

# Ni-Catalyzed Regioselective Three-Component Coupling of Alkyl Halides, Arylalkynes, or Enynes with Ar-M (M = MgX, ZnX)

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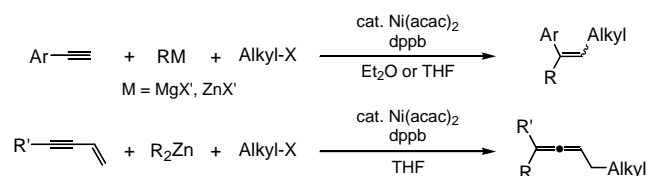
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A new method for the regioselective three-component cross-coupling of alkyl halides, alkynes, or enynes with organomagnesium or organozinc reagents in the presence of a nickel catalyst and a dppb ligand has been developed.

Transition-metal-catalyzed C-C bond formation via the reaction of organic halides with organometallic reagents or unsaturated hydrocarbons has been extensively studied and used in many applications in the field of organic chemistry.<sup>1</sup> These reactions are generally initiated by the oxidative addition of halides to low-valent metals such as Ni(0) and Pd(0); however, the scope of halides as substrates is restricted, partly because of the slow oxidative addition of alkyl halides to metal complexes and the facile  $\beta$ -elimination from the alkyl metal intermediates. With the aim of increasing the applicability of alkyl halides in transition-metal-catalyzed reactions, we recently developed a new method for the generation of alkyl radical species from a variety of alkyl halides (Alkyl-X; Alkyl = primary, secondary, or tertiary alkyl group; X = Cl, Br, or I) by single-electron transfer from anionic Ti and Ni complexes and successfully used this method for C-C bond formation among alkyl halides, unsaturated hydrocarbons, and Grignard reagents.<sup>2</sup> The addition of a variety of alkyl halides containing Cl, Br, and I to primary, secondary, and tertiary alkyl groups proceeds smoothly. However, the unsaturated hydrocarbon substrates that can be used in this reaction are restricted to styrenes and 1,3-butadienes. As an extension of these studies, we discuss herein the regioselective three-component coupling<sup>3</sup> of alkyl halides, arylalkynes, or enynes with organomagnesium or organozinc reagents by the combined use of a catalytic amount of Ni(acac)<sub>2</sub><sup>4</sup> and a phosphine ligand, bis(diphenylphosphino)butane (dppb) (Scheme 1).



Scheme 1

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We initially investigated the addition of phenylacetylene (0.5 mmol) to *t*-butyl iodide (1 mmol) and an ether solution of methylmagnesium bromide (MeMgBr; 1.0 mmol, 1.0 mL) in the presence of Ni(acac)<sub>2</sub> (0.08 mmol) and dppb (0.10 mmol). The reaction was completed within 1 h (at 25 °C) and afforded the coupling product **1a**, which possessed a methyl group at the benzylic carbon and a *t*-butyl group at the terminal carbon of the phenylacetylene unit, in 86% GC yield with perfect regio- and stereoselectivity. The crude product was purified by silica gel column chromatography using pentane as the eluent to afford pure **1a** in 73% yield. Increase in the reaction time did not lead to isomerization of the double bond in the product. When dppb was replaced with PPh<sub>3</sub>, dppe, dppp, dppf, and xantphos, **1a** was isolated in moderate yields (17%, 59%, 61%, 38%, and 56%, respectively). Under identical reaction conditions, 2-naphthyl, 3-tolyl, 4-methoxyphenyl, 4-perfluoromethylphenyl, and 2-thionyl substituted alkynes also gave the corresponding three-component coupling products in good yields (runs 2–8, 10). Tertiary alkyl bromides and

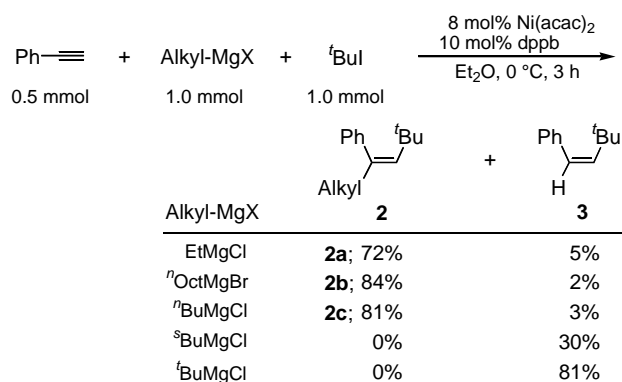
**Table 1** Ni-catalyzed regioselective three-component coupling of alkyl halides, arylalkynes, and R-M (M = MgX, ZnX)<sup>a</sup>

