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Cu-Catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenol derivatives†

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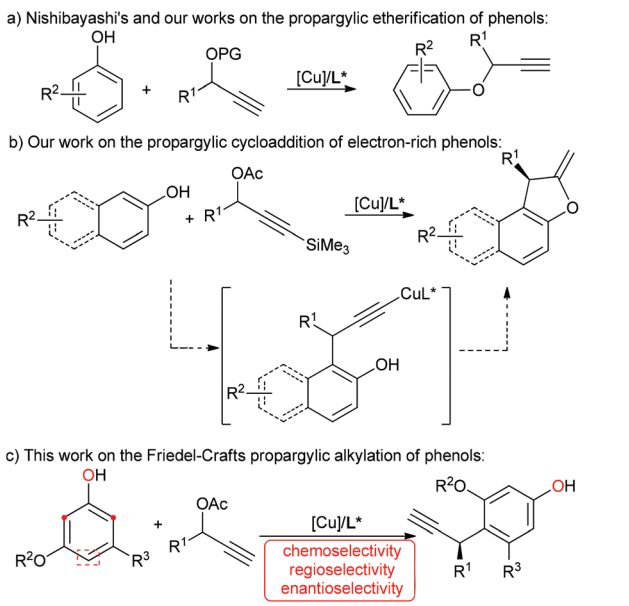
A copper-catalyzed asymmetric Friedel–Crafts propargylic alkylation of electron-rich phenol derivatives with a variety of propargylic esters has been described. With $Cu(OTf)_2$ decorated with a chiral tridentate ketimine P,N,N-ligand as the catalyst, asymmetric Friedel–Crafts propargylic alkylation of 3,5-dialkoxyphenol derivatives proceeded smoothly in high yields and with good to excellent enantioselectivities. The present study suggested that the presence of an electron-rich substituent on the *meta*-position of phenol is essential for the promotion of Friedel–Crafts propargylic alkylation, and the substrate bearing two electron-rich groups on both the 3,5-positions of phenol tends to give a satisfactory performance.

Introduction

Since van Maarseveen[1] and Nishibayashi[2] reported the first Cu-catalyzed asymmetric propargylic amination in 2008, copper-catalyzed asymmetric propargylic transformation,[3] featuring Cu-allenylidene complexes as the key intermediates, has attracted increasing attention due to its high potential in the enantioselective formation of C–C and C–heteroatom bonds[4] and the stereoselective construction of complex cyclic frameworks.[5] In the past decade, many C-, N-, and O-nucleophiles have proved to be suitable reaction partners for this important transformation. However, Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation with electron-rich aromatic compounds as C-nucleophiles remains less successful although catalytic asymmetric Friedel–Crafts alkylation has made significant achievements in the past few decades.[6] To our knowledge, only one example has been reported by van Maarseveen recently, in which a Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation of indole has been described.[7] However, Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenol derivatives is still unexplored. There is therefore an urgent need for the development of Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenol derivatives.

The challenge for the realization of Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenols is obvious since phenols readily underwent the propargylic *O*-alkylation with propargylic esters in the presence of a copper catalyst as reported by Nishibayashi's group and us (Scheme 1a).[8] Very recently, we disclosed a copper-catalyzed sequential Friedel–Crafts alkylation/intramolecular hydroalkoxylation process between electron-rich phenols and propargylic esters.[9] This reaction suggested that the development of a copper-catalyzed Friedel–Crafts propargylic alkylation should be possible if the last hydroalkoxylation process can be efficiently interrupted (Scheme 1b). Undoubtedly, if a Friedel–Crafts propargylic alkylation is controlled to take place at the *para*-position of phenol, the intramolecular hydroalkoxylation would be completely inhibited. Indeed, this strategy has been successfully employed by us in the Cu-catalyzed asymmetric



Scheme 1 Cu-Catalyzed asymmetric transformation between phenols and propargylic esters.

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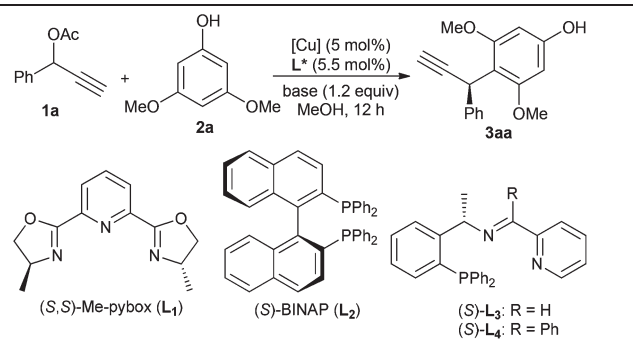
propargylic dearomatization of phenols very recently.[10] As part of our ongoing interest in the development of Cu-catalyzed asymmetric propargylic transformation, we herein wished to report our detailed studies on the copper-catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenols.

