Selective Halogen−Magnesium Exchange Reaction via Organomagnesium Ate Complex

Atsushi Inoue, Kazuya Kitagawa, Hiroshi Shinokubo, and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

oshima@fm1.kuic.kyoto-u.ac.jp

Halogen−magnesium exchange of various aryl halides is achieved with a magnesium ate complex at low temperatures. Tributylmagnesate ($^nBu_3MgLi$) induces facile iodine−magnesium exchange at −78 °C. Dibutylisopropylmagnesate ($^iPr^nBu_2MgLi$) is more reactive than $^nBu_3MgLi$, and this reagent accomplishes selective bromine−magnesium exchange at −78 °C. This procedure is utilized for the preparation of various polyfunctionalized arylmagnesium species. The exchange of alkenyl halides using this method proceeds with retention of configuration of the double bond.

Introduction

Organomagnesium reagents are synthetic tools of great importance, and numerous reports for the preparation of various organomagnesium compounds have been published.[1] Methods for the preparation of organomagnesium compounds are usually based on (1) direct metalation of organic halides with metallic magnesium, (2) deprotonation, (3) transmetalation from other organometallics, or (4) halogen−magnesium exchange. For the preparation of polyfunctional organomagnesium compounds, method 3 or 4 is particularly attractive. Very recently, Knochel et al. have shown that polyfunctional aryl- and alkenylmagnesium reagents can be prepared by the halogen−magnesium exchange reaction with ^iPrMgBr at low temperatures.[2−5] However, the substrates are limited to electron-deficient aryl halides or alkenyl halides having an oxygen functionality acting as a metal directing group.

The utility of organometallic ate complexes such as R_2-CuLi, R_3ZnLi, R_4AlLi, and R_3MnLi in organic synthesis is well-recognized,[6] and these complexes are known to induce halogen−metal exchange reactions in some cases.[7] Since a magnesium ate complex (R_3MgLi) was first reported in 1951, several investigations on its structure have been reported.[8] However, synthetic application of magnesate reagents still remains unexplored.[9] Herein we wish to report a versatile method for the preparation of various organomagnesium reagents which makes use of the magnesium ate complex.[10]

Results and Discussion

(1) Iodine−Magnesium Exchange of Aryl Iodides. Lithium tributylmagnesate ($^nBu_3MgLi$) was easily prepared by mixing butylmagnesium bromide and butyllithium in a 1:2 ratio in THF at 0 °C. Treatment of

* To whom correspondence should be addressed. Phone: +81-75-753-5523. Fax: +81-75-753-4863.

(1) (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (b) *Handbook of Grignard-Reagents*; Silverman, G. S., Rakita, P. E. Eds.; Marcel Dekker: New York, 1996. (c) *Grignard Reagents: New Developments*; Richey, H. G., Jr., Eds.; Wiley & Sons: New York, 1999.

(2) For review, see: (a) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 767. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

(3) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701. (b) Varchi, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Tetrahedron* **2000**, *56*, 2727. (c) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7449. (d) Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359. (e) Abarbri, M.; Knochel, P. *Synlett* **1999**, 1577. (f) Dehmel, F.; Abarbri, M.; Knochel, P. *Synlett* **2000**, 345. (g) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (h) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 4, **1080**. (i) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* 2000, *41*, 3319. (j) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, *1820*.

(4) (a) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407. (b) Smith, C. F.; Moore, G. J.; Tamborski, C. *J. Organomet. Chem.* **1971**, *33*, C21. (c) Paradies, H. H.; Görbing, M. *Angew. Chem.* **1969**, *81*, 293. (d) Martin, G. J.; Mechin, B.; Leroux, Y.; Paulmier, Cl.; Meunier, J. C.; *J. Organomet. Chem.* **1974**, *67*, 327. (e) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845. (f) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339.

(5) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428.

(6) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1.

(7) Halogen−metal exchange with trialkylzincate or dialkylcuprate have been reported. (a) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717. (b) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733. (c) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (d) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem.* **1996**, *108*, 818; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736. (e) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897.