run	Ar	R-M	Alkyl-X	yield (%) <sup>b</sup> [E/Z] <sup>c</sup>
1	Ph	Me-MgBr	<sup>t</sup> Bu-I	<b>1a</b> 73 [0/100]
2	2-Naphtyl	Me-MgBr	<sup>t</sup> Bu-I	<b>1b</b> 79 [0/100]
3		Me-MgBr	<sup>t</sup> Bu-Br	<b>1b</b> 60 [0/100]
4		Me-MgBr	<sup>s</sup> Bu-I	<b>1c</b> 54 [3/97]
5		Me-MgBr	<sup>n</sup> Bu-I	<b>1d</b> 7 [15/85]
6	3-MeC <sub>6</sub> H <sub>4</sub>	Me-MgBr	<sup>t</sup> Bu-I	<b>1e</b> 77 [0/100]
7	4-MeOC <sub>6</sub> H <sub>4</sub>	Me-MgBr	<sup>t</sup> Bu-I	<b>1f</b> 78 [0/100]
8	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Me-MgBr	<sup>t</sup> Bu-I	<b>1g</b> 68 [0/100]
9	Ph	PhCH <sub>2</sub> -MgCl	<sup>t</sup> Bu-I	<b>1h</b> 64 [0/100]
10	2-Thionyl	PhCH <sub>2</sub> -MgCl	<sup>t</sup> Bu-I	<b>1i</b> 80 [0/100]
11	Ph	Ph <sub>2</sub> Zn	<sup>t</sup> Bu-I	<b>1j</b> 82 [0/100]
12	3-MeCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph <sub>2</sub> Zn	<sup>t</sup> Bu-I	<b>1k</b> 68 [2/98]
13	3-NCC <sub>6</sub> H <sub>4</sub>	Ph <sub>2</sub> Zn	<sup>t</sup> Bu-I	<b>1l</b> 56 [4/96]
14	3-MeCOC <sub>6</sub> H <sub>4</sub>	Ph <sub>2</sub> Zn	<sup>t</sup> Bu-I	<b>1m</b> 40 [3/97]
15	Ph	4-EtCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ZnCH <sub>2</sub> TMS	<sup>t</sup> Bu-I	<b>1n</b> 47 [0/100]

<sup>a</sup> Ni(acac)<sub>2</sub> (0.08 mmol), dppb (0.10 mmol), aryl alkyne (0.5 mmol), Grignard reagent (1.0 mmol, 1 M in Et<sub>2</sub>O) or organozinc reagent (1.0 mmol, 1 M), and alkyl halide (1.0 mmol), 25 °C, 1 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by GC.

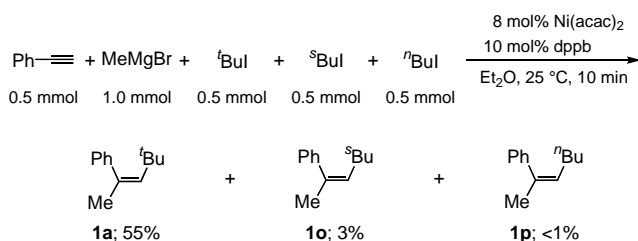
secondary alkyl iodides also gave the corresponding addition products in good yields (runs 3 and 4), whereas the desired coupling product was obtained in a poor yield (7%) when *n*-butyl iodide was used (run 5). The use of a benzyl Grignard reagent also afforded the corresponding products in good yields (runs 9 and 10). The reaction also proceeded readily when arylzinc halides were employed instead of Grignard reagents (run 11). This catalytic system was found to tolerate unsaturated heteroatom functional groups such as esters, nitriles, and ketones (runs 12–15).

Alkyl Grignard reagents having a  $\beta$ -hydrogen are also suitable for use in the proposed cross-coupling reaction (Scheme 2). In this reaction, two different alkyl groups can be introduced at adjacent alkyne carbons with good regio- and stereoselectivity. It is also noteworthy that the hydroalkylation product **3** is selectively formed when *s*- and *t*-butyl Grignard reagents are used. However, there is no evidence for the formation of the three-component coupling product **2**.



