

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

Xuan Wang,<sup>†,‡</sup> Shulin Wang,<sup>‡</sup> Weichao Xue,<sup>‡</sup> and Hegui Gong<sup>\*,†,‡</sup>

<sup>†</sup>School of Materials Science and Engineering and <sup>‡</sup>Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China

**S** Supporting Information

**ABSTRACT:** A mild Ni-catalyzed reductive arylation of tertiary alkyl halides with aryl bromides has been developed that 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 4-(dimethylamino)pyridine, while imidazolium salts slightly enhance the coupling efficiency.

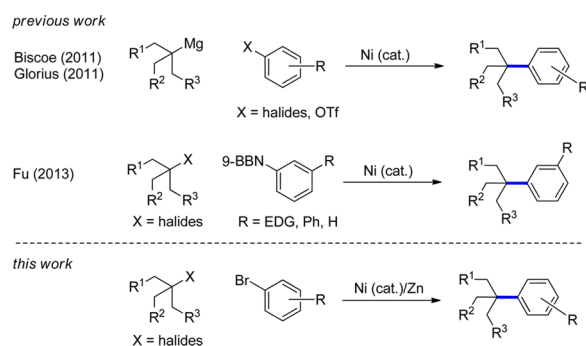
The catalytic formation of all-carbon quaternary centers remains a challenge in current nucleophile/electrophile cross-coupling methods.<sup>1–7</sup> This is particularly true for the construction of tertiary alkyl–aryl C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bonds.<sup>1d,e,2,4,5</sup> For instance, although strategies based on Cu- and Co-catalyzed coupling of tertiary alkyl nucleophiles with organic electrophiles have achieved important progress,<sup>1–4</sup> arylation of tertiary alkyl–M (M = Mg, Zn) succeeds only for certain aza-heteroaromatic halides.<sup>1d,e,2</sup> In contrast, the Ni/carbene-catalyzed Kumada protocol recently revealed by Glorius<sup>4a</sup> and Biscoe<sup>4b</sup> enables coupling of a wide range of aryl electrophiles with tertiary alkyl–Mg (Scheme 1). Biscoe's approach is much more efficient by

scope of nucleophiles, which were previously restrained to special allyl- and benzyl–M (M = Zn, Mg) reagents.<sup>6</sup> 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 a Ni catalyst to manipulate unactivated tertiary halides.<sup>5</sup>

We and others have recently demonstrated that Ni-catalyzed reductive approaches enable effective coupling of alkyl halides with other electrophiles.<sup>8–13</sup> These include the direct coupling of aryl halides with secondary alkyl bromides, which effectively affords alkyl–aryl compounds.<sup>13</sup> We have also disclosed that tertiary alkyl halides can be employed to form ketones when coupled with in situ-activated acids.<sup>14</sup> 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 4-(dimethylamino)pyridine (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 to a minor extent.

Initially the reaction of *t*BuBr (limiting reagent) with 2 equiv of methyl 4-bromobenzoate was tested. The pyridine-derived bidentate and tridentate ligands that were previously developed for secondary alkyl halides proved to be ineffective despite numerous efforts (e.g., Table 1, entries 1 and 2). In the presence of 1 equiv of pyridine, a combination of Ni(acac)<sub>2</sub>/Zn/MgCl<sub>2</sub> in dimethylacetamide (DMA) with the readily accessible carbene precursor **4a** gave product **1** (retaining the quaternary center) and the isomerization product **1'** in an overall yield of 61% with an 8:1 retention/isomerization (R/I) ratio (entry 3). Replacing pyridine with DMAP boosted the R/I ratio to 20:1 (entry 4). Switching the ratio of *t*BuBr to ArBr (*x*:*y*) from 1:2 to 2:1 enhanced the overall yield of **1** and **1'** to 81% with an 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 **4a** but with enhanced isomerization (entry 8). Other carbene precursors **5–7** did not improve the coupling yield or the R/I ratio (entries 9–13 and Table S1).<sup>15</sup> A control experiment in the absence of **4a** remarkably afforded **1** and **1'** in 75% overall yield with a 20:1 R/I ratio (entry 14), suggesting that