(8) (a) Wittig, G.; Meyer, F. J.; Lange, G. *Liebigs Ann. Chem.* **1951**, *571*, 167. (b) Thoennes, D.; Weiss, E. *Chem. Ber.* **1978**, *111*, 3726. (c) Coates, G. E.; Heslop, J. A. *J. Chem. Soc. (A)* **1968**, 514. (d) Greiser, T.; Kopf, J.; Thoennes, D.; Weiss, E. *Chem. Ber.* **1981**, *114*, 209.

(9) (a) Ashby, E. C.; Chao, L.-C.; Laemmle, J. *J. Org. Chem.* **1974**, *39*, 3258. (b) Richey, H. G., Jr.; Farkas, J., Jr. *Tetrahedron Lett.* **1985**, *26*, 275. (c) Richey, H. G., Jr.; Farkas, J., Jr. *Organometallics* **1990**, *9*, 1778. (d) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Synlett* **1998**, 899. (e) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1417. (f) Ide, M.; Yasuda, M.; Nakata, M. *Synlett* **1998**, 936. (g) Ide, M.; Yasuda, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491. (h) Kamienski, C. W.; Gastonia, N. C.; Eastham, J. F. U.S. Patent 3,847,883, 1974; *Chem. Abstr.* **1975**, *82*, 58590b. (i) Castaldi, G.; Borsotti, G. Eur. Pat. Appl. EP 491,326, 1992; *Chem. Abstr.* **1992**, *117*, 150667w. (j) Iida, T.; Wada, T.; Mase, T. Japan Application No. JP 2000-024613 20000202. (k) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.*, in press.

(10) A part of this paper was published in a communication. Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem.* **2000**, *112*, 2594; *Angew. Chem., Int. Ed.* **2000**, *39*, 2481.
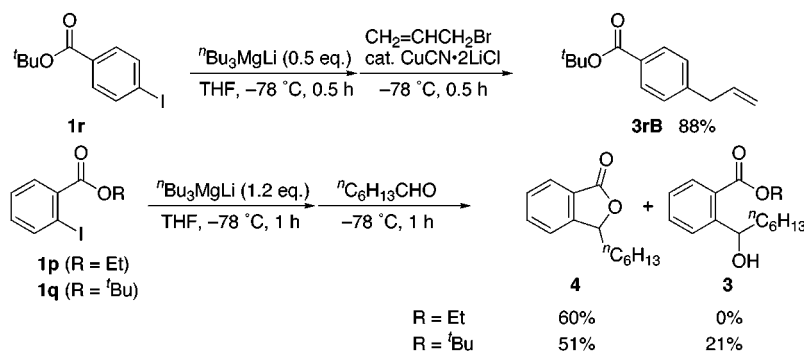
Scheme 1

Table 1. Iodine–Magnesium Exchange of Aryl Iodides

Entry	Substrate	Temp.	Electrophile	Product	Yield (%)
1	1a	0 °C	$^nC_6H_{13}CHO$	3aD	80
2	1c	−78 °C	EtCHO	3cC	75[a]
3	1e	−78 °C	PhCHO	3eE	92
4	1f	−78 °C	PhCHO	3fE	93
5	1g	−78 °C	$^nC_6H_{13}CHO$	3gD	94
6	1l	0 °C	$CH_2=CHCH_2Br$	3lB	87

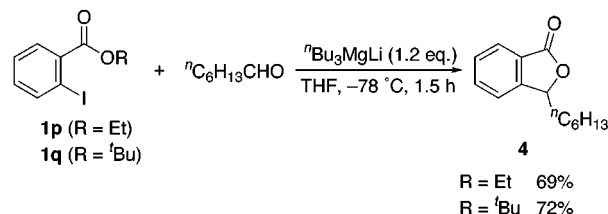[a] $^nBu_3MgLi$ (0.5 equiv) was used.

various aryl iodides **1** with 1.2 equiv of $^nBu_3MgLi$ followed by an addition of electrophiles afforded the desired products **3** in good to excellent yields (Table 1).[11]
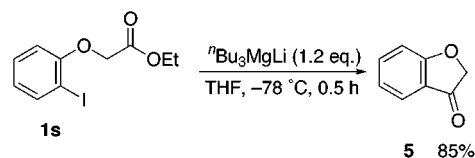
Electron-rich aryl iodides such as *o*-, *m*-, or *p*-iodoanisole can be converted into the corresponding arylmagnesates at −78 °C (entries 3–5). The amount of the magnesate reagent can be reduced to 0.5 equiv to the substrate (entry 2). This result indicates that two of the three butyl groups in the reagent can work for the exchange reaction.

