O-Aryloxime Ethers from the Copper(II)-Mediated Cross-Coupling of Oximes and Phenylboronic Acids

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Abstract: A direct approach to *O*-aryloxime ethers by means of the first copper-mediated cross-coupling of aromatic oximes and phenylboronic acids is reported. The O-arylation of acetophenone oximes with phenylboronic acids typically furnished *O*-aryloxime ethers in good to moderate yields.

Key words: *O*-aryloxime ether, oxime, phenylboronic acid, copper(II) acetate, cross-coupling

O-Aryloxime ethers are not only useful synthetic intermediates, being precursors to benzofurans[1] and benzisoxazoles,[2] but are present in a growing number of bioactive compounds. Examples include potent inhibitors of transthyretin amyloid fibril formation[3] and agents with significant in vitro activity against ecto- and endoparasites that afflict companion and production animals.[4]

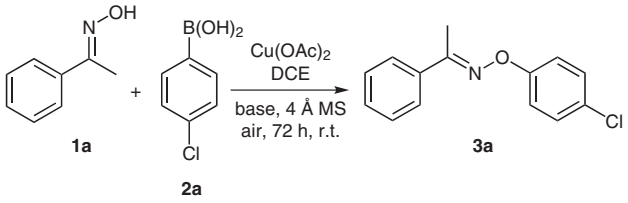
The *O*-aryloxime ether moiety is commonly prepared from a condensation reaction between aldehydes or ketones and *O*-aryloxyamines.[5] Although large numbers of aldehydes and ketones are commercially available, the *O*-aryloxyamines are not and in general must be prepared prior to use. A more direct approach to *O*-aryloxime ethers is based upon the O-arylation of alkali metal oxime salts with nitro- or fluoroarene derivatives,[6] although a limitation of this strategy is that haloarenes such as iodo- and bromobenzenes cannot be used.[7] Despite these methods, there is an ongoing need to develop general synthetic approaches to prepare *O*-aryloxime ethers.

An O-arylation process conducted under very mild reaction conditions is the oxidative cross-coupling of OH-containing substrates with phenylboronic acids, simultaneously reported by Chan[8] and Evans et al.[9] This process is mediated by a stoichiometric amount of a copper(II) salt in the presence of a weak base and atmospheric oxygen. We envisaged that such an O-arylation process between oximes and phenylboronic acids would provide a simple and general method for the synthesis of *O*-aryloxime ethers.

Acetophenone oxime (**1a**), readily obtained from acetophenone and hydroxylamine, and 4-chlorophenylboronic acid (**2a**) were used as model substrates to explore the conditions required for their copper-mediated cross-coupling (Table 1).

The conditions chosen were based upon those reported for the copper(II)-mediated cross-coupling of phenylboronic acids with phenols.[8] Thus, 1 equivalent of both acetophenone oxime (**1a**) and $Cu(OAc)_2$, and 2 equivalents of both the phenylboronic acid **2a** and an amine base, were allowed to react at room temperature in 1,2-dichloroethane with 4 Å molecular sieves for a period of 72 hours under an ambient atmosphere.

Table 1 Optimization of Bases, Solvents, and Copper Salts[a]



1a 2a 3a

Entry	Base	Equiv	Yield of **3a** (%)[b]
1	pyridine	1.1	36
2	pyridine	2	59
3	pyridine	5	27
4	Et_3N	2	22
5	DBU	2	55
6	DMAP	2	40
7	pyridine–Et_3N (1:1)	2	30
8	pyridine–DBU (1:1)	2	30
9	Cs_2CO_3	1.1	no reaction
10[c]	pyridine	2	trace[d]
11[e]	pyridine	2	trace[d]
12[f]	pyridine	2	35

[a] Conditions: **1a** (1.5 mmol), **2a** (3.0 mmol), $Cu(OAc)_2$ (1.5 mmol).
[b] Isolated yield (in some cases minor amounts of biaryl ether and/or phenol products were also isolated).
[c] MeOH as solvent.
[d] Deoximation of **1a** observed.
[e] DMF as solvent.
[f] Amount of CuCl used: 1.5 mmol.

