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Enantioselective Copper-Catalyzed Propargylic Etherification of Propargylic Esters with Phenols Promoted by Inorganic Base Additives

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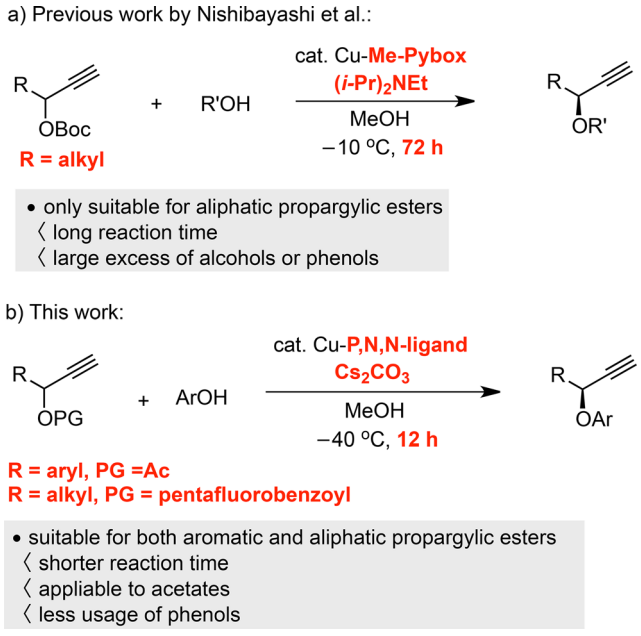
Abstract: An enantioselective copper-catalyzed propargylic etherification of both aromatic and aliphatic propargylic esters with phenols has been developed, in which the employment of inorganic base additives, in particular cesium carbonate (Cs_2CO_3), was found to significantly promote not only the reactivity but also the enantioselectivity of the reaction. By using a structurally hindered chiral ketimine P,N,N-ligand, a wide range of optically active propargylic ethers were prepared in high yields and with excellent enantioselectivities (up to 98% *ee*).

Keywords: asymmetric catalysis; copper; etherification; phenol; propargylic substitution

Catalytic asymmetric propargylic substitution, featuring metal-allenylidene complexes as the key intermediates, represents a versatile synthetic strategy for the enantioselective construction of C–C and C–heteroatom bonds.[1] In this context, the copper-catalyzed asymmetric propargylic substitution has attracted much attention since van Maarseveen[2] and Nishibayashi[3] independently reported the first copper-catalyzed asymmetric propargylic amination in 2008. To date, a variety of nitrogen and carbon nucleophiles have proved to be suitable reagents for the copper-catalyzed asymmetric propargylic substitution[4] and the related propargylic annulation.[5] In sharp contrast, oxygen nucleophiles such as alcohols and phenols had not yet been employed in the corresponding propargylic etherification until very recently. In 2015, Nishibayashi et al.[6] reported the first copper-catalyzed asymmetric propargylic etherification of propargylic carbonates with not only alcohols but also phenols as oxygen nucleophiles to give the corresponding propargylic ethers in good to high yields with a high to excellent enantioselectivity (Scheme 1a). However, only propargylic carbonates bearing an alkyl substituent at the propargylic position served as suitable substrates to the reaction, and a long reaction time was normally required to complete the reaction. The search for an alternative catalytic system with broad substrate scope, in particular with aromatic propargylic esters, for the copper-catalyzed asymmetric propargylic etherification is therefore highly desirable and remains a challenging task.

Given our recent success in the use of a chiral tridentate P,N,N-ligand for the copper-catalyzed asymmetric propargylic transformation,[4f,i–m,5b–f] we envisioned that this ligand type could also provide a pow-



