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A new type of ligand derived from N-terminal protected dipeptides in enantioselective addition of phenylacetylene to aromatic ketones at room temperature

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Abstract

A new type of ligand derived from N-terminal protected L-Phe-based dipeptides was found to be effective in catalyzing the enantioselective addition of phenylacetylene to aromatic ketones with up to 91% ee. The reaction required no other metal to promote than Et_2Zn. The whole process was completed at room temperature and proceeded under very mild reaction conditions.

Keywords: Alkynylzinc; Enantioselective addition; Ketones; Dipeptides

1. Introduction

Optically active propargyl alcohols are important precursors for the synthesis of many organic compounds and important pharmaceutical intermediates. The enantioselective addition of organometallic reagents to ketones is recognized as one of the most effective methods [1]. In the past few years, the enantioselective addition of alkynylzinc to aldehyde has been well developed [2]. Although there is enormous challenge for the addition of alkynylzinc to ketone, little work on the enantioselective addition of alkynylzinc to ketone has been reported. This is mostly due to the much lower reactivity of ketone and the difficulty in controlling facial stereoselectivity. To overcome the low reactivity of ketone, some activated ketones are used. For example, Tan et al. [3] reported a stoichiometric asymmetric addition of alkynylzinc to activated ketones for the synthesis of Efavirenz, a drug for AIDS treatment. Grabowski and coworkers [4] reported the direct approaches for the asymmetric addition of lithium cyclopropylacetylide to ketones. Jiang et al. [5] described the addition of alkynes to α-keto esters.

Cozzi [6] reported a catalytic asymmetric alkynylzinc addition to unactivated ketones by using Zn(salen) bifunctional catalyst **1** (20 mol%) and achieved moderate ee. Another pioneering work was done by Chan and coworkers [7]; in the presence of chiral camphorsulfonamide ligand **2** (Fig. 1), they used $Cu(OTf)_2$, a stronger Lewis acid, to promote the reaction and get the desired products with high enantioselectivities (up to 71–97% ee). In addition, we [8] found that (*S*)-BINOL (20 mol%) was an efficient catalyst for asymmetric alkynylation of aromatic ketones when the ratio of BINOL to Ti(O^iPr)4 was 1.0, achieving good to excellent enantioselectivities. At the same time, Cozzi and Alesi [9] developed a practical method for the synthesis of chiral tertiary propargyl alcohols in the presence of titanium phenylacetylide (obtained by the transmetalation of lithium alkynyl derivatives with $ClTi(O^iPr)_3$) and (*R*)-BINOL (25 mol%). The reaction was performed at −15 or −30 °C with up to 90% ee values.

Although excellent results have been achieved, in view of the importance of the tertiary propargyl alcohols as precursors of many important pharmaceuticals, the design and development of easily accessible and economical chiral ligands to promote asymmetric addition of phenylacetylene to ketone are still a worthwhile project. Recently, we reported a series of different ligands in the asymmetric addition of phenylacetylene to ketone: (a) the application of chiral oxazolidine ligand, which

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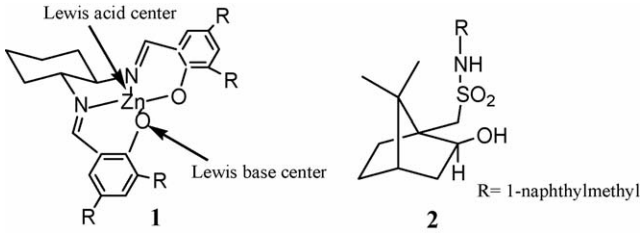


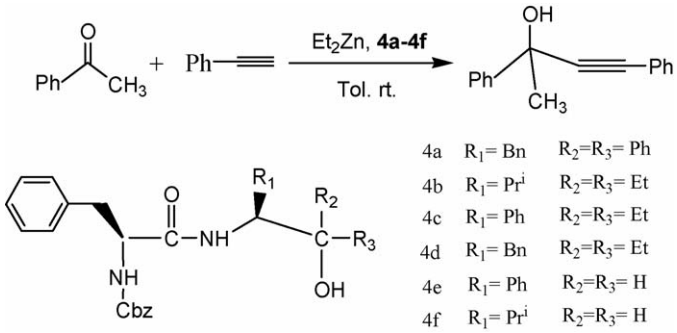
Fig. 1. Catalyst **1** and Ligand **2**.