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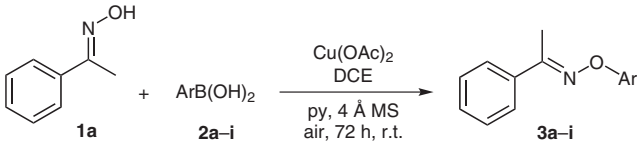
It is known that the amine plays a crucial role, acting as both a base and a ligand, and varies according to the specific copper-mediated cross-coupling process.[8–10] In this case, pyridine was found to be the best amine, with 2 equivalents required for optimal yields of **3a** (Table 1, entry 2).[11] Using either 1.1 or 5 equivalents of pyridine resulted in diminished yields (Table 1, entries 1 and 3). Amines such as triethylamine, DBU, and DMAP either suppressed or did not improve the cross-coupling reaction (Table 1, entries 4–6). It has also been reported that mixtures of amines can improve carbon–heteroatom cross-coupling processes.[9,10c] However, when 2 equivalents of an equimolar mixture of pyridine and triethylamine (or pyridine and DBU) was used no improvement in the yield of **3a** occurred (Table 1, entries 7 and 8). Furthermore, no reaction was observed when an inorganic base such as Cs_2CO_3 was used (Table 1, entry 9). A limited examination of solvents revealed that 1,2-dichloroethane was optimal when compared to methanol or DMF, which both gave only traces of **3a** and resulted in considerable deoximation of **1a** to the corresponding ketone (Table 1, entries 10 and 11). Finally, cuprous chloride was evaluated as a copper source, but failed to improve the yield of **3a** (Table 1, entry 12), despite this copper(I) salt being shown to effectively promote the O-arylation of *N*-hydroxyphthalimide with phenylboronic acids.[10a]

With a suitable set of cross-coupling conditions in hand,[11] we investigated the $Cu(OAc)_2$-mediated O-arylation of acetophenone oxime (**1a**) with a set of structurally and electronically diverse arylboronic acids (Table 2).

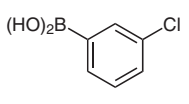
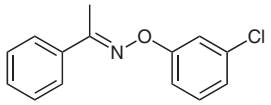
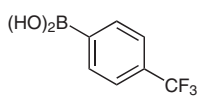
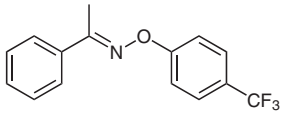
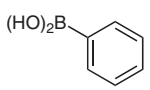
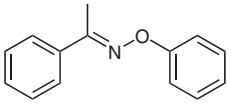
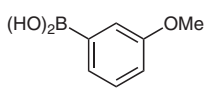
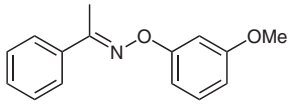
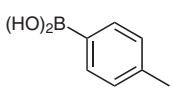
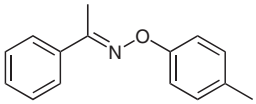
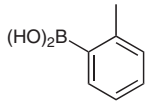
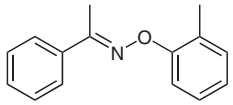
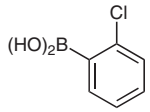
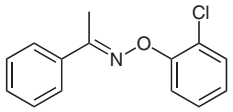
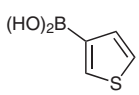
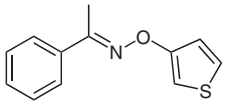
As discussed, **1a** and 4-chlorophenylboronic acid (**2a**) efficiently cross-coupled to give *O*-aryloxime ether **3a** (Table 2, entry 1). Similarly, **1a** reacted with 3-chlorophenylboronic acid (**2b**) to afford *O*-(3-chlorophenyl)acetophenone oxime (**3b**) in a satisfactory yield (Table 2, entry 2). Use of the more electron-deficient 4-trifluoromethylphenylboronic acid (**2c**) resulted in a slight decrease in yield (Table 2, entry 3). A significantly better O-arylating agent was phenylboronic acid (**2d**), which afforded *O*-aryloxime ether **3d** in 70% isolated yield (Table 2, entry 4). When the cross-coupling of **1a** with 3-methoxyphenylboronic acid (**2e**) and 4-methylphenylboronic acid (**2f**) was examined, it was found that the corresponding O-arylated products **3e** and **3f**, respectively, were formed in moderate yields (Table 2, entries 5 and 6). In contrast oxime **1a** did not efficiently cross-couple with 2-methylphenylboronic acid (**2g**, Table 2, entry 7) or 2-chlorophenylboronic acid (**2h**, Table 2, entry 8), and the isolated yields of *O*-aryloxime ethers **3g** and **3h**, respectively, were significantly depressed.[12] Lastly, the cross-coupling of **1a** and 3-thienylboronic acid (**2i**) resulted in the *O*-aryloxime ether product **3i** being isolated in very low yield (Table 2, entry 9).[12]

