## Ni-catalyzed regioselective three-component coupling of alkyl halides, arylalkynes, or enynes with R-M (M = MgX', ZnX')<sup>†</sup>

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A new method for the regioselective three-component crosscoupling 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  $\beta$ -hydrogen 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 $(acac)_2^4$  and a phosphine ligand, bis(diphenylphosphino)butane (dppb) (Scheme 1).

We initially investigated the addition of phenylacetylene (0.5 mmol) to *tert*-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) (Table 1). 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 *tert*-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-thienyl substituted alkynes also gave the corresponding three-component coupling products in good yields (runs 2, 6-8, 10). Tertiary alkyl bromides and 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 diorganozincs 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 alkynyl carbons with good regio- and stereoselectivity. It is also noteworthy that the hydroalkylation product **3** is selectively formed when *sec-* and *tert*-butyl Grignard reagents are used. However, there is no evidence for the formation of the three-component coupling product **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%), dppb (10 mol%), and equimolar amounts of *n*-, *sec*-, and *tert*-butyl iodides (0.5 mmol) was 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.

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Table 1 Ni-catalyzed regioselective three-component coupling of alkyl halides, arylalkynes, and R–M (M = MgX',  $ZnX')^a$ 

	$Ar \longrightarrow F R-M + Alkyl-X \longrightarrow B mol \% Ni(acac)_2 Ar AlkylM = MgX', ZnX' 25°C, 1 h R 1$						
Run	Ar	R–M	Alkyl–X	Yield (%)	6	$[E/Z]^c$	
1	Ph	Me-MgBr	<sup>t</sup> Bu–I	1a	73	[0/100]	
2	2-Naphthyl	Me-MgBr	<sup>t</sup> Bu–I	1b	79	[0/100]	
3	2-Naphthyl	Me-MgBr	<sup>t</sup> Bu–Br	1b	60	[0/100]	
4	2-Naphthyl	Me-MgBr	<sup>s</sup> Bu–I	1c	54	[3/97]	
5	2-Naphthyl	Me-MgBr	<sup>n</sup> Bu–I	1d	7	[15/85]	
6	$3-MeC_6H_4$	Me-MgBr	<sup><i>t</i></sup> Bu–I	1e	77	[0/100]	
7	4-MeOC <sub>6</sub> H <sub>4</sub>	Me-MgBr	<sup><i>t</i></sup> Bu–I	1f	78	[0/100]	
8	$4-CF_3C_6H_4$	Me-MgBr	<sup><i>t</i></sup> Bu–I	1g	68	[0/100]	
9	Ph	PhCH <sub>2</sub> –MgCl	<sup><i>t</i></sup> Bu–I	1h	64	[0/100]	
10	2-Thienyl	PhCH <sub>2</sub> -MgCl	<sup>t</sup> Bu–I	1i	80	[0/100]	
11	Ph	Ph <sub>2</sub> Zn	<sup>t</sup> Bu–I	1j	82		
12	$3-MeO_2CC_6H_4$	$Ph_2Zn$	<sup>t</sup> Bu–I	1k	68	[2/98]	
13	$3-NCC_6H_4$	Ph <sub>2</sub> Zn	<sup>t</sup> Bu–I	11	56	[4/96]	
14	3-MeOCC <sub>6</sub> H <sub>4</sub>	$Ph_2Zn$	<sup>t</sup> Bu–I	1m	40	[3/97]	
15	Ph	4-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> ZnCH <sub>2</sub> TMS	<sup><i>t</i></sup> Bu–I	1n	47	[0/100]	

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

tput10 mol% dppb
Et <sub>2</sub> O, 0 °C, 3 h
0 mmol
$\begin{array}{ccc} Ph & {}^{t}Bu & Ph & {}^{t}Bu \\ \searrow = / & + & \searrow = / \\ Alkyl & H \end{array}$
2 3
<b>2a</b> ; 72% 5%
<b>2b</b> ; 84% 2%
<b>2c</b> ; 81% 3%
0% 30%
0% 81%

Scheme 2

Ph-==	+ MeMgBr +	t <sub>Rul +</sub> s <sub>Rul +</sub> n <sub>Rul</sub>	8 mol% Ni(acac) <sub>2</sub> 10 mol% dppb			
		Bui Bui Bui		Et <sub>2</sub> O, 25 °C, 10 min		
0.5 mmol	1.0 mmol	0.5 mmol	0.5 mmol	0.5 mmol		
	Ph <sup>f</sup> Bu Me <b>1a</b> ; 55%	+	Ph <sup>s</sup> Bu Me <b>1o</b> ; 3%	+	Ph^Bu )/ Me <b>1p</b> ; <1%	
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 *tert*-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 cyclopentyl-idenemethyl radical in the C–C bond forming step.<sup>5</sup>

In this reaction system, (dppb)Ni(0) was assumed to be formed in situ by the reductive coupling of  $NiR_2$  and



subsequent coordination with the dppb 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 (dppb)Ni(0), which was formed by the *in situ* reaction of Ni(acac)<sub>2</sub> with 2 eq. MeMgBr in the presence of dppb, with *tert*-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 *tert*-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.

