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Enantioselective addition of phenylacetylene to aldehydes catalyzed by 1,3-aminophenol ligand

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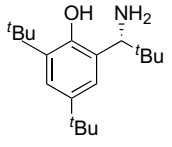
Abstract—The 1,3-aminophenol ligand (*R*)-**1** was found to be a good catalyst for the zinc phenylacetylene addition to aldehydes. The high activity and enantioselectivity could be improved upon by basic additives. The enantioselectivity follows a linear free energy relationship with higher enantioselectivity obtained for the more reactive aryl aldehydes.

1. Introduction

The enantioselective addition of alkynylzinc reagents to aldehydes is an important and simple method of synthesizing chiral propargyl alcohols, which are important precursors to many chiral organic compounds.[1] Carreira et al. discovered a highly enantioselective catalyst based on the chiral aminoalcohol *N*-methyl ephedrine for the alkynylzinc addition to (mostly) aliphatic aldehydes.[2] Pu et al. reported that BINOL/Ti(O^iPr)$_4$ can catalyze alkynylzinc addition to a broad range of substrates, including alkyl, aryl and α,β-unsaturated aldehydes.[3] Chan et al. reported that a 1:1 combination of BINOL with sulfonamide as the ligand can also catalyze this reaction giving the products with high ee values.[4]

However, the factors governing enantioselectivity remain the subject of speculation even in the reactions that have been extensively studied.[5] Enantioselectivity in a catalytic asymmetric reaction is usually interpreted in steric terms,[6] affected by the temperature and solvent, etc.[7] However, electronic effects have been reported recently. In the reported studies on electronic effects,[8] the underlying reasons are poorly understood in most cases. Herein, we report our findings on the enantioselective addition of zinc phenylacetylene to aldehydes in the presence of (*R*)-**1** with sterically bulky *tert*-butyl groups on the stereogenic carbon atom and 4,6-positions of phenol. In the catalytic enantioselective addition of zinc phenylacetylene to *para*- or *meta*-substituted aryl aldehydes catalyzed by chiral 1,3-aminophenol (*R*)-**1**, we have found for the first time that the enantioselectivity depends on the electronic nature of the aryl aldehydes in a linear free energy relationship and increases with more reactive substrates.



(*R*)-**1**

2. Results and discussion

Chiral 1,3-aminophenol (*R*)-**1** was prepared following the recently reported procedure.[9] To optimize the reaction conditions, we first studied the asymmetric reaction of phenylacetylene with *para*-chlorobenzaldehyde in the presence of diethylzinc. The results are summarized in Table 1. In all entries listed in Table 1, some amounts of ethylation product were also formed. We found that the reaction was strongly influenced by solvent. In CH_2Cl_2 or toluene, very good enantioselectivity (81% ee) was observed (entries 1 and 2). On the other hand, a low ee value was obtained in hexane or diethyl ether, and especially in THF (26% ee) (entries 3–5). Decreasing the reaction temperature from room temperature to 0 °C or −17 °C increased the reaction

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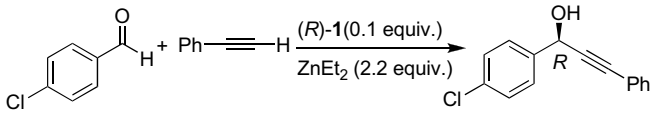
Table 1. Results for the reactions of phenylacetylene with *para*-chlorobenzaldehyde in the presence of (*R*)-**1**[a]



Entry	Reaction conditions	Additive (mol %)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2, rt, 4 h		95	81
2	Toluene, rt, 4 h		87	81
3	Hexane, rt, 4 h		91	64
4	Et_2O, rt, 4 h		88	61
5	THF, rt, 24 h		55	26
6	CH_2Cl_2, 0 °C, 24 h		83	74
7	Toluene, 0 °C, 10 h		82	81
8	Toluene, −17 °C, 48 h		81	67
9	CH_2Cl_2, rt, 4 h	DBU (10)	99	62
10	CH_2Cl_2, rt, 4 h	$^iPr_2NEt$ (10)	98	82
11	CH_2Cl_2, rt, 4 h	Et_3N (10)	96	86
12	**CH_2Cl_2, rt, 4 h**	**Proton sponge (10)**	**96**	**88**
13	CH_2Cl_2, rt, 4 h	Proton sponge (20)	92	81
14	CH_2Cl_2, rt, 4 h	Proton sponge (50)	94	86
15	CH_2Cl_2, 10 °C, 4 h	Proton sponge (10)	88	82

