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Nickel-Catalyzed Carbon–Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations

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Abstract

The first Suzuki cross-couplings of unactivated tertiary alkyl electrophiles are described, employing a readily accessible catalyst ($NiBr_2$·diglyme/4,4′-di-*t*-butyl-2,2′-bipyridine, both commercially available); this also represents the initial example of the use of a Group 10 catalyst to cross-couple unactivated tertiary electrophiles to form carbon–carbon bonds. This approach to the synthesis of all-carbon quaternary carbon centers does not suffer from isomerization of the alkyl group, in contrast with the umpolung strategy for this bond construction (cross-coupling a tertiary alkylmetal with an aryl electrophile). Preliminary mechanistic studies are consistent with the generation of a radical intermediate along the reaction pathway.

During the past decade, substantial progress has been accomplished in the development of metal-catalyzed cross-coupling reactions of alkyl electrophiles with organometallic reagents to form carbon–carbon bonds.[1,2] Nearly all reports have focused on couplings of primary and secondary electrophiles; in contrast, there have only been isolated examples of successful reactions with unactivated tertiary electrophiles. In particular, Oshima has described cross-couplings with indenyllithium (silver catalyst), cyclopentadienylmagnesium (copper), benzylmagnesium (silver), allylmagnesium (cobalt, copper, and silver), and allyl- and benzylzinc (silver) reagents.[3]

The difficulty in coupling tertiary alkyl electrophiles can be attributed to a variety of factors, including a low propensity to undergo oxidative addition via an S_N2 or a direct-insertion pathway. We and others have demonstrated that, for an array of nickel-catalyzed cross-coupling reactions of unactivated primary and secondary alkyl halides, oxidative addition likely proceeds through an inner-sphere electron-transfer pathway.[4-6] In view of the relative stability of tertiary radicals, this mechanism could be conducive to reactions of tertiary alkyl electrophiles. Indeed, we have recently established that carbon–*boron* bond formation can be achieved by coupling tertiary halides with diboron reagents.[7] In this report, we expand the scope of cross-coupling reactions of unactivated tertiary alkyl electrophiles by describing the first method for accomplishing carbon–*carbon* bond formation with the aid of a Group 10 catalyst (eq 1).

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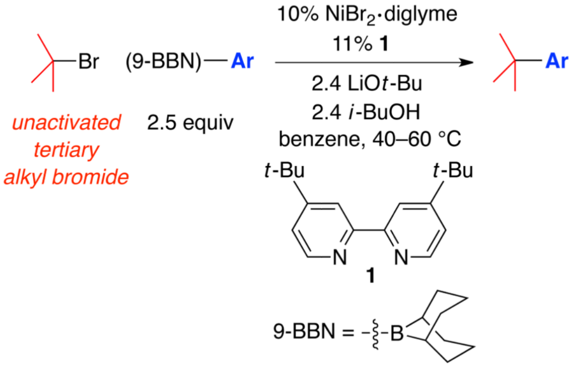
ASSOCIATED CONTENT

Supporting Information. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

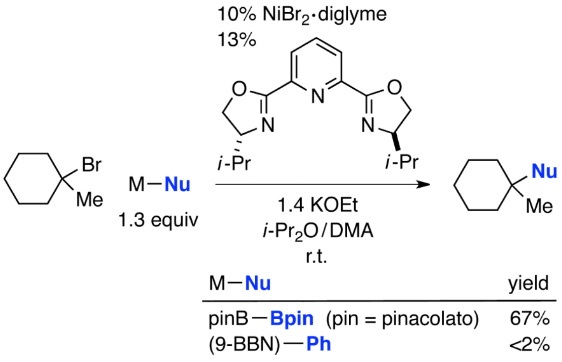
The authors declare no competing financial interest.



(1)

Early in this investigation, we decided to focus on organoboron reagents as coupling partners for two primary reasons. First, the Suzuki reaction is the most widely used cross-coupling method for the formation of carbon–carbon bonds.[8] Second, we have employed organo-(9-BBN) reagents (in conjuction with an alkoxide activator) as partners in an array of nickel-catalyzed Suzuki couplings of *primary* and *secondary* electrophiles,[9] and we have further established that the conditions are not highly Brønsted-basic, due to complexation of the alkoxide to the trivalent borane.[4] The propensity of many tertiary alkyl electrophiles to undergo elimination under basic or acidic conditions is a significant impediment to cross-coupling this family of reaction partners.

