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Construction of Multi-Substituted Benzenes via NHC-Catalyzed Reactions of Carboxylic Esters

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ABSTRACT A carbene-catalyzed ester activation reaction for the synthesis of multi-substituted benzenes is developed. Tetra-substituted benzene compounds are efficiently synthesized through this methodology. Compared with aldehyde substrates used in previous reports, the ester substrates used here are much more readily available and inexpensive. In addition, the TEMPO oxidant used here is more inexpensive than the quinones commonly used in related carbene-catalyzed reactions.

KEYWORDS *N*-heterocyclic carbene, carboxylic ester, benzene synthesis, organocatalysis, TEMPO oxidation

Introduction

Substituted benzenes are frequently found in both natural products and pharmaceuticals.[1] More than 70% of the best sold human medicines contain at least one benzene ring in their structures.[2] Therefore, the synthesis of substituted benzenes is important. Traditionally, benzene rings with different substituents were prepared through electrophilic substitutions on the benzene structures[3] or transition metal-catalyzed cross coupling reactions using halogenated benzenes.[4] The direct construction of the benzene rings through transition metal catalysis was disclosed more than 50 years ago.[5] Various excellent methodologies have been developed within this field including the transition metal catalyzed [2+2+2] and [4+2] reactions.[6] However, the construction of benzene rings through organocatalytic reactions has been much less developed.[7] Therefore, developing a range of organocatalytic methodologies that are complimentary to each other to provide multiple strategies in the synthesis of substituted benzenes is important.

We are interested in constructing various aromatic rings through metal-free organocatalytic reactions.[8] We have previously reported the *N*-heterocyclic carbene (abbreviated as NHC or carbene) catalyzed [3+3] oxidative reaction for the synthesis of multi-substituted benzene compounds.[9] *β*-Methyl substituted *α*,*β*-unsaturated aldehydes were used to react with oxadienes to afford 2,4,6-tri-substituted acetophenones in moderate to good yields. The activation of the *δ*-carbons on rationally designed vinylogous enals has also been developed to synthesize a variety of multi-substituted benzene molecules.[10] However, as a technical note, the aldehyde substrates used in these methods are routinely prepared from corresponding esters through a sequential reduction/oxidation process (Figure 1a, right part). Therefore, the direct activation of ester substrates in the benzene synthesis is interesting.[11] Herein, we report the construction of substituted benzene rings through NHC catalytic reactions using *β*-methyl substituted *α*,*β*-unsaturated esters as the starting materials (Figure 1a, left part). Mechanistically, the *α*,*β*-unsaturated carboxylic ester **1** is initially attacked by the carbene catalyst and gives the acyl azolium intermediate **I**, which could react with oxadiene **2** through Michael addition/enolization processs to form intermediate **II**. Intermediate **II** then goes through an intramolecular aldol reaction to form intermediate **III**, which leads to **IV** through lactone formation and liberates the NHC catalyst. Decarboxylation of **IV** delivers intermediate **V**, which finally afford the benzene product **3** through an additional oxidation step (Figure 1b).

