Diversity-Oriented Synthesis of Biaryl Derivatives Using Cross-Enyne Metathesis, Diels–Alder Reaction, and Suzuki–Miyaura Cross-Coupling as Key Steps

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Dedicated to the memory of Prof. K. D. Deodher

Abstract: Biaryl derivatives have been prepared by utilizing cross-enyne metathesis, Diels–Alder reaction followed by aromatization. These biaryl derivatives are further functionalized via Suzuki–Miyaura cross-coupling reaction to generate functionalized terphenyl derivatives.

Key Words: biaryl derivatives, cross-enyne metathesis, Suzuki–Miyaura cross-coupling, diversity-oriented synthesis

The biaryl unit is a core structural element present in naturally occurring products such as alkaloids, lignans, terpenes, and flavonoids.[1] In addition, the biaryl unit is found in several medicinally important compounds (e.g., antibiotics, anti-inflammatories, antihypertensives, anticancer, and antifungal agents).[2] For example, losartan[3] is one of the most prescribed drugs for antihypertension. Several important biaryl derivatives are shown in Figure 1.[4] The biaryl motif may also be a component of agrochemicals, liquid crystals, and molecular switches.[5] Several structural components of biaryls are natural pigments (e.g., gossypol).[6] Binaphthyl polyphenyls are used as male antifertility agents and polycholorobiphenyls (PCB) are recognized as environmental polluants.[7]

Transition-metal-catalyzed cross-coupling[8] of aryl halides with aryl organometallic species has been used for the development of synthetic methods allowing C–C coupling between two aryl groups. While the metathesis[9,10] protocol (Figure 2) and Diels–Alder chemistry is often used to create new C–C bonds, only a few reports describe biaryl preparation involving the Diels–Alder reaction as a key step.

