C–C Activation

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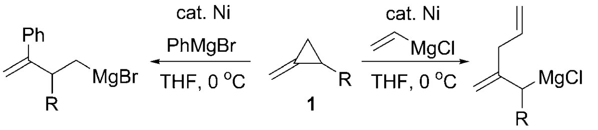
Nickel-Catalyzed Regioselective Carbomagnesation of Methylenecyclopropanes through a Site-Selective Carbon–Carbon Bond Cleavage**

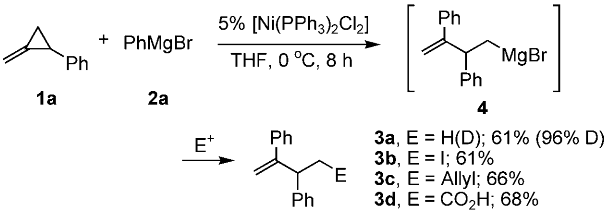
Jun Terao, Masahiro Tomita, Surya Prakash Singh, and Nobuaki Kambe**

Since the discovery of Grignard reagents (RMgX) by the reaction of organic halides (RX) with magnesium metal in 1900, numerous efforts have been devoted to revealing the reactivity of these species and to applying these reagents in organic synthesis. The addition of organomagnesium compounds across carbon–carbon unsaturated bonds (carbomagnesation) is one of the principal and important methods employed for the generation of Grignard reagents with concomitant C–C bond formation; this method provides a straightforward entry into Grignard reagents having a unique carbon skeleton.[1,2] Recently, we have realized the regioselective carbomagnesation of carbon–carbon unsaturated compounds such as alkenes, 1,3-butadienes, alkynes, and enynes with Grignard reagents in the presence of transition-metal "ate" complexes as key catalytic species.[3] We attempted to apply this methodology to methylenecyclopropanes (MCPs), because MCPs are readily accessible[4] and highly reactive unsaturated hydrocarbons which have served as useful building blocks in organic synthesis, especially in transition-metal-catalyzed reactions.[5] We report herein the nickel-catalyzed reaction of MCPs with Grignard reagents, wherein the selective cleavage of the proximal or the distal carbon–carbon bond of the MCPs[6] has been achieved by using Grignard reagents to give the corresponding carbomagnesation products regioselectively [Eq. (1)].



(1)

2-Phenyl-1-methylenecyclopropane (**1a**, 0.5 mmol) was reacted with phenylmagnesium bromide (**2a**, 1.0 mmol, 1 M in THF) in the presence of a catalytic amount of $[Ni(PPh_3)_2Cl_2]$ (0.025 mmol) at 0 °C for eight hours and then an aqueous workup was performed, delivering 2,3-diphenyl-1-butene (**3a**) in 83 % yield as determined by GC methods [Eq. (2)].



(2)

The pure form of **3a** was obtained in 61 % yield by recycling preparative HPLC methods using $CHCl_3$ as an eluent. The selective cleavage of a less sterically hindered proximal C–C bond was observed in this reaction. Under the same reaction conditions, the use of $NiCl_2$, $[Ni(PMe_3)_2Cl_2]$, and $[Ni(dppf)Cl_2]$, instead of $[Ni(PPh_3)_2Cl_2]$, gave **3a** in only 30 %, 20 %, and 11 % yields, respectively. Using $[Pd(PPh_3)_2Cl_2]$ was ineffective. Methyl and allyl Grignard reagents did not undergo this reaction. When the reaction mixture was quenched with D_2O before the usual aqueous workup, monodeutarated **3a** (deuterium content 96 %) was obtained. This result implies that the 2,3-diphenyl-1-butenyl Grignard reagent **4** was formed by the present reaction. Reagent **4** could be trapped with iodine, allyl bromide, and CO_2 to give the corresponding products **3b**, **3c**, and **3d** in 61 %, 66 %, and 68 % yields, respectively.