Results and discussion

We started our investigation by screening a series of chiral ligands for the model reaction of 1-phenyl-2-propynyl acetate **1a** with 3,5-dimethoxyphenol **2a** in methanol at room temperature in the presence of $Cu(OAc)_2{\cdot}H_2O$ and $^iPr_2NEt$, and the results are summarized in Table 1. 3,5-Dimethoxyphenol **2a** was selected as the standard substrate to examine the possibility of the Friedel–Crafts propargylic alkylation since we have recently disclosed that electron-rich phenols preferentially underwent the Friedel–Crafts-type reaction and the dearomatization reaction rather than the propargylic *O*-alkylation. Pleasingly, the ligand screening disclosed that the Friedel–Crafts propargylic alkylation took place smoothly by the use of chiral tridentate P,N,N-ligands developed within our group, in which the ketimine P,N,N-ligand (*S*)-**L$_4$** was identified as the most promising ligand in terms of yield and enantioselectivity (entries 1–4). A brief base-additive screening revealed that K_2CO_3 was the best base-additive for this transformation, affording **3aa** in 93% yield and with 87% ee (entries 4–8). The result also indicated that the base-additive was necessary for this transformation since very low conversion was observed in its absence (entry 9). Cu salts showed less influence on the reactivity and enantioselectivity. All of the Cu salts tested gave similar performance to that with $Cu(OAc)_2{\cdot}H_2O$. Lowering the reaction temperature could further improve the reaction performance, in which $Cu(OTf)_2$ displayed the best catalytic activity and enantioselectivity. In particular, when the reaction was performed at −20 °C, Friedel–Crafts propargylic alkylation product **3aa** could be obtained in 96% yield and with 93% ee (entry 16).

With the optimized reaction conditions in hand, we proceeded to investigate the applicability of propargylic acetates **1** in the Friedel–Crafts propargylic alkylation of 3,5-dimethoxyphenol **2a**, and the results are summarized in Table 2. In all cases, only Friedel–Crafts propargylic alkylation products were observed. These results indicated that the reaction was sensitive to the substitution pattern on the phenyl ring. Thus, the reactions with 3-Cl or 4-Cl substituted propargylic acetates (**1c** and **1d**) proceeded smoothly to give the desired products (**3ca** and **3da**) in high yields and with excellent enantioselectivities (95% and 92% ee, respectively) (entries 2 and 3), while the substrate **1b** with a 2-Cl substituent led to an obvious decrease in the enantioselectivity to 76% ee although good yield (86%) was maintained (entry 1). The electronic properties of the substituent at the *para*-position of the phenyl ring showed little influence on the reactivity and enantioselectivity, and all substrates **1d–i** gave rise to the corresponding Friedel–Crafts

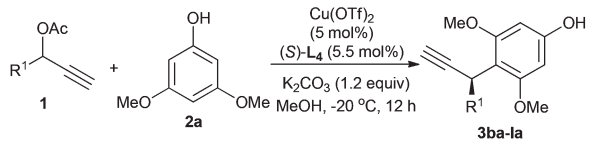
Table 1 Optimization of the reaction conditions[a]



Entry	[Cu]	L	Base	T (°C)	Yield[b] (%)	ee[c] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	**L$_1$**	$^iPr_2NEt$	rt	—	—
2	$Cu(OAc)_2{\cdot}H_2O$	**L$_2$**	$^iPr_2NEt$	rt	16	12
3	$Cu(OAc)_2{\cdot}H_2O$	**L$_3$**	$^iPr_2NEt$	rt	51	62
4	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	$^iPr_2NEt$	rt	82	87
5	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	DBU	rt	63	86
6	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	NEt_3	rt	55	87
7	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	K_2CO_3	rt	93	87
8	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	Cs_2CO_3	rt	66	84
9	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	—	rt	<10	—
10	$Cu(MeCN)_4BF_4$	**L$_4$**	K_2CO_3	rt	82	85
11	CuCl	**L$_4$**	K_2CO_3	rt	87	87
12	$Cu(OTf)_2$	**L$_4$**	K_2CO_3	rt	84	88
13	$Cu(OAc)_2{\cdot}H_2O$	**L$_4$**	K_2CO_3	0	87	91
14	CuCl	**L$_4$**	K_2CO_3	0	82	90
15	$Cu(OTf)_2$	**L$_4$**	K_2CO_3	0	93	91
16	$Cu(OTf)_2$	**L$_4$**	K_2CO_3	−20	96	93

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [Cu] (0.015 mmol, 5 mol%), **L*** (0.0165 mmol, 5.5 mol%), and base (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at indicated reaction temperature for 12 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase.

Table 2 Scope with respect to propargylic acetates[a]



Entry	Substrate (R^1)	Product (**3**)	Yield[b] (%)	ee[c] (%)
1	**1b**: R^1 = 2-ClC_6H_4	**3ba**	86	76
2	**1c**: R^1 = 3-ClC_6H_4	**3ca**	89	95
3	**1d**: R^1 = 4-ClC_6H_4	**3da**	88	92
4	**1e**: R^1 = 4-FC_6H_4	**3ea**	90	90
5	**1f**: R^1 = 4-BrC_6H_4	**3fa**	86	92
6	**1g**: R^1 = 4-MeC_6H_4	**3ga**	93	93
7	**1h**: R^1 = 4-$MeOC_6H_4$	**3ha**	86	87
8	**1i**: R^1 = 4-$CF_3C_6H_4$	**3ia**	87	92
9	**1j**: R^1 = 2-naphthyl	**3ja**	84	93
10	**1k**: R^1 = 2-thienyl	**3ka**	84	91
11[d]	**1l**: R^1 = Bn	**3la**	39	72