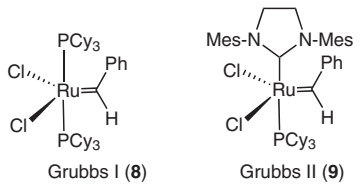

Figure 2 Various Grubbs catalysts used in cross-enyne metathesis

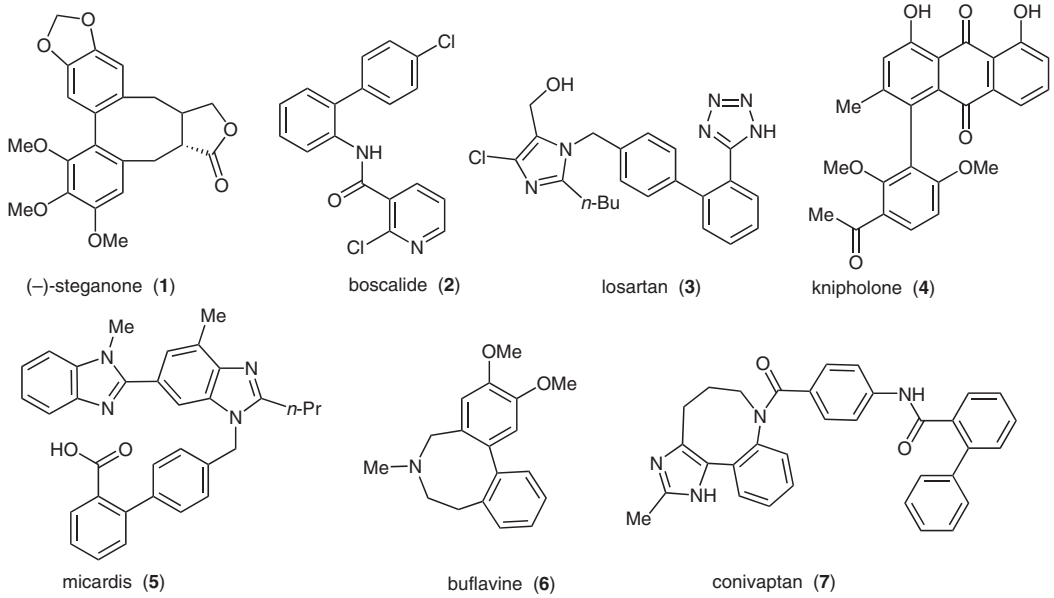

Figure 1 Various biaryl-containg molecules

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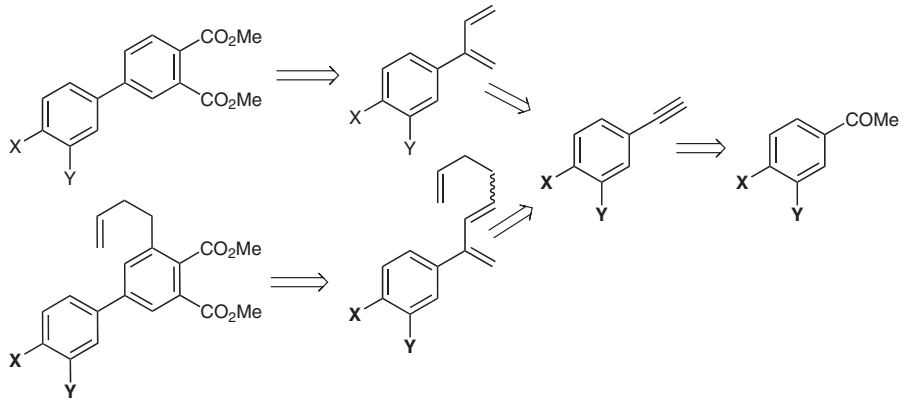
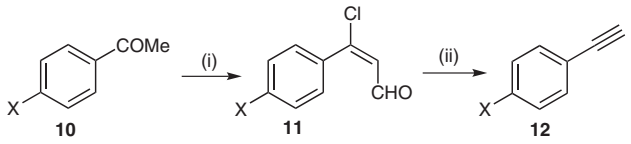


Figure 3 Retrosynthetic approaches towards biaryl derivatives

Herein, we report a new strategy for the synthesis of biaryl derivatives involving cross-enyne metathesis and Diels–Alder reaction[11,12] as key steps. The first step in the strategy involves cross-enyne metathesis with 1,5-hexadiene to generate homoallyl diene derivatives, and ethylene-mediated cross-metathesis to generate 1,3-diene derivatives (Figure 3).[13] These dienes are subjected to Diels–Alder reaction with a dienophile such as dimethyl acetylenedicarboxylate (DMAD)[14] followed by aromatization to generate highly substituted biaryl systems. Subsequently, Suzuki–Miyaura cross-coupling[15] with these biaryl systems can generate highly functionalized terphenyl derivatives.

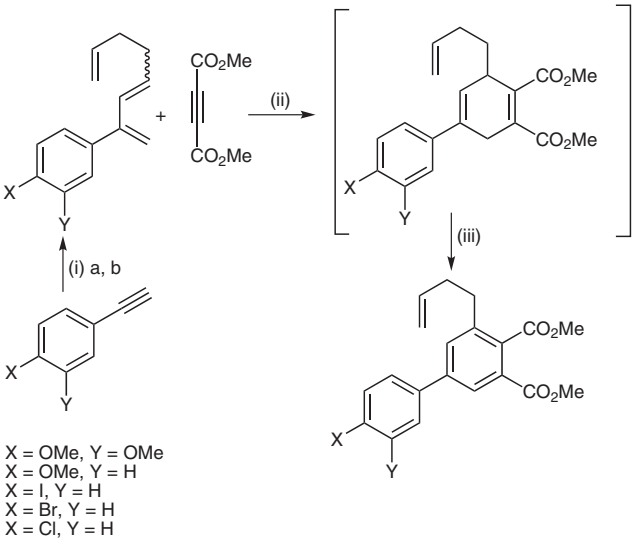
Various commercially available functionalized acetophenones **10** were converted into aryl acetylene derivatives **12** by using known methodology (Scheme 1).[16]



Scheme 1 Preparation of various phenyl acetylene derivatives. *Reagents and conditions*: (i) DMF, $POCl_3$; (ii) NaOH, 1,4-dioxane.