Table 1 summarizes the representative results obtained using substituted MCPs and aryl Grignard reagents. 4-Methoxyphenylmagnesium bromide (**2b**) gave the corresponding product **3e** in good yield (Table 1, entry 1). The reaction was sluggish with respect to the chloro-substituted phenylmagnesium bromide **2c** (Table 1, entry 2). 4-Tolyl and 2-naphthyl groups on **1** did not affect this reaction system, and the desired products **3g** and **3h** were obtained in 68 % and 62 % yields, respectively (Table 1, entries 3 and 4). An MCP bearing an alkyl substituent gave the corresponding product **3i** in a moderate yield (Table 1, entry 5).

Surprisingly, the use of a vinyl Grignard reagent instead of an aryl Grignard one led to the formation of a different carbomagnesation product through the selective distal C–C bond cleavage reaction of the MCPs. For example, the reaction of **1a** with vinylmagnesium chloride **5a** in the presence of 5 mol % of $NiCl_2$ at 0 °C for three hours with

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[*] Dr. J. Terao
Department of Energy and Hydrocarbon Chemistry
Graduate School of Engineering
Kyoto University, Nishikyo-ku, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2514
E-mail: terao@scl.kyoto-u.ac.jp
Homepage: http://twww.ehcc.kyoto-u.ac.jp/terao/
M. Tomita, Dr. S. P. Singh, Prof. Dr. N. Kambe
Department of Applied Chemistry, Graduate School of Engineering
Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871 (Japan)
E-mail: kambe@chem.eng.osaka-u.ac.jp

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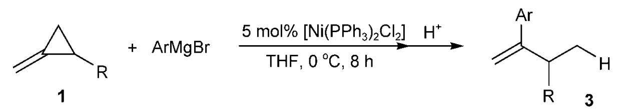
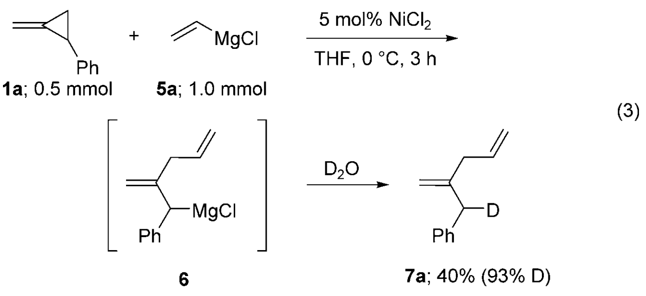
Table 1: Nickel-catalyzed reaction of MCPs with arylmagnesium bromide.[a]



Entry	MCP	Ar	Product	Yield [%][b]
1	**1a**	**2b** (Ar = 4-MeOC$_6$H$_4$)	**3e**	72
2	**1a**	**2c**	**3f**	37[c]
3	**1g** (R = 4-tolyl)	**2a**	**3g**	68
4	**1h** (R = 2-naphthyl)	**2a**	**3h**	62
5	**1i** (R = *n*-hexyl)	**2a**	**3i**	37[d]

[a] Reaction conditions: MCP (0.5 mmol), ArMgBr (1.0 mmol, 1 M in THF), [Ni(PPh$_3$)$_2$Cl$_2$] (0.025 mol), THF (3 mL), 0 °C, 8 h. [b] Yield of isolated product based on MCP. [c] Stirring for 20 h at 10 °C. [d] Stirring for 10 h at −20 °C.

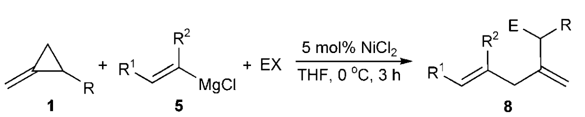
subsequent quenching with D$_2$O yielded monodeuterated **7a** in 40% yield with a deuterium atom at the benzylic position. No evidence was found for the presence of another possible carbomagnesation product arising from the proximal C−C bond cleavage reaction. This result suggests that the allylic benzyl Grignard reagent **6** was formed in situ [Eq. (3)].



