Award Accounts

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Highly Selective Synthetic Reactions by the Combined Use of Organometallic Reagents and Radical Species

Koichiro Oshima

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku katsura, Nishikyo-ku, Kyoto 615-8510

Received June 8, 2007; E-mail: oshima@orgrxn.mbox.media.kyoto-u.ac.jp

During these thirty years, we have pursued new methodologies in organic synthesis and developed many synthetically useful reactions. Among them, four topics are described in this article. (1) Regio- and stereoselective silylmetalation of acetylenes has been examined. Whereas platinum- or copper-catalyzed silylmagnesation of terminal acetylenes afforded (*E*)-1-silyl-1-alkene exclusively, palladium-catalyzed silylalumination with $PhMe_2Si$-$AlEt_2$ provided 2-silyl-1-alkenes with high regioselectivity. (2) Triethylborane induced radical addition of Ph_3SnH to acetylenes gave 1-triphenylstannyl-1-alkenes in the presence of small amount of oxygen. The reaction has two distinguishing characteristics. One feature is that Et_3B can initiate the radical reaction at low temperature, such as $-78\,^{\circ}C$. (3) The other distinctive feature of Et_3B-induced radical reaction is that many solvents could be used for the reaction. Thus, water was chosen as a solvent, and Et_3B-induced atom-transfer radical cyclization of iodo acetals and iodoacetates in water was examined. (4) Three types of organometallic ate complexes, $R_3MnMgBr$, R_3MgLi, and $R_3Co(L_2)MgBr$, were prepared and used for organic synthesis. Treatment of *gem*-dibromocyclopropane with trialkylmanganate provided alkylated cyclopropane after aqueous workup. Aryl and alkenyl halides could be converted into the corresponding magnesium reagents by the action of trialkylmagnesate via halogen–magnesium exchange. Finally, synthetic reactions catalyzed by cobalt complexes are described. Without suffering from β-elimination, cobalt complexes allow cross-coupling reactions of alkyl halides with Grignard reagents.

1. Silylmetalation of Acetylenes and Its Application to the Stereoselective Synthesis of Steroidal Side Chains

In 1982, we started an investigation on the stereoselective synthesis of the side chain of a plant growth steroidal hormone, brassinolide. Our synthesis route, which consists of three key reactions, is shown in Scheme 1.

We began by studying the last step (c), selective ring opening of α,β-epoxy alcohol. Among many organometallic compounds examined, organoaluminum reagents were found to be effective for the regio- and stereoselective ring opening of epoxy alcohol to give 1,2-diols.[1] The reaction proceeds with inversion at the reacting center. In the next step (b), we had to develop a new method of preparing threo epoxy alcohol **3** form (*E*)-allylic alcohol **2a**. The vanadium-catalyzed epoxidation of (*E*)-allylic alcohol gave the erythro isomer as a main product. On the other hand, *m*-CPBA epoxidation gave the threo isomer as a major product, but the selectivities of these reactions were rather low and not enough for our purpose. This problem was solved by substitution of an appropriate hydrogen on the double bond by a bulky Me_3Si group.[2] Treatment of **2b** with $VO(acac)_2$–*t*-BuOOH or *m*-CPBA gave threo epoxy alcohol **3** with high stereoselectivity (99%). The Me_3Si group was easily removed by treatment with *n*-Bu_4NF or CsF in DMSO, and the desilylation of epoxysilane proceeded with retention of configuration at the oxiranyl carbon.

We then faced the difficult problem (step a) of how to get an alkenylmetal species, (*Z*)-$R_3SiC(Me)$=CHMtl in order to obtain the desired silyl-substituted allylic alcohol **2b** from the readily available aldehyde **1**. Regio- and stereoselective addition of Si–metal compounds to propyne afforded the alkenylmetal compound. Thus, combined acid–base reagents, such as Si–Al or Si–Zn, were examined to solve the problem. This was the basis of our studies on the silylmetalation of acetylenes.

1.1 Silylmetalation of Acetylenes. In connection with an investigation of the stereoselective synthesis of the side chain of brassinolide, we had to develop a method for the formation of the alkenylmetal spiecies (**5**, $R = CH_3$) (Scheme 2). Although exclusive formation of 2-metallo-1-silyl-1-alkenes (**4**) by silylcupration,[3] silyltitanation,[4] or silylalumination[5] has previously been reported, the selective generation of 1-metallo-2-silyl isomer **5** has not been described to our knowledge. First, we investigated simultaneous addition of the silyl group and metal to acetylenes with regioselectivity using $PhMe_2SiLi$ and several metal compounds, such as MeMgI, Et_2AlCl, and $ZnBr_2$, in the presence of a couple of transition-metal catalyst.[6]

Platinum- or copper-catalyzed silylmagnesation, followed by aqueous quenching, provided exclusively (*E*)-1-silyl-1-

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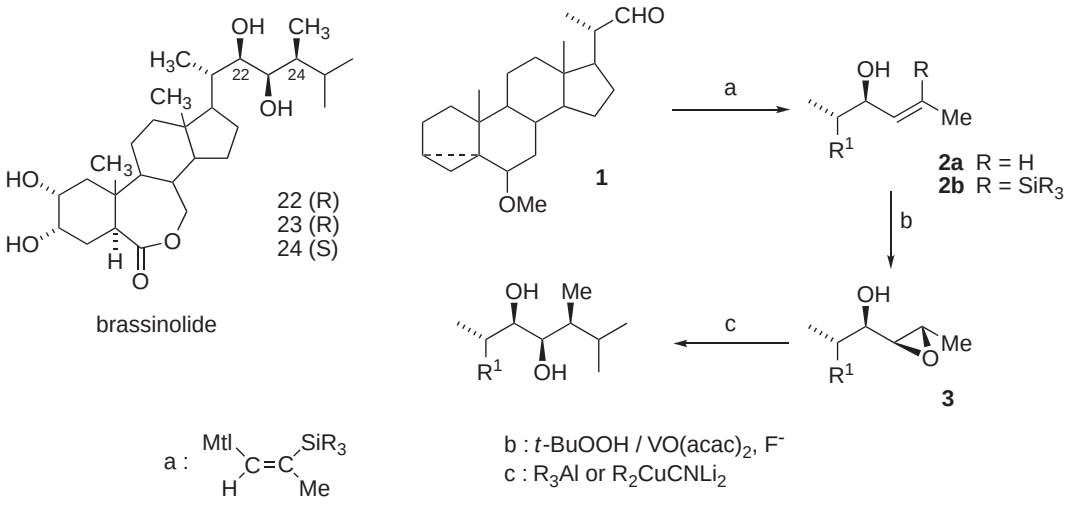
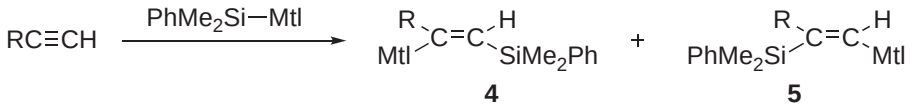


Scheme 1.



Scheme 2.

alkenes, which have previously been produced by stoichiometric silylcupration[3] or silyltitanation.[4] In contrast, the use of a Pd catalyst resulted in the formation of a mixture of two regioisomers. The reagent prepared from $PhMe_2SiLi$ and $ZnBr_2$ also added to acetylenes in *syn* fashion to give isomeric mixtures. In the presence of a Pt catalyst, 1-silyl-1-alkene was the main product. However, the Ru- or Pd-catalyzed reaction gave the 2-silyl isomer as the major product. The reagent derived from $PhMe_2SiLi$ and Et_2AlCl was added to 1-dodecyne without any catalyst after heating at 80 °C for 8 h to give 1-[dimethyl(phenyl)silyl]-1-dodecene almost exclusively. The Cu-catalyzed reaction provided two isomers in 50:50 ratio. Palladium-catalyzed silylalumination afforded 2-silyl-1-alkene with high regioselectivity. The results are summarized in Table 1.

The regiochemistry of the silylmetalation reaction depends heavily on the nature of the transition-metal catalysts as well as metallic species of silyl–metal reagents employed. Ligands on the palladium catalysts also play an important role in controlling the product distribution. The reaction of 1-dodecyne with $PhMe_2Si–AlEt_2$ in the presence of a variety of palladium catalysts was studied with ligand L of $PdCl_2L_2$ and the ratio of **6**/**7** being as follows: (m-$MeOC_6H_4)_3P$, 90/10; $Ph_2PCH_2CH_2PPh_2$, 65/35; (2-(diphenylphosphino)ferrocenyl)methyldimethylamine, 50/50; n-Bu_3P, 35/65; PPh_3, 30/70; (o-$CH_3C_6H_4)_3P$, 15/85.

