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Nickel-Catalyzed Reductive Coupling of Aryl Bromides with *Tertiary* Alkyl Halides

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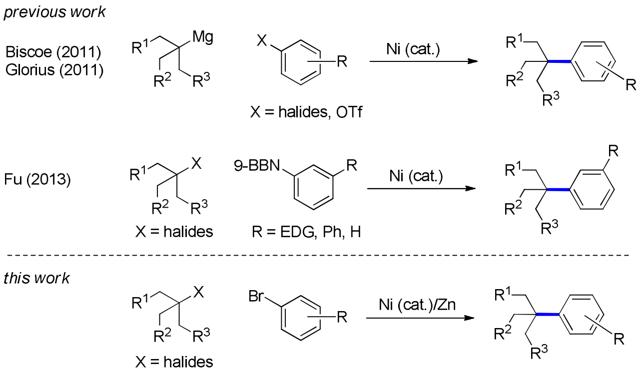
Supporting Information Placeholder

ABSTRACT: A mild Ni-catalyzed reductive arylation of *tertiary* alkyl halides with aryl halides has been developed, which delivers products bearing all-carbon quaternary centers in moderate to excellent yields with excellent functional group tolerance. Electron-deficient arenes are generally more effective in inhibiting alkyl isomerization. The reactions proceed successfully with pyridine or DMAP, while the imidazolium salts slightly enhance the coupling efficiency.

The catalytic formation of all-carbon quaternary centers remains a challenge in the current nucleophile/electrophile cross-coupling methods.[1–7] This is particular true for the construction of *tertiary* alkyl—aryl $C(sp^3)$—$C(sp^2)$ bonds. [1d–e,2,4–5] For instance, the strategies based on the Cu- and Co-catalyzed coupling of *tertiary* alkyl nucleophiles with organo electrophiles though have achieved important progress,[1–4] arylation of *tertiary* alkyl–M (M = Mg, Zn) only succeeds for certain aza-heteroaromatic halides.[1d-e,2] In contrast, the Ni/carbene-catalyzed Kumada protocol recently revealed by Glorius and Biscoe, permits a wide range of aryl electrophiles to couple with *tertiary* alkyl–Mg (Scheme 1).[4] Of note is Biscoe's approach that is much more efficient by virtue of broader substrate scope and excellent control of isomerization of *tertiary* alkyl groups. Using a different strategy, Fu has demonstrated that *tertiary* alkyl halides are competent for the coupling with aryl-9-BBN under Ni-catalyzed Suzuki conditions.[5] Of the very limited examples emphasizing unactivated *tertiary* alkyl halides as the coupling partners, Fu's method significantly expands the scope of nucleophiles that are previously restrained to special allyl– and benzyl–Zn, Mg reagents.[6] It also displays excellent functional group compatibility as opposed to the protocols using *tertiary* alkyl Grignard reagents. Although only phenyl- and arylborons bearing certain *meta*-substituted groups are viable, the Suzuki method represents the first use of Ni catalyst for manipulating unactivated *tertiary* halides.[5]

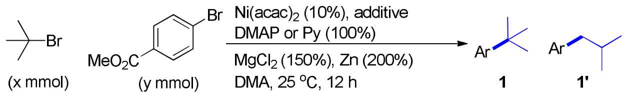
Recently, we and others have demonstrated that Ni-catalyzed reductive approaches enable effective coupling of alkyl halides with other elelctrophiles.[8–13] These include direct coupling of aryl halides with *secondary* alkyl bromides that effectively affords alkyl—aryl compounds.[13] We have also disclosed that *tertiary* alkyl halides can be employed to form ketones when coupled with in situ activated acids.[14] It would therefore be interesting to extend the reductive coupling protocol to generate *tertiary* alkyl—aryl products, which unfortunately remains very challenging. Herein, we present the synthesis of aryl-substituted all-carbon quaternary centers via Ni-catalyzed reductive coupling of *tertiary* alkyl halides with aryl halides, wherein DMAP or pyridine proves to be crucial for the catalytic process; moderate to high coupling efficiency is observed which may generally be promoted by imidazolium salts at minor extent.