[a] Reagent ratio: aldehyde/$ZnEt_2$/phenylacetylene/ligand = 1.0:2.2:2.4:0.1.
[b] Isolated yields.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H); absolute configuration was determined by comparison with the known compounds.[11a]

time and decreased the yield and ee (entries 6–8). Considering that (*S*)-**1** was a good ligand for the addition of diethylzinc to aldehydes,[9] we expected that the deprotonation of phenylacetylene by diethylzinc plays an important role in the ratio of the products of both ethylating and alkynylation. In fact, some reports also suggested that in the presence of the Lewis base diethylzinc reacted rapidly with phenylacetylene at room temperature to generate the corresponding alkynylzinc complex.[3c,d,10,11a] Therefore some Lewis bases were tested as an additive to the reaction (entries 9–12). Addition of 10 mol % of DBU improved the yield of the propargyl alcohol but gave lower ee (entry 9). Addition of 10 mol % of $^iPr_2NEt$ led to a small increase in ee (entry 10). When 10 mol % of Et_3N or proton sponge was added to facilitate the reaction of phenylacetylene with diethylzinc, the enantioselectivity was significantly improved (entries 11 and 12). Increasing the amount of proton sponge or decreasing the reaction temperature also reduced the enantioselectivity (entries 13–15 vs entry 12). Thus entry 12 was identified as the optimized procedure for this reaction because of its high enantioselectivity.

To demonstrate the influence of electronic and steric effects of the substrate for this asymmetric alkynylation reaction, a series of different aryl aldehydes were evaluated under the optimized condition. The results are summarized in Table 2. In all entries listed in Table 2, a small amount of ethylation product was also formed. Most remarkably, the enantioselectivity of the reactions is subject to an electronic effect. In Table 2, the substrates with electron-withdrawing groups in the *para*- or *meta*-positions of aryl aldehydes afforded higher enantioselectivity than those with electron-donating groups (entries 1–9). To evaluate the effects

Table 2. Results for the reactions of phenylacetylene with aryl aldehydes in the presence of (*R*)-**1**, proton sponge and Et_2Zn (rt, 4 h)[a]

Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1	C_6H_5CHO	94	69
2	*p*-$NO_2C_6H_4CHO$	75	99
3	*p*-ClC_6H_4CHO	96	88
4	*p*-BrC_6H_4CHO	98	89
5	*p*-MeC_6H_4CHO	90	60
6	*p*-$MeOC_6H_4CHO$	89	56
7	*m*-$NO_2C_6H_4CHO$	79	99
8	*m*-ClC_6H_4CHO	96	89
9	*m*-MeC_6H_4CHO	92	66
10	*o*-$NO_2C_6H_4CHO$	77	36
11	*o*-ClC_6H_4CHO	90	88
12	*o*-MeC_6H_4CHO	90	12
13	$C_6H_5CH_2CH_2CHO$	79	22
14	$C_6H_5CH(CH_3)CHO$	87	20
15	$C_6H_5CH{=}CHCHO$	85	36

[a] Reagent ratio: aldehyde/$ZnEt_2$/phenylacetylene/ligand = 1.0:2.2:2.4:0.1.
[b] Isolated yields.
[c] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OD-H); absolute configuration was determined by comparison with the known compounds.[3a,4b,11]

of the substituents, the results in Table 2 were analyzed by means of a Hammett plot (Fig. 1). A linear correlation was observed between enantioselectivity and electronic constant. As shown in Figure 1, the enantioselectivity increased following the sequence MeO < Me < H < Cl, Br < NO_2. This result suggested that the electronic property of a substituent had a significant influence on the reaction rate and enantioselectivity. It is well known that substituents with electron-withdrawing groups (positive Hammett constants σ) lead to an increase in Lewis acidity of the carbonyl carbon atom of aryl aldehydes, while such substituents with electron-donating groups (negative σ-values) diminish it. It is expected the substrates with an electron-withdrawing substituent afforded faster reaction leading to higher enantioselectivity. However, the substrates with electron-donating substituents had lower reaction rates and enantioselectivities. On the other hand, low ee values were obtained in the case of *ortho*-substituted aryl aldehydes except *ortho*-chlorobenzaldehyde (entries 10–12). These results suggested that the enantioselectivity of zinc

