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Pd-catalyzed oxidative acylation of 2-phenoxypyridines with alcohols via C–H bond activation

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ABSTRACT

A palladium-catalyzed oxidative acylation of 2-phenoxypyridines with benzylic and aliphatic alcohols via C–H bond activation is described. This protocol represents direct access to biologically active *ortho*-acylphenol derivatives, and provides new opportunities to use readily available alcohols as starting materials for catalytic acylation reactions.

1. Introduction

The *ortho*-acylphenols are widely distributed in a number of bioactive molecules ranging from natural products to drugs (Fig. 1).[1] They also serve as versatile building blocks for the formation of various pharmaceuticals, agrochemicals, and fragrances.[2]

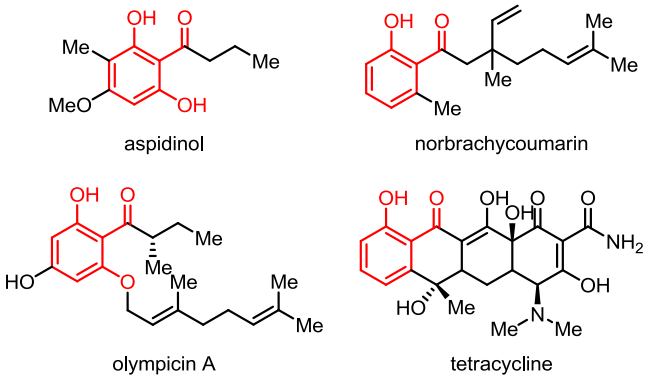

Fig. 1. Selected examples for bioactive molecules containing *ortho*-acylphenol framework.

Direct C-acylation of phenols[3] and anionic Fries rearrangement of phenyl esters[4] are common approaches for the synthesis of *ortho*-acylphenols. However, from a synthetic point of view, these approaches have intrinsic drawbacks, including the use of hazardous organometallic reagents, harsh reaction conditions, and the formation of undesired *para*-acylated compounds. Therefore, it is highly desirable to develop novel and efficient protocols involving fewer synthetic steps and readily available starting materials for the synthesis of *ortho*-acylphenols.

Transition metal-catalyzed cross-coupling reaction via selective C–H bond activation has emerged as an attractive alternative to traditional cross-coupling reactions due to the minimization of stoichiometric metallic waste and the costs associated with the preparation of starting materials.[5] Thus, cross-coupling reactions via C–H bond activation can lead to an improved overall efficiency of the desired transformation. Since the pioneering efforts of Murai,[6] remarkable progress on C–H bond activation has been focused on dehydrogenative cross-coupling between sp^2 C–H bonds and sp^2 or sp^3 C–H bonds.[7] In particular, various directing groups such as ketones, carboxylic acids, amides, pyrroles/pyridines, anilides, carbamates, ureas, and azine-*N*-oxides can provide an anchor for selective *ortho*-metalation on aromatic rings.

Recently, transition metal-catalyzed oxidative acylation[8] of aromatic C–H bonds with various directing groups, such as pyridines,[9] amides,[10] oximes,[11] acetanilides,[12] and indoles,[13] using aldehydes as acyl sources have been described. Catalytic decarboxylative acylations of acetanilides,[14] arylpyridines,[15] enamides,[16]

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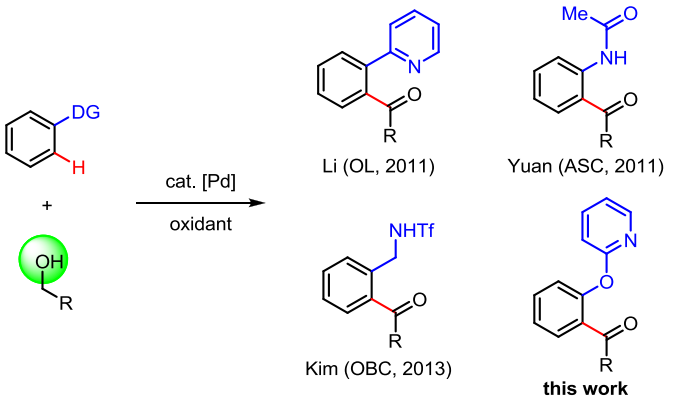
oximes,[17] acetamides,[18] carbamates,[19] indoles,[20] and formamides[21] using α-oxocarboxylic acids as acyl surrogates were also reported. Recently, a palladium-catalyzed acylation of 2-arylpyridines via C–C bond cleavage of α-diketones was demonstrated.[22] However, transition metal-catalyzed oxidative acylation on aromatic sp^2 C–H bonds from the alcohol oxidation level is relatively unexplored (Scheme 1). Li et al. first described a Pd-catalyzed oxidative *ortho*-acylation of arylpyridines with benzylic and aliphatic alcohols as acyl equivalents via C–H bond activation.[23] Yuan and co-workers also demonstrated a palladium-catalyzed oxidative C–H bond acylation of acetanilides with benzylic alcohols.[24] Recently, we reported a palladium-catalyzed oxidative *ortho*-acylation of *N*-benzyltriflamides with benzylic and aliphatic alcohols from the alcohol oxidation level.[25] Alcohols have long served as versatile substrates for carbon–carbon bond formation.[26] Notably, alcohols are available at low cost in great structural diversity, and are easy to handle and to store. Also, alcohols can be readily oxidized into aldehydes under metal catalysis.[27] Thus alcohols can be reliable candidates for the catalytic acylation reaction. 2-Pyridinyl groups are readily introduced to phenols via copper-catalyzed coupling between phenols and pyridines,[28] and have been used as directing groups in C–H bond activation protocols.[29]



Scheme 1. Pd-catalyzed oxidative acylation of sp^2 C–H bonds from the alcohol oxidation level.

As part of an ongoing research program directed toward the development of catalytic carbon–carbon bond forming reactions, we became interested in developing an efficient synthetic route to *ortho*-acylphenols via C–H bond activation. Herein we present the palladium-catalyzed *ortho*-acylation of 2-phenoxypyridines with benzylic and aliphatic alcohols under *tert*-butyl hydroperoxide (TBHP) as a convenient oxidant from the alcohol oxidation level.

