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A Unified Strategy for Iron-Catalyzed *ortho*-Alkylation of Carboxamides

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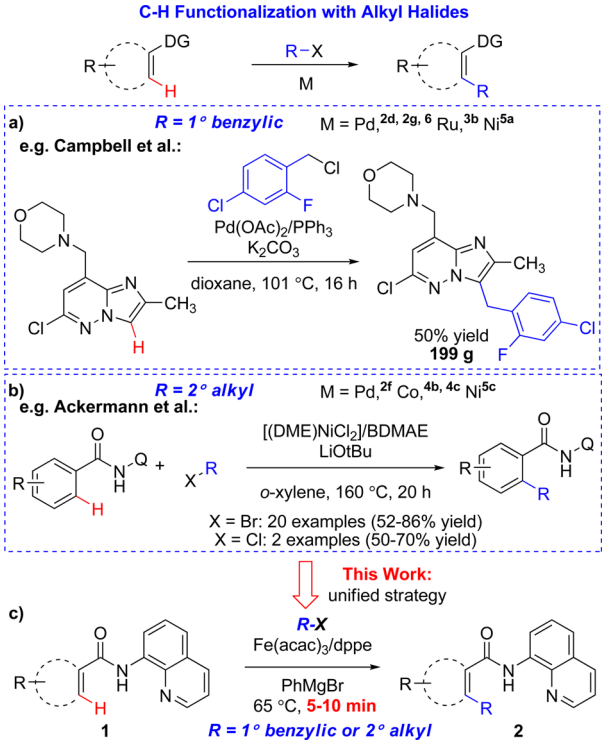
Supporting Information

ABSTRACT: Using 8-aminoquinoline-based aryl carboxamides, the direct *ortho*-alkylation can be achieved in high yields in the presence of an iron source, 1,2-bis(diphenylphosphino)ethane (dppe) and phenylmagnesium bromide. The reactions proceed without overalkylation and provide high levels of regioselectivity. The benzylation reactions can be performed in air with reagent-grade THF, while the alkylation works well with unactivated secondary bromides and iodides in 2-methyltetrahydrofuran. Moreover, the reactions only require 5−10 min.

The introduction of an alkyl group *ortho* to a carboxylic acid derivative is not trivial. Recently transition-metal-catalyzed, directed C−H bond functionalization has emerged as an attractive method for this bond construction.[1] While C_{sp^2} C−H alkylation examples exist with alkyl electrophiles using Pd,[2] Ru,[3] Co,[4] and Ni,[5] these approaches remain limited in electrophile scope. Furthermore, there exists a need to develop robust alkylation reactions capable of large-scale implementation (Scheme 1a).[6] While pioneering work by Nakamura et al. has enabled C−H functionalization with nucleophiles,[7] their investigations of electrophiles have just begun.[8] We recently reported a system to allow the use of primary electrophiles;[9] however, unactivated secondary electrophiles represent important coupling partners that currently require relatively harsh conditions or long reaction times with Pd,[2e] Co,[4b,c] and Ni[5c] (Scheme 1b). Here we report easily tunable conditions to allow the directed *ortho*-alkylation of 8-aminoquinoline-based[10] aryl carboxamides **1** to products **2** using inexpensive and benign iron salts under mild conditions in ≤10 min (Scheme 1c).

The iron-catalyzed *ortho*-benzylation of benzamides was optimized through the systematic evaluation of pertinent reaction parameters (see Supporting Information (SI)). A Grignard reagent proved uniquely effective as a base/reductant for the reaction, while zinc salts[8a,c] shut down the desired reaction, providing the direct coupling of the Grignard and benzamide substrate.[7,11] The reaction is performed by combining $Fe(acac)_3$ (10 mol %), dppe (15 mol %), and a benzylating agent (3 equiv) in reagent-grade THF at 65 °C, followed by the slow addition of the Grignard (usually 7 min, Table 1). Unlike most Pd,[2a,d,e,g] Co,[4a] and Ni[5a,b] methods, the reaction provided the monosubstituted products without any detectable bis-substitution (entries 1−11, 13−14, Table 1). As found previously,[9] *meta* substituents provided alkylation at the less hindered position. Impressively, even *m*-fluorobenzamide **7** provides product **23** with >20:1 regioselectivity (entry 5, Table 1). While highly selective for monoalkylation, this prevents the use of *ortho*-substituted benzamides (see SI), except in the case of *o*-fluorobenzamide **17** (entry 15, Table 1). Additionally, the benzylation reaction functions well with thiophene and pyrrole (entries 12 and 16, Table 1). Another significant finding of this work is the success of the reaction in the presence of aryl halides (entries 3−5, 8, and 15, Table 1), as such functional groups are incompatible with previously reported methods.[12] The reaction proceeds well on gram scale, providing **20** in 82% yield with 85% conversion (entry 2, Table 1). Importantly, the reaction proved particularly robust with all reactions performing well *open to air* (Table 1).