The fact that the iodine–magnesium exchange reaction proceeds at −78 °C encouraged us to investigate the reaction of functionalized aryl iodides. Indeed, the treatment of *tert*-butyl *p*-iodobenzoate (**1r**) with 0.5 equiv of

(11) In the trapping reaction of resultant magnesate (Ar$^nBu_2MgLi$) with electrophiles, no significant difference in the migratory attitude of the ligands (Ar vs ^nBu) was observed. For example, the reaction of Ar$^nBu_2MgLi$ (Ar = 4-methoxyphenyl) with 1.0 equiv of PhCHO provided a mixture of ArCH(OH)Ph and $^nBuCH(OH)Ph$ in a 1:2 ratio. Therefore, we recommend the use of more than 3 equiv of electrophiles.

Scheme 2

R = Et   69%
R = ^tBu 72%

Scheme 3

$^nBu_3MgLi$ at −78 °C furnished the desired magnesium compound which reacted with allyl bromide in the presence of CuCN·2LiCl[12] (Scheme 1). The reaction of *o*-iodobenzoates (**1p** and **1q**) with heptanal after the exchange provided 3-hexylphthalide (**4**) as a major product. Interestingly, this exchange reaction was much faster than the nucleophilic attack of the butyl group to an aldehyde. The addition of $^nBu_3MgLi$ to a mixture of *o*-iodobenzoate ester (**1p** or **1q**) and heptanal provided 3-hexylphthalide (**4**) as the single product (Scheme 2). The ester group of ethyl (2-iodophenoxy)acetate (**1s**) could survive under the reaction conditions, and 3-coumaranone (**5**) was obtained in 85% yield via the intramolecular attack of the resultant magnesium reagent (Scheme 3).

(2) Bromine–Magnesium Exchange of Aryl Bromides. We next turned our attention on the bromine–magnesium exchange reaction of aryl bromides, because it is desirable to use readily available aryl bromides as substrates. Various aryl bromides **6** could be efficiently converted into the corresponding arylmagnesium compounds with $^nBu_3MgLi$ at 0 °C. The resultant arylmagnesium species could be trapped by various electrophiles such as aldehydes or allyl bromide (Table 2). Several comments are worth noting. (1) Both electron-rich and electron-deficient aryl bromides give satisfactory results in this magnesate-induced reaction. In contrast, isopropylmagnesium bromide-induced exchange reaction often requires electron-withdrawing groups on the aromatic ring.[2,3c,4a,b] (2) In contrast to aryl iodides, the exchange reaction of aryl bromides does not go to completion at −78 °C in some cases. (3) A half-equivalent of the reagent

(12) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (c) Knochel, P. *Synlett* **1995**, 393.

Table 2. Bromine−Magnesium Exchange of Aryl Bromides

$$\text{ArBr} \xrightarrow[\text{THF, 0 °C, 0.5 h}]{^{n}\text{Bu}_3\text{MgLi (1.2 eq.)}} \text{Ar}^{n}\text{Bu}_2\text{MgLi} \xrightarrow{\text{Electrophile}} \text{ArE}$$
$$\quad\quad 6 \quad\quad\quad\quad\quad\quad\quad\quad\quad 2 \quad\quad\quad\quad\quad 3$$