2. Results and discussion

Our initial investigation focused on the coupling of phenol derivatives with benzyl alcohol (**2a**). After extensive screening of phenol derivatives with various protecting groups, including acetyl, pivaloyl, *N*,*N*-dimethylcarbamoyl, *p*-toluenesulfonyl, 2-pyrimidinyl and 2-pyridinyl, phenol derivative **1a** with 2-pyridinyl directing group was found to couple with 2 equiv of benzyl alcohol (**2a**) in the presence of 10 mol% of $Pd(OAc)_2$ and 3 equiv of *tert*-butyl hydrogperoxide (TBHP) in DCE solvent at 80 °C for 20 h to afford the desired product **3a** in 42% yield (Table 1, entry 1). Phenoxy-2-pyrimidine was also converted to the corresponding product in relatively low yield (14%), but phenol derivatives with other directing groups did not yield our desired *ortho*-acylphenol compounds under otherwise identical reaction conditions. Thus, phenol derivative **1a** was chosen as a model substrate for optimizing the reaction conditions. Screening of oxidants showed that TBHP is superior to other oxidants such as $(PhCOO)_2$, Ag_2O, $Cu(OAc)_2$, and $(NH_4)_2S_2O_8$ (Table 1, entries 2–5). After screening of solvents under otherwise identical conditions, DCE was found to be the most effective solvent in this coupling reaction, whereas other solvents such as DMF, THF, and MeCN were less effective (Table 1, entries 6–8). Further investigation of the effect of other palladium catalysts including $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, and $Pd(OTf)_2$ were performed (data not shown), and $Pd(OAc)_2$ was found to be most effective in this coupling reaction. Logically, it was thought that the formation of **3a** can be increased by the amount of alcohol and oxidant (Table 1, entries 9 and 10). Indeed, the use of 3 equiv of alcohol **2a** and 4 equiv of TBHP afforded our desired product **3a** in high yield (71%), as shown in entry 10. Further study revealed that a decreased loading of $Pd(OAc)_2$ was found to be less effective (Table 1, entry 11), and the use of AcOH additive failed to facilitate high levels of conversion (Table 1, entry 12). In addition, this coupling reaction did not proceed at room temperature, even for longer reaction time (Table 1, entry 13).

With the optimized reaction conditions in hand, the scope and limitation of the alcohol were explored (Table 2). The coupling of 2-(2-fluorophenoxy)pyridine (**1a**) and benzylic alcohols **2b**–**2i** with electron-donating and electron-withdrawing groups (OMe, Me, CO_2Me, CF_3, F, and Cl), regardless of substituent position on the aromatic ring, was found to be favored in the acylation reaction to afford the corresponding products **3b**–**3i** in good to high yields. Notably, *m*-chlorobenzyl alcohol (**2h**) was tolerated under these coupling conditions and offers versatile synthetic functionality for further elaboration. In addition, 1-naphthalenemethanol (**2j**) and 2-naphthalenemethanol (**2k**) smoothly underwent this coupling reaction to generate the corresponding products. To our delight, this reaction is not limited to benzylic alcohols. Aliphatic alcohols **2l** and **2m** also participated in the oxidative coupling to furnish **3l** and **3m** in 78% and 50% yields, respectively.

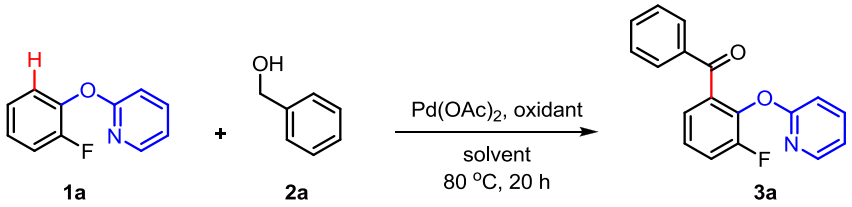
To further explore the substrate scope and limitations of this process, a broad range of phenoxy-2-pyridines was screened to couple with benzyl alcohol (**2a**), as shown in Table 3. The reaction of *meta*-substituted phenoxy-2-pyridines **1b**–**1d** preferentially occurred at the less hindered position to afford the corresponding product **4b**–**4d** in good yields as a single regioisomer owing to the steric effect that caused interference with either the formation of the cyclopalladated intermediate or the approach of the acyl radical into the cyclopalladated intermediate. In addition, this transformation also showed good reactivity toward *ortho*-substituted phenoxy-2-pyridines **1e**–**1g**. Notably, symmetrical phenoxy-2-pyridines **1h** and **1i** underwent smoothly the acylation reaction to afford the corresponding products **4h** and **4i** with a high to excellent level of monoselectivity. However, a symmetrical phenoxy-2-pyridine **1j** with an electron-donating group (OMe) gave the monoacylated product **4j** in 48% yield in conjunction with the bisacylated compound **4jj** in 14% yield.

To generate acylphenols, we next removed the 2-pyridinyl directing group based on the reported literature.[28] To our pleasure, a deprotection process smoothly underwent without affecting an acyl moiety to give the corresponding products **5a**–**5c** in high yields (Table 4).

3. Conclusion

In conclusion, a pyridinyl-directed Pd-catalyzed *ortho*-acylation of phenoxy-2-pyridines with benzylic and aliphatic alcohols from the alcohol oxidation level has been developed, which is an effective approach to access various *ortho*-acylphenol compounds. These transformations have been applied to a wide range of substrates, and typically proceed with excellent level of regio- and chemoselectivity as well as with high functional group tolerance.

Table 1
Selected optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Oxidant (equiv)	Solvent	Yield[b] (%)
1	TBHP (3)	DCE	42
2	$(PhCOO)_2$ (3)	DCE	11
3	Ag_2O (3)	DCE	N.R.
4	$Cu(OAc)_2$ (3)	DCE	N.R.
5	$(NH_4)_2S_2O_8$ (3)	DCE	N.R.
6	TBHP (3)	DMF	10
7	TBHP (3)	THF	8
8	TBHP (3)	MeCN	Trace
9[c]	TBHP (3)	DCE	56
10[c]	*TBHP (4)*	*DCE*	*71*
11[d]	TBHP (4)	DCE	52
12[e]	TBHP (4)	DCE	43
13[f]	TBHP (4)	DCE	N.R.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (quantity noted), solvent (1 mL) at 80 °C for 20 h in pressure tubes.
[b] Isolated yield by flash column chromatography.
[c] **2a** (0.6 mmol, 3 equiv).
[d] $Pd(OAc)_2$ (5 mol %).
[e] AcOH (50 mol %) was added as an additive.
[f] Room temperature, 40 h.