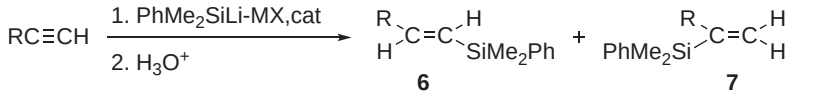
The *syn* addition of a silyl–metal component was confirmed by analyzing of the ^1H NMR spectrum of the product **6a** (J = 18.9 Hz) and also by comparing the GLPC with an authentic (*Z*) sample prepared from hydroalumination of 1-[dimethyl(phenyl)silyl]-1-dodecyne.[7] Silylalumination was also shown to proceed in *syn* fashion by examining of the ^1H NMR spectrum of (*E*)-1-deuterio-1-dodecyne, prepared by palladium-catalyzed silylalumination of 1-dodecyne, followed by quenching with D_2O and successive desilylation (Scheme 3). Deuterolysis of the intermediate derived from silylmetalation gave the monodeuterated alkenylsilanes. Thus, silyl reagents do not cause acetylenic proton–metal exchange (Scheme 4).

1.2 Application of Silylmetalation of Acetylenes to the Synthesis of Brassinolide. Palladium-catalyzed silylalumination of 1-dodecyne provided a mixure of two regioisomers in an 85/15 (**5**/**4**, R = Me) ratio. This ratio was the best so far and could not be improved in spite of various attempts. (This problem was solved later, see Section **1.3**). A combination of this method with our previous findings[1,2] provided us with an easy route to the stereoselective synthesis of the side chain of brassinolide.[8] Palladium-catalyzed silylalumination of propyne, followed by the addition of iodine, provided an 88:12 mixture of 2-[dimethyl(phenyl)silyl]-1-iodo-1-propene (**8a**) and its regioisomer. The desired 2-silylalkene **8a** was obtained in pure form by using silica-gel column chromatography.

Treatment of a mixture of an aldehyde **1**[9] and iodoalkene **8a** with butyllithium at −78 °C gave, after chromatography, (22*R*)-allylic alcohol **9** in 48% yield along with the (22*S*) isomer (16% yield, Scheme 5). Silyl-group-assisted stereoselective epoxidation[2] ($VO(acac)_2$–t-BuOOH), followed by elimination of $PhMe_2Si$ group with n-Bu_4NF, gave the key intermediate *threo*-α,β-epoxy alcohol **10a** exclusively (65% yield). Regio- and stereoselective ring opening[1] of epoxy alcohol with the organoaluminum compound $Et_2AlC{\equiv}CSiMe_3$ proceeded with inversion at the reacting center to give 1,2-diol **11a** in 60% yield. Removal of the Me_3Si group (KF and DMSO) and hydrogenation (H_2 and PtO_2) afforded **11b**. Reaction of benzyl ether **10b** with the higher order mixed cuprate[10] $(Me_2CH)_2Cu(CN)Li_2$ afforded **11c** (63% yield), which was transformed into **11d** (Li in liquid NH_3).[8b]

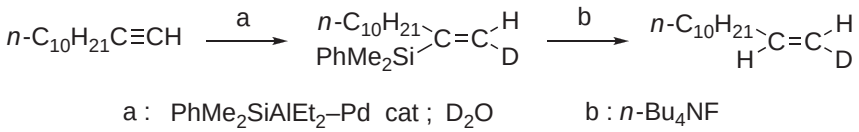
1.3 Development of $PhMe_2SiZnR_2Li$ Reagent and Its Characteristics. The previously reported reaction of Si–Mg, Si–Al, or Si–Zn reagents with an acetylenic linkage af-

Table 1. Transition-Metal-Catalyzed Silylmetalation[a)]

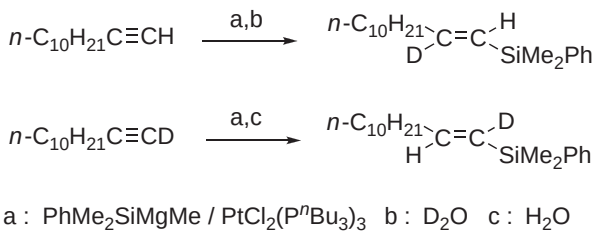


R	MX	Catalyst	Yield/%	**6**:**7**
a: *n*-$C_{10}H_{21}$	MeMgI	[*cis*-$PtCl_2$(P-*n*-Bu_3)$_2$]	90	>99:<1
		CuI[b)]	86	>99:<1
		[$PdCl_2(PPh_3)_2$]	76	60:40
	Et_2AlCl	—[c)]	60	97:3
		[$RhCl(PPh_3)_3$]	70	91:9
		CuI[b)]	78	55:45
		[$PdCl_2$(P(*o*-$CH_3C_6H_4$)$_3$)$_2$]	85	15:85
	$ZnBr_2$[d)]	[*cis*-$PtCl_2$(P-*n*-Bu_3)$_2$]	55	70:30
		[$PdCl_2(PPh_3)_2$]	71	30:70
		[$RuCl_2(PPh_3)_3$]	75	20:80
b: $PhCH_2OCH_2CH_2$	MeMgI	CuI[b)]	90	>99:<1
	Et_2AlCl	[$PdCl_2(PPh_3)_2$]	88	30:70

a) A mixture of acetylene substrate, $PhMe_2SiLi$–MX reagent, and a catalyst (1:2:0.01 mol ratio) was employed. The reactions were performed at 25 °C in THF and completed within 1 h. b) CuI (0.05 molar amount) was used. c) Pt or Ru catalyst did not accelerate the silylalumination reactions. The reaction mixture was heated at reflux for 8 h without catalyst. d) A reagent was produced by mixing the silyllithium with $ZnBr_2$ in a 2:1 ratio.



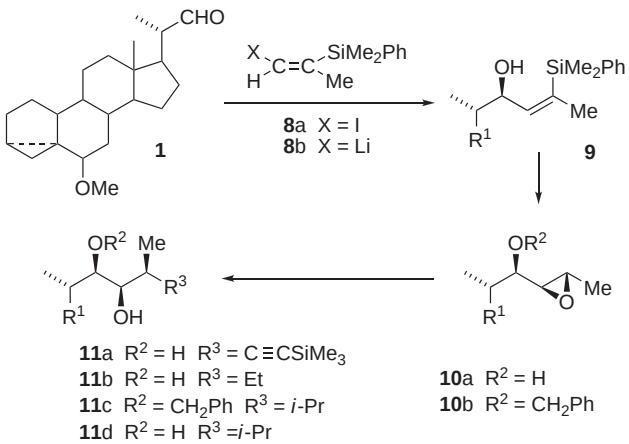
Scheme 3.



Scheme 4.

fords a simple and general method of vinylsilane synthesis (see Section **1.2**). The method, however, has two major drawbacks: (1) whereas the terminal acetylenes react with these reagents very easily, the internal acetylenes barely react, and (2) regioselective preparation of 1-silyl-1-alkenes from 1-dodecyne is easily performed with the combination of $PhMe_2SiMgMe$–CuI or $PhMe_2SiMgMe$–[$PtCl_2$(P-*n*-Bu_3)$_2$]. In contrast, it is difficult to obtain 2-silyl-1-alkenes with high regioselectivity. The combination of $PhMe_2SiAlEt_2$–[$PdCl_2$(P(*o*-tolyl)$_3$)$_2$] gave the best results so far and gave 2-silyl-1-dodecene as the main product (85%) along with the 1-silyl isomer (15%) upon treatment of 1-dodecyne. Here, we describe new silylmetalation reactions, which solve these problems.[11]

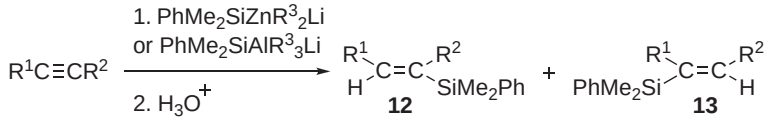
Extensive studies have been performed concerning the reactions of cuprates, such as conjugate addition or substitution.[12] In contrast, few examples are known for the synthetic utility of organozincate reagents.[13] It is well known that ate complexes,



Scheme 5.

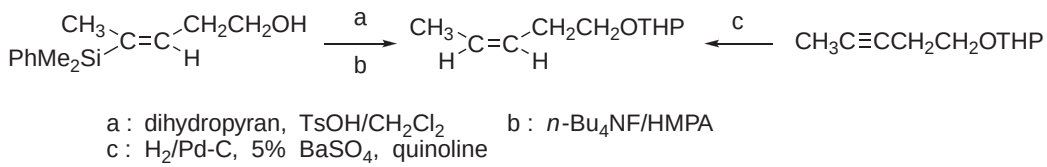
such as R_4BLi and R_4AlLi, are much more reactive than the corresponding organometallic reagents, R_3B and R_3Al.[14] Thus, the ate complexes, $PhMe_2SiZnR_2Li$ and $PhMe_2SiAlR_3Li$, were thought to be able to react with internal acetylenes as terminal ones. This was indeed the case, and representative results are shown in Table 2.[15] The reaction had following characteristics: (1) CuI, CuCN, and [$Pd(PPh_3)_4$] were effective catalysts for these silylmetalation reactions, whereas [$RhCl(PPh_3)_3$] and [$RuCl_2(PPh_3)_3$] were not efficient. The uncatalyzed reaction of silylzinc and silylaluminum compounds with

Table 2. Silylzincation and Silylalumination of Acetylenes[a)]