As shown in Table 2, acetophenone oxime (**1a**) most effectively cross-coupled with the parent phenylboronic acid (**2d**), which is somewhat unexpected given that **2d** is reputed to be relatively inefficient in copper-mediated carbon–heteroatom cross-coupling reactions.[13] Moreover, it was apparent that the O-arylation of oxime **1a** was sensitive to the presence of electron-withdrawing and -donating substituents on the phenylboronic acid. For example, the O-arylation of **1a** became progressively less efficient as the phenylboronic acid coupling partner became increasingly electron deficient. Thus, yields from cross-

Table 2 $Cu(OAc)_2$-Mediated O-Arylation of Acetophenone Oxime (**1a**) with Arylboronic Acids **2a–i**[11]



1a 2a–i 3a–i

Entry	Arylboronic acid	Product	Yield (%)[a]
1	**2a**	**3a**	59
2	 **2b**	 **3b**	59
3	 **2c**	 **3c**	42
4	 **2d**	 **3d**	70
5	 **2e**	 **3e**	50
6	 **2f**	 **3f**	50
7	 **2g**	 **3g**	18
8[b]	 **2h**	 **3h**	10
9[b]	 **2i**	 **3i**	3

[a] See Table 1.
[b] DBU as the amine and 7 d reaction time.

couplings involving 4- and 3-chlorophenylboronic acids (**2a** and **2b**) were somewhat diminished in comparison to the parent phenylboronic acid (**2d**), whereas the yield from the reaction of the highly electron-deficient phenylboronic acid **2c** was significantly reduced. It was also noticeable that the cross-coupling of phenylboronic acids bearing electron-donating substituents, 3-methoxyphenylboronic acid (**2e**) and 4-methylphenylboronic acid (**2f**), were also less efficient when compared to phenylboronic acid (**2d**). Furthermore, the *ortho*-substituted phenylboronic acids **2g** and **2h**, and the heteroarylboronic acid **2i**, appear not to be tolerated. It should be noted that the poor yield obtained when using 2-chlorophenylboronic acid (**2h**) was not surprising since it has been reported that 2-halophenylboronic acids do not participate in copper-mediated carbon–heteroatom cross-couplings.[9,10a,14]

In all cases the *O*-aryloxime ethers shown in Table 2 were found to be single isomers about the C=N bond by analysis of the associated NMR spectroscopic data. However, by virtue of insufficient through-space correlations, NOESY NMR experiments failed to indicate if these compounds existed as *E*- or *Z*-isomers about the C=N bond. The *O*-aryloxime ethers were subsequently confirmed as being *E*-isomers about the C=N bond by single-crystal X-ray diffraction (Figure 1).