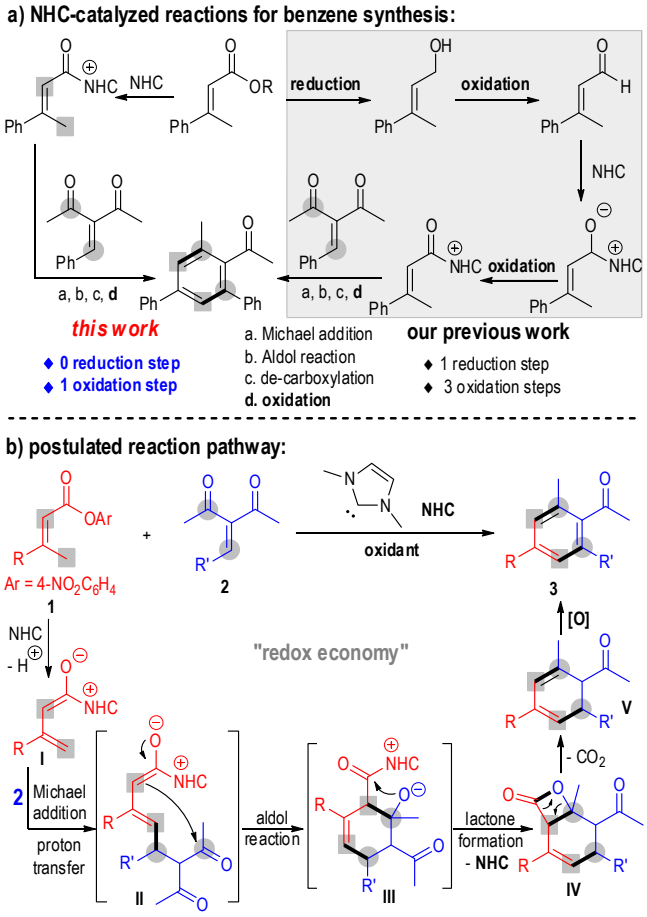

Figure 1 NHC-catalyzed ester activation for benzene synthesis.

Results and Discussion

The *β*-methyl substituted *α*,*β*-unsaturated ester **1a** was chosen as the model substrate to react with oxadiene **2a**. The substituted benzene product **3a** could be afforded in 28% yield with air as the oxidant with the use of NHC pre-catalyst **A** (Table 1, Entry 1). No or trace product could be observed when using **B**, **C** or **D** as the NHC pre-catalysts (Entry 2). The product yield could be dra-

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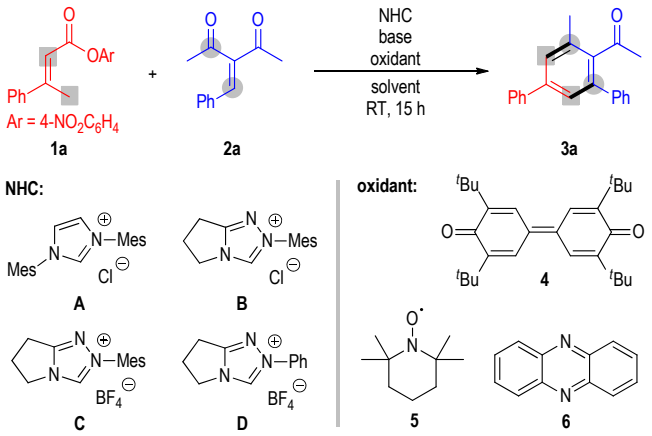
matically increased when oxidant **4**[12] was added into the catalytic system (Entry 3). A variety of oxidants were then examined for this catalytic process (Entries 3 to 6). The radical oxidant TEMPO **5**[13] could give the benzene product **3a** in 75% yield (Entry 4). The substituted benzene **3a** could also be afforded with phenazine **6** or MnO_2 as the oxidants, although the product yields were slightly lower. The yield of **3a** could be further improved to 86% when 2 equiv. of the TEMPO **5** was applied as the oxidative additive (Entry 7). We then decided to use 2 equiv. of **5** as the oxidant in the following examinations of different bases and solvents (Entries 8 to 11). Switching the base additives from Cs_2CO_3 to other organic/inorganic bases led to drops of the product yields (*e.g.*, Entries 8 to 9). A variety of organic solvents could be used for this transformation (*e.g.*, Entries 10 to 11), but the product yields did not show further improvements comparing with the reaction using THF as the solvent (Entry 7). It is worth noting that the radical oxidant TEMPO **5** ($ 20/g, TCI) used in this methodology is less expensive than the oxidant **4** ($ 146/g, TCI) used in our previous aldehyde activation approaches.[9,10]

Table 1 Condition optimization[a]

