

## Functional Group Tolerant Kumada–Corriu–Tamao Coupling of Nonactivated Alkyl Halides with Aryl and Heteroaryl Nucleophiles: Catalysis by a Nickel Pincer Complex Permits the Coupling of Functionalized Grignard Reagents

Oleg Vechorkin, Valérie Proust, and Xile Hu\*

Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), ISIC-LSCI, BCH 3305, Lausanne, CH 1015, Switzerland

Received April 6, 2009; E-mail: xile.hu@epfl.ch

**Abstract:** A nickel(II) pincer complex  $[(^{\text{Me}}\text{NN}_2)\text{NiCl}]$  (**1**) catalyzes Kumada–Corriu–Tamao cross coupling of nonactivated alkyl halides with aryl and heteroaryl Grignard reagents. The coupling of octyl bromide with phenylmagnesium chloride was used as a test reaction. Using 3 mol % of **1** as the precatalyst and THF as the solvent, and in the presence of a catalytic amount of TMEDA, the coupling product was obtained in a high yield. The reaction conditions could be applied to cross coupling of other primary and secondary alkyl bromides and iodides. The coupling is tolerant to a wide range of functional groups. Therefore, alkyl halides containing ester, amide, ether, thioether, alcohol, pyrrole, indole, furan, nitrile, conjugated enone, and aryl halide moieties were coupled to give high isolated yields of products in which these units stay intact. For the coupling of ester-containing substrates, O-TMEDA is a better additive than TMEDA. The reaction protocol proves to be efficient for the coupling of Knochel-type functionalized Grignard reagents. Thus aryl Grignard reagents containing electron-deficient and/or sensitive ester, nitrile, amide, and  $\text{CF}_3$  substituents could be successfully coupled to nonactivated and functionalized alkyl iodides. The catalysis is also efficient for the coupling of alkyl iodides with functionalized heteroaryl Grignard reagents, giving rise to pyridine-, thiophene-, pyrazole-, furan-containing molecules with additional functionalities. Concerning the mechanism of the catalysis,  $[(^{\text{Me}}\text{NN}_2)\text{Ni}(\text{heteroAr})]$  was identified as an intermediate, and the activation of alkyl halides was found to take place through a radical-rebound process.

### Introduction

C–C cross coupling is one of the most straightforward and versatile methods in organic synthesis.<sup>1</sup> Over the past three decades, advances in transition metal catalysis make it possible to couple an organic electrophile with an organometallic nucleophile with high efficiencies and broad substrate scopes. Whereas the nucleophiles can be alkyl, alkenyl, aryl, alkynyl, allyl, and benzyl groups, the electrophilic coupling partners are often limited to contain aryl, alkenyl, and certain activated alkyl units.<sup>1</sup> For a long time, the coupling of nonactivated alkyl halides, especially those containing  $\beta$ -hydrogens, has been challenging for the following reasons: (i) Oxidative addition of alkyl halides is generally more difficult than that of aryl and alkenyl halides. (ii) If oxidative addition occurs, the resulting metal alkyl species can suffer from unproductive  $\beta$ -H elimination.<sup>2–4</sup> In recent years, however, significant progress has been made by a number of groups on

the cross coupling of nonactivated and  $\beta$ -H containing alkyl halides.<sup>5–23</sup> Continuous developments in the area will likely

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make this coupling methodology part of the standard repertoire in synthetic chemistry.

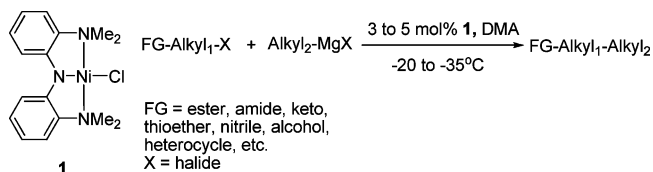
The Kumada–Corriu–Tamao coupling, in which an organic electrophile is coupled to a Grignard nucleophile, was discovered at the very early stage of modern cross-coupling chemistry.<sup>24</sup> The high reactivity of Grignard reagents, however, results in poor compatibility with functional groups. Subsequently, alternative coupling protocols employing less reactive organometallic reagents such as Zn, B, Sn, and Si nucleophiles were developed.<sup>1,25</sup> Even so, Grignard reagents remain desirable coupling partners because they are economical and easy to synthesize, and many of them are commercially available. Furthermore, many other organometallic coupling partners are prepared from the corresponding Grignard reagents. Thus, the Kumada–Corriu–Tamao coupling provides more direct access to the same desired products.<sup>17,26–29</sup> Improvements of functional group tolerance in the Kumada–Corriu–Tamao coupling will encourage the application of this atom-economic<sup>30</sup> coupling reaction in synthesis.

Several recent developments demonstrate that good functional group compatibility can be achieved in the Kumada–Corriu–Tamao coupling. A few catalytic systems based on Mn/Cu,<sup>6</sup>

Cu,<sup>8</sup> Pd,<sup>16,17</sup> Ni,<sup>9,19</sup> Co,<sup>20–23</sup> and particularly Fe<sup>12,13,15,31</sup> are active enough that the coupling can be carried out at mild conditions (e.g., room temperature and below). Consequently, a large number of alkyl halides containing reactive functional groups such as keto, ester, amide, nitrile, alcohol, heterocycles, etc. were selectively coupled to simple sp<sup>3</sup> or sp<sup>2</sup> Grignard reagents. In terms of the electrophilic coupling partner, the scope of these reactions is comparable to that of Negishi coupling,<sup>32</sup> and in some cases approaches that of Suzuki–Miyaura coupling.<sup>3,33</sup> Nonetheless, the nucleophiles are limited to conventional Grignard reagents. Parallel to this, the pioneer work of Knochel and co-workers on the preparation of functional Grignard reagents makes these nucleophiles readily available for further reactions.<sup>26,34</sup> Unfortunately, under most circumstances, these compounds cannot be directly used for cross-coupling reactions because they are unstable under the conditions required for such reactions (e.g., elevated temperature). Only a few exceptions are known so far. Knochel et al. showed that aryl Grignard reagents containing ester and nitrile groups and pyridyl Grignard reagents could be coupled to alkenyl halides, halopyridones, and lately aryl bromides.<sup>29,35,36</sup> Buchwald et al. developed a Pd-catalyzed sp<sup>2</sup>–sp<sup>2</sup> Kumada–Corriu–Tamao coupling process that tolerates a wide range of functional groups in either coupling partners using Knochel-type Grignard reagents.<sup>28</sup> Coupling of these reagents to alkyl halides, however, has been scarce prior to the current study.

Our group has been exploring the applications of a new Ni<sup>II</sup> pincer complex,<sup>37,38</sup> [(<sup>Me</sup>NN<sub>2</sub>)NiCl] (**1**), in catalytic C–C bond forming reactions.<sup>18,19,39</sup> We found that **1** was an efficient catalyst for the Kumada–Corriu–Tamao coupling of nonactivated alkyl halides with alkyl Grignard reagents at low temperatures (–20 to –35 °C) (Figure 1).<sup>19</sup> The same protocol, however, is inefficient for the coupling of alkyl halides with

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**Figure 1.** Alkyl–alkyl Kumada–Corriu–Tamao coupling catalyzed by **1**; DMA = dimethylacetamide. Yields are from 55% to 99%.