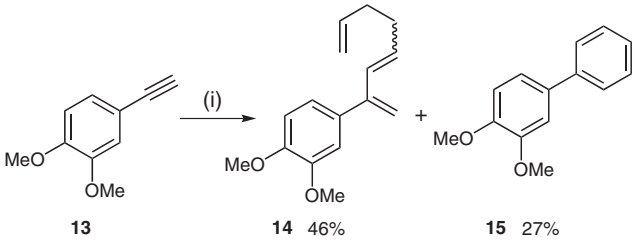
Initially, the cross-enyne metathesis was performed starting with 3,4-di-methoxyphenylacetylene **13** and 1,5-hexadiene as a cross-coupling partners in the presence of Grubbs first-generation catalyst **8** in CH_2Cl_2 (Scheme 2). After considerable experimentation, we found that the highest yield of the cross-metathesis product was obtained at 90 °C in toluene. In toluene at reflux, two products were observed: the expected cross-enyne metathesis product **14** and another benzoanulated product **15**. The cross-enyne product **14** was converted into the 3,4-dimethoxybiaryl system **15** (Scheme 3) by an intramolecular metathesis and aromatization sequence.

During the cross-enyne metathesis in toluene at 90 °C the products were obtained as an inseparable mixture of *cis*/*trans* isomers.[17] When the halogenated acetylene derivatives were subjected to cross-enyne metathesis with 1,5-hexadiene in toluene at 90 °C and under reflux, starting



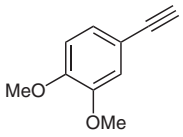
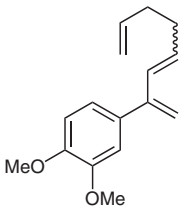
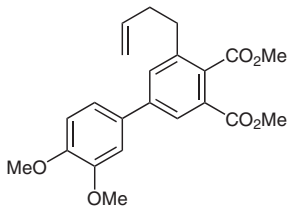
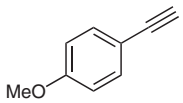
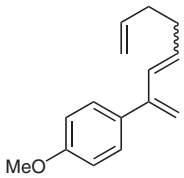
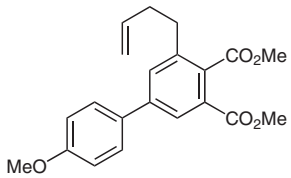
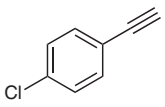
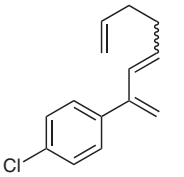
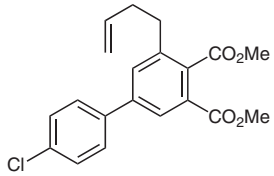
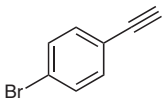
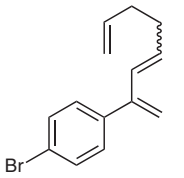
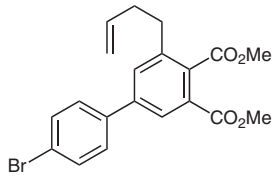
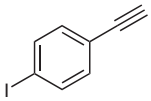
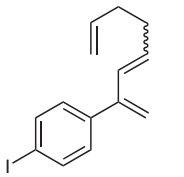
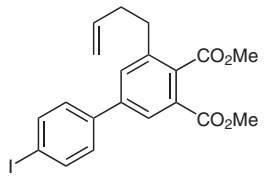
Scheme 2 *Reagents and conditions*: (i) (a) Grubbs II, 1,5-hexadiene, toluene 90 °C, 24 h; (b) Grubbs I, 1,5-hexadiene, CH_2Cl_2, 12 h; (ii) toluene, 90 °C, 24 h; (iii) DDQ, toluene, reflux, 36 h.

material was not completely consumed. The reaction was subsequently carried out using Grubbs first-generation catalyst **8** in CH_2Cl_2 at room temperature under nitrogen, and it was found that the reaction rate was much faster and that the reaction proceeded to completion within 12 hours. Again, an inseparable mixture of *cis*/*trans* isomers of diene **14** was obtained in good yield. Since the dienes are used to generate aromatic products by a Diels–Alder reaction and aromatization sequence, the geometry of the double bond present in **14** is of no consequence in the present study.