Further applications of this method to the synthesis of biologically active compounds are in progress.

4. Experimental

4.1. General methods

Commercially available reagents were used without additional purification, unless otherwise stated. Sealed tubes (13×100 mm^2) were purchased from Fischer Scientific and dried in oven for overnight and cooled under a stream of nitrogen prior to use. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker Unity 400 MHz and 700 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.24 ppm) and $CDCl_3$ δ_C (77.2 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

4.2. General procedure for the synthesis of phenoxy-2-pyridines

A mixture of cesium carbonate (3.2 g, 10 mmol), 2-chloropyridine (567 mg, 10 mmol), CuCl (25 mg, 2.5 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (92 mg, 0.5 mmol), and phenols (10 mmol) in NMP (8 mL) was degassed and filled with nitrogen three times. After the slurry was heated at 120 °C under nitrogen for 24 h, it was cooled to room temperature and diluted with EtOAc. The organic layer was washed subsequently with 2 M NaOH (30 mL) and saturated brine (3×30 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2: *n*-hexanes/EtOAc) to give the corresponding phenoxy-2-pyridines.

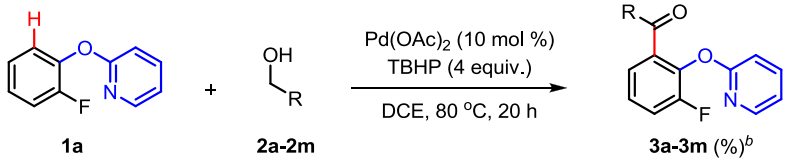
4.3. Typical procedure for the acylation of phenoxy-2-pyridines (3a–m and 4b–j)

To an oven-dried sealed tube with *o*-fluorophenoxy-2-pyridine (**1a**) (37.8 mg, 0.2 mmol, 100 mol %), $Pd(OAc)_2$ (4.8 mg, 0.02 mmol, 10 mol %), benzyl alcohol (**2a**) (64.9 mg, 0.6 mmol, 300 mol %) in DCE (1 mL) was added TBHP (0.146 mL, 0.8 mmol, 400 mol %). The reaction mixture was allowed to stir at 80 °C for 20 h. After cooling at room temperature, the reaction mixture was evaporated onto silica gel. Purification of the product by flash column chromatography (SiO_2: *n*-hexanes/EtOAc) provided **3a** (41.6 mg, 0.142 mmol) in 71% yield.

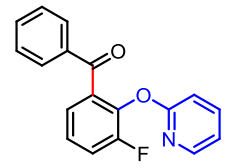
*4.3.1. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**3a**).* R_f=0.55 (*n*-hexanes/EtOAc=4:1); white solid; mp 82–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.74 (d, J=7.1 Hz, 2H), 7.54 (t, J=8.4 Hz, 1H), 7.46 (t, J=7.4 Hz, 1H), 7.35–7.27 (m, 5H), 6.91 (t, J=5.3 Hz, 1H), 6.68 (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 161.9, 155.1 (d, J_{C-F}=249.8 Hz), 146.3, 139.7, 139.0 (d, J_{C-F}=13.2 Hz), 136.9, 134.8, 133.1, 129.8, 128.0, 125.8 (d, J_{C-F}=7.4 Hz), 125.0 (d, J_{C-F}=3.6 Hz), 119.1 (d, J_{C-F}=18.9 Hz), 118.7, 110.7; IR (KBr) υ 2939, 2830, 1669, 1597, 1463, 1429, 1271, 1190, 1143, 1068, 887, 777 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{12}FNO_2$ $[M]^+$ 293.0852; found 293.0851.

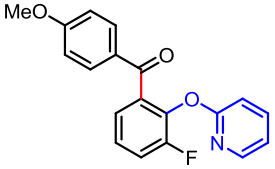
*4.3.2. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(4-methoxyphenyl)methanone (**3b**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=5.0 Hz, 1H), 7.74 (d, J=9.2 Hz, 2H), 7.52 (t, J=7.2 Hz, 1H), 7.33–7.24 (m, 3H), 6.89–6.86 (m, 1H), 6.79 (d, J=8.9 Hz, 2H), 6.71 (d, J=8.3 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 163.6, 162.3, 155.1 (d, J_{C-F}=249.4 Hz), 146.8, 139.2, 138.7 (d, J_{C-F}=13.6 Hz), 135.4, 132.9, 132.4, 129.8, 125.6

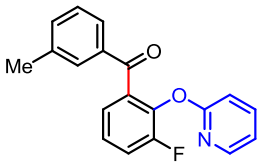
Table 2
Scope of alcohols[a]

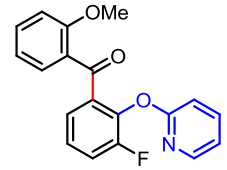


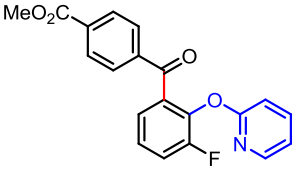
1a + **2a-2m** → **3a-3m** (%)[b]

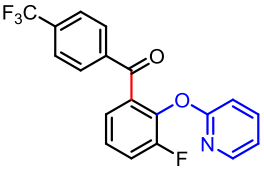

3a (71%)

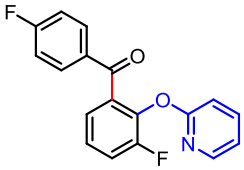

3b (72%)

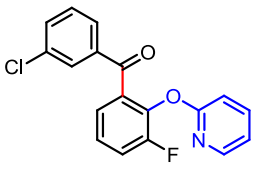

3c (71%)

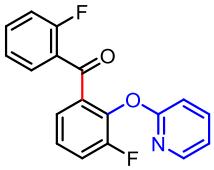

3d (84%)

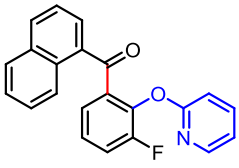

3e (61%)

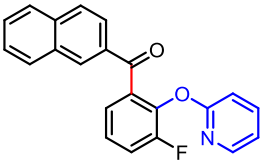

3f (87%)

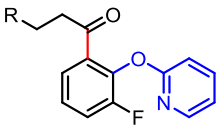

3g (76%)


3h (87%)


3i (72%)


3j (61%)


3k (75%)


3l (78%, R = Ph)
3m (50%, R = Me)

[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), TBHP (0.8 mmol), DCE (1 mL) at 80 °C for 20 h in pressure tubes. [b] Isolated yield by flash column chromatography.

