Synthesis Y. Wang et al. Paper

One-Pot Synthesis of Quinolin-4(1*H*)-one Derivatives by a Sequential Michael Addition–Elimination/Palladium-Catalyzed Buchwald–Hartwig Amination Reaction

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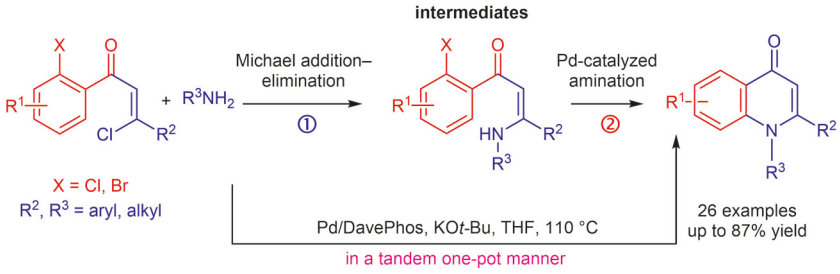

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Abstract A convenient approach has been developed for the construction of quinolin-4(1*H*)-one frameworks, starting from (*Z*)-β-chlorovinyl aromatic ketones and amines. Intermolecular Michael addition of an amine to a (*Z*)-β-chlorovinyl ketone was followed by elimination of a chloride anion to give enamine intermediates, with full retention of the initial *Z*-configuration. The enamine intermediates were transformed into quinolin-4(1*H*)-one products by a palladium-catalyzed intramolecular N-arylation in a tandem one-pot manner, with good to excellent yields.

Key words quinolines, ketones, Michael additions, aminations, tandem reactions, cyclizations

Quinolin-4-one frameworks are frequently found in a diverse array of compounds, including natural products,[1] synthetic building blocks,[2] and therapeutically active molecules (Figure 1), such as antibacterial,[3] antitumor,[4] antimalarial,[5] or antimitotic agents[6] or HIV-1 integrase inhibitors.[7] Consequently, the construction of this valuable structural unit has received considerable attention, and much effort has been focused on the development of new and efficient synthetic methods.[8] The classical synthetic approaches are based on various cyclocondensation strategies, such as the Camps,[9] Conrad–Limpach,[10] or Niementowski cyclization.[11] Although these methods have been widely used in the preparation of quinolin-4-ones, they require harsh reaction conditions (high temperatures and/or strong bases), dramatically limiting their scope. To develop milder processes for assembling the quinolin-4-one ring system, methods mediated by transition metals, such as palladium,[12] copper,[13] or gold,[14] have been extensively investigated.

As part of our continuing efforts in relation to sequential one-pot syntheses of nitrogen heterocycles by palladium-catalyzed reactions,[15] we set out to develop a new protocol for the synthesis of quinolin-4-ones from the corresponding (*Z*)-β-chlorovinyl aromatic ketones (Scheme 1). These ketones are readily prepared by regio- and stereoselective addition of acid chlorides to alkynes in the presence of low-cost iron catalysts[16] and they are valuable intermediates for the synthesis of various heterocyclic compounds.[17] We surmised that β-chloroalkenyl aryl ketones **1**, derived from the appropriate 2-chlorobenzoyl chlorides and terminal alkynes, might react with amines in the presence of a palladium complex and a base to give the corresponding N-substituted quinolones. Because of the versatile chemical properties of the β-chlorovinyl ketone moiety, we initially wondered whether enones **1** might serve as both the aryl chloride and the vinyl chloride electrophilic coupling part-

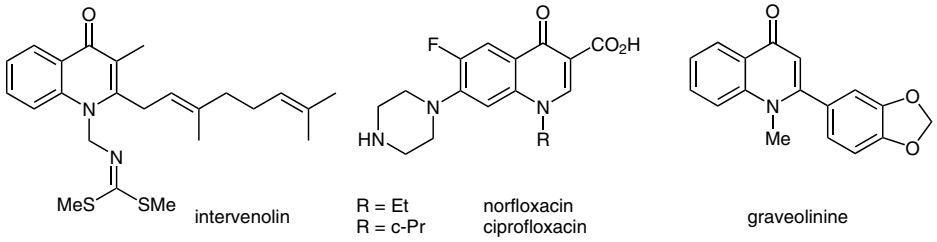
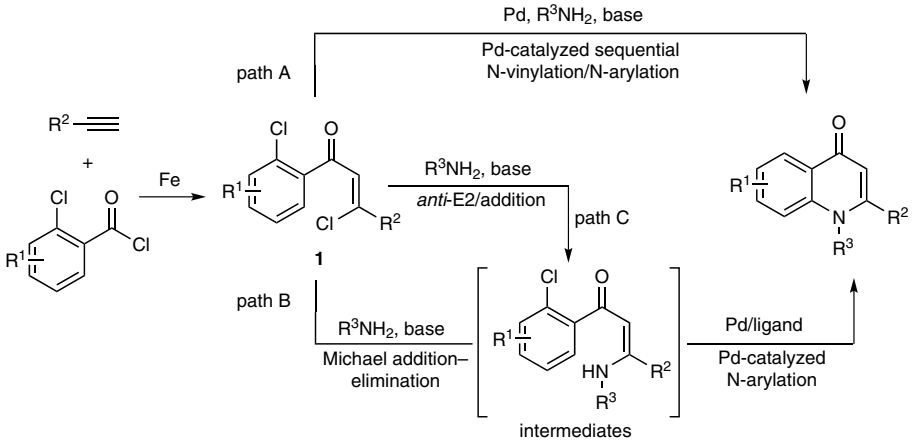


Figure 1 Representative quinolin-4-one moieties in pharmaceuticals and natural products

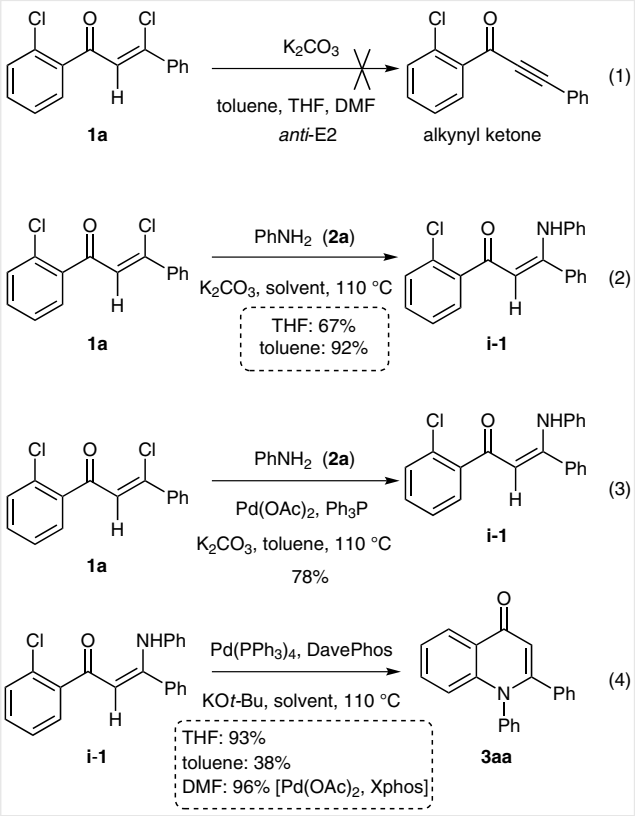


Scheme 1 Possible pathways to quinolin-4-ones from β-chlorovinyl ketones and amines

ners[18] in a palladium-catalyzed double Buchwald–Hartwig amination reaction to give the target molecules (Scheme 1; path A);[19] Alternatively, enones **1** might serve Michael acceptors that would undergo a base-promoted tandem conjugate addition–elimination process[20] to give the corresponding enamine intermediates. (An alternative pathway involving an elimination–Michael addition reaction could not be ruled out.)[12e,21] The enamine intermediates could then be transformed into quinolin-4-ones through a palladium-catalyzed intramolecular N-arylation reaction (Scheme 1; paths B and C).