was derived conveniently from natural amino acids [10]; (b) the application of the catalyst, generated from commercially available Cinchona alkaloids and industrially available triethylaluminum, gave the expected tertiary alcohols with good enantiomeric excess (70–89%) and yields (60–83%) [11]; (c) the application of the novel C_2-symmetrical bissulfonamide ligands, which were easily prepared in three simple steps, in the enantioselective addition of alkynylzinc reagents to aldehydes and ketones [12]; (d) the application of (*S*)-phenylalanine-derived β-amino alcohol, which was readily available from L-Phe, in catalyzing the addition reaction of alkynylzinc reagent to aromatic ketones with up to 80% ee of the thus produced chiral tertiary propargylic alcohols [13].

Although many types of ligands had been developed, using peptide or the analogs of peptide as ligand was still a challenging field [14]. Gong and coworkers [15] used L-Pro-based amides ligands in the aldol reaction. Jacobsen and coworkers [16] reported the application of the peptides in the asymmetric Strecker reaction. Based on our studies on the asymmetric addition of alkynylzinc to aldehyde and ketone [17], we herein report the application of a new type of ligand **4a–f** derived from the L-Phe-based N-terminal protected dipeptides in the asymmetric addition reaction of phenylacetylene to acetophenone in the presence of Et_2Zn for the first time.

2. Results and discussions

Series of ligands **4a–f** were conveniently prepared according the classic DCC (*N*,*N*′-dicyclohexylcarbodiimide)/HOBt (1-hydroxybenzotriazole) method [18] (Scheme 1). Using the DCC/HOBt protocol, we first obtained the activated ester Cbz (benzyloxycaronyl)-Phe-OBt. This ester could easily react with



Scheme 2. Asymmetric addition of phenylacetylene to acetophenone catalyzed by ligands **4a–f**.

Table 1
Asymmetric addition of phenylacetylene to acetophenone catalyzed by ligands **4a–f** using toluene as solvent

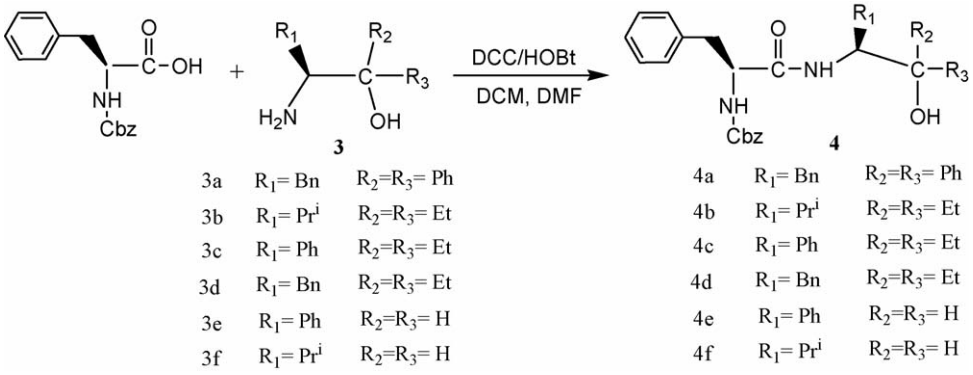
Entry	Ligand	Yields[a] (%)	Ee[b] (%)
1	**4a**	83	47
2	**4b**	75	20
3	**4c**	73	25
4	**4d**	51	3
5	**4e**	63	10
6	**4f**	82	45

[a] Yield of isolated product.
[b] The ee values were determined by chiral HPLC with Chiracel OD-H column.

β-amino alcohols **3a–f**. Ligands **4a–f** were obtained successfully according to this classic peptides synthesis method.

We studied the catalytic properties of ligands **4a–f** in the reaction of phenylacetylene with acetophenone in the presence of Et_2Zn. The alkynylzinc reagents were generated in situ from phenylacetylene with diethylzinc at room temperature and were successfully used in the asymmetric alkynylation of ketone. In addition, there were no additional metal centers as a promoter in this asymmetric addition reaction.

