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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 15 May 2020

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Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Chlorides with Primary Alkyl Chlorides

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Supporting Information Placeholder

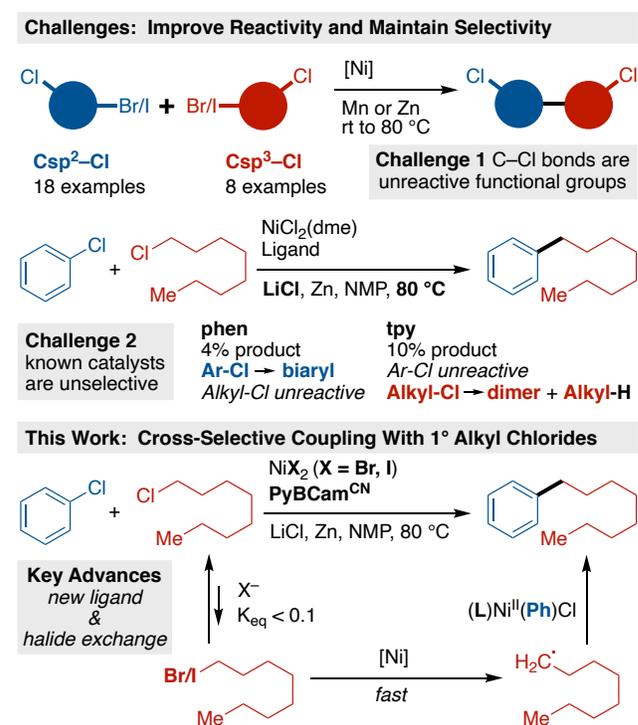
ABSTRACT: Alkyl chlorides and aryl chlorides are among the most abundant and stable carbon electrophiles. Although their coupling with carbon nucleophiles is well developed, the cross-electrophile coupling of aryl chlorides with alkyl chlorides has remained a challenge. We report here the first general approach to this transformation. The key to productive, selective cross-coupling is the use of a small amount of iodide or bromide along with a recently reported ligand, pyridine-2,6-bis(*N*-cyanocarboxamide) (PyBCam^{CN}). The scope of the reaction is demonstrated with 35 examples (63% ±16% ave yield) and we show that the Br⁻ and I⁻ additives act as co-catalysts, generating a low, steady-state concentration of more-reactive alkyl bromide/iodide.

Cross-electrophile coupling has rapidly become an important approach to the synthesis of Csp²-Csp³ bonds,¹ but engaging less reactive C-Cl bonds, outside of activated systems² or intramolecular reactions,³ has proven challenging. Indeed, unactivated C-Cl bonds are well-tolerated functional groups⁴ in cross-electrophile coupling methods (Scheme 1).^{5,6} The ability to cross-couple with organic chlorides is valuable for several reasons – first, organic chlorides are more abundant than organic bromides or organic iodides;⁷ second, the low reactivity of the C-Cl bond allows it to be introduced early in a synthesis and later diversified.^{8,9,10}

The central challenge presented by C-Cl bonds in cross-electrophile coupling is the need for *higher reactivity without sacrificing selectivity* (Scheme 1). While the homodimerization of alkyl chlorides¹¹ and aryl chlorides^{8c} has been reported, no general cross-selective approach has yet been found.¹² Recently, Zhang reported couplings of a variety of aryl chlorides, but only with an excess of ClCF₂R reagents.¹³ Several groups have reported on the coupling of aryl chlorides with alkyl bromides¹⁴ or tertiary alkyl oxalate esters.¹⁵ However, the coupling of chlorobenzene with a simple alkyl bromide provided less than 25% yield of cross-coupled product.^{14a} Switching to an alkyl chloride further diminishes selectivity and yield using our standard conditions (Scheme 1).¹⁶

Based upon our proposed mechanism for the coupling of aryl iodides with alkyl iodides,¹⁷⁻¹⁹ overcoming this dual reactivity-selectivity challenge requires a catalyst that selectively reacts with the Ar-Cl over the Alkyl-Cl, yet can slowly generate an alkyl radical from the Alkyl-Cl starting material. Herein we show that this can be accomplished through the use of salt additives to maintain a very low, steady-state concentration of an alkyl bromide/iodide and a uniquely selective pyridine-2,6-bis(*N*-cyanocarboxamide) (PyBCam^{CN})^{20,21} ligated nickel catalyst (Scheme 1).