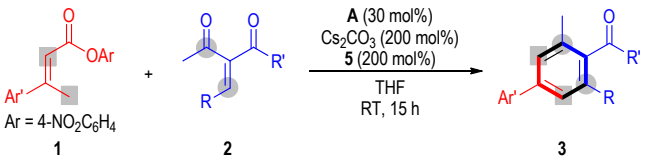


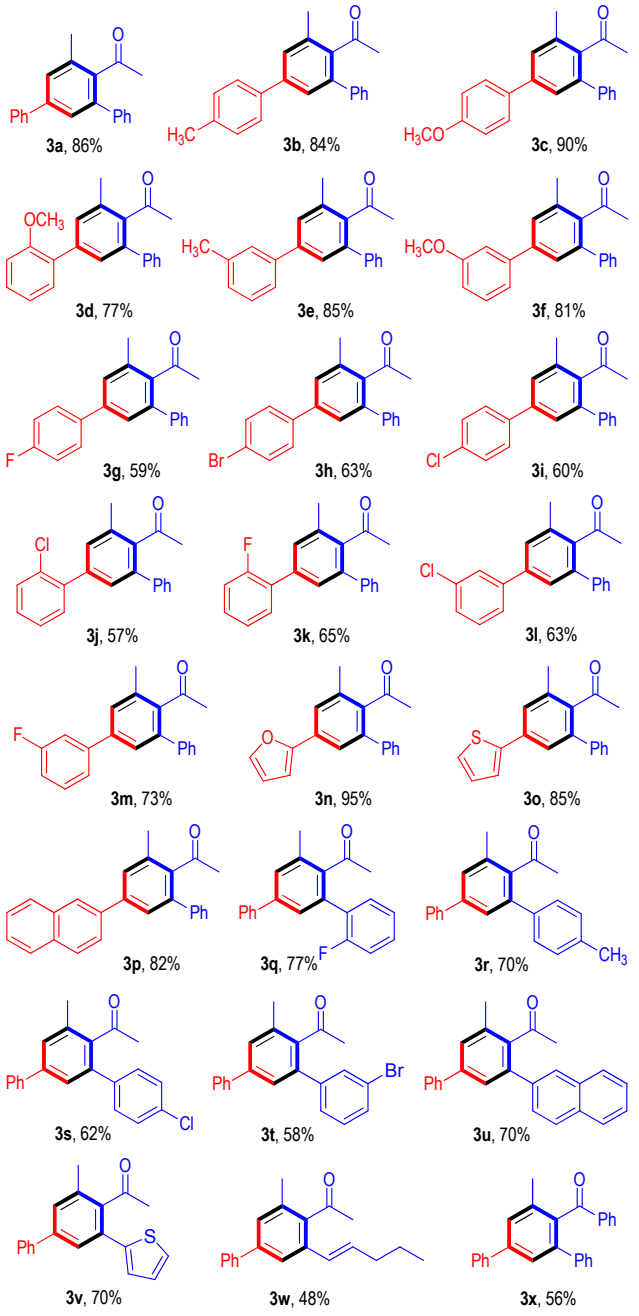
Entry	Cat.	Base	Oxidant	Solvent	Yield[b]/%
1	**A**	Cs_2CO_3	—[c]	THF	28
2	**B/C/D**	Cs_2CO_3	—[c]	THF	<5
3	**A**	Cs_2CO_3	**4**	THF	69
4	**A**	Cs_2CO_3	**5**	THF	75
5	**A**	Cs_2CO_3	**6**	THF	62
6	**A**	Cs_2CO_3	MnO_2	THF	52
7[d]	**A**	Cs_2CO_3	**5**	THF	86
8[d]	**A**	DBU	**5**	THF	44
9[d]	**A**	TEA	**5**	THF	0
10[d]	**A**	Cs_2CO_3	**5**	CH_2Cl_2	70
11[d]	**A**	Cs_2CO_3	**5**	CH_3CN	68

[a] 1.0 equiv. **1a** (0.1 mmol), 1.0 equiv. **2a**, 30 mol% NHC, 200 mol% base, 1.0 equiv. oxidant, 1.2 mL THF, r.t., 15 h. [b] Yields were isolated yields via SiO_2 column chromatography. [c] Under air. [d] 2.0 equiv. oxidant **5** was used.