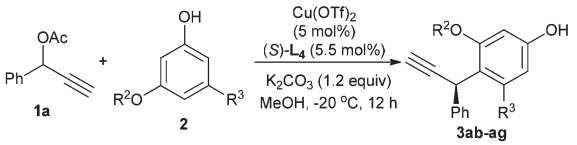
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol, 5 mol%), (*S*)-**L$_4$** (0.0165 mmol, 5.5 mol%), and K_2CO_3 (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at −20 °C for 12 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] The corresponding pentafluorobenzoate was used instead of acetate.

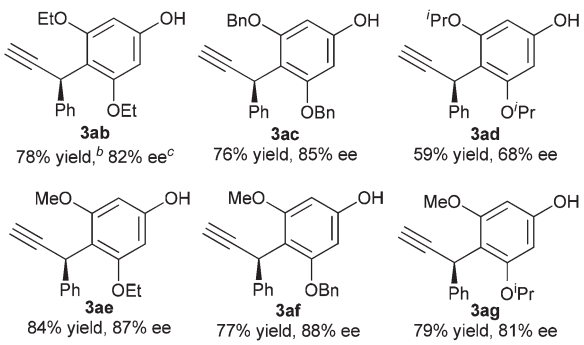
propargylic alkylation products **3da–ia** in good yields (86–93% yield) and with good enantioselectivities (87–93% ee) (entries 3–8). 2-Naphthyl-substituted substrate **1j** served as a suitable reaction partner, giving **3ja** in 84% yield and with 93% ee (entry 9). 2-Thienyl substituted heterocyclic substrate **1k** also worked well for the reaction, producing **3ka** in 83% yield and with 91% ee (entry 10). However, aliphatic substrate **1l** proved to be less suitable for the reaction, with which only low yield and moderate enantioselectivity were obtained (entry 11).

Table 3 shows the scope and limitation with regard to phenol derivatives that underwent the Friedel–Crafts propargylic alkylation. In general, the presence of the alkoxy group on both the 3,5-positions of phenols tended to give satisfactory yield and enantioselectivity, in which only Friedel–Crafts propargylic alkylation products were observed. However, the increased steric hindrance of the alkoxy group significantly decreased the reactivity and enantioselectivity of Friedel–Crafts propargylic alkylation. Thus, 3,5-diisopropoxyphenol **2d** led to the corresponding Friedel–Crafts propargylic alkylation product in 59% yield and with 68% ee. Different alkoxy groups on the 3,5-positions of phenols were well tolerated, and the corresponding Friedel–Crafts propargylic alkylation products (**3ae–ag**) were obtained in good yields (77–84%) and with good enantioselectivities (81–88% ee). However, when 3,5-dimethoxyaniline was used as the substrate, no Friedel–Crafts propargylic alkylation product was detected.

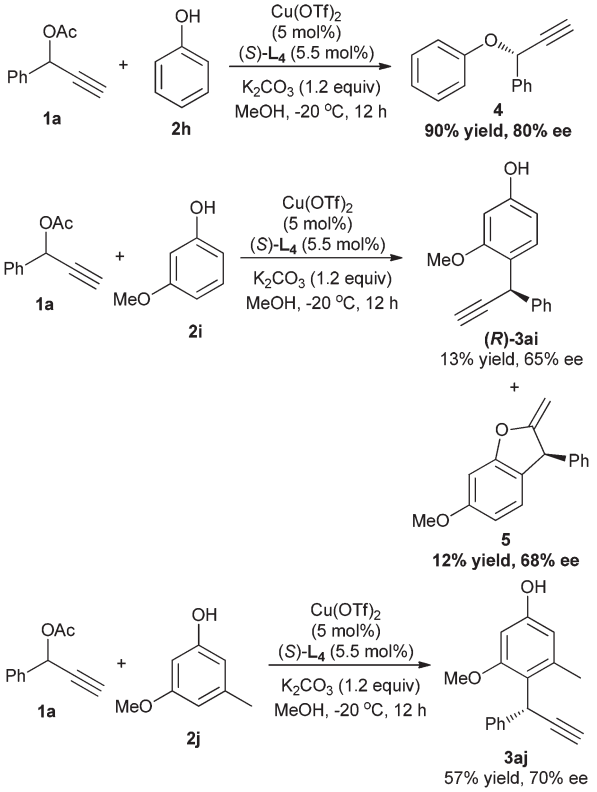
To investigate the role of the substituent on phenols, some control experiments were performed as shown in Scheme 2. With phenol as the substrate, only *O*-alkylation product **4** was observed. The introduction of a methoxy group at the *meta*-position of phenol significantly inhibited the propargylic

Table 3 Scope with respect to phenol derivatives[a]





[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $Cu(OTf)_2$ (0.015 mmol, 5 mol%), (*S*)-**L**$_4$ (0.0165 mmol, 5.5 mol%), and K_2CO_3 (0.36 mmol, 1.2 equiv.) in 3 mL of MeOH at −20 °C for 12 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase.



