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Nickel-Catalyzed Kumada Cross-Coupling Reactions of Tertiary Alkylmagnesium Halides and Aryl Bromides/Triflates

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S Supporting Information

ABSTRACT: We report a Ni-catalyzed process for the cross-coupling of tertiary alkyl nucleophiles and aryl bromides. This process is extremely general for a wide range of electrophiles and generally occurs with a ratio of retention to isomerization >30:1. The same procedure also accommodates the use of aryl triflates, vinyl chlorides, and vinyl bromides as the electrophilic component.

The development of transition metal-catalyzed C−C bond-forming cross-coupling reactions has profoundly altered the paradigms by which we approach the synthesis of organic structures.[1] Although research into these cross-coupling reactions is largely focused on the creation of $C(sp^2)-C(sp^2)$ bonds, transition metal-catalyzed processes that permit the use of $C(sp^3)$ nucleophiles and electrophiles have also been developed.[1b,2] However, the use of secondary and tertiary nucleophiles in C−C bond-forming cross-coupling reactions still suffers from limitations.[3] Recently, we reported a general Ni-catalyzed Negishi reaction that permits the cross-coupling of acyclic secondary alkylzinc halides and aryl iodides without isomerization of the secondary nucleophile.[3k] In an attempt to build upon this work, we investigated the possibility that a nickel-based catalytic system could support the direct cross-coupling of tertiary alkyl nucleophiles and aryl halides to form aryl-substituted quaternary centers. Carrying out such a reaction in an effective and efficient manner is indeed a significant challenge; the procedure would need to support transmetallation of a sterically hindered tertiary nucleophile, while additionally promoting facile oxidative addition and reductive elimination such that β-hydride elimination is averted (see Figure 1).[4] The few existing reports of Pd- and Ni-catalyzed cross-coupling reactions employing tertiary nucleophiles have led to the exclusive formation of isomerized cross-coupling products (via intermediates analogous to **2b**)[5−7] due to rapid β-hydride elimination. Recently, Hintermann has developed an elegant copper-catalyzed protocol for the cross-coupling of tertiary alkylmagnesium halides and certain polychlorinated aza−aryl electrophiles.[8] However, this method has not been successfully extended to a wider range of electrophiles. Herein, we report an efficient Ni-catalyzed Kumada cross-coupling reaction of tertiary alkylmagnesium halides and aryl bromides, using commercially available N-heterocyclic carbenes (NHC) as supporting ligands.[9] This process permits the formation of aryl-substituted quaternary centers without extensive formation of inseparable isomerization byproducts. In these reactions, no dependence on the electronic nature of the electrophilic component is observed. Aryl triflates, vinyl bromides, and vinyl chlorides can be additionally employed as an electrophilic partner, which significantly broadens the utility of this cross-coupling process.

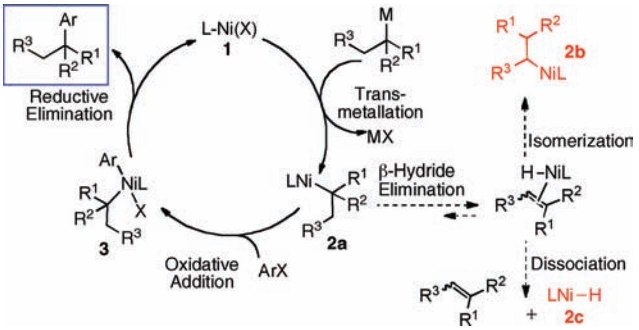

Figure 1. Proposed catalytic cycle for the Ni-catalyzed cross-coupling of tertiary alkyl nucleophiles and aryl halides.

We concentrated our initial investigation on the Ni-catalyzed cross-coupling of *t*-BuMgCl and 4-bromoanisole (**4**). 4-Bromoanisole (**4**) was selected as a model substrate because it is electronically deactivated (i.e., electron-rich), which makes it a challenging electrophile, and because its potential products (**5**−**8**) are readily analyzed by gas chromatography. Test reactions were conducted using 10 mol % Ni and 10 mol % ligand at 0 °C for 1 h in THF. In an initial screen of ligand classes, NHCs were identified as the most promising candidate for this cross-coupling reaction. Thereafter, the effect of steric and electronic perturbations of the NHC backbone was extensively investigated (Figure 2). Bulky NHC ligands were ineffective at supporting the desired transformation, leading mainly to products resulting from isomerization (**6**), reduction (**7**), or homocoupling (**8**). Fortunately, less hindered, electron-rich ligands such as **18** and **19** afforded mainly the desired cross-coupling product **5** while significantly decreasing the formation of byproducts (**6**-**8**).