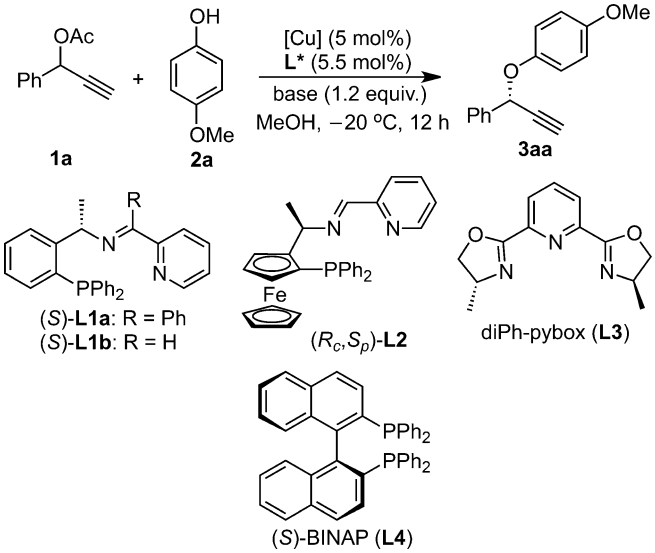
Scheme 1. Copper-catalyzed asymmetric propargylic etherification.

erful solution to the copper-catalyzed asymmetric propargylic etherification of propargylic esters, in particular aromatic propargylic esters. As a result, herein we report a highly enantioselective and efficient copper-catalyzed propargylic etherification of both aromatic and aliphatic propargylic esters with phenols as oxygen nucleophiles. In this reaction, inorganic base additives, in particular Cs_2CO_3, were found to significantly promote not only the reaction rate but also the enantioselectivity, and a structurally rigid tridentate ketimine P,N,N-ligand was identified as the best choice. This method provides an efficient access to a variety of optically active propargylic aryl ethers with high enantioselectivities (up to 98% *ee*).

We commenced our study with the examination of the reaction of 1-phenylprop-2-yn-1-yl acetate (**1a**) with 4-methoxyphenol (**2a**) in the presence of a structurally hindered P,N,N-ligand (*S*)-**L1a** and $(i\text{-Pr})_2$NEt, the best combination in Cu-catalyzed asymmetric propargylic transformations used by us previously.[4,5] Unfortunately, very poor result was achieved when the reaction was performed at room temperature (Table 1, entry 1), where a complex mixture was achieved besides the desired propargylic ether **3aa**. The presence of some competitive side reactions such as Friedel–Crafts alkylation, cycloaddition and so on could be responsible for this poor result. We surmised that lowering the reaction temperature may suppress these side reactions. In fact, increased yields and enantioselectivity were observed on lowering the reaction temperature to 0 °C, although the result was still far from satisfactory (entries 2 and 3). With other organic bases such as Et_3N, much worse performance was achieved even at −20 °C (entry 4). To our delight, we found that the introduction of inorganic bases additives into the present catalytic system could significantly promote the reaction rate and enantioselectivity (entries 5–8). In particular, when Cs_2CO_3 was used instead of $(i\text{-Pr})_2$NEt, excellent performance (87% yield and 95% *ee*) was achieved (entry 8). We speculated that the irreversible deprotonation with Cs_2CO_3 by loss of CO_2 accelerated the reaction. However, the exact reason for this promotion remains unclear. As a comparison, we also examined some other ligands including Me-Pybox that proved to be efficient in the etherification of aliphatic propargylic esters reported by Nishibayashi very recently,[6] however, poor results were achieved (entries 9–12). Copper salts displayed less influence on the reaction outcomes, in all cases, good performance was achieved with CuOTf·1/2 C_6H_6 identified as the best choice (entries 13–15). Lowering the reaction temperature to −40 °C further improved the reaction performance to afford 92% yield and 96% *ee* (entry 16).

Under the optimized reaction conditions, the scope of propargylic esters for the catalytic asymmetric etherification with phenol **2a** was first examined, and the results are summarized in Table 2. The results disclosed that the present catalytic system was highly efficient for the aromatic propargylic acetates, providing the corresponding propargylic ethers in high yields with good to excellent enantioselectivities. The substitution pattern of the functionality on the phenyl ring was well tolerated, thus, all three substrates bearing a Cl group on the different positions of the phenyl ring gave similarly high performances (entries 2–4).