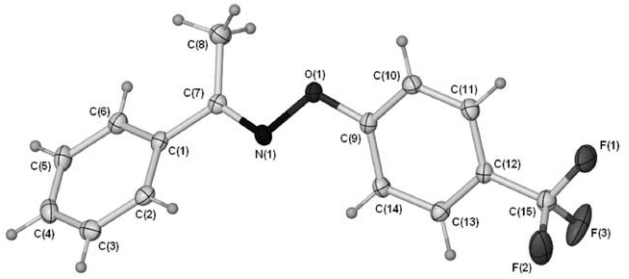
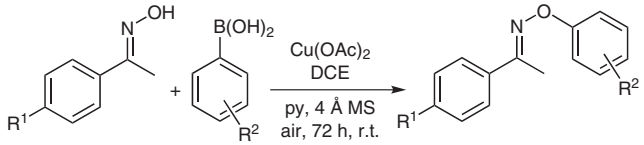


Figure 1 ORTEP diagram of the single-crystal X-ray structure of (*E*)-*O*-(4-trifluoromethylphenyl)acetophenone oxime (**3c**)

To probe the reaction scope further, we investigated the O-arylation of acetophenone oximes containing both electron-withdrawing and -donating substituents. Thus, the O-arylation of 4′-chloro-, 4′-nitro- and 4′-methoxyacetophenone oximes **1b–d** with phenylboronic acids **2a–f** was explored, with the overall results tending to mirror those involving acetophenone oxime (**1a**, Table 3).

Once again the best yields were generally obtained when using 4- and 3-chlorophenylboronic acids (**2a** and **2b**, Table 3, entries 1, 2, 7, 8, 13, and 14) and phenylboronic acid (**2d**, Table 3, entries 4, 10, and 16), with the O-arylation process being less efficient when 4-trifluoromethylphenylboronic acid (**2c**) was employed (Table 3, entries 3, 9, and 15). In a similar manner to **1a**, acetophenone oximes **1b–d** cross-coupled with 3-methoxyphenylboronic acid (**2e**) to afford the corresponding *O*-aryloxime ethers in modest (Table 3, entries 5 and 17) or good isolated yield (Table 3, entry 11). Cross-couplings of **1b–d** with 4-methylphenylboronic acid (**2f**) gave yields analogous to

Table 3 $Cu(OAc)_2$-Mediated O-Arylation of 4′-Substituted Acetophenone Oximes **1b–d** with Phenylboronic Acids **2a–f**[11]



1b, R^1 = Cl **2a–f** **4a–r**
1c, R^1 = NO_2
1d, R^1 = OMe

Entry	R^1	R^2	Product	Yield (%)[a]
1	Cl	4-Cl	**4a**	52
2	Cl	3-Cl	**4b**	52
3	Cl	4-CF_3	**4c**	32
4	Cl	H	**4d**	53
5	Cl	3-OMe	**4e**	40
6	Cl	4-Me	**4f**	53
7	O_2N	4-Cl	**4g**	56[b]
8	O_2N	3-Cl	**4h**	62[b]
9	O_2N	4-CF_3	**4i**	40
10	O_2N	H	**4j**	63[b]
11	O_2N	3-OMe	**4k**	60
12	O_2N	4-Me	**4l**	50
13	MeO	4-Cl	**4m**	66
14	MeO	3-Cl	**4n**	54
15	MeO	4-CF_3	**4o**	39
16	MeO	H	**4p**	65
17	MeO	3-OMe	**4q**	49
18	MeO	4-Me	**4r**	49

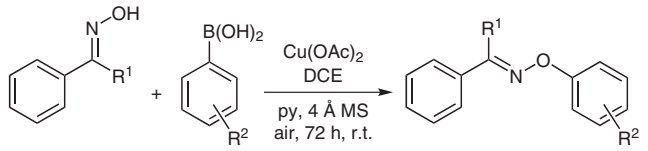
[a] See Table 1.
[b] Includes the isolation of a minor amount (ca. 5%) of the corresponding *(Z)*-isomer.

that obtained from the reaction of **1a** and **2f** (Table 3, entries 6, 12, and 18). Overall, these results suggest that the efficacy of this copper-mediated cross-coupling process is not greatly influenced by the electronic nature of the acetophenone oxime, but significantly affected by the presence of electron-withdrawing and -donating substituents on the phenylboronic acid coupling partner.