Entry	Substrate	Electrophile	Product	Yield (%)
1	6a	EtCHO	3aC	87
2	6b	EtCHO	3bC	88
3	6c	EtCHO	3cC	85
4	6d	EtCHO	3dC	78
5	6e	$CH_2{=}CHCH_2Br$	3eB	83
6	6g	$CH_2{=}CHCH_2Br$	3gB	84
7	6g	EtCHO	3gC	90[a]
8	6g	$^{n}C_6H_{13}CHO$	3gD	100
9	6g	PhCHO	3gE	90 (85)[a]
10	6h	$CH_2{=}CHCH_2Br$	3hB	74
11	6i	EtCHO	3iC	94
12	6j	$^{n}C_6H_{13}CHO$	3jD	76
13	6k	EtCHO	3kC	52 (62)[b]
14	6l	$CH_2{=}CHCH_2Br$	3lB	97
15	6m	$CH_2{=}CHCH_2Br$[c]	3mB	93
16	6n	$CH_2{=}CHCH_2Br$[c]	3nB	100
17	6n	D_2O	3nA	93

[a] $^{n}Bu_3MgLi$ (0.5 eq.) was used. [b] $^{n}BuMe_2MgLi$ was used. [c] $CuCN\cdot2LiCl$ (30 mol %) was added.

is sufficient. (4) Sterically hindered halides such as **6m** and **6n** can be also metalated efficiently. In these cases, a catalytic amount of $CuCN\cdot2LiCl$ improves efficiency of the trapping reaction with allyl bromide.[12]

This magnesate-induced exchange reaction was compared with the conventional bromine−lithium exchange (Scheme 4). Treatment of allyl 2-bromophenyl ether (**6o**) with $^{n}BuLi$ in THF at 0 °C afforded a complex mixture containing dihydrobenzofuran derivative **7** which resulted from bromine−lithium exchange and subsequent intramolecular carbolithiation.[13] In contrast, the magnesate reagent induced the clean bromine−magnesium exchange providing the magnesium species **2o**.[14]

With this successful exchange procedure in hand, we examined the preparation of functionalized arylmagnesium compounds from the corresponding aryl bromide. The reaction of aryl bromides with $^{n}Bu_3MgLi$ did not go to completion under the same conditions as the reaction of aryl iodides. To enhance the reactivity of a magnesate reagent, an isopropyl group was introduced on magnesium as a ligand. The reagent $^{i}Pr^{n}Bu_2MgLi$ was prepared by mixing $^{i}PrMgBr$ and $^{n}BuLi$ in a 1:2 ratio. With this reagent the exchange reaction proceeded smoothly at −78 °C, and the subsequent addition of various electrophiles provided the desired coupling products in moderate to good yields (Table 3). Functional groups such as ester, amide and cyano groups are tolerable during the exchange procedure. The addition of a catalytic amount of $CuCN\cdot2LiCl$ was necessary when allyl bromide was employed as an electrophile.[12] The cyano group was tolerable at even −40 °C and, therefore, the exchange reaction of bromobenzonitriles with $^{n}Bu_3MgLi$ was performed at −40 °C (Scheme 5). Aryl bromide **6y** containing a bromo acetal moiety at the proper position provided 2-alkoxy-substituted coumaran **8** in moderate yield via intramolecular nucleophilic substitution without decomposition of the acetal moiety (Scheme 6).

(3) Halogen−Magnesium Exchange of Dihaloarenes. The preparation of polymetalated aromatic compounds has been a topic of organometallic chemistry.[15] In addition, selective metalation of polyhaloarenes provides an efficient methodology to synthesize substituted aromatic compounds. We then investigated the selective exchange reaction of dihalogenated aromatics (Table 4). In the case of *p*-bromoiodobenzene (**9a**), none of the bromide−magnesium exchange proceeded (entry 1). Only one of two bromines of *m*- or *p*-dibromobenzene was exchanged (entries 2 and 3). On the other hand, *p*-diiodobenzene (**9d**) was converted into dimagnesiated benzene upon treatment with 1.0 equiv of $^{n}Bu_3MgLi$ (entry 4), while dimetalation of *m*-diiodobenzene (**9e**) required 2.0 equiv of the reagent to furnish *m*-dimagnesiobenzene (entry 6). The reagent $^{n}BuMe_2MgLi$ was employed to induce selective monomagnesiation of *p*-diiodobenzene (entry 5). Because the methyl ligand on magnesium is less reactive than the butyl group, the second exchange is enough slow to be controlled. In contrast to *p*-dibromobenzene (entry 3), dimagnesiated biphenyl was formed quantitatively via the double exchange reaction of 4,4′-dibromobiphenyl (**10**) (entry 7).