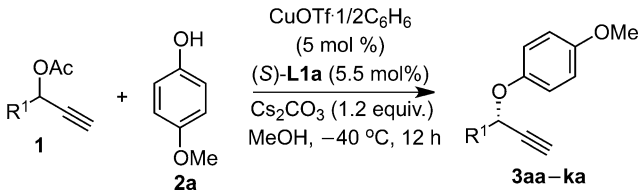
Table 1. Optimization of the reaction conditions.[a]



Entry	[Cu]	L*	Base	Yield [%][b]	*ee* [%][c]
1[d]	$Cu(OAc)_2·H_2O$	**L1a**	$(i\text{-Pr})_2$NEt	45	7
2[e]	$Cu(OAc)_2·H_2O$	**L1a**	$(i\text{-Pr})_2$NEt	73	44
3	$Cu(OAc)_2·H_2O$	**L1a**	$(i\text{-Pr})_2$NEt	77	78
4	$Cu(OAc)_2·H_2O$	**L1a**	Et_3N	24	<5
5	$Cu(OAc)_2·H_2O$	**L1a**	K_3PO_4	84	88
6	$Cu(OAc)_2·H_2O$	**L1a**	Na_2CO_3	80	88
7	$Cu(OAc)_2·H_2O$	**L1a**	K_2CO_3	85	91
8	$Cu(OAc)_2·H_2O$	**L1a**	Cs_2CO_3	87	95
9	$Cu(OAc)_2·H_2O$	**L1b**	Cs_2CO_3	85	84
10	$Cu(OAc)_2·H_2O$	**L2**	Cs_2CO_3	43	50
11	$Cu(OAc)_2·H_2O$	**L3**	Cs_2CO_3	39	68
12	$Cu(OAc)_2·H_2O$	**L4**	Cs_2CO_3	18	65
13	$Cu(OTf)_2$	**L1a**	Cs_2CO_3	80	92
14	CuCl	**L1a**	Cs_2CO_3	84	94
15	CuOTf·1/2 C_6H_6	**L1a**	Cs_2CO_3	90	95
16[f]	CuOTf·1/2 C_6H_6	**L1a**	Cs_2CO_3	92	96

[a] The reaction was carried out using **1a** (0.3 mmol), **2a** (0.36 mmol), [Cu] (0.015 mmol, 5 mol%), **L*** (0.0165 mmol, 5.5 mol%), base (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at −20 °C for 12 h unless otherwise noted.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Performed at room temperature.
[e] Performed at 0 °C.
[f] Performed at −40 °C.

Table 2. Substrate scope of propargylic esters.[a]

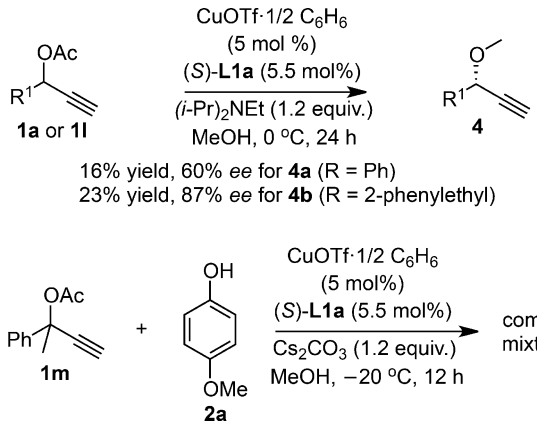


Entry	1 (R^1)	3	Yield [%][b]	*ee* [%][c]
1	**1a**: R^1 = Ph	**3aa**	92	96
2	**1b**: R^1 = 2-ClC_6H_4	**3ba**	93	90
3	**1c**: R^1 = 3-ClC_6H_4	**3ca**	87	94
4	**1d**: R^1 = 4-ClC_6H_4	**3ad**	85	96
5	**1e**: R^1 = 4-FC_6H_4	**3ea**	90	95
6	**1f**: R^1 = 4-BrC_6H_4	**3fa**	83	96
7	**1g**: R^1 = 4-MeC_6H_4	**3ga**	92	95
8	**1h**: R^1 = 4-$MeOC_6H_4$	**3ha**	86	84
9	**1i**: R^1 = 2-naphthyl	**3ia**	87	91
10[d]	**1j**: R^1 = Me	**3ja**	91	98
11[d]	**1k**: R^1 = Bn	**3ka**	88	98

[a] The reaction was carried out using **1** (0.3 mmol), **2a** (0.36 mmol), CuOTf·1/2 C_6H_6 (0.015 mmol, 5 mol%), (*S*)-**L1a** (0.0165 mmol, 5.5 mol%), Cs_2CO_3 (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at −40 °C for 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Pentafluorobenzoates were used instead of the corresponding acetates.