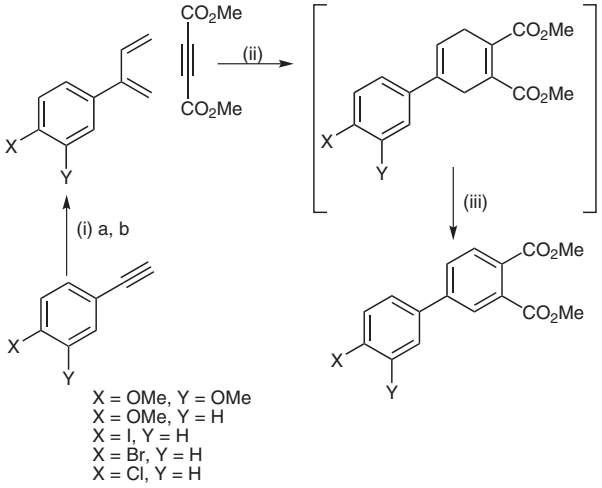
Scheme 3 *Reagents and conditions*: (i) 1,5-hexadiene, Grubbs II, toluene, reflux.

Table 1 Preparation of Homoallyl 1,3-Dienes and Aromatized Products

Substrate	Product (Yield)	Product (Yield)
 **13**	 **14** (73%)	 **24** (75%)
 **16**	 **20** (65%)	 **25** (66%)
 **17**	 **21** (75%)	 **26** (60%)
 **18**	 **22** (88%)	 **27** (72%)
 **19**	 **23** (86%)	 **28** (82%)

The dienes **14** were then subjected to Diels–Alder reaction with dienophiles in toluene under reflux to deliver the corresponding adducts. Even though we used a catalytic amount of 1,4-hydroquinone during the cycloaddition reaction to prevent polymerization of the diene, the results were not encouraging. However, when the reaction was carried out in toluene at 90 °C for 24 hours, formation of the Diels–Alder adduct was observed (TLC monitoring). The adduct was then subjected directly to aromatization with MnO_2 in 1,4-dioxane and also with DDQ in toluene. We observed that the DDQ/toluene conditions gave better yields of the aromatized products (Table 1).

In a second strategy, 1-ethynyl-4-methoxybenzene (**16**) was subjected to an ethylene-mediated (1 bar pressure) cross-metathesis sequence using the Grubbs second-generation catalyst **9** in toluene at 90 °C to generate the required diene. The disappearance of the acetylenic proton and the appearance of new peaks at δ = 5.12–5.29 ppm and at δ = 6.66 ppm in ^{1}H NMR spectral data indicated the

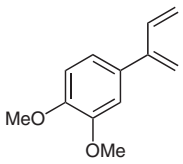
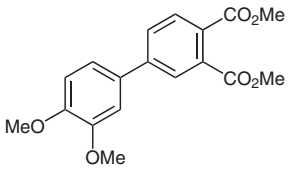
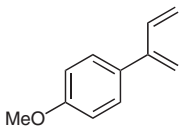
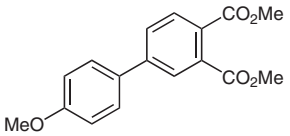
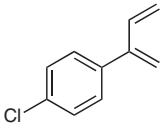
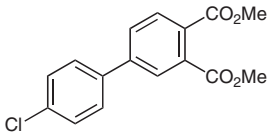
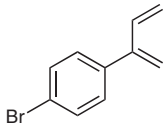
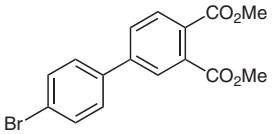
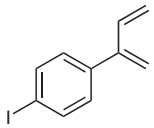
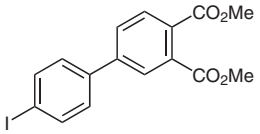


