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Synthetic Methods

Nickel-Catalyzed Cross-Coupling of Non-activated and Functionalized Alkyl Halides with Alkyl Grignard Reagents**

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Non-activated alkyl halides are difficult substrates for metal-catalyzed C−C coupling reactions because of their reluctance to undergo oxidative addition, and because metal alkyl intermediates are prone to unproductive β-hydride eliminations.[1,2] Despite these challenges, recent progress in Ni and Pd catalysis has resulted in a number of efficient protocols for catalytic C−C coupling of non-activated primary and secondary alkyl halides.[1–8] With the use of zinc, boron, and silicon nucleophiles, even functionalized alkyl halides can be coupled.[2–4,8] Grignard nucleophiles are seldom used for the coupling of functionalized organic halides because of their high reactivity.[9] The use of Grignard reagents, is however, desirable as they are economical, easy to synthesize, and many of them are commercially available.[9,10] The emergence of Fe catalysis has expanded the scope of coupling reactions between alkyl halides and Grignard reagents.[11] Because of the high activities of the Fe-based catalysts, the coupling can be carried out at low temperatures wherein the functional groups of the alkyl halides do not react with the Grignard reagents.[12] This improvement is however limited to alkyl–aryl/alkenyl coupling,[12,13] as iron-catalyzed sp^3–sp^3 coupling is less developed.[14] We only found two prior reports of a metal-catalyzed cross-coupling of functionalized alkyl halides with alkyl Grignards.[15,16] Several keto and ester derivatives were successfully alkylated using a Mn/Cu[16] or Cu[15] catalyst, but the scope of these transformations was not fully developed. Presented herein is a nickel-catalyzed Kumada–Corriu–Tamao coupling[17] of non-activated and functionalized alkyl bromides and iodides with alkyl Grignard reagents. The (pre)catalyst is an isolated and well-defined Ni^{II} coordination compound. The catalysis is general, highly efficient, and tolerates a wide range of important functional groups.

We recently reported the synthesis, structure, and reactivity of a series of Ni complexes having a pincer amidobis(amine) ligand.[18,19] The Ni^{II}–Cl complex $[(^{Me}NN_2)Ni^{II}\text{-Cl}]$ (**1**) catalyzed the sp^3–sp^3 coupling of non-activated and unfunctionalized alkyl halides with Grignard reagents (Figure 1) under very mild conditions (−20 °C).[19,20] Since Grignard reagents are known to tolerate a wide range of functional groups at such a low temperature, we thought it might be possible to couple the functionalized alkyl halides with alkyl Grignards by employing similar protocols. Initial tests were carried out for the coupling of 5-bromopentyl acetate with *n*BuMgCl (Table 1). To our delight, the coupling succeeded in 60 % yield under the conditions previously used for the coupling of the unfunctionalized alkyl halides (9 mol % catalyst, 1 equiv Grignard, dimethylacetamide (DMA) as the solvent, −20 °C; Table 1, entry 1). The yield was additionally improved when the reaction was carried out at −35 °C, just above the melting point of the reaction mixture (Table 1, entries 2 and 3).[21] A catalyst loading of 3 mol % was adequate to ensure a good conversion (Table 1, entry 3). Increasing the amount of the Grignard reagent used led to a lower yield, probably because of the reaction of the excess Grignard with the acetate group (Table 1, entry 4). The yields were lower at higher temperatures (Table 1, entries 5 and 6) and other solvents gave lower yields, even *N*-methylpyrrolidone (NMP), a solvent widely used to promote C−C coupling reactions (Table 1, entries 7 and 8).[1,15]

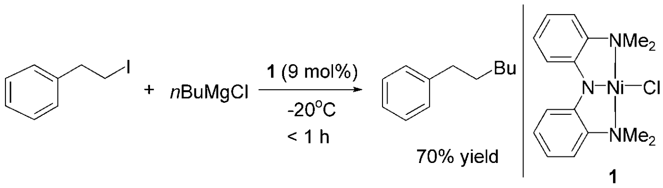
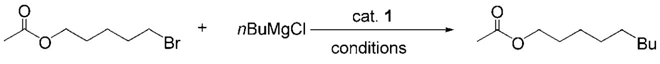


Figure 1. The structure of complex **1** and a representative example of catalytic C−C coupling of unfunctionalized alkyl halides.