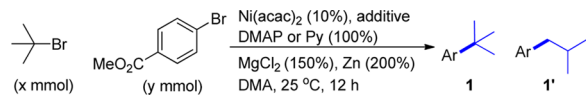
## Scheme 1. Ni-Catalyzed Methods for Tertiary Alkyl–Aryl Compounds<sup>4,5</sup>



virtue of broader substrate scope and excellent control of isomerization of tertiary alkyl groups. Using a different strategy, Fu demonstrated that tertiary alkyl halides are competent for the coupling with 9-borabicyclo[3.3.1]nonyl-substituted arenes (Ar-9-BBN) under Ni-catalyzed Suzuki conditions.<sup>5</sup> Of the very limited examples emphasizing unactivated tertiary alkyl halides as the coupling partners, Fu's method significantly expands the

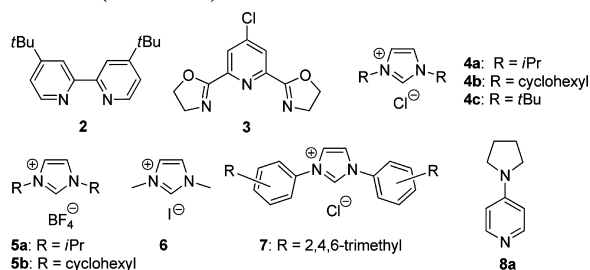
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Table 1. Optimization of the Formation of **1**<sup>a,b</sup>


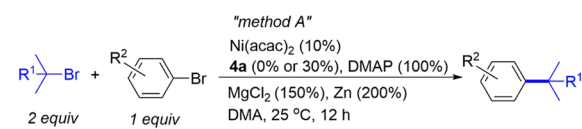
entry	x:y	ligand or additive	DMAP or Py	% yield (1:1')
1	1:2	2	Py	12 <sup>c</sup>
2	1:2	3	Py	trace
3	1:2	4a	Py	61 (8:1)
4	1:2	4a	DMAP	60 (20:1)
5	2:1	4a	DMAP	81 (40:1) <sup>d</sup>
6	2:1	4a	Py	45 (5:1)
7	2:1	4b	DMAP	68 (45:1)
8	2:1	4c	DMAP	82 (15:1)
9	2:1	5a	DMAP	78 (25:1)
10	2:1	5b	DMAP	63 (13:1)
11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

<sup>a</sup>Reaction conditions: *t*BuBr or ArBr as the limiting reagent (0.3 mmol), Ni(acac)<sub>2</sub> (10 mol %), 2–3 (10 mol %) or 4–7 (30 mol %), MgCl<sub>2</sub> (150 mol %), pyridine or DMAP (100 mol %), Zn (200 mol %), DMA (1 mL). <sup>b</sup>Yields for **1** and **1'** and **1:1'** ratios were determined from a mixture containing other impurities by <sup>1</sup>H NMR analysis using 2,5-dimethylfuran as the internal reference after a quick flash column chromatography. <sup>c</sup>30 mol % TBAB was added. <sup>d</sup>Isolated yield = 82% (R/I = 40:1).



the carbene precursors may serve as additives rather than ligands. A screen of other pyridine derivatives (e.g., **8**) did not result in better results (entry 15 and Table S1).<sup>15</sup> Both DMAP and MgCl<sub>2</sub> were found to be indispensable (entries 16 and 17). While the former may function as a labile ligand,<sup>16</sup> the latter may accelerate the reduction of Ni species.<sup>14</sup>

Next, a range of aryl bromides was subjected to the optimized conditions (method A; Table 1, entry 5), as shown in Table 2. Electron-withdrawing groups generally furnished good to excellent yields when coupled with *t*BuBr, as evidenced by 9–14 (Table 2). A good yield and R/I ratio were obtained even for **11**, allowing installation of *t*Bu at the ortho position of an ester group, although an additional 2 equiv of *t*BuBr was necessary to drive the aryl bromide to completion. The meta and ortho substitution patterns seemingly resulted in lower coupling yields than the para modes. Unprotected 4-bromobenzaldehyde afforded only 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 at the para position, aryl bromides bearing additional meta substituents, including ester and methoxy, gave good yields, as evidenced by **16** and **17**. By