Scheme 2 The substituent effect in the Cu-catalyzed asymmetric transformation between phenols and propargylic esters.

O-alkylation, promoting the Friedel–Crafts propargylic alkylation at the *para*-position and the sequential Friedel–Crafts alkylation/intramolecular hydroalkoxylation at the *ortho*-position. Further introduction of an electron-rich group at the 5-position of **2i** led to the Friedel–Crafts propargylic alkylation as the only observed reaction. Thus, 3-methoxy-5-methylphenol **2j** gave the Friedel–Crafts propargylic alkylation product **3aj** in 57% yield and with 70% ee. These results suggested that the presence of electron-rich substituents on the 3,5-positions of phenol should be necessary to efficiently promote the Friedel–Crafts propargylic alkylation of phenol. The absolute configuration of **3ai** was determined as *R*-configuration by the derivatization and comparison to the known compound.[11]

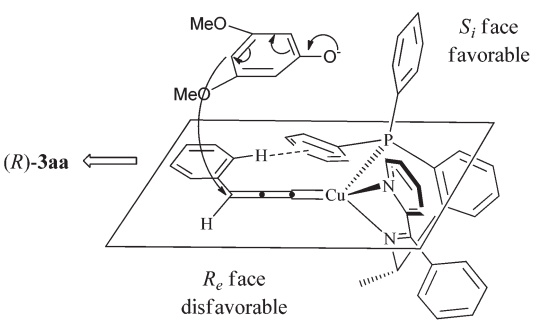


Fig. 1 Proposed transition state for observed stereochemistry.

Based on the experimental results and an edge-to-face aromatic interaction between a phenyl group of the substrate and a phenyl group of the ligand, a transition state of a Cu-acetylide complex with chiral P,N,N-ligand (*S*)-**L$_4$** is proposed to explain the observed stereochemistry as shown in Fig. 1. Due to the steric hindrance of the ligand, the attack of the γ-carbon atom happened favourably from the Si face to form (*R*)-**3aa** while the Re face was hampered.

Conclusions

In conclusion, we have realized an enantioselective copper-catalyzed Friedel–Crafts propargylic alkylation of phenol derivatives with propargylic esters. The research indicated that the presence of an electron-rich substituent on the *meta*-position of phenol is essential for the realization of the Friedel–Crafts propargylic alkylation of phenol, and phenol derivatives bearing two electron-rich groups on both the 3,5-positions tend to give a satisfactory performance. With $Cu(OTf)_2$ in combination with a structurally rigid chiral tridentate ketimine P,N,N-ligand as the catalyst, the Friedel–Crafts propargylic alkylation of 3,5-dialkoxyphenols proceeded smoothly, therefore giving rise to a variety of Friedel–Crafts propargylic alkylation products in good to high yields with high to excellent enantioselectivities (up to 95% ee). To our knowledge, the present research represents the first successful example of Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation of phenol derivatives.

Experimental

General methods

Commercially available compounds were used without further purification. Solvents were purified by a standard procedure before use. Flash chromatography was performed on silica gel 60 (40–63 μm, 60 Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with an F254 indicator. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26 or DMSO = δ 2.50). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 100 MHz spectrometer. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.23 or DMSO = δ 39.60). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), integration. Only the most important and relevant frequencies are reported. Enantiomeric ratios were determined by chiral HPLC with *n*-hexane and i-PrOH as solvents. IR was recorded on a Nicolet-is50 infrared spectrometer. Optical rotations were recorded on a JASCO P-1020 polarimeter.

General procedure for Cu-catalyzed asymmetric Friedel–Crafts propargylic alkylation reaction

A solution of $Cu(OTf)_2$ (5.4 mg, 0.015 mmol) and (*S*)-**L$_4$** (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. A solution of propargylic esters **1** (0.3 mmol), phenol derivatives **2** (0.36 mmol) and K_2CO_3 (49.8 mg, 0.36 mmol) in 2 mL of anhydrous methanol was added. The mixture was stirred at −20 °C for 12 h. The reaction mixture was then concentrated under vacuum, and the residue was purified by silica gel chromatography to afford the desired products **3**.

3,5-Dimethoxy-4-[(*R*)-1-phenylprop-2-yn-1-yl]phenol (3aa). Employing the general procedure afforded compound **3aa** as a pale-yellow oil (77.2 mg, 96% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 8.7 min (major enantiomer), t_R = 10.0 min (minor enantiomer); 93% ee. $[\alpha]_D^{21}$ = +97.4 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.53 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.1 Hz, 1H), 6.09 (s, 2H), 5.48 (s, 1H), 3.65 (s, 6H), 2.99 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 141.4, 128.2, 127.4, 126.3, 108.3, 93.0, 85.0, 71.8, 56.0, 30.5. IR (KBr): 3428, 3280, 2937, 2845, 2112, 1597, 1473, 1116, 996, 814, 730, 633 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}O_3$ [M + H] 269.1178, found 269.1174.