Further optimizations of reaction conditions were initially hindered by poor reproducibility of the results shown in Figure 2. When new sources of NiCl$_2$ were employed alongside ligand **18**, increased formation of reduction product was observed, and the reactions often failed to reach completion. Closer examination of the NiCl$_2$ source led to the conclusion that a hydrated nickel species was necessary to reproducibly achieve the results of Figure 2.[10] Samples of initially anhydrous NiCl$_2$ that had been

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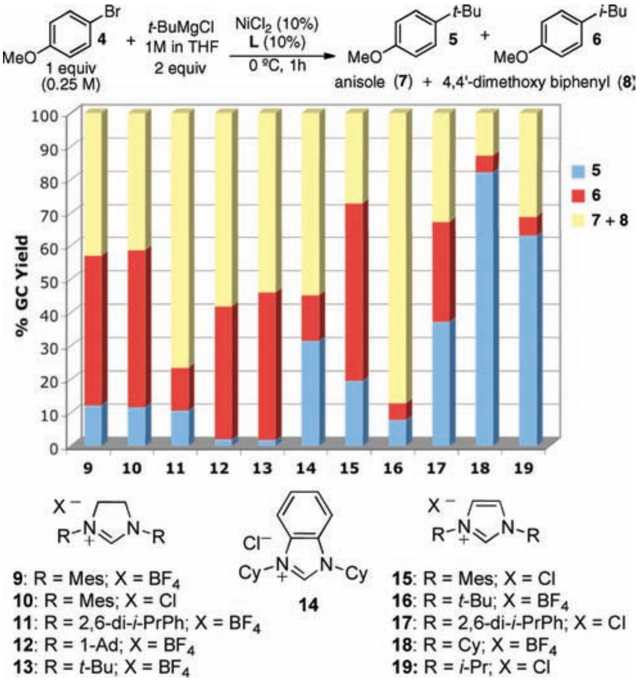


Figure 2. NHC ligand screen for the Ni-catalyzed cross-coupling of *t*-BuMgCl and 4-bromoanisole.

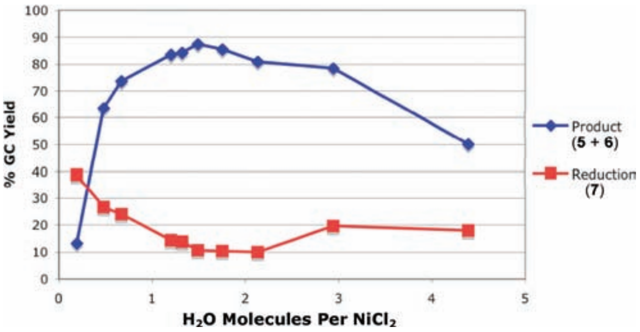
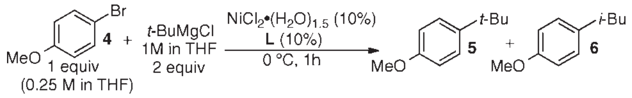


Figure 3. The influence of $NiCl_2 \cdot (H_2O)_n$ hydration on the cross-coupling of *t*-BuMgCl and 4-bromoanisole as shown in Figure 2.