To determine the nature of the synthetic pathways, we chose (*Z*)-3-chloro-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (**1a**) and aniline (**2a**) as model substrates and we conducted several control experiments (Scheme 2). First, treatment of enone **1a** with potassium carbonate, a mild base, in the absence of aniline in toluene, tetrahydrofuran, or *N*,*N*-dimethylformamide did not give the conjugated alkynyl ketone through *anti*-elimination of hydrogen chloride (Scheme 2; reaction 1), and enone **1a** was completely recovered from the reaction mixture. This result appears to preclude the possibility of a reaction pathway involving a tandem *anti*-E2/Michael addition process to enamine intermediates (Scheme 1; path C). When we examined the reaction of enone **1a** with aniline (**2a**) in tetrahydrofuran or toluene containing potassium carbonate as a base, the enamine intermediate **i-1** was obtained in 67% and 92% yield, respectively (Scheme 2; reaction 2). When **1a** and **2a** were treated in the presence of a palladium catalyst, the reaction gave the same product, **i-1** (Scheme 2; reaction 3). Compared with the palladium-free reaction in toluene, the use of palladium catalyst gave a lower yield of the enamine product **i-1** (78% versus 92%). Furthermore, the oxidative addition of an aryl chloride (a similar electrophilic coupling reagent to a vinyl chloride) to palladium did not proceed to give the product **3aa** through a N-arylation reaction under the same reaction conditions (Scheme 2; reaction 3). These results show that a Michael addition–elimination process (Scheme 1; path B) is more reasonable than a palladium-catalyzed N-vinylation process (Scheme 1; path A). However, at this point, path A could not be completely ruled out. Finally, by using a Buchwald-type ligand[22] {[2′-(dicyclohexylphosphino)biphenyl-2-yl]dimethylamine (DavePhos) or dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (Xphos)} for aromatic C–Cl bond activation, with potassium *tert*-butoxide as the base, intermediate **i-1** was efficiently transformed into the quinolin-4-one **3aa** in good yield (Scheme 2; reaction 4). Therefore, a two-step procedure involving reactions 2 and 4 is a practicable method for the synthesis of quinolin-4-ones in a tandem one-pot fashion.

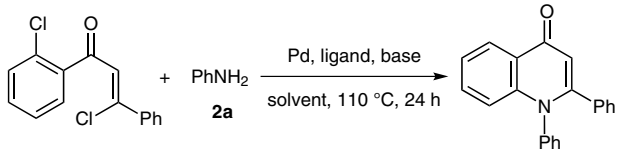
Next, we conducted extensive experiments on the one-pot preparation of quinolin-4-one **3aa** through a sequential Michael addition–elimination/palladium-catalyzed intramolecular amination reaction (Table 1). We first examined the model reaction in tetrahydrofuran for 24 hours with tetrakis(triphenylphosphine)palladium as the catalyst and potassium *tert*-butoxide as the base, and we obtained the desired product **3aa** in 40% and 15% yields at 110 and 80 °C, respectively (Table 1, entry 1). We then examined the effects of various Buchwald-type or bidentate phosphorus ligands in an attempt to increase the yield (entries 2–5). DavePhos performed best, and the yield was increased to 60% (entry 4). Screening of various sources of palladium [for example, palladium(II) chloride, palladium(II) acetate, or tris(dibenzylideneacetone)dipalladium] in tetrahydrofuran, showed that DavePhos with tetrakis(triphenylphosphine)palladium was the best catalyst system and potassium *tert*-butoxide was the best base (entries 4 and 6–8). A survey of reaction media showed that tetrahydrofuran as a solvent gave better results than 1,4-dioxane, toluene, or *N*,*N*-dimethylformamide (entries 9–11). Finally, we focused on the choice of a suitable base for this tandem process (entries 12–16). The nature of the base was found to be very important in determining the outcome of the reaction. Use



Scheme 2 Investigations of possible synthetic pathways

of milder bases, such as potassium carbonate, sodium carbonate, or tripotassium phosphate (entries 13–15) gave inferior results to those achieved with strong bases such as potassium or sodium *tert*-butoxide (entries 4 and 12). For the Michael addition–elimination process, a mild base provides the enamine intermediate **i-1** in good yields [Scheme 2; Reaction 2]; however, a strong base is more suitable for the palladium-catalyzed C–N cross-coupling process (Scheme 2; Reaction 4 and Table 1, entry 4). On the other hand, the moderate yields of the target **3aa** (40–60%; Table 1) made us wonder whether a strong base, such as potassium or sodium *tert*-butoxide, would be more suitable for the nucleophilic addition–elimination process. In fact, when (*Z*)-β-chlorovinyl ketone **1a** was treated with potassium *tert*-butoxide in tetrahydrofuran, partial decomposition of (*Z*)-**1a** occurred to give an unidentifiable mixture.[21b] We therefore conducted the synthesis of **3aa** as a one-pot two-step process using potassium carbonate as the base for the formation of enamine intermediate and potassium *tert*-butoxide as the base for the intramolecular C–N bond formation; this tandem reaction gave a high yield [82% for $Pd(PPh_3)_4$–DavePhos, 73% for $Pd(OAc)_2$–Xphos; Table 1, entry 16].