4-(1-(2-Chlorophenyl)prop-2-yn-1-yl)-3,5-dimethoxyphenol (3ba). Employing the general procedure afforded compound **3ba** as a pale-yellow solid (77.8 mg, 86% yield). M.p. 42–44 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 8.7 min (major enantiomer), t_R = 10.3 min (minor enantiomer); 76% ee. $[\alpha]_D^{22}$ = +99.3 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.37–7.20 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.01 (s, 2H), 5.80 (d, *J* = 2.4 Hz, 1H), 5.44 (s, 1H), 3.63 (s, 6H), 2.28 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.5, 137.8, 133.0, 131.5, 129.2, 127.6, 125.7, 108.8, 93.0, 84.3, 69.7, 55.8, 29.8. IR (KBr): 3421, 3302, 2930, 2926, 2113, 1600, 1472, 1149, 1120, 995, 800, 757, 640 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_3Cl$ [M + H] 303.0788, found 303.0780.

4-(1-(3-Chlorophenyl)prop-2-yn-1-yl)-3,5-dimethoxyphenol (3ca). Employing the general procedure afforded compound **3ca** as a pale-yellow solid (81.1 mg, 89% yield). M.p. 52–54 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 7.6 min (major enantiomer), t_R = 10.5 min (minor enantiomer); 95% ee. $[\alpha]_D^{22}$ = +109.7 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.28 (d, *J* = 6.9 Hz, 1H), 7.23–6.94 (m, 2H), 6.02 (s, 2H), 5.62 (d, *J* = 2.3 Hz, 1H), 5.57 (s, 1H), 3.64 (s, 6H), 2.29 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.6, 143.0, 133.6, 129.1, 127.4, 126.2, 125.5, 109.8, 93.0, 84.1, 69.8, 55.9, 30.3. IR (KBr): 3518, 3288, 2972, 2112, 1594, 1470, 1227, 1097, 720, 664, 620 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_3Cl$ [M + H] 303.0788, found 303.0779.

4-(1-(4-Chlorophenyl)prop-2-yn-1-yl)-3,5-dimethoxyphenol (3da). Employing the general procedure afforded compound **3da** as a

colourless oil (79.9 mg, 88% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 85/15, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 13.8 min (major enantiomer), t_R = 15.2 min (minor enantiomer); 92% ee. $[\alpha]_D^{24}$ = +115.6 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.04 (s, 2H), 5.62 (d, *J* = 2.5 Hz, 1H), 5.32 (s, 1H), 3.68 (s, 6H), 2.27 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.5, 139.5, 131.6, 128.6, 127.8, 110.1, 92.8, 84.3, 69.4, 55.9, 30.1. IR (KBr): 3412, 3294, 2931, 2115, 1602, 1475, 1431, 1216, 1122, 995, 780, 630 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_3Cl$ [M + H] 303.0788, found 303.0783.

4-(1-(4-Fluorophenyl)prop-2-yn-1-yl)-3,5-dimethoxyphenol (3ea). Employing the general procedure afforded compound **3ea** as a pale-yellow solid (77.5 mg, 90% yield). M.p. 76–78 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 20.1 min (major enantiomer), t_R = 21.8 min (minor enantiomer); 90% ee. $[\alpha]_D^{24}$ = +120.9 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.34–7.31 (m, 2H), 7.09–7.04 (m, 2H), 6.09 (s, 2H), 5.46 (s, 1H), 3.66 (s, 6H), 3.02–3.01 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.0 (d, *J* = 241.7 Hz), 158.8, 158.4, 137.5 (d, *J* = 2.9 Hz), 129.1 (d, *J* = 8.1 Hz), 115.0, 114.8, 108.1, 93.0, 84.8, 72.1, 56.0, 29.9. IR (MeOH): 3360, 3280, 2950, 1600, 1510, 1470, 1220, 1120, 1020, 778, 630, 562 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_3F$ [M + H] 287.1083, found 287.1079.

4-(1-(4-Bromophenyl)prop-2-ynyl)-3,5-dimethoxyphenol (3fa). Employing the general procedure afforded compound **3fa** as a pale-yellow oil (89.5 mg, 86% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 85/15, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 14.7 min (major enantiomer), t_R = 16.6 min (minor enantiomer); 92% ee. $[\alpha]_D^{22}$ = +80.7 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.04 (s, 2H), 5.60 (d, *J* = 2.5 Hz, 1H), 5.30 (s, 1H), 3.67 (s, 6H), 2.27 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.6, 140.0, 130.8, 129.1, 119.7, 110.0, 92.8, 84.2, 69.5, 55.9, 30.2. IR (KBr): 3419, 2966, 2950, 2936, 2113, 1600, 1486, 1430, 1344, 777, 633 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_3Br$ [M + H] 347.0283, found 347.0273.