Scheme 4 *Reagents and conditions*: (i) (a) Grubbs II, C_2H_4, CH_2Cl_2, r.t., 24 h; (b) Grubbs II, C_2H_4, toluene, 90 °C 24 h; (ii) toluene, 90 °C, 24 h; (iii) DDQ toluene, reflux, 36 h.

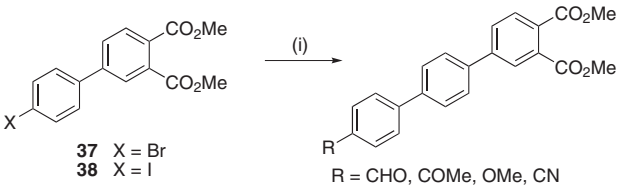
formation of the diene **30**. Along similar lines, 1-ethynyl-4-iodobenzene (**19**) was subjected to cross-metathesis with ethylene using the Grubbs second-generation catalyst **9** in CH_2Cl_2 at room temperature for 24 hours under nitrogen, and complete conversion of the starting material was observed. Next, 4-chloro- and 4-bromophenylacetylene derivatives were subjected to cross-enyne metathesis with ethylene in the presence of the Grubbs second-generation catalyst to generate the corresponding dienes (Scheme 4).

Based on the above experiments it was concluded that toluene is a better solvent for cross-enyne metathesis under ethylene as well as 1,5-hexadiene conditions with substrates such as 3,4-dimethoxyphenylacetylene (**13**) and 4-methoxyphenylacetylene (**16**), whereas CH_2Cl_2 seems to be a better solvent for halogenated phenylacetylene substrates **17**–**19**. The dienes obtained during the cross-metathesis were subjected to Diels–Alder reaction with a dienophile such as DMAD in toluene, at 90 °C for 24 hours to deliver the corresponding adducts.

Table 2 Aromatization of Diels–Alder Products with DDQ in Toluene at Reflux

Substrate	Product (Yield)	Product (Yield)
13	 **29** (75%)	 **34** (66%)
16	 **30** (81%)	 **35** (62%)
17	 **31** (70%)	 **36** (65%)
18	 **32** (83%)	 **37** (82%)
19	 **33** (63%)	 **38** (86%)

The Diels–Alder products were subjected to aromatization with DDQ in toluene at reflux (Table 2). Finally, these aromatized products were subjected to Suzuki–Miyaura cross-coupling (Scheme 5) with boronic acids such as 4-methoxyphenyl boronic acid, 4-cyanophenyl boronic acid, 4-acetylphenyl boronic acid, and 4-formylphenyl boronic acid using a Pd(0) catalyst in toluene and THF (1:1 ratio, Figure 4) to generate terphenyl derivatives.



Scheme 5 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, 4-R-$C_6H_4B(OH)_2$, Na_2CO_3.

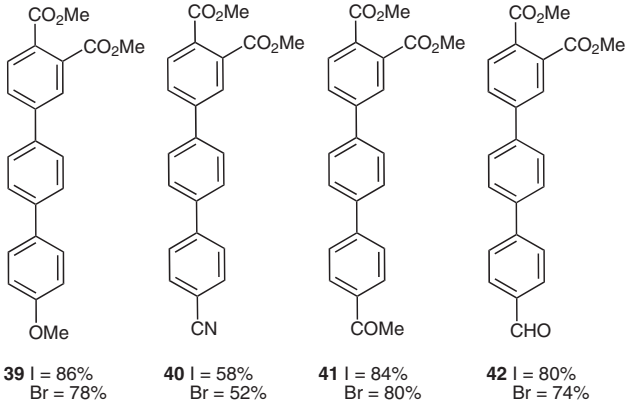


Figure 4 Preparation of terphenyl derivatives via SM cross-coupling starting with **37** or **38**