**Scheme 2**

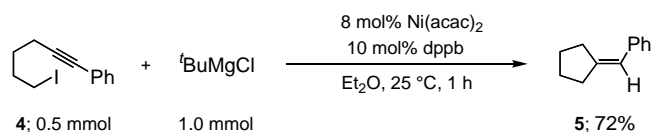
We carried out control experiments to elucidate the reaction pathway. First, we examined the relative reactivities of alkyl halides via competitive experiments. To a mixture of phenylacetylene (0.5 mmol), Ni(acac)<sub>2</sub> (8 mol%), dpbb (10 mol%), and equimolar amounts of *n*-, *s*-, and *t*-butyl iodides (0.5 mmol) were added an ether solution of MeMgBr (1.0 mmol, 1 mL) (Scheme 3). After stirring for 10 min, **1a**, **1o**, and **1p** were formed in 55%, 3%, and <1% yields, respectively. This result indicated the conversion of the alkyl groups into radical or cationic species.



**Scheme 3**

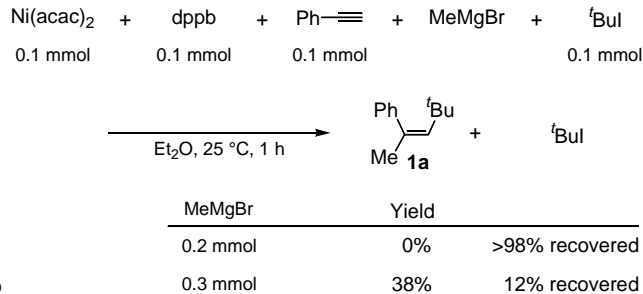
In order to examine the possibility of the coupling reaction proceeding via a radical mechanism, the reaction of 6-iodo-1-phenyl-1-hexyne **4** with a *t*-butyl Grignard reagent was carried out. This reaction afforded cyclopentylidenemethylbenzene **5** in 72% yield (Scheme 4). The formation of **5** strongly

suggested the possibility of a radical mechanism, i.e., 5-exo cyclization of the 6-hexynyl radical to afford the cyclopentylidenemethyl radical in the C-C bond forming step.<sup>5</sup>



**Scheme 4**

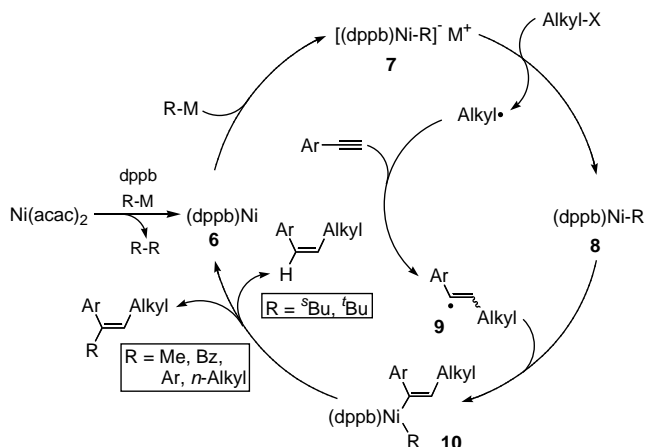
In this reaction system, (dpbb)Ni(0) was assumed to be formed in situ by the reductive coupling of NiMe<sub>2</sub> and subsequent coordination with the dpbb ligand. Since under the present catalytic conditions, oxidative addition of alkyl halides to Ni(0) could proceed via a radical pathway,<sup>6</sup> we investigated the reaction of (dpbb)Ni(0), which was formed by the in situ reaction of Ni(acac)<sub>2</sub> with 2 eq MeMgBr in the presence of dpbb, with *t*-butyl iodide and phenylacetylene (Scheme 5). After stirring for 1 h at 25 °C, the reaction was quenched with 1 N aqueous HCl. GC and NMR analysis of the resulting mixture confirmed that no alkylation products were formed, and *t*-butyl iodide was recovered intact. On the other hand, when the same reaction was carried out employing 3 eq of MeMgBr (with respect to Ni(acac)<sub>2</sub>), **1a** was obtained in 38% yield, indicating that the addition of excess MeMgBr facilitated the C-I bond cleavage.



