

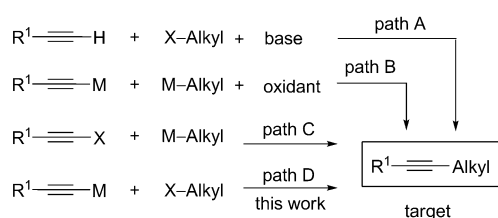
Cross-Coupling of Nonactivated Alkyl Halides with Alkynyl Grignard Reagents: A Nickel Pincer Complex as the Catalyst**

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Alkynes are an important class of organic molecules because they are frequently used as synthetic intermediates and precursors for natural products, biologically active molecules, and organic materials.^[1,2] Alkynes are also essential coupling partners for the azide–alkyne Huisgen cycloaddition reaction.^[3,4] The streamlined synthesis of alkynes containing various functional groups is therefore highly desirable.

Alkynes containing nonactivated alkyl groups, especially those with β -hydrogen atoms, are difficult to synthesize. Reactions of alkali metal acetylides with alkyl halides in liquid ammonia, or with hexamethylphosphoramide (HMPA) as the solvent or cosolvent at a low temperature (e.g., -78°C), have long been used for the alkylation of alkynes. These reactions suffer from the limited solubility of acetylides in liquid ammonia, the carcinogenic effect of HMPA, and the inconvenience of working at low temperatures.

The limitations of uncatalyzed nucleophilic alkylation of alkali metal acetylides motivate the search for alternative, transition-metal-catalyzed alkyl–alkynyl coupling methods. However, the alkyl–alkynyl cross-coupling is among the most challenging coupling reactions for two reasons: 1) the metal alkyl intermediates have a tendency to undergo unproductive β -hydride elimination; 2) the metal alkynyl moieties are weakly nucleophilic and are subject to oxidative dimerization. As a result, only a few methods for alkyl–alkynyl coupling have been reported. These methods can be classified into four categories (Scheme 1).



Scheme 1. Four types of transition-metal-catalyzed cross-coupling methods for the synthesis of alkyl-substituted alkynes. X = halide, M = metal.

The first three paths to an alkylated alkyne are: 1) Coupling of alkyl halides with terminal alkynes under Sonogashira-type conditions (path A, Scheme 1);^[5–7] 2) Palladium-catalyzed oxidative alkyl–alkynyl coupling (path B, Scheme 1);^[8–11] 3) Cross-coupling of alkynyl halides with organometallic alkyl reagents (path C, Scheme 1).^[12–15] Only a small number of protocols have been developed based on these reactions. Thus, the scope remains limited. Furthermore, most of these protocols have one or more of the following drawbacks: 1) Copper-catalyzed or cocatalyzed reactions have a low tolerance for functional groups that have a high affinity for copper, such as sulfur-containing groups; 2) Oxidative coupling so far requires two organometallic reagents as coupling partners, or excess amounts of alkyl zinc reagents; 3) Functionalized alkyl Grignard reagents are scarce.

A fourth method for constructing the alkyl–alkynyl bond is the coupling of nonactivated alkyl halides with alkynyl organometallic reagents (path D, Scheme 1). Despite recent progress in the cross-coupling of nonactivated alkyl electrophiles,^[16–21] there are only two prior reports of successful cross-coupling reactions of nonactivated alkyl halides with alkynyl Grignard reagents.^[22,23] Only a narrow range of alkynyl Grignard reagents could be used, namely phenylethynyl- and trimethylsilylethynyl magnesium halide (Br, I) for the palladium-based system, and trimethylsilylethynyl magnesium bromide for the cobalt-based system.

We find that by using a well-defined nickel pincer complex^[24–26] as the catalyst, general and efficient cross-coupling of nonactivated alkyl halides with alkynyl Grignard reagents can be achieved. Herein, we describe the development of this nickel-catalyzed coupling method, the exploration of its scope, and the investigation of its mechanism.