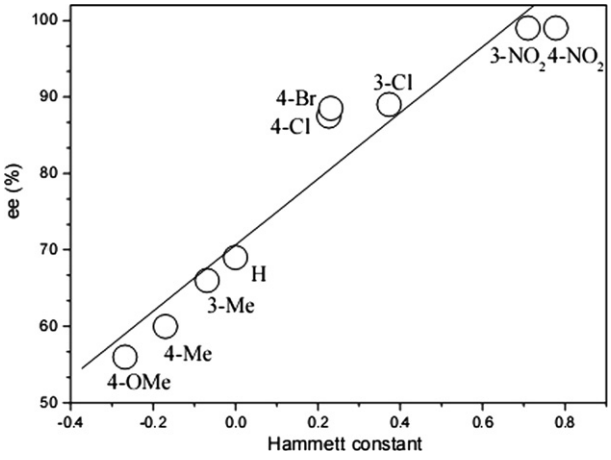
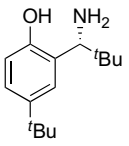


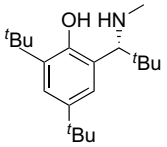
Figure 1. Correlation of the enantiomeric excess of the alkynylation of *para*- or *meta*-substituted aryl aldehydes versus Hammett constant σ.

phenylacetylene to *ortho*-substituted aldehydes was affected not only by electronic effect but also by steric effect.[12] Lower chemical yields were obtained for NO_2-substituted benzaldehydes (entries 2, 7 and 10), and some by-products were observed by TLC analysis. The reaction was also tested with aliphatic aldehydes (entries 13–15) and provided the corresponding propargyl alcohols with 20–36% ees in spite of good chemical yields.

The effect of the *tert*-butyl group at the *ortho*-position on the phenolic hydroxy group should be mentioned. That is, in the case of the use of 10 mol % of aminophenol ((*R*)-**2**) without a *tert*-butyl group at the *ortho*-position, the opposite enantiomer (*S*) was obtained in 98% yield and 11% ee (Scheme 1). On the other hand, only 13% ee (92% yield) was obtained by using *N*-methyl aminophenol ((*R*)-**3**) whereas some N-substituted amino alcohols or aminophenols are effective in the addition of alkynylzinc reagents or asymmetric addition reaction of diethylzinc with aldehydes.[3b,13]

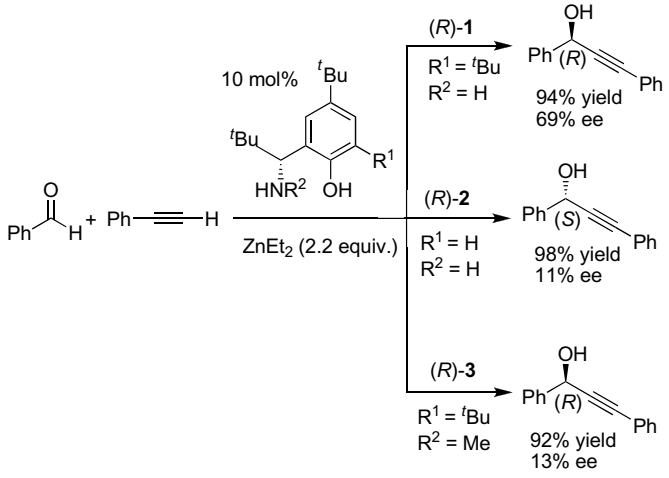


(*R*)-**2**



(*R*)-**3**

Although the reaction mechanism is not exactly clear, a possible mechanism for this asymmetric alkynylation of aldehydes was proposed according to the well-known mechanism for asymmetric alkylation of aldehydes with diethylzinc.[14] As for an analogy with the ethylation,[9] we can then presume that in the alkynylation with (*R*)-**1**, the two most stable TS's are *anti*-(*Si*) and *anti*-(*Re*) (Fig. 2) and therefore that the enantioselectivity of the reaction is primarily determined by their energy difference. From Figure 2, we can see that in *anti*-(*Re*) the $^{t}Bu^{\#}$ and alkynyl groups are on the same side, while in *anti*-(*Si*) the $^{t}Bu^{\#}$ and the alkynyl groups are on the opposite sides. The latter



Scheme 1. Effect of the *tert*-butyl group at the *ortho*-position on the phenolic hydroxy group and the methyl group on the nitrogen atom of the ligand.