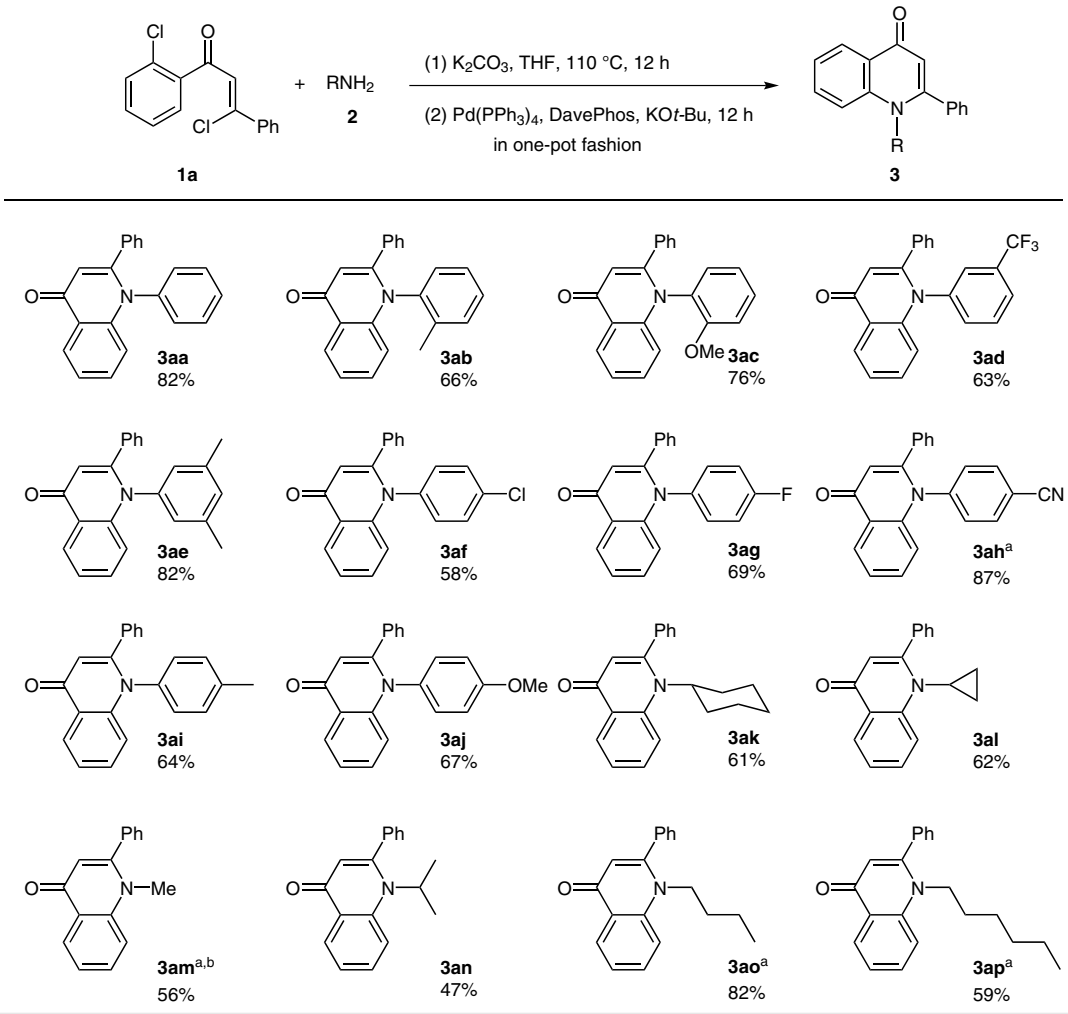
Table 1 Optimization of the Conditions for the One-Pot Reaction[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(PPh_3)_4$	-	*t*-BuOK	THF	40 (15)[c]
2	$Pd(PPh_3)_4$	*t*-BuMephos[d]	*t*-BuOK	THF	56
3	$Pd(PPh_3)_4$	MePhos[e]	*t*-BuOK	THF	36
4	$Pd(PPh_3)_4$	DavePhos[f]	*t*-BuOK	THF	60
5	$Pd(PPh_3)_4$	dppf[g]	*t*-BuOK	THF	44
6	$PdCl_2$	DavePhos	*t*-BuOK	THF	30 (24)[h]
7	$Pd(OAc)_2$	DavePhos	*t*-BuOK	THF	48 (39)[i]
8	$Pd_2(dba)_3$	DavePhos	*t*-BuOK	THF	36
9	$Pd(PPh_3)_4$	DavePhos	*t*-BuOK	1,4-dioxane	44
10	$Pd(PPh_3)_4$	DavePhos	*t*-BuOK	toluene	36
11	$Pd(PPh_3)_4$	DavePhos	*t*-BuOK	DMF	trace
12	$Pd(PPh_3)_4$	DavePhos	*t*-BuONa	THF	46
13	$Pd(PPh_3)_4$	DavePhos	K_2CO_3	THF	42
14	$Pd(PPh_3)_4$	DavePhos	Na_2CO_3	THF	25
15	$Pd(PPh_3)_4$	DavePhos	K_3PO_4	THF	22
16[j]	$Pd(PPh_3)_4$	DavePhos	K_2CO_3/*t*-BuOK	THF	82 (73)[k]

[a] *Reaction conditions*: **1a** (0.2 mmol, 1.0 equiv), $PhNH_2$ (**2a**; 0.3 mmol, 1.5 equiv), base (3.0 equiv), Pd catalyst (5 mol%), ligand (10 mol%), solvent (2 mL), 110 °C, 24 h.
[b] Isolated yield after chromatography.
[c] At 80 °C.
[d] Dicyclohexyl(2′-methylbiphenyl-2-yl)phosphine.
[e] Di-*tert*-butyl(2′-methylbiphenyl-2-yl)phosphine.
[f] [2′-(Dicyclohexylphosphino)biphenyl-2-yl]dimethylamine.
[g] 1,1′-Bis(diphenylphosphinyl)ferrocene
[h] Ligand = PPh_3.
[i] 5 mol% of ligand was used.
[j] The reaction was carried out in a one-pot, two-step manner. **1a** and **2a** were treated with K_2CO_3 (1.5 equiv) in THF for 12 h; $Pd(PPh_3)_4$, DavePhos, and *t*-BuOK (1.5 equiv) were added; and the mixture was kept for another 12 h.
[k] $Pd(OAc)_2$ and Xphos were used in the second step.

Having determined the optimal conditions for the one-pot reaction, we next explored its scope and generality. As shown in Scheme 3, a variety of simple primary amines can be used as starting materials, giving good yields of the corresponding products **3aa**–**ap**. The reaction conditions were compatible with various functional groups on the benzene ring of aromatic amines, including methyl, methoxy, fluoro, trifluoromethyl, chloro, and cyano (Scheme 3; **3ab**–**ap**). Steric hindrance by *ortho*-substituents on the aryl ring did not appear to hamper the reaction and the corresponding quinolin-4-ones **3ab** and **3ac** were obtained in 66% and 76% yield, respectively. Alicyclic primary amines such as cyclohexylamine (**2k**) or cyclopropylamine (**2l**) were also toler-



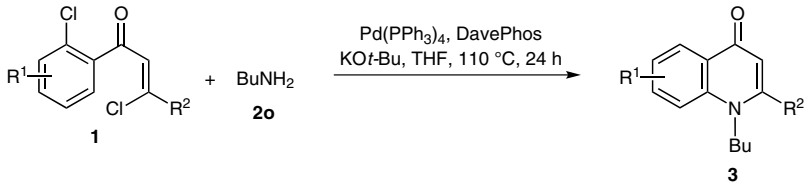
Scheme 3 Scope of amine reactants. *Reagents and conditions* (one-pot, two-step operation): **1a** (0.2 mmol), amine **2** (0.3 mmol), K_2CO_3 (0.3 mmol), THF (2 mL), 110 °C, 12 h; then $Pd(PPh_3)_4$ (0.01 mmol), DavePhos (0.02 mmol), *t*-BuOK (0.3 mmol), 12 h. The yields are those of the isolated product after chromatography. [a] The reaction was carried out in a one-pot, one-step manner. [b] $MeNH_2 \cdot H_2O$ was used.

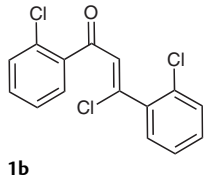
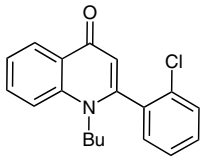
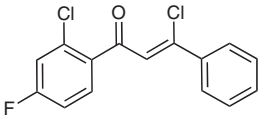
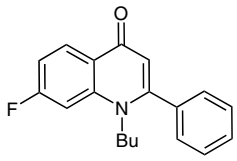
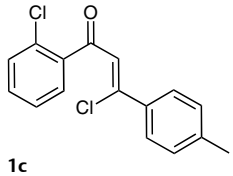
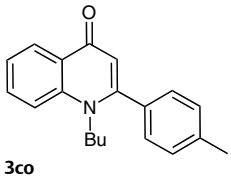
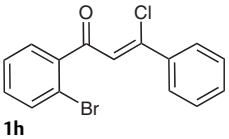
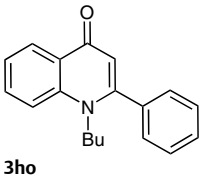
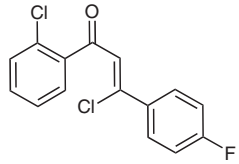
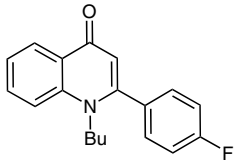
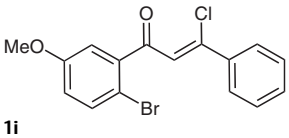
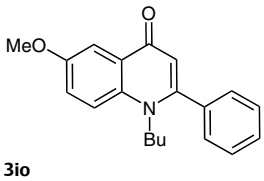
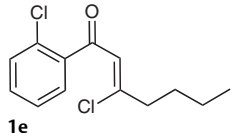
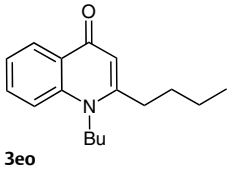
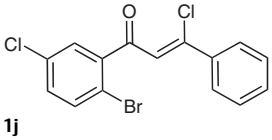
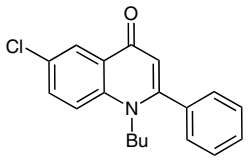
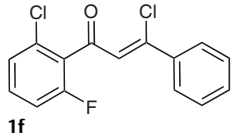
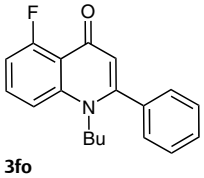
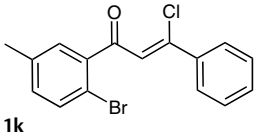
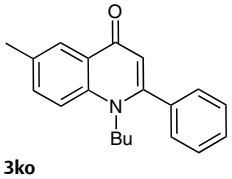
ated in the process, giving good yields of the corresponding products **3ak** and **3al**. Furthermore, various aliphatic amines (methylamine monohydrate, isopropylamine, butylamine, or hexylamine) were smoothly converted into the desired products in moderate to good yields.