Entry	Substrate R^1	Substrate R^2	Reagent[b)]	Yield/%	Ratio of **12**:**13** **12**	**13**
1	*n*-$C_{10}H_{21}$	H	$PhMe_2SiZnEt_2Li$[c)]	80	75	25
2			$PhMe_2SiZnEt_2Li$	81	58	42
3			$PhMe_2SiZnEt_2Li$[d)]	60	30	70
4			$PhMe_2SiZn$-*t*-Bu_2Li	92	1	99
5	$THPOCH_2CH_2$	H	$PhMe_2SiZnEt_2Li$	80	67	33
6			$PhMe_2SiZn$-*i*-Pr_2Li	97	30	70
7			$PhMe_2SiZn$-*t*-Bu_2Li	87	1	99
8	$PhCH_2OCH_2CH_2$	H	$PhMe_2SiZnEt_2Li$	78	67	33
9			$PhMe_2SiZn$-*i*-Pr_2Li	91	33	67
10			$PhMe_2SiZn$-*t*-Bu_2Li	98	5	95
11	$HOCH_2CH_2$	H	$PhMe_2SiZn$-*t*-Bu_2Li[e)]	83	47	53
12	$HOCH_2$	CH_3	$PhMe_2SiZnEt_2Li$[e)]	85	100	0
13	$HOCH_2CH_2$	CH_3	$(PhMe_2Si)_3ZnLi$[e)]	89	100	0
14	*n*-$C_{10}H_{21}$	H	$PhMe_2SiAlMe_3Li$	78	67	33
15			$PhMe_2SiAlEt_3Li$[c)]	73	64	36
16			$PhMe_2SiAl$-*t*-Bu_3Li[c)]	65	40	60
17			$PhMe_2SiAl$-*t*-Bu_3Li	45	17	83
18	$PhCH_2OCH_2CH_2$	H	$PhMe_2SiAlEt_3Li$	72	83	17
19	$HOCH_2$	H	$PhMe_2SiAlEt_3Li$	89	100	0
20	$HOCH_2$	CH_3	$PhMe_2SiAlEt_3Li$[e)]	90	100	0
21	*n*-Bu(HO)CH	*n*-C_3H_7	$PhMe_2SiAlEt_3Li$[d),e)]	63	100	0

a) The reactions were performed at 25 °C in THF. Reagent (2.0 mmol), acetylene (1.0 mmol), and catalyst (CuCN, 0.02 molar amount) were employed. b) Prepared from $PhMe_2SiLi$ and the corresponding dialkylzinc (1:1) or trialkylaluminium (1:1) at 25 °C. c) $[Pd(PPh_3)_4]$ was used as a catalyst. d) $[CoCl_2(PPh_3)_2]$ was used as a catalyst. e) Reagent (3.0 mmol) and acetylene (1.0 mmol) were employed.



Scheme 6.

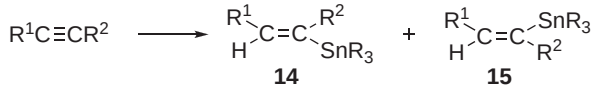
acetylenes proceeded very slowly to provide silylated olefins in low yield after prolonged reaction time. For instance, the reaction of $PhMe_2SiZnEt_2Li$ with 1-dodecyne gave a mixture of 1-[dimethyl(phenyl)silyl]-1-dodecene and the 2-silyl isomer (5:3) in 13% combined yield after stirring at 25 °C for 20 h. (2) The regioselectivity of the reaction was strongly affected by the nature of the dialkylzinc and trialkylaluminum employed. The use of bulky alkyl group favors the formation of 2-silyl-1-alkenes. The silylzinc reagent $PhMe_2SiZn$–*t*-Bu_2Li[16] gave higher regioselectivity than the silylalanate, $PhMe_2SiAl$–*t*-Bu_3Li.[17] In the case of the former reagent, high selectivity (>95%) was achieved for all examined substrates, except Entry 11 in Table 2. The selective preparation of 1-[dimethyl(phenyl)silyl]-1-alkenes has already been achieved with $PhMe_2SiMgMe$ in the presence of CuI or $[PtCl_2(P$-*n*-$Bu_3)_2]$ catalyst. Thus, we succeeded in obtaining both regioisomers with high selectivity (>95%). (3) Regioselective silylmetalation was performed for 2-propynyl and 3-pentynyl alcohols. As shown in Table 2 (Entries 12 and 13), 2-butyn-1-ol or 3-pentyn-1-ol gave (*E*)-3-[dimethyl(phenyl)silyl]-2-buten-1-ol or (*E*)-4-[dimethyl(phenyl)silyl]-3-penten-1-ol as a single product. The silylanion attacked the remote acetylenic carbon from the hydroxy group exclusively.

The *syn* mode of the addition was confirmed by comparing the tetrahydropyranyl ether of (*Z*)-3-penten-1-ol derived from the silylzincation product of 3-pentyn-1-ol (Entry 13 in Table 2) with an authentic sample (Scheme 6).

2. Et_3B-Induced Radical Addition of R_3SnH and R_3GeH to Acetylenes

During the course of our studies on various ate complexes, the behavior of *n*-Bu_3SnBEt_3Li was examined. The addition of the ate complex to acetylenes required the presence of a proton source, such as methanol, so that the intermediary vinylborane

Table 3. Et_3B-Induced Hydrostannylation of Acetylenes



Acetylene	Reagent	Reaction time/h	Yield/%	Ratio of **14**:**15**
n-$C_{10}H_{21}C{\equiv}CH$	Ph_3SnH	0.3	80	79:21
	n-Bu_3SnH	2.0	40	80:20
$PhCH_2OCH_2CH_2C{\equiv}CH$	Ph_3SnH	0.3	79	69:31
	n-Bu_3SnH	10	71	90:10
$THPOCH_2CH_2C{\equiv}CH$	Ph_3SnH	0.3	81	80:20
	n-Bu_3SnH	2.0	49	90:10
$HOCH_2CH_2C{\equiv}CH$	Ph_3SnH	0.3	87	82:18
	n-Bu_3SnH	2.0	40	69:31
$PhC{\equiv}CH$	Ph_3SnH	0.3	75	100:0
$Me_3SiC{\equiv}CH$	Ph_3SnH	0.3	83[b)]	100:0
n-$C_5H_{11}C{\equiv}C$-n-C_5H_{11}	Ph_3SnH	10	86[c)]	0:100
$PhC{\equiv}CCH_3$	Ph_3SnH	1.0	74	25:75

a) Acetylene (1.0 mmol), R_3SnH (1.2 mmol), and Et_3B (0.1 mmol) were employed. b) Excess of (trimethylsilyl)acetylene (5.0 mmol) and Ph_3SnH (1.0 mmol) were employed and the yield was based on Ph_3SnH. c) Excess of Ph_3SnH (5.0 mmol) was used.

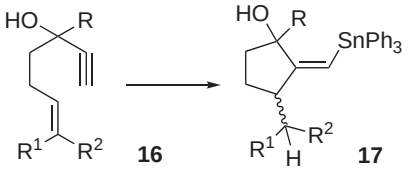
species could not be used for further transformation.[18] Next, we studied the reaction of acetylenes with a reagent that was prepared from Et_3B and Ph_3SnH and believed to be Ph_3SnBEt_2. Treatment of 1-dodecyne with the reagent gave a mixture of (*E*)- and (*Z*)-1-(triphenylstannyl)-1-dodecene. However, the expected intermediary vinylborane could not be trapped by any electrophiles, such as D_2O, MeI or allyl bromide. The ^{11}B NMR spectrum of a solution of Et_3B showed no change upon treatment with Ph_3SnH. These facts indicated that the reagent did not have the structure of Ph_3SnBEt_2, and it turned out that the reaction proceeded via free radical chain mechanism.

2.1 Et_3B-Induced Radical Addition of R_3SnH to Acetylenes and Its Application to Cyclization Reactions. The cyclization of vinyl acetylene to methylene-substituted five-membered rings has been described by Stork and Mook.[19] We have studied this reaction further and reported that trialkylborane mediates a facile addition of R_3SnH to an acetylenic bond to give vinylstannane regioselectively and that this new method has been applied to vinyl radical cyclization reactions[20,21] effectively.

The hydrostannylation of acetylenes[22] takes place readily either in the absence of a catalyst or in the presence of a catalytic amount of free radical initiator such as azobisisobutyronitrile (AIBN),[23] but these reaction conditions (without solvent, heat to 80–100 °C) may not always be suitable for an intramolecular radical cyclization reaction.[21f]

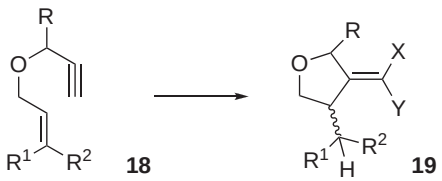
We found that an addition of a catalytic amount of Et_3B to a solution of acetylenic compound and Ph_3SnH (or n-Bu_3SnH) in toluene promotes the formation of vinylstannanes effectively.[24] Representative results are summarized in Table 3. The triphenylstannyl group adds to the terminal acetylenic carbon regioselectively, but non-stereoselectively, to give a mixture of (*E*)- and (*Z*)-1-(triphenylstannyl)-1-alkenes. The *E*/*Z* ratios of double bonds were generally 8/2–7/3 and were not affected by solvents and reaction temperature. The ratios of (*E*)-1-(triphenylstannyl)-1-dodecene and the *Z* isomer were 79/21, 80/20, 77/23, and 63/37 in toluene, benzene, Et_2O, and THF, respectively. In contrast, Corey et al. have reported[23] that the *E*/*Z* ratios depend on the reaction temperature in the case of uncatalyzed hydrostannylation. Heating a mixture of 1-dodecyne and Ph_3SnH at 80 °C for 1.5 h gave a mixture of (*E*)- and (*Z*)-1-(triphenylstannyl)-1-dodecene (*E*/*Z* = 22/78) in 53% combined yield. A mixture of the *E* and *Z* isomer (*E*/*Z* = 75/25, 65% yield) was obtained after 5 h at 150 °C. Phenylacetylene and (trimethylsilyl)acetylene afforded (*E*)-vinylstannanes exclusively. Addition of n-Bu_3SnH required a longer reaction time and gave the corresponding vinylstannanes in poor yields.