Scheme 1. Ni-catalyzed methods to t-R$_{alkyl}$–Ar compounds.[4,5]



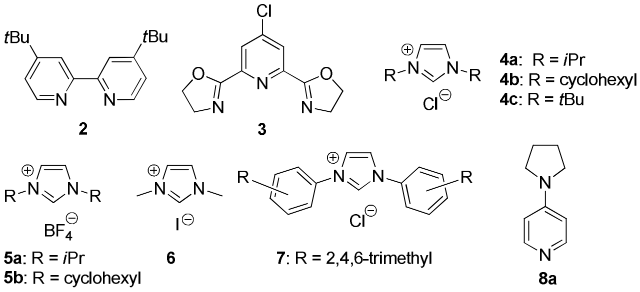
To begin with, the reaction of *t*BuBr (limiting reagent) with 2 equiv of methyl 4-bromobenzoate was tested. The pyridine-derived bidentate and tridentate ligands that are previously developed for *secondary* alkyl halides proved to be ineffective albeit with numerous efforts (e.g., Table 1, entries 1–2). In the presence of 1 equiv of pyridine, a combination of Ni(acac)$_2$/Zn/MgCl$_2$ in DMA with the readily accessible carbene precursor **4a** gave product **1** (retaining the quaternary center) and the isomerization product **1'** in an overall 61% yield with a 8:1 retention/isomerization (R/I) ratio (entry 3). Replacing pyridine with DMAP boosted the R/I ratio to 20:1 (entry 4). By switching the ratio of *t*BuBr to the ArBr (x/y) from 1:2 to 2:1, the overall yield for **1** and **1'** was enhanced to 81% with a R/I ratio of 40:1 (entry 5). Under equivalent conditions, pyridine was not effective (entry 6). While **4b** did not generate a better yield (entry 7), the more hindered *t*BuIm-HCl salt **4c** gave a similar overall yield to that with **4a** but with enhanced isomerization (entry 8). Other carbene precursors **5**–**7** did not improve the coupling yields, nor the R/I ratios (entries 9–13 and Table S1).[15] A control experiment in the absence of **4a** remarkably afforded **1** and **1'** in a 75% overall yield and a 20:1 R/I ratio (entry 14), *suggesting that the carbene precursors may not serve as ligands, but additives*. A screen of other pyridine derivatives e.g., **8** did not result in better results (entry 15 and Table S1).[15] Both DMAP and MgCl$_2$ were found to be indispensable (entries 16–17). While the former may function as a labile ligand,[16] the latter may accelerate the reduction of Ni species.[14]

Table 1. Optimization for the formation of 1.[a,b]



entry	x/y	ligand or additive	DMAP or Py	yield% (**1**:**1'**)
1	1/2	**2**	Py	12[c]
2	1/2	**3**	Py	trace
3	1/2	**4a**	Py	61 (8:1)
4	1/2	**4a**	DMAP	60 (20:1)
5	**2/1**	**4a**	**DMAP**	**81 (40:1)**[d]
6	2/1	**4a**	Py	45 (5:1)
7	2/1	**4b**	DMAP	68 (45:1)
8	2/1	**4c**	DMAP	82 (15:1)
9	2/1	**5a**	DMAP	78 (25:1)
10	2/1	**5b**	DMAP	63 (13:1)
11	2/1	**6a**	DMAP	79 (32:1)
12	2/1	**7a**	DMAP	78 (25:1)
13	2/1	**7b**	DMAP	61 (6:1)[c]
14	2/1	**none**	DMAP	75 (20:1)
15	2/1	**none**	**8a**	62 (18:1)
16	2/1	**4a**, w/o MgCl$_2$	DMAP	trace
17	2/1	**4a**	none	6 %