A preliminary study was conducted with the aim of determining the catalytic properties of ligands **4a–f** in asymmetric alkynylation of ketone (Scheme 2). The results summarized in Table 1 (entries 1–6) showed that ligands **4a** and **4f** gave the very high yield among the six ligands. But the ee values were very low.



Scheme 1. Synthesis of ligands **4a–f**.

Table 2
Asymmetric addition of phenylacetylene to acetophenone catalyzed by ligands **4a–f** using dichloromethane as solvent

Entry	Ligand	Yields[a] (%)	Ee[b] (%)
1	**4a**	85	10
2	**4b**	72	10
3	**4c**	66	6
4	**4d**	76	15
5	**4e**	43	5
6	**4f**	72	72

[a] Yield of isolated product.
[b] The ee values were determined by chiral HPLC with Chiracel OD-H column.

When we used dichloromethane (DCM) as solvent in the reaction, the best ligand **4f** gave a satisfactory result (Table 2, entry 6).

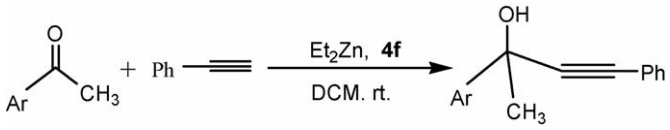
Then, the conditions of the asymmetric alkynylation of acetophenone in the presence of chiral ligand **4f** were optimized as summarized in Table 3.

We found that our reaction system proceeded under mild reaction conditions. It was strongly influenced by the solvents. Other conditions slightly influenced the ee values. Dichloromethane (DCM) was the best solvent, and using other solvents led to a decreased ee (Table 3, entries 1–3). THF obviously made the reaction sluggish and undesired side products were obtained (Table 3, entry 2). Decreasing the volume of DCM from 1.5 to 1.0 ml, resulted in no change in the ee values. But it led to an increased yield and shortened the time of reaction. 10 mol% **4f** was the best choice, increasing or decreasing the amount of ligand led to the lower ee (Table 3, entries 9 and 11). We then examined the effect of the amount of Et_2Zn, and found 3 equiv. Et_2Zn was the best amount (Table 3, entries 4, 7, and 10). When the amount of Et_2Zn was increased from 3 to 4 equiv. (Table 3, entry 6) or decreased from 3 to 2 equiv. (Table 3, entry 5), the speed of reaction changed but the ee was not influenced. When the temperature of reaction was decreased from room temperature to 0 °C, the reaction slowed down but the ee value was not influenced (Table 3, entry 10).

Table 3
Asymmetric addition of phenylacetylene to acetophenone using **4f** as ligands[a]

Entry	Ligand (%)	Et_2Zn (mol%)	Solvent	$V_{Sol.}$ (ml)	Yields[b] (%)	Ee[c] (%)
1	10	300	Hexane	1.5	65	26
2	10	300	THF	1.5	5	5
3	10	300	Ether	1.5	53	15
4	10	300	CH_2Cl_2	1.5	72	72
5	10	200	CH_2Cl_2	1.5	70	69
6	10	400	CH_2Cl_2	1.5	82	67
7[d]	10	300	CH_2Cl_2	1.0	85	72
8[e]	10	300	CH_2Cl_2	1.0	79	61
9	20	300	CH_2Cl_2	1.0	75	65
10[f]	10	300	CH_2Cl_2	1.0	55	72
11	5	300	CH_2Cl_2	1.0	69	67

[a] All the reactions, unless otherwise stated, were carried out for 48 h at room temperature.
[b] Yield of isolated product.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiracel OD-H column.
[d] The result was carried out for 24 h at room temperature.
[e] Et_2Zn was diluted with dichloromethane.
[f] The reaction was performed at 0 °C.



Scheme 3. Asymmetric addition of phenylacetylene to aromatic ketones catalyzed by ligand **4f**.