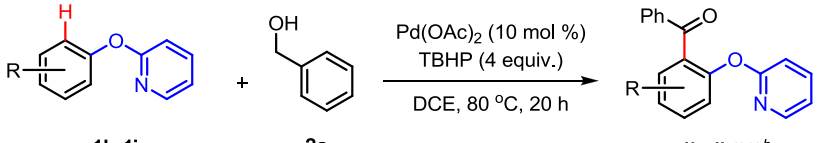
(d, J_{C-F}=7.3 Hz), 124.6 (d, J_{C-F}=3.6 Hz), 118.5 (d, J_{C-F}=19.0 Hz), 113.5, 110.6, 55.4; IR (KBr) υ 2939, 2841, 1661, 1598, 1462, 1429, 1238, 1169, 1031, 887, 776 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{14}FNO_3$ $[M]^+$ 323.0958; found 323.0965.

*4.3.3. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(m-tolyl)methanone (**3c**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); pale yellow sticky solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J=4.9 Hz, 1H), 7.56–7.49 (m, 3H), 7.35–7.24 (m, 4H), 7.21–7.17 (m, 1H), 6.88 (t, J=5.5 Hz, 1H), 6.67 (d, J=8.3 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 162.2, 155.2 (d, J_{C-F}=249.8 Hz), 146.8, 139.3, 139.1 (d, J_{C-F}=13.5 Hz), 137.9, 135.1, 133.9, 130.3, 128.0, 127.1, 125.6 (d, J_{C-F}=7.3 Hz), 124.9 (d, J_{C-F}=3.6 Hz), 118.9 (d, J_{C-F}=19.0 Hz), 118.6, 110.6, 21.1; IR (KBr) υ 2938, 2841, 1669, 1599, 1462, 1429, 1271, 1238, 1169, 1033, 883, 775 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{14}FNO_2$ $[M]^+$ 373.1009; found 373.1013.

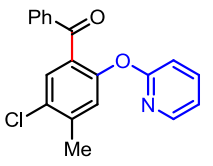
*4.3.4. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(2-methoxyphenyl)methanone (**3d**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (700 MHz, $CDCl_3$) δ 7.98 (d, J=5.0 Hz, 1H), 7.47–7.44 (m, 2H), 7.31–7.28 (m, 2H), 7.27–7.24 (m, 2H), 6.83–6.82 (m, 1H), 6.80–6.75 (m, 2H), 6.45 (d, J=8.3 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 193.4, 162.3, 158.1, 155.1 (d, J_{C-F}=249.4 Hz), 146.7, 139.3 (d, J_{C-F}=13.7 Hz), 138.9, 136.0, 132.8, 130.1, 129.1, 125.5 (d, J_{C-F}=7.0 Hz), 125.2 (d, J_{C-F}=2.6 Hz), 120.1, 119.4 (d, J_{C-F}=19.1 Hz), 118.2, 111.0, 110.2, 55.5; IR (KBr) υ 2946, 2844, 1666, 1599, 1464, 1380, 1270, 1241, 1049, 887, 756 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{14}FNO_3$ $[M]^+$ 373.0958; found 373.0954.

*4.3.5. Methyl 4-(3-fluoro-2-(pyridin-2-yloxy)benzoyl)benzoate (**3e**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (m, 3H), 7.76 (d, J=6.8 Hz, 2H), 7.49 (t, J=7.2 Hz, 1H), 7.37–7.28 (m, 3H), 6.87 (t, J=5.8 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 166.2, 162.0, 155.1 (d, J_{C-F}=249.7 Hz), 146.8, 140.6, 139.4, 139.3 (d, J_{C-F}=13.3 Hz), 134.3, 133.6, 129.5, 129.2, 125.8 (d, J_{C-F}=7.3 Hz), 125.1 (d, J_{C-F}=3.4 Hz), 119.6 (d, J_{C-F}=18.9 Hz), 118.6, 110.6, 52.4; IR (KBr) υ 2953, 1725, 1674, 1596, 1463, 1430, 1275, 1107, 964, 887,

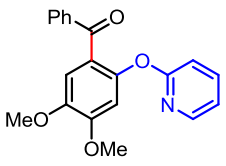
Table 3
Scope of phenoxy-2-pyridines[a]



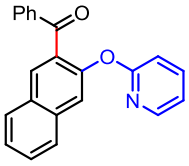
1b-1j **2a** **4b-4j** (%)[b]



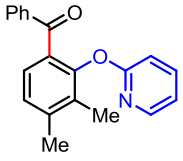
4b (65%)



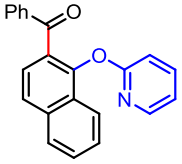
4c (58%)



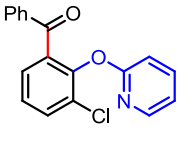
4d (66%)



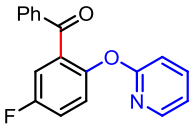
4e (82%)



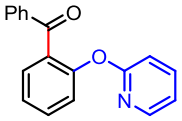
4f (61%)



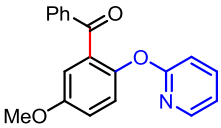
4g (67%)



4h (61%)



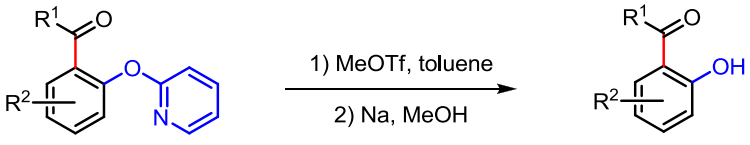
4i (71%)[c]



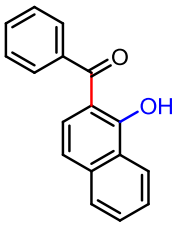
4j (48%)[d]

[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), TBHP (0.8 mmol), DCE (1 mL) at 80 °C for 20 h in pressure tubes. [b] Isolated yield by flash column chromatography. [c] Bisacylated compound **4ii** was also obtained in 9% yield. [d] Bisacylated compound **4jj** was also obtained in 14% yield.