(13) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960, and references therein.

(14) Carbomagnesiation has been reported to be slow. Richey, H. G., Jr.; Veale, H. S. *Tetrahedron Lett.* **1975**, *615*, and references therein.

(15) (a) Rot, N.; Bickelhaupt, F. *Organometallics* **1997**, *16*, 5027. (b) Bickelhaupt, F. *Chem. Soc. Rev.* **1999**, *28*, 17.
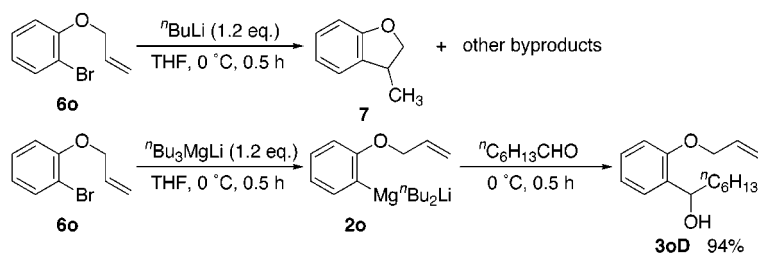
Scheme 4

Table 3. Bromine−Magnesium Exchange of Aryl Bromides Bearing Reactive Functionalities
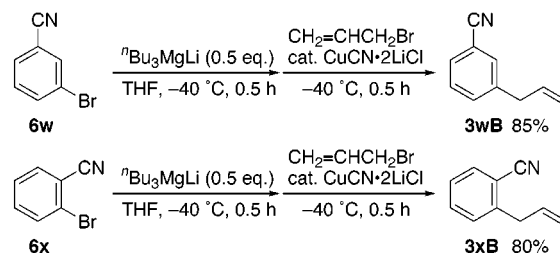
Entry	Substrate	Electrophile	Product	Yield (%)
1	6q	CH₂=CHCH₂Br[b]	3qB	99
2	6q	ⁿC₆H₁₃CHO	4	61
3	6r	CH₂=CHCH₂Br[b]	3rB	66
4	6r	ⁿC₆H₁₃CHO	3rD	71 (50)[a]
5	6t	CH₂=CHCH₂Br[b]	3tB	80
6	6t	EtCHO	3tC	66
7	6u	CH₂=CHCH₂Br[b]	3uB	79
8	6u	EtCHO	3uC	37
9	6v	CH₂=CHCH₂Br[b]	3vB	87
10	6v	ⁿC₆H₁₃CHO	3vD	60 (44)[a]

[a] ⁿBu₃MgLi was used. [b] CuCN·2LiCl (30 mol %) was added.

Scheme 5

Scheme 6

Table 4. Halogen−Magnesium Exchange of Dihaloarenes

Entry	Substrate	Conditions	Electrophile	Product	Yield (%)
1	9a	ⁱPrⁿBu₂MgLi (1.0) −78 °C, 0.5 h	EtCHO	11a	65
2	9b	ⁱPrⁿBu₂MgLi (1.0) 0 °C, 0.5 h	EtCHO	11b	78
3	9c	ⁿBu₃MgLi (1.0) 0 °C, 0.5 h	EtCHO	11a	85
4	9d	ⁿBu₃MgLi (1.0) −78 °C, 0.5 h	EtCHO	12a	80
5	9d	ⁿBuMe₂MgLi (1.0) −78 °C, 0.5 h	EtCHO	11c	64
				12a	9
6	9e	ⁿBu₃MgLi (2.0) −78 °C, 0.5 h	EtCHO	12b	48
7	10	ⁿBu₃MgLi (1.0) 0 °C, 1 h	D₂O	13	100

Treatment of *o*-dibromobenzene (**9f**) with ⁿBu₃MgLi yielded 2-butylphenylmagnesium **15**. The formation of **15** arises from the addition of the butyl group to benzyne which is derived from 2-bromophenylmagnesium **14** via 1,2-elimination.[16] (Scheme 7).

