Nickel-Catalyzed Regioselective Three Component Coupling Reaction of Alkyl Halides, Butadienes, and Ar-M ($M = MgX, ZnX$)

Jun Terao, Shinsuke Nii, Firoz A. Chowdhury, Akifumi Nakamura,
Nobuaki Kambe*

Department of Molecular Chemistry & Science and Technology Center for Atoms, Molecules and Ions Control, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan
Fax: (+81)-6-6879-7390, e-mail: kambe@chem.eng.osaka-u.ac.jp

Received: February 13, 2004; Accepted: May 25, 2004

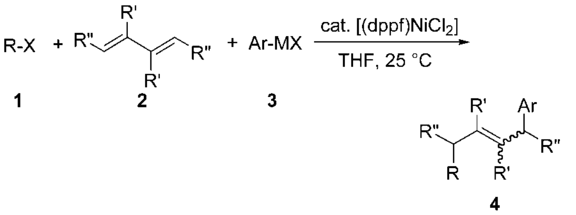
Dedicated to Prof. Noboru Sonoda (Professor Emeritus at Osaka University) on the occasion of his retirement from Kansai University.

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A new method for the regioselective three component cross-coupling reaction of alkyl halides, 1,3-butadienes, and aryl-Grignard reagents has been developed by the use of a nickel catalyst. This reaction proceeds efficiently at 25 °C using (dppf) $NiCl_2$ as a catalyst. Alkyl chlorides, bromides, and iodides can be used as suitable alkylating reagents. The reaction also proceeds when arylzinc halides are used instead of Grignard reagents. Competitive reactions of a mixture of primary, secondary, and tertiary alkyl bromides showed that the reactivities of the halides increase in the order primary < secondary < tertiary. A possible reaction pathway involving single electron transfer from a nickelate complex to alkyl halides is proposed.

Keywords: alkyl halides; butadiene; C–C bond formation; cross-coupling; Grignard reagents; multicomponent reactions; nickel

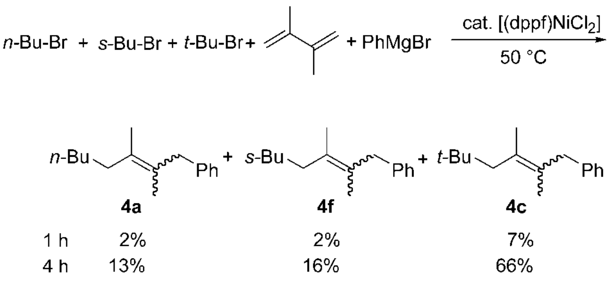
The transition metal catalyzed coupling reaction of organic halides with organometallic reagents or alkenes has been extensively studied and employed in wide areas of organic synthesis.[1] These types of reactions are initiated generally by the oxidative addition of halides to low-valent metals such as Ni^0 and Pd^0 and the scope of the halides as substrates has been limited to aryl, vinyl, allyl, and benzyl halides,[2,3] partly, due to the slow oxidative addition of alkyl halides to metal complexes. Facile β-elimination from the alkylmetal intermediates also restricted the application of alkyl halides. In pursuit of finding novel uses for alkyl halides in transition metal catalyzed reaction, we have recently developed a new type of Ni[4] or Pd[5] catalyzed cross-coupling reaction of alkyl halides with Grignard reagents in the presence of 1,3-butadiene where bisallylmetalate complexes play important roles as active catalytic species. When we examined this reaction using [(dppf)$NiCl_2$], we found an unprecedented three component coupling reaction of alkyl halides, 1,3-butadienes, and arylmagnesium or arylzinc reagents [Eq. (1)].