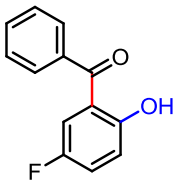
Table 4
Removal of directing group[a]



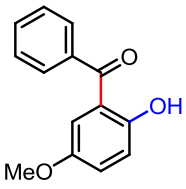
4f, 4h, 4j **5a-5c** (%)[b]



5a (89%)



5b (80%)



5c (88%)

[a] *Reaction conditions:* 1) **4f, 4h** and **4j** (0.3 mmol), MeOTf (0.51 mmol), toluene (10 mL) at 100 °C for 2 h under N_2; 2) Na (7.2 mmol), MeOH (10 mL) at 80 °C for 15 min under N_2. [b] Isolated yield by flash column chromatography.

777 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{14}FNO_4$ $[M]^+$ 351.0907; found 351.0916.

*4.3.6. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(4-(trifluoromethyl)phenyl)methanone (**3f**).* R_f=0.56 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=4.8 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 2H), 7.53–7.47 (m, 3H), 7.40–7.28 (m, 3H), 6.90 (t, *J*=5.6 Hz, 1H), 6.59 (d, *J*=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 161.8, 155.1 (d, J_{C-F}=250.0 Hz), 146.6, 140.2, 139.4, 139.2 (d, J_{C-F}=13.5 Hz), 134.1, 134.0 (q, J_{C-F}=32.6 Hz), 129.7, 125.9 (d, J_{C-F}=7.4 Hz), 125.1 (d, J_{C-F}=3.5 Hz), 124.9 (d, J_{C-F}=3.6 Hz), 123.5 (q, J_{C-F}=271.0 Hz), 119.6 (d, J_{C-F}=19.0 Hz), 118.8, 110.5; IR (KBr) υ 2947, 2846, 1677, 1596, 1463, 1403, 1327, 1271, 1171, 1130, 1015, 888, 765 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{11}F_4NO_2$ $[M]^+$ 361.0726; found 361.0730.

*4.3.7. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(4-fluorophenyl)methanone (**3g**).* R_f=0.60 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J*=5.0 Hz, 1H), 7.97–7.75 (m, 2H), 7.53 (t, *J*=8.4 Hz, 1H), 7.36–7.27 (m, 3H), 6.97 (t, *J*=8.6 Hz, 2H), 6.89 (t, *J*=5.0 Hz, 1H), 6.67 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 165.7 (d, J_{C-F}=253.6 Hz), 162.1, 155.1 (d, J_{C-F}=249.9 Hz), 146.7, 139.4, 138.9 (d, J_{C-F}=13.2 Hz), 134.6, 134.8, 133.5 (d, J_{C-F}=2.8 Hz), 132.5 (d, J_{C-F}=9.3 Hz), 125.8 (d, J_{C-F}=7.3 Hz), 124.7 (d, J_{C-F}=3.6 Hz), 119.1 (d, J_{C-F}=18.9 Hz), 118.7, 115.2 (d, J_{C-F}=21.8 Hz), 110.6; IR (KBr) υ 2946, 1671, 1597, 1462, 1429, 1271, 1237, 1153, 1068, 888, 776 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{11}F_2NO_2$ $[M]^+$ 311.0758; found 311.0758.

*4.3.8. (3-Chlorophenyl)(3-fluoro-2-(pyridin-2-yloxy)phenyl)methanone (**3h**).* R_f=0.50 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J*=4.9 Hz, 1H), 7.69 (s, 1H), 7.61 (d, *J*=7.7 Hz, 1H), 7.53 (t, *J*=7.2 Hz, 1H), 7.41–7.21 (m, 5H), 6.89 (t, *J*=5.4 Hz, 1H), 6.66 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 161.9, 155.1 (d, J_{C-F}=250.0 Hz), 146.87, 139.4, 139.1 (d, J_{C-F}=13.3 Hz), 138.7, 134.3, 134.2, 132.8, 129.6, 129.3, 127.7, 125.8 (d, J_{C-F}=7.4 Hz), 124.9 (d, J_{C-F}=3.5 Hz), 119.4 (d, J_{C-F}=18.9 Hz), 118.7, 110.5; IR (KBr) υ 2841, 1674, 1596, 1463, 1429, 1270, 1237, 1143, 1073, 890, 752 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{11}ClFNO_2$ $[M]^+$ 327.0462; found 327.0463.

*4.3.9. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(2-fluorophenyl)methanone (**3i**).* R_f=0.58 (*n*-hexanes/EtOAc=4:1); white solid; mp 43–46 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=5.0 Hz, 1H), 7.49–7.45 (m, 2H), 7.43–7.26 (m, 4H), 7.03–6.94 (m, 2H), 6.87 (t, *J*=5.0 Hz, 1H), 6.52 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 162.1, 160.7 (d, J_{C-F}=254.3 Hz), 155.1 (d, J_{C-F}=248.8 Hz), 146.8, 139.5 (d, J_{C-F}=13.6 Hz), 139.2, 135.1, 133.7 (d, J_{C-F}=8.4 Hz), 130.7 (d, J_{C-F}=1.6 Hz), 127.3 (d, J_{C-F}=12.2 Hz), 125.8 (d, J_{C-F}=7.3 Hz), 125.2 (d, J_{C-F}=3.4 Hz), 123.8 (d, J_{C-F}=3.6 Hz), 120.1 (d, J_{C-F}=19.1 Hz), 118.5, 116.0 (d, J_{C-F}=21.7 Hz), 110.2; IR (KBr) υ 2841, 1673, 1609, 1463, 1429, 1307, 1271, 1236, 1103, 1070, 888, 774 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{11}F_2NO_2$ $[M]^+$ 311.0758; found 311.0754.

*4.3.10. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(naphthalen-1-yl)methanone (**3j**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); yellow sticky solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J*=9.7 Hz, 1H), 7.90 (d, *J*=5.0 Hz, 1H), 7.77–7.71 (m, 2H), 7.50 (d, *J*=7.1 Hz, 1H), 7.46–7.43 (m, 3H), 7.38–7.16 (m, 4H), 6.72–6.70 (m, 1H), 6.24 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 161.9, 155.4 (d, J_{C-F}=249.3 Hz), 146.6, 139.7 (d, J_{C-F}=13.2 Hz), 138.9, 136.0, 135.5, 133.4, 132.3, 130.3, 129.8, 128.1, 127.6, 126.2, 125.8 (d, J_{C-F}=3.5 Hz), 125.7 (d, J_{C-F}=7.3 Hz), 125.5, 123.9, 119.8 (d, J_{C-F}=19.1 Hz), 118.4, 110.3; IR (KBr) υ 2946, 2844, 1739, 1665, 1594, 1462, 1429, 1270, 1235, 1143, 1064, 888, 777 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{14}FNO_2$ $[M]^+$ 343.1009; found 343.1013.