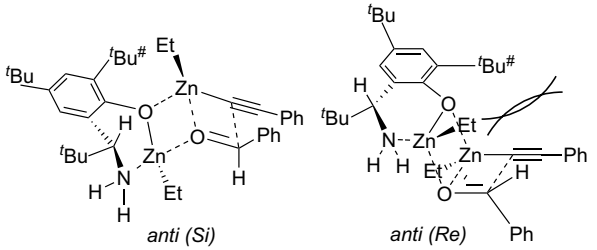


Figure 2.

transition state, which leads to an alkynyl transfer on the *Si* face of the carbonyl is therefore the more stable one. Additionally, the energy differences between these two transition states, which lead to the opposite enantiomers by means of semi-empirical PM5 calculations[15] show that the structure *anti*-(*Si*) is more stable, with a large difference of 14.05 kcal/mol. This value supports the experimental result, which shows the (*R*)-1,3-diphenyl-prop-2-yn-1-ol as the major product (Table 2, entry 1).

3. Conclusions

In summary, (*R*)-**1** has been shown to catalyze the addition of phenylacetylene to aryl aldehydes with moderate to high enantioselectivity using proton sponge as an additive. Most importantly, this enantioselectivity follows a linear free energy relationship with higher enantioselectivity obtained for more reactive aryl aldehydes. Further modification of these ligands as well as applications in asymmetric catalysis is in progress.

4. Experimental

Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck Silica Gel plates (60F-254). NMR spectra were recorded on Bruker AC300 or DPX400 spectrophotometer, operating at 300 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR (Molecular Analysis and Life-Science Center of Saitama University). Chemical shifts were reported in parts per million downfield from Me_4Si in $CDCl_3$ solution and the coupling constants were given in Hertz. Enantiomeric excess determination was carried out using a set of JASCO LC 900 series with chiral columns. Optical rotations were measured with a JASCO DIP-370 polarimeter. All reagents commercially available were purchased at the highest quality and were purified by distillation when necessary. Dichloromethane was distilled and stored on sodium wire before use.

Chiral 1,3-aminophenols (*R*)-**1** and (*R*)-**2** were synthesized according to the literature procedure.[9]

4.1. Characterization of 2-(1-amino-2,2-dimethylpropyl)-4,6-di-*tert*-butylphenol 1

A white solid. Mp: 108–110 °C. (*S*)-**1**: $[\alpha]_D^{20} = +22.0$ (*c* 0.5, $CH_3COOCH_2CH_3$); (*R*)-**1**: $[\alpha]_D^{20} = -12.7$ (*c* 1.0, MeOH). Enantiomeric purity >99% ee was determined by HPLC

analysis (CHIRALCEL OJ, 15% IPA in hexane, 0.5 mL/min, 254 nm UV detector) at retention time: $t_S = 8.63$ min, $t_R = 13.2$ min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, $J = 2.6$ Hz, 1H, ArCH), 6.75 (d, $J = 2.2$ Hz, 1H, ArH), 3.87 (s, 1H, $(CH_3)_3CHAr$), 1.43 (s, 9H, $(CH_3)_3ArOH$), 1.29 (s, 9H, $(CH_3)_3Ar$), 0.98 (s, 9H, $(CH_3)_3CHAr$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 138.7, 136.3, 125.8, 122.5, 122.4, 67.4, 36.2, 34.9, 33.9, 31.7, 29.6, 26.9. IR (KBr) 3485, 2977, 2957, 1693, 1627, 1604, 1454, 1376, 1353, 1331, 1268, 1244, 1151, 969, 958, 794 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.81. Found: C, 78.41; H, 11.31; N, 4.90.