The coupling of *n*-octyliodide with 1-propynyl magnesium bromide was chosen as the test reaction (Table 1). Surprisingly, the reported palladium- and cobalt-based methods failed to effect this seemingly simple coupling reaction.^[27] No reaction occurred between the two substrates in the absence of a catalyst or additive after 1 hour in THF at room temperature (entry 1, Table 1). Amines are known to promote the reactivity of metal acetylides,^[23] therefore upon addition of a chelating amine, bis[2-(*N,N*-dimethylamino-ethyl)]ether (O-TMEDA) there was an increase in the conversion of *n*-octyliodide to 31%. However, the yield of the cross-coupling product was only 3% (entry 2, Table 1). Upon adding 5 mol % of [(^{Me}N₂N)NiCl] (**1**, Nickamine)^[28–30] as the catalyst, the conversion was 38%, and the yield of the cross-coupling product was 20% (entry 3, Table 1). The combination of the catalyst **1** and an amine additive (TMEDA or O-TMEDA) significantly improved both the

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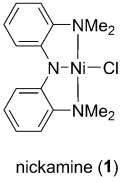
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Table 1: Optimization of the reaction conditions for the coupling of *n*-octyliodide with 1-propynyl magnesium bromide.^[a]

$\text{CH}_3\text{—C}\equiv\text{C—MgBr} + \text{I—}n\text{Oct}$
 1.2 equiv

$\xrightarrow[\text{THF, RT, 1–3 h}]{\text{conditions}}$

$\text{CH}_3\text{—C}\equiv\text{C—}n\text{Oct}$


 nickamine (1)

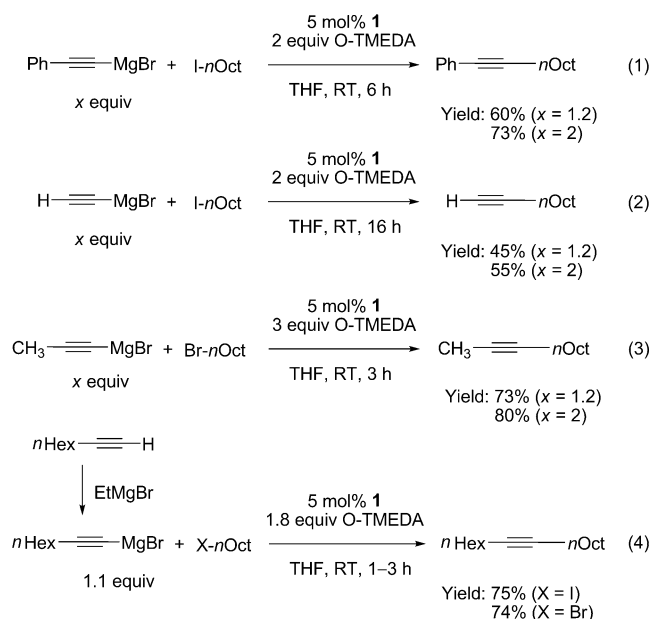
Entry	Conditions	Conversion ^[b] [%]	Yield ^[c] [%]
1	no catalyst, no additive ^[d]	0	0
2	2 equiv of O-TMEDA	31	3
3	5 mol % 1 , no additive	38	20
4	5 mol % 1 , 2 equiv of TMEDA	68	44
5	5 mol % 1 , 2 equiv of O-TMEDA	85	68
6	5 mol % 1 , 3 equiv of O-TMEDA ^[d]	100	93

[a] Reaction conditions unless otherwise specified: 1-propynyl magnesium bromide (0.6 mmol) was added over a 1 h period to a THF solution of [(ⁱMeN₂N)Ni-Cl] (0.025 mmol), O-TMEDA, and *n*-octyliodide (0.5 mmol). [b] Conversion of *n*-octyliodide. [c] Yield as determined by GC analysis of the crude reaction mixture using decane as an internal standard. [d] Addition of Grignard reagent at once.

conversion and yield (entries 4 and 5, Table 1). O-TMEDA is a better additive than TMEDA (compare entries 4 and 5, Table 1). Additional optimization showed that the best result for this reaction was achieved using 5 mol % of **1** and 3 equivalents of O-TMEDA (entry 6, Table 1).^[31] The Grignard reagent could be added at once, which gave a slightly better yield than adding it over a period of 1 hour. Under these reaction conditions, the conversion was 100 % and the yield was 93 %. Additional details on the influence of various reaction parameters on the transformation can be found in Table S1 in the Supporting Information.^[31]

Several additional test reactions were carried out to examine the generality of this catalytic system. With some minor modifications, the optimized protocol used in Table 1 could be extended to other substrates (Scheme 2).^[31] The coupling of *n*-octyliodide with 2-phenylethynyl magnesium bromide required 6 hours [Eq. (1), Scheme 2]. The slower reaction rate is likely due to the reduced nucleophilicity of aryl-substituted alkynyl anions. Interestingly, ethynyl magnesium bromide was coupled to give a terminal alkyne in a modest yield [Eq. (2), Scheme 2]. This reaction obviates the need of protecting groups for alkynes, and provides easy access to alkyl-substituted terminal alkynes. The coupling of *n*-octylbromide with 1-propynyl magnesium bromide was complete after 3 hours [Eq. (3), Scheme 2]. For these three reactions, the employment of an excess of the Grignard reagent was slightly beneficial.

