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Enantioselective alkynylation of aromatic ketones promoted by (*S*)-phenylalanine-derived β-amino alcohol

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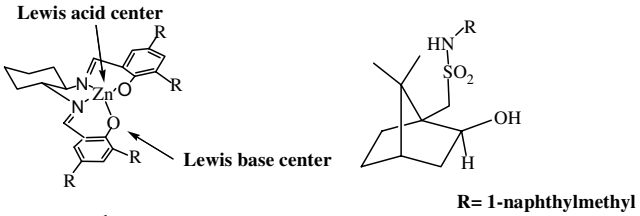
Abstract—(*S*)-(−)-2-Amino-1,1,3-triphenylpropanol **3c**, which is readily available from L-Phe, was found to be effective in catalyzing the addition reaction of an alkynylzinc reagent to aromatic ketones with up to 80% ee of the thus produced chiral tertiary propargylic alcohols. Unlike previous reports, **3c** does not require the use of an additional central metal (other than zinc itself) and the pre-preparation of an alkynylzinc. This has greatly simplified the experimental procedure for this reaction.

1. Introduction

Asymmetric alkynylzinc addition to ketones is a useful method for the production of chiral tertiary propargylic alcohols, which are important pharmaceutical intermediates. It is known that the enantioselective addition of alkynylzinc to aldehydes has been achieved with excellent enantioselectivity.[1] In sharp contrast, the use of ketones as electrophilic substrates has proven much more challenging. Direct approaches to the synthesis of chiral tertiary propargylic alcohols involve the asymmetric addition of lithium cyclopropylacetylide to ketones reported by Grabowski et al.[2] and the addition of alkynes to α-keto esters described by Jiang and Chen.[3] However, good yields and enantioselectivities have been achieved only in the cases of ketones activated by the electron withdrawing groups. When the substrates are unactivated ketones, only two catalysts have very recently been developed to catalyze the asymmetric alkynylzinc addition to ketones. Cozzi[4] reported a Zn(salen) bifunctional catalyst, **1** (20 mol%), promoting alkynylation of ketones with moderate yields and enantioselectivities.

However, the pre-preparation of an alkynylzinc is required and the catalytic system is substantially less effective on aromatic substrates (ee values range from 53% to 70% and yields from 45% to 81% for aryl methyl ketones). In the same year, Chan and co-workers[5] described the alkynylzinc addition to ketones in the presence of chiral camphorsulfonamide ligand **2** using $Cu(OTf)_2$ as a promoter with high enantioselectivities and yields (ee values range from 82% to 97% and yields from 49% to 92% for aryl methyl ketones).



1 **2**

Although significant results have been achieved by Chan, the design and development of easily accessible and economical chiral reagents are still a worthwhile project. Many amino alcohol ligands have been developed in asymmetric catalysis, and have shown powerful utilities in epoxidation reactions,[6] Diels–Alders reactions,[7] asymmetric reduction of prochiral ketones,[8] organozinc addition to carbonyl compounds,[9] and others. Based on the behavior of amino alcohol in catalytic asymmetric reactions and our recent studies on the

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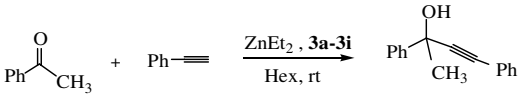
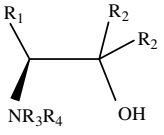
asymmetric addition of alkynylzinc to aldehydes,[10] we herein report our results for the enantioselective addition of alkynylzinc to ketones without the preparation of an alkynylzinc in advance or additional central metal (other than zinc itself) catalyzed by readily available *N*-nonsubstituted amino alcohol ligands.

2. Results and discussion

Initially, the catalytic properties of ligands (*S*)-**3a**–**i** in asymmetric alkynylation were tested (Scheme 1). The results showed that when the substituents at the carbon of the hydroxyl group are more rigid, the enantioselectivity and yields are higher (Table 1). Ligand **3a** has the most flexible substitute and gives the lowest ee, while ligand **3c** possesses the most rigid substituent and gives the highest ee value. We also compared the effect when the substituents at the nitrogen are nonsubstituted **3c** and **3f**, monosubstituted **3e** and bisubstituted **3d** and found when the ligand was *N*-nonsubstituted amino alcohol, the best enantiomeric excess was obtained. Then we examined the effect of the substituents at the carbon of the amino group, with ligand **3c** being found to be superior to others both in yields and ee's.