Table 4
Asymmetric addition of phenylacetylene to aromatic ketones promoted by ligand **4f**[a,b]

Entry	Ketones	Time (h)	Yield[c] (%)	Ee[d] (%)
1	Acetophenone	48	85	72
2	2′-Fluoroacetophenone	48	90	75
3	4′-Fluoroacetophenone	48	69	61
4	2′-Chloroacetophenone	48	88	83
5	4′ -Chloroacetophenone	48	70	64
6	2′-Bromoacetophenone	48	85	86
7	3′-Bromoacetophenone	48	85	51
8	2′-Methylacetophenone	72	65	91
9	3′-Methylacetophenone	48	83	71
10	4′-Methylacetophenone	48	73	74
11	3′-Methoxyacetophenone	48	79	65
12	4′-Methoxyacetophenone	72	60	52
13	2′-Naphthacetophenone	48	81	52

[a] In all of the entries, the Et_2Zn:phenylacetylene:ketones:**4f** ratio was 3.0:3.0:1.0:0.1
[b] All the reactions were processed under argon and at room temperature.
[c] Yield of isolated product.
[d] The ee values were determined by HPLC analysis of the corresponding products with a Chiracel OD-H column.

Under the optimized reaction conditions, ligand **4f** was employed to induce the enantioselective addition of phenylacetylene to a family of aromatic ketones (Scheme 3).

The ee values were up to 91% while yields up to 90% were obtained (Table 4). Under the same conditions, we also used ligands **4f** in the addition of phenylacetylene to the aliphatic ketone: isopropyl methyl ketone. The enantioselectivity was found to be 54% (yield 80%).

3. Conclusions

In conclusion, we have successfully used the ligands derived from the N-terminal protected dipeptide as chiral ligand in the asymmetric catalytic addition of phenylacetylene to aromatic ketones under very mild conditions for the first time and achieved desired results. Our studies developed a novel use of the analogs of dipeptides, which were conventionally only applied to the aldol and Strecker reactions. Furthermore, the ligand **4f** retained high enantioselectivity from 0 °C to room temperature, showing potential for industrial application.

4. Experimental

4.1. General methods

All 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 ketones 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 was recorded on a X-4 melting point apparatus and uncorrected. ^{1}H NMR spectra were measured on DRX-200MHz spectrometers (with TMS as an internal standard). IR spectra were obtained on a Nicolet NEXUS 670 FT-IR spectrometer. 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 a Daicel Chiracel OD-H column on a Waters HPLC instrument with a 996 UV-detector.

4.2. Preparation of *4a–f*

Ligands **4a–f** were synthesized according to the literature procedures [18].

4.2.1. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-benzyl-2,2-diphenylethyl)-amide (*4a*)

N-carbobenzyloxy-L-phenylalanine (Cbz-Phe)(1.57 g, 5.0 mmol) and HOBt (0.89 g, 6.0 mmol) were dissolved in dry DCM (30 ml); a small amount of DMF was added to enhance the dissolvability of substrates. DCC (1.24 g, 6.0 mmol) was dissolved in dry DCM (5 ml). Both solutions were cooled down to 0 °C and mixed. The resulting solution was stirred at 0 °C for 30 min and at room temperature for 10 h. The solution was filtrated in order to remove the side product DCU (*N*,*N*-dicyclohexylurea). β-Amino alcohol **3a** (1.52 g, 5 mmol) was dissolved in dry DCM (10 ml) and cooled down to 0 °C. To the solution was added the filtrate of Cbz-Phe-OBt. The resulting solution was stirred at 0 °C for 30 min and at room temperature for 24 h. The solvent was distilled under vacuum. The residue was dissolved in ester acetate. The solution was washed with 5% citric acid aqueous solution, saturated $NaHCO_3$ aqueous solution, and saturated NaCl aqueous solution and then dried (Na_2SO_4). The solvent was distilled under reduced pressure. The residue was purified through column chromatography on silica gel (eluent: petroleum:ethyl acetate = 5:1) to give **4a**.

A colorless crystal, yield 63%; mp 201–202 °C; $[\alpha]_D^{20} = -107.0$ (c 0.31 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.11–7.59 (m, 25H, Ph–H), 6.20–6.24 (d, 1H, –NH–), 5.32–5.36 (d, 1H, –NH–), 4.96 (s, 2H, $PhCH_2$–O–), 4.05–4.18 (2m, 2H, –CHN), 2.70–2.75 (d, 2H, $PhCH_2$), 2.57–2.61 (d, 2H, $PhCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.67, 37.85, 56.34, 58.79, 66.94, 80.62, 125.51, 125.74, 126.33, 126.76, 127.02, 127.95, 128.21, 128.28, 128.48, 128.52, 128.57, 129.18, 129.21, 136.05, 136.57, 138.50, 155.43, 170.88; IR (KBr): 3300, 3060, 3028, 2924, 2853, 1687, 1645, 1600, 1565, 1538, 1494, 1446, 1347, 1301, 1264, 1193, 1170, 1060, 1036, 955, 911, 744, 696 cm^{-1}; MS(ESI): *m*/*z*: 585 $[M+H]^+$.