(3)

Since it is known that allylic Grignard reagents are more reactive nucleophiles toward chlorosilanes than vinyl Grignard reagents,[7] we carried out the reaction of **1a** (0.5 mmol) with **5a** (1.0 mmol) in the presence of tributylchlorosilane (0.75 mmol) as an electrophile to quench **6** in situ; the same reaction conditions as those in Equation (3) were used for this experiment. As expected, the three-component-coupling product **8a** was formed regioselectively and isolated in 56% yield based on **1a**. NMR and GC analyses of the resulting reaction mixture showed no evidence for the direct coupling of vinyl Grignard reagents with tributylchlorosilane. Optimization of the reaction conditions revealed that use of **1a** (0.75 mmol), **5a** (1.0 mmol), tributylchlorosilane (0.5 mmol), and NiCl$_2$ (0.025 mmol) at 0 °C for three hours afforded coupling products **8a** in 86% upon isolation, based on tributylchlorosilane (Table 2, entry 1). [Ni(acac)$_2$] (acac = acetylacetonate), [Ni(PPh$_3$)$_2$Cl$_2$], and [Ni(dppf)Cl$_2$] (dppf = 1,1-bis(diphenylphosphino)ferrocene) also afforded **8a** in 84%, 63%, and 60% yields, respectively, under the same reaction conditions, indicating phosphine-free conditions are more suitable for the vinylation reaction. PdCl$_2$ was not effective. When 1-bromooctane was employed as an electrophile, the corresponding product **8b** was obtained in 70% yield (Table 2, entry 2). α-Methyl- and β-methyl-substituted vinyl Grignard reagents also underwent the present coupling reaction (Table 2, entries 3 and 4). 2-Naphthyl-, 4-tolyl-, and 4-methoxyphenyl-substituted MCPs also gave the corresponding products in good yield (Table 2, entries 5–7).

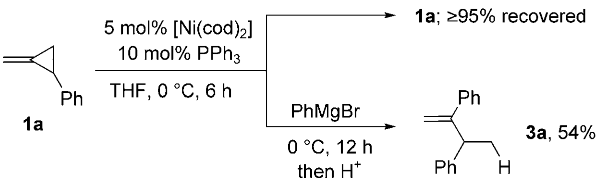
Table 2: Nickel-catalyzed reaction of MCPs with vinylmagnesium chloride in the presence of electrophiles.[a]



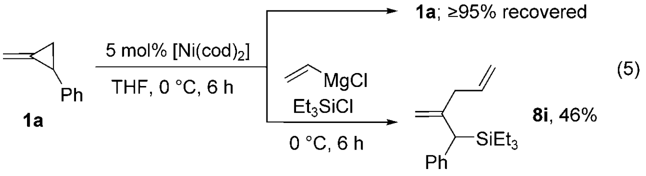
Entry	MCP	R^{1}CH=CR^{2}MgCl	EX	Product	Yield [%][b]
1	**1a** (R = Ph)	**5a** (CH$_2$=CHMgCl)	*n*Bu$_3$SiCl	**8a**	86
2	**1a**	**5a**	*n*OctBr	**8b**	70
3	**1a**	**5c** (CH$_2$=CMeMgCl)	*n*Pr$_3$SiCl	**8c**	72
4	**1a**	**5c** (MeCH=CHMgCl)	*n*Pr$_3$SiCl	**8d**	63
5	**1e** (R = 2-naphthyl)	**5a**	*n*Bu$_3$SiCl	**8e**	73
6	**1g** (R = 4-MeOC$_6$H$_4$)	**5a**	*n*Bu$_3$SiCl	**8f**	87
7	**1h** (R = 4-ClC$_6$H$_4$)	**5a**	*n*Bu$_3$SiCl	**8h**	85

[a] Reaction conditions: MCP (0.75 mmol), R^{1}CH=CR^{2}MgCl (1.0 mmol), EX (0.5 mmol), NiCl$_2$ (0.025 mol), THF (3 mL), 0 °C, 3 h. [b] Yield of isolated product based on EX.