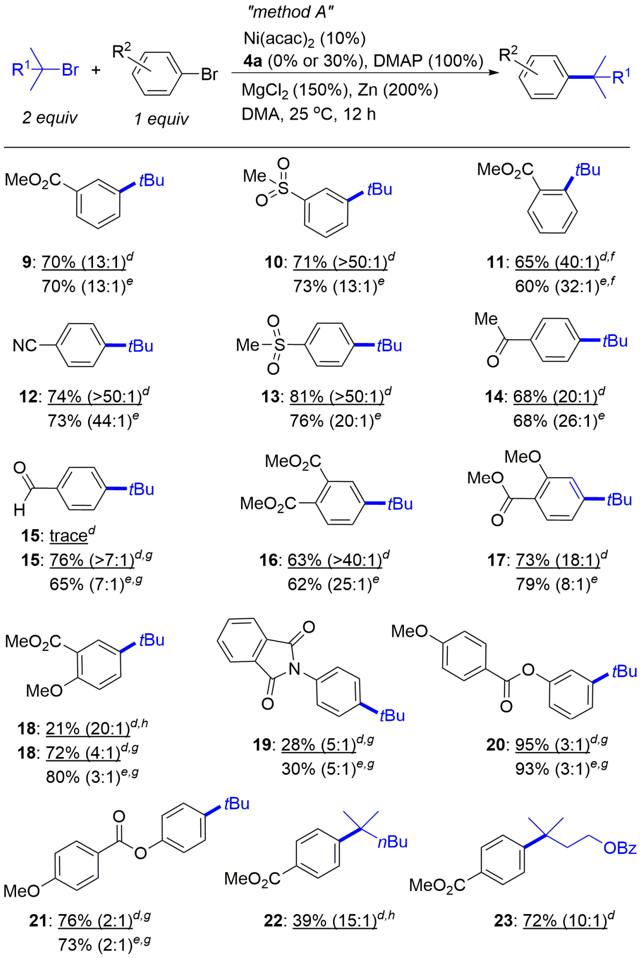
[a] Reaction Conditions: *t*BuBr or ArBr as the limiting reagent (0.3 mmol), Ni(acac)$_2$ (10 mol %), **2**–**3** (10 mol %) or **4**–**7** (30 mol %), MgCl$_2$ (150 mol %), pyridine or DMAP (100 mol %) was used, Zn (200 mol %), DMA (1 mL). [b] Yield for **1** and **1'**, and **1/1'** ratio were determined from a mixture containing other impurities by ^{1}H NMR using 2,5-dimethylfuran as the internal reference after a quick flash column chromatography. [c] 30 mol % of TBAB was added. [d] Isolated yield: 82% (R/I = 40:1).



Next, a range of aryl bromides was subjected to the optimized conditions (*method A*, Table 1, entry 5) as shown in Table 2. It was disclosed that electron-withdrawing groups generally furnished good to excellent yields when coupled with *t*BuBr as evident in **9–14** (Table 2). Good yield and R/I ratio were even obtained for **11** allowing installation of *t*Bu to the *ortho*-position of an ester group, although 2 more equivalents of *t*BuBr was necessary to drive the arylbromide to completion. The *meta*- and *ortho*-substitution patterns seemingly resulted in lower coupling yields than the *para*-modes. Unprotected 4-bromobenzaldehyde only revealed a trace amount of product **15** along with substantial unreacted aryl bromide. However, when pyridine was a surrogate for DMAP, a good yield as well as a good R/I ratio was obtained. With an electron-withdrawing group on the *para* position, arylbromides bearing additional *meta*-substituents including ester and methoxy gave good yields as evident in **16** and **17**. By comparison, 4-methoxyphenylbromide containing *m*-ester substituent generated **18** in a poor yield, albeit high R/I ratio. Use of pyridine in lieu of DMAP again promoted the overall coupling yield to 72%, but the R/I ratio decreased to 4:1. Likewise, under the DMAP conditions, less electron-donating groups including benzoyloxy and phthalimidyl on the *para* and *meta*-positions resulted in **19**–**21** in trace amounts, wherein majority of the aryl halides were recovered. The yields arising from these less reactive arene derivatives particularly for **20** were boosted significantly by replacing DMAP with pyridine, although low R/I ratios were produced. At this time, the reason why pyridine and DMAP exhibit profound impacts on the reactivities of substrates and the isomerization side paths remains unclear.

With the standard *method A*, sterically more hindered 2-bromo-2-methylhexane only resulted in **22** in 39% yield with a 15:1 R/I ratio. In contrast, 3-bromo-3-methylbutyl benzoate generated **23** in a good yield and a good R/I ratio, possibly due to the pendent OBz group enhanced the reactivity of the C–Br bond, albeit two carbons away from the reactive carbon center.[17]