Table 2. Scope of Alkyl and Aryl Bromides Using Method A<sup>a,b,c</sup>


entry	Yield (%)	R/I ratio
9	70%	(13:1) <sup>d</sup> 70% (13:1) <sup>e</sup>
10	71%	(>50:1) <sup>d</sup> 73% (13:1) <sup>e</sup>
11	65%	(40:1) <sup>d,f</sup> 60% (32:1) <sup>e,f</sup>
12	74%	(>50:1) <sup>d</sup> 73% (44:1) <sup>e</sup>
13	81%	(>50:1) <sup>d</sup> 76% (20:1) <sup>e</sup>
14	68%	(20:1) <sup>d</sup> 68% (26:1) <sup>e</sup>
15	trace <sup>d</sup>	
16	76%	(>7:1) <sup>d,g</sup> 65% (7:1) <sup>e,g</sup>
17	63%	(>40:1) <sup>d</sup> 62% (25:1) <sup>e</sup>
18	21%	(20:1) <sup>d,h</sup>
18	72%	(4:1) <sup>d,g</sup> 80% (3:1) <sup>e,g</sup>
19	28%	(5:1) <sup>d,g</sup> 30% (5:1) <sup>e,g</sup>
20	95%	(3:1) <sup>d,g</sup> 93% (3:1) <sup>e,g</sup>
21	76%	(2:1) <sup>d,g</sup> 73% (2:1) <sup>e,g</sup>
22	39%	(15:1) <sup>d,h</sup>
23	72%	(10:1) <sup>d</sup>

<sup>a</sup>Reaction conditions: see Table 1, entry 5. <sup>b</sup>Isolated yields for product/isomer mixtures. <sup>c</sup>R/I ratios (in parentheses) were determined by <sup>1</sup>H NMR analysis after purification. <sup>d</sup>4a (30%). <sup>e</sup>4a (0%). <sup>f</sup>An additional 2 equiv of *t*BuBr was loaded after 8 h. <sup>g</sup>Pyridine was used instead of DMAP. <sup>h</sup>NMR yield using 2,5-dimethylfuran as the internal reference due to contamination with inseparable hydrodehalogenated arene.

comparison, 4-methoxyphenyl bromide containing an *m*-ester substituent generated **18** in a poor yield but with a 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, weaker electron-donating groups including benzyloxy and phthalimidyl at the para and meta positions resulted in **19**–**21** in trace amounts, wherein the majority of the aryl halide was 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.

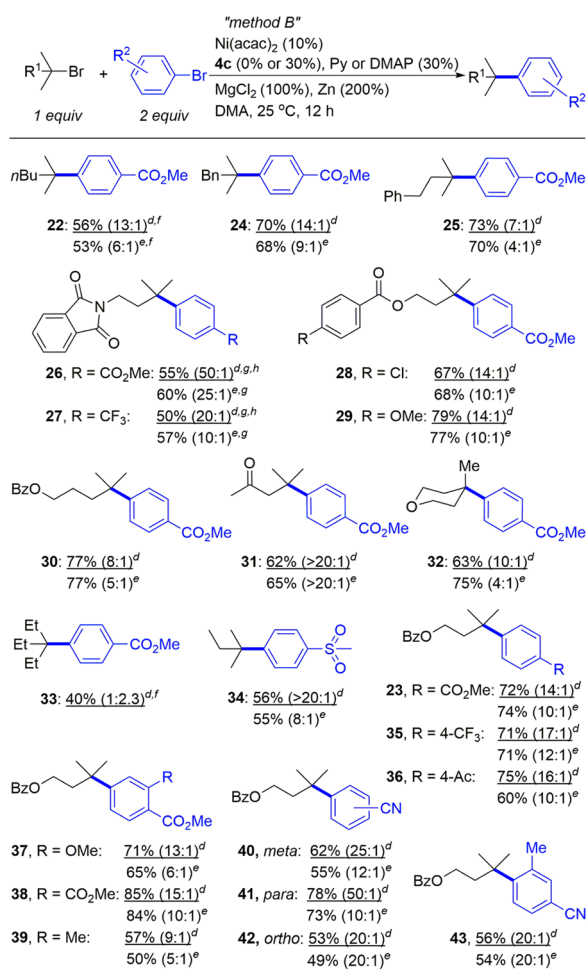
With the standard method A, sterically more hindered 2-bromo-2-methylhexane gave **22** in only 39% yield with a 15:1 R/I ratio. In contrast, 3-bromo-3-methylbutyl benzoate generated **23** in a good yield with a good R/I ratio, possibly because the pendent OBz group enhanced the reactivity of the C–Br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

To gain more details about the impact of imidazolium salts, equivalent reaction conditions without **4a** were employed for 9–

21. It was generally found that the yields and R/I ratios decreased slightly compared with those using **4a** (Table 2). This observation consistently supports the conclusion that DMAP or pyridine is crucial for the coupling process, although the imidazolium salt may play a minor role.<sup>16</sup>