3,5-Dimethoxy-4-(1-(*p*-tolyl)prop-2-yn-1-yl)phenol (3ga). Employing the general procedure afforded compound **3ga** as a pale-yellow oil (78.9 mg, 93% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 17.4 min (major enantiomer), t_R = 18.9 min (minor enantiomer); 93% ee. $[\alpha]_D^{24}$ = +93.7 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.00 (s, 2H), 5.63 (s, 1H), 5.47 (s, 1H), 3.64 (s, 6H), 2.28 (s, 3H), 2.24 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 156.3, 137.8, 135.5, 128.6, 127.1, 110.7, 93.0, 85.2, 68.9, 56.0, 30.2, 21.0. IR (MeOH): 3275, 3029, 2836, 2116, 1595, 1505, 1452, 1292, 1194, 1033, 952, 831, 699 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_3$ [M + H] 283.1134, found 283.1132.

3,5-Dimethoxy-4-(1-(4-methoxyphenyl)prop-2-yn-1-yl)phenol (3ha). Employing the general procedure afforded compound **3ha** as a pale-yellow solid (77.4 mg, 86% yield). M.p. 124–126 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 20.7 min (minor enantiomer), t_R = 26.3 min (major enantiomer); 87% ee. $[\alpha]_D^{24}$ = +104.7 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.09 (s, 2H), 5.43 (s, 1H), 3.68 (d, *J* = 12.1 Hz, 9H), 2.94 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.6, 158.4, 157.9, 133.3, 128.4, 113.6, 108.6, 93.0, 85.4, 71.5, 56.0, 55.4, 29.7. IR (KBr): 3354, 3281, 2932, 2116, 1596, 1511, 1475, 1239, 1118, 1000, 630 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_4$ [M + H] 299.1283, found 299.1280.

3,5-Dimethoxy-4-(1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl) phenol (3ia). Employing the general procedure afforded compound **3ia** as a colourless oil (88.2 mg, 87% yield). HPLC (Chiralcel OD-H, *n*-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 12.9 min (major enantiomer), t_R = 14.2 min (minor enantiomer); 92% ee. $[\alpha]_D^{24}$ = +91.3 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 6.10 (s, 2H), 5.56 (s, 1H), 3.66 (s, 6H), 3.10 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8 (d, *J* = 70.2 Hz), 146.2, 128.1, 127.1 (d, *J* = 31.6 Hz), 126.2, 125.2 (d, *J* = 3.9 Hz), 123.5, 107.5, 93.0, 84.0, 72.7, 56.0, 30.5. IR (MeOH): 3360, 3280, 2830, 1600, 1470, 1320, 1220, 1110, 1020, 630 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}O_3F_3$ [M + H] 347.0283, found 347.0273.

3,5-Dimethoxy-4-(1-(naphthalen-2-yl)prop-2-yn-1-yl)phenol (3ja). Employing the general procedure afforded compound **3ja** as a colourless oil (80.1 mg, 84% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 10.3 min (major enantiomer), t_R = 13.5 min (minor enantiomer); 93% ee. $[\alpha]_D^{21}$ = +187.9 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.87–7.59 (m, 3H), 7.51–7.26 (m, 3H), 5.96 (s, 2H), 5.81 (d, *J* = 1.5 Hz, 1H), 5.59 (s, 1H), 3.56 (d, *J* = 3.8 Hz, 6H), 2.34 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 156.5, 138.3, 133.3, 132.1, 127.9, 127.5, 127.3, 126.0, 125.7, 125.4, 125.2, 110.4, 92.9, 84.8, 69.4, 56.0, 30.7. IR (MeOH): 3340, 3290, 2950, 2940, 1600, 1480, 1220, 1110, 1020, 998, 816, 633 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}O_3$ [M + H] 319.1334, found 319.1311.

3,5-Dimethoxy-4-(1-(thiophen-2-yl)prop-2-ynyl)phenol (3ka). Employing the general procedure afforded compound **3ka** as a colourless oil (69.1 mg, 84% yield). HPLC (Chiralcel OJ-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 9.7 min (minor enantiomer), t_R = 12.3 min (major enantiomer); 91% ee. $[\alpha]_D^{21}$ = +52.8 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 4.6 Hz, 1H), 6.87 (d, *J* = 3.4 Hz, 1H), 6.77 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.93 (s, 2H), 5.74 (d, *J* = 1.7 Hz, 1H), 5.47 (s, 1H), 3.59 (s, 6H), 2.17 (d, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 156.6, 145.2, 126.4, 124.4, 123.5, 109.8, 93.0, 84.7, 68.5, 56.0, 26.7. IR (MeOH): 3390, 3290, 2940, 2840, 1600, 1470, 1430, 1210, 1110, 995, 815, 701, 630 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}O_3S$ [M + H] 275.0742, found 275.0741.

3,5-Dimethoxy-4-(1-phenylbut-3-yn-2-yl)phenol (3la). Employing the general procedure afforded compound **3la** as a colourless oil (32.8 mg, 39% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 12.5 min (major enantiomer), t_R = 13.8 min (minor enantiomer); 72% ee. $[\alpha]_D^{24}$ = +(*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (m, 5H), 5.99 (s, 2H), 5.04 (s, 1H), 4.49–4.46 (m, 1H), 3.71 (d, *J* = 22.9 Hz, 6H), 3.25 (dd, *J* = 13.0, 8.0 Hz, 1H), 3.02 (dd, *J* = 12.8, 7.7 Hz, 1H), 2.02–2.01 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.0, 140.2, 129.2, 127.9, 126.0, 109.4, 94.3, 92.7, 86.9, 67.3, 55.9, 55.4, 40.0, 27.9. IR (MeOH): 3310, 2940, 2830, 1410, 1120, 1020, 691, 614 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_3$ [M + H] 283.1334, found 283.1329.