When we applied our recently reported method for nickel-catalyzed carbon–*boron* bond formation with tertiary alkyl bromides to a corresponding Suzuki cross-coupling, we observed essentially no carbon–carbon bond formation (eq 2). Similarly, the conditions that we had developed for Suzuki arylations of primary and secondary alkyl bromides were not effective for tertiary bromides (<2% yield).[10]



M—Nu	yield
pinB—Bpin (pin = pinacolato)	67%
(9-BBN)—Ph	<2%

(2)

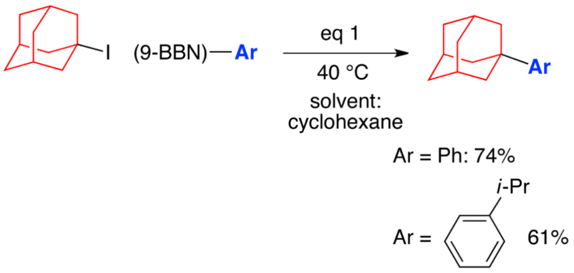
Notwithstanding this result, we continued our pursuit of a method for the synthesis of all-carbon quaternary centers via the cross-coupling of unactivated tertiary halides. In view of the steric demand of tertiary electrophiles, we chose to focus on the use of smaller ligands. Ultimately, we determined that Ni/4,4′-di-*t*-butyl-2,2′-bipyridine (**1**) serves as an effective catalyst for the coupling of 1-bromo-1-methylcyclohexane with a phenylborane, furnishing the target compound in 88% yield (Table 1, entry 1). A variety of bioactive compounds, including oxycodone (OxyContin™),[11] include an all-carbon quaternary center with one aryl substituent.

As illustrated in Table 1, in the absence of $NiBr_2$˙ diglyme, ligand **1**, or LiOt-Bu, little or no Suzuki cross-coupling of the unactivated tertiary alkyl bromide occurs (entries 2–4). The use of 2,2′-bipyridine or bathophenanthroline,[10a] rather than ligand **1**, leads to a somewhat lower yield (entries 5 and 6). For every other nickel-catalyzed Suzuki reaction of 9-BBN reagents that we have described (couplings of primary and secondary electrophiles), a 1,2-diamine has been the ligand of choice;[9] however, this is not the case for this Suzuki cross-coupling of a tertiary alkyl electrophile (entry 7). The counterion of the base plays a critical role in the efficiency of the coupling process (entry 8). Carbon–carbon bond formation proceeds in lower yield in solvents such as toluene, cyclohexane, and Et_2O (entries 9–11), and the use of less organoborane or less catalyst leads to less product (entries 12 and 13). Finally, the cross-coupling is not highly moisture-sensitive (entry 14).

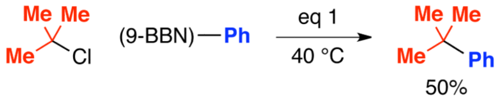
We have established that this method can be applied to Suzuki reactions of an array of unactivated tertiary alkyl bromides, generating the desired carbon–carbon bond in good yield (Table 2).[12] Thus, both 1-bromo-1-methylcyclohexane and *t*-butyl bromide are suitable substrates (entries 1 and 2), as is 3-bromo-3-ethylpentane, which is significantly more hindered (entry 3). Furthermore, a tertiary cyclobutyl bromide can be cross-coupled (entry 4). Importantly, functional groups such as an aromatic ring, ether, alkene, and primary alkyl chloride are compatible with this method for Suzuki cross-coupling of tertiary alkyl bromides (entries 5–8).

Although this method for cross-coupling unactivated tertiary alkyl halides is versatile with respect to the electrophile (Table 2), it has limitations with respect to the nucleophile (Table 3).[13] Specifically, ortho- and para-substituted aryl-(9-BBN) reagents generally do not couple in useful yield; on the other hand, a range of meta-substituted compounds serve as suitable Suzuki cross-coupling partners. Fortunately, this set of products is particularly useful, since they are not available through direct Friedel-Crafts alkylation.