(1)

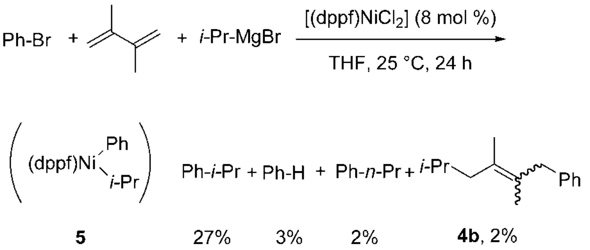
For example, into a mixture of isopropyl bromide (1.2 mmol), 2,3-dimethyl-1,3-butadiene (1 mmol), and [(dppf)$NiCl_2$] (0.08 mmol) was added a THF solution of PhMgBr (1.5 mmol, 1.5 mL). The solution was stirred at 25 °C for 24 h. Usual work-up and NMR analysis of the crude mixture indicated the formation of a coupling product **4b** ($R = i$-Pr, $R' = Me$, $R'' = H$, $Ar = Ph$) bearing isopropyl and phenyl groups at the terminal carbons of the 1,3-butadiene unit in 99% yield by NMR ($E/Z = 67/33$) (Table 1, run 2). The product was obtained in pure form in 91% yield by recycling preparative HPLC using $CHCl_3$ as an eluent. Neither regioisomers of **4b** nor isopropylbenzene (direct coupling product of *i*-PrBr with PhMgBr) were formed. The elongation of reaction time did not lead to isomerization of the double bond of the product. The use of [$(PPh_3)_2NiCl_2$] and [(dppp)$NiCl_2$] in place of [(dppf)$NiCl_2$] afforded **4b** in poor yields (18% and 33%, respectively), along with 2–3% yields of 1,2-adduct as a by-product, while [(dppf)PdCl$_2$] was ineffective. Under similar conditions primary and tertiary alkyl bromides also gave the corresponding addition products in good yields (runs 1 and 3). Phenyl-substituted 1,3-butadienes also gave the coupling products in good yields (runs 4 and 5), but unsubstituted 1,3-butadiene failed to afford the corresponding product. It should be noted that secondary and tertiary alkyl chlorides can also be used as suitable alkylating reagents (runs 6 and 7) whereas the desired coupling product was not obtained when 1-chlorooctane was used. The reaction also proceeded when arylzinc halides were employed instead of Grignard reagents (run 8). This system can allow the introduction of a carbon moiety carrying an ester group (run 9). Under the same conditions, $CH_2{=}CHMgBr$, $PhB(OH)_2$, and $PhC{\equiv}CSn(n\text{-}Bu)_3$ were ineffective.

We carried out some control experiments in order to elucidate the reaction pathway. First we examined the relative reactivities of alkyl halides by competitive experiments. To a mixture of equimolar amounts of *n*-butyl, *s*-butyl, *t*-butyl bromides and 2,3-dimethyl-1,3-butadiene were added a THF solution of PhMgBr (1.5 equivs.) and 8 mol % of [(dppf)NiCl$_2$] [Eq. (2)]. After stirring for 4 h, **4a**, **4f**, and **4c** were formed in 13%, 16% and 66% yields, respectively. This result implies that alkyl groups are transferred as radical or cationic species.



(2)

As shown in Table 1, run 2, the combined use of *i*-PrBr and PhMgBr with 2,3-dimethyl-1,3-butadiene afforded the corresponding coupling product **4b** efficiently. Then we examined the similar reaction depicted in Eq. (3) employing a reverse combination of the reagents, i.e., PhBr and *i*-PrMgCl, under otherwise identical conditions. Interestingly, but not unexpectedly, cumene was formed in 27% yield as the major product probably by Tamao–Kumada coupling *via* an intermediate **5**. The three component coupling product **4b** was formed only in 2% yield along with small amounts of benzene and propylbenzene. This result suggests that the present three component coupling reaction may not proceed through **5**.