Scheme 1. (a) A Process-Scale Example of C−H Benzylation; (b) Alkylation of C−H Bonds with Secondary Electrophiles Remain Rare; (c) This Work Demonstrates How Iron Catalysis Can Be Used for a Range of Alkylations[a]



[a]DG = directing group; Q = 8-quinolinyl; BDMAE = bis(2-dimethylaminoethyl)ether; DME = dimethoxyethane.

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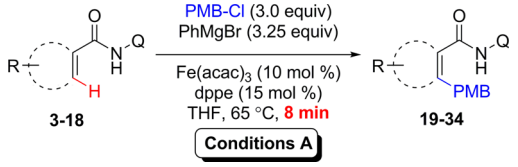
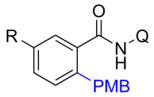
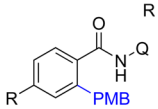
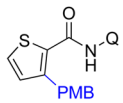
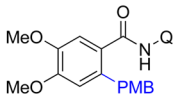
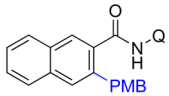
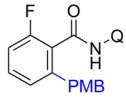
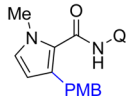
Table 1. *ortho*-Benzylation of Various Benzamides with *p*-Methoxybenzyl Chloride (PMB-Cl)



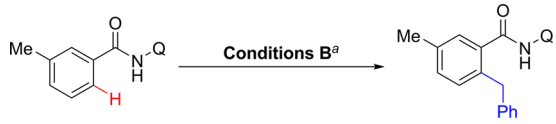
entry	product			under N_2 % yield (conv)[a]	under air[b] % yield (conv)[a]
1		R = H	**19**	83 (87)	82 (89)
2[d]		Me	**20**	85 (86)	77 (78)
3		Cl	**21**	81 (92)	84 (91)
4		Br	**22**	76 (100)	82 (86)
5		F	**23**	63 (72)	73 (74)
6		CF_3	**24**	64 (70)[c]	45 (64)[c]
7		R = OMe	**25**	77 (85)	76 (84)
8		I	**26**	45 (74)[c]	41 (67)[c]
9		SMe	**27**	80 (88)	86 (91)
10		*t*-Bu	**28**	81 (89)	75 (87)
11		NMe_2	**29**	93 (100)[c]	91 (100)[c]
12			**30**	79 (100)	61 (76)
13			**31**	87 (89)	86 (91)
14			**32**	89 (93)	70 (74)
15			**33**	60 (81)[c]	47 (63)[c]
16			**34**	61 (100)[c]	-

[a]Isolated yields after silica chromatography. [b]Open flask. [c]Conditions B: $Fe(acac)_3$ (20 mol %), dppe (30 mol %), PMBCl (3.5 equiv), PhMgBr (4.1 equiv). [d]Reaction run on 1.0 g scale of **4** yielded 82% (1.19 g, 85% conv) of **20** PMB = *p*-methoxybenzyl, Q = 8-quinolinyl.

To test the scope of electrophiles in the benzylation, various benzyl electrophiles were evaluated under our optimized reaction conditions (Table 2). To our surprise, benzyl chloride **35** was significantly better than benzyl bromide **36** (entries 1 and 2, Table 2), while benzyl iodide **37** (entry 3, Table 2) provided only a trace yield of desired product **41**. Moreover, benzyl mesylate **38**, tosylate **39**, and phosphate **40** proved competent in the reaction, delivering low yields of desired product **41** (entries 4–6, Table 2). While this demonstrates the breadth of electrophiles competent in the reaction, they may be proceeding through a common intermediate.[13]

Next, various benzyl chloride derivatives were evaluated in the reaction (Table 3). While the reaction provided moderate-to-high yields with 10 mol % iron loading, the products proved difficult to separate from the starting *m*-tolylbenzamide **4**. The use of a higher catalyst loading and additional phenylmagnesium bromide, however, provided complete conversion (entries 1–3 and 5, Table 3). Interestingly, the reaction appears