4.2. Characterization of 2-(1-amino-2,2-dimethylpropyl)-4-*tert*-butylphenol 2

A white solid. Mp: 99–101 °C. (*S*)-**2**, $[\alpha]_D^{20} = -6.8$ (*c* 0.326, diethyl ether); (*R*)-**2**, $[\alpha]_D^{20} = +8.4$ (*c* 0.330, diethyl ether). Enantiomeric purity >99% ee was determined by HPLC analysis (CHIRALCEL OD-H, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector) at retention time: $t_S = 12.7$ min; $t_R = 13.8$ min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (dd, $J = 8.5$ Hz, $J = 2.6$ Hz, 1H, ArCH), 6.88 (d, $J = 2.6$ Hz, 1H, ArH), 6.74 (d, $J = 8.5$ Hz, 1H, ArH), 3.85 (s, 1H, $(CH_3)_3CHAr$), 1.27 (s, 9H, $(CH_3)_3Ar$), 0.98 (s, 9H, $(CH_3)_3CHAr$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 140.3, 127.8, 125.1, 122.9, 116.6, 66.9, 36.2, 33.8, 31.5, 26.8. IR (KBr) 3067, 2983, 1598, 1485, 1448, 1386, 1298, 1137, 913, 868 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.67; H, 10.85; N, 6.01.

Chiral 1,3-aminophenol (*R*)-**3** was synthesized according to the literature procedure.[16]

4.3. Characterization of (*R*)-2,4-di-*tert*-butyl-6-(2,2-dimethyl-1-(methylamino)propyl)phenol (*R*)-3

A white solid. Mp: 115–117 °C. $[\alpha]_D^{20} = -31.7$ (*c* 0.328, $CH_3COOCH_2CH_3$). Enantiomeric purity >99% ee was determined by HPLC analysis (CHIRALCEL OJ, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector) at retention time: $t_R = 7.627$ min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.19 (br, 1H), 7.16 (d, $J = 2.6$ Hz, 1H, ArCH), 6.71 (d, $J = 2.6$ Hz, 1H, ArH), 3.27 (s, 1H, $(CH_3)_3CHAr$), 2.41 (s, 3H, $NHCH_3$), 1.40 (s, 9H, $(CH_3)_3ArOH$), 1.28 (s, 9H, $(CH_3)_3Ar$), 0.94 (s, 9H, $(CH_3)_3CHAr$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 138.5, 135.3, 126.6, 122.1, 120.0, 77.2, 36.2, 35.1, 34.8, 33.9, 31.7, 29.6, 27.3.

4.4. General procedure for enantioselective alkynylation procedure

To a solution of ligand (29.2 mg, 0.1 mmol) in dry CH_2Cl_2 (1 mL) under a nitrogen atmosphere at room temperature was added a solution of Et_2Zn in hexane (1.0 M, 2.2 mL, 2.2 mmol). The mixture was stirred for 30 min, then proton sponge (21.4 mg, 0.1 mmol) was added, and after further 1 h, a solution of phenylacetylene (0.27 mL, 2.4 mmol) in dry CH_2Cl_2 (1 mL) was added. After the solution was stirred at room temperature for 1 h, the solution of an aryl aldehyde (1 mmol) in dry CH_2Cl_2 (2 mL) was added. The mixture was monitored by TLC and when no more traces of the aldehyde were detected, the reaction mixture was quenched by saturated aq NH_4Cl. The mixture was extracted with ethyl acetate and the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel to give the enantiomer enriched propargylic alcohol. The enantiomeric purity of the product was determined by chiral HPLC Chiralcel OD-H column.

The propargylic alcohols are known and their ^{1}H NMR spectra agreed with those in the literature cited below.[4b,10] The enantiomeric excess (ee) of the products was determined by HPLC using Chiracel OD-H column. The absolute configuration of the adducts was assigned by comparison with the literature data.[4b,11]

4.4.1. (*R*)-1,3-Diphenyl-prop-2-yn-1-ol.[11a] 94% isolated yield. 69% ee determined by HPLC analysis (Chiralcel OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 17.097$ and $t_{minor} = 23.528$ min. $[\alpha]_D^{23} = +3.2$ (*c* 0.668, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.46–7.19 (m, 8H), 5.64 (s, 1H), 2.81 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 131.7, 128.6, 128.5, 128.3, 128.2, 126.7, 122.4, 88.8, 86.5, 64.9.