(3)

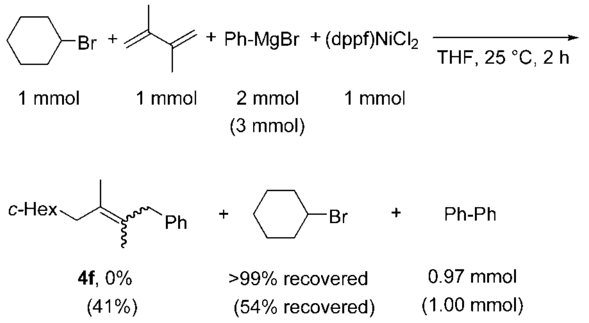
When [(dppf)NiCl$_2$] was treated with two equivalents of PhMgBr at 25 °C for 2 h, biphenyl was obtained in almost quantitative yield. In this reaction system, [(dppf)Ni(0)] is formed in solution by the reductive coupling of [(dppf)NiPh$_2$]. Since oxidative addition of alkyl halides to Ni^0 may take place under these conditions *via* a radical pathway,[6] we then examined the reaction of the thus formed [(dppf)Ni(0)] with a stoichiometric amount of cyclohexyl bromide in the presence of 2,3-dimethyl-1,3-butadiene [Eq. (4)]. After stirring the THF solution for 2 h at 25 °C, the reaction was quenched with 1 N aqueous HCl. GC and NMR analysis of the resulting mixture indicated no formation of alkylation products and cyclohexyl bromide was recovered unchanged. On the other hand, a similar reaction employing one equivalent of additional PhMgBr {i.e., 3 equiva-

Table 1. Ni-catalyzed three component coupling reaction.

Run	R-X	R′	R″	Ar-MX	Isolated yield [%]	[*E/Z*][a]
1	*n*-Bu-Br	Me	H	Ph-MgBr	**4a**; 69	59/41
2	*i*-Pr-Br	Me	H	Ph-MgBr	**4b**; 91	67/33
3	*t*-Bu-Br	Me	H	Ph-MgBr	**4c**; 74	56/44
4	*c*-Hex-Br	Ph	H	Ph-MgBr	**4d**; 73	79/21
5	*c*-Hex-Br	H	Ph	Ph-MgBr	**4e**; 60	100/0
6	*s*-Bu-Cl	Me	H	Ph-MgBr	**4f**; 63	57/43
7	*t*-Bu-Cl	Me	H	Ph-MgBr	**4c**; 81	52/48
8	*c*-Hex-I	Me	H	Ph-ZnCl	**4g**; 72	72/28
9	*t*-Bu-Br	Me	H	*p*-$EtO_2CC_6H_4$-ZnI	**4h**; 69	52/48

Conditions: **1** (1.2 mmol), **2** (1 mmol), **3** (1.5 mmol), [(dppf)NiCl$_2$] (8 mol %), THF (1.5 mL), 25 °C, 24 h.
[a] Determined by GC.

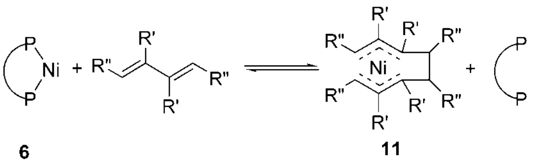
lents to [(dppf)$NiCl_2$]} afforded three component coupling product **4f** (R = *c*-Hex, R′ = Me, Ar = Ph) in 41% yield. This finding indicates that excess PhMgBr does, in fact, promote the C–Br bond cleavage.



(4)