In contrast to the O-arylation of acetophenone oximes, the cross-coupling of benzaldehyde oxime (**5a**) with a select group of phenylboronic acids was considerably less efficient (Table 4). The best isolated yield was obtained from the cross-coupling reaction involving phenylboronic acid (**2d**, Table 4, entry 3), whereas the electron-deficient phenylboronic acids **2a** and **2b**, and also 3-methoxyphenylboronic acid (**2e**), all gave O-arylated products in poor yields

(Table 4, entries 1, 2, and 4). Similarly, benzophenone oxime (**5b**) cross-coupled poorly with 4-chlorophenylboronic acid (**2a**, Table 4, entry 5), although the O-arylation of **5b** with phenylboronic acid (**2d**) was somewhat more efficacious (Table 4, entry 6). Moreover, in both cases significant deoximation of benzophenone oxime (**5b**) occurred under the reaction conditions [the deoximation of oximes by Cu(II) salts has been reported previously].[7,15]

Table 4 $Cu(OAc)_2$-Mediated O-Arylation of Benzaldehyde Oxime (**5a**) or Benzophenone Oxime (**5b**) with Phenylboronic Acids **2a**,**b**,**d**,**e**[11]



5a, R^1 = H
5b, R^1 = Ph

2a,**b**,**d**,**e**

6a–f

Entry	R^1	R^2	Product	Yield (%)[a]
1	H	4-Cl	**6a**	28
2	H	3-Cl	**6b**	30
3	H	H	**6c**	43
4	H	3-MeO	**6d**	29[b]
5	Ph	4-Cl	**6e**	32
6	Ph	H	**6f**	51

[a] See Table 1.
[b] Slowly isomerizes in $CDCl_3$ to give a mixture of *E*- and *Z*-isomers.

In summary, we report a concise method to prepare *O*-aryloxime ethers by means of the first copper-mediated cross-coupling of aromatic oximes and phenylboronic acids using stoichiometric $Cu(OAc)_2$ with pyridine as base. In most cases the O-arylation of acetophenone oximes with phenylboronic acids furnished *O*-aryloxime ethers in good to moderate yields, although when the phenylboronic acid coupling partner contained a highly electron-deficient moiety the reaction did not proceed as smoothly. It was also found that the cross-coupling was not greatly influenced by the electronic nature of the acetophenone oxime. Studies to optimize and improve the scope of this method are being actively investigated within our laboratories and will be reported in due course.

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(11) All products showed analytical and spectral characteristics consistent with their structure.

Representative Pocedure for the Copper-Mediated Cross-Coupling of Aromatic Oximes and Phenylboronic Acids

To a mixture of acetophenone oxime (**1a**, 200 mg, 1.48 mmol), $Cu(OAc)_2$ (269 mg, 1.48 mmol) and 4-chlorophenylboronic acid (**2a**, 463 mg, 2.96 mmol) in DCE (12 mL) was added pyridine (239 μL, 2.96 mmol). This resulted in a light green colored solution to which freshly activated, and partially crushed, 4 Å MS (ca. 350 mg) were added. The reaction was open to the atmosphere. The progress of the reaction was followed by TLC. The color of the reaction mixture changed from light to deep green as the reaction proceeded. After stirring at r.t. for 72 h the reaction mixture was filtered through a small pad of silica gel (eluting with CH_2Cl_2) and the solvent removed under reduced pressure. The resulting brown oil was purified by radial chromatography (eluting with 5–10% CH_2Cl_2–PE) to afford (*E*)-*O*-(4-chlorophenyl)acetophenone oxime (**3a**, 215 mg, 59%) as a white solid; mp 69–71 °C (lit.[7] 54–56 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (m, 2 H), 7.43 (m, 3 H), 7.29 (d, *J* = 9.2 Hz, 2 H), 7.23 (d, *J* = 9.2 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2 (C), 158.1 (C), 135.7 (C), 129.9 (CH), 129.1 (CH), 128.5 (CH), 126.9 (C), 126.5 (CH), 116.0 (CH), 13.4 (CH_3). HRMS: *m/z* calcd for $C_{14}H_{12}ClNO$: 245.0607; found: 245.0599.