In an attempt to simplify the operational procedure, we examined the reaction of various (*Z*)-β-haloalkenyl aromatic ketones **1** with butylamine (**2o**) in the presence of the palladium catalyst and base in a one-pot, one-step fashion. As shown in Table 2, various functional groups R^1 and R^2 on enone **1** were well tolerated. In the case of substituent R^2, substrates with aryl groups showed higher reactivities than did those with alkyl groups, and good yields were obtained with either electron-donating or electron-withdrawing substituents on the aromatic ring (Table 2, entries 1–4). 2-Chloro aromatic ketones (Table 2, entries 5 and 6) or 2-bromo aromatic ketones (Table 2, entries 8–10) bearing *ortho*-, *meta*-, or *para*-substituents R^1 were also smoothly transformed into the corresponding products **3fo**–**ko** in good yields. Note that the compatibility of the chloro functional group in substrates **1** is particularly appealing because this substituent offers a considerable range of opportunities for further synthetic manipulations (Table 2, entries 1 and 9).

Our proposed reaction mechanism is shown in Scheme 4. Nucleophilic Michael addition of amine **2** to (*Z*)-β-chlorovinyl aromatic ketone **1** gives intermediate **4**, which undergoes elimination of a halide anion in the presence of a base to give the *Z*-configured enamine intermediate **5**. Oxidative addition of the C–X bond of intermediate **5** to palladium(0) followed by intramolecular reaction of the enamine and base give intermediate **6**. Complex **6** undergoes a C–N bond-forming reductive elimination to give the desired product **3** with regeneration of the active catalytic species.

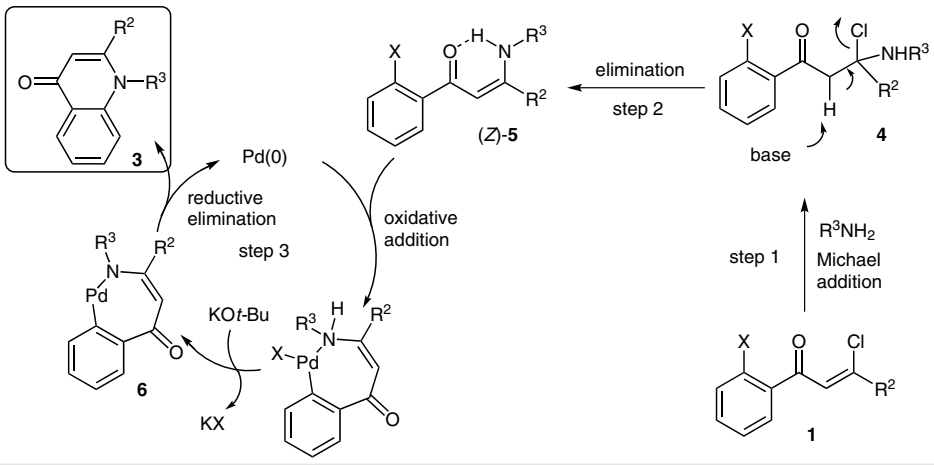
Table 2 Scope of β-Chlorovinyl Aromatic Ketones[a]



Entry	Substrate **1**	Product **3**	Yield[b] (%)	Entry	Substrate **1**	Product **3**	Yield[b] (%)
1	 **1b**	 **3bo**	43	6	 **1g**	 **3go**	80
2	 **1c**	 **3co**	56	7	 **1h**	 **3ho**	67
3	 **1d**	 **3do**	62	8	 **1i**	 **3io**	58
4	 **1e**	 **3eo**	49	9	 **1j**	 **3jo**	81
5	 **1f**	 **3fo**	68	10	 **1k**	 **3ko**	87

[a] Reaction conditions (one-pot, one-step operation): **1** (0.2 mmol), $BuNH_2$ (**2o**; 0.3 mmol), *t*-BuOK (0.6 mmol), $Pd(PPh_3)_4$ (0.01 mmol), DavePhos (0.02 mmol), THF (2 mL), 110 °C, 24 h.
[b] Yield of isolated product after chromatography.

In conclusion, we have developed an efficient protocol for the sequential one-pot synthesis of quinolin-4-one derivatives. The process is based on the intermolecular Michael addition of an amine to a (*Z*)-β-chlorovinyl aromatic ketone, subsequent elimination of a chloride anion to give a *Z*-enamine, and, finally, a palladium-catalyzed intramolecular N-arylation. The result presented here, together with previous research, have potential applications in the synthesis of valuable molecules in medicinal science.



Scheme 4 Proposed mechanism for the sequential Michael addition–elimination/palladium-catalyzed N-arylation process

Chemicals were all purchased from commercial suppliers and were used without further purification unless otherwise stated. Before use, solvents were dried and purified by the standard procedures. (*Z*)-β-Chlorovinyl aromatic ketones were prepared from the corresponding acid chlorides and alkynes by the reported methods.[16] All reactions were carried out in dried glassware, and monitored by TLC. Yields refer to isolated yields of compounds. Melting points were determined on a melting-point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer with $CDCl_3$ as solvent. The reported chemical shifts are relative to $CDCl_3$ (^{1}H NMR: $CDCl_3$, δ = 7.26 ppm; ^{13}C NMR: $CDCl_3$, δ = 77.2 ppm). High-resolution mass spectra were recorded on a Bruker Bio TOF-Q mass spectrometer.

Quinolin-4(1*H*)-ones 3; General Procedures

Method A: One-Pot Two-Step Procedure

A 25 mL Schlenk tube equipped with a magnetic stirrer bar was charged with β-chlorovinyl aromatic ketone **1** (0.2 mmol, 1.0 equiv), amine **2** (0.3 mmol, 1.5 equiv), and K_2CO_3 (42 mg, 0.3 mmol, 1.5 equiv). THF (2.0 mL) was added from a syringe at r.t., and the tube was sealed and placed in a preheated oil bath at 110 °C for 12 h. $Pd(PPh_3)_4$ (0.01 mmol, 11.5 mg), DavePhos (0.02 mmol, 6.9 mg), *t*-BuOK (34 mg, 0.3 mmol, 1.5 equiv) were then added and the mixture was heated at 110 °C for a further 12 h.

Method B: One-Pot One-Step Procedure

A 25 mL Schlenk tube equipped with a magnetic stirrer bar was charged with β-chlorovinyl aromatic ketone **1** (0.2 mmol, 1.0 equiv), amine **2** (0.3 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.01 mmol, 11.5 mg), DavePhos (0.02 mmol, 6.9 mg), and *t*-BuOK (68 mg, 0.6 mmol, 3.0 equiv). THF (2.0 mL) was added from a syringe at r.t., and the tube was sealed and placed in a preheated oil bath at 110 °C for 24 h. The mixture was then cooled to r.t. and the reaction was quenched with H_2O (5 mL). The mixture was diluted with EtOAc (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 20–40% EtOAc–PE).