*4.3.11. (3-Fluoro-2-(pyridin-2-yloxy)phenyl)(naphthalen-2-yl)methanone (**3k**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.00 (d, *J*=5.0 Hz, 1H), 7.90 (d, *J*=8.5 Hz, 1H), 7.80–7.75 (m, 3H), 7.53 (t, *J*=6.9 Hz, 1H), 7.47–7.30 (m, 5H), 6.80–6.77 (m, 1H), 6.59 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 162.1, 155.1 (d, J_{C-F}=249.5 Hz), 146.7, 139.2, 139.1 (d, J_{C-F}=13.3 Hz), 135.4, 135.1, 134.2, 132.6, 132.0, 129.4, 128.5, 128.0, 127.6, 126.5, 125.8 (d, J_{C-F}=7.3 Hz), 125.0 (d, J_{C-F}=3.5 Hz), 124.6, 118.9 (d, J_{C-F}=18.9 Hz), 118.6, 110.5; IR (KBr) υ 2842, 1739, 1665, 1626, 1596, 1462, 1429, 1270, 1238, 1143, 1068, 882, 772 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{14}FNO_2$ $[M]^+$ 343.1009; found 343.1014.

*4.3.12. 1-(3-Fluoro-2-(pyridin-2-yloxy)phenyl)-3-phenylpropan-1-one (**3l**).* R_f=0.55 (*n*-hexanes/EtOAc=4:1); pale yellow oil; ^1H NMR (700 MHz, $CDCl_3$) δ 8.10 (d, *J*=5.0 Hz, 1H), 7.75 (t, *J*=7.2 Hz, 1H), 7.55 (d, *J*=7.8 Hz, 1H), 7.31–7.24 (m, 2H), 7.22–7.20 (m, 2H), 7.11 (d, *J*=7.3 Hz, 1H), 7.08 (d, *J*=8.2 Hz, 2H), 7.02–7.00 (m, 2H), 3.18 (t, *J*=7.4 Hz, 2H), 2.94 (t, *J*=7.7 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.2, 162.3, 155.2 (d, J_{C-F}=249.2 Hz), 147.4, 140.8, 139.9 (d, J_{C-F}=13.2 Hz), 139.7, 135.4, 134.4, 132.6, 128.3, 128.1, 125.9, 125.8 (d, J_{C-F}=7.2 Hz), 124.7 (d, J_{C-F}=3.5 Hz), 119.9 (d, J_{C-F}=18.5 Hz), 119.0, 110.7, 44.0, 29.8; IR (KBr) υ 2966, 2877, 1691, 1597, 1462, 1430, 1270, 1236, 1143, 884, 777 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{16}FNO_2$ $[M]^+$ 321.1165; found 321.1161.

*4.3.13. 1-(3-Fluoro-2-(pyridin-2-yloxy)phenyl)butan-1-one (**3m**).* R_f=0.55 (*n*-hexanes/EtOAc=4:1); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J*=5.0 Hz, 1H), 7.72 (t, *J*=7.2 Hz, 1H), 7.54 (d, *J*=7.2 Hz, 1H), 7.31–7.21 (m, 2H), 7.04–6.98 (m, 2H), 2.79 (t, *J*=7.2 Hz, 2H), 1.62–1.58 (m, 2H), 0.81 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 162.3, 155.2 (d, J_{C-F}=248.7 Hz), 147.4, 139.7, 139.6 (d, J_{C-F}=13.2 Hz), 134.7, 125.8 (d, J_{C-F}=7.3 Hz), 124.7 (d, J_{C-F}=3.4 Hz), 119.7 (d, J_{C-F}=19.0 Hz), 118.9, 110.6, 44.6, 17.3, 13.6; IR (KBr) υ 2986, 2848, 1691, 1595, 1460, 1430, 1271, 1238, 1143, 990, 888, 775 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{14}FNO_2$ $[M]^+$ 259.1009; found 259.1003.

*4.3.14. (5-Chloro-4-methyl-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4b**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); white solid; mp 84–88 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=5.0 Hz, 1H), 7.69 (d, *J*=8.1 Hz, 2H), 7.52 (s, 1H), 7.50–7.43 (m, 2H), 7.30 (t, *J*=8.0 Hz, 2H), 7.13 (s, 1H), 6.85 (t, *J*=5.0 Hz, 1H), 6.54 (d, *J*=8.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 162.7, 149.8, 146.8, 140.7, 139.7, 137.2, 132.8, 131.0, 130.5, 130.3, 129.6, 128.0, 125.1, 118.5, 113.3, 20.4; IR (KBr) υ 2976, 2864, 1740, 1667, 1591, 1462, 1428, 1375, 1262, 1241, 1131, 1011, 897, 779 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{14}ClNO_2$ $[M]^+$ 323.0713; found 323.0714.

*4.3.15. (4,5-Dimethoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4c**).* R_f=0.35 (*n*-hexanes/EtOAc=4:1); pale yellow sticky solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J*=5.1 Hz, 1H), 7.62 (d, *J*=8.4 Hz, 2H), 7.56 (t, *J*=8.5 Hz, 1H), 7.43 (t, *J*=7.4 Hz, 1H), 7.29 (t, *J*=7.8 Hz, 2H), 7.12 (s, 1H), 6.93 (t, *J*=5.5 Hz, 1H), 6.76 (s, 1H), 6.49 (d, *J*=8.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.8, 162.5, 152.5, 146.3, 145.7, 145.3, 140.6, 138.0, 132.4, 129.4, 127.9, 123.2, 118.2, 112.5, 113.3, 106.2, 56.3, 56.2; IR (KBr) υ 2976, 2864, 1659, 1599, 1512, 1449, 1428, 1271, 1241, 1216, 1106, 1006, 868, 780 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{17}NO_4$ $[M]^+$ 335.1158; found 335.1157.