**Table 1.** Kumada–Corriu–Tamao Coupling of Octyl Bromide with PhMgCl<sup>a</sup>

Octyl-Br + PhMgCl		cat. <b>1</b> conditions		Octyl-Ph	
entry	solvent	cat. (mol %)	T (°C)	additive <sup>c</sup>	yield <sup>b</sup> (%)
1	DMA	9	−35		36
2	THF	5	20	1 equiv of TMEDA	84
3	THF	9	20		20
4	THF	5	20	1 equiv of TMEDA	63 <sup>c</sup>
5	THF	0	20	1 equiv of TMEDA	0
6	THF	0 (5 mol % (dme)NiCl <sub>2</sub> )	20	1 equiv of TMEDA	23
7	THF	0 (5 mol % (PPh <sub>3</sub> ) <sub>2</sub> NiCl <sub>2</sub> )	20	1 equiv of TMEDA	15
8	THF	3	20	0.03 equiv of TMEDA	85
9	THF	3	20	0.3 equiv of TMEDA	81 <sup>d</sup>

<sup>a</sup> 0.6 mmol (1.2 equiv) of PhMgCl in THF (3 mL, 2 M) was added dropwise via a syringe pump (1 h) to a solution (1 mL) of **1** and octyl-Br (0.5 mmol) according to the conditions specified in Table 1. The reaction time was 30 min to 1 h. <sup>b</sup> GC yields relative to the organic halides. <sup>c</sup> PhMgCl was added at once. <sup>d</sup> 1 equiv of PhMgCl was used.

sp<sup>2</sup> Grignard reagents. Because aryl and heteroaryl groups are ubiquitous in natural products, biologically active small molecules, and organic materials, we focus our efforts on alternative processes that permit the coupling of sp<sup>2</sup> Grignard nucleophiles. Here we show that by judicious choices of reaction conditions and additives, the Kumada–Corriu–Tamao coupling of non-activated alkyl halides with aryl and heteroaryl Grignard reagents can be achieved using the same Ni<sup>II</sup> precatalyst **1**. The catalysis tolerates a wide variety of functional groups in both coupling partners, and allows the use of Knochel-type functionalized Grignard reagents in sp<sup>3</sup>–sp<sup>2</sup> coupling.

## Results

**1. Optimization of Reaction Conditions for Coupling of Alkyl Halides with Aryl Grignard Reagents.** Under the same conditions previously employed for alkyl–alkyl Kumada–Corriu–Tamao coupling, the reactions of alkyl halides with aryl Grignard reagents gave low yields of coupling products. For instance, in the presence of 9 mol % **1**, coupling of octyl-Br with PhMgCl produced octyl-Ph only in 36% yield (entry 1, Table 1). However, the yields of cross-coupling reactions can be significantly improved by judicious choice of solvent, temperature, and additives (see Supporting Information for additional entries for the optimization of reaction conditions). In the presence of 1 equiv of TMEDA in THF at room temperature, 86% of coupling product could be obtained using 5 mol % of **1** (entry 2, Table 1). In the absence of TMEDA, the coupling gave only a 20% yield (entry 3, Table 1). The main side products in this case are Ph-Ph (55%) and octyl-octyl (50%). Slow addition of PhMgCl (during 1 h) is slightly beneficial (compare entries 2 and 4). Other amine additives, such as NEt<sub>3</sub>, NEt<sup>t</sup>Pr<sub>2</sub>, HMTA (hexamethylenetetraamine), had only modest effects (see Supporting Information). In the absence

of **1**, no coupling product was observed (entry 5, Table 1). The use of 5 mol % of another soluble Ni<sup>II</sup> compound, Ni(dme)Cl<sub>2</sub> or Ni(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, as the precatalyst resulted in ~20% coupling products (entries 6 and 7, Table 1). This underscores the unique activity of complex **1** for this catalysis.

The catalyst loading can be reduced to 3 mol % catalyst, and the amounts of TMEDA could be decreased without sacrificing the yields (entry 8, Table 1). 0.03 equiv of TMEDA relative to the alkyl halide, or 1 equiv relative to the catalyst is enough to ensure a high yield. For further reactions, 0.3 equiv of TMEDA is used for convenience in sample handling.<sup>40</sup> The yield of reaction remains satisfactory with 1 equiv of PhMgCl (entry 9, Table 1).

**2. Scope of Kumada–Corriu–Tamao Coupling of Alkyl Halides with Aryl and Heteroaryl Grignard Reagents. 2.1. Alkyl–Aryl Coupling Using Common Grignard Reagents.** We explored the scope of this new coupling protocol for a wide range of alkyl halides and aryl Grignard reagents. Primary alkyl bromides and iodides could be coupled in high yields (Table 2). Thus, Grignard reagents containing fluorine, methoxy and amino groups could be used (entries 1–26, Table 2). Aniline derivatives could be prepared starting from bis(trimethylsilyl)amino-substituted Grignard reagents (entries 3, 13, 17, 25, Table 2). Branching at the β-position of the alkyl halides was tolerated (entries 15–19, Table 2). Cyclohexyl iodide and bromide could also be coupled in modest to high yields (entries 23–26, Table 2). Noncyclic secondary alkyl halides could only be coupled in low yields (entries 27 and 28, Table 2); coupling of alkyl chloride was inefficient (entry 30, Table 2), likely due to the high C–Cl bond energy. Both 4- and 3-substituted Grignards reagents could be coupled; the coupling of 2-substituted Grignard reagents did not occur (entry 31, Table 2). Tertiary iodide cannot be coupled (entry 29, Table 2). The GC yields are close to the isolated yields (e.g., entries 1 and 11, Table 2).

We next applied the same conditions to the coupling of functionalized alkyl halides. To our delight, a wide range of functional groups are tolerated. The desired cross-coupling products could be easily separated from the reaction mixture in high isolated yields. Nitrile, ether, thioether, acetal, and amide groups did not interfere with the C–C coupling (entries 1–8, Table 3). Coupling of alkyl-Br is selective in the presence of alkyl-Cl, aryl-Cl, and aryl-Br groups (entries 9–11, Table 3). An alcohol-containing substrate could be used without protecting groups (entry 12, Table 3). Alkyl halides containing heterocyclic groups could be coupled to give furan, indole, and pyrrole derivatives (entries 13–16, Table 3). Coupling of an aromatic conjugate enone containing substrate was also effective (entry 16, Table 3). The coupling of ester containing substrates was successful, but required the use of bis[2-(*N,N*-dimethylaminoethyl)]ether (O-TMEDA) rather than TMEDA as the additive (entries 15–19, Table 3). Functionalized secondary cyclic iodides were coupled similarly (entries 19–20, Table 3). More reactive keto groups however cannot be tolerated (entry 21, Table 3). We found that coupling of alkyl iodides containing ester, amide, and nitrile groups is more efficient than of the respective alkyl bromides (data not shown).

**2.2. Alkyl–Aryl Coupling Using Knochel-Type Grignard Reagents.** The mild conditions and the good functional group compatibility of this coupling method encouraged us to explore

(40) In the current scale of reactions, 0.3 equiv of TMEDA corresponds to 25 μL of liquid sample.