When *n*-Bu(Me)<sub>2</sub>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 of **22** to 52% as opposed to 37% using method A (Table 2). The amounts of DMAP and MgCl<sub>2</sub> 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. With 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 evidenced by **23**–**32** (Table 3). The R/I ratios were generally high. Phthalimidyl-pendant alkyl bromide required pyridine as the additive because

**Table 3. Coupling of Alkyl Halides and Electron-Deficient Aryl Bromides<sup>a,b,c</sup>**

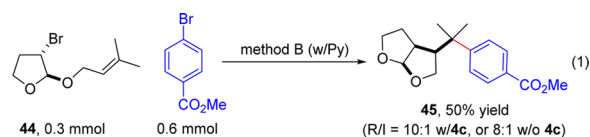


<sup>a</sup>Reaction conditions: *t*RBr (0.3 mmol, 100 mol %), 0.15 M in DMA, Ni(acac)<sub>2</sub> (10 mol %), **4c** (30 mol %), MgCl<sub>2</sub> (100 mol %), Zn (200 mol %), DMA (1 mL), and DMAP, unless otherwise noted. <sup>b</sup>R/I ratios (in parentheses) were determined by <sup>1</sup>H NMR analysis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

of cleavage of the amide bonds by DMAP, which resulted in a moderate R/I ratio for **26** but a high ratio for **27**. In both cases the isomerization products can be partially separated out (Table 3). This indicates that more electron-deficient aryl bromides produced good R/I ratios even when pyridine was utilized, as supported by **15** (Table 2). However, more sterically bulky 3-bromo-3-ethylpentane (Et<sub>3</sub>CBr) was less satisfactory, giving a poor yield of **33** with a low R/I ratio, indicating one limitation of this method. The compatibility of aryl halides bearing electron-deficient substituents was examined for **34**–**43**, which effectively delivered good yields and R/I ratios. Of note is a good result for **43** even though it contains an *o*-methyl group. In the absence of **4c**, the coupling yields and R/I ratios again were 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 method A and method B revealed that the alkyl bromide was consumed more rapidly than the aryl bromide in both cases.<sup>15</sup> In addition, substitution of Zn with Mn also provided **1** in >40% yield,<sup>15</sup> suggesting that a Negishi mechanism is unlikely.<sup>13b</sup>

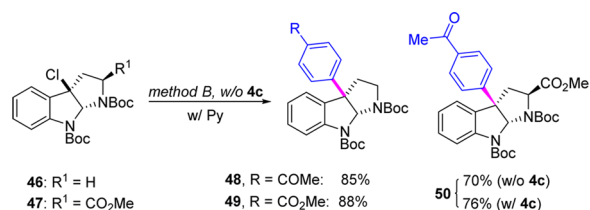
Similar to the previously disclosed Ni-catalyzed reductive cyclization/coupling of alkyl halides,<sup>9a–c</sup> coupling of **44** with methyl 4-bromobenzoate using method B and pyridine as the additive provided the desired cyclization/arylation product **45** in 50% yield with a R/I ratio of 10:1 or 8:1 without **4c** (eq 1). This



result indicates the possible participation of in situ-generated tertiary alkyl radicals, which is consistent with the observations for a variety of Ni-catalyzed couplings of alkyl halides.<sup>14,18,19</sup> It is unclear whether the present method follows Weix's radical chain mechanism.<sup>18b</sup>

Finally, this reductive coupling strategy enabled the facile synthesis of cyclotryptamine analogues, which have attracted widespread synthetic interest over the past decades.<sup>20</sup> Using method B without **4c**, tertiary benzyl chlorides were efficiently converted into **48**–**50** in good to excellent yields when coupled with electron-deficient aryl bromides (Scheme 2). Pyridine appeared to be much more effective than DMAP (Scheme S1).<sup>15</sup> 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.<sup>21</sup>

**Scheme 2. Synthesis of Cyclotryptamine Analogues**





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, imidazolium salts only slightly promoted the efficiency. The present reductive protocol exhibits excellent functional group compatibility, which generally enables 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 analogues. Finally, although the reaction mechanism is still under investigation, the possible involvement of a radical process is in line with general profiles for Ni-catalyzed reductive couplings of alkyl halides.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06255.

Experimental procedures and characterization data (PDF)  
Crystallographic data for **50** (CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*hegui\_gong@shu.edu.cn

### Notes

The authors declare no competing financial interest.

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