3a: R_1=Bn, R_2=Et, R_3=R_4=H
3b: R_1=Bn, R_2=Bn, R_3=R_4=H
3c: R_1=Bn, R_2=Ph, R_3=R_4=H
3d: R_1=Bn, R_2=Ph, R_3=R_4=Me
3e: R_1=MePr^i, R_2=Ph, R_3=Bn, R_4=H
3f: R_1=MePr^i, R_2=Ph, R_3=R_4=H
3g: R_1=MeCH$_2$Pr^i, R_2=Ph, R_3=R_4=H
3H: R_1=Me, R_2=Ph, R_3=R_4=H
3i: R_1=Ph, R_2=Ph, R_3=R_4=H

Scheme 1. Asymmetric addition of phenylacetylene to acetophenone catalyzed by β-amino alcohols **3a**–**i**.

Table 1. Asymmetric addition of phenylacetylene to acetophenone using **3a**–**i** as ligands

Entry	Ligand	Yields[a] (%)	Ee[b] (%)
1	**3a**	41	19
2	**3b**	53	45
3	**3c**	75	66
4	**3d**	50	12
5	**3e**	63	43
6	**3f**	53	50
7	**3g**	60	44
8	**3h**	45	20
9	**3i**	55	42

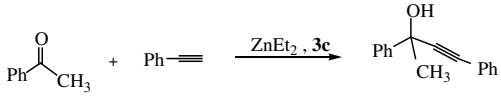
[a] Yield of isolated product.
[b] The ee values were determined by chiral HPLC with Chiracel OD column.

The conditions of the asymmetric alkynylation of acetophenone in the presence of chiral ligand **3c** (Scheme 2) were optimized with the results summarized in Table 2. We found that the reaction was strongly influenced by the solvents. Hexane was the best (entry 6), while THF obviously made the reaction sluggish and undesired side products were obtained (entry 3). Decreasing the reaction temperature from room temperature to 0 °C led to an increased ee (entry 9), while at −15 °C the ee was decreased (entry 10). Increasing the amount of ligand from 10 to 20 mol% resulted in a low ee of 56% (entry 11). When the amount of diethylzinc was increased from 1.4 to 3 equiv, the reaction proceeded faster but the ee was not influenced (entries 6–8). A variety of additives, such as methanol,[9c] phenol, binol, and ephedrine were also added to the reaction mixture, but with no improvement of the enantiomeric excess (entries 12–15).

Table 2. Asymmetric addition of phenylacetylene to acetophenone using **3c** as ligand[a]

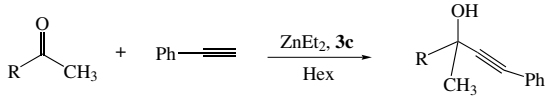
Entry	Ligand (%)	$ZnEt_2$ (mol%)	Solvent	Additive	Yield[b] (%)	Ee[c] (%)
1	10	200	Toluene		70	56
2	10	200	Ether		58	53
3	10	200	THF		10	3
4	10	200	CH_2Cl_2		63	47
5	10	200	Benzene		60	57
6	10	200	Hexane		75	66
7	10	140	Hexane		68	58
8	10	300	Hexane		78	66
9[d]	10	200	Hexane		70	71
10[e]	10	200	Hexane		53	57
11	20	200	Hexane		80	56
12	10	200	Hexane	(*R*,*R*)-Binol	61	50
13	10	200	Hexane	Phenol	51	54
14	10	200	Hexane	Methanol	53	51
15	10	200	Hexane	Ephedrine	58	50

[a] All the reactions, unless otherwise stated, were carried out for 30 h at room temperature.
[b] Yield of isolated product.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on Chiracel OD column.
[d] The reaction was performed at 0 °C.
[e] The reaction was performed at −15 °C.