In conclusion, we have demonstrated that cross-enyne metathesis of 1,5-hexadiene or ethylene with phenylacetylene derivatives followed by a Diels–Alder reaction and aromatization sequence furnishes biaryl derivatives. These biaryl derivatives are useful intermediates to prepare highly functionalized terphenyl derivatives via Suzuki–Miyaura cross-coupling. The strategy demonstrated here has several diversity points.[18] Firstly, the cross-metathesis partners can be varied and a second diversity point involves the utilization of various dienophiles during the Diels–Alder reaction. A third diversity point is the variation of the boronic acids during the Suzuki–Miyaura reaction. Since more than thousand boronic acids are commercially available, our approach to biaryl (or terphenyl) building blocks can provide a library of these privileged molecules.

General Procedure for the Preparation of Homoallyl Dienes

To a degassed solution of 4-ethynyl-1,2-dimethoxybenzene (**13**, 100 mg, 0.61 mmol) and 1,5-hexadiene (100 mg, 1.22 mmol) in toluene (10 mL) was added Grubbs second-generation catalyst (20 mg, 4 mol%), and the reaction mixture was heated at reflux for 1 h. At the conclusion of the reaction (TLC monitoring) the reaction mixture was concentrated, and the crude product was purified by a flash

column chromatography using PE as eluent to afford **14** (110 mg, 74%) as a colorless liquid.

General Procedure for the Diels–Alder Reaction of Homoallyl Butadiene Derivatives Followed by Aromatization

To a solution of the diene **14** (110 mg, 0.45 mmol) in toluene (5 mL) was added dimethyl acetylene dicarboxylate (128 mg, 0.9 mmol), and the reaction mixture was heated at 90 °C for 15 h. At the conclusion of the reaction (TLC monitoring) the solvent was removed under reduced pressure, and the crude product was purified by a silica gel column chromatography (EtOAc–PE, 0.5:9.5) to afford the adduct as a semisolid. Oxidation of the adduct was carried out with MnO_2 (116 mg, 13.05 mmol) in refluxing 1,4-dioxane (14 mL) for 30 h. The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel column chromatography (EtOAc–PE, 0.5:9.5) to afford the aromatized product **24** (130 mg, 75%) as a semisolid.

General Procedure for the Preparation of 1,3-Dienes and Diels–Alder Reaction Followed by Aromatization

A solution of **13** (100 mg, 0.61 mmol) in toluene (10 mL) was degassed with N_2 for 10 min and then Grubbs second-generation catalyst (26 mg, 5 mol%) was added. The reaction mixture was kept under 1 atm pressure of ethylene (balloon pressure) and stirred at 90 °C for 24 h. At the conclusion of the reaction (TLC monitoring) the solvent was concentrated, and the crude product was purified by a flash silica gel column chromatography (EtOAc–PE, 0.5:9.5) to afford **29** (85 mg, 73%) as a brownish liquid. Later, diene **29** (95 mg, 0.5 mmol) was dissolved in toluene (10 mL), dimethyl acetylene dicarboxylate (142 mg, 1.0 mmol) was added, and the mixture was heated at 90 °C for 24 h. At the conclusion of the reaction (TLC monitoring) the adduct was oxidized with DDQ (181 mg, 0.79 mmol) in refluxing toluene (10 mL) for 36 h. The solvent was removed under reduced pressure, and the crude product obtained was purified by flash silica gel column chromatography with 5% EtOAc–PE to afford the aromatized product **34** (110 mg, 66%) as a semisolid.