Taking into account these results, we propose a possible reaction pathway for the proposed reaction, as shown in Scheme 6. Accordingly,  $Ni(acac)_2$  reacts with R-M





(M = MgX', ZnX') and dppb to generate the zero valent complex 6, which further reacts with R-M to afford the nickelate complex 7.7 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(1) complex 8, the resulting alkyl radical adds to the terminal carbon of the arylalkynes to yield the vinyl radical intermediate 9. The combination of 8 with 9 affords the vinyl-NiR 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 sec- and tert-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.

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 *tert*-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 *tert*-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 2–8). This reaction also proceeded satisfactorily when *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).

We have developed a nickel-catalyzed regioselective threecomponent 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 a

**Table 2** Ni-catalyzed regioselective three component coupling reaction of alkyl halides, enynes, and  $R_2Zn^a$ 

R' <b>-=</b> _∫	+ R <sub>2</sub> Zn ·	+ Alkyl-X —	8 mol % Ni(acac) <sub>2</sub> 10 mol % dppb THF	R' R 11	-Alkyl
Run	R′	R	Alkyl–X	Yield (%	6) <sup>b</sup>
1 <sup>c</sup>	Ph	Me	<sup>t</sup> Bu–I	11a	77
$2^c$	"Hex	Me	<sup>s</sup> Bu–I	11b	78
$3^d$	"Hex	Me	<sup>n</sup> Bu–I	11c	50
$4^d$	"Hex	Me	<sup><i>t</i></sup> Bu–Br	11d	70
5 <sup>e</sup>	"Hex	Me	<sup>s</sup> Bu–Br	11b	60
6 <sup>c</sup>	"Hex	PhCH <sub>2</sub>	<sup>t</sup> Bu–I	11e	54
$7^c$	"Hex	CH <sub>2</sub> =CH	CH <sub>2</sub> <sup>t</sup> Bu–I	11f	56
8 <sup>c</sup>	"Hex	"Bu	<sup>2</sup> <sup>t</sup> Bu–I	11g	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.

new method for the generation of alkyl radical species and is expected to act as a scaffold for the development of novel transition-metal-catalyzed radical reactions.

## Notes and references

- 1 For reviews of transition metal-catalyzed cross-coupling reactions, see: International Symposium on 30 years of the Cross-coupling Reaction, J. Organomet. Chem., 2002, 653(1); Metal-Catalyzed Cross-Coupling Reactions, ed. A. de Meijere and F. Diederich, Wiley-VCH, New York, 2004; Transition Metals for Organic Synthesis, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2004; Handbook of Organopalladium Chemistry for Organic Synthesis, ed. E. Negishi, Wiley-Interscience, New York, 2002.
- 2 For Ti-catalyzed regioselective alkylations of styrenes or butadienes using alkyl halides, see: (a) J. Terao, K. Saito, S. Nii, N. Kambe and N. Sonoda, J. Am. Chem. Soc., 1998, 120, 11822; (b) S. Nii, J. Terao and N. Kambe, J. Org. Chem., 2000, 65, 5291; (c) J. Terao, H. Watabe, M. Miyamoto and N. Kambe, Bull. Chem. Soc. Jpn., 2003, 76, 2209; (d) S. Nii, J. Terao and N. Kambe, J. Org. Chem., 2004, 69, 573; (e) Y. Fujii, J. Terao, Y. Kato and N. Kambe, Chem. Commun., 2008, 5836; (f) J. Terao, Y. Kato and N. Kambe, Chem.-Asian J., 2008, 3, 1472. For Ni three-component coupling reactions using butadienes, Grignard reagents, and alkyl halides, see: (g) J. Terao, S. Nii, F. A. Chowdhury, A. Nakamura and N. Kambe, Adv. Synth. Catal., 2004, 346, 905.
- 3 For Co-catalyzed three-component coupling reactions using dienes, Grignard reagents, and alkyl halides via the generation of alkyl radical species from alkyl halides by single-electron transfer from anionic Co complexes, see: K. Mizutani, H. Shinokubo and K. Oshima, Org. Lett., 2003, 5, 3959.
- 4 For recent reviews of Ni-catalyzed multiple-component coupling reactions, see: (a) J. Montgomery, Acc. Chem. Res., 2000, 33, 467;
  (b) S. Ikeda, Acc. Chem. Res., 2000, 33, 511; (c) M. Kimura, J. Synth. Org. Chem., 2006, 64, 130; (d) M. Jeganmohan and C.-H. Cheng, Chem. Commun., 2008, 3101.
- 5 A. L. J. Beckwith and C. H. Schiesser, Tetrahedron, 1985, 41, 3925.
- 6 It is suggested that the oxidative addition of alkyl halides to Ni(0) may proceed via a radical pathway, see: C. W. Weston, A. W. Verstuyft, J. H. Nelson and H. B. Jonassen, *Inorg. Chem.*, 1977, 16, 1313.
- 7 For magnesium nickelate complexes, see: W. Kaschube, K. R. Pörschke, K. Angermund, C. Krüger and G. Wilke, *Chem. Ber.*, 1988, **121**, 1921.
- 8 For addition of alkyl radical to enynes, see: E. Ghera and S. Shoua, *Tetrahedron Lett.*, 1974, 15, 3843.