Scheme 1. Challenges in the Cross-Electrophile Coupling of Organic Chlorides.

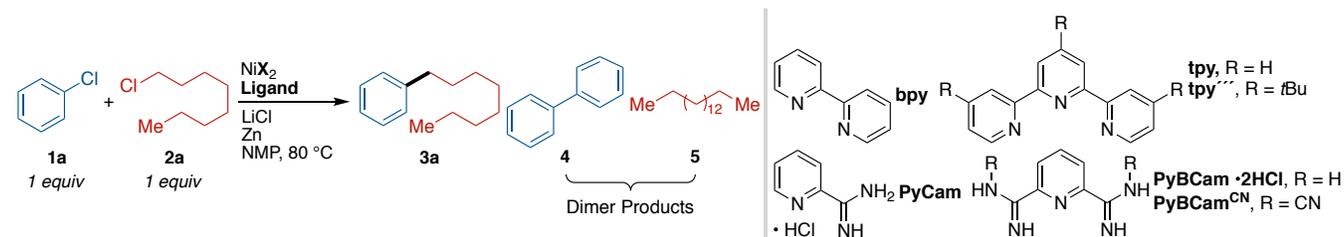


During reaction development, we observed a strong synergistic effect between the catalyst and the presence of sub-stoichiometric amounts (10-30 mol%) of bromide or iodide (Table 1 and Supporting Information Figures S1, S3-S6). While no catalysts were found that provided high yields of product in the absence of bromide or iodide, high selectivity

could be achieved in reactions with PyBCam^{CN} ligand and NiBr₂(dme) or NiI₂•4H₂O; and in reactions with PyBCam ligand and NiBr₂(dme) (Table 1, bold-faced entries). Reactions with bipyridine (bpy) or pyridine 2-carboxamide (PyCam) ligands, which are optimal for the coupling of aryl bromides with alkyl bromides,^{20,22} favored formation of aryl dimer products (bpy) or hydrodehalogenated arene (PyCam) without consuming the alkyl chloride. Reactions with terpyridine (tpy), which is useful for the dimerization of

alkyl halides,²³ converted alkyl chloride to dimeric and hydrodehalogenated products without consuming aryl chloride. In contrast to tpy, reactions with 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (tpy'''), which is useful in Negishi cross-coupling reactions of alkyl halides,²⁴ consumed both substrates but formed approximately 1:1:1 product/alkyl dimer/aryl dimer.²⁵ See also Chart S1 in the Supporting Information.

Table 1. The Effect of Ligands and Additives on the Cross-Electrophile Coupling of Chlorobenzene with Chlorooctane.^a



Ligand	X	Yield 3a (%) ^b	Yield 4 (%) ^b	Yield 5 (%) ^b	Ligand	X	Yield 3a (%) ^b	Yield 4 (%) ^b	Yield 5 (%) ^b
bpy	Cl	2	48	1	PyCam	Cl	16	19	6
	Br	9	43	4		Br	43	9	5
	I	17	39	17		I	19	2	3
tpy	Cl	10	0	25	PyBCam·2HCl	Cl	11	0	0
	Br	4	2	40		Br	53	0	2
	I	1	0	16		I	18	0	23
tpy'''	Cl	38	28	16	PyBCam ^{CN}	Cl	46	1	7
	Br	22	26	19		Br	65	0	9
	I	4	33	8		I	87 (82)^c	0	6

^aReaction conditions: chlorobenzene (0.5 mmol), 1-chlorooctane (0.5 mmol), NiX₂ = NiI₂•4H₂O/NiBr₂(dme)/NiCl₂(dme) (0.05 mmol), ligand (0.05 mmol), LiCl (0.5 mmol), Zn (1.0 mmol), and NMP (1 mL) were assembled in a N₂ filled glovebox and heated for 24 h. ^bYields were determined by GC analysis calibrated against 1,3,5-trimethoxybenzene as an internal standard. ^cIsolated yield after column chromatography.