The reaction was successfully applied to the radical cyclization reactions shown in Schemes 7–9. The concentration of Ph_3SnH affected the yield and distribution of the products. An uncyclized product was obtained in addition to the cyclized desired compound in a higher concentration. For instance, compound **16a** gave cyclized product **17a** exclusively at 0.02 M concentration of Ph_3SnH, whereas, at 0.30 M concentration, **17a** and uncyclized product $Me_2C{=}CHCH_2CH_2C(OH)MeCH{=}CHSnPh_3$ were obtained in 60 and 15% yield, respectively. Heating a mixture of **16a** and Ph_3SnH without solvent at 80 °C for 15 h gave a complex mixture consisting of (*E*)- and (*Z*)-vinylstannanes ($Me_2C{=}CHCH_2CH_2C(OH)MeCH{=}CHSnPh_3$, 46%), a regioisomer ($Me_2C{=}CHCH_2CH_2C(OH)MeC(SnPh_3){=}CH_2$, 9%) and the desired cyclized product **17a** (38% yield). It is worth noting that the serious limitation, i.e., the non-stereoselectivity, shown in Table 3, was overcome in these cyclization reactions and the cyclized products consist of only the *Z* isomer without contamination by the other stereoisomer. The formation of a single isomer may be explained by assuming the rapid cyclization of the intermediary radical **A**, which is generated by the kinetically favored *anti* addition of the triphenylstannyl radical. Isomerization of **A** to **B** can be slow compared to cyclization (Scheme 10). Com-



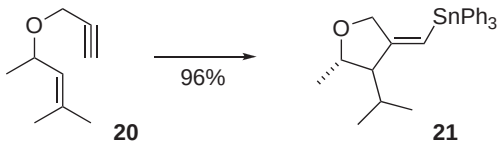
a : R = Me $R^1 = R^2$ = Me 75% (78/22)
b : R = Me $R^1 = R^2$ = H 50% (80/20)
c : R = Me R^1 = Me $R^2 = CH_2CH_2CH{=}CMe_2$ 78% (79/21)
d : R = n-C_5H_{11} R^1 = H R^2 = Ph 87% (63/37)

Scheme 7.

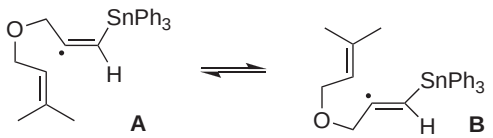


a : R = H $R^1 = R^2$ = Me
X = $SnPh_3$ Y = H (78%)
b : R = H R^1 = H $R^2 = n$-C_3H_7
X = $SnPh_3$ Y = H (85%)
c : R = n-Bu $R^1 = R^2$ = Me
X = $SnPh_3$ Y = H (69%, 64/36)
d : R = H $R^1 = R^2$ = Me X = Ha Y = Hb
e : R = H $R^1 = R^2$ = Me X = $SnPh_3$ Y = D
f : R = H $R^1 = R^2$ = Me X = H Y = D

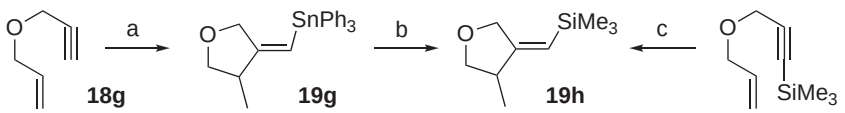
Scheme 8.



Scheme 9.



Scheme 10.



a : Ph_3SnH, Et_3B b : n-BuLi/Me_3SiCl c : $ZrCp_2$

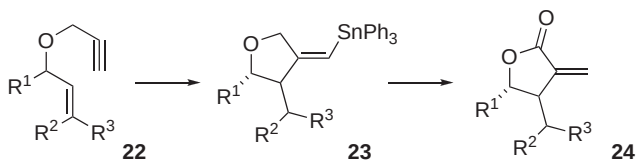
Scheme 11.

pound **19d** derived from **19a** by destannylation (n-BuLi/THF, H_2O)[25] showed ^{1}H NMR signals at δ 5.00 (m, H_a) and 4.95 (m, H_b). Treatment of deuterated acetylene **18a** ($DC{\equiv}CCH_2OCH_2CH{=}CMe_2$) with Ph_3SnH followed by destannylation provided **19f**, of which the ^{1}H NMR spectrum showed only one signal in the olefinic region at δ 4.99. The complete disappearance of the higher field signal is consistent with the formation of single stereoisomer **19e**.

The structure of the cyclized product was also confirmed as follows (Scheme 11). Treatment of **18g** ($R = R^1 = R^2 = H$) with our new method provided **19g** (32% yield) along with the six-membered ring product 3-(triphenylstannyl)methylene-tetrahydropyran (45%). Vinylstannane **19h** was identical with the sample prepared from allyl 3-(trimethylsilyl)-2-propynyl ether following Negishi's procedure.[26]

Compounds **16a**–**16d** and **18c** provided *cis*–*trans* stereoisomeric mixtures concerning the substituents on a five-membered ring. In contrast, compound **20** gave *trans* isomer **21** as a single product. This stereoselective cyclization reaction was applied[27] to the synthesis of α-methylene-γ-butyrolactones, which represent a major class of known natural products and possess wide-ranging biological activities.[28] The results are summarized in Table 4. Cyclized products **23a**–**23d** consist of only (*Z*)-*trans*-isomers, independently of the stereochemistry of the double bond in the starting enynes **22a** and **22d**. In contrast, treatment of **22e** with Ph_3SnH gave *cis*-fused oxolane **23e** exclusively, which is thermodynamically more stable than the *trans*-isomer. Destannylation, followed by oxidation with $CrO_3{\cdot}2py$,[29] gave the desired α-methylene-γ-butyrolactones **24** (Scheme 12).

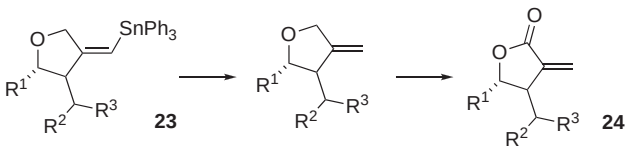
Table 4. Synthesis of α-Methylene-γ-butyrolactones



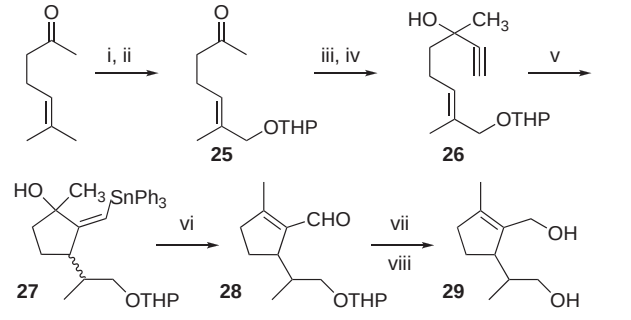
				Yield/%	
22	R^1	R^2	R^3	**23**	**24**[a)]
a	Ph	Ph	Me	84	57
b	Ph	Me	Me	70	39
c	n-C_4H_9	H	n-C_3H_7	83	41
d	Me	n-C_4H_9	H	75	59
e	$-(CH_2)_4-$		H	71[b)]	31

a) Overall yield from **22**. b) *cis*-Product was obtained.

Scheme 13 illustrates the synthesis of dehydroiridodiol and



Scheme 12.



i) SeO_2/EtOH-H_2O ii) Dihydropyran, TsOH iii) $Me_3SiC{\equiv}CLi$
iv) KF/DMSO v) Ph_3SnH, Et_3B vi) $CrO_3{\cdot}2Py$ vii) *i*-Bu_2AlH
viii) TsOH/MeOH

Scheme 13.

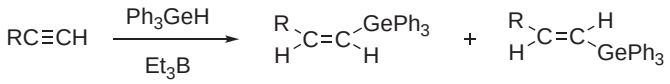
isodehydroiridodiol. The triethylborane-induced triphenyltin radical addition–cyclization process gave vinylstannane **27** (84%) starting from readily available 2-propynyl alcohol **26**. Collins oxidation of **27** gave **28** (54%). Diisobutylaluminum hydride reduction, followed by treatment with *p*-TsOH, afforded a mixture of dehydroiridodiol ($3R^*$, $8S^*$) and isodehydroiridodiol ($3R^*$, $8R^*$) (26/74, 58% overall yield from **28**),[30] which was easily separated by preparative TLC on silica gel.