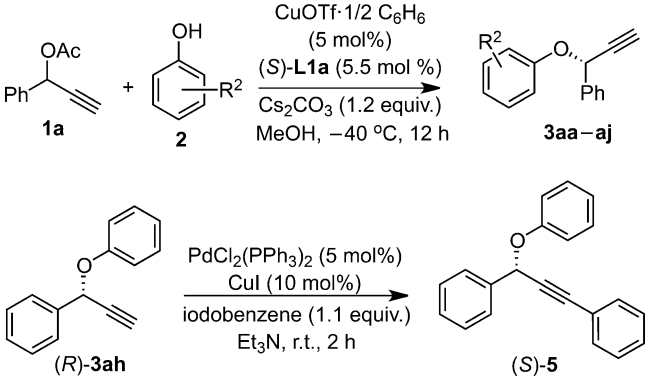
The reaction was some sensitive to the electronic property of the substituent on the phenyl ring. For example, a 4-methoxy group on the phenyl ring led to a decrease in enantioselectivity to 84% *ee* (entry 8). To our delight, the catalytic system was also highly effective for aliphatic substrates, giving rise to the corresponding propargylic ethers in high yields and with up to 98% *ee* although pentafluorobenzoates were used instead of the corresponding acetates in these cases (entries 10 and 11). However, the present catalytic system was less efficient in the reaction of both aromatic and aliphatic acetates with alcohols, such as methanol, giving methyl propargylic ethers **4a** and **4b** in only low yields. The reaction did not tolerate the tertiary propargylic acetate **1m**, leading to a complex mixture (Scheme 2).

The scope of the catalytic propargylic etherification with regard to phenols was next investigated, and the results are listed in Table 3. The reaction proceeded smoothly for all substrates, giving the corresponding propargylic ethers in good results. The substitution pattern showed some influence on the reactivity (entries 2–4). With the substrate **2d** bearing a 2-methyl group, a decreased yield of 78% was achieved but with maintained enantioselectivity of 96% *ee* (entry 4). The results indicated that an electron-withdrawing group on the substrates led to decreased enantioselectivity. Thus, the substrate with a Cl (**2i**) or



Scheme 2. Reactions of methanol and tertiary propargylic acetate.

Table 3. Substrate scope of phenols.[a]



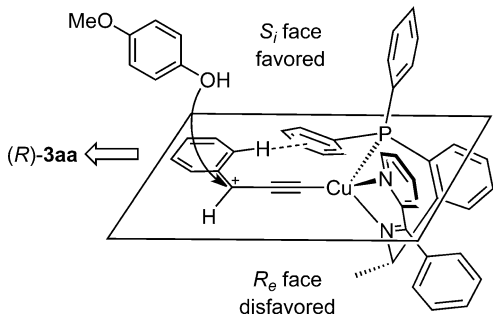
Entry	2 (R^2)	3	Yield [%][b]	*ee* [%][c]
1	**2a**: R^2 = 4-OMe	**3aa**	92	96
2	**2b**: R^2 = 4-Me	**3ab**	98	95
3	**2c**: R^2 = 3-Me	**3ac**	83	93
4[e]	**2d**: R^2 = 2-Me	**3ad**	78	96
5	**2e**: R^2 = 4-NHAc	**3ae**	87	95
6	**2f**: R^2 = 4-NMe_2	**3af**	85	94
7[e]	**2g**: R^2 = 4-OH	**3ag**	81	93
8	**2h**: R^2 = H	**3ah**	86	95 (*R*)[d]
9	**2i**: R^2 = 4-Cl	**3ai**	95	83
10[f]	**2j**: R^2 = 4-F	**3aj**	87	86

[a] The reaction was carried out using **1a** (0.3 mmol), **2** (0.36 mmol), CuOTf·1/2 C_6H_6 (0.015 mmol, 5 mol%), (*S*)-**L1a** (0.0165 mmol, 5.5 mol%), Cs_2CO_3 (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at −40 °C for 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The absolute configuration of **3ah** was determined by comparison with the known compound **5** after derivatization.
[e] 24 h.
[f] −20 °C.