**Table 2.** Kumada–Corriu–Tamao Coupling of Alkyl Halides with Aryl Grignard Reagents<sup>a</sup>

		$\text{Alkyl}^1\text{-X} + \text{Aryl}^2\text{-MgX} \xrightarrow[\text{THF, RT, 1 hr}]{\substack{3 \text{ mol\% } \mathbf{1} \\ 30 \text{ mol\% TMEDA}}}$				$\text{Alkyl}^1\text{-Aryl}^2$	
Entry	Alkyl <sup>1</sup> -X	Aryl <sup>2</sup> -MgX	Yield (%) <sup>b</sup>	Entry	Alkyl <sup>1</sup> -X	Aryl <sup>2</sup> -MgX	Yield (%) <sup>b</sup>
1	Octyl-I (2a)		88/92 <sup>c</sup>	16	2e		86
2	2a		98	17	2e		99 <sup>d</sup>
3	2a		99 <sup>d</sup>	18	2e		72
4	2a		80	19			77
5	Octyl-Br (2b)		87	20	<sup>n</sup> Bu-I (2f)		99
6	2b		86	21	2f		85
7	2b		82	22	2f		85
8	2b		67	23			62
9			74	24	2g		51
10	2c		72	25	2g		92
11			91/90 <sup>c</sup>	26			65
12	2d		78	27			18
13	2d		99 <sup>d</sup>	28			11
14	2d		85	29			-
15			86	30	Octyl-Cl		22 <sup>e</sup>
				31	2a		-

<sup>a</sup> Reaction procedure unless otherwise specified: 0.6 mmol (1.2 equiv) of ArMgX and 0.17 mmol of TMEDA in THF (3 mL) was added dropwise via a syringe pump (1 h) to a solution (1 mL) of **1** (5.2 mg, 0.015 mmol) and alkyl-X (0.5 mmol) at room temperature. The reaction time was 1 h. <sup>b</sup> Unless otherwise specified, GC yields relative to the organic halides. <sup>c</sup> Isolated yields relative to the organic halides. <sup>d</sup> Amine was formed after workup. <sup>e</sup> At 40 °C and with 9 mol % catalyst.

the coupling of alkyl halides with functionalized Grignard reagents. Knochel et al. developed two different general procedures for the preparation of Grignard nucleophiles containing nitrile, ester, and CF<sub>3</sub> groups. In method A, a functionalized aryl halide undergoes a halide/Mg exchange with an isopropyl Grignard reagent to yield a functionalized Grignard reagent and an isopropyl halide; in method B, with the aid of LiCl, Mg inserts into the same aryl halide precursor to form the desired Grignard reagent (Figure 2).

We prepared the Knochel-type Grignard reagents in a slightly modified procedure (see Experimental Section) and used them in situ for alkyl–aryl coupling reactions employing the newly developed protocol. We initially chose octyl-I as the test

substrate. When method A was used to make the Grignard reagents, isopropyl bromide or iodide was present as a side-product in the reaction mixture. They reacted slightly faster than other alkyl electrophiles, leading to low yields of cross-coupling products (entry 1, Table 4). This problem was remediated using an excess of the electrophilic coupling partners, and a 5:1 ratio of alkyl halide versus Grignard reagent was enough to ensure an efficient coupling. As reported by Wang et al., O-TMEDA increased the stability of the functionalized Grignard reagents.<sup>41</sup> Thus, octyl-I could be coupled to ester, nitrile, and amide

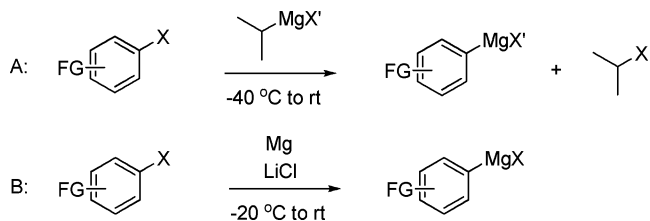
(41) Wang, X. J.; Sun, X. F.; Zhang, L.; Xu, Y. B.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305–307.



**Table 3.** Kumada–Corriu–Tamao Coupling of Functionalized Alkyl Halides with Aryl Grignard Reagents<sup>a</sup>

$\text{FG-Alkyl}^1\text{-X} + \text{Aryl}^2\text{-MgX} \xrightarrow[\text{THF, RT, 1 hr}]{\substack{3 \text{ mol\% } \mathbf{1} \\ 30 \text{ mol\% TMEDA}}} \text{FG-Alkyl}^1\text{-Aryl}^2$									
Entry	FG-Alkyl <sup>1</sup> -X	Aryl <sup>2</sup> -MgX	Product	Yield (%) <sup>b</sup>	Entry	FG-Alkyl <sup>1</sup> -X	Aryl <sup>2</sup> -MgX	Product	Yield (%) <sup>b</sup>
1				80	13				83
2				89	14				81
3				99	15				81 <sup>d</sup>
4				89	16				62 <sup>d</sup>
5				66	17				75 <sup>d</sup>
6				96	18				63 <sup>d</sup>
7				85	19				65 <sup>d</sup>
8				84	20				73
9				76	21			-	-
10				98					
11				98					
12				74 <sup>c</sup>					

<sup>a</sup> Reaction procedure unless otherwise specified: 1.2 mmol (1.2 equiv) of ArMgX and 0.34 mmol of TMEDA in THF (6 mL) was added dropwise via a syringe pump (1 h) to a solution (2 mL) of **1** (10.4 mg, 0.03 mmol) and alkyl-X (1 mmol) at room temperature. The reaction time was 1 h. <sup>b</sup> Isolated yields relative to the organic halides. <sup>c</sup> 2.4 equiv of **3a** used. <sup>d</sup> 60 mol % O-TMEDA was used in place of TMEDA.

**Figure 2.** The Knochel procedures for the synthesis of functionalized Grignard reagents.

containing Grignard nucleophiles in high isolated yields (entries 2–6, Table 4). The preparation of Grignard reagents via method B is more attractive because it does not require a pre-made Grignard reagent, but just Mg. However, among Grignard reagents prepared by this method, only those containing CF<sub>3</sub> and nitrile groups can be further used in the coupling reactions; and a 1:2 ratio of alkyl halide versus Grignard reagent was necessary for high yields (entries 7 and 8, Table 4).

The modified procedure is efficient for the coupling of other alkyl halides, including functionalized alkyl halides, with the Knochel-type Grignard reagents. Homobenzylic iodide, primary iodides containing heterocyclic, nitrile, enone, ester, and amide groups could be readily coupled (entries 9–14, Table 4). Alkyl-I is selectively arylated in the presence of alkyl-Cl and aryl-Cl groups (entries 15–17, Table 4). Grignard reagents containing ester, amide, tertiary amine, and CF<sub>3</sub> groups could be readily coupled. Although 5 equiv of alkyl halides were needed when employing method A, these coupling partners could be recycled from the final product mixtures in high purity. For instance, we recovered about 2.5–3.7 equiv of the starting alkyl halides for reactions in entries 10–12, 14, 19, 20, Table 4. Gratifyingly, secondary cyclic iodides could also be used (entries 18–20, Table 4). Coupling of octyl-Br was less efficient (entries 21 and 22, Table 4).