Table 1. Final Optimization of the Ni-Catalyzed Cross-Coupling of *t*-BuMgCl and 4-Bromoanisole



entry	L	variation from conditions of Figure 2	yield (%)[a]	**5**:**6**[a]
1	**18**	0 50 M in THF	84	25:1
2	**18**	0 50 M in THF; 5% cat.; 5% **L**	77	24:1
3	**18**	0 50 M in THF; −10 °C	90	40:1
4	**18**	0 50 M in THF; −10 °C; Ni(COD)$_2$ (10%)	<5	–
5	**18**	0 50 M in THF; −10 °C; NiBr$_2$(10%)	17	18:1
6	**18**	0 50 M in THF; −10 °C; NiBr$_2$−H$_2$O (10%)	83	38:1
7	**18**	0 50 M in THF; −10 °C; Ni(acac)$_2$-H$_2$O (10%)	69	25:1
8	**18**	0 50 M in THF; −10 °C; NiCl$_2$-glyme (10%)	78	42:1
9	**18**	0.50 M in THF; −10 °C; Ni(OH)$_2$(10%)	<5	–
10	**18**	0.50 M in THF; −10 °C, NiCl$_2$(10%); KOH[b]	<5	–
11	**18**	0.50 M in THF; −10 °C, NiCl$_2$(10%); NaO*t*-Bu	32	35:1
12	none	0.50 M in THF; −10 °C	17	3:1

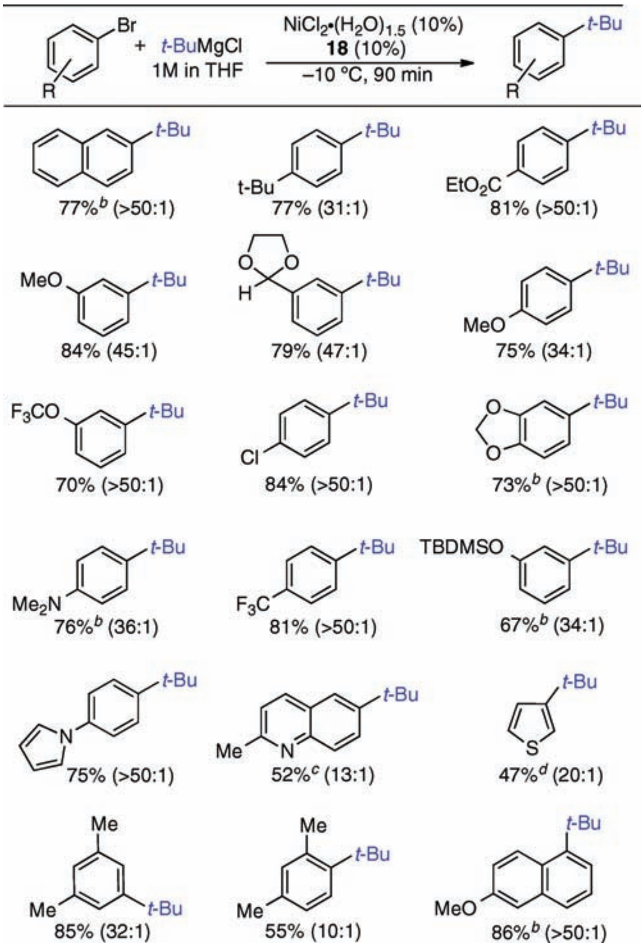
[a] Yields and selectivities determined by GC. [b] 0.4 equiv.

stored outside of the glovebox for several months performed significantly better in these reactions than samples of anhydrous NiCl$_2$ removed from the glovebox immediately prior to use. Furthermore, the addition of exogenous substoichiometric water to reactions that employed anhydrous NiCl$_2$ directly from the glovebox led to enhanced yields of cross-coupling product and decreased reduction. However, the best yields obtained by addition of water to fresh anhydrous NiCl$_2$ were consistently ∼20% lower than the best yields obtained when hydrated samples of NiCl$_2$ were employed. In order to determine the optimal water content for this reaction, we prepared a series of NiCl$_2$ samples with different water content by heating $NiCl_2 \cdot (H_2O)_6$ under vacuum. These samples were then employed in the cross-coupling reaction of *t*-BuMgCl and 4-bromoanisole, giving the results shown in Figure 3. The most efficient catalytic systems were obtained when the nickel source consisted of 1.2−1.8 equivalents of water per molecule of NiCl$_2$.[10] When less than one equivalent of water was present per molecule of NiCl$_2$, the yield of cross-coupling product dramatically decreased while the yield of reduction product increased.