(2*Z*)-3-Anilino-1-(2-chlorophenyl)-3-phenylprop-2-en-1-one (i-1)

White solid; yield: 122.5 mg (92%); mp 122–124 °C.

IR (KBr): 3450, 1609, 1588, 1567, 1481, 1325, 756, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.65 (s, 1 H), 7.59–7.56 (m, 1 H), 7.43–7.29 (m, 8 H), 7.14 (t, *J* = 8.0 Hz, 2 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 6.82 (d, *J* = 7.6 Hz, 2 H), 5.79 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 161.4, 140.9, 139.2, 135.3, 131.0, 130.5, 130.3, 129.9, 129.5, 128.8, 128.6, 128.5, 126.8, 124.5, 123.5, 100.9.

ESI-MS: *m/z* = 333 [M$^+$], 334 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{16}ClNNaO$: 356.0818; found: 356.0821.

1,2-Diphenylquinolin-4(1*H*)-one (3aa)[13b]

White solid; yield: 48.7 mg (82%); mp 279–281 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53–8.51 (m, 1 H), 7.50–7.47 (m, 1 H), 7.46–7.33 (m, 4 H), 7.20–7.15 (m, 7 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.44 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 153.9, 142.6, 139.2, 135.7, 131.9, 130.0, 129.6, 129.2, 128.9, 128.6, 127.9, 126.3, 126.1, 123.8, 118.1, 112.6.

2-Phenyl-1-(2-tolyl)quinolin-4(1*H*)-one (3ab)[12h]

Yellow solid; yield: 41.1 mg (66%); mp 253–255 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.0 Hz, 1 H), 7.48 (t, *J* = 6.4 Hz, 1 H), 7.39 (t, *J* = 6.4 Hz, 1 H), 7.24–7.17 (m, 9 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.46 (s, 1 H), 1.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 153.9, 141.8, 137.9, 136.6, 135.3, 132.1, 131.5, 130.5, 129.4, 128.8, 128.7, 127.8, 127.0, 126.4, 126.1, 123.8, 117.5, 112.7, 17.5.

1-(2-Methoxyphenyl)-2-phenylquinolin-4(1*H*)-one (3ac)[12e]

Yellow solid; yield: 49.7 mg (76%); mp 222–224 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 7.37–7.28 (m, 2 H), 7.19–7.11 (m, 6 H), 6.94–6.83 (m, 3 H), 6.42 (s, 1 H), 3.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 155.6, 154.9, 142.5, 136.0, 132.1, 131.3, 131.0, 128.9, 128.7, 127.9, 127.7, 126.4, 123.8, 121.0, 117.8, 112.5, 112.2, 55.6.

2-Phenyl-1-[3-(trifluoromethyl)phenyl]quinolin-4(1*H*)-one (3ad)[13b]

White solid; yield: 46 mg (63%); mp 234–236 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.55–7.48 (m, 2 H), 7.44–7.38 (m, 3 H), 7.21–7.20 (m, 3 H), 7.15–7.12 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 153.8, 142.4, 140.0, 135.3, 133.7, 132.5 (q, J_{C-F} = 22 Hz), 132.4, 130.5, 129.3, 129.1, 128.3, 127.5 (d, 127.50, 127.47, J_{C-F} = 3 Hz), 126.8, 126.1, 125.9 (d, 125.93, 125.90, J_{C-F} = 3 Hz), 124.3, 123.3 (d, 124.2, 122.4, J_{C-F} = 180 Hz), 117.7, 113.0.

1-(3,5-Dimethylphenyl)-2-phenylquinolin-4(1*H*)-one (3ae)

White solid; yield: 53.3 mg (82%); mp 214–216 °C.

IR (KBr): 1630, 1596, 1479, 1462, 1404, 1306, 1133, 766, 711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.48–7.46 (m, 1 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 7.21–7.18 (m, 5 H), 6.97–6.93 (m, 2 H), 6.76 (s, 2 H), 6.42 (s, 1 H), 2.24 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 142.6, 139.3, 138.9, 135.8, 131.7, 130.4, 129.7, 129.1, 128.5, 127.7, 127.5, 126.2, 126.1, 123.6, 118.3, 112.5, 21.0.

ESI-MS: *m/z* = 325 [M^+], 326 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{19}NNaO$: 348.1364; found: 348.1366.

1-(4-Chlorophenyl)-2-phenylquinolin-4(1*H*)-one (3af)[12e]

White solid; yield: 38.4 mg (58%); mp 206–208 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.0 Hz, 1 H), 7.49 (m, 1 H), 7.40–7.10 (m, 10 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 153.9, 142.6, 137.9, 135.6, 135.1, 132.3, 131.5, 130.1, 129.3, 129.1, 128.3, 126.6, 126.3, 124.2, 117.9, 113.0.

1-(4-Fluorophenyl)-2-phenylquinolin-4(1*H*)-one (3ag)[12h]

White solid; yield: 43.5 mg (69%); mp 219–221 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.0 Hz, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.23–7.14 (m, 6 H), 7.05 (t, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 163.1, 161.4 (d, $^1J_{C-F}$ = 174 Hz), 154.0, 142.7, 135.6, 135.2, 132.1, 131.9, 131.8 (d, $^3J_{C-F}$ = 6 Hz), 129.2, 128.8, 128.1, 126.5, 126.2, 124.0, 117.8, 116.8, 116.7 (d, $^2J_{C-F}$ = 15 Hz), 112.8.

4-(4-Oxo-2-phenylquinolin-1(4*H*)-yl)benzonitrile (3ah)[13b]

White solid; yield: 56 mg (87%); mp 254–255 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.72–7.64 (m, 3 H), 7.55–7.46 (m, 6 H), 7.43–7.39 (m, 3 H), 6.25 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 154.6, 140.6, 136.1, 132.2, 132.1, 131.9, 129.4, 128.8, 128.7, 128.6, 128.4, 128.3, 127.5, 127.1, 123.5, 116.2, 112.9.

2-Phenyl-1-(4-tolyl)quinolin-4(1*H*)-one (3ai)[12e]

Yellow solid; yield: 39.8 mg (64%); mp 211–213 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.48–7.44 (m, 1 H), 7.39–7.35 (m, 1 H), 7.23–7.13 (m, 7 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.43 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 154.2, 142.8, 139.0, 136.5, 135.8, 131.8, 130.2, 129.7, 129.2, 128.6, 127.9, 126.3, 126.1, 123.7, 118.2, 112.6, 21.2.

1-(4-Methoxyphenyl)-2-phenylquinolin-4(1*H*)-one (3aj)[12h]

Yellow solid; yield: 43.8 mg (67%); mp 198–200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.52–7.46 (m, 1 H), 7.40–7.36 (m, 1 H), 7.22–7.17 (m, 5 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 6.44 (s, 1 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 159.4, 154.5, 143.0, 135.8, 132.3, 131.9, 131.8, 129.2, 128.6, 127.9, 126.3, 126.1, 123.8, 118.1, 114.6, 112.5, 55.5.

1-Cyclohexyl-2-phenylquinolin-4(1*H*)-one (3ak)[13b]

White solid; yield: 37 mg (61%); mp 197–199 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.96 (d, *J* = 8.8 Hz, 1 H), 7.63 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.50–7.48 (m, 3 H), 7.40–7.36 (m, 3 H), 6.22 (s, 1 H), 4.19–4.13 (m, 1 H), 2.46–2.37 (m, 2 H), 1.88–1.80 (m, 4 H), 1.63–1.60 (m, 1 H), 1.23–0.86 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 155.7, 141.0, 137.3, 130.9, 129.3, 128.8, 128.1, 127.6, 127.1, 123.3, 118.8, 113.4, 63.5, 31.1, 26.5, 25.1.