**2.3. Alkyl–Heteroaryl Kumada–Corriu–Tamao Coupling.** We next explored the coupling of alkyl halides with heteroaryl Grignard reagents. The reactions took place smoothly and gave

**Table 4.** Kumada–Corriu–Tamao Coupling of Alkyl Halides with the Knochel-Type Aryl Grignard Reagents<sup>a</sup>

		$\text{Alkyl}^1\text{-X} + \text{FG-Aryl}^2\text{-MgX} \xrightarrow[\text{THF, RT, 1 hr}]{\text{3 mol\% 1, additive}}$									
Entry	Alkyl <sup>1</sup> -X	FG-Aryl <sup>2</sup> MgX	Product	Method <sup>b,c</sup>	Isolated Yield (%)	Entry	Alkyl <sup>1</sup> -X	FG-Aryl <sup>2</sup> MgX	Product	Method <sup>b,c</sup>	Isolated Yield (%)
1	Octyl-I (2a)			A	27	12				A	72 <sup>d</sup>
2	2a			A	83 <sup>d</sup>	13				B	69 <sup>e</sup>
3	2a			A	75 <sup>d</sup>	14				A	86 <sup>d</sup>
4	2a			A	70 <sup>d</sup>	15				A	76 <sup>d</sup>
5	2a			A	58 <sup>d</sup>	16				A	86 <sup>d</sup>
6	2a			A	86 <sup>d</sup>	17				B	72 <sup>e</sup>
7	2a			B	62 <sup>e</sup>	18				A	61 <sup>d</sup>
8	2a			B	70 <sup>e</sup>	19				A	60 <sup>d</sup>
9				A	88 <sup>d</sup>	20				A	58 <sup>d</sup>
10				A	74 <sup>d</sup>	21	Octyl-I-Br (2b)			A	31 <sup>d</sup>
11				A	70 <sup>d</sup>	22	2b			B	32 <sup>e</sup>

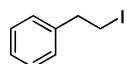
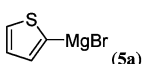
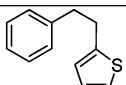
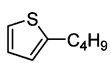

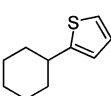
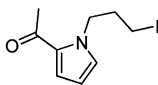
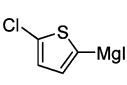
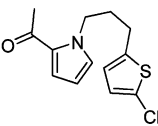
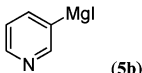
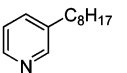
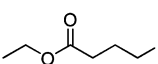
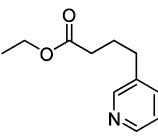
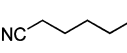
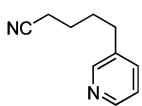
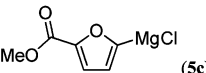
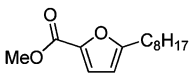
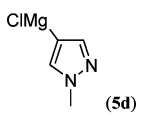
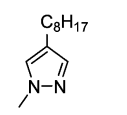
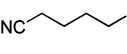
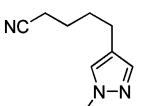
<sup>a</sup> Reaction procedure unless otherwise specified: ArMgX (prepared by method A or B) and TMEDA or O-TMEDA in THF (8 mL) was added dropwise via a syringe pump (1 h) to a solution (2 mL) of **1** (10.4 mg, 0.03 mmol) and alkyl-X (1 mmol) at room temperature (see Experimental Section for details). The reaction time was 1 h. <sup>b</sup> Method A: The Grignard reagent was prepared by X/Mg exchange; ArMgX:alkyl-X = 1:5 except in entry 1, where ArMgX:alkyl-X = 1:1. <sup>c</sup> Method B: The Grignard reagent was prepared by Mg insertion; ArMgX:alkyl-X = 2:1. <sup>d</sup> Isolated yields relative to the Grignard reagents. <sup>e</sup> Isolated yields relative to the organic halides.

the coupling products in high yields. Thiophen-2-yl-MgBr was coupled in the same fashion as simple aryl Grignard reagents, except that the coupling with alkyl bromide was not successful (entries 1–4, Table 5). The Knochel-type heteroaryl Grignard

reagents could also be coupled. Again, either method A or method B was employed for the preparation of these reagents in situ. The coupling with pyridine- and thiophene-containing Grignard reagents was possible with method B (entries 5–8,

**Table 5.** Kumada–Corriu–Tamao Coupling of Alkyl Halides with the Heteroaryl Grignard Reagents<sup>a</sup>

$$\text{Alkyl}^1\text{-X} + \text{heteroAryl}^2\text{-MgX} \xrightarrow[\text{THF, RT, 1 hr}]{\substack{3 \text{ mol\% } 1 \\ \text{additive}}} \text{Alkyl}^1\text{-Aryl}^2\text{-hetero}$$

Entry	Alkyl <sup>1</sup> -X	heteroAryl <sup>2</sup> MgX	Product	Method <sup>b,c</sup>	Yield (%)
1				-	99 <sup>d</sup>
2	<sup>n</sup> Bu-I	5a		-	93 <sup>d</sup>
3		5a		-	54 <sup>d</sup>
4	Octyl-Br	5a	-	-	-
5				B	62 <sup>e</sup>
6	Octyl-I (2a)			B	76 <sup>e</sup>
7		5b		B	69 <sup>e</sup>
8		5b		B	78 <sup>e</sup>
9	2a			A	65 <sup>f</sup>
10	2a			A	91 <sup>f</sup>
11		5d		A	74 <sup>f</sup>
12	Octyl-Br	5b	-	B	-

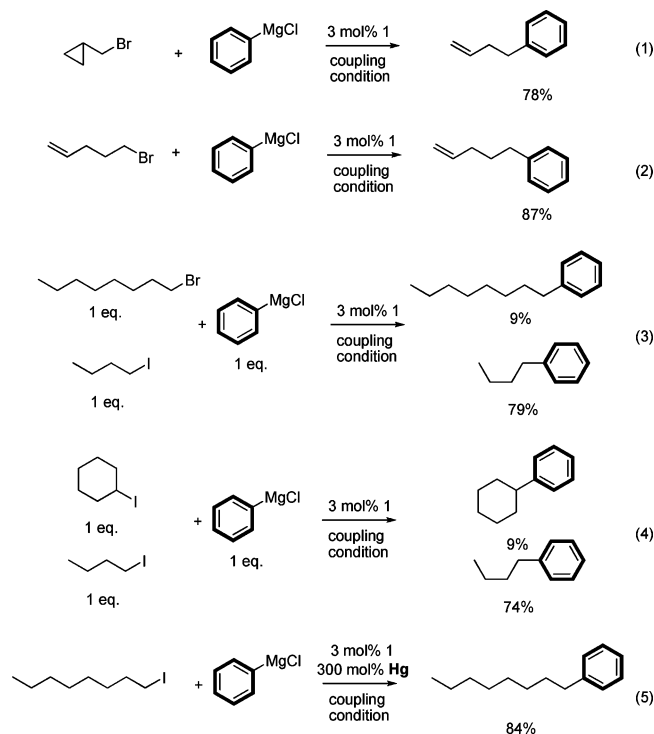
<sup>a</sup> Reaction procedures are the same as the coupling of alkyl halides with simple aryl Grignard reagents (Table 2) or with the Knochel-type Grignard reagents (Table 4) (see Experimental Section for more details). <sup>b</sup> Method A: The Grignard reagent was prepared by X/Mg exchange; ArMgX:alkyl-X = 1:5. <sup>c</sup> Method B: The Grignard reagent was prepared by Mg insertion; ArMgX:alkyl-X = 2:1. <sup>d</sup> GC yields relative to the organic halides. <sup>e</sup> Isolated yields relative to the organic halides. <sup>f</sup> Isolated yields relative to the Grignard reagents.