Commercially unavailable alkynyl Grignard reagents are normally synthesized by reaction of a terminal alkyne with EtMgBr. These in situ prepared alkynyl Grignard reagents are also suitable coupling partners. For example, cross-coupling of 1-octynyl magnesium bromide with *n*-octylhalide (Br, I) proceeded with yields of approximately 74 % [Eq. (4), Scheme 2]. Unfortunately, *n*-octylchloride or secondary alkyl iodides like cyclohexyliodide could not be coupled.



Scheme 2. Optimized reaction conditions for testing reactions of catalytic alkyl–alkynyl cross-coupling. Reported yields were determined by GC analysis of the reaction mixture using decane as an internal standard.

After establishing the nickel-catalyzed alkyl–alkynyl Kumada coupling method, we explored its scope. As shown in Table 2 and Table S2 in the Supporting Information, a wide range of nonactivated alkyl iodides and bromides are suitable substrates. Modest to high yields (45–91 %) of isolated products were obtained within 1–6 hours at room temperature. Not only robust chloride and ether groups (entries 1–3, Table S2),^[31] but also sensitive amide, ester, and nitrile groups (entries 1–5, Table 2; entries 4–6, Table S2) were tolerated. Amine groups did not pose a problem, regardless of whether they were Boc protected (entries 6 and 7, Table 2; entry 7, Table S2), or present as a tertiary amine (entry 8, Table 2). Acetal and olefinic groups did not interfere with the coupling (entries 9 and 10, Table 2). Gratifyingly, substrates containing important N and O heterocycles were successfully coupled (entries 11–13, Table 2; entries 8 and 9, Table S2). An aromatic enone was also coupled (entry 14, Table 2). Sulfur-containing thioether and thiophene groups could be tolerated (entries 3, 15, and 16, Table 1). The scope of the alkynyl coupling partner is impressive. Alkyl-, aryl-, vinyl-, and silyl-substituted alkynyl Grignard reagents were all readily coupled. The alkynyl coupling partner can contain various sensitive functional groups. The results show that functionalized alkynyl Grignard reagents are easily prepared, stable, and attractive reagents for cross-coupling reactions.

One major advantage of this nickel catalysis is its high functional group tolerance. It is sometimes possible to find conditions for alkylation of lithium acetylides in THF at room or elevated temperature even without HMPA.^[32] In our hands, reaction of 1-hexynyllithium (prepared by deprotonation of 1-hexyne with *n*BuLi) with octyliodide took place slowly to give 5-tetradecyne in a yield of 84 % after 24 hours [Eq. (S1) in the Supporting Information].^[31] However, this

Table 2: Cross-coupling of nonactivated alkyl halides with alkynyl Grignard reagents.^[a]

$R^1 \equiv \text{MgBr} + \text{X-Alkyl} \xrightarrow[\text{THF, RT, 1-6 h}]{5 \text{ mol\% } \mathbf{1}, 1.5-3 \text{ equiv O-TMEDA}}$		$R^1 \equiv \text{Alkyl}$	
Entry	X-Alkyl	Product	Yield ^[b] [%]
1			69
2			78
3			73
4			45
5			56
6			73
7			90
8			70
9			77
10			83
11			91
12			65
13			85
14			52
15			88
16			54

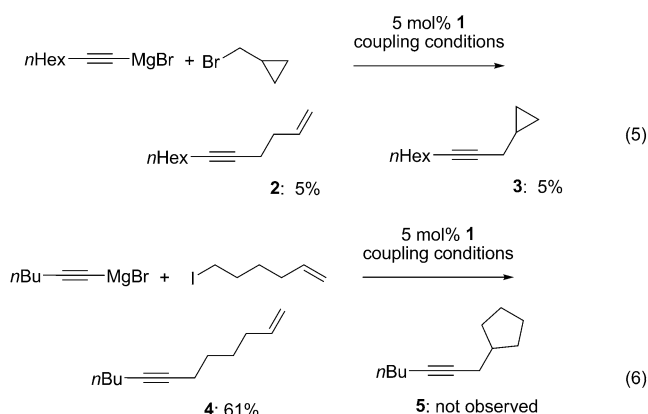
[a] See the Supporting Information for experimental details. [b] Yield of isolated product. Boc = *tert*-butoxycarbonyl.