F group (**2j**) gave lower enantioselectivity in comparison with those bearing an electron-donating group

(entries 9–10 *vs.* entries 1–7). The absolute configuration of the propargylic ether **3ah** was determined by the comparison with the known compound **5**[7] after the derivatization as shown in Table 3, to which an *R*-configuration was assigned (entry 8).

A preformed catalyst, prepared from the reaction of CuOTf·1/2 C_6H_6 and (*S*)-**L1a** according to Nishibayashi's method for the dinuclear copper-pybox complex,[6] was submitted to the reaction. However, no expected reaction was detected, suggesting that the reactive species with the present catalytic system may not be the dinuclear copper complex as in Nishibayashi's catalytic system. An attempt to detect the formation of a Cu-allenylidene complex by IR failed. Based on the experimental results and an edge-to-face aromatic interaction[8] between a phenyl group of the substrate and a phenyl group of the ligand, a transition state of Cu-acetylide complex with chiral P,N,N-ligand (*S*)-**L1a**, is proposed to explain the observed stereochemistry as shown in Scheme 3. Due to the steric hindrance of the ligand, the attack of the γ-carbon atom by the oxygen atom of hydroxy group on **2a** happened favorably from the S_i face to form (*R*)-**3aa** while the R_e face was hampered.



Scheme 3. Proposed stereochemical pathway.

In conclusion, we have developed an efficient and highly enantioselective copper-catalyzed propargylic etherification of both aliphatic and aromatic propargylic esters with phenols as oxygen nucleophiles. The present study disclosed that the use of inorganic base additives, in particular Cs_2CO_3 instead of organic bases such as $(i\text{-Pr})_2$NEt significantly increased the reaction rate and enantioselectivity presumably due to the irreversible deprotonation by loss of CO_2 during the reaction. With a structurally rigid chiral tridentate ketimine P,N,N-ligand, a variety of aryl propargylic ethers could be prepared in good to high yields with a high to excellent enantioselectivity (up to 98% *ee*). However, the present catalytic system didn't tolerate tertiary propargylic acetates and alcohols as the reaction partners.

Experimental Section

General Remarks

^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.26$ or DMSO, $\delta = 2.50$). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (101 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, $\delta = 77.0$ or DMSO, $\delta = 39.60$). The enantiomeric excesses (*ee*) were determined by HPLC analysis on commercial chiral columns. Optical rotations were reported as follows: $[\alpha]_D^T$ (c = g/100 mL, in solvent). HR-MS were recorded on a commercial apparatus (ESI source). All reagents and solvents were obtained from commercial suppliers and used without further purification except as indicated below. All catalytic reactions were run in dried Schlenk tubes under a nitrogen atmosphere and the solvents were purified by standard procedures before use.

General Procedure for Cu-Catalyzed Asymmetric Propargylic Etherification

A solution of CuOTf·1/2 C_6H_6 (7.6 mg, 0.015 mmol) and (*S*)-**L1a** (7.8 mg, 0.0165 mmol) in 1 mL of anhydrous methanol placed in an oven-dried Schlenk flask was stirred at room temperature under a nitrogen atmosphere for 1 h. The reaction mixture was then cooled to −40 °C, and a solution of propargylic ester **1** (0.3 mmol) in 2 mL of anhydrous methanol, phenol **2** (0.36 mmol) and Cs_2CO_3 (117.3 mg, 0.36 mmol) were added successively. After being stirred at −40 °C for 12 h, the reaction mixture was concentrated under vacuum, and the residue was purified by silica gel chromatography to afford the desired product **3**.