Table 5), whereas the coupling with the other functionalized heteroaryl Grignard reagents required method A (entries 9–11, Table 5). The coupling tolerates functional groups in both coupling partners, and primary and cyclic secondary alkyl iodides were selectively coupled.

**3. Mechanistic Investigations.** A few experiments were conducted to probe the mechanism for this sp<sup>3</sup>–sp<sup>2</sup> cross coupling. When bromomethylcyclopropane was coupled to PhMgCl, the ring-opening product 4-phenyl-1-butene was isolated as the main product in 78% yield. When 5-bromo-1-pentene was coupled to PhMgBr, 5-phenyl-1-pentene was isolated in 87% yield (eqs 1 and 2). Under identical and

competing catalytic conditions, coupling of butyl iodide with PhMgCl is about 8 times higher in yield than coupling of octyl bromide; coupling of butyl iodide is about 7 times higher in yield than coupling of cyclohexyl iodide (eqs 3 and 4). When the coupling of octyl-I with PhMgCl was conducted in the presence of 100 equiv of Hg (relative to the catalyst), octyl-Ph was produced in a 84% yield, nearly identical to the coupling in the absence of Hg (eq 5). This suggests that heterogeneous metal particles are not responsible for the catalysis.<sup>42</sup>

We attempted to identify the metal-containing species after the catalysis. In the coupling of octyl-I with PhMgCl, when 3

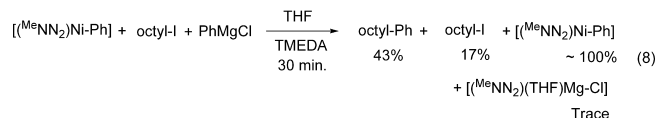
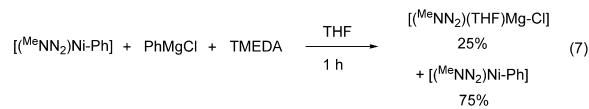


mol% of  $[(\text{MeNN}_2)\text{NiCl}]$  (**1**) was used as the precatalyst, we isolated  $[(\text{MeNN}_2)\text{Ni-Ph}]$  (**6**) in 72% yield (relative to **1**) from the catalysis mixture after acidic workup in air. Complex **6** was previously synthesized by reaction of **1** with  $\text{PhMgCl}$ ,<sup>39</sup> and it is apparently stable under air and in protic solutions. We then tested a pre-made sample of **6** for the coupling of octyl-I and octyl-Br with  $\text{PhMgCl}$  following our optimized protocol. Using 3 mol % of **6** as the precatalyst, the reactions produced octyl-Ph in 92% and 72% yields, respectively. These results are comparable to those obtained using 3 mol % of **1** as the precatalyst.

We previously showed that  $[(\text{MeNN}_2)\text{Ni-Ph}]$  (**6**) failed to react with alkyl halides to give C–C coupled products.<sup>39</sup> We reinvestigated the reaction of **6** with 20 equiv of octyl-I under catalytically relevant conditions (in THF in the presence of TMEDA) by NMR, but again no reaction was observed over 24 h (eq 6). Complex **6** did react with  $\text{PhMgCl}$  under the same conditions slowly to give the previously reported Mg complex  $[(\text{MeNN}_2)(\text{THF})\text{Mg-Cl}]$  (**7**), with 25% conversion after 2 h (eq 7). The rate of this reaction is roughly 2 times slower in the presence than in the absence of TMEDA. The reaction seems too slow to be relevant to the catalysis, which finishes within 1 h with more than 30 turnovers. Additionally, when **7** was used as the precatalyst for the coupling of octyl-I with  $\text{PhMgCl}$ , only 2% of octyl-Ph was formed under the same conditions, suggesting that **7** is not a competent catalyst for this catalysis.

Interestingly, when **6** was mixed with an equal mixture of  $\text{PhMgCl}$ , octyl-I, and TMEDA (all 1 equiv relative to **6**) in THF, a rapid reaction occurred, which gave the C–C coupled product octyl-Ph (eq 8). When the addition of  $\text{PhMgCl}$  was slow (20 min), only a trace of **7** was formed. When the addition was fast (in one portion), 25% of **7** was formed. Thus, the benefit of slow addition of Grignard reagents for some coupling reactions

(vide supra) might be due to the suppression of eq 7, which leads to the decomposition of the active catalyst. No paramagnetic species in the catalysis mixture could be detected by EPR at both room temperature and 25 K.



## Discussion

**1.  $\text{sp}^3\text{-sp}^2$  Kumada–Corriu–Tamao Coupling Catalyzed by  $[(\text{MeNN}_2)\text{NiCl}]$  (**1**).** The protocol optimized for alkyl–alkyl Kumada–Corriu–Tamao coupling was inefficient for alkyl–aryl coupling. Amine ligands<sup>23</sup> and additives such as TMEDA<sup>12–14</sup> were widely used to promote alkyl–aryl Kumada–Corriu–Tamao coupling, especially in Fe-catalyzed systems. We thus investigated the influence of TMEDA in our catalysis. The addition of TMEDA significantly improved the yields of coupling in THF. The synergy of THF and TMEDA is well documented in Fe catalysis,<sup>12–14</sup> but is less reported in Ni catalysis. A catalytic amount of TMEDA was sufficient. The coupling of some cyclic secondary halides is efficient, whereas that of noncyclic secondary alkyl halides is not. This could be attributed to the less steric hindrance in cyclic alkyl halides for C–X activation, and the higher stability of the corresponding metal cycloalkyl intermediates against  $\beta$ -H elimination.<sup>22</sup> Coupling of sterically demanding tertiary alkyl iodides or 2-substituted Grignard reagents was not possible. This should be a consequence of having a tridentate chelating ligand ( $\text{NN}_2$ ) on the Ni center, which leaves limited space for interaction with the coupling partners.

The reaction conditions are mild enough that they can be applied to the coupling of functionalized alkyl halides. The coupling is selective for alkyl-I and alkyl-Br moieties over alkyl-Cl, aryl-Br, and aryl-Cl moieties, giving rise to products containing the latter groups, which could be subject to further functionalization. In terms of functional group compatibility on the alkyl halides, the current Ni-system is in line with the most tolerant Pd,<sup>16,17</sup> Fe,<sup>13</sup> and Co<sup>20,22,23</sup> systems.

The extension to include the Knochel-type functionalized aryl Grignard reagents as coupling partners posed several challenges. These nucleophiles have limited stability at room temperature and above, and thus they should be used at lower temperature. However, they contain electron withdrawing groups (CN, RCO,  $\text{CF}_3$ ) which in turn make them less nucleophilic. A highly active catalyst is thus required, which might explain why there are only very few reports succeeding in the coupling of these Grignard reagents.<sup>28,29,35</sup> All prior examples concern  $\text{sp}^2\text{-sp}^2$  C–C coupling. The coupling of alkyl halides could be more difficult due to the possibility of unproductive  $\beta$ -H elimination. Gratifyingly, complex **1** was able to catalyze the  $\text{sp}^3\text{-sp}^2$  Kumada–Corriu–Tamao coupling of alkyl iodides with these Grignard reagents. Even though the Knochel-type Grignard reagents could be prepared by halogen/Mg exchange or by LiCl-assisted Mg insertion (method A or B, Figure 2),<sup>26,34</sup> not all Grignard reagents prepared by method B can be successfully

(42) (a) Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819–1830. (b) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855–859.