type of alkylation method is not efficient using alkyl bromides. Reaction of 1-octynyllithium with octylbromide gave 7-hexadecyne in a yield of only 8% after 24 h [Eq. (S2)].^[31] The biggest drawback of this alkylation method is its poor functional group tolerance. For example, reaction of 1-octynyllithium with an ester-containing substrate, ethyl 4-iodobutanoate, gave no coupling product [Eq. (S3)].^[31]

We reported earlier that complex **1** was an efficient catalyst for nickel-catalyzed Sonogashira coupling of non-activated alkyl halides with terminal alkynes.^[7] The Sonogashira method required a temperature of 100 °C to 140 °C whereas the present Kumada coupling method can be conducted at room temperature. As a consequence, the Kumada coupling is significantly more tolerant. For example, indoles containing an H atom at the 2-position could not be used for the Sonogashira coupling, but could be used for the Kumada coupling (entries 12 and 16, Table 2; entry 9, Table S2). Furthermore, because no copper cocatalyst is required for the Kumada coupling, sulfur-containing groups are now tolerated (entries 3, 15, and 16, Table 2). The improved group compatibility is important for applications in medicinal and materials chemistry.

A number of experiments were conducted to give insight into the mechanism of the nickel catalysis. The mercury test suggests that the catalysis is homogeneous, that is, in the presence of 100 equivalents of mercury (relative to the catalyst), a coupling reaction gave a nearly identical yield of product as the reaction conducted without mercury.^[31]

Activation of alkyl halides in nickel-catalyzed cross-coupling reactions often proceeds through a radical mechanism.^[16,20,21,33,34] To ascertain that this is the case for the current nickel catalysis, coupling reactions with radical-probe-type substrates were carried out (Scheme 3). The


Scheme 3. Nickel-catalyzed alkyl-alkynyl Kumada coupling of radical-probe-type substrates.

reaction of cyclopropylmethylbromide with octynyl magnesium bromide gave both **2** and **3** as the cross-coupling products, albeit with low yields [Eq. (5), Scheme 3]. The reaction of 1-iodo-5-hexene with hexynyl magnesium bromide gave **4**, but not **5**, as the coupling product [Eq. (6),

Scheme 3]. These results suggest that alkyl halides are also activated through a radical mechanism. The recombination of the alkyl radical with the catalyst has a rate that is comparable to the ring-opening rearrangement of the cyclopropylmethyl radical, which has a first-order rate constant of 10^8 s^{-1} .^[35] The recombination is much faster than the ring-closing rearrangement of 5-hexenyl radical, which has a first-order rate constant of 10^5 s^{-1} .^[35]

To probe as to whether nickel/alkynyl species are intermediates in the catalysis, $[(^{\text{Mc}}\text{N}_2\text{N})\text{Ni}-\text{C}\equiv\text{CCH}_3]$ (**6**) was synthesized. The identity of **6** was confirmed by X-ray crystallography, which revealed the square-planar structure of **6** (Figure 1). Using 5 mol% of **6** as the catalyst, the

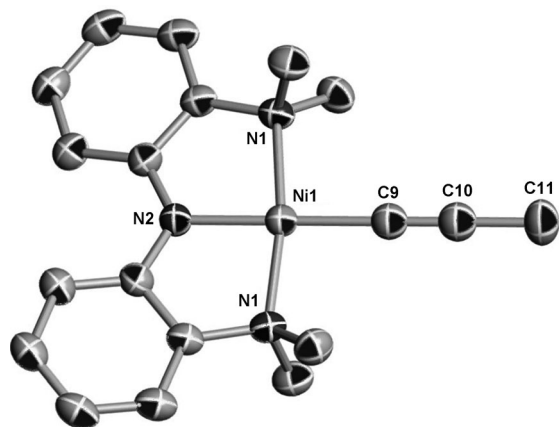
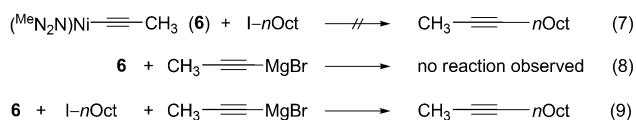


Figure 1. Molecular structure of complex **6**. The thermal ellipsoids are displayed in 50% probability. Selected bond lengths [Å] and angles [deg.]: Ni1–N1 1.9703(17), Ni1–N2 1.853(3), Ni1–C9 1.890(4); C9–C10 1.193(6); N2–Ni1–C9 180.0, Ni1–C9–C10 180.0.^[37]

coupling of *n*-octyl iodide with 1-propynyl magnesium bromide gave an 86% yield of 2-undecyne, a yield that is comparable to the result obtained using **1** as the catalyst (entry 6, Table 1). Therefore, a nickel/alkynyl species is likely involved in the catalytic cycle.