We selected $NiCl_2 \cdot (H_2O)_{1.5}$ to be the nickel source for our next series of optimization efforts.[11] By reducing the reaction temperature to −10 °C and increasing the concentration of the aryl bromide to 0.5 M, we obtained the best conditions for this transformation. These conditions afforded the cross-coupling product in 90% yield with a 40:1 ratio of retention product (**5**) to isomerization product (**6**).[12] The use of alternative nickel sources resulted in inferior yields, although the importance of water was again demonstrated (see Table 1, entries 5 and 6). The addition of NaO*t*-Bu and KOH to reactions with anhydrous NiCl$_2$ did not result in improvement of the reaction (entries 10 and 11).[13]

The conditions developed in Table 1 are general for substrates typically compatible with Grignard reactions. Both electron-rich and electron-deficient aryl substrates performed well in this reaction (Table 2). Thus, this reaction does not demonstrate sensitivity to the electronic properties of the aryl bromide. The catalytic system also displayed complete selectivity for an aryl bromide over an aryl chloride, as indicated by selective transformation of 4-bromo-chlorobenzene to 4-*t*-butyl-chlorobenzene. Therefore, chloroaryl-substituted quaternary centers can be easily generated for use in follow-up cross-coupling reactions. The presence of acetals, esters, pyrroles, silyl-protected alcohols, and trifluoromethoxy groups was also tolerated by the reaction conditions. When heteroaryl bromides were employed in this reaction, cross-couplings generally occurred more slowly and failed to undergo complete conversion. Despite this, products from cross-coupling reactions involving a bromoquinoline and a bromothiophene could still be generated in reasonable yields.

Table 2. Ni-Catalyzed Cross-Coupling Reactions of *t*-BuMgCl and Aryl Bromides[a]

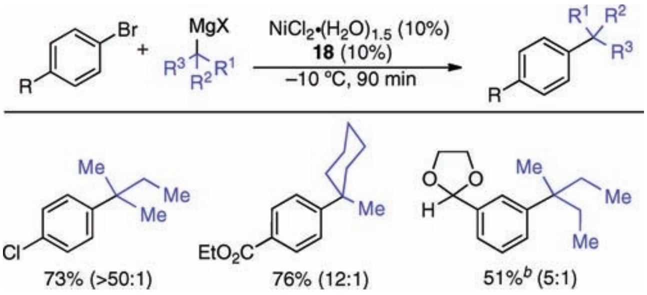


[a] ArBr (1 mmol), *t*-BuMgCl (2 mmol); average isolated yields of two runs. Ratio (determined by ^{1}H NMR spectroscopy) of retention product to isomerization product in parentheses. [b] Isolated alongside an additional ~10% reduction product. [c] Yield determined by ^{1}H NMR; 90% conversion by GC after 24 h. [d] Calibrated GC yield; 64% conversion by GC after 24 h.

Since sensitivity to steric effects is expected for a cross-coupling reaction involving a tertiary alkyl nucleophile, we were delighted to observe excellent reactivity when the bromide was located in the sterically hindered α-position of naphthalene. Even the presence of an ortho methyl group on the electrophile could be tolerated, although the formation of reduction product was significant in this case. *In general, insignificant isomerization of the tertiary nucleophile was observed in these reactions.* The ratio of retention product to isomerization product was greater than 30:1 for most substrates. Thus, the formation of inseparable isomerization products was, for the most part, unproblematic. The major byproduct formed in these reactions was the reduced aryl bromide.

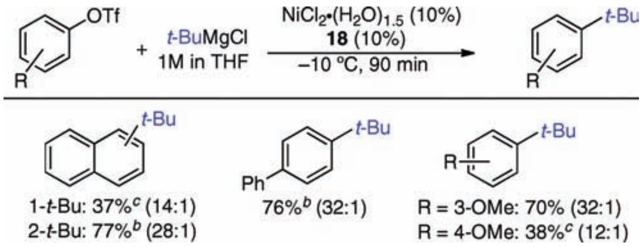
In order to verify that tertiary alkylmagnesium halides could be employed in this Ni-catalyzed cross-coupling process in a general fashion, we performed cross-coupling reactions with nucleophiles other than *t*-BuMgCl. The presence of a mono-α-branched nucleophile (e.g., *t*-amylMgCl) was well tolerated in these reactions (Table 3) and resulted in negligible isomerization. The use of a cyclic tertiary nucleophile was also successful. While an acyclic bis-α-branched nucleophile could be successfully employed, ~15% of the total product was the isomerized species. These results suggest that the use of bulkier nucleophiles tends to increase the concurrent formation of isomerization products.