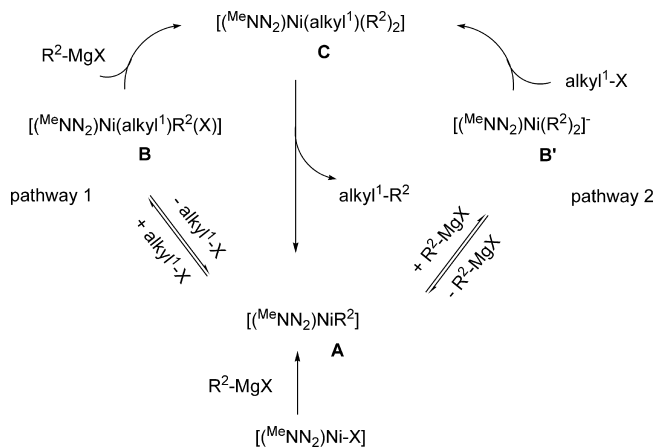
coupled. We suspect that it is caused by the difference in the stability of a given Grignard reagent prepared via either method. Whereas the coupling of alkyl bromides with simple aryl Grignard reagents is efficient, the coupling of them with the Knochel-type Grignard reagents was not successful. This is probably due to the higher barrier in C–Br bond activation, which makes the C–C coupling slower than the competing side reactions such as reaction with isopropyl halides (for method A), HX elimination, and/or decomposition of the Grignard reagents.

When a functionalized Grignard reagent is prepared via halogen/Mg exchange (method A), a stoichiometric amount of isopropyl halide is generated as a byproduct. This complicated the cross coupling of such Grignard reagent with other alkyl halide because, under the same conditions, reactions with the isopropyl halide dominated. No isopropyl–aryl cross-coupling product was found. We suspect that the main side reaction is HX elimination from the isopropyl halide. Using an excess of alkyl halide coupling partners (5 equiv), cross-coupling products were formed and isolated in high yields. In cases where the electrophilic coupling partner is cheap and readily available (such as octyl-I), this method is sufficient. If the alkyl halides are expensive and require several steps to prepare, then an improvement is warranted. It is thus satisfying to find that about 2.5–3.7 equiv of the unreacted alkyl halides can be recycled from the product mixtures in high purity. When the Grignard reagents are prepared via direct Mg insertion (method B), the coupling employs a one-pot procedure using Mg, LiCl, catalyst **1**, and the coupling partners. No reactive reagents are required, and thus the method is interesting with respect to process chemistry.

The coupling protocol is also effective for alkyl–heteroaryl coupling. Whereas a number of reports on cross coupling of alkyl halides with aryl nucleophiles have been published in recent years,<sup>2,3</sup> coupling of alkyl halide with heteroaryl nucleophiles is rare.<sup>10,14,43</sup> Coupling of various alkyl halides with heteroaryl Grignard reagents, including those of the Knochel-type, gives pyridine-, thiophene-, pyrazole-, furan-containing molecules that may have interesting applications as ligands, organic materials, and biologically active small molecules. The potentially coordinating pyridine and pyrazole groups do not inhibit the catalysis, likely because they are unable to displace the chelating NN<sub>2</sub> ligand even when in large excess.

As shown in Tables 3–5, a large number of functionalized small molecules are accessible in a straightforward and rapid fashion via this sp<sup>3</sup>–sp<sup>2</sup> Kumada–Corriu–Tamao coupling protocol. To the best of our knowledge, this is the first general protocol for the coupling of nonactivated alkyl halides with functionalized aryl and heteroaryl Grignard reagents. In terms of functional group compatibility in both coupling partners, the scope of this Kumada–Corriu–Tamao catalysis is in line with those of the very few reported examples of Negishi<sup>32</sup> and Suzuki–Miyaura<sup>33</sup> sp<sup>3</sup>–sp<sup>2</sup> coupling of alkyl halides.<sup>7,10</sup> The advantages of using Grignard reagents as coupling partners include their low cost, ease and atom-economy in preparation, and high reactivity resulting in short reaction time.

**2. Mechanism of the sp<sup>3</sup>–sp<sup>2</sup> Kumada–Corriu–Tamao Coupling.** Taking into consideration that [(Me<sub>2</sub>NN<sub>2</sub>)Ni–Ph] (**6**) is an active catalyst and is also the resting state of the catalysis in the coupling reactions of alkyl halides with PhMgCl, we



**Figure 3.** Proposed catalytic cycles for sp<sup>3</sup>–sp<sup>2</sup> coupling; R<sup>2</sup> represents an aryl or heteroaryl group.

propose that an analogous Ni<sup>II</sup>–(hetero)aryl species [(Me<sub>2</sub>NN<sub>2</sub>)Ni–R<sup>2</sup>] (**A**, R<sup>2</sup> is an aryl or heteroaryl group) is an intermediate in the Ni-catalyzed sp<sup>3</sup>–sp<sup>2</sup> coupling reactions (Figure 3). This intermediate is formed by transmetalation of the [(Me<sub>2</sub>NN<sub>2</sub>)Ni–Cl] precatalyst with a Grignard reagent. It reacts with a mixture of alkyl halide and Grignard reagent to give a six-coordinate complex [(Me<sub>2</sub>NN<sub>2</sub>)Ni(alkyl)(R<sup>2</sup>)<sub>2</sub>] (**C**). Reductive elimination then gives the alkyl–aryl coupling product and regenerates **A**. The high yield of alkyl–aryl coupling suggests that alkyl–aryl reductive elimination is faster than aryl–aryl reductive elimination. Whereas a DFT study found that sp<sup>2</sup>–sp<sup>2</sup> reductive elimination is faster than its sp<sup>3</sup>–sp<sup>3</sup> counterparts,<sup>44</sup> it was recently shown that the two reactions can become competitive in pincer complexes.<sup>45</sup> Thus, the observed higher selectivity for alkyl–aryl coupling does not necessarily contradict the proposed mechanism.

From **A** to **C**, there are two conceivable pathways. **A** could react with alkyl halide to form [(Me<sub>2</sub>NN<sub>2</sub>)Ni(alkyl)(R<sup>2</sup>)X] (**B**), which could then be transmetalated by the Grignard reagent to give **C** (pathway 1). Alternatively, **A** could react with a Grignard reagent to give an anionic species [(Me<sub>2</sub>NN<sub>2</sub>)Ni(R<sup>2</sup>)<sub>2</sub>]<sup>–</sup> (**B'**), which then reacts with alkyl halide to form **C** (pathway 2). Model reactions between **6** and octyl-I or PhMgCl did not produce **B** or **B'** in a detectable amount (eqs 6 and 7). However, this does not exclude either pathway, as the transformation from **A** to **B** or **B'** can be fast and reversible but thermodynamically uphill. Thus, **B** or **B'** exists in a very small percentage but, upon treatment with a second coupling partner, quickly forms **C** and then the coupling product. This is supported by the fact that **6** reacted rapidly with a mixture of octyl-I and PhMgCl to give octyl-Ph (eq 8).