Table 1: Catalytic coupling of 5-bromopentyl acetate with *n*BuMgCl.[a]



Entry	*T* [°C]	*n*BuMgCl [equiv]	Cat. [mol %]	*t* [h]	Yield [%][b]
1	−20	1	9	0.5	62
2	−35	1	9	1	75
3	−35	1	3	0.5	73/78[c]
4	−20	1.8	9	0.75	32
5	0	1	9	1	47
6	20	1	9	1	38
7	−35	1	9	0.5	30[d]
8	−35	1	9	0.5	67[e]

[a] General reaction conditions: *n*BuMgCl in THF (2 M) was added dropwise into a DMA (0.75 mL) solution of **1** and 5-bromopentylacetate (0.5 mmol) according to the conditions specified in Table 1. [b] Yields determined by GC methods and are relative to the organic halides. [c] Yield of isolated product. [d] THF was used as the solvent. [e] NMP was used as the solvent. DMA = dimethylacetamide.

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Encouraged by these findings, we explored the scope of this catalysis. As shown in Table 2, an array of non-activated and functionalized alkyl bromides and iodides can be coupled under similar conditions.[22] Although a catalyst loading of 3 mol % is sufficient to afford a high coupling yield for most substrates, several substrates demand a catalyst loading of 9 mol %. The ester, amide, ether, acetal, nitrile, and thioether groups did not interfere with the cross-coupling reaction (Table 2, entries 1–10). Substrates containing reactive keto groups were successfully coupled (Table 2, entries 11–14), which is rather unusual since the addition of Grignard reagents to keto groups is a popular method for the generation of tertiary alcohols. This reaction underscores the high activity of the cross-coupling reactions, despite the potential reaction of the Grignard reagent with other functional groups. An alcohol-containing substrate reacted when two equivalents of the Grignard were used (Table 2, entry 15), and an alkyl–Cl bond was inert during the coupling of an alkyl–Br unit (Table 2, entry 16). The coupling of activated alkyl (allylic, benzylic, and α-halocarbonyl) halides is inefficient (data not shown). The current system is thus complementary to the Ni(pybox) (pybox = pyridylbis(oxazoline)) system, which is highly active for the coupling of activated alkyl halides.[23]

Gratifyingly, alkyl halides containing heterocyclic groups could be coupled to give indole, pyrrole, and furan derivatives in high yields upon isolation (Table 2, entries 17–20). Importantly, the scope of the electrophile was expanded to include cyclic secondary alkyl iodides (Table 2, entries 21–23). The alkylation of a secondary alkyl iodide is selective in the presence of an aryl–bromide bond (Table 2, entry 23). Therefore, the Ni catalysis improves significantly upon the copper-catalyzed alkylation protocol,[15] which was ineffective for secondary alkyl halides. Such reactivity is consistent with the previous finding in which Ni complexes were uniquely situated to the cross-coupling catalysis of secondary alkyl halides whereas Pd catalysis is limited to primary alkyl halide substrates.[3] Unfortunately the coupling of a noncyclic secondary alkyl halide was less efficient (35 % yield, see the Supporting Information).

Furthermore, the nucleophile for this coupling is not limited to nonbranched alkyl Grignards. Steric bulk at the β position of the Grignard partner was tolerated (Table 2, entries 23 and 24). Phenyl ethyl Grignards were effective (Table 2, entries 25 and 26), as well as acetal functionalized Grignard reagents (Table 2, entry 27). Interestingly, dialkylation using a bis(alkyl Grignard) was also successful (Table 2, entry 28).

The mechanism of the catalysis should be the same as that of the Kumada–Corriu–Tamao coupling of nonfunctionalized alkyl halides by **1**. We showed previously that the latter catalysis likely started with the transmetalation of **1** with an alkyl Grignard to give a Ni^{II}–alkyl intermediate. The Ni^{II}–alkyl species then reacted with alkyl halides to form an alkyl radical, which recombined with the metal to give a Ni–bis(alkyl) intermediate. The C–C reductive elimination then led to the coupling product and a Ni^{II}–halide, thereby re-entering the catalytic cycle.[19] A similar "radical-rebound" mechanism was proposed earlier for the alkyl–alkyl Negishi

Table 2: Catalytic coupling of functionalized alkyl bromides and iodides with alkyl Grignard reagents.[a]

$$R^1X + R^2MgCl \xrightarrow[\text{DMA, -35°C, 0.5 h}]{\mathbf{1}\text{ (3 mol\%)}} R^1R^2$$

