaldehyde	6	90	86
9	3-Tolaldehyde	5	91	91
10	3-Nitrobenzaldehyde	8	60	96
11	α-Naphthaldehyde	8	90	85
12	β-Naphthaldehyde	9	90	93
13	2-Chlorobenzaldehyde	5	92	85
14	2-Anisaldehyde	5	89	81
15	Butylaldehyde	8	70	75
16	Cinnamicaldehyde	8	60	78

[a] Isolated yield.
[b] Determined by chiral HPLC on a Daicel Chiracel OD column.
[c] The absolute configurations were based on determination of the specific rotation and in comparison with literature [13].

cinnamicaldehyde yielded good enantioselectivity (entry 16).

4. Conclusion

In conclusion, simple derivatives of L-leucine were successfully used as chiral ligands in the catalytic asymmetric addition of phenylacetylene to aldehydes. Ligand **3b** gave higher enantioselectivity and chemical yield. The results showed that the *R* group of the α-carbon greatly influenced the enantioselectivity.

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