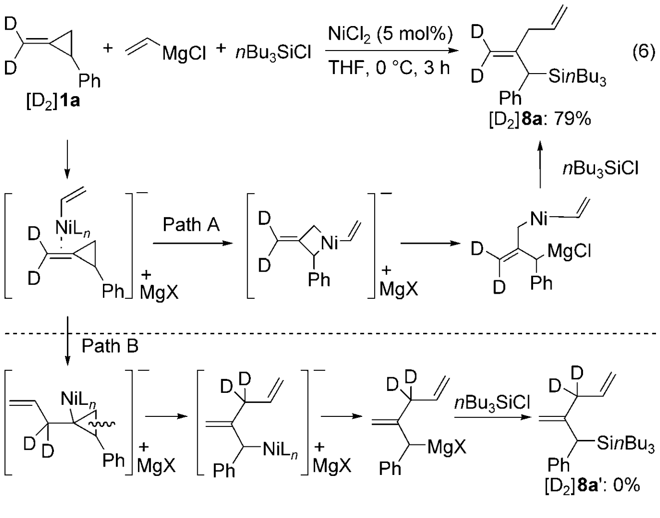
To study the effect of Grignard reagents on the C−C bond-cleavage reaction, we carried out the reaction of **1a** with a catalytic amount of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) in the presence and in the absence of PPh$_3$ [Eqs. (4) and (5)]; the C−C bond-cleavage reaction of a cyclopropane ring of an MCP was reported to occur in the presence of Ni^0 to give oligomerization products.[8] After the THF solution had been stirred for six hours at 0 °C, the reaction was quenched with 1 N HCl (aq.). GC and NMR analyses of the resulting reaction mixture did not indicate the formation of dimerization or oligomerization products, and **1a** was recovered unchanged [Eqs. (4) and (5); top arrow]. In contrast, when PhMgBr or CH$_2$=CHMgCl and Et$_3$SiCl were added to these reaction mixtures, a phenylmagnesation product **3a** and the three-component-coupling product **8i** were obtained in 54% and 46% yields, respectively [Eqs. (4) and (5); bottom arrow]. This result indicates that Grignard reagents promote the C−C bond-cleavage reaction.



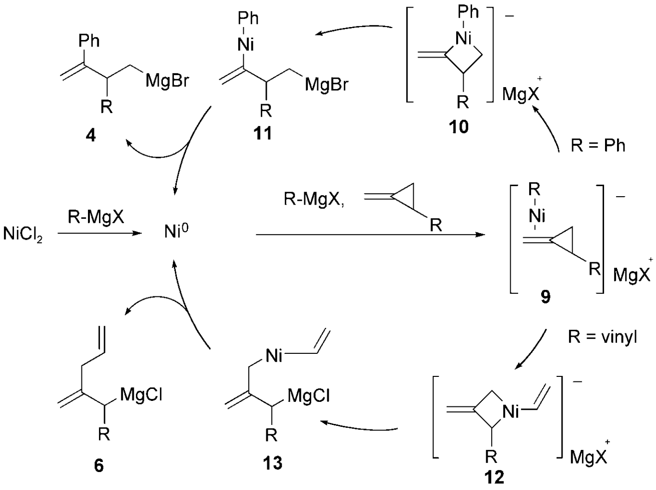
(4)



It is known that the C–C bond-cleavage reaction of MCPs proceeds through the oxidative addition or migratory insertion of a C=C bond and subsequent β-carbon elimination.[5,9] To investigate the reaction mechanism, the following labeling experiment was performed. The reaction of an MCP containing deuterium at the terminal vinylic carbon atom ($[D_2]$**1a**) with a vinyl Grignard reagent and tributylchlorosilane was conducted in THF at 0°C for three hours in the presence of $NiCl_2$. Compound $[D_2]$**8a** was formed in 79% yield with deuterium atoms at the geminal vinylic position [Eq. (6)]. No evidence was found for the formation of $[D_2]$**8a′**, which can possibly be obtained by migratory insertion and subsequent β-carbon elimination (Path B). This result indicates that the present carbomagnesation reaction could proceed through the oxidative addition of a C–C bond of an MCP to a Ni catalyst (Path A).