1-Iodoadamantane can also be cross-coupled, generating 1-aryladamantanes, a motif found in a number of pharmaceuticals (eq 3).[14-16] Furthermore, in a preliminary study we have determined that carbon–carbon bond formation can be achieved with an unactivated tertiary alkyl chloride as the electrophile (eq 4; yield determined by GC analysis).[16]

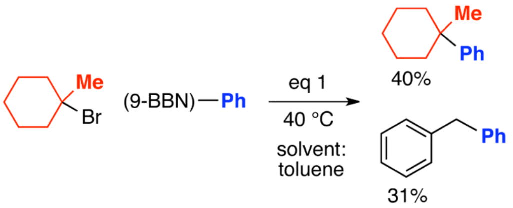


(3)



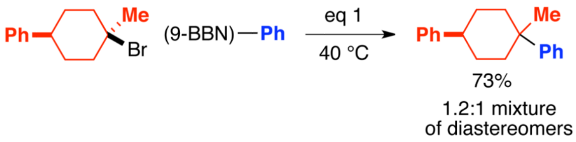
(4)

A possible mechanism for this nickel-catalyzed Suzuki cross-coupling, illustrated for the reaction of 1-bromo-1-methylcyclohexane with Ph-(9-BBN), is provided at the top of Figure 1.[4-6] As for our couplings of unactivated secondary alkyl halides, our initial mechanistic observations are consistent with a radical pathway for the oxidative addition of an unactivated tertiary halide to nickel. For example, when we conduct a Suzuki reaction in toluene, rather than benzene, we obtain a significant amount of diphenylmethane (eq 5), likely due to hydrogen-atom abstraction from toluene by radical **B** to form a benzyl radical, which then enters the catalytic cycle (bottom of Figure 1).



(5)

Furthermore, a nickel-catalyzed Suzuki reaction of a single diastereomer of a tertiary alkyl bromide leads to the formation of a mixture of diastereomeric cross-coupling products (eq 6). This observation can also be accommodated by a radical pathway for oxidative addition.



(6)

In conclusion, we have developed a method for the Suzuki arylation of tertiary alkyl bromides, using commercially available catalyst components ($NiBr_2$·diglyme and 4,4′-di-*t*-butyl-2,2′-bipyridine). To the best of our knowledge, these represent the first examples of the use of organoboron reagents as cross-coupling partners with unactivated tertiary electrophiles, as well as the first time that a Group 10 catalyst has been employed in cross-couplings of unactivated tertiary alkyl halides to form carbon–carbon bonds. In contrast with the umpolung approach (coupling a tertiary organometallic reagent with an aryl halide) to this bond construction, our method does not suffer from isomerization of the alkyl group.[17] Preliminary observations are consistent with a radical intermediate along the pathway of this new cross-coupling process. Additional studies directed at expanding the scope of this reaction, as well as enhancing our understanding of the mechanism, are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(2). For a recent application of an asymmetric Negishi cross-coupling of an alkyl electrophile in a total synthesis of carolacton, see: Schmidt T, Kirschning A. Angew. Chem., Int. Ed. 2012; 51:1063–1066.

(3). For examples of cross-couplings (not Heck reactions or other related processes) that provide >50% yield with an unactivated tertiary alkyl halide other than a 1-haloadamantane (which cannot eliminate HX), see: (a) allylmagnesium (cobalt): Tsuji T, Yorimitsu H, Oshima K. Angew. Chem., Int. Ed. 2002; 41:4137–4139. Ohmiya H, Tsuji T, Yorimitsu H, Oshima K. Chem. Eur. J. 2004; 10:5640–5648. [PubMed: 15457521] (b) allyl- and benzylmagnesium (silver): Someya H, Ohmiya H, Yorimitsu H, Oshima K. Org. Lett. 2008; 10:969–971. [PubMed: 18247499] Mitamura Y, Someya H, Yorimitsu H, Oshima K. Synlett. 2010:309–312. (c) cyclopentadienylmagnesium (copper): Sai M, Someya H, Yorimitsu H, Oshima K. Org. Lett. 2008; 10:2545–2547. [PubMed: 18481867] (d) allylmagnesium (copper): Sai M, Yorimitsu H, Oshima K. Bull. Chem. Soc. Jpn. 2009; 82:1194–1196. (e) allyl- and benzylzinc (silver): Mitamura Y, Asada Y, Murakami K, Someya H, Yorimitsu H, Oshima K. Chem. Asian J. 2010; 5:1487–1493. [PubMed: 20446338] (f) indenyllithium (silver): Someya H, Yorimitsu H, Oshima K. Tetrahedron. 2010; 66:5993–5999.