Table 3. Ni-Catalyzed Cross-Coupling Reactions of Aryl Bromides with Different Tertiary Alkylmagnesium Halides[a]



[a] ArBr (1 mmol), RMgX (2 mmol); average isolated yields of two runs. Ratio (determined by ^{1}H NMR spectroscopy) of retention product to isomerization products in parentheses. [b] The reaction was warmed to rt and stirred overnight (10 h).

Table 4. Ni-Catalyzed Cross-Coupling Reactions of Aryl Triflates with *t*-BuMgCl[a]



[a] ArBr (1 mmol), *t*-BuMgCl (2 mmol); average isolated yields of two runs. Ratio (determined by ^{1}H NMR spectroscopy) of retention product to isomerization product in parentheses. [b] Isolated alongside an additional ~10% reduction product. [c] Calibrated GC yield.

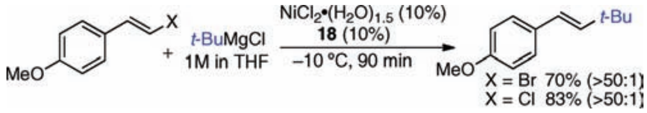


Figure 4. Ni-catalyzed cross-coupling reaction of *t*-BuMgCl and vinyl electrophiles (ratio of retention product to isomerization product in parentheses).

Although aryl bromide substrates constitute the major focus of this study, we also investigated the performance of other electrophiles in this cross-coupling reaction. Nonhindered, nondeactivated aryl triflates gave good yields under reaction conditions identical to those used with aryl bromides (Table 4), but electron-rich 4-methoxy phenyl triflate and sterically hindered 1-naphthyl triflate performed poorly compared to their corresponding aryl bromides. Thus, reactions employing aryl triflates appear to be more sensitive to steric and electronic effects than the analogous aryl bromide reactions. Good yields were also obtained in cross-coupling reactions involving vinyl chlorides and vinyl bromides (Figure 4).[14,15] The ability to employ such a wide variety of electrophiles without altering the reaction conditions gives this process excellent overall utility and operational simplicity.

In summary, we have developed a general Ni-catalyzed process for the cross-coupling of tertiary alkylmagnesium halides and aryl bromides. This process permits the efficient construction of aryl-substituted quaternary centers with nominal concurrent isomerization of the tertiary nucleophile. We have demonstrated that the same conditions used with aryl bromides can be successfully employed with aryl triflates and vinyl halides, resulting in a high degree of utility and simplicity for this process. Finally, we have shown that this process is highly dependent on the extent of $NiCl_2$ hydration. Detailed mechanistic and kinetic studies of this reaction, and the role of water therein, are currently in progress.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Samples of $NiCl_2 \cdot (H_2O)_n$ where $n = 1.4{-}1.7$ were easily prepared on large scale by grinding $NiCl_2 \cdot (H_2O)_6$ with a mortar and pestle and heating the powder under high vacuum in an oil bath at 100 °C for 20 min, then at 120 °C for an additional 5−10 min (see Supporting Information for more details). The powder was rapidly stirred to ensure homogeneous heating. The extent of dehydration can be readily determined by the mass change before/after heating under vacuum.

(12) In contrast to our original report on the Ni-catalyzed Negishi cross-coupling of secondary alkylzinc halides and aryl iodides with terpyridine as the ligand (ref 3k), the addition of LiCl (1 equiv) does not inhibit catalytic turnover or promote isomerization of the nucleophile.

(13) The failure of NaO*t*-Bu to facilitate the reaction suggests that kinetically slow in situ deprotonation of the NHC by the Grignard reagent is not responsible for the failure of the anhydrous reactions.

(14) Use of the vinyl bromide resulted in the formation of more reduction product than with use of the vinyl chloride.

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