4.4.2. (*R*)-1-(4-Nitrophenyl)-3-phenyl-prop-2-yn-1-ol.[11b] 79% isolated yield. 99% ee determined by HPLC analysis (Chiralcel OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 19.258$ and $t_{minor} = 58.84$ min. $[\alpha]_D^{23} = +13.3$ (*c* 0.15, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19–8.18 (m, 2 H), 8.17–8.16 (m, 2H), 8.15–7.18 (m, 5H), 5.71 (s, 1H), 2.65 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 131.8, 129.1, 128.4, 127.4, 123.8, 121.7, 87.6, 87.4, 64.0. The racemic compound was prepared by using the same procedure as the preparation of the optically active compound except that racemic **1** was used in place of (*R*)-**1**.

4.4.3. (+)-1-(3-Nitrophenyl)-3-phenyl-prop-2-yn-1-ol.[4b,11c] 79% isolated yield. 99% ee determined by HPLC analysis (Chiralcel OD-H column, 50% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 10.632$ and $t_{minor} = 67.348$ min. $[\alpha]_D^{23} = +9.4$ (*c* 0.276, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 8.13 (d, 1H, $J = 8.1$ Hz), 7.88 (d, 1H, $J = 7.7$ Hz), 7.53–7.19 (m, 6H), 5.726 (d, $J = 5.1$ Hz, 1H), 2.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 132.6, 131.7, 129.5, 129.0, 128.4, 123.2, 121.7, 87.6, 87.4, 63.9. The racemic compound was prepared by using the same procedure as the preparation of the optically active compound except that racemic **1** was used in place of (*R*)-**1**.

4.4.4. (−)-1-(2-Nitrophenyl)-3-phenyl-prop-2-yn-1-ol.[11c,e] 77% isolated yield. 36% ee determined by HPLC analysis (Chiralcel OD-H column, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 28.442$ and $t_{minor} = 36.715$ min. $[\alpha]_D^{23} = -2.9$ (*c* 0.34, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01–7.97 (m, 2H), 7.97–7.69 (m, 1 H), 7.68–7.43 (m, 3H), 7.33–7.26 (m, 3H), 6.21 (s,

1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 133.8, 131.9, 129.6, 129.4, 128.9, 128.3, 125.1, 121.9, 86.9, 86.5, 61.9.

4.4.5. (*R*)-1-(4-Methylphenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 90% isolated yield. 60% ee as determined by HPLC analysis (Chiralcel OD-H column, 15% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 16.345$ and $t_{minor} = 28.673$ min. $[\alpha]_D^{23} = +2.2$ (c 0.452, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.37 (m, 4H), 7.24–7.22 (m, 3H), 7.16–7.11 (m, 2H), 5.56 (s, 1H), 2.28 (s, 3H), 2.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 137.8, 131.7, 129.3, 128.5, 128.3, 126.7, 122.5, 88.9, 86.5, 64.9, 21.2.

4.4.6. (*R*)-1-(3-Methylphenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 92% isolated yield. 66% ee determined by HPLC analysis (Chiralcel OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 15.545$ and $t_{minor} = 28.54$ min. $[\alpha]_D^{23} = +2.8$ (c 0.36, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.41 (m, 4H), 7.40–7.24 (m, 4H), 7.16 (d, $J = 7.4$ Hz, 1H), 5.65 (d, $J = 5.5$ Hz, 1H), 2.38 (s, 3H), 2.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 138.5, 131.8, 129.2, 128.6, 128.3, 127.4, 123.8, 122.5, 88.8, 86.6, 65.2, 21.5.

4.4.7. (*R*)-1-(2-Methylphenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 90% isolated yield. 12% ee as determined by HPLC analysis (Chiralcel OD-H column, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 19.34$ and $t_{minor} = 41.925$ min. $[\alpha]_D^{23} = -3.6$ (c 0.436, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.726 (d, $J = 3.7$ Hz, 1H), 7.708 (d, $J = 3.7$ Hz, 2H), 7.47–7.17 (m, 6H), 5.82 (s, 1H), 2.48 (s, 3H), 2.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 136.0, 131.7, 130.8, 128.5, 128.3, 126.9, 126.2, 122.5, 88.5, 86.5, 62.9, 19.0.

4.4.8. (*R*)-1-(4-Chlorophenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 96% isolated yield. 88% ee determined by HPLC analysis (Chiralcel OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 13.813$ and $t_{minor} = 29.845$ min. $[\alpha]_D^{23} = +8.5$ (c 0.4, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.26 (m, 9H), 5.66 (s, 1H), 2.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 139.2, 133.0, 131.7, 128.7, 128.5, 128.3, 128.1, 127.3, 122.2, 88.4, 86.8, 64.2.