With an optimized reaction condition in hand, we then tested the scope of this benzene constructing process using substrates with different substitution patterns (Table 2). Electron donating substitutents were well torlerated on each position of the *β*-benzene rings of the ester substrates **1**, with the corresponding tetra-substituted benzene products afforded in good isolated yields (**3b** to **3f**). Electron withdrawing groups also worked well in this transformation, although the product yields were slightly lower (**3g** to **3m**). The substituted benzene rings on substrates **1** could even be switched to a variety of hetero aromatic groups (**3n** to **3o**) or a napthyl group (**3p**) and the products could be isolated

Table 2 Substrate scope[a]





[a] Reactions were carried out under conditions as stated in Table 1, Entry 7. The product yields indicated isolated yields after column chromatography.

in good to excellent yields. However, no products could be observed when the *β*-aryl groups on the ester substrates **1** were replaced with alkyl groups. This might be because that the C—H bond on the *β*-dialkyl ester is not sufficiently acidic to be activated by the NHC catalyst to react with the oxadiene substrates. Substituents with different electronic properties could also be installed on the *β*-benzene rings of the oxadiene substrates **2**, with all the products afforded in moderate to good isolated yields (**3q** to **3u**). Notably, the aryl groups on substrates **2** could be replaced with

either a hetero aromatic thiophenyl group (**3v**) or even an aliphatic alkene group with a conjugated double bond installed next to the β-position of oxadiene substrate (**3w**). One of the methyl groups attached to the ketone moieties of the substrate **2** could be replaced with an aromatic benzene substituent, although the corresponding product could only be afforded in moderate yield under the current catalyic reaction condition (**3x**).

Conclusions

In summary, we have developed a carbene catalyzed ester activation reaction for the construction of substituted benzene rings. 2,4,6-Tri-substituted acetophenones (tetra-substituted benzenes) could be efficiently synthesized in up to 95% isolated yields through this strategy. This newly developed methodology processes certain advantages over the previous aldehyde activation approaches because the ester substrates used here are easily prepared and inexpensive. Moreover, the TEMPO oxidant used in this method is much more inexpensive than the quinone oxidant **4** that has been frequently used in the aldehyde oxidative activations. Further investigations on the synthesis of multi-substituted aromatic compounds through organocatalytic reactions are currently in progress in our laboratory.

Experimental

General information

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker (500 or 400 MHz) spectrometer. Chemical shifts were recorded (δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26, singlet). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), *etc*. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (126 MHz) (101 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Thermo Fisher Q Exactive mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on pre-coated silica gel plate (0.2 mm thickness). Melting Point (m.p.): Melting points were measured on a Beijing Tech XT-4 micro melting point apparatus and are uncorrected. Visualization was performed using a UV lamp.

General procedure for the preparation of substrates 1

To a 100 mL round bottom flask containing NaH (46 mmol, 60% mineral dispersion) and anhydrous THF (92 mL) at 0 °C, was added triethyl phosphonoacetate (49.6 mmol) dropwise via an addition funnel. The reaction mixture was gradually warmed to r.t., followed by a dropwise addition of the ketone solution (20 mmol, in 46 mL anhydrous THF). The reaction mixture was stirred for 12 h, and then quenched with water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (50 mL×2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography [*V*(hexanes)/*V*(EtOAc)=95/5] to afford the corresponding α,β-unsaturated ester **S2**. To a 100 mL round bottom flask was added α,β-unsaturated ester **S2** (15 mmol), 0.5 N aqueous KOH (42 mL) and the reaction mixture was stirred at 100 °C until the oil layer disappeared. After cooling to rt, 1 mol/L aqueous HCl solution (200 mL) was carefully added and the reaction mixture was extracted with diethyl ether (100 mL×3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and filtered, the solvent was removed under reduced pressure to afford the desired α,β-unsaturated acid **S3**, which was used in the next reaction without further purification. To a 50 mL round bottom flask containing α,β-unsaturated acids **S3** (10 mmol) and EtOAc (15 mL) was successively added 4-nitrophenol (11 mmol), DCC (11 mmol) and DMAP (0.4 mmol), and the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the precipitate was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was subjected to flash chromatography [*V*(hexanes)/*V*(EtOAc)=5/1] to give substrate **1**.