Scheme 2. Asymmetric addition of phenylacetylene to acetophenone catalyzed by ligand **3c**.

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



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

Most ketones afforded high yields (up to 90%) and the ee values were up to 80% (Table 3). The reactions of the phenylacetylene addition to dialkyl ketones, such as isobutyl methyl ketone, were also observed, but only 48% ee was obtained with 81% yield.

Table 3. Asymmetric addition of phenylacetylene to aromatic ketones promoted by ligand **3c**[a,b]

Entry	Ketones	Time (h)	Yield[c] (%)	Ee[d] (%)
1	Acetophenone	30	70	71 (+)
2	2′-Fluoroacetophenone	30	90	77 (+)
3	2′-Naphthacetophenone	36	77	75 (+)
4	1′-Naphthacetophenone	48	58	80
5	4′-Methylacetophenone	36	75	72 (+)
6	3′-Methylacetophenone	36	80	68 (+)
7	4′-Fluoroacetophenone	36	73	68
8	4′-Methoxyacetophenone	48	51	66
9	4′-Chloroacetophenone	30	78	65 (+)
10	2′-Methoxyacetophenone	48	59	63
11	3′-Bromoacetophenone	30	88	60 (+)

[a] In all of the entries: Et_2Zn:phenylacetylene:ketones:**3c** = 2.0:2.0:1.0:0.1.
[b] All the reactions were processed under argon and at 0 °C.
[c] Yield of isolated product.
[d] The ee values were determined by chiral HPLC with Chiracel OD column.

3. Conclusion

We have successfully described the third catalyst in the asymmetric alkynylzinc addition to ketones under very mild conditions catalyzed by (*S*)-(−)-2-amino-1,1,3-triphenylpropanol **3c**, which is readily available. Our catalytic system is more effective for aromatic substrates than that of Cozzi, and employs no additional central metal (other than zinc itself). We are currently examining the scope of this catalyst and improving the enantioselectivity of this methodology through the design of more efficient ligands.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere and 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 hexane to 1.0 M. Melting points was uncorrected and recorded on X-4 melting point apparatus. ^{1}H NMR spectra were measured on DRX-200 MHz spectrometers (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 3a–i

Amino alcohols **3a**–**d** and **3f**–**i** were synthesized according to literature procedures.[11] Amino alcohol ligand **3e** was synthesized according to a literature procedure.[11a]

4.2.1. (*S*)-2-Amino-3-ethyl-1-phenylpentan-3-ol 3a. A pale yellow oil, yield 63%; $[\alpha]_D^{19} = -39.0$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.19–7.35 (m, 5H, Ph–H), 2.97–3.00 (q, 1H, CHN, $J = 3.5$ Hz, $J = 9.0$ Hz), 2.29–2.35 (q, 2H, $PhCH_2$, $J = 12.0$ Hz), 1.44–1.57 (m, 4H, CH_2), 1.11 (s, 2H, NH_2), 0.97 (t, 3H, CH_3, $J = 7.3$ Hz), 0.96 (t, 3H, CH_3); IR (KBr): 3391, 3059, 3026, 2964, 2926, 2851, 1595, 1494, 1457, 1397, 1376, 1316, 1260, 1153, 1076, 1028, 952, 750, 697 cm^{-1}; HR-MS calcd for $(M+H)^+$: 208.1696. Found: 208.1701.

4.2.2. (*S*)-3-Amino-2-benzyl-1,4-diphenylbutan-2-ol 3b. A colorless crystal, yield 66%; mp 130–131 °C; $[\alpha]_D^{18} = +19.0$ (*c* 1.38, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 6.96–7.40 (m, 15H, Ph–H), 3.87 (s, 1H, OH), 2.66–3.29 (m, 6H, $PhCH_2$), 2.416 (t, 1H, CHN, $J = 12.4$ Hz), 0.81 (br, 2H, NH_2); IR (KBr): 3377, 3315, 3026, 2935, 1600, 1493, 1450, 1388, 1078, 1054, 1030, 876, 838, 752, 719, 698, 625 cm^{-1}; MS (ESI): *m*/*z*: 332$[M+H]^+$.