(4). For leading references to mechanistic studies of nickel-catalyzed Suzuki reactions of unactivated alkyl electrophiles, see: Wilsily A, Tramutola F, Owston NA, Fu GC. J. Am. Chem. Soc. 2012; 134:5794–5797. [PubMed: 22443409]

(5). For early mechanistic studies of nickel-catalyzed *Negishi* reactions of unactivated alkyl electrophiles, see: Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA. J. Am. Chem. Soc. 2006; 128:13175–13183. [PubMed: 17017797] Phapale VB, Buñuel E, García-Iglesias M, Cárdenas D. J. Angew. Chem., Int. Ed. 2007; 46:8790–8795. Lin X, Phillips DL. J. Org. Chem. 2008; 73:3680–3688. [PubMed: 18410144]

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(7). Dudnik AS, Fu GC. J. Am. Chem. Soc. 2012; 134:10693–10697. [PubMed: 22668072]

(8). For leading references, see: Suzuki A. Angew. Chem., Int. Ed. 2011; 50:6722–6737. (b) *Metal-Catalyzed Cross-Coupling Reactions;* de Meijere A, Diederich F. 2004Wiley–VCHNew York Negishi, E.-i.Handbook of Organopalladium Chemistry for Organic Synthesis. 2002Wiley InterscienceNew York

(9). For recent examples and leading references, see: (a) Reference 4. Zultanski SL, Fu GC. J. Am. Chem. Soc. 2011; 133:15362–15364. [PubMed: 21913638]

(10). (a) Ligand = bathophenanthroline: Zhou J, Fu GC. J. Am. Chem. Soc. 2004; 126:1340–1341. [PubMed: 14759182] (footnote 15: “Under our standard conditions, primary and tertiary alkyl bromides…are not suitable substrates.”). (b) Ligand = amino alcohol: González-Bobes F, Fu GC. J. Am. Chem. Soc. 2006; 128:5360–5361. [PubMed: 16620105]

(11). For leading references, see: James KS, Colette R, Forbes K, Hanks G. Palliative Medicine. 2011; 25:454–470. [PubMed: 21708852]

(12). Under our standard conditions: (a) when the cross-coupling illustrated in entry 1 of Table 2 was conducted in a capped vial under an atmosphere of air, the desired product was generated in 31% yield; (b) an unactivated primary or secondary alkyl bromide/iodide, 1-bromoadamantane, and an acyclic tertiary iodide were not suitable cross-coupling partners; (c) PhBpin, $PhB(OH)_2$, and $PhBF_3$ did not afford significant amounts of coupling product (<5% yield).

(13). Several other meta-substituted aryl-(9-BBN) reagents, including several halogenated compounds, were not effective coupling partners.

(14). Adapalene (Differin™) is an example of a pharmaceutical drug that includes a 1-aryladamantane.

(15). For a review of the use of the adamantyl group in medicinal chemistry, see: Lamoureux G, Artavia G. Curr. Med. Chem. 2010; 17:2967–2978. [PubMed: 20858176]

(16). Essentially no cross-coupling product is observed in the absence of $NiBr_2$·diglyme.

(17). For two recent advances and for leading references, see: Joshi-Pangu A, Wang C-Y, Biscoe MR. J. Am. Chem. Soc. 2011; 133:8478–8481. [PubMed: 21553878] Lohre C, Dröge T, Wang C, Glorius F. Chem. Eur. J. 2011; 17:6052–6055. [PubMed: 21509842]

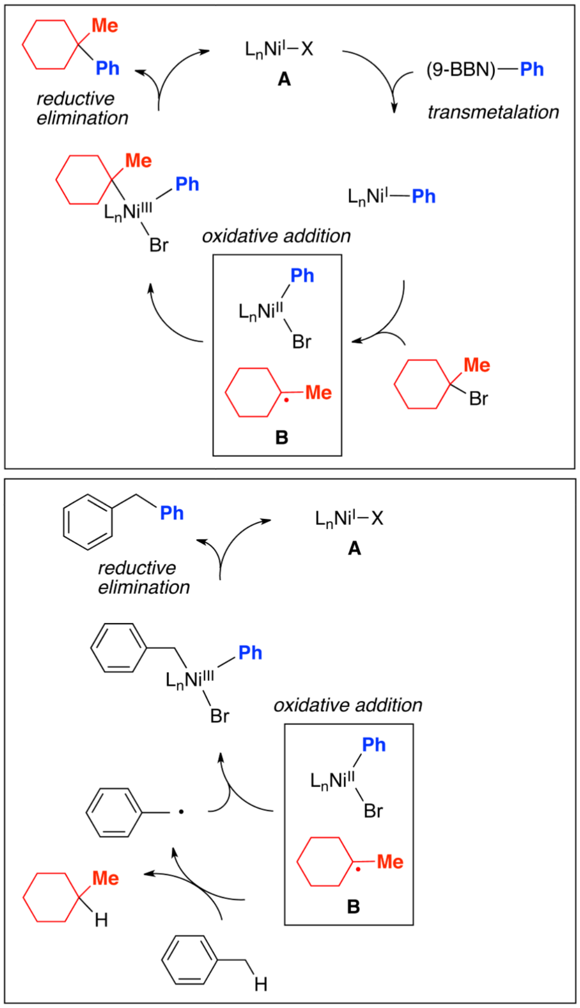
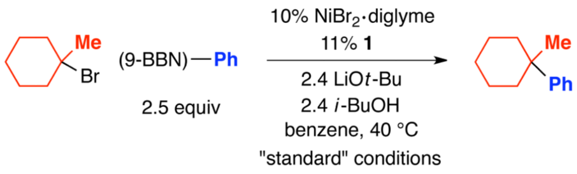