General Procedure for Cross-Coupling Reactions

A solution of **37** (74 mg, 0.21 mmol) in THF–toluene (1:1) mixture, 4-methoxy phenylboronic acid (63 mg, 0.48 mmol) and aq Na_2CO_3 (44 mg, 0.42 mmol) was degassed with N_2 for 20 min, and $Pd(PPh_3)_4$ (9.7 mg, 4 mol%) was added. The reaction mixture was then heated for 6 h at 90 °C. At the conclusion of the reaction (TLC monitoring) the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. The solvent was evaporated, and the crude product was purified by silica gel column chromatography EtOAc–PE, 0.5:9.5) to give the desired cross-coupling product **39** (68 mg, 86%) as a white solid.

Compound 15

IR (neat): 790, 1220, 1590, 2985 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 3.95 (s, 3 H), 6.95 (d, *J* = 4.4 Hz, 2 H), 7.11–7.16 (m, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.42 (t, *J* = 8.2 Hz, 2 H), 7.56 (d, *J* = 4.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5, 56, 110, 111, 119, 127, 128, 134, 141, 148, 149. HRMS(Q-ToF): *m/z* calcd for $C_{14}H_{15}O_2$ $[M + H]^+$: 215.1078; found: 215.1072.

Compound 20

IR (neat): 742, 811, 1263, 1514, 1601, 2929 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.23 (m, 4 H), 3.81 (s, 3 H), 4.95–5.03 (m, 3 H), 5.12 (d, *J* = 1.6 Hz,1 H), 5.64–5.71 (m, 1 H), 5.78–5.85 (m, 1 H), 6.30 (d, *J* = 15.6 Hz, 1 H), 6.86 (d, *J* = 1.2 Hz, 2 H), 7.25 (d, *J* = 0.9 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 32.4, 33.6, 55.3, 60.5, 113.5, 114.1, 114.3, 115.0, 126.8, 128.2, 128.8, 129.4, 132.1, 133.5, 138.2, 147.5. HRMS(Q-ToF): *m/z* calcd for $C_{15}H_{19}O$ $[M + H]^+$: 215.1436; found: 215.1433.

Compound 24

IR (neat): 1025, 1262, 1519, 1729, 2925 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (dd, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 2 H), 2.76 (t, *J* = 2.4 Hz, 2 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 3.97 (s, 3 H), 4.92–5.07 (m, 2 H), 5.81–5.89 (m, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 7.08 (d, *J* = 2.0 Hz, 1 H), 7.13–7.17 (m, 1 H), 7.58 (d, *J* = 2.0 Hz, 1 H), 8.02 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0, 35.4, 52.8, 56.14, 56.18, 56.2, 110.4, 111.6, 115.6, 119.8, 126.2. 128.9, 132.0, 132.4, 133.2, 137.5, 142.2, 149.5, 166.6, 169.8. HRMS(Q-ToF): *m/z* calcd for $C_{22}H_{24}O_6$ $[M + Na]^+$: 407.1471; found: 407.1482.

Compound 26

IR (neat): 1013, 1266, 1435, 1640, 2952 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 2 H), 3.80 (t, *J* = 4.8 Hz, 2 H), 3.92 (s, 3 H), 3.96 (s, 3 H), 4.99–5.30 (m, 1 H), 5.81–5.89 (m, 1 H), 7.43 (d, *J* = 4.8 Hz, 1 H), 7.43 (d, *J* = 4.8 Hz, 1 H), 7.53 (d, *J* = 4.4 Hz, 1 H), 7.59 (d, *J* = 2.0 Hz, 2 H), 8.03 (d, *J* = 2.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.9, 35.3, 52.7, 53.6, 115.7, 126.4, 128.5, 128.8, 129.2, 132.2, 134.0, 134.4, 137.3, 137.8, 140.3, 140.9, 166.3, 169.7. HRMS(Q-ToF): *m/z* calcd for $C_{20}H_{19}O_4Cl$ $[M + Na]^+$: 381.0882; found: 381.0870.