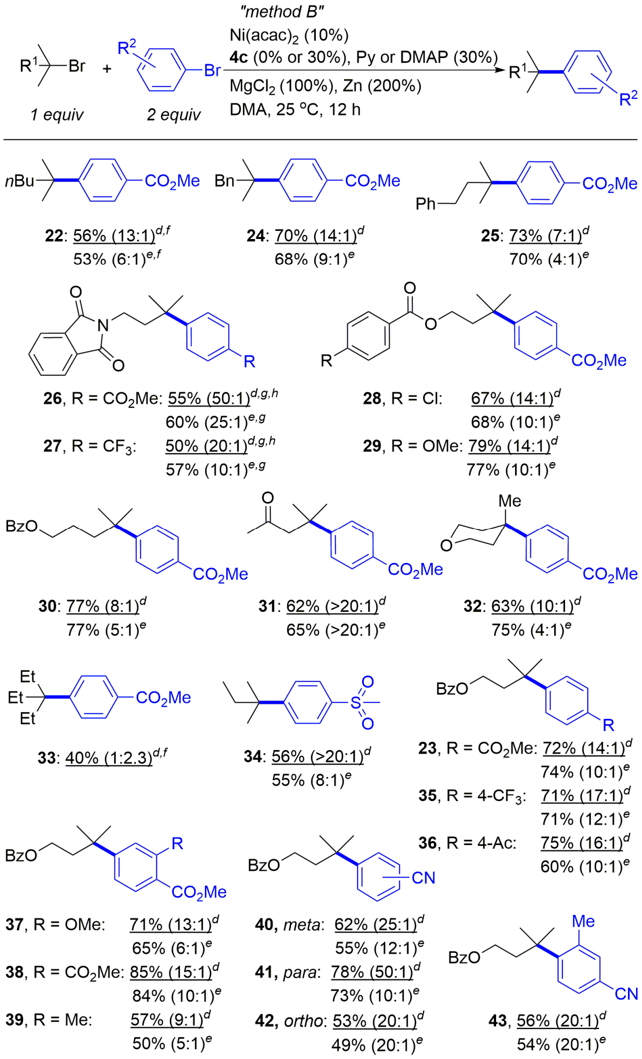
Table 2. Scope of alkyl and aryl bromides using method A.[a,b,c]



[a] Reaction Conditions: as in Table 1, entry 5. [b] Isolated yields for a mixture of product and isomer. [c] R/I ratios in the parenthesis were determined by ^{1}H NMR after purification. [d] **4a** (30%). [e] **4a** (0%). [f] Additional 2 equivalents of *t*BuBr were loaded after 8 h. [g] Pyridine was used instead of DMAP. [h] NMR yield using 2,5-dimethylfuran as the internal reference due to contamination with inseparable hydrodehalogenated arene.

To gain more details about the impact of imidazolium salts, equivalent reaction conditions without **4a** was conducted for **9**–**21**. It was generally found that the yields and R/I ratios decreased slightly as compared to those with **4a** (Table 2). This observation consistently supports that DMAP or pyridine was crucial for the coupling process, although the imidazolium salts may play some minor roles.[16]

Table 3. Coupling of alkyl halides and electron-deficient aryl bromides[a,b,c]

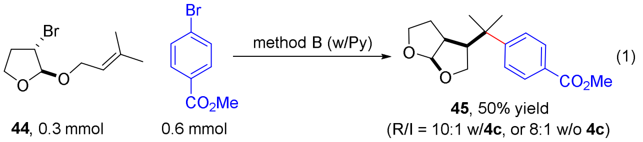


[a] Reaction Conditions: *tert*-RBr (0.3 mmol, 100 mol %, 0.15 M in DMA), Ni(acac)$_2$ (10 mol %), **4c** (30 mol %), MgCl$_2$ (100 mol %), Zn (200 mol %), DMA (1 mL), DMAP was used unless otherwise noted. [b] R/I ratios in the parenthesis were determined by ^{1}H NMR after purification. [c] Isolated yields for a mixture of product and isomer. [d] **4a** (30%). [e] **4a** (0%). [f] NMR yield using 2,5-dimethylfuran as the internal standard. [g] Pyridine was used instead of DMAP. [h] The initial R/I ratios for **26** and **27** prior to purification were determined to be 4:1 and 9:1 , respectively.