Routine optimization with PyBCam and PyBCam^{CN} demonstrated that PyBCam^{CN} was superior, that reactions were best conducted at 60-80 °C, and that a variety of iodide and bromide additives provide similar results.²⁵ Reactions with bromide additive provided the highest yields when the alkyl chloride was added slowly, either portionwise via syringe or dropwise through an addition funnel. Reactions with iodide additive did not benefit from slow addition. The primary side products in both cases are the alkyl dimer and aryl hydrodehalogenated product.

The optimized conditions were then applied to a variety of primary alkyl chlorides and chloroarenes (Scheme 2). Electron-rich aryl chlorides, which were unreactive under our previously published conditions, coupled in 69-72% yield (**3b**, **3f**, **3g**, **3r**). However, a more sterically hindered aryl chloride, 2-chlorotoluene, coupled poorly (**3e**, 15% yield). While we had coupled electron-poor aryl chlorides with alkyl

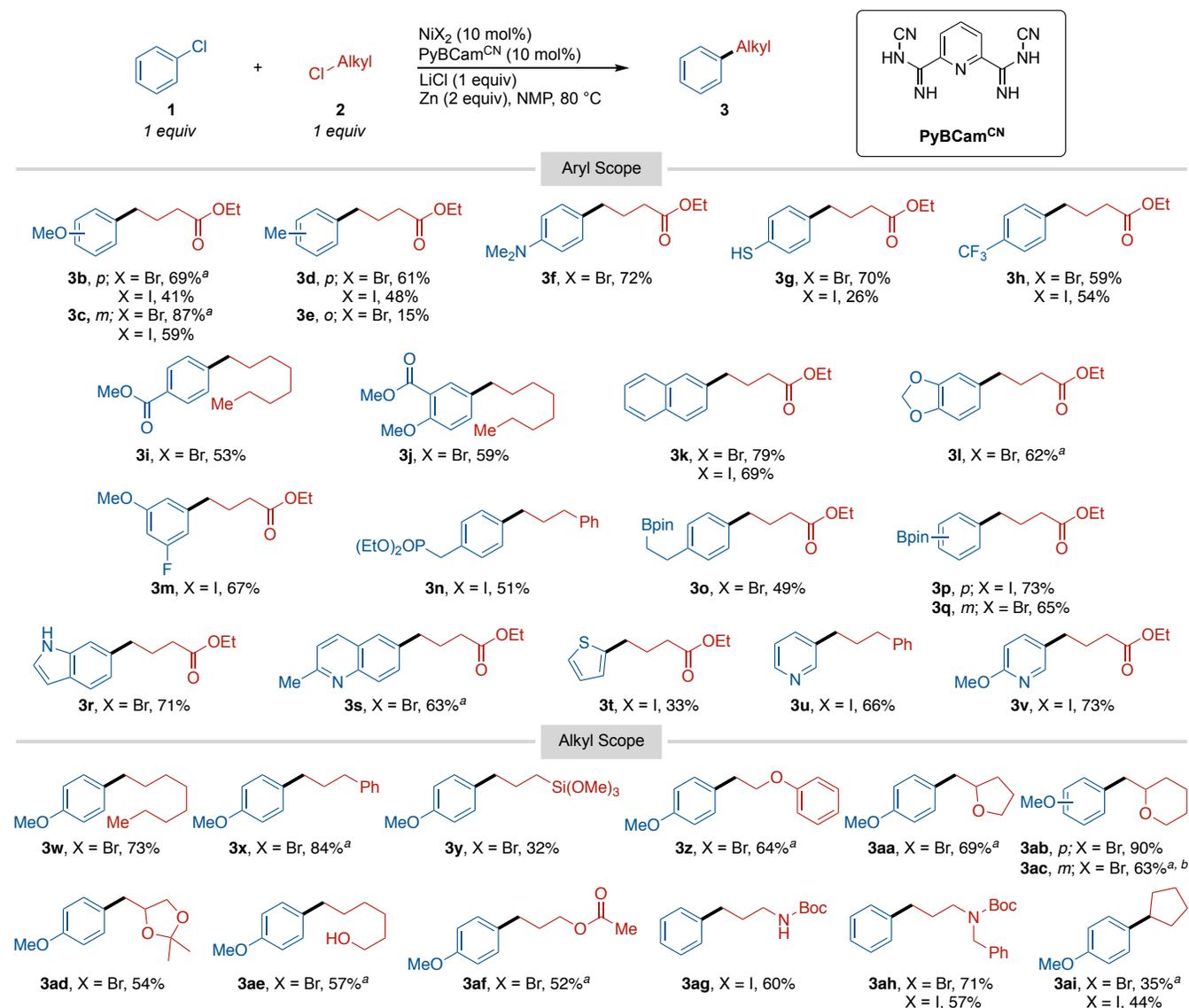
bromides previously,¹⁴ under these conditions electron-poor aryl chlorides could be coupled with alkyl chlorides for the first time, with yields ranging from 53-73% yield (**3c**, **3h**, **3i**, **3s**, **3u**, **3v**). As expected with PyBCam ligands,²⁰ a variety of heterocycles could be coupled, including both electron-poor quinoline (**3s**, 63%) and pyridine (**3u**, 66% and **3v**, 73%); and electron-rich indole (**3r**, 71%) and thiophene (**3t**, 33%). A particular advantage of cross-electrophile coupling is tolerance for alkyl halides with β-leaving groups (**3z-3ad**). The analogous organometallic reagents would be prone to elimination. Finally, secondary alkyl chlorides do couple under these conditions, but in lower yield (**3ai**, 44%).