**Scheme 4**

Taking into account these results, we propose a possible reaction pathway for the proposed reaction, as shown in Scheme 6. Accordingly, Ni(acac)<sub>2</sub> reacts with R-M (M = MgX, ZnX) and dpbb to generate the zerovalent complex **6**, which further reacts with R-M to afford the nickelate complex **7**. This nickelate complex acts as an active electron-transfer reagent. Electron transfer from **7** to the alkyl halide results in the formation of an alkyl radical, along with the concomitant generation of the nickel(I) complex **8**, the resulting alkyl radical adds to the terminal carbon of the arylalkenes to yield the vinyl radical intermediate **9**. The combination of **8** with **9** affords the allylaryl-Ni(II) intermediate **10**, which then undergoes reductive elimination to afford the three-component coupling product along with **6** to complete the catalytic cycle. The intriguing result shown in Scheme 2 that different products are obtained when using Grignard reagents containing *s*- and *t*-alkyl groups can be explained as follows. In the presence of the aforementioned Grignard reagents, **10**

preferentially undergoes  $\beta$ -hydrogen elimination to afford a hydroalkylation product rather than reductive elimination to afford the three-component coupling product.



**Scheme 5**

We found that enynes efficiently underwent the proposed three-component coupling reaction as well.<sup>8</sup> For example, the reaction of 4-phenyl-1-buten-3-yne (0.5 mmol) with dimethylzinc (1.0 mmol, 1 M in THF) and *t*-butyl iodide (0.6 mmol) at 25 °C for 12 h afforded the three-component coupling product **11a**, which had a methyl group at the benzylic carbon and a *t*-butyl group at the terminal olefinic carbon, in 77% yield (Table 2, run 1). Alkyl substituted enynes also afforded the desired product in good yields (runs 15 2–8). This reaction also proceeded satisfactorily when *sec*-alkyliodides, *n*-alkyliodides, *t*-alkylbromides, and *sec*-alkylbromides were used (runs 2–5). The use of benzyl, allyl, and *n*-butyl zinc reagents also afforded the corresponding products in good yields (runs 6–8).

## Conclusions

We have developed a nickel-catalyzed regioselective three-component reaction for the one-pot coupling of alkyl halides, arylacetylenes, or enynes with organomagnesium or organozinc reagents. In this reaction, alkyl radical species are generated in situ from a variety of alkyl halides by single electron transfer from a nickelate complex. The present reaction involves two different C-C forming steps: (1) the addition of alkyl radicals to unsaturated C-C bonds and (2) reductive elimination of Ni(II) intermediates. This reaction is expected to act as a scaffold for the development of novel transition-metal-catalyzed radical reactions.

## Notes and references

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**Table 2** Ni-Catalyzed regioselective three component coupling reaction of alkyl halides, enynes, and  $R_2Zn$ <sup>a</sup>

run	R	R'	Alkyl-X	yield (%) <sup>b</sup>
1 <sup>c</sup>	Ph	Me	<sup>t</sup> Bu-I	<b>11a</b> 77
2 <sup>c</sup>	<sup>n</sup> Hex	Me	<sup>s</sup> Bu-I	<b>11b</b> 78
3 <sup>d</sup>	<sup>n</sup> Hex	Me	<sup>n</sup> Bu-I	<b>11c</b> 50
4 <sup>d</sup>	<sup>n</sup> Hex	Me	<sup>t</sup> Bu-Br	<b>11d</b> 70
5 <sup>e</sup>	<sup>n</sup> Hex	Me	<sup>s</sup> Bu-Br	<b>11b</b> 60
6 <sup>c</sup>	<sup>n</sup> Hex	PhCH <sub>2</sub>	<sup>t</sup> Bu-I	<b>11e</b> 54
7 <sup>c</sup>	<sup>n</sup> Hex	CH <sub>2</sub> =CHCH <sub>2</sub>	<sup>t</sup> Bu-I	<b>11f</b> 56
8 <sup>c</sup>	<sup>n</sup> Hex	<sup>n</sup> Bu	<sup>t</sup> Bu-I	<b>11g</b> 66

<sup>a</sup> Ni(acac)<sub>2</sub> (0.08 mmol), dppb (0.10 mmol), diorganozinc reagent (1.0 mmol, 1 M in THF), and alkyl halide (1.0 mmol)<sup>b</sup> Isolated yield. <sup>c</sup> At 25 °C for 12 h. <sup>d</sup> At 50 °C for 20 h. <sup>e</sup> Refluxing in THF for 12 h.

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