1-Cyclopropyl-2-phenylquinolin-4(1*H*)-one (3al)[12h]

Yellow solid; yield: 32.4 mg (62%); mp 166–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.73–7.64 (m, 1 H), 7.55–7.46 (m, 5 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 6.35 (s, 1 H), 3.37–3.33 (m, 1 H), 0.94 (d, *J* = 1.6 Hz, 2 H), 0.58 (d, *J* = 1.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 155.6, 143.1, 136.9, 131.8, 129.3, 128.6, 128.4, 126.7, 126.5, 123.7, 117.9, 113.2, 32.5, 12.9.

1-Methyl-2-phenylquinolin-4(1*H*)-one (3am)[23]

White solid; yield: 26.3 mg (56%); mp 61–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 7.6 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.58–7.51 (m, 4 H), 7.46–7.43 (m, 3 H), 6.32 (s, 1 H), 3.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 154.8, 142.0, 135.9, 132.4, 130.9, 129.6, 128.6, 128.5, 126.8, 123.7, 115.9, 112.7, 37.3.

1-Isopropyl-2-phenylquinolin-4(1*H*)-one (3an)[8h]

White solid; yield: 24.7 mg (47%); mp 95–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.85–7.82 (m, 1 H), 7.69–7.61 (m, 1 H), 7.56–7.36 (m, 6 H), 6.20 (s, 1 H), 4.72–4.65 (m, 1 H), 1.60 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 154.4, 139.1, 136.1, 130.0, 128.3, 127.9, 127.2, 126.7, 126.3, 122.4, 117.5, 112.1, 52.6, 20.4.

1-Butyl-2-phenylquinolin-4(1*H*)-one (3ao)[13b]

Yellow solid; yield: 45.4 mg (82%); mp 73–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.72–7.65 (m, 2 H), 7.56–7.46 (m, 4 H), 7.43–7.38 (m, 2 H), 6.25 (s, 1 H), 4.02 (t, *J* = 8.0 Hz, 2 H), 1.72–1.64 (m, 2 H), 1.28–1.13 (m, 2 H), 0.76 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 154.6, 140.6, 136.0, 132.2, 129.4, 128.7, 128.3, 127.3, 127.1, 123.6, 116.3, 112.8, 47.9, 30.8, 19.7, 13.4.

1-Hexyl-2-phenylquinolin-4(1*H*)-one (3ap)

Yellow solid; yield: 36 mg (59%); mp 75–77 °C.

IR (KBr): 2964, 2935, 2878, 1627, 1595, 1486, 1464, 1417, 1304, 1175, 764, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.0 Hz, 1 H), 7.73–7.68 (m, 1 H), 7.55–7.50 (m, 4 H), 7.43–7.39 (m, 3 H), 6.26 (s, 1 H), 4.01 (t, *J* = 8.0 Hz, 2 H), 1.68–1.63 (m, 2 H), 1.45–1.11 (m, 6 H), 0.84 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 153.6, 139.5, 135.0, 131.3, 128.4, 127.7, 127.3, 126.3, 126.1, 122.5, 115.2, 111.8, 47.2, 29.9, 27.6, 25.0, 21.3, 12.8.

ESI-MS: *m/z* = 305 [M^+], 306 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{23}NNaO$: 328.1677; found: 328.1681.

1-Butyl-2-(2-chlorophenyl)quinolin-4(1*H*)-one (3bo)[8h]

Yellow solid; yield: 26.8 mg (43%); mp 141–143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.0 Hz, 1 H), 7.73–7.69 (m, 1 H), 7.56–7.52 (m, 2 H), 7.49–7.41 (m, 4 H), 6.22 (s, 1 H), 4.18–4.11 (m, 1 H), 3.78–3.75 (m, 1 H), 1.77–1.68 (m, 1 H), 1.51–1.48 (m, 1 H), 1.18–1.11 (m, 2 H), 0.77 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 151.3, 140.4, 134.8, 132.9, 132.3, 131.0, 130.6, 129.9, 127.3, 127.2, 127.1, 123.7, 116.2, 112.7, 47.8, 30.5, 19.7, 13.4.

1-Butyl-2-(4-tolyl)quinolin-4(1*H*)-one (3co)

Yellow solid; yield: 32.6 mg (56%); mp 85–87 °C.

IR (KBr): 2961, 2932, 2871, 1627, 1597, 1508, 1484, 1465, 1421, 1379, 841 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.71–7.67 (m, 1 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.42–7.38 (m, 1 H), 7.31–7.27 (m, 4 H), 6.25 (s, 1 H), 4.04 (t, *J* = 8.0 Hz, 2 H), 2.44, (s, 3 H), 1.67–1.64 (m, 2 H), 1.26–1.14 (m, 2 H), 0.77 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 154.9, 140.6, 139.5, 133.2, 132.1, 129.3, 128.2, 127.3, 127.0, 123.5, 116.3, 112.9, 47.9, 30.8, 21.4, 19.7, 13.5.

ESI-MS: *m/z* = 291 [M^+], 292 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO$: 314.1521; found: 314.1524.

1-Butyl-2-(4-fluorophenyl)quinolin-4(1*H*)-one (3do)[8h]

Yellow solid; yield: 36.6 mg (62%); mp 98–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 8.0 Hz, 1 H), 7.73–7.68 (m, 1 H), 7.55–7.52 (m, 1 H), 7.44–7.38 (m, 3 H), 7.22–7.18 (m, 2 H), 6.23 (s, 1 H), 4.01 (t, *J* = 8.0 Hz, 2 H), 1.65 (m, 2 H), 1.22–1.17 (m, 2 H), 0.79 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 163.2 (d, $^1J_{C-F}$ = 249 Hz), 153.5, 140.6, 132.3, 132.1 (d, $^4J_{C-F}$ = 3.0 Hz), 130.3 (d, $^3J_{C-F}$ = 8.0 Hz), 127.4, 127.1, 123.7, 116.2, 115.9 (d, $^2J_{C-F}$ = 22.0 Hz), 113.1, 47.9, 30.8, 19.7, 13.4.

1,2-Dibutylquinolin-4(1*H*)-one (3eo)

Yellow solid; yield: 25.2 mg (49%); mp 91–93 °C.

IR (KBr): 2959, 2931, 2872, 1629, 1599, 1488, 1466, 1429, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 8.4 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 6.28 (s, 1 H), 4.14 (t, *J* = 8.0 Hz, 2 H), 2.70 (t, *J* = 7.6 Hz, 2 H), 1.71–1.68 (m, 4 H), 1.51–1.48 (m, 4 H), 1.10–0.90 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 154.9, 141.1, 132.3, 127.2, 127.1, 123.5, 115.9, 111.3, 46.0, 33.9, 31.5, 31.0, 22.4, 20.1, 14.0, 13.8.

ESI-MS: *m/z* = 257 [M^+], 258 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{23}NNaO$: 280.1677; found: 280.1681.

1-Butyl-5-fluoro-2-phenylquinolin-4(1*H*)-one (3fo)

Yellow solid; yield: 40.1 mg (68%); mp 164–166 °C.

IR (KBr): 2962, 2931, 2873, 1629, 1597, 1509, 1483, 1465, 1422, 847, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.8, 6.8 Hz, 1 H), 7.52–7.50 (m, 3 H), 7.40–7.38 (m, 2 H), 7.19–7.11 (m, 2 H), 6.22 (s, 1 H), 3.94 (t, *J* = 8.0 Hz, 2 H), 1.67–1.63 (m, 2 H), 1.23–1.13 (m, 2 H), 0.77 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 165.3 (d, $^1J_{C-F}$ = 249 Hz), 155.0, 142.1 (d, $^3J_{C-F}$ = 11.0 Hz), 135.7, 130.0 (d, $^3J_{C-F}$ = 11.0 Hz), 129.6, 128.8, 128.3, 124.1, 113.2, 112.3 (d, $^2J_{C-F}$ = 22.0 Hz), 102.4 (d, $^2J_{C-F}$ = 27.0 Hz), 48.2, 30.5, 19.6, 13.4.