3,5-Diethoxy-4-(1-phenylprop-2-yn-1-yl)phenol (3ab). Employing the general procedure afforded compound **3ab** as a pale-yellow solid (69.2 mg, 78% yield). M.p. 82–84 °C. HPLC (Chiralcel OJ-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 8.3 min (major enantiomer), t_R = 13.0 min (minor enantiomer); 82% ee. $[\alpha]_D^{20}$ = +122.3 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 2H), 7.23 (dd, *J* = 8.7, 6.3 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 5.95 (d, *J* = 4.0 Hz, 2H), 5.71 (d, *J* = 2.3 Hz, 1H), 5.16 (s, 1H), 3.91 (dt, *J* = 14.1, 7.1 Hz, 2H), 3.81 (dd, *J* = 14.9, 7.9 Hz, 2H), 2.25 (d, *J* = 2.7 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 156.1, 141.1, 127.7, 127.4, 125.8, 110.9, 93.3, 84.9, 69.3, 64.3, 30.6, 14.6. IR (KBr): 3380, 3306, 2982, 2926, 2115, 1597, 1458, 1229, 1150, 1120, 696 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}O_3$ [M + H] 297.1491, found 297.1489.

3,5-Bis(benzyloxy)-4-(1-phenylprop-2-ynyl)phenol (3ac). Employing the general procedure afforded compound **3ac** as a pale-yellow solid (95.2 mg, 76% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 11.8 min (major enantiomer), t_R = 13.3 min (minor enantiomer); 85% ee. $[\alpha]_D^{20}$ = +(*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.35–7.00 (m, 13H), 6.02 (s, 2H), 5.83 (s, 1H), 5.63 (s, 1H), 4.92 (d, *J* = 12.0 Hz, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 2.22 (dd, *J* = 2.6, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 156.3, 140.8, 136.8, 128.5, 127.9, 127.8, 127.5, 127.4, 126.0, 111.0, 94.1, 84.9, 70.4, 69.8, 30.8. IR (KBr): 3360, 3280, 2930, 1600, 1450, 1230, 1110, 1020, 730, 695, 631 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{29}H_{25}O_3$ [M + H] 421.1804, found 421.1801.

3,5-Diisopropoxy-4-(1-phenylprop-2-ynyl)phenol (3ad). Employing the general procedure afforded compound **3ad** as a colorless oil (57.2 mg, 59% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 85/15, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 7.5 min (major enantiomer), t_R = 8.3 min (minor enantiomer); 68% ee. $[\alpha]_D^{31}$ = +140.6 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.21 (dd, *J* = 12.2, 4.9 Hz, 2H), 7.13 (d, *J* = 7.3 Hz, 1H), 5.98 (s, 2H), 5.68 (d, *J* = 2.2 Hz, 1H), 5.40 (s, 1H), 4.38 (dt, *J* = 12.1, 6.0 Hz, 2H), 2.23 (d, *J* = 2.7 Hz, 1H), 1.32–1.26 (m, 6H), 1.06 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 156.0, 141.4, 127.5, 127.5, 125.7, 112.5, 94.0, 84.8, 70.4, 69.4, 30.8, 22.0, 21.7. IR (MeOH): 3260, 2980, 1600, 1460, 1370, 1100, 1060, 1020, 720, 654 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}O_3$ [M + H] 325.1804, found 325.1804.

3-Ethoxy-5-methoxy-4-(1-phenylprop-2-ynyl)phenol (3ae). Employing the general procedure afforded compound **3ae** as a colourless oil (70.7 mg, 84% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 7.2 min (major enantiomer), t_R = 8.1 min (minor enantiomer); 87% ee. $[\alpha]_D^{20}$ = +123.4 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 5.92 (dd, *J* = 10.0, 2.2 Hz, 2H), 5.61 (d, *J* = 1.9 Hz, 1H), 4.64 (s, 1H), 3.85–3.78 (m, 1H), 3.67 (d, *J* = 16.9 Hz, 1H), 3.57 (s, 3H), 2.31–2.05 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.9, 156.4, 141.0, 127.8, 127.3, 125.9, 110.6, 93.6, 92.7, 84.9, 69.2, 64.3, 55.9, 30.6, 14.6. IR (MeOH): 3350, 3280, 2940, 2930, 1600, 1470, 1120, 1022, 699, 636 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}O_3$ [M + H] 283.1334, found 283.1359.

3-(Benzyloxy)-5-methoxy-4-(1-phenylprop-2-ynyl)phenol (3af). Employing the general procedure afforded compound **3af** as a colorless oil (79.2 mg, 77% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 13.6 min (major enantiomer), t_R = 16.7 min (minor enantiomer); 88% ee. $[\alpha]_D^{30}$ = +97.3 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.34–7.00 (m, 8H), 6.10–5.93 (m, 2H), 5.87 (s, 1H), 5.74 (s, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 3.57 (s, 3H), 2.23 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 157.6, 156.4, 140.8, 136.8, 128.4, 127.4, 126.1, 110.8, 94.0, 93.2, 85.0, 70.4, 69.7, 56.0, 30.7. IR (MeOH): 3300, 2940, 2830, 1600, 1450, 1110, 1020, 698, 630 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}O_3$ [M + H] 345.1491, found 345.1484.