4.2.2. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-isopropyl-2,2–diethylethyl)amide (*4b*)

The same general procedure as for **4a** was followed, the ratio of eluent (petroleum:ethyl acetate) being 2:1.

A colorless crystal, yield 66%; mp 139–140 °C; $[\alpha]_D^{20} = -14.0$ (c 0.35 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.26–7.33 (m, 10H, Ph–H), 5.36–5.40, 6.05–6.10 (d, 1H, –NH–), 4.41–4.52 (m, 1H, –CHN), 3.74–3.80 (m, 1H, –CH–Pr^i), 3.08–3.12 (d, 2H, Ph–CH^2), 1.99–2.05 (m, 1H, C–CH–C), 0.96–1.49 (2m, 4H, –CH_2), 0.65–0.83 (m, 12H, –CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.79, 16.67, 22.00, 27.36, 27.67, 28.28, 38.29, 56.71, 67.06, 127.04, 128.07, 128.18, 128.51, 128.74, 129.30, 136.15, 136.61, 155.73, 170.88; IR (KBr): 3340, 3074, 3032, 2961, 2921, 2852, 1695, 1652, 1536, 1456, 1375, 1284, 1258, 1231, 1148, 1029, 928, 821, 744, 697 cm^{-1}; MS(ESI): *m*/*z*: 441 $[M+H]^+$.

4.2.3. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-phenyl-2,2–diethylethyl)amide (*4c*)

The same general procedure as for **4a** was followed, the ratio of eluent (petroleum:ethyl acetate) being 2:1.

A colorless needle crystal, yield 63%; mp 130–132 °C; $[\alpha]_D^{20} = -4.0$ (c 0.52 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.16–7.31 (m, 15H, Ph–H), 6.89–6.93 (d, 1H, –NH–), 5.22–5.26 (d, 1H, –NH–), 4.97 (s, 2H, $PhCH_2$–O), 4.77–4.81 (d, 1H, PhCHN), 4.45–4.48 (d, 1H, CHN), 3.01–3.05 (d, 2H, $PhCH_2$–), 0.95–1.33 (2m, 4H, –CH_2–), 0.69–0.79 (m, 6H, –CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.71, 26.97, 28.24, 38.36, 56.33, 57.86, 67.02, 126.94, 127.44, 128.07, 128.16, 128.25, 128.29, 128.50, 128.72, 129.25, 136.11, 136.31 139.03, 155.71, 169.82; IR (KBr):3733, 3308, 3062, 3031, 2967, 2938, 2880, 1700, 1654, 1582, 1531, 1493, 1454, 1385, 1326, 1298, 1256, 1134, 1029, 980, 932, 906, 837, 739, 698 cm^{-1}; MS(ESI): *m*/*z*: 475 $[M+H]^+$.

4.2.4. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-benzyl-2,2–diethylethyl)amide (*4d*)

The same general procedure as for **4a** was followed, the ratio of eluent (petroleum:ethyl acetate) being 2:1.

A colorless crystal, yield 77%; mp 166–168 °C; $[\alpha]_D^{20} = -87.0$ (c 0.53 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.08–7.34 (m, 15H, Ph–H), 5.94–5.99 (d, 1H, –NH–), 5.05 (s, 2H, $PhCH_2$–O), 4.88–4.92 (d, 1H, –NH–), 4.08–4.28 (2m, 2H, –CHN–), 2.85–3.04 (m, 2H, $PhCH_2$), 2.49–2.61 (m, 2H, $PhCH_2$–), 1.46–1.59 (m, 2H, –CH_2–), 1.15–1.29 (m, 2H, –CH_2–), 0.73–0.91 (m, 6H, –CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.72, 27.51, 35.22, 38.09, 55.41, 56.57, 56.62, 67.03, 126.24, 126.88, 127.45, 128.22, 128.25, 128.54, 128.65, 129.20, 136.11, 136.54, 138.51, 155.75, 170.47; IR(KBr): 3406, 3336, 3085, 3065, 3028, 2964, 2930, 2877, 1949, 1878, 1805, 1689, 1648, 1550, 1520, 1495, 1451, 1382, 1324, 1284, 1232, 1197, 1159, 1134, 1079, 1032, 995, 980, 931, 912, 836, 749, 697, 605, 567, 544, 496, 464 cm^{-1}; MS(ESI): *m*/*z*: 489 $[M+H]^+$.