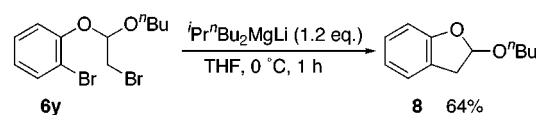**(4) Halogen−Magnesium Exchange of Heteroaryl Halides.** The bromine−magnesium exchange of 3-bro-

(16) Ghosh, T.; Hart, H. *J. Org. Chem.* **1988**, *53*, 3555, and references therein.

mopyridine with ⁿBu₃MgLi at 0 °C followed by an addition of propanal furnished the desired product in low yield along with various byproducts. To prevent side reactions induced by an excess butyl group, the ate complex ⁿBuMe₂MgLi was employed. This reagent gave satisfactory results for the preparation of pyridylmagnesiums (Table 5).[3d,g,4c−f] 2-Iodo-, 2-bromo-, and 3-bromopyridine were converted into the corresponding pyridylmagnesiums (entries 1−4). The reaction of 2-chloropyridine

Scheme 7

Table 5. Halogen−Magnesium Exchange of Heteroaryl Halides

Entry	Substrate	Electrophile	Product	Yield (%)
1	**17**	EtCHO	**20a**	58
2	**18a**	EtCHO	**20a**	67
3	**18b**	EtCHO	**20b**	73 (56)[a]
4	**18b**	$^nC_5H_{11}$CO$^nC_5H_{11}$	**21**	49
5	**19**	PhCHO[b]	**22**	78[a]

[a] nBu$_3$MgLi was used. [b] Trapping reaction was performed at −78 °C.

Table 6. Iodine−Magnesium Exchange of Alkenyl Iodides

Entry	Substrate	Electrophile	Product	Yield (%)
1	**23a** R = $^nC_{10}H_{21}$	D$_2$O	**24aA**	93
2	**23a**	Me$_3$SiCl	**24aB**	93 (95)[a] (88)[b]
3	**23a**	CH$_2$=CHCH$_2$Br[c]	**24aC**	70
4	**23a**	^{n}BuI[c]	**24aD**	76[b]
5	**23a**	PhCHO	**24aG**	69
6	**23a**	CH$_3$COCH$_3$	**24aH**	75
7	**23b** R = $^nC_{10}H_{21}$	Me$_3$SiCl	**24bB**	87 (83)[a] (78)[b]
8	**23b**	CH$_2$=CHCH$_2$Br[c]	**24bC**	70
9	**23b**	PhCHO	**24bG**	69
10	**23b**	CH$_3$COCH$_3$	**24bH**	75
11	**23c** R = $^nC_5H_{11}$	D$_2$O	**24cA**	87
12	**23c**	EtCHO	**24cF**	65
13	**23c**	PhCHO	**24cG**	87
14	**23d** R = $^nC_5H_{11}$	Me$_3$SiCl	**24dA**	88
15	**23d**	PhSSPh	**24dE**	77
16	**23d**	PhCHO	**24dG**	70

[a] The exchange reaction was performed at −78 °C. [b] nBu$_3$MgLi was used. [c] CuCN·2LiCl (30 mol %) was added.

Scheme 8

provided a complex mixture.[17] Thienylmagnesium can be prepared in good yield via the exchange reaction with ^{n}Bu$_3$MgLi at 0 °C (entry 5).

(5) Halogen−Magnesium Exchange of Alkenyl Halides. This new procedure is also applicable for the preparation of alkenylmagnesates from alkenyl iodides (Table 6). The iodine−magnesium exchange of alkenyl iodides **23** proceeds with complete retention of configuration of the double bond. The reaction of nonactivated iodoalkene with ^{i}PrMgBr is reported to require increased reaction time at room temperature.[3h] In contrast, this method can achieve the complete exchange within 1 h at −78 °C. The presence of an ester functionality is compatible with the formation of alkenylmagnesate at −78 °C (Scheme 8).