Figure 1.

Top: Outline of a possible mechanism for the nickel/**1**-catalyzed Suzuki cross-coupling of an unactivated tertiary alkyl bromide. Bottom: Possible pathway for the formation of diphenylmethane, when toluene is employed as the solvent (the early steps of the catalytic cycle are as illustrated at the top, and are omitted for simplicity).

Table 1

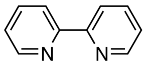
Suzuki Arylation of an Unactivated Tertiary Alkyl Bromide: Effect of Reaction Parameters



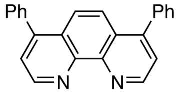
entry	variation from the “standard” conditions	yield (%)[a]
1	none	**88**
2	no NiBr$_2$·diglyme	<2
3	no **1**	8
4	no LiO*t*-Bu	<2
5	**2**, instead of **1**	72
6	**3**, instead of **1**	63
7	**4**, instead of **1**	7
8	KO*t*-Bu or NaO*t*-Bu, instead of LiO*t*-Bu	<2
9	toluene, instead of benzene	45
10	cyclohexane, instead of benzene	34
11	Et$_2$O, instead of benzene	13
12	1.8 equiv of (9-BBN)–Ph[b]	62
13	5% NiBr$_2$·diglyme, 5.5% **1**	53
14	0.1 equiv H$_2$O	89

[a] The yield was determined by GC analysis versus a calibrated internal standard (average of two experiments).

[b] 1.7 LiO*t*-Bu, 1.7 *i*-BuOH.



2



3

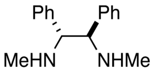


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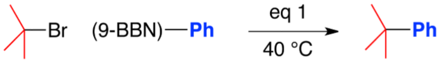
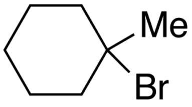
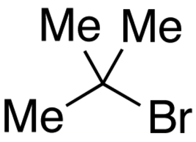
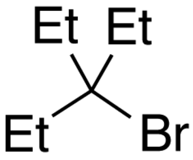
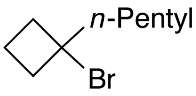
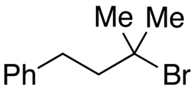
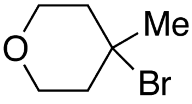
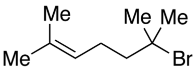
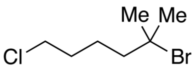
Table 2

Suzuki Cross-Couplings of Unactivated Tertiary Alkyl Bromides: Scope with Respect to the Electrophile



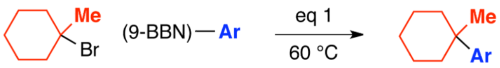
entry	tertiary alkyl bromide	yield (%) [a]
1		84
2		71 (84) [b]
3		70
4		53
5		86
6		57
7		76
8		67

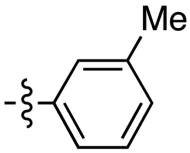
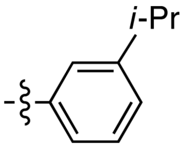
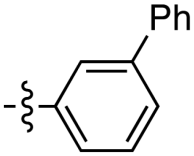
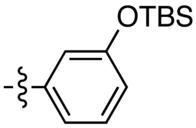
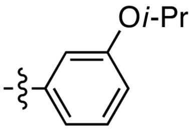
[a] Yield of purified product (average of two experiments).

[b] Due to the volatility of the product, the yield in parentheses was determined by GC analysis with the aid of a calibrated internal standard.

Table 3

Suzuki Cross-Couplings of Unactivated Tertiary Alkyl Bromides: Scope with Respect to the Nucleophile



entry	Ar	yield (%) [a]
1		60
2		61
3		74
4		57
5		54

[a] Yield of purified product (average of two experiments).