(*R*)-1-Chloro-2-[1-(4-methoxyphenoxy)prop-2-yn-1-yl]-benzene (3ba): White solid; mp 26–28 °C); yield: 76.4 mg (93%); 90% *ee*; $[\alpha]_D^{23}$: −85.8 ($c = 1.00$ in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 12.3 min, t_2 (minor) = 13.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 7.4$ Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.34–7.26 (m, 2H), 7.03 (d, $J = 8.9$ Hz, 2H), 6.83 (d, $J = 8.9$ Hz, 2H), 6.10 (s, 1H), 3.73 (s, 3H), 2.66 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 154.9$, 151.3, 135.3, 133.2, 130.2, 129.7, 129.1, 127.4, 117.8, 114.6, 80.5, 76.5, 68.1, 55.6; HR-MS: $m/z = 273.0673$, calcd. for $C_{16}H_{14}ClO_2$ $[M+H]^+$: 273.0682.

(*R*)-1-Chloro-3-[1-(4-methoxyphenoxy)prop-2-yn-1-yl]-benzene (3ca): Pale yellow solid; mp 28–30 °C; yield: 71.1 mg (87%); 94% *ee*; $[\alpha]_D^{20}$: −73.7 ($c = 1.00$ in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 8.0 min, t_2 (minor) = 8.8 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$ (s, 1H), 7.39–7.38 (m, 1H), 7.24 (dd, J = 4.9, 1.5 Hz, 2H), 6.93–6.91 (m, 2H), 6.78–6.74 (m, 2H), 5.61 (d, $J = 1.9$ Hz, 1H), 3.68 (s, 3H), 2.61 (d, $J = 2.1$ Hz, 1H);

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 151.1, 139.6, 134.6, 123.0, 129.0, 127.5, 125.4, 117.9, 114.6, 80.7, 77.0, 70.4, 55.7; HR-MS: m/z = 273.0656, calcd. for $C_{16}H_{14}ClO_2$ $[M+H]^+$: 273.0682.

(*R*)-1-Chloro-4-[1-(4-methoxyphenoxy)prop-2-yn-1-yl]-benzene (3da): Pale yellow solid; mp 62–64 °C; yield: 71.1 mg (85%); 96% *ee*; $[\alpha]_D^{20}$: −60.9 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralpak AS-H, *n*-hexane/*i*-PrOH = 85/15, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 18.8 min, t_2 (minor) = 26.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.68 (d, J = 1.7 Hz, 1H), 3.74 (s, 3H), 2.68 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 151.2, 136.2, 134.7, 128.9, 128.7, 117.9, 114.6, 80.9, 76.9, 70.4, 55.7; HR-MS: m/z = 273.0668, calcd. for $C_{16}H_{14}ClO_2$ $[M+H]^+$: 273.0682.

(*R*)-1-Fluoro-4-[1-(4-methoxyphenoxy)prop-2-yn-1-yl]-benzene (3ea): White solid; mp 52–54 °C; yield: 69.1 mg (90%); 95% *ee*; $[\alpha]_D^{23}$: −72.9 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralpak AS-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (minor) = 30.1 min, t_2 (major) = 32.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 8.5, 5.4 Hz, 2H), 7.07 (t, J = 8.7 Hz, 2H), 7.01–6.99 (m, 2H), 6.84–6.82 (m, 2H), 5.69 (d, J = 1.7 Hz, 1H), 3.75 (s, 3H), 2.68 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.0 (d, J = 247.5 Hz), 154.9, 151.2, 133.5 (d, J = 3.2 Hz), 129.3 (d, J = 8.4 Hz), 117.9, 115.6 (d, J = 21.7 Hz), 114.6, 81.1, 76.8, 70.5, 55.6; HR-MS: m/z = 257.0970, calcd. for $C_{16}H_{14}FO_2$ $[M+H]^+$: 257.0978.