The reaction was not so effective for the formation of a six-membered ring. For instance, treatment of $HC{\equiv}CCH_2OCH_2CH_2CH{=}CHCH_2CH_3$ gave the desired cyclized product in only 28% yield along with uncyclized vinylstannane (49%). Addition of galvinoxyl to a reaction mixture of 1-dodecyne, Ph_3SnH, and Et_3B resulted in the recovery of the acetylene (73%). Organoboranes are known to be excellent sources of free radicals in the presence of oxygen.[31] Thus, we think a radical chain mechanism may be occurring. Trace oxygen could be in a reaction mixture and initiate the free-radical reaction, although the reactions have been achieved under an argon atmosphere.[32]

2.2 Et_3B-Induced Stereoselective Radical Addition of Ph_3GeH to Acetylenes and Its Application to the Isomerization of Olefins. Free radical reactions have increasingly been used in recent years for the synthesis of organic molecules. The hydrogermylation[33] or hydrostannylation of acetylenes takes place readily either in the absence of a catalyst or in the presence of catalytic amount of free radical initiator, such as azobisisobutyronitrile (AIBN). These reactions producing the corresponding alkenyltrialkylgermane or alkenyltrialkylstannane are of particular synthetic interest; however, they have a serious limitation. Thus, the reactions are generally not highly regio- and stereoselective. Moreover, the mechanism of the reactions does not appear to have been well established, mainly because the products can undergo isomerization under hydrogermylation or hydrostannylation reaction conditions. Here, we want to show that trialkylborane facilitates the addition of Ph_3GeH to acetylenes to give (*E*)- or (*Z*)-alkenyltriphenylgermanes, respectively, under excellent control of regio- and stereoselectivities.[34]

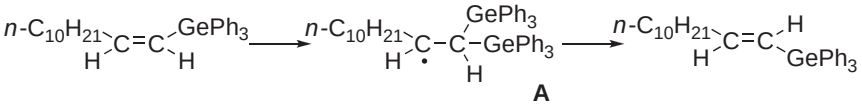
Representative results are summarized in Table 5. The isomeric ratios of the products heavily depended on the reaction temperature and the ratio of [acetylene]/[Ph_3GeH]. This is a big difference from the Et_3B-induced addition reactions of Ph_3SnH to acetylenes. In the case of Ph_3SnH, the ratios of the products, (*E*)-alkenyltriphenylstannane and its (*Z*)-isomer,

Table 5. Stereoselective Hydrogermylation of Acetylenes

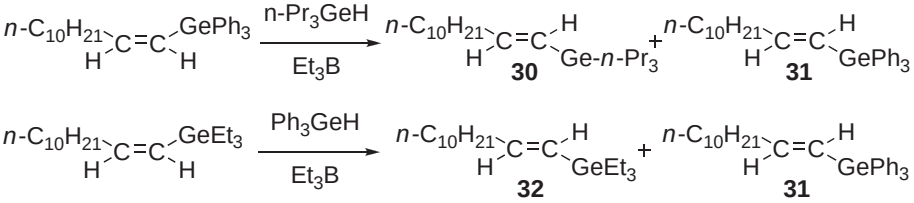


Entry	Acetylene R	Reaction conditions Temperature/°C		Time/h	Product Yield/%[a]	Z/E[b]
1	*n*-$C_{10}H_{21}$	−78[c]		3	76	>20/1
2		−20[d]		2	78	2/1
3		25[d]		2	77	1/9
4		60[d]		2	99	<1/20
5		0[d]	(THF)	2	84	8/1
6		0[d]	($PhCH_3$–MeOH)	2	80	10/1
7	CH_3	−78[e]		2	65	>20/1
8	$HOCH_2CH_2$	−78[c]		5	80	>20/1
9		60[d]		15	75	<1/20
10	$HOCH_2CH_2CH_2CH_2$	−78[c]		5	80	>20/1
11	$EtOOC(CH_2)_9$	−78[c]		12	64	>10/1
12		60[d]		15	93	<1/20
13	6-Dodecyne	−78[c]		8	65	>20/1

a) Isolated yields. b) Determined by GC and/or NMR. c) Acetylene (1.1 mmol), Ph_3GeH (1.0 mmol), and Et_3B (1.0 mmol) were employed. Toluene was used as solvent. d) Acetylene (1.0 mmol), Ph_3GeH (1.1 mmol), and Et_3B (1.0 mmol) were employed. Benzene was used as solvent unless otherwise noted. e) Propyne (3.0 mmol), Ph_3GeH (1.0 mmol), and Et_3B (1.0 mmol) were employed.



Scheme 14.



Scheme 15.

were always 8/2–7/3 and not affected by the reaction temperature and the ratio of [acetylene]/[Ph_3SnH]. In contrast, the reaction of Ph_3GeH at $-78\,^{\circ}C$ in toluene in the presence of slight excess of the acetylene afforded (*Z*)-alkenyltriphenylgermane exclusively, whereas the reaction at $60\,^{\circ}C$ in benzene with slight excess of Ph_3GeH gave (*E*)-alkenyltriphenylgermane as a single product. Solvent also affects the isomeric ratio of the products. In polar solvents, the (*Z*)-isomer was obtained as the major product. For instance, treatment of 1-dodecyne with Ph_3GeH–Et_3B in THF at $0\,^{\circ}C$ for 2 h gave a mixture of (*Z*)-1-triphenylgermyl-1-dodecene and (*E*)-isomer ($Z/E = 8/1$) in 84% yield. Addition of methanol (10 mmol per 1.0 mmol of substrate) to toluene was also effective for the selective formation of (*Z*)-isomer (Entry 6 in Table 5).

Et_3B-induced additon of *n*-Pr_3GeH to acetylenes did not give high stereoselectivity as compared to the addition of Ph_3GeH. For instance, the reaction of 1-dodecyne with *n*-Pr_3GeH at $60\,^{\circ}C$ in the presence of Et_3B gave an isomeric mixture of (*E*)-1-tripropylgermyl-1-dodecene and (*Z*)-isomer in 79% yield ($E/Z = 2/1$). The amount of Et_3B could be reduced to 0.1 mol per 1.0 mol of acetylene without any decrease in the yield and the reaction rate at the temperature above $0\,^{\circ}C$. However, the reaction rate drops considerably at low temperature, such as $-78\,^{\circ}C$. Thus, the use of stoichiometric amounts of Et_3B is recommended in these cases. *i*-Pr_3B and (*n*-$C_8H_{17})_3B$ were as effective as Et_3B. Et_3B initiates the radical reaction at low temperature, such as $-78\,^{\circ}C$, which is a great advantage. Ordinary radical initiators, such as AIBN and *t*-BuOO-*t*-Bu, require the reaction mixture be heated (80–130 °C) to promote the reaction, so that the isomerization of the produced alkenylgermanes easily takes place under such conditions.

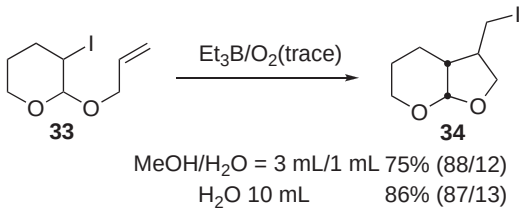
It was anticipated that the *anti* addition products (i.e., (*Z*)-isomers) were kinetic-controlled products and isomerized into (*E*)-isomers under thermodynamic conditions. This was indeed the case as demonstrated by the isomerization of (*Z*)-1-triphenylgermyl-1-dodecene into the (*E*)-isomer. Heating a benzene solution of (*Z*)-1-triphenylgermyl-1-dodecene at $60\,^{\circ}C$ in the presence of catalytic amounts of Ph_3GeH and Et_3B gave (*E*)-isomer exclusively. The isomerization is explained by addition–elimination sequences of the triphenylgermyl radical (Scheme 14). The germyl radical, $Ph_3Ge\bullet$, attacks the olefin to give a radical intermedeate **A**. Free rotation scrambles the stereochemistry, so that the composition of the mixture reaches the thermodynamic equilibrium.[35] This mechanism is supported by the following facts that treatment of (*Z*)-1-triphenylgermyl-1-dodecene (1.0 mmol) with *n*-Pr_3GeH–Et_3B (1.0 mmol each) at $60\,^{\circ}C$ gave a mixture of (*E*)-1-tripropylgermyl-1-dodecene (**30**) and (*E*)-1-triphenylgermyl-1-dodecene (**31**) (**30**/**31** = 2/5) and that treatment of (*Z*)-1-triethylgermyl-1-dodecene with Ph_3GeH–Et_3B gave (*E*)-1-triethylgermyl-1-dodecene (**32**) and (*E*)-1-triphenylgermyl-1-dodecene (**31**) (**32**/**31** = 2/5, Scheme 15).