When *n*-Bu(Me)$_2$CBr was set as the limiting reagent, its coupling with 2 equiv of methyl 4-bromobenzoate using DMAP and **4c** as the additives (*method B*) improved the yield for **22** to 52% as opposed to 37% with *method A* (Table 2). The amount of DMAP and MgCl$_2$ can be lowered to 30% and 100%, respectively. It should be noted that *method B* is less effective for *t*BuBr, which generated **1** in 69% yield with a 15:1 R/I ratio. Using methyl 4-bromobenzoate as the coupling partner, *method B* proved to be effective for a wide set of other sterically more bulky alkyl halides (with respect to *t*BuBr) as evident in **23–32** (Table 3). The R/I ratios were generally high. Phthalimidyl-pendent alkyl bromide required pyridine as the additive due to cleavage of the amide bonds by DMAP, which resulted in a moderate R/I ratio for **26**, but high for **27**. In both cases the isomerization products can be partially separated out (Table 3). This agrees with that more electron-deficient aryl bromides produced good R/I ratios even when pyridine was utilized, as supported in **15** (Table 1). However, more sterically bulky 3-bromo-3-ethylpentane (Et$_3$CBr) was less satisfactory wherein a poor yield for **33** with a low R/I ratio was disclosed, indicating one limitation of this method. The compatibility of aryl halides bearing electron-deficient substituents was examined for **34–43**, wherein good yields and R/I ratios were effectively delivered. Of note is a good result for **43** albeit containing an *ortho*-methyl group. In the absence of **4c**, the coupling yields and R/I ratios again diminished slightly for most of the examples in Table 3, which reinforces the notion that carbene precursors are not essential for the coupling event.

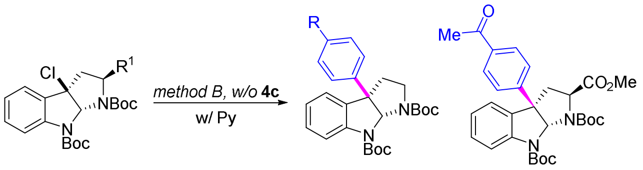
In general, the side reactions for alkyl halides arose from hydrodehalogenation and β-H elimination, whereas dimerization and hydrodehalogenation of aryl halides accounted for the major mass balance for the aryl partners. Tracking the coupling process for **23** with both *methods A and B* revealed that the alkyl bromide consumed more rapidly than the aryl bromide in both cases.[15] In addition, substitution of Zn with Mn also provided **1** in >40% yield,[15] suggesting a Negishi mechanism is unlikely.[13b]

Similar to the previously disclosed Ni-catalyzed reductive cyclization/coupling of alkyl halides,[9a-c] coupling of **44** with methyl 4-bromobenzoate using *method B* and pyridine as the additive provided the desired cyclization/arylation product **45** in 50% yield with a R/I ratio of 10:1 or 8:1 without **4c** (eq 1). This result indicates possible participation of in situ generated *tertiary* alkyl radical, which is consistent with the observations for a variety of Ni-catalyzed coupling on alkyl halides.[14,18–19] It is unclear whether the present method follows Weix's radical chain mechanism.[18b]



Finally, this reductive coupling strategy enabled facile synthesis of cylcotryptamine analogs, which have attracted widespread synthetic interest over the past decades.[20] Using *method B without* **4c**, *the tertiary* benzyl chlorides were efficiently converted into **48–50** in good to excellent yields when coupled with the electron-deficient aryl bromides (Scheme 2). Pyridine appeared to be much more effective than DMAP (Scheme S1).[15] Notably, no isomerization byproducts were detected, demonstrating potential applications of this work to the construction of complex molecules. This method differs from the Friedel–Crafts synthesis that is suited for electron-rich aryl compounds.[21]

Scheme 2. Synthesis of cyclotryptamine analogs.



46: R^1 = H
47: R^1 = CO_2Me

48, R = COMe: 85%
49, R = CO_2Me: 88%

50 70% (w/o **4c**)
76% (w/ **4c**)

In summary, this easy-to-operate method features direct coupling of a wide range of readily accessible *tertiary* alkyl and aryl halides under mild Ni-catalyzed conditions. While pyridine and DMAP proved to be pivotal for the feasibility of this coupling event, the imidazolium salts only slightly promoted the efficiency. The present reductive protocol exhibits excellent functional group compatibility, which generally enables the electron-deficient aryl halides to deliver arylated quaternary products in good to excellent yields with low isomerization/retention ratios. In contrast, electron-rich aryl halides are less effective. The practicability of this reductive coupling approach is further manifested in the synthesis of cyclotryptamine analogs. Finally, although the insight into the reaction mechanism is still under investigation, the possible involvement of a radical process is in line with the general profiles for Ni-catalyzed reductive coupling of alkyl halides.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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