4.2.3. (*S*)-2-Amino-1,1,3-triphenylpropan-1-ol 3c. A colorless crystal, yield 70%; mp 134–136 °C; $[\alpha]_D^{18} = -85.0$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 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, $CDCl_3$): δ 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*)-1,1,3-Triphenyl-2-(*N*,*N*-dimethylamino)propan-1-ol 3d. A pale yellow oil, yield 81%; $[\alpha]_D^{20} = +32.0$ (*c* 0.85, $CH_3COOC_2H_5$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 7.45–7.52 (m, 5H, Ph–H), 7.20–7.32 (m, 10H, Ph–H), 3.86–3.92 (d, 1H, CHN, $J = 11.8$ Hz), 3.03–3.10 (d, 1H, $PhCH_2$, $J = 14.6$ Hz), 2.65–2.78 (dd, 1H, $PhCH_2$, $J = 14.6$ Hz), 1.98 (s, 6H, CH_3); IR (KBr): 3314, 3085, 3059, 3026, 2933, 2844, 2792, 1600, 1494, 1471, 1448, 1370, 1287, 1265, 1160, 1069, 1032, 946, 911, 758, 741, 725, 699 cm^{-1}; HR-MS calcd for $(M+H)^+$: 332.2009. Found: 332.2014.

4.2.5. (*S*)-3-Methyl-2-benzylamino-1,1-diphenylbutan-1-ol 3e. A colorless crystal, yield 76%; mp 132–134 °C; $[\alpha]_D^{25} = -34.0$ (*c* 1.24, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 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, $CDCl_3$): δ 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.

4.2.6. (*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol 3f. A colorless needle crystal, yield 65%; mp 95–97 °C; $[\alpha]_D^{18} = -124.0$ (*c* 1.27, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 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, $CDCl_3$): δ 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]$^+$.

4.2.7. (*S*)-2-Amino-4-methyl-1,1-diphenylpentan-1-ol 3g. A colorless needle crystal, yield 55%; mp 132–134 °C; $[\alpha]_D^{18} = -105.0$ (*c* 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 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, $CDCl_3$): δ 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]$^+$.

4.2.8. (*S*)-2-Amino-1,1-diphenylpropan-1-ol 3h. A colorless needle crystal, yield 52%; mp 100–102 °C; $[\alpha]_D^{25} = -83.0$ (*c* 0.814, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.61 (d, 2H, Ph–H, $J = 7.5$ Hz), 7.48 (d, 2H, Ph–H, $J = 7.8$ Hz), 7.15–7.34 (m, 6H, Ph–H), 4.14 (q, 1H, CHN, $J = 6.0$ Hz), 0.94 (d, 3H, CH_3, $J = 6.0$ Hz); IR (KBr): 3436, 3392, 3328, 3024, 2985, 2891, 1591, 1489, 1446, 1366, 1175, 969,835, 764, 707, 646 cm^{-1}; MS (ESI): *m/z*: 228[M+H]$^+$.

4.2.9. (*S*)-2-Amino-1,1,3-triphenylethan-1-ol 3i. A colorless needle crystal, yield 67%; mp 113–115 °C; $[\alpha]_D^{18} = -212.0$ (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.75–7.78 (m, 2H, Ph–H), 7.60–7.63 (m, 1H, Ph–H), 7.39–7.48 (m, 3H, Ph–H), 7.26–7.31 (m, 1H, Ph–H), 7.09–7.14 (m, 6H, Ph–H), 7.01–7.08 (m, 2H, Ph–H), 5.02 (s, 1H, PhCHN), 4.68 (s, 1H, OH), 1.61 (s, 2H, NH_2); IR (KBr): 3381, 3311, 3059, 3029, 2888, 1445, 1367, 1173, 1046, 893, 754, 725, 697 cm^{-1}; MS (ESI): *m/z*: 290[M+H]$^+$.