3. Synthetic Radical Reactions in Aqueous Media

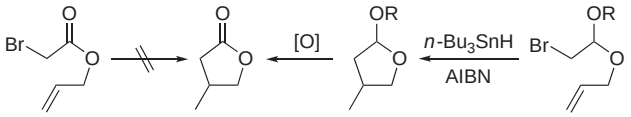
The choice of a solvent, which is crucial for controlling ionic reaction, had been mostly neglected for radical reactions. Benzene is a standard solvent for radical reaction because of the absence of easily transferable hydrogen. The accepted wisdom that most radical reactions show small solvent effects has been widespread.[36] Some organic chemists, who were interested in basic studies, focused on the influence of the solvent on radicals,[37] and many synthetic chemists have accepted the standard solvent system.

Water has special physical properties and has, therefore, provided fascinating solvent effects in conventional ionic reactions, such as the S_N1 reaction. In 1982, the solvent effect of water on the Diels–Alder reactions, a concerted reaction, was discovered.[38] Since then, reactions in aqueous media have attracted much attention from economical, environmental, and scientific points of view.[39] However, synthetic radical reactions in aqueous media have been scarcely investigated.[40] We anticipated interesting solvent effects of water on the radical reaction and began to develop radical reactions of synthetic use in aqueous media in 1997.

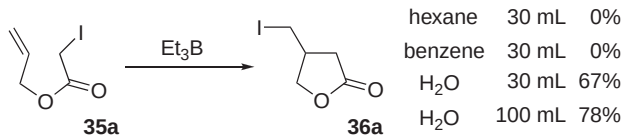
3.1 Triethylborane-Induced Iodine Atom Transfer Radical Cyclization of Iodo Acetals and Allylic Iodoacetates in Aqueous Media.[41] At the beginning of this project, we needed to choose the initiator to be employed. Triethylborane seemed the most attractive to avoid conceivable solvolysis of the substrates and products, because triethylborane-induced reactions can be performed at ambient temperature. To explore the application of water as a solvent, a methanol solution of triethylborane was used as a suitable initiator for its easy handling as well as for minimizing the influence of an additional solvent. We were initially anxious about the stability of triethylborane in methanol. Trialkylboranes are said to be stable in a protic medium, except in carboxylic acids, whereas triethylborane is well known for spontaneous ignition on expo-



Scheme 16.



Scheme 17.



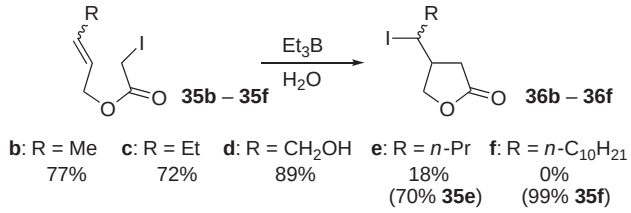
Scheme 18.

sure to air. It was doubtful that triethylborane, a very flammable liquid, could be safely diluted with methanol. Fortunately, we were able to safely prepare a methanol solution of triethylborane under argon. The stability of triethylborane in methanol was checked by examining the ^{1}H NMR spectrum of a CD_3OD solution of triethylborane. The solution worked as well for several months when stored under an argon atmosphere.

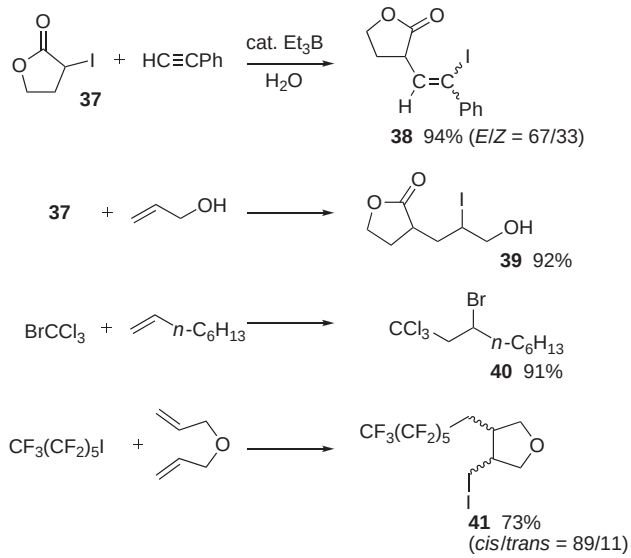
We performed the iodine atom transfer radical cyclization[42] of iodo acetals in aqueous methanol as the first trial since the system was homogeneous and tin-free (Scheme 16). Iodo acetal **33** was dissolved in aqueous methanol, and triethylborane in methanol was added to the homogeneous solution to afford the corresponding tetrahydrofuran derivative **34** in good yield. This success prompted us to perform this reaction in water, in which a heterogeneous reaction medium was formed. A similar reaction in water provided **34** in comparable yield. We confirmed that radical reaction could be performed in water, irrespective of the homogeneity of the reaction.

Our attention moved to atom transfer radical cyclization of allyl iodoacetate. An indirect halo acetal method has been developed by Stork et al. and Ueno et al.,[43] because direct cyclization of α-halo esters into γ-butyrolactones is an inefficient process. Lactones are usually synthesized by means of this strategy, by oxidation of the products prepared from radical cyclization of bromo acetal (Scheme 17).

Indeed, treatment of allyl iodoacetate (**35a**) with triethylborane in benzene or hexane at room temperature did not yield lactone **36a** (Scheme 18). The iodide was consumed, and polymeric products formed. In contrast, in water, **35a** cyclized much more smoothly in the presence of triethylborane at ambient temperature, and the reaction yielded lactone **36a** in high yield. The yield of **36a** increased at lower concentration. This powerful solvent effect also operated in a related system (Scheme 19). 2-Butenyl iodoacetate (**35b**) and 2-pentenyl iodoacetate (**35c**) provided the corresponding lactones **36b** and **36c**, respectively, in satisfactory yield. In contrast, iodoacetates **35e** and **35f**, which have longer alkyl substituents, such as propyl



Scheme 19.



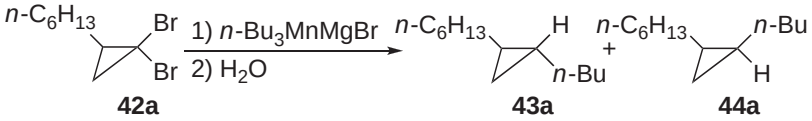
Scheme 20.

and decyl groups, on the terminal olefinic carbon, afforded the corresponding lactones in very poor yields. Most of the starting material was recovered. In this reaction, the yields of lactone might be parallel to the solubility of α-iodo ester in water.

3.2 Atom Transfer Radical Addition of Halogenated Compounds in Water.[44] We continued to investigate triethylborane-induced radical reaction in water. The next target was intermolecular addition of halogenated compounds to carbon–carbon multiple bonds. Triethylborane effected radical addition of α-iodo lactone **37** to phenylacetylene in water. Adduct **38** was obtained quantitatively (Scheme 20). It is worth noting that the reactions in water were much more effective than the reactions without solvent (**38**, 32%, 3 days).

4. Synthetic Use of ate Complexes (R_3MnLi and R_3MgLi) and Catalytic Reactions Mediated by Manganese or Cobalt Complexes

4.1 Synthetic Reactions with Organomanganese Reagents. Organomanganese reagents are among the less expensive organo transition metal compounds due to the low cost of manganese metal. However, contrary to organocopper reagents, which have been extensively studied in organic synthesis, organomanganese compounds have been almost ignored until 1976. Then, professors J. F. Normant and G. Cahiez reported studies on the preparation of organomanganese reagents and subsequent synthetic applications of these compounds.[45] They have introduced procedures for preparation of three types of organomanganese reagents: organomanganese halide (RMnX), dialkylmanganese (R_2Mn), and organomanganate



Scheme 21.

(R_3MnMtl). Among them, trialkylmanganate is the most stable reagent, and it is stable at room temperature. Meanwhile, dialkylmanganese compounds, such as n-Bu_2Mn is unstable and decomposes at $-30\,^{\circ}C$. The stability of RMnX is between dialkylmanganese and trialkylmanganate. Taking into account the stability and reactivity, we chose trialkylmanganate and examined several reactions.

4.1.1 Dialkylation of *gem*-Dibromocyclopropanes with Trialkylmanganate and Manganese(II) Chloride-Catalyzed Reaction with Alkylmagnesium Bromide: Cyclopropane derivatives are versatile synthetic intermediates. Double alkylation of *gem*-dihalocyclopropanes, which can be easily prepared by the addition of dihalocarbene to olefins, provides us with an effective route to a variety of functionalized cyclopropane derivatives. The transformation of *gem*-dihalocyclopropanes into 1-alkyl-1-butylcyclopropanes has been reported to proceed by successive treatment with dibutylcuprate[46] or tributylzincate[47,48] and several electrophiles. Here, we show that the reaction of *gem*-dibromocyclopropanes with trialkylmanganate, followed by treatment with electrophiles, affords dialkylated cyclopropanes as in the case of the reaction with cuprates or zincates and also that the reaction of *gem*-dibromocyclopropanes with alkylmagnesium halides takes place in the presence of a catalytic amount of manganese(II) chloride.

Treatment of *gem*-dibromocyclopropane **42a** with tributylmanganate, generated from $MnCl_2$ and 3.0 molar amount of butylmagnesium bromide, gave a mixture of *trans*-1-butyl-2-hexylcyclopropane (**43a**) and *cis*-isomer **44a** in 89% combined yield (**43a**/**44a** = 71/29) (Scheme 21).