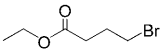
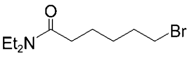
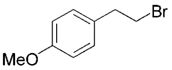
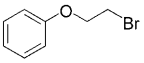
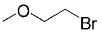
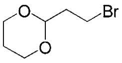
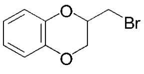
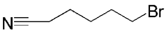
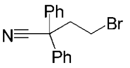
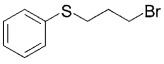
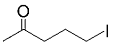
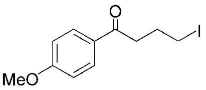
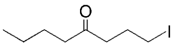
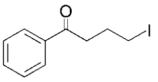
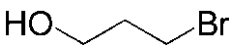
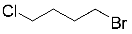
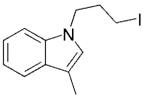
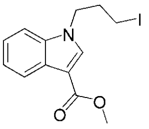
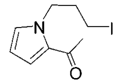
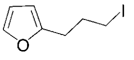
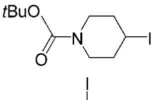
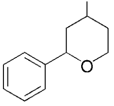
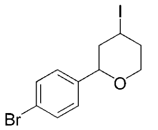
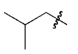
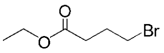
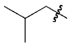
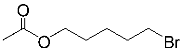
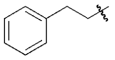
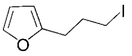
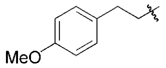
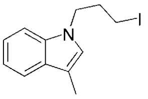
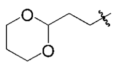
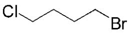
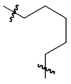
Entry	R^1X	R^2	Yield [%][b]
1		*n*Bu	85
2		*n*Bu	78
3		*n*Bu	80
4		*n*Bu	97
5		*n*Oct	98
6		*n*Bu	99
7		*n*Bu	71[c]
8		*n*Bu	77[c]
9		*n*Bu	99
10		*n*Bu	56[c]
11		*n*Pent	60
12		*n*Bu	68[c]
13		*n*Bu	75
14		*n*Bu	74
15		*n*Oct	79[c,d]
16		*n*Pent	91[e]
17		*n*Bu	95
18		*n*Bu	91
19		*n*Bu	93
20		*n*Bu	99
21		*n*Bu	86
22		*n*Bu	79

Table 2: (Continued)

Entry	R^{1}X	R^2	Yield [%][b]
23			89[f]
24			71
25			65
26			87
27			60[g]
28			66[e,g]

[a] General reaction conditions unless specified otherwise: 1 equiv of R^{2}MgCl in THF (1–3 M) was added dropwise into a DMA (0.75 mL) solution of **1** (3 mol%) and R^{1}X (0.5 mmol) at −35 °C. The reaction mixture was then removed from the cold bath and reacted for an additional 30 min. [b] Yield of isolated product. [c] Used 9 mol% catalyst. [d] Used 2 equiv of Grignard. [e] Only the alkyl–Br bond was coupled. [f] Only the alkyl–I bond was coupled. [g] R^{2}MgBr instead of R^{2}MgCl was used. X = halide.

coupling by Ni(pybox) and analogous Ni(terpy) (terpy = 2,2′:6′,2″-terpyridine) catalysts, which operated by a Ni^{I}/Ni^{III} cycle.[7,8] The current system however appears to operate by a formal Ni^{II}/Ni^{IV} cycle,[24] which shares common features with the system developed by Kambe et al.[5] This hypothesis is supported by the fact that Ni^{II}–methyl complex is a competent catalyst for alkyl–alkyl coupling,[19] and that Ni^{II}–alkyl complexes react cleanly with alkyl halides to form Ni^{II}–halides and C–C coupled organic products.[18,19]

In summary, the [(^{Me}NN$_2$)Ni^{II}-Cl] complex has enabled us to achieve a highly efficient catalytic coupling of non-activated and functionalized alkyl bromides and iodides with alkyl Grignard reagents. The work expands significantly the substrate scopes of C–C cross-coupling reactions using Grignard nucleophiles, making these readily available reagents useful for the synthesis of organic molecules containing reactive functional groups.

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Keywords: C–C coupling · cross-coupling · Grignard reaction · homogeneous catalysis · nickel

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