4.3. Characterization of the tertiary propargyl alcohols

4.3.1. 2-(4-Chloro-phenyl)-4-phenyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68–7.31 (m,2H), 7.49–7.44 (m, 2H), 7.35–7.31 (m, 5H), 2.60 (br s, 1H), 1.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.2, 133.5, 131.7, 128.6, 128.4, 128.3, 126.5, 122.3, 91.9, 85.2, 69.9, 33.35; IR (KBr) 3366, 3059, 2985, 2921, 2235, 1672, 1596, 1576, 1488, 1444, 1399, 1366, 1138, 1091, 1048, 1014, 939, 905, 829, 780, 756, 733, 691 cm^{-1}. Anal. Calcd for $C_{16}H_{13}OCl$: C, 74.85; H, 5.10; Cl, 13.81. Found: C, 74.69; H, 5.21; Cl, 13.72.

4.3.2. 2-(2-Fluoro-phenyl)-4-phenyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78–7.70 (m, 1H), 7.48–7.44 (m, 2H), 7.32–7.25 (m, 4H), 7.19–7.04 (m, 2H), 2.79 (br s, 1H), 1.98 (s, 3H); ^{13} C NMR (50 MHz, $CDCl_3$): δ 131.7, 129.7, 129.5, 128.5, 128.3, 124.0, 123.9, 116.6, 116.1, 92.6, 84.1, 68.1, 30.6; IR (KBr) 3585, 3396, 3060, 2924, 2854, 2235, 1679, 1610, 1581, 1487, 1449, 1371, 1275, 1222, 1198, 1110, 1073, 1033, 941, 897, 824, 757, 691 cm^{-1}. Anal. Calcd for $C_{16}H_{13}OF$: C, 79.98; H, 5.45; F, 7.91. Found: C, 79.86; H, 5.50; F, 8.01.

4.3.3. 4-Phenyl-2-*m*-tolyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54–7.45 (m, 4H), 7.32–7.23 (m, 4H), 7.12 (d, 1H), 2.38 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.6, 138.0, 131.7, 128.4, 128.2, 125.6, 122.6, 122.1, 119.8, 92.7, 84.7, 70.3, 33.2, 21.5; IR (KBr) 3533, 3375, 3056, 2984, 2926, 2862, 2232, 1949, 1881, 1674, 1602, 1488, 1444, 1365, 1327, 1268, 1172, 1137, 1084, 1051, 940, 918, 845, 788, 756, 696 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.33; H 6.87.

4.3.4. 2,4-Diphenyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, 2H), 7.47–7.26 (m, 8H), 2.5 (s,1H), 1.87 (s, 3H). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.41; H, 6.42.

4.3.5. 2-(3-Bromo-phenyl)-4-phenyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (m, 3H), 7.66–7.20 (m, 8H), 2.55 (br s, 1H), 1.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.9, 131.7, 130.8, 129.9, 128.6, 128.3, 123.7, 122.4, 122.2, 92.3, 85.0, 69.9, 33.4; IR (KBr) 3556, 3371, 3060, 2985, 2929, 2857, 2235, 1950, 1881, 1754, 1679, 1594, 1568, 1489, 1470, 1443, 1415, 1366, 1328, 1277, 1205, 1140, 1071, 1053, 939, 909, 837, 787, 756, 692 cm^{-1}. Anal. Calcd for $C_{16}H_{13}OBr$: C, 63.81; H, 4.35; Br, 26.53. Found: C, 63.63; H, 4.43; Br, 26.39.

4.3.6. 2-Naphthalen-2-yl-4-phenyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.87–7.77 (m, 4H), 7.52–7.45 (m, 4H), 7.34–7.30 (m, 3H), 2.68 (br s, 1H), 1.95 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.9, 133.0, 132.9, 131.8, 128.5, 128.3, 128.2, 126.2, 126.1, 122.6, 92.5, 85.1, 70.5, 33.1; IR (KBr) 3542, 3366, 3056, 2984, 2929, 2852, 2232, 1630, 1599, 1570, 1506, 1489, 1442, 1357, 1272, 1180, 1128, 1076, 1048, 940, 909, 859, 819, 752, 691 cm^{-1}. Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.15; H, 5.98.