Unfortunately, the bromine−magnesium exchange of alkenyl bromides[3i] was disappointing. Because the exchange was slow, the dehydrobromination and deprotonation afforded magnesium acetylides. The results are shown in Table 7. Especially in the case of the *Z* isomer **25b**, the acetylenic products **26A** and **26B** were obtained predominantly.
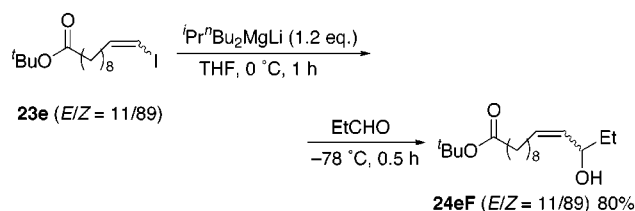
The results of the exchange reaction of 1-silyl-1-haloalkenes are shown in Table 8. In the case of alkenyl

iodides **27**, considerable isomerization[18] was observed in the preparation of trimethylsilyl-substituted alkenyl-magnesium (entries 1 and 2). For *tert*-butyldimethylsilyl-

---

(17) The deprotonation at 5-position of 2-chlorothiophene occurred under the same conditions.

(18) Silyl-substituted alkenyl halides have been reported to isomerize easily in the presence of organometallic reagents. (a) Zweifel, G.; Murray, R. E.; On, H. P. *J. Org. Chem.* **1981**, *46*, 1292. (b) Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 3402.

Table 7. Bromine−Magnesium Exchange of Alkenyl Bromides

Entry	Substrate	Electrophile	Yield (%)			
1	**25a** R = $^nC_{10}H_{21}$	D$_2$O	**24aA** 64	**26A** 25		
2	**25a**	Me$_3$SiCl	**24aB** 71	**26B** 29		
3	**25b** R = $^nC_{10}H_{21}$	D$_2$O	**24bA** 24	**26A** 54	**25b** 10	
4	**25b**	Me$_3$SiCl	**24bB** 27	**26B** 59	**25b** 10	

Table 8. Halogen−Magnesium Exchange of 1-Silylalkenyl Halides

Entry	Substrate[a]	Electrophile	Product	E / Z	Yield (%)
1	**27a** (E/Z = 85/15)	D$_2$O	**29aA**	32/68	98
2		CH$_2$=CHCH$_2$Br[b]	**29aC**	29/71	95
3	**27b** (E/Z = 84/16)	D$_2$O	**29bA**	96/ 4	89
4		CH$_2$=CHCH$_2$Br[b]	**29bC**	94/ 6	99
5	**28a** (E/Z = 100/0)	D$_2$O	**29aA**	93/ 7	90
6		CH$_2$=CHCH$_2$Br[b]	**29aC**	93/ 7	92
7	**28b** (E/Z = 84/16)	D$_2$O	**29bA**	93/ 7	86
8		CH$_2$=CHCH$_2$Br[b]	**29bC**	96/ 4	80
9	**28a** (E/Z = 35/65)	D$_2$O	**29aA**	94/ 6	99
10		CH$_2$=CHCH$_2$Br[b]	**29aC**	94/ 6	98

^{a} R = $^nC_6H_{13}$. ^{b} CuCN·2LiCl (30 mol %) was added.

Scheme 9

Scheme 10

undergo metalation reactions.[19] We investigated the halogen−magnesium exchange reaction of cyclopropyl halides. Treatment of cyclopropyl bromide (**30**) with 1.0 equiv of ^{n}Bu$_3$MgLi for 0.5 h at 0 °C followed by an addition of benzaldehyde furnished α-cyclopropylbenzyl alcohol (**31**) in 91% yield. Two-fold amount of 1-phenyl-pentanol (**32**), which was separable from the desired product by silica gel column chromatography, was also obtained. An attempt to reduce the amount of the magnesate reagent decreased the yield of **31** (Scheme 10).

Conclusions

We have demonstrated that a magnesium ate complex, R$_3$MgLi, induces the facile halogen−magnesium exchange of various aryl halides and alkenyl halides. The reaction proceeded smoothly at low temperatures. The reactivity of magnesate reagents is tunable by a proper choice of ligands on magnesium. Because of these notable characteristics of the reaction, one can prepare functionalized organomagnesium reagents using the magnesate-induced halogen−magnesium exchange reaction.