We prefer pathway 1 because the analogous Ni<sup>II</sup>–alkyl complexes [(Me<sub>2</sub>NN<sub>2</sub>)Ni–alkyl] reacted with alkyl halides to give alkyl–alkyl coupled products in the absence of a Grignard reagent.<sup>18,39</sup> The Ni<sup>II</sup>–(hetero)aryl complexes are less electron-rich, and the same reactions with alkyl halides may become thermodynamically unfavored, as is suggested by the catalytic cycle shown in Figure 3. The fact that reductive elimination occurs from **C** but not from **B** is unusual and suggests that the

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axial ligand (phenyl versus  $\text{Cl}^-$ ) has a big impact in the compound's reactivity.

The oxidation state of Ni in intermediates **B** and **C** warrants a few further notes. If the ligand is redox-innocent, then the Ni center is formally  $\text{Ni}^{\text{IV}}$ . However, it has been shown that pincer amido ligands can be redox-active. For example, the  $[(\text{PNP})\text{NiCl}](\text{OTf})$  complex ( $\text{PNP} = \text{N}[2\text{-P}(\text{CHMe}_2)_2\text{-4-methylphenyl}]_2$ ) is best formulated as a  $\text{Ni}^{\text{II}}$  center coordinated to a ligand cation.<sup>38</sup> Therefore, **B** and **C** are perhaps better described as  $\text{Ni}^{\text{III}}$  ligand cation complexes. If this is the case, the Ni center would have 19 electrons, which is less common but not unprecedented for organometallic complexes.<sup>46</sup> On the other hand, the Ni center has a stable 18-electron configuration in the  $\text{Ni}^{\text{IV}}$  formulation, and thus such possibility cannot be excluded. Several stable  $\text{Ni}^{\text{IV}}$  alkyl complexes have been recently reported.<sup>47</sup>

The oxidative addition of alkyl halide to **A** or **B'** likely takes place via single-electron transfer. Thus, **A** or **B'** reacts with the alkyl halide to form an alkyl radical which quickly recombine to form  $[(^{\text{Me}}\text{NN}_2)\text{Ni}(\text{alkyl})(\text{R}^2)\text{X}]$  (**B**) or  $[(^{\text{Me}}\text{NN}_2)\text{Ni}(\text{alkyl})(\text{R}^2)_2]$  (**C**). This radical-rebound mechanism is supported by the result of the coupling of  $\text{PhMgCl}$  with the radical clock, bromomethylcyclopropane, which yielded 4-phenyl-1-butene (eq 1, vide supra). The radical recombination process hence is slower than the ring-opening of cyclopropanylmethyl radical ( $k \approx 10^7 \text{ s}^{-1}$ ).<sup>11</sup> It is however faster than the cyclization of 4-pentenyl radical ( $k \approx 10^5 \text{ s}^{-1}$ ),<sup>11</sup> as the coupling of 5-bromo-1-pentene with  $\text{PhMgCl}$  yielded 5-phenyl-1-pentene (eq 2). The radical mechanism may also explain why aryl halides could not be coupled under the same conditions.

Competing experiments show that, under the same catalytic conditions, activation of alkyl iodides is faster than bromides, consistency with the relative strength of alkyl–X bonds. Activation of primary alkyl halides is faster than secondary alkyl halides. This probably has a steric origin, since secondary alkyl radicals tend to be more stable than their primary counterparts.

In a number of reactions, the coupling is efficient for alkyl iodides but less so for alkyl bromides. This would be consistent with the turnover determining step being the activation of alkyl halides, although it does not prove it. Since the activation of the more inert alkyl bromides is slower, side reactions compete favorably and the coupling yields diminish.

The addition of TMEDA or O-TMEDA suppresses the homocoupling of both coupling partners (vide supra). As in other reported systems,<sup>12–14</sup> how these additives are involved in the catalysis is not clear at this moment. A recent study suggested that in Fe-catalysis, TMEDA can serve as the ligand for the Fe center.<sup>48</sup> Since the Ni center is coordinated by a strong pincer chelate, it is not likely that the additives serve as ligands for Ni ions. They can however bind to Mg and make the Grignard reagents more nucleophilic. It was reported that in the presence of amine ligands like PMDTA ( $N,N,N',N'',N'''$ -pentamethyldiethylenetriamine), the Schlenk equilibrium of Grignard reagents

is shifted to the side of dismutation ( $\text{RMgX}$ ).<sup>49</sup> Similar effects might be induced by TMEDA and O-TMEDA in the current system. Furthermore, O-TMEDA is known to stabilize functionalized Grignard reagents.<sup>41</sup> The beneficial effects of TMEDA and O-TMEDA likely have multiple origins.

It is possible that the amido nitrogen in complex **1** is involved in the catalytic cycle. Like TMEDA and O-TMEDA, it could complex the Mg ion of Grignard reagents and enhances their reactivity. It may also act as a nucleophile toward alkyl halides. Since the activation of alkyl halides involves radical intermediates, the latter possibility is however not very likely.

## Conclusion

Applying a newly developed and straightforward protocol, we show here that a preformed, stable, and easy to handle  $\text{Ni}^{\text{II}}$  complex  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (**1**) catalyzes efficiently the  $\text{sp}^3\text{–sp}^2$  Kumada–Corriu–Tamao coupling of nonactivated and  $\beta\text{-H}$  containing alkyl halides with aryl and heteroaryl Grignard reagents. The catalysis demands only a relatively low loading of catalyst (3 mol %) and is completed within a short period of time (1 h). Primary iodides and bromides and certain secondary iodides can be coupled in high yields. Thanks to the mild conditions employed, the reactions tolerate a wide range of sensitive functional groups. Alkyl halides containing ester, amide, nitrile, ether, thioether, acetal, alcohol, indole, pyrrole, furan, pyrazole, NBoc groups are selectively coupled. Furthermore, functionalized aryl and heteroaryl Grignard reagents, including those of the Knochel-type, could be coupled to nonactivated alkyl halides for the first time. With the demonstration of efficient coupling between functionalized alkyl halides and functionalized Grignard reagents, the work expands significantly the scope of Kumada–Corriu–Tamao coupling, making this atom-economic and cost-effective cross-coupling technology attractive for the construction of more complex molecules and materials. We are currently exploiting further applications of **1** in cross-coupling catalysis and interrogating the mechanistic details of these reactions.

## Experimental Section

**A. Chemicals and Reagents.** All manipulations were carried out under an inert  $\text{N}_2(\text{g})$  atmosphere using standard Schlenk or glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ) and transferred to the glovebox without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless otherwise noted, all other reagents and starting materials were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze–pump–thaw procedures prior to use. Ligand  $\text{H}^{\text{Me}}\text{NN}_2$  and complexes  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (**1**),  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Me}]$ ,  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Ph}]$  (**6**), and  $[(^{\text{Me}}\text{NN}_2)(\text{THF})\text{Mg-Cl}]$  (**7**) were prepared as described previously.<sup>39</sup>

**B. Physical Methods.** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer.  $^1\text{H}$  NMR chemical shifts were referenced to residual solvent as determined relative to  $\text{Me}_4\text{Si}$  ( $\delta = 0$  ppm). The  $^{13}\text{C}\{^1\text{H}\}$  chemical shifts were reported in ppm relative to the carbon resonance of  $\text{CDCl}_3$  (77.00 ppm). GC–MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRESI-MS measurements were conducted at the EPFL

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ISIC Mass Spectrometry Service with a Micro Mass QTOF Ultima spectrometer. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. The temperature of reactions below room temperature was regulated by a Julabo FT-902 chiller. Room temperature ESR measurements were performed using a CW X-band ESR spectrometer (model ESP300E), from Bruker BioSpin GmbH, Karlsruhe, Germany, equipped with a standard rectangular TE102 cavity. Low temperature ESR measurements were performed using a CW X-band ESR spectrometer, Model EleXsys 500, from Bruker BioSpin GmbH, Karlsruhe, Germany, equipped with a Gunn diode-based microwave bridge (model SuperX), super high-Q cylindrical cavity (model ER4122SHQE), and helium gas-flow cryostat (model ESR900), from Oxfords Instruments (Great Britain).