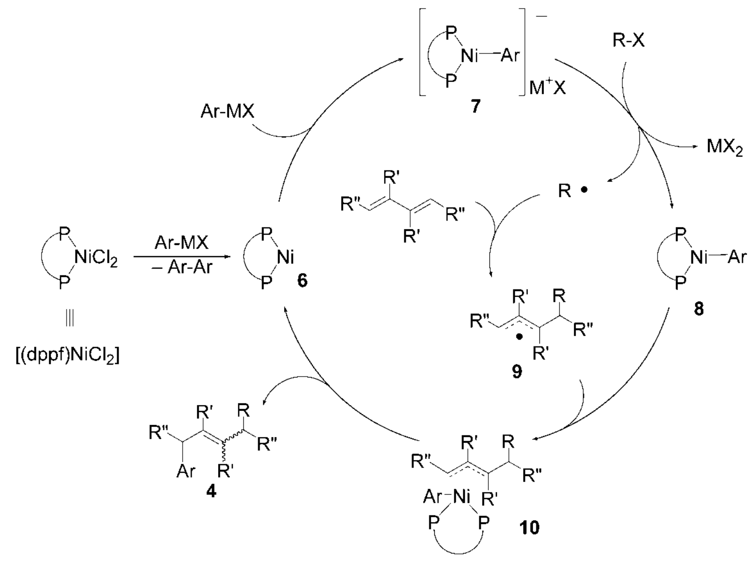
Taking into account these results, we propose the possible reaction pathway shown in Scheme 1. Nickel dichloride reacts with 2 equivalents of Ar-MX (M = Mg, Zn) to generate the zero-valent complex **6**, which reacts with Ar-MX to give the nickelate complex[7] **7**. This ate complex would act as an active electron transfer reagent.[8,9] An alkyl radical is formed by the electron transfer from **7** to alkyl halides with concomitant generation of an arylnickel(I) complex **8**, and adds to the terminal carbon of butadienes yielding an allyl radical intermediate **9**. Combination of **8** with **9** gives allylaryl-Ni(II) intermediate **10** which then undergoes reductive elimination to afford the three component coupling product **4** along with **6** to complete the catalytic cycle.

As mentioned above, the present reaction proceeds efficiently to afford three component coupling products **4** when disubstituted 1,3-butadienes are used, whereas the cross-coupling product (R-Ar) was obtained under the same conditions when unsubstituted 1,3-butadiene or isoprene were employed in the absence of phosphine ligands. These phenomena may be explained as follows, i.e., bidentate dppf ligand is bound strongly on Ni resulting in the suppression of the formation of bis-allylnickel complexes **11** [Eq. (5)], which are key intermediates for the cross-coupling reaction.[4] As for the structures of butadienes, the active catalytic species **6** of the present reaction would be generated efficiently when substituted butadienes are used since formation of **11** from Ni^0 and butadienes becomes thermodynamically less favorable by introduction of substituents on the butadiene skeleton.[10]



(5)

In conclusion, we have developed for the first time a nickel-catalyzed, regioselective three component cross-coupling reaction of alkyl halides, 1,3-butadienes, and ArMgX or ArZnX.[11] In this reaction, alkyl radical species are generated *in situ* from a variety of alkyl halides (R-X; R = primary, secondary, and tertiary alkyl; X = Cl, Br, and I) by single electron transfer from a nickelate complex. This reaction will provide a new method for the generation of alkyl radical species and open up a new field of Ni-catalyzed radical reactions.[12]



Scheme 1. A plausible reaction pathway.

Experimental Section

Three Component Product 4b

To a mixture of isopropyl bromide (149 mg, 1.2 mmol), 2,3-dimethyl-1,3-butadiene (82 mg, 1.0 mmol), and a catalytic amount of [(dppf)NiCl$_2$] (54 mg, 0.08 mmol) was added a THF solution of PhMgBr (1.0 M, 1.5 mL, 1.5 mmol) at 0 °C under nitrogen. After stirring for 24 h at 25 °C, 1 N aqueous HCl was added to the solution. A saturated aqueous NaHCO$_3$ solution (10 mL) was added, and the product was extracted with ether (10 mL). The organic layer was dried over MgSO$_4$, and evaporated to give a pale yellow crude product (99% NMR yield). Purification by HPLC with CHCl$_3$ as an eluent afforded **4b**; yield: 182 mg (91%). ^{1}H NMR showed a mixture of stereoisomers with an *E/Z* ratio of 67/33. IR (neat): $\nu = 2953$, 2866, 1602, 1493, 1452, 1382, 1365, 723 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ (*E* isomer) = 7.28–7.24 (m, 2H), 7.18–7.15 (m, 3H), 3.41 (s, 2H), 2.00 (d, $J = 7.2$ Hz, 2H), 1.88–1.79 (m, 1H), 1.76 (s, 3H), 1.59 (s, 6H), 0.90 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (*E* isomer) = 140.7, 129.2, 128.1, 127.9, 127.4, 125.3, 43.6, 40.5, 27.3, 22.6, 18.9, 18.5; ^{1}H NMR (400 MHz, CDCl$_3$): δ (*Z* isomer) = 7.28–7.24 (m, 2H), 7.18–7.15 (m, 3H), 3.41 (s, 2H), 2.06 (d, $J = 7.2$ Hz, 2H), 1.88–1.79 (m, 1H), 1.70 (s, 3H), 1.57 (s, 6H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ (*Z* isomer) = 140.7, 129.2, 128.2, 127.8, 126.9, 125.3, 43.5, 39.8, 27.3, 22.6, 18.8, 18.4; MS (EI): *m/z* (relative intensity, %) 202 = (M$^+$, 80), 159 (67), 145 (78), 131 (25), 117 (100), 111 (15), 91(42), 69 (13), 43 (16); HR-MS: calcd. for C$_{15}$H$_{22}$: 202.1721; found: 202.1726; anal. calcd. for C$_{15}$H$_{22}$: C 88.78, H 10.85; found: C 89.04, H 10.96.