(*R*)-1-Bromo-4-[1-(4-methoxyphenoxy)prop-2-yn-1-yl]-benzene (3fa): Pale yellow solid; mp 52–54 °C; yield: 79.0 mg (83%); 96% *ee*; $[\alpha]_D^{20}$: −73.7 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 8.3 min, t_2 (minor) = 10.2 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.66 (d, J = 1.5 Hz, 1H), 3.73 (s, 3H), 2.67 (d, J = 1.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 151.2, 136.7, 131.8, 129.0, 122.9, 117.9, 114.6, 80.8, 77.0, 70.5, 55.7; HR-MS: m/z = 338.9999, calcd. for $C_{16}H_{13}BrNaO_2$ $[M+Na]^+$: 338.9997.

(*R*)-1-Methoxy-4-{[1-(*p*-tolyl)prop-2-yn-1-yl]oxy}benzene (3ga): White solid; mp 30–32 °C; yield: 69.8 mg (92%); 95% *ee*; $[\alpha]_D^{22}$: −53.5 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 7.8 min, t_2 (minor) = 9.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 9.1 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 5.68 (d, J = 1.7 Hz, 1H), 3.73 (s, 3H), 2.65 (d, J = 2.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 151.5, 138.7, 134.8, 129.4, 127.4, 117.8, 114.5, 81.5, 76.4, 71.0, 55.7, 21.3; HR-MS: m/z = 253.1236, calcd. for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1229.

(*R*)-2-[1-(4-Methoxyphenoxy)prop-2-yn-1-yl]naphthalene (3ia): White solid; mp: 58–60 °C; yield: 75.1 mg (87%); 91% *ee*; $[\alpha]_D^{21}$: −27.4 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 98/2, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 17.3 min, t_2 (minor) = 19.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.88–7.81 (m, 3H), 7.69 (d, J = 8.5 Hz, 1H), 7.49–7.47 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.88 (s, 1H), 3.73 (s, 3H), 2.72 (d, J = 1.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8, 151.4, 135.0, 133.5, 133.2, 128.7, 128.4, 127.8, 126.6, 126.5, 126.4, 125.0, 118.0, 114.6, 81.3, 76.9, 71.3, 55.7; HR-MS: m/z = 289.1241, calcd. for $C_{20}H_{17}O_2$ $[M+H]^+$: 289.1229.

(*R*)-1-Methyl-3-[(1-phenylprop-2-yn-1-yl)oxy]benzene (3ac): Yellow oil; yield: 55.5 mg (83%); 93% *ee*; $[\alpha]_D^{20}$: −99.5 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 99/1, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 10.0 min, t_2 (minor) = 16.5 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 7.4 Hz, 2H), 7.33–7.26 (m, 3H), 7.11–7.07 (m, 1H), 6.82–8.80 (m, 2H), 6.73 (d, J = 7.3 Hz, 1H), 5.72 (s, 1H), 2.58 (d, J = 1.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 139.6, 137.6, 129.2, 128.9, 128.8, 127.3, 122.7, 117.1, 112.9, 81.2, 76.6, 69.8, 21.6; HR-MS: m/z = 223.1116, calcd. for $C_{16}H_{15}O$ $[M+H]^+$: 223.1123.

(*R*)-*N*-{4-[(1-Phenylprop-2-yn-1-yl)oxy]phenyl}acetamide (3ae): Pale yellow solid; mp 90–92 °C; yield: 68.9 mg (87%); 95% *ee*; $[\alpha]_D^{20}$: −68.7 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralpak AS-H, *n*-hexane/*i*-PrOH = 70/30, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 15.0 min, t_2 (minor) = 23.6 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H), 7.58 (d, J = 6.8 Hz, 2H), 7.41–7.33 (m, 5H), 6.99 (d, J = 8.9 Hz, 2H), 5.76 (d, J = 1.9 Hz, 1H), 2.68 (d, J = 2.1 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.9, 154.0, 137.3, 132.3, 128.9, 128.8, 127.3, 121.9, 116.7, 81.0, 76.9, 70.4, 24.2; HR-MS: m/z = 266.1181, calcd. for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181.