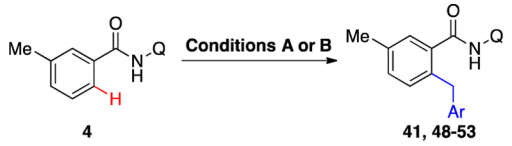
Table 2. Comparison of Different Benzyl Electrophiles



entry	electrophile		% yield[b]
1	BnCl	**35**	99
2	BnBr	**36**	43
3	BnI	**37**	< 5
4	BnOMs	**38**	23
5	BnOTs	**39**	38
6	$BnOPO(OEt)_2$	**40**	34

[a]Conditions same as described in Table 1 except reaction performed over 10 min. [b]^{1}H NMR yields calculated using 1,3,5-trimethoxybenzene as internal standard. Q = 8-quinolinyl.

Table 3. *ortho*-C–H Functionalization of *m*-Tolylbenzamide 3 with Benzyl Chloride Derivatives

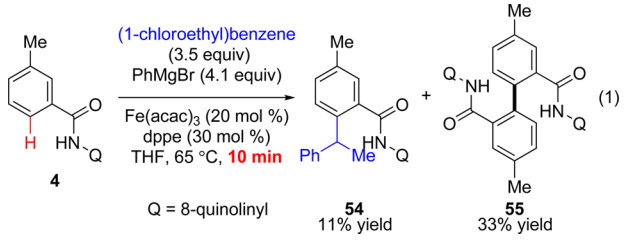


entry	electrophile		Conditions A[a] % yield[b]	Conditions B[a] % yield[c]
1	BnCl	**35**	95	99
2	4-ClBnCl	**42**	59	98
3	4-FBnCl	**43**	89	96
4	4-(MeS)BnCl	**44**	54	78
5	4-MeBnCl	**45**	83	97[d]
6	2-MeBnCl	**46**	44	52
7	2,4,6-TriMeBnCl	**47**	20	48

[a]Conditions same as described in Table 1 except reaction performed over 10 min. [b]^{1}H NMR yields calculated using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yields after silica chromatography. [d]$Fe(acac)_3$ (10 mol %), dppe(15 mol %), PhMgBr (4.25 equiv). Q = 8-quinolinyl.

particularly sensitive to steric encumbrance at the benzylic center. For example, while *p*-methylbenzyl chloride **45** produced a 97% yield of **52** with 10 mol % iron, *o*-methylbenzyl chloride **46** provided only a 52% yield of **53** with 20 mol % catalyst (entries 5 and 6, Table 3). Additionally, the more sterically hindered mesitylbenzyl chloride **47** yielded only 48% of product **54** (entry 7, Table 3).

Interestingly, secondary benzyl chloride 1-chloroethylbenzene provided product **54** without isomerization (eq 1). This represents the first example of directed C–H functionalization with a secondary benzylic electrophile. Moreover, starting benzamide **3** underwent a dehydrogenative biaryl coupling to form **55** in 33% yield. Dimer **55** was not detected in any previous reaction, suggesting a unique mechanistic pathway for secondary benzylic chlorides. Future efforts will be dedicated to unraveling the unique reactivity in eq 1.



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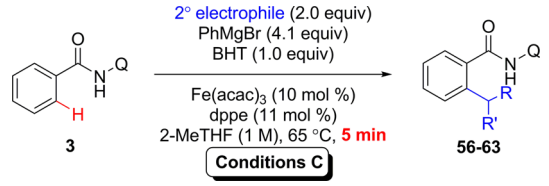
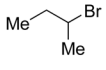
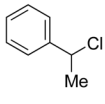
Attempts to expand this chemistry to unactivated alkyl chlorides proved unviable. Bromocyclohexane, however, showed product formation along with significant overalkylation products. Since the overalkylation products could stem from formation of transient secondary radicals, the radical inhibitor butylated hydroxytoluene (BHT) was added to the reaction. With one equivalent of BHT, overalkylation was suppressed. Moreover, simply switching the solvent to 2-methyltetrahydrofuran, increasing the concentration to 1 M, and shortening the addition time of phenylmagnesium bromide provided generally useful yields across a variety of secondary bromides (Table 4).