Acknowledgements

This research was financially supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan. Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for MS and HRMS measurements as well as elemental analyses.

References and Notes

[1] For reviews of transition metal catalyzed cross-coupling reactions, see: a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) International Symposium on 30 years of the Cross-coupling Reaction, *J. Organomet. Chem.*, **2002**, *653*, 1–291; c) *Cross-Coupling Reactions. A Practical Guide*, (Ed.: N. Miyaura), *Top. Curr. Chem.* Vol. 219; Springer, Berlin, **2002**; d) *Metal-catalyzed Cross-coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**.

[2] a) For recent reviews of transition metal-catalyzed cross-coupling reaction of alkyl halides with organometallic reagents, see: D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2003**, *42*, 384–387; b) T.-Y. Luh, M.-K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187–3204; c) D. J. Cárdenas, *Angew. Chem. Int. Ed.* **1999**, *38*, 3018–3020.

[3] For Heck-type reactions of alkyl halides with styrenes, see: Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.*, **2002**, *124*, 6514–6515 and references cited therein.

[4] a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. b) J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647.

[5] J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, *Chem. Lett.*, **2003**, *32*, 890–891.

[6] C. W. Weston, A. W. Verstuyft, J. H. Nelson, H. B. Jonassen, *Inorg. Chem.* **1977**, *16*, 1313–1317.

[7] For magnesium nickelate complexes, see: W. Kaschube, K. R. Pörschke, K. Angermund, C. Krüger, G. Wilke, *Chem. Ber.* **1988**, *121*, 1921–1929.

[8] We have reported several synthetic reactions involving alkyl radical intermediates generated from alkyl halides by single electron transfer from titanate complexes, see: a) J. Terao, K. Saito, S. Nii, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.* **1998**, *120*, 11822–11823; b) S. Nii, J. Terao, N. Kambe, *J. Org. Chem.* **2000**, *65*, 5291–5297; c) J. Terao, N. Kambe, *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1044–1051; d) J. Terao, H. Watabe, M. Miyamoto, N. Kambe, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2209–2214; e) S. Nii, J. Terao, N. Kambe, *J. Org. Chem.* **2004**, *69*, 573–576.

[9] For the generation of alkyl radicals by single electron transfer from a cobaltate complex to alkyl halides and its application to benzyl-substituted heterocycles, see: K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374–5375.

[10] P. W. Jolly, G. Wilke, *The Organic Chemistry of Nickel*, Vol. 2, Academic Press, New York, **1975**.

[11] For the Co-catalyzed three component coupling reaction of alkyl halides, 1,3-dienes, and trimethylsilylmethylmagnesium chloride, see: K. Mizutani, H. Shinokubo, K. Oshima, *Org. Lett.* **2003**, *21*, 3959–3961.

[12] For the Ni-catalyzed radical cyclization, see: A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 5743–5753.