Although the detailed mechanism of the present carbomagnesation reaction has not yet been clarified, we would like to propose the reaction pathways as shown in Scheme 1. $[L_nNiCl_2]$ could be reduced by two equivalents of Grignard reagents to afford $[L_nNi^0]$ by the reductive elimination of $[L_nNiR_2]$. The subsequent reaction of $[L_nNi^0]$ with a Grignard reagent and an MCP would yield the nickelate complex **9**.[9] In the case of aryl Grignard reagents, the direct oxidative addition of a proximal C–C bond of the MCP to the nickel catalyst might occur to yield **10**. In contrast, when vinyl Grignard reagents were employed, the distal bond cleavage of the MCP might predominate to form **12**. The subsequent isomerization of **10** and **12** into **11** and **13**, respectively, and then reductive coupling would afford the corresponding carbomagnesation products **4** and **6**, respectively, along with Ni^0 to complete the catalytic cycle. An alternative pathway proceeding by the insertion of the double bond of MCP into the Ph–Ni bond and subsequent β-carbon elimination cannot be ruled out in the case of PhMgBr.



Scheme 1. A plausible reaction pathway.

In conclusion, we report the first example of the nickel-catalyzed carbomagnesation of MCPs, wherein the appropriate aryl or vinyl Grignard reagents lead to the site-selective C–C bond cleavage reaction of the proximal or the distal C–C bonds of the MCPs. The present reaction provides a new method for the preparation of substituted homoallyl or allyl Grignard reagents from an aryl or a vinyl Grignard reagent and MCPs in the presence of a nickel catalyst.

Experimental Section

2,3-Diphenyl-1,6-heptadiene (**3c**): $[Ni(PPh_3)_2Cl_2]$ (16.3 mg, 0.025 mmol) was added to a mixture of 2-phenyl-1-methylenecyclopropane (65.0 mg, 0.5 mmol), phenylmagnesium bromide (1.0 M, 1.0 mL, 1.0 mmol), and THF (2 mL) which was maintained at 0°C under a nitrogen atmosphere. After the reacton mixture had been stirred for 8 h, allyl bromide (133.1 mg, 1.1 mmol) was added to the solution at 0°C, and the mixture was warmed to 20°C. A saturated aqueous NH_4Cl solution (50 mL) was added, and the product was extracted with diethyl ether (50 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a yellow residue containing the crude products (78% GC yield). Purification by HPLC methods using $CHCl_3$ as an eluent afforded 71.3 mg (66%) of **3c** as a colorless oil.

2-[Phenyl(tributylsilyl)methyl]-1,4-pentadiene (**8a**): Vinylmagnesium chloride (1.25 M, 0.8 mL, 1.0 mmol) was added to a mixture of 2-phenyl-1-methylenecyclopropane (65.0 mg, 0.75 mmol), tributylchlorosilane (117.4 mg, 0.5 mmol), $NiCl_2$ (3.2 mg, 0.025 mmol), and THF (2 mL) which was maintained at 0°C under a nitrogen atmosphere. After the reaction mixture had been stirred for 3 h, a saturated aqueous NH_4Cl solution was added to the solution and the products were extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and evaporated to give a yellow residue containing the crude products (92% GC yield). Purification by HPLC methods using $CHCl_3$ as an eluent afforded 153.2 mg (86%) of **8a** as a colorless oil.

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