Data for Selected Compounds

(*E*)-*O*-(3-Chlorophenyl)acetophenone Oxime (3b)

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (m, 2 H), 7.43 (m, 3 H), 7.35 (m, 1 H), 7.24 (m, 1 H), 7.15 (m, 1 H), 7.01 (m, 1 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C), 158.5 (C), 135.6 (C), 134.7 (C), 130.0 (CH), 129.9 (CH), 128.5 (CH), 126.5 (CH), 122.2 (CH), 115.2 (CH), 113.0 (CH), 13.4 (CH_3). HRMS: *m/z* calcd for $C_{14}H_{12}ClNO$: 245.0607; found: 245.0606.

(*E*)-*O*-(4-Chlorophenyl)-4′-chloroacetophenone Oxime (4a)

Colorless solid; mp 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 2.42 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.0 (C), 157.1 (C), 136.0 (C), 134.1 (C), 129.2 (CH), 128.8 (CH), 127.7 (CH), 127.1 (C), 116.0 (CH), 13.3 (CH_3). HRMS: *m/z* calcd for $C_{14}H_{11}Cl_2NO$: 279.0218; found: 279.0207.

(*E*)-*O*-(4-Methylphenyl)-4′-chloroacetophenone Oxime (4f)

Yellow solid; mp 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.14 (m, 4 H), 2.42 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (C), 156.2 (C), 135.6 (C), 134.5 (C), 131.7 (C), 129.7 (CH), 128.7 (CH), 127.7 (CH), 114.7 (CH), 20.6 (CH_3), 13.1 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{14}ClNO$: 259.0764; found: 259.0766.

(*E*)-*O*-(4-Chlorophenyl)-4′-nitroacetophenone Oxime (4g)

Colorless solid; mp 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.2 Hz, 2 H), 7.93 (d, *J* = 9.2 Hz, 2 H), 7.30 (d, *J* = 9.2 Hz, 2 H), 7.22 (d, *J* = 9.2 Hz, 2 H), 2.49 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8 (C), 156.2 (C), 148.5 (C), 141.6 (C), 129.3 (CH), 127.6 (C), 127.2 (CH), 123.7 (CH), 116.1 (CH), 13.3 (CH_3). HRMS: *m/z* calcd for $C_{14}H_{11}ClN_2O_3$: 290.0458; found: 290.0446.

(*E*)-*O*-(3-Methoxyphenyl)-4′-nitroacetophenone Oxime (4k)

Colorless solid; mp 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 8.8 Hz, 2 H), 7.96 (d, *J* = 8.8 Hz, 2 H), 7.26 (m, 1 H), 6.89 (m, 2 H), 6.64 (m, 1 H), 3.84 (s, 3 H), 2.50 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.7 (C), 160.3 (C), 155.7 (C), 148.5 (C), 141.9 (C), 129.9 (CH), 127.2 (CH), 123.7 (CH), 108.2 (CH), 107.2 (CH), 101.1 (CH), 55.4 (CH_3), 13.2 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{14}N_2O_4$: 286.0954; found: 286.0945.

(*E*)-*O*-(4-Chlorophenyl)-4′-methoxyacetophenone Oxime (4m)

Colorless solid; mp 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 9.2 Hz, 2 H), 7.21 (d, *J* = 9.2 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.41 (s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0 (C), 158.2 (C), 157.8 (C), 129.1 (CH), 128.1 (C), 127.9 (CH), 126.7 (C), 116.0 (CH), 113.9 (CH), 55.3 (CH_3), 13.3 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{14}ClNO_2$: 275.0713; found: 275.0698.

(12) In the case of compounds **3h** and **3i**, DBU (2.0 equiv) was found to be a more effective amine than pyridine.

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