Despite the higher temperatures, functional group compatibility remained broad. The low basicity of the conditions allowed us to tolerate both aryl and alkyl pinacol boronic acid esters (**3o-3q**, 49-73% yield), providing opportunities for further elaboration of the products. Acidic N-H (**3ag**, 60%)

and O-H (**3ae**, 57%) groups are tolerated, which would be a challenge for organomagnesium or organozinc reagents.²⁶ As a testament to the low basicity of the conditions, a free thiol was tolerated (**3g**, 70% yield), avoiding competing S_N2 with the alkyl electrophile and S-arylation (pK_a of thiophenol in DMSO is 10.3,²⁷ which makes it more acidic than acetic acid).²⁸ On the other hand, despite the presence of Lewis acids (Zn^{II} salts, Li⁺ salts) at 60-80 °C, Boc groups on nitrogen were still tolerated (**3ag**, 60%; **3ah**, 71%). While esters were tolerated, we did observe scrambling when two different esters were present due to transesterification (for example, me-

thyl and ethyl ester exchange). For this reason, we coupled chloroarenes bearing esters (**3i**, **3j**) with 1-chlorooctane. Other functional group highlights include a benzylic diethylphosphonate ester (**3n**, 51%) and a trimethoxysilane (**3y**, 32%). Despite the low yield, the cross-coupling to form trimethoxysilane product **3y** is notable because it is a different approach^{29,30} to forming functionalized silanes that could be useful in attaching molecules to glass or silica.³¹ As in our previous studies on cross-electrophile coupling reactions with less reactive substrates, this chemistry can be scaled up using standard techniques (**3ac**).³²

Scheme 2. Reaction Scope for the Nickel-Catalyzed Coupling of Aryl Chlorides with Alkyl Chlorides.