3-Isopropoxy-5-methoxy-4-(1-phenylprop-2-ynyl)phenol (3ag). Employing the general procedure afforded compound **3ag** as a colorless oil (69.3 mg, 79% yield). HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 6.0 min (major enantiomer), t_R = 6.8 min (minor enantiomer); 81% ee. $[\alpha]_D^{30}$ = +139.0 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.37 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 5.98 (dd, *J* = 11.1, 1.9 Hz, 2H), 5.75 (s, 1H), 5.67 (d, *J* = 2.2 Hz, 1H), 4.50–4.18 (m, 1H), 3.62 (s, 3H), 2.24 (d, *J* = 2.7 Hz, 1H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 156.6, 156.2, 141.1, 127.7, 127.4, 125.8, 111.6, 94.5, 92.6, 84.9, 70.5, 69.4, 55.9, 30.68 (s), 22.0, 21.6. IR (MeOH): 3360, 3280, 2980, 2940, 1600, 1470, 1110, 1020, 697, 632 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}O_3$ [M + H] 297.1491, found 297.1490.

3-Methoxy-4-(1-phenylprop-2-ynyl)phenol (3ai). Employing the general procedure afforded compound **3ai** as a white solid (9.3 mg, 13% yield). M.p. 96–97 °C. HPLC (Daicel Chiralpak AD-H, *n*-hexane/i-propanol = 80/20, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 8.2 min (minor enantiomer), t_R = 9.8 min (major enantiomer); 65% ee. $[\alpha]_D^{31}$ = +55.4 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.17 (s, 1H), 6.34 (dd, *J* = 12.4, 5.3 Hz, 2H), 5.53 (s, 1H), 5.36 (d, *J* = 1.9 Hz,

1H), 3.67 (s, 3H), 2.36 (dd, J = 1.8, 0.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 155.8, 141.4, 129.6, 128.4, 127.7, 126.7, 122.2, 107.3, 99.2, 85.5, 71.5, 55.6, 35.4. IR (KBr): 3407, 3274, 3025, 2838, 2114, 1596, 1506, 1455, 1203, 1037, 952, 699 cm^{-1}; HRMS (ESI): m/z calcd for $C_{16}H_{15}O_2$ [M + H] 239.1072, found 239.1076.

3-Methoxy-5-methyl-4-(1-phenylprop-2-ynyl)phenol (3aj). Employing the general procedure afforded compound **3aj** as a colorless oil (42.8 mg, 57% yield). HPLC (Daicel Chiralpak AD-H, n-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 16.0 min (major enantiomer), t_R = 19.8 min (minor enantiomer); 70% ee. $[\alpha]_D^{31}$ = +64.1 (c = 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 7.5 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.17 (s, 1H), 6.32 (d, J = 2.3 Hz, 1H), 6.22 (d, J = 2.2 Hz, 1H), 5.87 (s, 1H), 5.46 (s, 1H), 3.73 (s, 3H), 2.36 (d, J = 2.7 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 155.3, 140.1, 140.1, 128.2, 127.0, 126.2, 120.2, 110.5, 97.1, 84.0, 71.2, 56.0, 31.9, 20.3. IR (MeOH): 3290, 2940, 1610, 1460, 1340, 1090, 1020, 725, 630 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{17}O_2$ [M + H] 253.1229, found 253.1255.

(*S*)-2,3-Dihydro-5-methoxy-2-methylene-1-phenyl-1*H*-indene (5). Employing the general procedure afforded compound **5** as a white solid (8.7 mg, 12% yield). M.p. 68–70 °C. HPLC (Chiralcel OJ-H, n-hexane/i-propanol = 90/10, flow rate 0.8 mL min^{-1}, detection at 230 nm): t_R = 11.3 min (major enantiomer), t_R = 16.4 min (minor enantiomer); 68% ee. $[\alpha]_D^{31}$ = −102.4 (c = 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (t, J = 7.4 Hz, 2H), 7.27 (d, J = 7.2 Hz, 1H), 7.22 (t, J = 10.3 Hz, 2H), 6.92 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.3, 2.2 Hz, 1H), 5.24 (s, 1H), 4.73 (d, J = 2.4 Hz, 1H), 4.14 (t, J = 2.3 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 160.7, 158.4, 143.2, 129.2, 128.2, 127.4, 125.7, 122.0, 108.5, 96.4, 87.2, 55.9, 49.4. IR (MeOH): 1690, 1590, 1490, 1440, 1290, 1090, 950, 820, 693, 565, 439 cm^{-1}; HRMS (ESI): m/z calcd for $C_{16}H_{15}O_2$ [M + H] 239.1072, found 239.1082.

Conflicts of interest

There are no conflicts to declare.

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