4.4.9. (*R*)-1-(3-Chlorophenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 96% isolated yield. 89% ee determined by HPLC analysis (Chiralcel OD-H column, 15% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 16.135$ and $t_{minor} = 46.14$ min. $[\alpha]_D^{23} = +9.8$ (c 0.408, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.39 (s, 3H), 7.24–7.17 (m, 5H), 5.58 (s, 1H), 2.41 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 134.5, 131.8, 129.9, 129.7, 128.8, 128.5, 128.4, 127.6, 126.9, 124.9, 122.1, 88.0, 87.1, 64.4.

4.4.10. (−)-1-(2-Chlorophenyl)-3-phenyl-prop-2-yn-1-ol.[11d,e] 90% isolated yield. 88% ee determined by HPLC analysis (Chiralcel OD-H column, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 20.955$ and $t_{minor} = 24.5$ min. $[\alpha]_D^{20} = -31.9$ (c 0.514, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.45–7.31 (m, 8H), 6.04 (s, 1H), 2.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 131.8, 129.8, 129.7, 128.7, 128.5, 128.3, 127.3, 122.3, 87.6, 86.7, 62.5.

4.4.11. (*R*)-1-(4-Bromophenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 98% isolated yield. 89% ee determined by HPLC analysis (Chiralcel OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 14.268$ and $t_{minor} = 32.198$ min. $[\alpha]_D^{23} = +3.9$ (c 0.568, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.44 (m, 6H), 7.35–7.19 (m, 3H), 5.65 (s, 1H), 2.44 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 131.8, 131.5, 128.8, 128.4, 127.7, 122.4, 122.1, 88.2, 87.0, 64.4.

4.4.12. (*R*)-1-(4-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol.[11a] 89% isolated yield. 56% ee determined by HPLC analysis (OD-H column, 15% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 22.093$ and $t_{minor} = 42.388$ min. $[\alpha]_D^{23} = +0.9$ (c 0.442, DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.45 (m, 4H), 7.33–7.25 (m, 3H), 6.95–6.91 (m, 2H), 5.64 (s, 1H), 3.82 (s, 3H), 2.28 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 133.0, 131.7, 128.6, 128.3, 128.2, 122.5, 114.0, 113.8, 88.9, 86.5, 64.7, 55.4.

4.4.13. (*R*)-1,5-Diphenyl-pent-1-yn-3-ol.[3a] 79% isolated yield. 22% ee determined by HPLC analysis (OD-H column, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 33.655$ and $t_{minor} = 70.75$ min. $[\alpha]_D^{23} = -13.9$ (c 0.458, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.32–7.19 (m, 8H), 4.59 (t, $J = 6.6$ Hz, 1H), 2.86 (t, $J = 7.7$ Hz, 2H), 2.16–2.10 (m, 2H), 2.03 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 131.6, 129.5, 129.4, 128.4, 128.3, 128.2, 127.0, 124.3, 88.6, 86.5, 62.1, 39.8, 31.8.

4.4.14. (+)-1,4-Diphenyl-pent-1-yn-3-ol. 87% isolated yield. 20% ee determined by HPLC analysis (OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 15.87$ and $t_{minor} = 19.08$ min. $[\alpha]_D^{23} = +15.5$ (c 1.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 10H), 4.66 (dd, $J = 6.9$ Hz, $J = 9.7$ Hz, 1H), 3.17–3.09 (m, 1H), 1.46 (dd, $J = 2.6$ Hz, $J = 4.9$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 131.6, 128.9, 128.6, 128.4, 128.3, 128.2, 127.5, 127.0, 122.6, 88.6, 86.3, 67.9, 46.5, 16.8.

4.4.15. (+)-1,5-Diphenyl-pent-1-en-4-yn-3-ol.[3a] 85% isolated yield. 36% ee determined by HPLC analysis (OD-H column, 20% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention time: $t_{major} = 21.775$ and $t_{minor} = 61.163$ min. $[\alpha]_D^{23} = +0.7$ (c 0.722, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.20 (m, 10H), 6.82 (d, $J = 15.8$ Hz, 1H), 6.41–6.34 (m, 1H), 5.27 (s, 1H), 1.80 (s, 1H).

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