*4.3.16. Phenyl(3-(pyridin-2-yloxy)naphthalen-2-yl)methanone (**4d**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); pale yellow sticky solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.94 (d, *J*=4.8 Hz, 1H),

7.81–7.88 (m, 2H), 7.77 (d, *J*=8.4 Hz, 2H), 7.68 (s, 1H), 7.46–7.57 (m, 4H), 7.35 (t, *J*=7.8 Hz, 2H), 6.83 (t, *J*=5.0 Hz, 1H), 6.68 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 163.2, 148.7, 146.9, 139.3, 137.5, 135.2, 132.7, 132.0, 131.2, 130.1, 130.0, 128.6, 128.0, 127.9, 127.3, 126.0, 119.4, 118.4, 111.4; IR (KBr) υ 2974, 1666, 1592, 1468, 1427, 1335, 1244, 1213, 1144, 1024, 847, 749 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{22}H_{15}NO_2$ [M]$^+$ 325.1103; found 325.1106.

*4.3.17. (3,4-Dimethyl-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4e**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J*=4.1 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 2H), 7.58 (t, *J*=6.7 Hz, 1H), 7.46 (t, *J*=7.4 Hz, 1H), 7.32 (t, *J*=7.7 Hz, 2H), 7.25 (d, *J*=7.7 Hz, 1H), 7.13 (d, *J*=7.7 Hz, 1H), 6.88 (t, *J*=5.9 Hz, 1H), 6.64 (d, *J*=8.3 Hz, 1H), 2.38 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 162.6, 149.1, 145.7, 142.3, 140.3, 137.6, 132.6, 130.9, 130.1, 129.9, 127.9, 127.5, 126.6, 117.9, 111.0, 20.5, 12.7; IR (KBr) υ 2923, 1664, 1598, 1468, 1430, 1291, 1245, 1143, 1080, 822, 779 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{20}H_{17}NO_2$ [M]$^+$ 303.1259; found 303.1262.

*4.3.18. Phenyl(1-(pyridin-2-yloxy)naphthalen-2-yl)methanone (**4f**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); pale yellow solid; mp 110–112 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.01 (d, *J*=8.4 Hz, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 7.88 (d, *J*=4.9 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.72 (d, *J*=8.2 Hz, 2H), 7.60 (d, *J*=8.4 Hz, 1H), 7.57–7.56 (m, 1H), 7.51–7.47 (m, 2H), 7.35–7.32 (m, 3H), 6.82 (t, *J*=5.7 Hz, 1H), 6.64 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.5, 163.3, 147.9, 147.1, 139.3, 137.6, 136.0, 132.7, 129.8, 128.5, 128.0, 127.9, 127.6, 127.0, 126.9, 125.9, 125.1, 123.3, 118.2, 110.5; IR (KBr) υ 2939, 2830, 1664, 1595, 1464, 1427, 1372, 1345, 1283, 1240, 1139, 1033, 891, 785 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{22}H_{15}NO_2$ [M]$^+$ 325.1103; found 325.1105.

*4.3.19. (3-Chloro-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4g**).* R_f=0.55 (*n*-hexanes/EtOAc=4:1); white solid; mp 60–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=4.9 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 2H), 7.62 (d, *J*=8.0 Hz, 1H), 7.53–7.46 (m, 2H), 7.40 (d, *J*=7.6 Hz, 1H), 7.33 (t, *J*=7.8 Hz, 2H), 7.26 (t, *J*=8.0 Hz, 1H), 6.84 (t, *J*=5.2 Hz, 1H), 6.66 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 162.2, 147.4, 146.8, 139.3, 136.8, 134.9, 133.0, 132.7, 129.9, 129.0, 128.2, 128.0, 125.6, 118.4, 110.6; IR (KBr) υ 2977, 2858, 1680, 1590, 1463, 1430, 1377, 1261, 1242, 1130, 1012, 897, 777 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{12}ClNO_2$ [M]$^+$ 309.0557; found 309.0547.

*4.3.20. (5-Fluoro-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4h**).* R_f=0.50 (*n*-hexanes/EtOAc=4:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=4.9 Hz, 1H), 7.72 (d, *J*=8.4 Hz, 2H), 7.50–7.45 (m, 2H), 7.32 (t, *J*=7.5 Hz, 2H), 7.26–7.24 (m, 3H), 6.87–6.84 (m, 1H), 6.54 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 162.7, 155.7, 147.2, 146.8, 139.3, 136.8, 133.0, 129.7, 128.0, 124.6 (d, J_{C-F}=7.9 Hz), 122.1, 118.8, 118.6 (d, J_{C-F}=13.0 Hz), 116.6 (d, J_{C-F}=24.0 Hz), 111.2; IR (KBr) υ 2956, 2844, 1670, 1596, 1466, 1429, 1269, 1248, 1189, 1142, 879, 780 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{12}FNO_2$ [M]$^+$ 293.0852; found 293.0856.

*4.3.21. Phenyl(2-(pyridin-2-yloxy)phenyl)methanone (**4i**).* R_f=0.45 (*n*-hexanes/EtOAc=4:1); white solid; mp 77–79 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.02 (d, *J*=4.9 Hz, 1H), 7.72 (d, *J*=7.1 Hz, 2H), 7.58–7.53 (m, 3H), 7.46 (t, *J*=7.4 Hz, 1H), 7.34–7.29 (m, 3H), 7.25 (d, *J*=8.1 Hz, 1H), 6.90 (t, *J*=5.4 Hz, 1H), 6.62 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 191.9, 162.6, 151.3, 146.1, 140.3, 137.3, 132.8, 132.2, 132.1, 130.3, 129.8, 128.0, 124.9, 122.7, 118.5, 111.6; IR (KBr) υ 2956, 1666, 1597, 1467, 1428, 1292, 1244, 1144, 1024, 886, 777 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{13}NO_2$ [M]$^+$ 275.0946; found 275.0950.

*4.3.22. (2-(Pyridin-2-yloxy)-1,3-phenylene)bis(phenylmethanone) (**4ii**).* R_f=0.42 (*n*-hexanes/EtOAc=4:1); colorless sticky solid; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J*=4.8 Hz, 1H), 7.71 (d, *J*=7.7 Hz, 6H), 7.43 (t, *J*=7.6 Hz, 3H), 7.27 (d, *J*=7.8 Hz, 5H), 6.72 (t, *J*=5.4 Hz, 1H), 6.16 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 201.6, 161.8, 148.5, 145.5, 139.5, 137.0, 133.0, 132.9, 132.5, 129.7, 128.0, 124.9, 118.4, 110.9; IR (KBr) υ 2956, 2844, 1666, 1598, 1465, 1453, 1291, 1247, 1032, 885, 777 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{25}H_{17}NO_3$ [M]$^+$ 379.1208; found 379.1226.