4.2.5. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-phenylethyl) amide (**4e**)

The same general procedure as for **4a** was followed, the ratio of eluent (petroleum:ethyl acetate) being 1:1.

A colorless crystal, yield 71%; mp 143–144 °C; $[\alpha]_D^{20} = +8.0$ (c 0.41 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.08–7.33 (m 15H, Ph–H), 6.37–6.40 (d, 1H, –NH–), 5.44–5.47 (d, 1H, –NH–), 5.06 (s, 2H, $PhCH_2$–O), 4.90–4.98 (m, 1H, –CHN), 4.44–4.47 (m, 1H, $PhCH_2$), 3.61–3.66 (m, 2H, $–CH_2$–O), 2.94–3.20 (m, 2H, $PhCH_2$), 2.19 (b, 1H, –OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.84, 55.69, 56.63, 65.91, 67.15, 126.62, 127.16, 127.83, 128.08, 128.25, 128.54, 128.78, 128.84, 129.35, 136.02, 136.43, 138.40, 155.93, 170.88; IR (KBr): 3296, 3061, 3029, 2920, 2851, 1688, 1645, 1530, 1494, 1450, 1371, 1286, 1256, 1232, 1190, 1142, 1115, 1077, 1039, 909, 846, 741, 697 cm^{-1}; MS(ESI): *m/z*: 419 $[M+H]^+$.

4.2.6. (2S,1′S)-Benzyloxycaronyl-phenylalanine acid (2-hydroxy-1-isopropylethyl) amide (**4f**)

The same general procedure as for **4a** was followed, the ratio of eluent (petroleum:ethyl acetate) being 1:1.

A pale yellow crystal, yield 75%; mp 98–100 °C; $[\alpha]_D^{20} = -18.0$ (c 0.60 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.26–7.34 (m, 10H, Ph–H), 5.73–5.76 (d, 1H, –NH–), 5.43–5.47 (d, 1H, –NH–), 5.09 (s, 2H, $PhCH_2$–O), 4.34–4.38 (m, 1H, CHN), 3.56–3.60 (m, 1H, –CH–Pr^i), 3.42–3.44 (m, 2H, $–CH_2$–O), 3.00–3.04 (d, 2H, $PhCH_2$), 1.70–1.77 (m, 1H, –CH–C_2), 0.75–0.87 (m, 6H, $–CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.08, 22.62, 38.72, 56.83, 57.18, 63.26, 67.16, 127.16, 128.10, 128.26, 128.54, 128.85, 129.29, 136.04, 136.58, 155.52, 171.14; IR(KBr): 3309, 3063, 3031, 2959, 2924, 2874, 2853, 1702, 1656, 1538, 1455, 1389, 1340, 1258, 1149, 1051, 1028, 912, 847, 821, 743, 698 cm^{-1}; MS(ESI): *m/z*: 385 $[M+H]^+$.

4.3. General procedures for the addition of phenylacetylene to ketones

General addition procedure: under argon, ligand **4f** (7.68 mg, 0.02 mmol) and a solution of Et_2Zn (1.0 M in toluene, 0.6 ml) were added to dry DCM (1.0 ml) at room temperature and the mixture was stirred for 1 h. Phenylacetylene (66.1 μl) was then added. After the mixture was stirred at room temperature for 2 h, it was treated with ketones at room temperature. The resulting mixture was stirred for 24–48 h at room temperature. After the reaction was complete (monitored with TLC), it was quenched with aqueous HCl (5%). The mixture was then 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 to give the product.

Acknowledgments

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