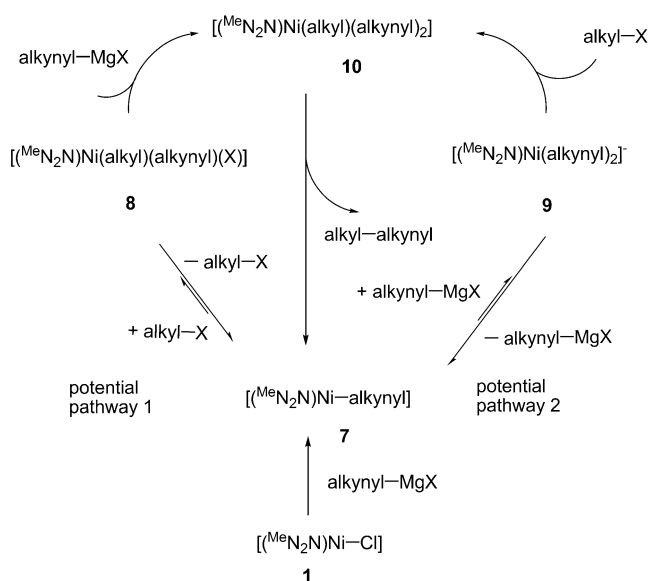
Under catalytically relevant conditions (in the presence of O-TMEDA, in THF at room temperature), the reaction of **6** with *n*-octyl iodide did not give 2-undecyne [Eq. (7), Scheme 4]. In fact, no reaction was observed that would be kinetically relevant to the catalysis. And no reaction was



Scheme 4. Stoichiometric reactions of complex **6**. All reactions were conducted in the presence of 1 equiv of O-TMEDA.

observed by NMR analysis of a mixture of **6** and 1-propynyl magnesium bromide [Eq. (8), Scheme 4]. However, when equal amounts of **6**, *n*-octyl iodide, and 1-propynyl magnesium bromide were mixed in THF, 2-undecyne was produced in a 73 % yield [Eq. (9), Scheme 4].

Based on the aforementioned results, a catalytic cycle can be proposed (Scheme 5). Reaction of the complex **1** with an



Scheme 5. Proposed catalytic cycles for the nickel-catalyzed alkyl–alkynyl coupling reactions.

alkynyl Grignard reagent yields the nickel/alkynyl complex **7**. There are two possible reactions of **7** that would lead to the key intermediate species **10**. In the potential pathway 1, **7** reacts with an alkyl halide to form a [Ni(alkyl)(alkynyl)] species (**8**), which is transmetalated by the alkynyl Grignard reagent to form **10**. In pathway 2, **7** reacts with a second molecule of the Grignard reagent to form a nickel/bis-(alkynyl) species (**9**). **9** has enhanced nucleophilicity compared to **7**, and it reacts with the alkyl halide to give the intermediate **10**. Reductive elimination from **10** produces the alkyl-alkynyl coupling product and regenerates **7**. According to Equations (7) and (8), the transformation from **7** into **8** or **9** must be thermodynamically uphill, and thus cannot be observed in stoichiometric reactions. The role of O-TMEDA may be multifold. It may coordinate to Mg and activate the Grignard reagents for transmetalation. In the case of functionalized alkynyl Grignard reagents, it may stabilize the reagents against decomposition. It may suppress homocoupling, as found in nickel-catalyzed alkyl-aryl coupling.^[25] The details of the mechanism are the subject of a future study.

In summary, we have disclosed the first general nickel-catalyzed cross-coupling of nonactivated alkyl halides with alkynyl Grignard reagents. The wide scope and high functional group tolerance makes the method attractive for the streamlined preparation of alkynes containing nonactivated alkyl groups. At this moment, only primary alkyl halides can be coupled. Methods to couple secondary alkyl halides are currently being developed in our lab.^[36]

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