Experimental Section

^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in CDCl$_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. Mass spectra were determined on a JEOL JMS-700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merk Silica gel 60F$_{254}$. Column chromatography was done with silica gel (Wakogel 200 mesh). The analyses were carried out at the Elemental Analysis Center of Kyoto University. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Grignard reagents were prepared from the corresponding alkyl halide and Mg turning (Nacalai tesque, INC), and the concentration was titrated with 2-butanol using 1,10-phenanthroline as the indicator. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Aldehydes were distilled and stocked under argon.

Procedure for the Bromine−Magnesium Exchange of Aryl Bromides. To a solution of butylmagnesium bromide (1.2 mL, 1.0 M solution in THF, 1.2 mmol) in THF (2 mL) was added butyllithium (1.5 mL, 1.6 M solution in hexane, 2.4 mmol) at 0 °C, and the mixture was stirred for 10 min. A solution of 4-bromoanisole (**6g**, 187 mg, 1.0 mmol) in THF (2 mL) was introduced dropwise. After stirring for 0.5 h at 0 °C, the mixture was cooled to −78 °C and benzaldehyde (0.37 mL, 3.6 mmol) was added. After stirring for 0.5 h at −78 °C, the reaction was quenched with saturated aqueous NH$_4$Cl. The

substituted alkenylmagnesium, almost perfect isomerization was observed (entries 3 and 4). Obviously, these results reflect strong preference of the bulky silyl group in the trans orientation to the alkyl group. On the other hand, the bromine−magnesium exchange is slower than the isomerization of bromosilylalkenes. Therefore, (E)-silylalkenylmagnesiums were obtained regardless of the bulkiness of the silyl groups (entries 5−10). The resulting 1-silylalkenylmagnesiums could be trapped with chlorotrimethylsilane in the presence of a catalytic amount of CuCN·2LiCl[12] to afford 1,1-disilylalkene (Scheme 9).

(6) Bromine−Magnesium Exchange of Cyclopropyl Bromide. Because a bond of strained cyclopropyl rings has significant s-character, cyclopropyl halides can

(19) (a) Lukina, M. Yu. *Russ. Chem. Rev. (Engl. Transl.)* **1962**, *31*, 419. (b) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Walborski, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283.

mixture was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration and purification by chromatography provided 1-(4-methoxyphenyl)-1-phenylmethanol (**3gE**, 193 mg, 0.90 mmol) in 90% yield.

Preparation of Polyfunctional Arylmagnesiums from Aryl Bromides. To a solution of isopropylmagnesium bromide (1.2 mL, 1.0 M solution in THF, 1.2 mmol) in THF (2 mL) was added butyllithium (1.5 mL, 1.6 M solution in hexane, 2.4 mmol) at 0 °C, and the mixture was stirred for 10 min. The resulting yellow solution was cooled to −78 °C, and a solution of *tert*-butyl 2-bromobenzoate (**6q**, 304 mg, 1.0 mmol) in THF (2 mL) was introduced dropwise. After the mixture was stirred for 1 h, CuCN·2LiCl (0.3 mL, 1.0 M solution in THF, 0.3 mmol) and allyl bromide (0.35 mL, 4.0 mmol) were sequentially added. After stirring for 0.5 h at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane, and the combined organic layers were dried over anhydrous Na_2SO_4. Concentration and purification by chromatography provided *tert*-butyl 2-allylbenzoate (**3qB**, 215 mg, 0.99 mmol) in 99% yield: $R_f = 0.74$ (hexane/ethyl acetate = 5/1); IR (neat) 1711 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.59 (s, 9H), 3.73 (d, $J = 6.3$ Hz, 2H), 5.01 (d, $J = 16.8$ Hz, 1H), 5.03 (d, $J = 10.5$ Hz, 1H), 6.02 (ddt, $J = 10.5$, 16.8, 6.3 Hz, 1H), 7.22−7.29 (m, 2H), 7.36−7.43 (m, 1H), 7.78 (dd, $J = 1.5$, 8.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 28.07, 38.22, 81.16, 115.53, 126.10, 130.32, 130.78, 131.41, 132.00, 137.59, 140.66, 167.33. Found: C, 76.98; H, 8.49%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

Supporting Information Available: Characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO015597V