Various *gem*-dibromocyclopropanes were allowed to react first with trialkylmanganate, triallylmanganate, or tris(dimethylphenylsilyl)manganate[49] and then with a variety of electrophiles. The results are summarized in Table 6. Among the solvent systems examined (THF, ether, and DME), THF gave the best results. Several observations are worth noting: (1) In contrast to the reaction with cuprate or zincate, which was performed at -48 or $-85\,^{\circ}C$, the reaction with manganate could be performed conveniently at $0\,^{\circ}C$. The reaction of **42a** with n-Bu_3MnLi at $-78\,^{\circ}C$ for 30 min provided 1-bromo-2-hexylcyclopropane[50] (*cis*/*trans* = 2/1) in 65% yield in addition to an isomeric mixture of 1-butyl-2-hexylcyclopropane (**43a**/**44a** = 76/24, 30% yield). Moreover, treatment of **42a** with n-$Bu_3MnMgBr$ at $-78\,^{\circ}C$ for 30 min resulted in almost complete recovery of **42a**. (2) Tributylmanganesemagnesium bromide, derived from $MnCl_2$ and 3.0 molar amount of butylmagnesium bromide, afforded better yields of butylated cyclopropanes **43** and **44** than tributylmanganeselithium generated from butyllithium (Entry 1 vs. 2, 11 vs. 12). (3) Triphenylmanganate $Ph_3MnMgBr$ or Ph_3MnLi gave phenylated cyclopropane in 34% or 30% yield, respectively, upon treatment of **42a**. (4) $(CH_2{=}CH)_3MnMgBr$ and $(Me_3Si{-}C{\equiv}C)_3MnMgBr$ gave a minimal amount of the corresponding alkenyl- or alkynylcyclopropanes (<5%). Manganates having secondary and tertiary alkyl ligands, such as i-$Pr_3MnMgBr$ and t-$Bu_3MnMgCl$, gave 1-bromo-2-hexylcyclopropane in 50–55% yield along with an unidentified complex mixture, which did not contain the desired isopropylcyclopropane or *tert*-butylcyclopropane. (5) The intermediary cyclopropylmanganese reagents **46** could be trapped by acid chloride,[51] iodine, and vinyl bromide (in the presence of $[Pd(PPh_3)_4]$ (0.10 molar amout))[52] as well as methyl iodide and allyl bromide. (6) 1,1-Dichlorocyclopropanes, such as 9,9-dichlorobicyclo[6.1.0]-nonane, were found to be unreactive.

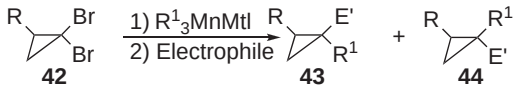
We are tempted to assume a similar reaction mechanism for the reaction with cuprates and zincates (Scheme 22): (1) initial halogen–manganese exchange at the less hindered bromine to affords **45**, (2) alkyl migration under Br^- elimination producing **46** (inversion at the cyclopropane carbon), and (3) the second alkylation by R^2X with retention of the configuration. The stereoselective formation of **43** might be attributed to the bulkiness of the manganese reagents which attack the less hindered halogen selectively.

Moreover, the reaction proceeded in the presence of a catalytic amount of manganese(II) chloride. For instance, addition of a solution of dibromocyclopropane **42a** to a THF solution of butylmagnesium bromide and manganese(II) chloride (0.10 molar amout) at $0\,^{\circ}C$ gave 1-butyl-2-hexylcyclopropane **43a** and **44a** in 75% combined yield after aqueous workup. In contrast, the reaction of **42a** with butylmagnesium bromide without manganese(II) chloride gave 1,2-nonadiene in 95% yield. Representative results of the catalytic reactions are shown in Table 7.

4.1.2 Reaction of *gem*-Dibromoalkanes with Trialkylmanganate(II): Treatment of 1,1-dibromodecane **47** with tributylmanganate, generated from $MnCl_2$ and three molar amounts of butyllithium, gave a mixture of 4-tetradecene (**48**, $E/Z = 92/8$) and 5-tetradecene (**49**, $E/Z = 92/8$) in 95% combined yield (**48**/**49** = 1/1) (Scheme 23). The use of butylmagnesium bromide in place of butyllithium gave the same isomeric mixture **48** and **49** (**48**/**49** = 1/1) in 91% yield. The reaction proceeded in the presence of a catalytic amount of manganese(II) chloride. Thus, addition of a solution of **47** (1.0 mmol) to a THF solution of butylmagnesium bromide (3.0 mmol) and manganese chloride (0.1 mmol) at $0\,^{\circ}C$ gave **48** and **49** in 83% combined yield.

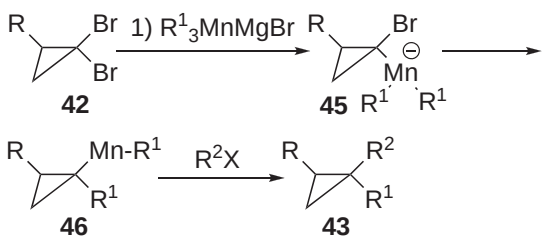
The reaction was applied to the preparation of alkenylsilanes,[53] and representative results are shown in Table 8 and Scheme 24. Several results are worth noting. (1) Both the stoichiometric reaction and the catalytic reaction were equally effective for the formation of 1-trialkylsilyl-1-alkenes.[54] (2) (*E*)-Alkenylsilanes were obtained exclusively, and no trace of the *Z*-isomers could be detected in the reaction mixture. (3) Among various manganese salts examined, $MnCl_2$, $Mn(acac)_3$, and $Mn_2(CO)_{10}$ proved to be good catalysts. For instance, treatment of i-$Pr_3SiCHBr_2$ with ethylmagnesium bromide in the presence of these catalysts gave (*E*)-1-triisopropylsilyl-1-

Table 6. Stereoselective Dialkylation of *gem*-Dibromocyclopropanes[a)]



Entry	Substrate **1**	$R^1{}_3MnMtl$	Electrophile	Yield/%	Isomeric ratio of **43**/**44**
1		*n*-Bu_3MnLi	EtOH[b)]	53	68/32
2		*n*-$Bu_3MnMgBr$	H_2O	89	71/29
3		*n*-$Bu_3MnMgBr$	CH_2=$CHCH_2Br$	77	89/11
4	*n*-C_6H_{13} Br Br **42a**	*n*-$Bu_3MnMgBr$	MeI	65	94/6
5		*n*-$Bu_3MnMgBr$	PhCOCl	72	83/17
6		*n*-$Bu_3MnMgBr$	I_2	54	72/28
7		*n*-$Bu_3MnMgBr$	CH_2=$CHBr$[c)]	58	99/1
8		*n*-$Hex_3MnMgBr$	H_2O	61	86/14
9		*n*-$Hex_3MnMgBr$	CH_2=$CHCH_2Br$	69	88/12
10		$(PhMe_2Si)_3MnLi$	H_2O	84	58/42
11	Br Br **42b**	*n*-Bu_3MnLi	H_2O	56	87/13
12		*n*-$Bu_3MnMgBr$	H_2O	82	97/3
13		*n*-$Bu_3MnMgBr$	CH_2=$CHCH_2Br$	88	97/3
14	Br Br **42c**	*n*-$Bu_3MnMgBr$	H_2O	64	87/13
15		*n*-$Bu_3MnMgBr$	PhCOCl	75	84/16
16		$(CH_2$=$CHCH_2)_3MnMgBr$	H_2O	64	83/17
17	Ph Br Br **42d**	*n*-$Bu_3MnMgBr$[d)]	H_2O	78	87/13
18		*n*-$Bu_3MnMgBr$[d)]	CH_2=$CHCH_2Br$	50	92/8
19	$PhCH_2OCH_2$ Br Br **42e**	*n*-$Bu_3MnMgBr$	H_2O	75	88/12
20		*n*-$Bu_3MnMgBr$	CH_2=$CHCH_2Br$	66	88/12
21	Me Me Me Br Br Me **42f**	$(PhMe_2Si)_3MnLi$	H_2O	62	—

a) The reactions were performed at 0 °C unless otherwise stated. b) Quenching the reaction with EtOH or H_2O gave the same results (yield and isomeric ratio of **43**/**44**). c) [$Pd(PPh_3)_4$] (0.1 molar amount) was added. d) The reaction was performed at −48 °C.



Scheme 22.

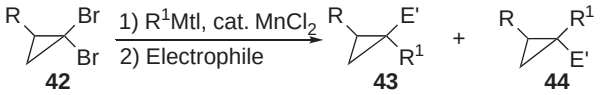
propene in 88%, 74%, or 85% yield, respectively. (4) Diiodide (*t*-$BuMe_2SiCHI_2$) was as reactive as dibromide **50b** and afforded the 1-*t*-butyldimethylsilyl-1-pentene in 88% yield upon treatment with *n*-Bu_3MnLi. Dichloride (*t*-$BuMe_2SiCHCl_2$) was less reactive than **50b**, and the reaction with *n*-Bu_3MnLi gave the same alkenylsilane in 57% yield after prolonged reaction time (25 °C, 21 h). (5) The reaction of 1,1-dibromodecane **47** with tris(trimethylsilylmethyl)manganate gave 1-trimethylsilyl-1-undecene exclusively, and no isomeric allylic silane (1-trimethylsilyl-2-undecene) could be detected (Scheme 24). The hydrogen on the carbon-bearing trimethylsilyl group was eliminated selectively.