Table 4. *ortho*-C−H Functionalization of Benzamide 3 with Secondary Electrophiles



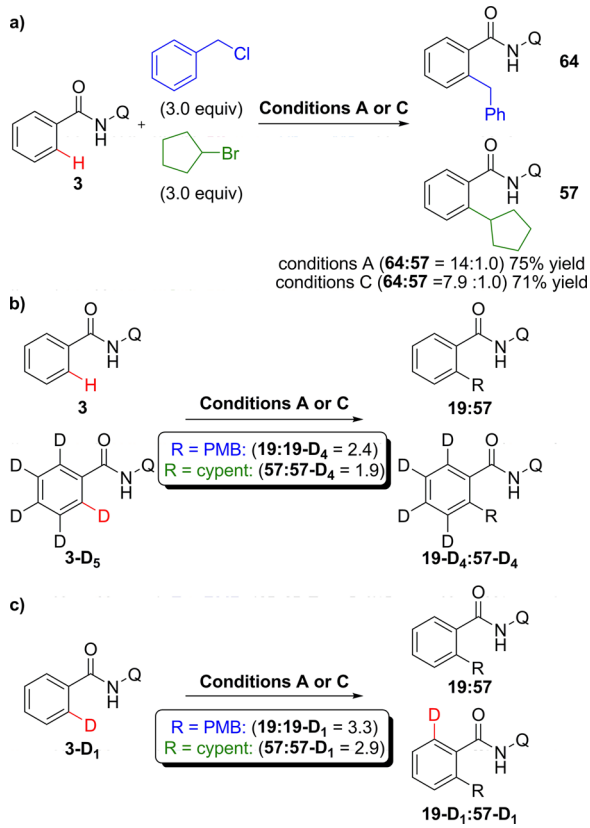
entry	2°electrophile	product		% yield[a]
1	bromocyclobutane	n = 1	**56**	26
2	bromocyclopentane	2	**57**	73
3	bromocyclohexane	3	**58**	55
4	iodocyclohexane	3	**58**	50
5			**59**	59
6			**60** (*exo* :*endo* = 7.6:1.0)	63
7		X = Br	**61** (*b*:*l* = 5:1)	58
8		I	**61** (*b*:*l* = 10:1)	36
9			**62** (*b*:*l* = 1.0:0.8)[b]	41
10			**63**	27

[a]Isolated yields after silica chromatography. [b]7 min addition leads to a 38% yield of **62** (*b*:*l* = 1.00:0.55) Q = 8-quinolinyl, *b*:*l* = *branched*:*linear*.

Interestingly, some substrates produced a mixture of linear and branched products (entries 7−9, Table 4). To probe the origin of this effect, the reaction was run in the presence of various olefins. While no crossover products were observed, β-hydride elimination products may not escape the coordination complex.

To gain insight into the course of the reaction, we conducted a series of competition experiments. As expected, benzyl chloride outcompetes bromocyclopentane under either of our standard reaction conditions (Scheme 2a). Moreover, the intermolecular KIE for benzylation is 2.4 while the intramolecular KIE is 3.3. Similarly, the intermolecular KIE for

Scheme 2. (a) Competition Experiments between Benzyl Chloride and Bromocyclopentane; (b) Intermolecular KIE for PMB-Cl and Cyclopentyl Bromide; (c) Intramolecular KIE for PMB-Cl and Cyclopentyl Bromide



bromocyclopentane is 1.9 while the intramolecular KIE is 2.9. Collectively, these data suggest that C−H cleavage is the product-determining step for both reactions. Since it is unlikely that C−H cleavage is reversible, the primary KIE values suggest that either C−H cleavage is the turnover-limiting step or the turnover-limiting step occurs prior to C−H cleavage and does not involve the carboxamide.[14]

In summary, we have developed a unified strategy for C−H alkylation reactions. The iron-catalyzed conditions can be rapidly tuned to accommodate a range of important electrophiles. The reactions generally proceed in high yields with exceptional regioselectivity on gram scale. The reaction is complete in ≤10 min, and the benzylations and can be performed in air with reagent-grade solvent. Further efforts will be directed toward understanding the reaction mechanism and expanding the scope of this interesting transformation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) For Pd examples of cross reactivity with aryl iodides, see ref 2f. For Fe examples of cross reactivity with aryl iodides, see refs 7b and 7g.

(13) Similar yields among the oxygen-based electrophiles might suggest in situ formation of benzyl bromides under the reaction conditions.

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