*4.3.23. (5-Methoxy-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone (**4j**).* R_f=0.40 (*n*-hexanes/EtOAc=4:1); pale yellow solid; mp 97–100 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (d, *J*=4.7 Hz, 1H), 7.70 (d, *J*=8.0 Hz, 2H), 7.41–7.43 (m, 2H), 7.28 (t, *J*=7.4 Hz, 2H), 7.16 (d, *J*=8.7 Hz, 1H), 7.08–7.04 (m, 2H), 6.81 (t, *J*=6.0 Hz, 1H), 6.48 (d, *J*=8.3 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.0, 163.2, 156.3, 146.8, 144.7, 139.1, 137.3, 132.8, 132.7, 129.7, 127.9, 124.0, 118.0, 114.3, 111.0, 55.7; IR (KBr) υ 2946, 2844, 1655, 1582, 1461, 1420, 1374, 1285, 1193, 1145, 1002, 949, 836 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{19}H_{15}NO_3$ [M]$^+$ 305.1052; found 305.1060.

*4.3.24. (5-Methoxy-2-(pyridin-2-yloxy)-1,3-phenylene)bis(phenylmethanone) (**4jj**).* R_f=0.35 (*n*-hexanes/EtOAc=4:1); yellow sticky solid; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (d, *J*=4.9 Hz, 1H), 7.70 (d, *J*=8.0 Hz, 4H), 7.41 (t, *J*=8.5 Hz, 2H), 7.25 (t, *J*=7.9 Hz, 6H), 7.18–7.15 (m, 1H), 6.68–6.65 (m, 1H), 6.02 (d, *J*=8.3 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 201.6, 161.8, 148.5, 145.5, 139.5, 137.0, 133.0, 132.9, 132.5, 129.7, 128.0, 124.9, 118.4, 110.9; IR (KBr) υ 3306, 2946, 2844, 1655, 1582, 1461, 1420, 1374, 1285, 1193, 1145, 1002, 949, 836 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{26}H_{19}NO_4$ [M]$^+$ 409.1314; found 409.1318.

4.4. Typical procedure for the removal of 2-pyridinyl directing group

To a solution of phenyl(1-(pyridin-2-yloxy)naphthalen-2-yl) methanone (**4f**) (97.6 mg, 0.3 mmol) in toluene (10 mL) under N_2 was added MeOTf (60 μL, 0.52 mmol). The reaction mixture was stirred under N_2 at 100 °C for 2 h. The reaction mixture was allowed to cool to ambient temperature. The solvent was evaporated to obtain the residue, which was dissolved in dry methanol (5.0 mL) and was added to a solution of Na (165 mg, 7.2 mmol) in dry methanol (5.0 mL) under N_2. The reaction mixture was heated at 80 °C for 15 min. The reaction mixture was allowed to cool to ambient temperature and the solvent was evaporated in vacuo. Water was added, and the resulting mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$. After filtration and evaporation of the solvents in vacuo, the residue was purified by column chromatography on silica gel (*n*-hexanes/EtOAc=40:1–20:1) to yield **5a** (66.3 mg) in 89% yield.

*4.4.1. (1-Hydroxynaphthalen-2-yl)(phenyl)methanone (**5a**).* R_f=0.50 (*n*-hexanes/EtOAc=6:1); yellow oil; ^{1}H NMR (700 MHz, $CDCl_3$) δ 13.93 (s, 1H), 8.51 (d, *J*=8.4 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.70 (d, *J*=8.1 Hz, 2H), 7.64 (t, *J*=7.4 Hz, 1H), 7.59–7.50 (m, 3H), 7.21 (d, *J*=8.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 201.4, 163.9, 138.1, 137.3, 131.6, 130.3, 129.0, 128.3, 127.4, 127.3, 125.9, 125.2, 124.4, 117.8, 112.5; IR (KBr) υ 3330, 2944, 2844, 1657, 1588, 1468, 1374, 1285, 1192, 1001, 951, 838 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{17}H_{12}O_2$ [M]$^+$ 248.0837; found 248.0832.

*4.4.2. (5-Fluoro-2-hydroxyphenyl)(phenyl)methanone (**5b**).* R_f=0.6 (*n*-hexanes/EtOAc=6:1); yellow solid; mp 77–79 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 11.72 (s, 1H), 7.66 (d, *J*=8.1 Hz, 2H), 7.60 (t, *J*=7.5 Hz, 1H), 7.51 (t, *J*=7.5 Hz, 2H), 7.27–7.22 (m, 2H), 7.03 (dd, *J*=9.1, 4.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 200.6 (d, J_{C-F}=2.4 Hz), 159.3, 154.4 (d, J_{C-F}=238.4 Hz), 137.3, 132.3, 129.0, 128.5, 123.9 (d, J_{C-F}=23.6 Hz), 119.7 (d, J_{C-F}=7.6 Hz), 118.6

(d, J_{C-F}=6.7 Hz), 118.3 (d, J_{C-F}=23.7 Hz); IR (KBr) υ 3332, 2946, 1654, 1588, 1462, 1375, 1288, 1192, 1003, 944, 832 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{13}H_9FO_2$ $[M]^+$ 216.0587; found 216.0585.

*4.4.3. (2-Hydroxy-5-methoxyphenyl)(phenyl)methanone (**5c**).* R_f=0.6 (*n*-hexanes/EtOAc=8:1); yellow oil; ^1H NMR (700 MHz, $CDCl_3$) δ 11.56 (s, 1H), 7.68 (d, *J*=8.1 Hz, 2H), 7.57 (t, *J*=7.8 Hz, 1H), 7.49 (t, *J*=7.8 Hz, 2H), 7.12 (d, *J*=9.0 Hz, 1H), 7.04 (s, 1H), 7.00 (d, *J*=9.1 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 201.1, 157.4, 151.3, 137.8, 131.9, 129.0, 128.3, 124.0, 119.2, 118.6, 116.3, 55.8; IR (KBr) υ 3336, 2942, 2845, 1655, 1458, 1377, 1286, 1194, 1150, 1004, 951, 844 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{14}H_{12}NO_3$ $[M]^+$ 228.0786; found 228.0788.

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Supplementary data

^1H NMR and ^{13}C NMR copies of all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.008.

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