ESI-MS: *m/z* = 295 [M^+], 296 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{18}FNNaO$: 318.1270; found: 318.1272.

1-Butyl-7-fluoro-2-phenylquinolin-4(1*H*)-one (3go)

Yellow solid; yield: 47.2 mg (80%); mp 162–165 °C.

IR (KBr): 2961, 2932, 2871, 1626, 1598, 1507, 1485, 1467, 1421, 844, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.8, 6.8 Hz, 1 H), 7.52–7.50 (m, 3 H), 7.40–7.38 (m, 2 H), 7.20–7.16 (m, 1 H), 7.15–7.10 (m, 1 H), 6.22 (s, 1 H), 3.94 (t, *J* = 8.0 Hz, 2 H), 1.66–1.63 (m, 2 H), 1.18–1.13 (m, 2 H), 0.76 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 165.2 (d, $^1J_{C-F}$ = 166 Hz), 155.0, 142.1 (d, $^3J_{C-F}$ = 8.0 Hz), 135.7, 129.9 (d, $^3J_{C-F}$ = 7.0 Hz), 129.6, 128.8, 128.3, 124.0, 113.1 (d, $^4J_{C-F}$ = 3.0 Hz), 112.3 (d, $^2J_{C-F}$ = 15.0 Hz), 102.5 (d, $^2J_{C-F}$ = 18.0 Hz), 48.2, 30.5, 19.6, 13.4.

ESI-MS: *m/z* = 295 [M^+], 296 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{18}FNNaO$: 318.1270; found: 318.1273.

1-Butyl-6-methoxy-2-phenylquinolin-4(1*H*)-one (3io)

Yellow solid; yield: 35.6 mg (58%); mp 108–111 °C.

IR (KBr): 2953, 2933, 2870, 2837, 1623, 1601, 1507, 1483, 1420, 1380, 840 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 3.2 Hz, 1 H), 7.54–7.49 (m, 4 H), 7.41–7.38 (m, 2 H), 7.32 (dd, *J* = 9.2, 3.2 Hz, 1 H), 6.24 (s, 1 H), 4.02 (t, *J* = 8.0 Hz, 2 H), 3.96 (s, 3 H), 1.67–1.63 (m, 2 H), 1.19–1.12 (m, 2 H), 0.75 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 156.1, 153.7, 136.1, 135.2, 129.4, 128.7, 128.6, 128.4, 122.9, 118.0, 111.9, 105.9, 55.8, 48.1, 30.9, 19.7, 13.4.

ESI-MS: *m/z* = 307 [M^+], 308 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO_2$: 330.1470; found: 330.1472.

1-Butyl-6-chloro-2-phenylquinolin-4(1*H*)-one (3jo)

Yellow solid; yield: 50.4 mg (81%); mp 87–89 °C.

IR (KBr): 2967, 2935, 2874, 2858, 1627, 1593, 1502, 1482, 1453, 1436, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47–8.46 (m, 1 H), 7.63–7.60 (m, 1 H), 7.54–7.48 (m, 4 H), 7.40–7.38 (m, 2 H), 6.24 (s, 1 H), 4.00 (t, *J* = 8.0 Hz, 2 H), 1.65–1.61 (m, 2 H), 1.17–1.12 (m, 2 H), 0.75 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 154.9, 139.0, 135.7, 132.4, 129.8, 129.6, 128.8, 128.4, 128.3, 126.3, 118.2, 113.0, 48.2, 30.7, 19.6, 13.4.

ESI-MS: *m/z* = 311 [M^+], 312 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{18}ClNNaO$: 334.0975; found: 334.0977.

1-Butyl-6-methyl-2-phenylquinolin-4(1*H*)-one (3ko)

Viscous yellow liquid; yield: 50.7 mg (87%).

IR (KBr): 2965, 2937, 2875, 2859, 1628, 1595, 1481, 1417, 1175, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.53–7.44 (m, 5 H), 7.40–7.38 (m, 2 H), 6.23 (s, 1 H), 4.00 (t, *J* = 8.0 Hz, 2 H), 2.49 (s, 3 H), 1.66–1.62 (m, 2 H), 1.17–1.12 (m, 2 H), 0.77 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 154.3, 138.7, 136.1, 133.6, 133.5, 129.3, 128.7, 128.4, 127.2, 126.4, 116.2, 112.5, 47.9, 30.8, 20.8, 19.7, 13.4.

ESI-MS: *m/z* = 291 [M^+], 293 [M + 1]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{21}NNaO$: 314.1521; found: 314.1523.

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Supporting Information

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References

(1) (a) Höfle, G.; Kunze, B. *J. Nat. Prod.* **2008**, *71*, 1843. (b) Abe, H.; Kawada, M.; Inoue, H.; Ohba, S.-i.; Nomoto, A.; Watanabe, T.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 2124. (c) Jadulco, R. C.; Pond, C. D.; Van Wagoner, R. M.; Koch, M.; Gideon, O. G.; Matainaho, T. K.; Piskaut, P.; Barrows, L. R. *J. Nat. Prod.* **2014**, *77*, 183.

(2) (a) Krishnamurthy, M.; Gooch, B. D.; Beal, P. A. *Org. Lett.* **2004**, *6*, 63. (b) Krishnamurthy, M.; Simon, K.; Orendt, A. M.; Beal, P. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7044. (c) Cross, R. M.; Manetsch, R. *J. Org. Chem.* **2010**, *75*, 8654. (d) Audisio, D.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2011**, *76*, 4995. (e) Chen, F.; Feng, Z.; He, C.-Y.; Wang, H.-Y.; Guo, Y.-l.; Zhang, X. *Org. Lett.* **2012**, *14*, 1176. (f) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584.

(3) (a) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374. (b) Asahina, Y.; Iwase, K.; Iinuma, F.; Hosaka, M.; Ishizaki, T. *J. Med. Chem.* **2005**, *48*, 3194. (c) Odagiri, T.; Inagaki, H.; Sugimoto, Y.; Nagamochi, M.; Miyauchi, R. N.; Kuroyanagi, J.; Kitamura, T.; Komoriya, S.; Takahashi, H. *J. Med. Chem.* **2013**, *56*, 1974.

(4) (a) Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-S.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **1994**, *37*, 3400. (b) Nakamura, S.; Kozuka, M.; Bastow, K. F.; Tokuda, H.; Nishino, H.; Suzuki, M.; Tatsuzaki, J.; Natschke, S. L. M.; Kuo, S.-C.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 4396. (c) Chang, Y.-H.; Hsu, M.-H.; Wang, S.-H.; Huang, L.-J.; Qian, K.; Morris-Natschke, S. L.; Hamel, E.; Kuo, S.-C.; Lee, K.-H. *J. Med. Chem.* **2009**, *52*, 4883.

(5) (a) Cross, R. M.; Monastyrskyi, A.; Mutka, T. S.; Burrows, J. N.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2010**, *53*, 7076. (b) Cross, R. M.; Namelikonda, N. K.; Mutka, T. S.; Luong, L.; Kyle, D. E.; Manetsch, R. *J. Med. Chem.* **2011**, *54*, 8321. (c) Zhang, Y.; Clark, J. A.; Connelly, M. C.; Zhu, F.; Min, J.; Guiguemde, W. A.; Pradhan, A.; Iyer, L.; Furimsky, A.; Gow, J.; Parman, T.; Mazouni, F. E.; Phillips, M. A.; Kyle, D. E.; Mirsalis, J.; Guy, R. K. *J. Med. Chem.* **2012**, *55*, 4205.