General procedure for the preparation of substrates 2

$AlCl_3$ (0.2 mmol) was added to a solution of the β-diketone (1.0 mmol) in DCM (2 mL) and the mixture was stirred at room temperature for 5 min. Then the aldehyde (1.0 mmol) was added and the resulting system was stirred at room temperature until the reaction was complete (determined by TLC). Then the reaction was quenched with saturated $NaHCO_3$ solution. After extraction with DCM (10 mL×3), the organic phase was collected and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by silica gel column chromatography.

1-(5'-Methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3a). Light yellow oil, 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64—7.62 (m, 2H), 7.38—7.64 (m, 10H), 2.41 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.69, 141.96, 140.68, 140.43, 139.49, 134.67, 129.23, 129.22, 129.21, 129.08, 128.91, 128.55, 128.09, 127.99, 127.43, 126.41, 32.38, 20.02; HRMS (ESI) calcd for $C_{21}H_{19}O$ $[M+H]^+$: 287.1430, found 287.1431.

1-(4,5'-Dimethyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3b). Light yellow powder, 84% yield; m.p.: 143—144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54—7.52 (m, 2H), 7.44—7.39 (m, 7H), 2.41 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.66, 141.68, 140.56, 139.95, 139.28, 137.65, 137.30, 134.47, 129.57, 128.99, 128.67, 128.13, 127.82, 127.02, 125.99, 32.19, 21.14, 19.82; HRMS (ESI) calcd for $C_{22}H_{21}O$ $[M+H]^+$: 301.1587, found 301.1586.

1-(4-Methoxy-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3c). Light yellow oil, 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.58—7.56 (m, 2H), 7.43—7.39 (m, 7H), 7.00—6.98 (m, 2H), 3.86 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.90, 141.87, 140.63, 140.36, 140.31, 137.67, 137.57, 135.88, 133.14, 129.39, 129.21, 128.90, 128.32, 128.10, 128.06, 127.77, 127.29, 127.25, 126.22, 19.95; HRMS (ESI) calcd for $C_{22}H_{20}O_2Na$ $[M+Na]^+$: 339.1356, found 339.1361.

1-(2-Methoxy-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3d). Light yellow oil, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45—7.30 (m, 9H), 7.07—6.95 (m, 2H), 3.84 (s, 3H), 2.37 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.85, 156.56, 140.75, 139.98, 139.27, 138.52, 133.67, 130.95, 130.79, 129.79, 129.57, 129.15, 128.67, 127.73, 120.99, 117.38, 111.31, 55.71, 32.26, 19.85; HRMS (ESI) calcd for $C_{22}H_{21}O_2$ $[M+H]^+$: 317.1536, found 317.1528.

1-(3,5'-Dimethyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3e). Light yellow oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (t, *J*=3.8 Hz, 4H), 7.42—7.37 (m, 5H), 7.33 (t, *J*=7.8 Hz, 1H), 7.21—7.17 (m, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.64, 141.92, 140.56, 140.22, 140.16, 139.28, 138.50, 134.45, 129.03, 128.78, 128.69, 128.53, 128.37, 127.99, 127.85, 126.24, 124.33, 32.19, 21.54, 19.81; HRMS (ESI) calcd for $C_{22}H_{21}O$ $[M+H]^+$: 301.1587, found 301.1587.

1-(3-Methoxy-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3f). Light yellow oil, 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (dd, *J*=6.8, 3.7 Hz, 3H), 7.42—7.38 (m, 4H), 7.38—7.34 (m, 1H), 7.23—7.18 (m, 1H), 7.16—7.12 (m, 1H), 6.93—6.91 (m, 1H), 3.86 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.62, 160.11, 141.84, 141.74, 140.54, 140.46, 139.36, 134.57,

129.96, 129.10, 128.78, 128.48, 127.96, 126.34, 119.79, 113.28, 113.03, 55.45, 32.24, 19.88; HRMS (ESI) calcd for $C_{22}H_{21}O_2$ $[M+H]^+$: 317.1536, found 317.1528.