(*R*)-*N*,*N*-Dimethyl-4-[(1-phenylprop-2-yn-1-yl)oxy]aniline (3af): Yellow oil; yield: 64.1 mg (85%); 94% *ee*; $[\alpha]_D^{20}$: −70.2 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH = 85/15, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 6.7 min, t_2 (minor) = 7.4 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.5 Hz, 2H), 7.41–7.34 (m, 3H), 7.00 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 5.70 (s, 1H), 2.86 (s, 6H), 2.66 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.4, 146.6, 137.9, 128.7, 128.7, 127.4, 117.9, 114.2, 81.6, 76.4, 71.3, 41.5; HR-MS: m/z = 252.1388, calcd. for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388.

(*R*)-4-[(1-Phenylprop-2-yn-1-yl)oxy]phenol (3ag): Colorless oil; yield: 54.4 mg (81%); 93% *ee*; $[\alpha]_D^{20}$: −55.8 (c = 0.50 in CH_2Cl_2); HPLC (Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 30.6 min, t_2 (minor) = 32.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 7.4 Hz, 2H), 7.42–7.36 (m, 3H), 6.96 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 5.71 (s, 1H), 4.77 (s, 1H), 2.68 (d, J = 1.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.4, 150.6, 137.6, 128.9, 128.7, 127.4, 118.1, 116.0, 81.2, 76.6, 71.2; HR-MS: m/z = 247.0735, calcd. for $C_{15}H_{12}NaO_2$ $[M+Na]^+$: 247.0735.

(*R*)-1-Fluoro-4-[(1-phenylprop-2-yn-1-yl)oxy]benzene (3aj): Pale yellow oil; yield: 59.0 mg (87%); 86% *ee*; $[\alpha]_D^{23}$: −74.7 (c = 1.00 in CH_2Cl_2); HPLC (Daicel chiralpak AS-H, *n*-hexane/*i*-PrOH = 99/1, flow rate 0.8 mL min^{-1}, λ = 230 nm, 40 °C): retention time: t_1 (major) = 13.0 min, t_2 (minor) = 14.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 6.9 Hz, 2H), 7.35–7.26 (m, 3H), 6.95–6.87 (m, 4H), 5.66 (d, J = 1.8 Hz, 1H), 2.60 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.0 (d, J = 239.7 Hz), 153.4 (d, J = 2.2 Hz), 137.2, 129.0, 128.8, 127.4, 117.8 (d, J = 8.0 Hz), 115.9

(d, $J=23.1$ Hz), 80.9, 76.9, 70.9; HR-MS: $m/z=227.0877$, calcd. for $C_{15}H_{12}FO$ $[M+H]^+$: 227.0872.

Procedure for Sonogashira Cross-Coupling of 3ah with PhI for the Synthesis of 5[7]

A solution of CuI (4.6 mg, 0.024 mmol), $PdCl_2(PPh_3)_2$ (8.4 mg, 0.012 mmol), PhI (53.0 mg, 0.26 mmol) and (*R*)-**3ah** (50.0 mg, 0.24 mmol) in 3 mL of Et_3N placed in an oven-dried Schlenk flask was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated under vacuum, and the residue was purified by silica gel chromatography to afford the desired product (*S*)-(3-phenoxyprop-1-yne-1,3-diyl)dibenzene (**5**)[7] as a pale yellow solid; yield: 55.2 mg (65%); mp 46–48 °C); 95% *ee*; $[\alpha]_D^{20}$: −76.5 ($c=1.00$ in CH_2Cl_2); HPLC (Daicel chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90/10, flow rate 0.8 mL min^{-1}, $\lambda=254$ nm, 40 °C): retention time: t_1 (minor) = 21.3 min, t_2 (major) = 26.4 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$ (d, $J=7.3$ Hz, 2H), 7.35–7.28 (m, 5H), 7.25–7.19 (m, 5H), 7.06 (d, $J=8.1$ Hz, 2H), 6.92 (t, $J=7.3$ Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=157.7$, 138.1, 131.9, 129.5, 128.8, 128.8, 128.3, 127.5, 122.3, 121.7, 116.4, 88.5, 86.4, 70.8.

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