(6) (a) Sui, Z.; Nguyen, V. N.; Altom, J.; Fernandez, J.; Hilliard, J. J.; Bernstein, J. I.; Barrett, J. F.; Ohemeng, K. A. *Eur. J. Med. Chem.* **1999**, *34*, 381. (b) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932. (c) Hadjeri, M.; Peiller, E. L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. *J. Med. Chem.* **2004**, *47*, 4964.

(7) (a) Cecchetti, V.; Parolin, C.; Moro, S.; Pecere, T.; Filipponi, E.; Calistri, A.; Tabarrini, O.; Gatto, B.; Palumbo, M.; Fravolini, A.; Palu, G. *J. Med. Chem.* **2000**, *43*, 3799. (b) Sato, M.; Motomura, T.; Aramaki, H.; Matsuda, T.; Yamashita, M.; Ito, Y.; Kawakami, H.; Matsuzaki, Y.; Watanabe, W.; Yamataka, K.; Ikeda, S.; Kodama, E.; Matsuoka, M.; Shinkai, H. *J. Med. Chem.* **2006**, *49*, 1506. (c) Pasquini, S.; Mugnaini, C.; Tintori, C.; Botta, M.; Trejos, A.; Arvela, R. K.; Larhed, M.; Witvrouw, M.; Michiels, M.; Christ, F.; Debyser, Z.; Corelli, F. *J. Med. Chem.* **2008**, *51*, 5125.

(8) (a) Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 43. (b) López, S. E.; Rebollo, O.; Salazar, J.; Charris, J. E.; Yánez, C. *J. Fluorine Chem.* **2003**, *120*, 71. (c) Boteva, A. A.; Krasnykh, O. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2009**, *45*, 757. (d) Romek, A.; Opatz, T. *Eur. J. Org. Chem.* **2010**, 5841. (e) Liu, Q.-L.; Li, Q.-L.; Fei, X.-D.; Zhu, Y.-M. *ACS Comb. Sci.* **2011**, *13*, 19. (f) Zhao, J.; Zhao, Y.; Fu, H. *Org. Lett.* **2012**, *14*, 2710. (g) Iaroshenko, V. O.; Knepper, I.; Zahid, M.; Dudkin, S.; Kuzora, R.; Villinger, A.; Langer, P. *Org. Biomol. Chem.* **2012**, *10*, 2955. (h) Shao, J.; Huang, X.; Hong, X.; Liu, B.; Xu, B. *Synthesis* **2012**, *44*, 1798. (i) Victor, N. J.; Muraleedharan, K. M. *Adv. Synth. Catal.* **2014**, *356*, 3600.

(9) Camps, R. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3228.

(10) (a) Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms*, 2nd ed.; Springer: Berlin, **2003**, 81. (b) Zewge, D.; Chen, C.-y.; Deer, C.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2007**, *72*, 4276.
(11) (a) Niementowski, S. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1394. (b) Fuson, R. C.; Burness, D. M. *J. Am. Chem. Soc.* **1946**, *68*, 1270. (c) Son, J. K.; Kim, S. I.; Jahng, Y. *Heterocycles* **2001**, *55*, 1981.
(12) (a) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373. (b) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773. (c) Haddad, N.; Tan, J.; Farina, V. *J. Org. Chem.* **2006**, *71*, 5031. (d) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609. (e) Zhao, T.; Xu, B. *Org. Lett.* **2010**, *12*, 212. (f) Takahashi, I.; Morita, F.; Kusagaya, S.; Fukaya, H.; Kitagawa, O. *Tetrahedron: Asymmetry* **2012**, *23*, 1657. (g) Iaroshenko, V. O.; Knepper, I.; Zahid, M.; Kuzora, R.; Dudkin, S.; Villinger, A.; Langer, P. *Org. Biomol. Chem.* **2012**, *10*, 2955. (h) Fei, X.-D.; Zhou, Z.; Li, W.; Zhu, Y.-M.; Shen, J.-K. *Eur. J. Org. Chem.* **2012**, 3001. (i) Iaroshenko, V. O.; Zahid, M.; Mkrtchyan, S.; Gevorgyan, A.; Altenburger, K.; Knepper, I.; Villinger, A.; Sosnovskikh, V. Y.; Langer, P. *Tetrahedron* **2013**, *69*, 2309.
(13) (a) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (b) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Synthesis* **2009**, 1209.
(14) Seppänen, O.; Muuronen, M.; Helaja, J. *Eur. J. Org. Chem.* **2014**, 4044.
(15) (a) Peng, J.; Shang, G.; Chen, C.; Miao, Z.; Li, B. *J. Org. Chem.* **2013**, *78*, 1242. (b) Chen, C.; Shang, G.; Zhou, J.; Yu, Y.; Li, B.; Peng, J. *Org. Lett.* **2014**, *16*, 1872. (c) Peng, J.; Zhao, Y.; Zhou, J.; Ding, Y.; Chen, C. *Synthesis* **2014**, *46*, 2051.
(16) (a) Wang, B.; Wang, S.; Li, P.; Wang, L. *Chem. Commun.* **2010**, *46*, 5891. (b) Gandeepan, P.; Parthasarathy, K.; Su, T.-H.; Cheng, C.-H. *Adv. Synth. Catal.* **2012**, *354*, 457.
(17) (a) Pohland, A. E.; Benson, W. R. *Chem. Rev.* **1966**, *66*, 161. (b) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9592; *Angew. Chem.* **2009**, *121*, 9770.
(18) For selected examples in which β-halovinyl ketones or analogues are used as electrophilic coupling reagents, see: (a) Xiang, J. S.; Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4284. (b) Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Ventura, M. P.; Weers, H. L.; Fernández de la Pradilla, R.; Castro, S.; Dorado, R.; Morente, M. *J. Org. Chem.* **1997**, *62*, 6326. (c) Xi, C.; Kotora, M.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2000**, *65*, 945. (d) Kotora, M.; Matsumura, H.; Gao, G.; Takahashi, T. *Org. Lett.* **2001**, *3*, 3467. (e) Haack, T.; Kurtkaya, S.; Snyder, J. P.; Georg, G. I. *Org. Lett.* **2003**, *5*, 5019. (f) Bekele, T.; Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 8471. (g) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (h) Liang, G.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 819. (i) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 1268.
(19) For selected examples of syntheses of nitrogen heterocycles through Pd-catalyzed double aminations, see: (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 403. (b) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851. (c) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764. (d) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413. (e) Zhang, X.; Yang, Y.; Liang, Y. *Tetrahedron Lett.* **2012**, *53*, 6406. (f) Ueno, A.; Kitawaki, T.; Chida, N. *Org. Lett.* **2008**, *10*, 1999. (g) Zhou, Y.; Verkade, J. G. *Adv. Synth. Catal.* **2010**, *352*, 616.
(20) (a) Chen, Q.-H.; Geng, Z. *Chin. Sci. Bull.* **1993**, *38*, 791. (b) Esteban, J.; Costa, A. M.; Gómez, À.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 65. (c) Kashiwabara, T.; Fuse, K.; Hua, R.; Tanaka, M. *Org. Lett.* **2008**, *10*, 5469. (d) Souibgui, A.; Gaucher, A.; Marrot, J.; Bourdreux, F.; Aloui, F.; Ben Hassine, B.; Prim, D. *Tetrahedron* **2014**, *70*, 3042. (e) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, **2001**, Chap. 23, 585.
(21) (a) Eaton, P. E.; Stubbs, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 5722. (b) Kim, H. Y.; Li, J.-Y.; Oh, K. *J. Org. Chem.* **2012**, *77*, 11132.
(22) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.
(23) Shim, S. C.; Chae, S. A.; Lee, D. Y.; Lim, H. S.; Kalinin, V. N. *J. Korean Chem. Soc.* **1994**, *38*, 774.