**C. Typical Procedure for the Synthesis of Alkyl-R from Alkyl-X and RMgCl.** Note: For all entries in Tables 3–5, the coupling products were isolated and the yields were determined by the masses of the products. Their identification was achieved by one of the following two methods:

**Method I.** For previously reported or commercially available compounds, their identity and purity were confirmed by comparing their  $^1\text{H}$  and/or  $^{13}\text{C}$  NMR spectra with the reported values. The references to literature data are given.

**Method II.** For new compounds, their  $^1\text{H}$  and  $^{13}\text{C}$  data are reported together with elemental analysis or high resolution mass spectrometric data (within 5 ppm of calculated value).

See Supporting Information for the coupling procedure, separation method, spectroscopic and analytical data for all the products.

**C.1. Typical Procedures for Reactions Shown in Table 2.** A mixture of an alkyl halide (0.5 mmol),  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (5.2 mg, 0.015 mmol), and TMEDA (25  $\mu\text{L}$ , 0.17 mmol) was dissolved in 1 mL of THF. A solution of an aryl Grignard reagent (0.6 mmol) in THF (3 mL) was added dropwise with a syringe pump (1 h) to this solution. After the addition was completed, the reaction mixture was stirred for 1 h. The reaction was quenched with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (15 mL). The resulting solution mixture was then extracted with ether (3 times, 10 mL each), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and subjected to GC analysis. 60  $\mu\text{L}$  of dodecane was used as an internal standard.

**C.2. Typical Procedure for Reactions Shown in Table 3.** A mixture of an alkyl halide (1 mmol),  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (10.4 mg, 0.03 mmol), and TMEDA (50  $\mu\text{L}$ , 0.34 mmol) or O-TMEDA (114  $\mu\text{L}$ , 0.6 mmol) was dissolved in 2 mL of THF (O-TMEDA was used for substrates containing ester or ketone functional group). A solution of an aryl Grignard reagent (1.2 mmol) in 6 mL of THF was added dropwise with a syringe pump (1 h) to the above solution. After the addition was completed, the reaction mixture was stirred for 1 h. The reaction was then quenched with a saturated solution of  $\text{NH}_4\text{Cl}$  (30 mL). The resulting solution mixture was then extracted with ether (3 times, 20 mL each), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica gel.

**C.3. Typical Procedure for Reactions Shown in Tables 4 and 5, Including the Preparation of Functionalized Grignard Reagents in Situ.** **Method A.** To a solution of O-TMEDA (228  $\mu\text{L}$ , 1.2 mmol) in 6 mL of THF was added a 2.0 M solution of  $^{150}\text{PrMgCl}$  (600  $\mu\text{L}$ , 1.2 mmol) at 0  $^\circ\text{C}$ . The mixture was stirred for 20 min and a solution of an aryl iodide or aryl bromide (1 mmol) in 2 mL of THF was added by one portion. The resulting mixture was stirred at room temperature for 10 min and then was added by syringe pump (1 h) to a solution containing an alkyl halide (5 mmol) and  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (10.4 mg, 0.03 mmol) in THF (2 mL). After

the addition was completed, the reaction mixture was stirred for 1 h. The reaction was then quenched with a saturated solution of  $\text{NH}_4\text{Cl}$  (30 mL). The resulting solution mixture was extracted with ether (3 times, 20 mL each), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica gel.

**Method B.** Magnesium (122 mg, 5 mmol) was placed in a vial to which a 0.5 M solution of  $\text{LiCl}$  (5.0 mL, 2.5 mmol) was added. The magnesium was activated by adding a small amount of diisobutylaluminum hydride (20  $\mu\text{L}$ , 1 M in THF, 0.02 mmol). The resulting mixture was stirred for 5 min, and a solution of an aryl iodide or aryl bromide (2 mmol) in 2 mL of THF was added at room temperature. The reaction mixture was stirred for 30 min (or 2 h in case of 4-bromobenzonitrile) and added by syringe pump (1 h) to a solution of an alkyl halide (1 mmol), and  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Cl}]$  (10.4 mg, 0.03 mmol) and TMEDA (50  $\mu\text{L}$ , 0.34 mmol) or O-TMEDA (114  $\mu\text{L}$ , 0.6 mmol) in 2 mL of THF (O-TMEDA was used for substrates containing ester or ketone functional group). After the addition was completed, the reaction mixture was stirred for 1 h. The reaction was quenched with a saturated solution of  $\text{NH}_4\text{Cl}$  (30 mL). The resulting solution mixture was then extracted with ether (3 times, 20 mL each), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica gel.

**D. Mechanistic Investigation.** For catalysis using complexes **6** and **7** as the precatalysts, the same procedures as described in section C.1 were used. Stoichiometric reactions of **6** with  $\text{PhMgCl}$  and octyl-I were carried out under catalytically relevant conditions.

For eq 6,  $[(^{\text{Me}}\text{NN}_2)\text{Ni-Ph}]$  (complex **6**, 20 mg, 0.05 mmol) was dissolved in  $\text{THF-}d_8$  (1 mL), and TMEDA (7.5  $\mu\text{L}$ , 0.05 mmol) and 20 equiv of octyl-I (180  $\mu\text{L}$ , 1 mmol) were added to this solution. The reaction mixture was transferred to an NMR tube and analyzed by NMR.

For eq 7, **6** (20 mg, 0.05 mmol) was dissolved in  $\text{THF-}d_8$  (1 mL), and TMEDA (7.5  $\mu\text{L}$ , 0.05 mmol) was added to this solution. A 2.0 M solution of  $\text{PhMgCl}$  (25  $\mu\text{L}$ , 0.05 mmol) was added in one portion. After the addition was finished, the reaction mixture was transferred to an NMR tube and analyzed by NMR.

For eq 8, **6** (20 mg, 0.05 mmol) was dissolved in  $\text{THF-}d_8$  (1 mL), and TMEDA (7.5  $\mu\text{L}$ , 0.05 mmol) and octyl-I (9  $\mu\text{L}$ , 0.05 mmol) were added to this solution. A 2.0 M solution of  $\text{PhMgCl}$  (25  $\mu\text{L}$ , 0.05 mmol) was then added to the resulting mixture (in one portion for fast addition or dissolved in 1 mL of  $\text{THF-}d_8$  and added with a syringe pump during 20 min for slow addition). After the addition was finished, the reaction mixture was stirred for 15 min, filtered, transferred to an NMR tube, and checked by NMR. After the NMR analysis was finished, the composition of the organic products was checked by GC using 10  $\mu\text{L}$  of dodecane as an internal standard.

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**Supporting Information Available:** Preparation procedures for substrates, additional entries for Table 1, detailed coupling procedures, separation methods, spectroscopic ( $^1\text{H}$  and  $^{13}\text{C}$ ) and analytical data for all the products shown in Tables 3–5. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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