4.3.7. 2-(4-Methoxy-phenyl)-4-phenyl-but-3-yn-2-ol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.64 (m, 2H), 7.50–7.47 (m, 2H), 7.35–7.26 (m, 3H), 6.94–6.90 (m, 2H), 3.818 (s, 3H), 1.86 (s, 3H). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.91; H, 6.45.

4.3.8. 4-Phenyl-2-*p*-tolyl-but-3-yn-2-ol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, 2H), 7.50–7.45 (m, 2H), 7.33–7.29 (m, 3H), 7.18 (d, 2H), 2.50 (s, 1H), 2.34 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.8, 137.4, 131.7, 129.0, 128.4, 128.3, 124.9, 119.2, 92.1, 85.4, 70.2, 33.2, 21.0; IR (KBr) 3548, 3391, 3056, 2982, 2925, 2856, 2246, 1905, 1671, 1602, 1574, 1510, 1489, 1446, 1369, 1326, 1266, 1205, 1182, 1138, 1109, 1085, 1045, 938, 908, 819, 756, 733, 691, 648 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.28; H, 6.90.

4.4. General procedures for the addition of phenylacetylene to ketones

General addition procedure: Under argon, ligand **3c** (7.6 mg, 0.025 mmol) and a solution of Et_2Zn (1.0 M in hexane, 0. 5 mL) were mixed in dry hexane (2.0 mL) at room temperature and stirred for 1 h. Phenylacetylene (55 μL, 0. 05 mmol) was then added. After the mixture was stirred at room temperature for another 1 h, the orange solution was cooled to 0 °C and treated with ketones (0.25 mmol). The resulting mixture was stirred for 30–48 h at 0 °C. After the reaction was complete (monitoring 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 (silica gel, 20% EtOAc in hexane) to give the product.

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References

1. (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886; (b) Lu, G.; Li, X. S.; Zhou, Z. Y.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147–2152; (c) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381; (d) Xu, M. H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555–4557; (e) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; (f) Lu, G.; Li, X. S.; Chen, G.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 449–452; (g) Moore, D.; Huang, W. S.; Xu, M. H.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831–8834; (h) Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413–10416; (i) Li, M.; Zhu, X. Z.; Yuan, K.; Cao, B. X.; Hou, X. L. *Tetrahedron: Asymmetry* **2004**, *15*, 219–222.
2. (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937–8940; (b) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038; (c) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212–11218.
3. Jiang, B.; Chen, Z. L. *Org. Lett.* **2002**, *4*, 3451–3453.
4. Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895–2898.
5. Lu, G.; Li, X. S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057–5058.
6. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.
7. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.
8. Corey, E. J.; Bakshi, R. K.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
9. (a) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824; (b) see ref. 11b; (c) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446; (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287; (e) Garcia, C.; Larochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971; (f) Falorni, M.; Collu, C.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 293–299; (g) See Ref. 11a.
10. (a) Xu, Z. Q.; Wang, R.; Xu, J. K.; Da, C. S.; Yan, W. J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747–5749; (b) Xu, Z. Q.; Chen, C.; Xu, J. K.; Miao, M. B.; Yan, W. J.; Wang, R. *Org. Lett.* **2004**, *6*, 1193–1195; (c) Zhou, Y. F.; Wang, R.; Xu, Z. Q.; Yan, W. J.; Liu, L.; Gao, Y. F.; Da, C. S. *Tetrahedron: Asymmetry* **2004**, *15*, 589–591; (d) Kang, Y. F.; Liu, L.; Wang, R.; Yan, W. J.; Zhou, Y. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3155–3159.
11. (a) Wu, Y.-J.; Yun, H.-Y.; Wu, Y.-S.; Ding, K.-L.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543–3552; (b) Da, C. S.; Han, Z. J.; Ni, M.; Yang, F.; Liu, D. X.; Zhou, Y. F.; Wang, R. *Tetrahedron: Asymmetry* **2003**, *14*, 659–665.