^aReaction was conducted with 1.25 equiv of alkyl chloride (0.75 mmol) with either NiBr₂(dme) or NiI₂•4H₂O as NiX₂. ^bReaction was run on a 7.0 mmol scale.

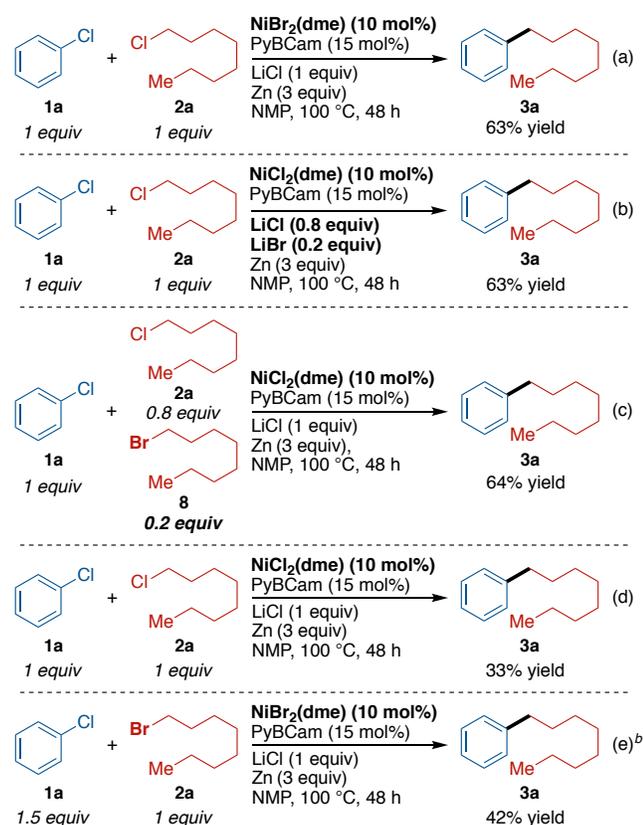
The distinctive feature of this reaction, when compared to other cross-electrophile couplings of aryl halides with alkyl halides, is the ability to engage two relatively unreactive substrates in a selective manner (Scheme 1). There are three keys to the success of this method.

First, LiCl was essential for efficient reduction of the nickel catalyst by the zinc surface. We have recently noted that ZnCl₂ can have an inhibitory effect on reduction of nickel catalysts and that lithium chloride is among the best agents for overcoming inhibition,³³ consistent with previous reports

on reduction of organic molecules.³⁴ Here too, reactions conducted without LiCl resulted in 3% formation of the cross-coupled product and primarily returned both substrates (Supporting Information Figure S2). We also verified that neither organic chloride reacts directly with zinc to form an organozinc reagent (Supporting Information Figure S2).

Second, halide exchange plays a key role by increasing the reactivity of the alkyl chloride. We found that 10-30% of bromide or iodide, regardless of how it was introduced, was essential for reasonable reaction rates (Scheme 3 and Supporting Information Figures S4-S7). Importantly, the low concentration of bromide was essential; reactions run without any bromide (Scheme 3d) or with only alkyl bromide (Scheme 3e) provided lower yields than reactions with a catalytic amount of bromide (Scheme 3a – Scheme 3c and Table 1).

Scheme 3. Evidence for Bromide Co-Catalysis.^a



^aReactions were run on a 0.5 mmol scale. Yields were determined by GC analysis calibrated against 1,3,5-trimethoxybenzene as an internal standard. ^bReaction run with DIPEA (20 mol%). DIPEA had no effect on reaction outcome.