1-(4-Fluoro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3g). Light yellow oil, 59% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60—7.57 (m, 2H), 7.43—7.39 (m, 7H), 7.16—7.12(m, 2H), 2.40 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.47, 162.82 (d, J_{cf}=247.2 Hz), 140.84, 140.45, 140.34, 139.48, 136.46, 134.69, 129.07, 128.87 (d, J_{cf}=8.1 Hz), 128.78, 128.27, 128.00, 126.14, 115.83 (d, J_{cf}=21.4 Hz), 32.20, 19.84; ^{19}F NMR (471 MHz, $CDCl_3$) δ: –114.75; HRMS (ESI) calcd for $C_{21}H_{18}OF$ $[M+H]^+$: 305.1336, found 305.1338.

1-(4-Bromo-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3h). Light yellow powder, 63% yield; m.p.: 176—177 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61—7.55 (m, 2H), 7.51—7.47 (m, 2H), 7.45—7.37 (m, 7H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.53, 140.60, 140.32, 139.54, 139.21, 134.81, 132.07, 129.06, 128.87, 128.83, 128.18, 128.07, 126.06, 122.19, 32.23, 19.89; HRMS (ESI) calcd for $C_{21}H_{18}OBr$ $[M+H]^+$: 365.0536, found 365.0642.

1-(4-Chloro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3i). Light yellow powder, 60% yield; m.p.: 159—160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.57—7.54 (m, 2H), 7.44—7.42 (m, 2H), 7.42—7.39 (m, 7H), 2.40 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.39, 140.57, 140.37, 139.53, 138.76, 134.76, 134.01, 129.10, 129.06, 128.79, 128.51, 128.21, 128.03, 126.10, 32.18, 19.84; HRMS (ESI) calcd for $C_{21}H_{18}OCl$ $[M+H]^+$: 321.1041, found 321.1040.

1-(2-Chloro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3j). Light yellow oil, 57% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51—7.47 (m, 1H), 7.42—7.34 (m, 6H), 7.34—7.29 (m, 4H), 2.38 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.68, 140.48, 140.24, 139.93, 139.61, 138.47, 133.79, 132.43, 131.34, 130.57, 130.07, 129.04, 128.88, 128.67, 128.54, 127.85, 126.93, 32.17, 19.70; HRMS (ESI) calcd for $C_{21}H_{18}OCl$ $[M+H]^+$: 321.1041, found 321.1028.

1-(2-Fluoro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3k). Light yellow oil, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (td, J=7.7, 1.8 Hz, 1H), 7.43—7.30 (m, 8H), 7.24—7.13 (m, 2H), 2.39 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.47, 160.00, 157.53, 139.55, 139.23, 137.87, 135.37, 133.07, 129.69 (d, J=3.3 Hz), 129.13 (d, J=2.9 Hz), 128.39 (d, J=8.3 Hz), 128.00, 127.64, 127.21, 127.08, 127.01 (d, J=2.8 Hz), 126.83, 123.41 (d, J=3.7 Hz), 115.15 (d, J=22.7 Hz), 31.09, 18.69; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –117.61; HRMS (ESI) calcd for $C_{21}H_{18}OF$ $[M+H]^+$: 305.1336, found 305.1332.

1-(3-Chloro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3l). Light yellow oil, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (t, J=1.6 Hz, 1H), 7.49 (dt, J=7.3, 1.7 Hz, 1H), 7.45—7.32 (m, 9H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.38, 142.08, 140.77, 140.32, 140.21, 139.46, 134.79, 134.72, 130.10, 129.00, 128.75, 128.28, 128.00, 127.78, 127.34, 126.18, 125.37, 32.13, 19.78; HRMS (ESI) calcd for $C_{21}H_{18}OCl$ $[M+H]^+$: 321.1041, found 321.1032.

1-(3-Fluoro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3m). Light yellow oil, 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48—7.36 (m, 9H), 7.35—7.28 (m, 1H), 7.12—7.02 (m, 1H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.16 (d, J=246.0 Hz), 141.47 (d, J=7.6 Hz), 129.31 (d, J=8.4 Hz), 113.53 (d, J=21.2 Hz), 113.08 (d, J=22.1 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ: –112.68; HRMS (ESI) calcd for $C_{21}H_{18}OF$ $[M+H]^+$: 305.1336, found 305.1349.