Compound 34

IR (neat): 738, 1025, 1266, 1731, 2954 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 3.93 (s, 3 H), 3.95 (d, *J* = 7.2 Hz, 6 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 1.2 Hz, 1 H), 7.18 (d, J_1 = 5.2 Hz, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H), 7.83 (d, *J* = 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.8, 52.9, 56.1, 56.2, 110.2, 110.3, 111.5, 119.9, 126.9, 129.1, 131.8, 133.9, 144.4, 149.5, 149.7, 167.6, 168.8. HRMS(Q-ToF): *m/z* calcd for $C_{18}H_{19}O_6$ $[M + H]^+$: 331.1182; found: 331.1185.

Compound 38

IR (neat): 748, 819, 1735, 2853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 3.94 (s, 3 H), 7.26–7.36 (m, 2 H), 7.69–7.79 (m, 1 H), 7.78–7.86 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 52.9, 94.7, 127.2, 129.1, 130.0, 133.3, 138.5, 138.6, 143.3, 167.6, 168.3. HRMS(Q-ToF): *m/z* calcd for $C_{16}H_{14}O_4I$ $[M + H]^+$: 393.9937; found: 393.9933.

Compound 39

Mp 150–152 °C. IR (KBr): 743, 819, 1734, 2852 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 7.01, (d, *J* = 4.0 Hz, 2 H), 7.58 (d, *J* = 4.8 Hz, 2 H), 7.67 (d, *J* = 2.0 Hz, 2 H), 7.80 (d, *J* = 1.6 Hz, 2 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 7.94 (d, *J* = 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 29.7, 55.4, 114.3, 126.7, 126.8, 127.3, 127.4, 127.8, 128.2, 128.8, 129.0, 129.1, 133.9, 140.9, 159.2. HRMS(Q-ToF): *m/z* calcd for $C_{23}H_{21}O_5$ $[M + H]^+$: 377.1398; found: 377.1389.

Compound 40

Mp 138–140 °C. IR (KBr): 743, 819, 1734, 2852 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 3.96 (s, 3 H), 7.71–7.94 (m, 5 H), 7.81 (d, *J* = 2.0 Hz, 2 H), 7.87 (d, J_1 = 8.4 Hz, 2 H), 7.95 (d, *J* = 2.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 55.5,114.4, 114.5, 119.0, 127.3, 127.6, 128.0, 128.7, 129.8, 132.9, 133.3, 137.3, 139.4, 141.1, 143.5, 153.6, 156.8. HRMS(Q-ToF): *m/z* calcd for $C_{23}H_{17}NO_4$ $[M + Na]^+$: 394.1068; found: 394.1055.

Compound 41

Mp 157–159 °C. IR (KBr): 740, 823, 1682, 1730, 2853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 7.73–7.74 (m, 7 H), 7.83 (dd, J_1 = 2.8 Hz, J_2 = 8.0 Hz, 1 H), 7.96

(s, 1 H), 8.06 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 52.9, 127.2, 128.0, 129.1, 129.3, 129.9, 130.3, 133.3, 136.2, 138.9, 140.0, 143.6, 144.9, 167.7, 168.4, 197.8. HRMS(Q-ToF): *m/z* calcd for $C_{24}H_{20}O_5$ [M + Na]$^+$: 411.1208; found: 411.1198.

Compound 42

Mp 156–160 °C. IR (KBr): 780, 840, 1726, 2953 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 3.96 (s, 3 H), 7.77 (d, J = 16.0 Hz, 2 H), 7.80–7.81 (m, 4 H), 7.84 (d, J = 18.4 Hz, 3 H), 7.79 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 2 H), 10.08 (s 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 52.9, 127.7, 127.9, 128.1, 129.3, 130.5, 133.3, 135.6, 135.1, 139.1, 139.9, 143.5, 146.3, 167.7, 168.4, 191.9. HRMS(Q-ToF): *m/z* calcd for $C_{23}H_{19}O_5$ [M + H]$^+$: 375.1232; found: 375.1233.

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