Studies on halide exchange showed that it is fast compared to the rate of reaction (reaching equilibrium in 1-2 h vs 24 h for reaction time) and unfavorable (Supporting Information Figure S8-S16). Significantly, the presence of zinc and lithium salts altered the equilibrium to more strongly favor alkyl iodide/bromide. This led to the counterintuitive outcome that increasing total chloride concentration increased alkyl iodide concentration. Under concentrations of salts chosen

to mimic those present catalytic reactions, we found that the amount of alkyl iodide increased as the concentration of ZnCl₂ increased, although the ratio of alkyl-Cl/alkyl-I remained large in all cases ($\geq 98:2$, Figure S10 and S16). We tentatively attribute this phenomenon to the favorable formation of LiZnCl₃ over LiZnCl₂Br or LiZnCl₂I, resulting in sequestration of chloride as the concentration of Zn²⁺ increases at later reaction times.³⁵ The halogen exchange is also somewhat faster than reported for exchanges in amide solvents with only sodium bromide, but this process could be catalyzed by zinc: catalysis of alkyl halogen exchange by titanium, zirconium, rhodium, and iron salts has been reported.³⁶

While iodide exchange to enhance the reactivity of alkyl bromides,¹⁴ sulfonic acid esters,³⁷ epoxides,³⁸ and chlorides¹¹ in cross-coupling reactions is now well established, the use of bromide is more rare.³⁹ In cases where iodide co-catalysis isn't practical, the use of bromide co-catalysis should be considered.

Finally, studies with a variety of ligands revealed that PyBCam nickel catalysts are unique in being able to react with both substrates at similar rates, even with activation by halide exchange (Table 1 and Supporting Information Figure S1). Compared to nickel complexes of tpy''', which could also react with both substrates but formed both biaryl and bialkyl, nickel PyBCam catalysts avoid biaryl formation entirely and form only small amounts of alkyl dimer. The origin of these differences in reactivity are not yet clear and are the subject of ongoing studies, but it is clear that PyBCam and PyBCam^{CN} are a distinctive, new class of tridentate ligands for nickel catalysis.⁴⁰

In conclusion, the first selective cross-electrophile coupling reaction of aryl chlorides with primary alkyl chlorides has been developed by the synergistic effect of three changes: a new, selective ligand (PyBCam^{CN}), LiCl to enhance catalyst turnover, and bromide/iodide co-catalysis. The mechanism by which PyBCam^{CN} improves yields is under investigation and will be reported in due course. We expect that the generally unreactive nature of alkyl and aryl chlorides should make this new method to functionalize them a useful addition to synthesis.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Additional tables of optimization data, mechanistic studies, detailed experimental procedures, characterization of products, copies of product NMR spectra (PDF)

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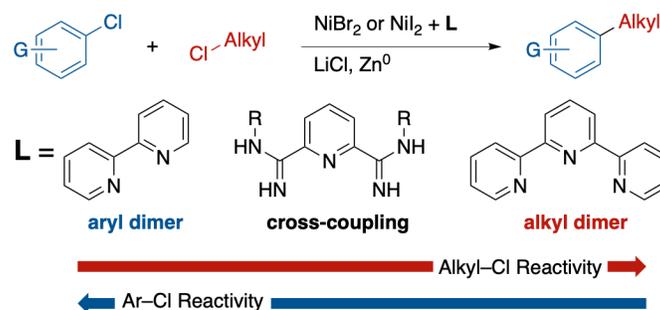
3 **ACKNOWLEDGMENT**

4 Research reported in this publication was supported by the Na-
5 tional Institute of General Medical Sciences of the National
6 Institutes of Health under award number R01GM097243
7 (DJW) and F32GM122362 (MJG). Analytical data were ob-
8 tained from the CENTC Elemental Analysis Facility at the Uni-
9 versity of Rochester, funded by NSF CHE-0650456. The fol-
10

lowing instrumentation in the PBCIC was supported by: Ther-
mo Q Exactive™ Plus by NIH 1S10 OD020022; Shimadzu
GCMS-QP2010S by the Department of Chemistry; Bruker
Avance III 400 by NSF CHE-1048642; Bruker Avance III 500
by a generous gift from Paul J. and Margaret M. Bender.

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(25) See the Supporting Information for extensive ligand reactivity and selectivity data (Figure S1) as well as additional optimization data (Figures S3, S4, S6).

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