1-(5-(Furan-2-yl)-3-methyl-[1,1'-biphenyl]-2-yl)ethanone (3n). Light yellow oil, 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (d, J=5.6 Hz, 2H), 7.48 (d, J=1.0 Hz, 1H), 7.42—7.38 (m, 5H), 6.71 (d, J=3.3 Hz, 1H), 6.49 (dd, J=3.1, 1.7 Hz, 1H), 2.36 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.41, 153.19, 142.66, 140.43, 140.23, 139.47, 134.69, 131.30, 129.02, 128.77, 128.00, 124.80, 122.82, 111.89, 106.18, 32.20, 19.87; HRMS (ESI) calcd for $C_{19}H_{17}O_2$ $[M+H]^+$: 277.1223, found 277.1223.

1-(3-Methyl-5-(thiophen-2-yl)-[1,1'-biphenyl]-2-yl)ethanone (3o). Light yellow oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49—7.42 (m, 3H), 7.42—7.35 (m, 5H), 7.32 (dd, J=5.1, 1.1 Hz, 1H), 7.10 (dd, J=5.1, 3.6 Hz, 1H), 2.37 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.23, 143.30, 140.35, 140.24, 139.56, 134.90, 134.83, 128.97, 128.74, 128.15, 128.00, 126.97, 125.53, 124.84, 123.84, 32.12, 19.75; HRMS (ESI) calcd for $C_{19}H_{17}OS$ $[M+H]^+$: 293.0995, found 293.0992.

1-(3-Methyl-5-(naphthalen-2-yl)-[1,1'-biphenyl]-2-yl)ethanone (3p). Light yellow powder, 82% yield; m.p.: 110—111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J=1.4 Hz, 1H), 7.97—7.85 (m, 3H), 7.78 (dd, J=8.5, 1.9 Hz, 1H), 7.59 (dd, J=3.5, 0.5 Hz, 2H), 7.56—7.47 (m, 2H), 7.46—7.41 (m, 5H), 2.44 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.56, 141.66, 140.51, 140.31, 139.45, 137.52, 134.65, 133.64, 132.86, 129.06, 128.73, 128.58, 128.26, 127.92, 127.69, 126.46, 126.22, 126.07, 125.37, 32.20, 19.86; HRMS (ESI) calcd for $C_{25}H_{21}O$ $[M+H]^+$: 337.1587, found 337.15

1-(2''-Fluoro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3q). Light yellow oil, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (dd, J=8.3, 1.2 Hz, 2H), 7.49—7.44 (m, 4H), 7.39—7.37 (m, 2H), 7.30 (td, J=7.5, 1.7 Hz, 1H), 7.23—7.14 (m, 2H), 2.43 (s, 3H), 2.09 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.48, 159.47 (d, J=246.8 Hz), 141.69, 140.94, 140.13, 134.61, 132.88, 132.06, 130.06 (d, J=8.1 Hz), 129.03 (d, J=25.5 Hz), 127.89, 127.79, 127.24 (d, J=20.9 Hz), 124.40, 124.37, 116.02 (d, J=22.1 Hz), 31.78, 20.03; ^{19}F NMR (471 MHz, $CDCl_3$) δ: –114.97; HRMS (ESI) calcd for $C_{21}H_{18}OF$ $[M+H]^+$: 305.1336, found 305.1328.

1-(4'',5'-Dimethyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3r). Light yellow oil, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64—7.58 (m, 2H), 7.48—7.40 (m, 4H), 7.36 (td, J=7.1, 3.2 Hz, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.22 (d, J=7.9 Hz, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.81, 141.83, 140.41, 140.28, 139.40, 137.80, 137.64, 134.54, 129.49, 128.96, 128.93, 128.23, 127.81, 127.30, 126.31, 32.28, 21.29, 19.90; HRMS (ESI) calcd for $C_{22}H_{21}O$ $[M+H]^+$: 301.1587, found 301.1586.

1-(4''-Chloro-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3s). Light yellow oil, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (dd, J=8.3, 1.3 Hz, 2H), 7.52—7.42 (m, 3H), 7.42—7.31 (m, 6H), 2.39 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.35, 141.94, 140.22, 140.07, 138.89, 137.89, 134.59, 134.16, 130.31, 128.91, 128.90, 128.68, 127.88, 127.21, 126.09, 32.31, 19.74; HRMS (ESI) calcd for $C_{21}H_{18}OCl$ $[M+H]^+$: 321.1041, found 321.1039.

1-(3''-Bromo-5'-methyl-[1,1':3',1''-terphenyl]-4'-yl)ethanone (3t). Light yellow oil, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (dt, J=3.7, 1.5 Hz, 3H), 7.56—7.50 (m, 1H), 7.50—7.42 (m, 3H), 7.39 (dd, J=4.4, 2.8 Hz, 2H), 7.35—7.27 (m, 2H), 2.39 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.11, 142.53, 141.96, 140.15, 139.99, 137.61, 134.66, 131.78, 130.96, 130.15, 128.91, 128.88, 127.91, 127.83, 127.22, 126.12, 122.81, 32.35, 19.79; HRMS (ESI) calcd for $C_{21}H_{18}OBr$ $[M+H]^+$: 365.0536, found 365.0532.

1-(3-methyl-5-(naphthalen-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (3u). Light yellow powder, 70% yield; m.p.: 100—101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03—7.83 (m, 4H), 7.69—7.62 (m, 2H), 7.58—7.50 (m, 4H), 7.49—7.44 (m, 3H), 7.39 (dt, J=9.4, 4.3 Hz, 1H), 2.43 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.62, 141.87, 140.43, 140.26, 139.24, 137.92, 134.67, 133.27, 132.69, 128.90, 128.49, 128.46, 128.29, 128.13, 127.82, 127.74, 127.26, 126.96, 126.61, 126.56, 126.46, 32.30, 19.87; HRMS (ESI) calcd for $C_{25}H_{21}O$ $[M+H]^+$: 337.1587, found 337.1587.

1-(3-Methyl-5-(thiophen-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (3v). Light yellow oil, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60

(d, J=7.9 Hz, 2H), 7.52 (s, 1H), 7.48—7.33 (m, 3H), 7.11—6.99 (m, 2H), 2.37 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.53, 141.97, 141.43, 140.32, 140.08, 134.59, 131.50, 128.96, 127.95, 127.86, 127.30, 126.62, 126.56, 125.25, 122.65, 31.87, 19.73; HRMS (ESI) calcd for $C_{19}H_{17}OS$ $[M+H]^+$: 293.0995, found 293.0990.

(*E*)-1-(3-Methyl-5-(pent-1-en-1-yl)-[1,1'-biphenyl]-4-yl)ethanone (3w). Light yellow oil, 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62—7.53 (m, 2H), 7.50—7.41 (m, 3H), 7.37 (d, J=7.3 Hz, 1H), 7.28 (d, J=0.7 Hz, 1H), 6.39 (dd, J=23.0, 13.5 Hz, 1H), 6.19 (dt, J=15.6, 6.9 Hz, 1H), 2.49 (s, 3H), 2.31 (s, 3H), 2.19 (dd, J=14.6, 7.0 Hz, 2H), 1.49 (dd, J=14.7, 7.3 Hz, 2H), 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.34, 141.68, 140.65, 139.69, 135.09, 134.49, 133.21, 128.78, 127.74, 127.59, 127.19, 126.91, 122.58, 35.34, 32.76, 22.37, 19.31, 13.72; HRMS (ESI) calcd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743, found 279.1743.

1-(5'-Phenyl-[1,1':3',1''-terphenyl]-2'-yl)ethanone (3x). Light yellow oil, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74—7.60 (m, 3H), 7.59—7.45 (m, 4H), 7.41 (dd, J=7.2, 1.8 Hz, 2H), 7.34—7.27 (m, 3H), 7.23—7.10 (m, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.90, 141.87, 140.63, 140.36, 140.31, 137.67, 137.57, 135.88, 133.14, 129.39, 129.21, 128.90, 128.32, 128.10, 128.06, 127.77, 127.29, 127.25, 126.22, 19.95; HRMS (ESI) calcd for $C_{26}H_{21}O$ $[M+H]^+$: 349.1587, found 349.1577.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201700773.

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