We propose the following reaction mechanism for the stoichiometric reaction: (1) initial halogen–manganese exchange to give **52**, (2) alkyl migration under Br^- elimination providing **53**, and (3) elimination of Mn and hydrogen at the β-position[55] (Scheme 25).

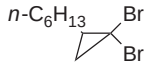
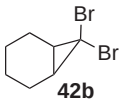
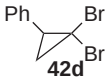
Meanwhile, the reaction mechanism for the catalytic pathway could be as follows: Low-valent manganese species Mn^0, generated from *n*-BuMnH, inserts into one of the carbon–bromine bonds to give $R_3SiCH(Br)MnBr$.[56] Attack of two molar amounts of *n*-BuMgBr on $R_3SiCH(Br)MnBr$ regenerates **52** (Scheme 26).[57]

The facility of Mn–H elimination depended on the nature of

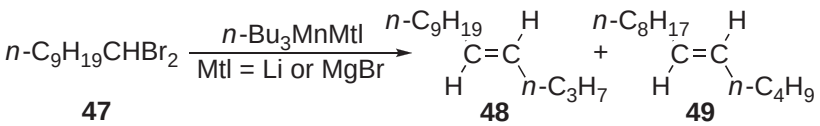
Table 7. Manganese(II) Chloride-Catalyzed Reaction of *gem*-Dibromocyclopropanes[a)]



42 **43** **44**

Entry	Substrate **42** (1.0 mmol)	R^1Mtl (3.0 mmol)	Electrophile (3.0 mmol)	Yield/%	Isomeric ratio of **43**/**44**
1		*n*-BuLi	H_2O	68	66/34
2		*n*-BuMgBr	H_2O	75	79/21
3	 **42a**	*n*-BuMgBr	CH_2=$CHCH_2Br$	57	81/19
4		CH_2=$CHCH_2MgBr$	H_2O	79	58/42
5		CH_2=$CHCH_2MgBr$	CH_2=$CHCH_2Br$	47	—
6		$PhMe_2SiLi$	EtOH	43	79/21
7	 **42b**	*n*-BuLi	H_2O	62	85/15
8		*n*-BuMgBr	EtOH	51	93/7
9	 **42d**	*n*-BuMgBr	H_2O	51	77/23

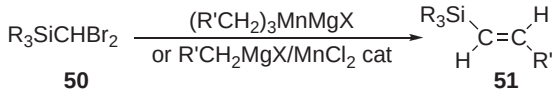
a) The reactions were performed in the presence of 0.1 mmol of $MnCl_2$.



47 **48** **49**

Scheme 23.

Table 8. Preparation of (*E*)-1-Trialkylsilyl-1-alkene[a)]

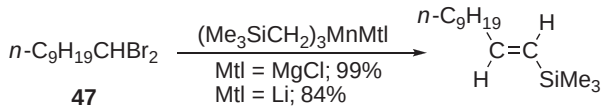


50 **51**

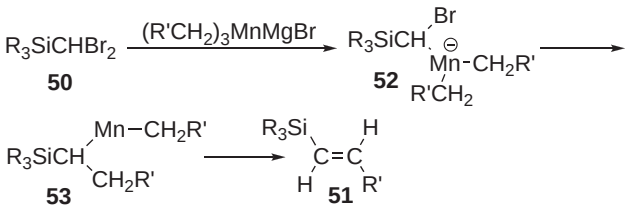
Entry		Substrate	Reagent	Time/h	Yield/%
1	**50a**	$Ph_2MeSiCHBr_2$[b)]	Me_3MnMgI	2	89
2	**50a**	$Ph_2MeSiCHBr_2$[b)]	$Et_3MnMgBr$	2	76
3	**50a**	$Ph_2MeSiCHBr_2$[b)]	*n*-Bu_3MnLi	2	95
4	**50a**	$Ph_2MeSiCHBr_2$[b)]	$(PhCH_2)_3MnMgBr$	2	88
5	**50b**	*t*-$BuMe_2SiCHBr_2$	$(Me_3SiCH_2)_3MnMgCl$	1	57
6	**50b**	*t*-$BuMe_2SiCHBr_2$	*n*-$Bu_3MnMgBr$	1	72
7	**50b**	*t*-$BuMe_2SiCHBr_2$	*n*-Bu_3MnLi	1	96
8	**50c**	*i*-$Pr_3SiCHBr_2$	$Et_3MnMgBr$	1	79
9	**50a**	$Ph_2MeSiCHBr_2$[b)]	*n*-$BuMgBr/MnCl_2$	12	67
10	**50a**	$Ph_2MeSiCHBr_2$[b)]	*n*-$C_{16}H_{33}MgBr/MnCl_2$	12	62
11	**50b**	*t*-$BuMe_2SiCHBr_2$	*n*-$BuMgBr/MnCl_2$	2	87
12	**50c**	*i*-$Pr_3SiCHBr_2$	$EtMgBr/MnCl_2$	2	88
13	**50c**	*i*-$Pr_3SiCHBr_2$	$MeMgI/MnCl_2$	2	75
14	**50d**	$Me_3SiCHBr_2$	*n*-$C_8H_{17}MgBr/MnCl_2$	2	76
15	**50e**	(*c*-$C_6H_{11})_2MeSiCHBr_2$[c)]	*n*-$BuMgBr/MnCl_2$	2	95

a) Stoichiometric reactions were performed with $R_3SiCHBr_2$ (1.0 mmol) and manganate (1.2 mmol) at 0 °C unless otherwise noted. In the catalytic reactions, Grignard reagent (3.0 mmol), $R_3SiCHBr_2$ (1.0 mmol), and $MnCl_2$ (0.05 mmol) were employed. b) The reactions were performed at 25 °C. c) *c*-C_6H_{11} = cyclohexyl.

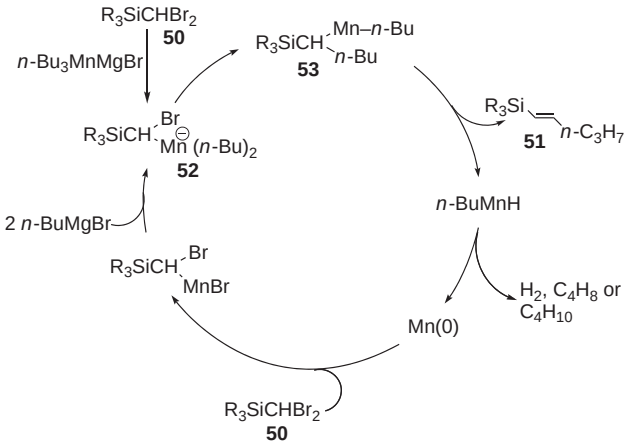
the substituents on the silicon. In the case of trialkylsilyldibromomethane, such as **50b**, **50c**, **50d**, and **50e**, elimination took place easily at 0 °C for 2 h. On the other hand, the elimination from $Ph_2MeSiCH(MnEt)Et$, derived from the reaction of **50a** with triethylmanganate, was slow and methyldiphenylpropylsilane was obtained in 17% yield along with alkenylsilane (47%). Thus, the reaction temperature was raised, and the reaction mixture of **50a** and $Et_3MnMgBr$ was stirred at 25 °C for



Scheme 24.



Scheme 25.



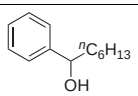
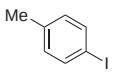
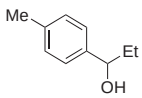
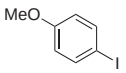
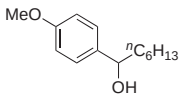
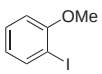
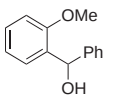
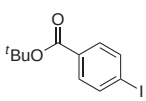
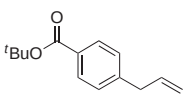
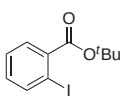
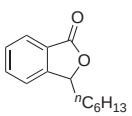
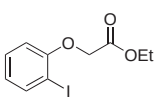
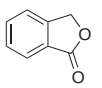
Scheme 26.

2 h to suppress the formation of methyldiphenylpropylsilane (<5%).

4.2 Trialkylmagnesate-Induced Halogen–Magnesium Exchange Reaction.[58,59] Organomagnesium compounds have a high reactivity toward functional groups, such as esters. Thus, the generation of polyfunctional organomagnesium reagents is achieved only at low temperatures. Knochel et al. have reported the halogen–magnesium exchange for the preparation of polyfunctional organomagnesium reagents.[60,61] Aryl, heteroaryl, and alkenyl halides bearing electron-withdrawing groups or metal-directing groups can be converted into the corresponding magnesium reagents by treating with *i*-PrMgBr or *i*-Pr_2Mg in THF at low temperatures. However, substrates are often limited to rather electron-poor aryl or alkenyl halides, particularly in the case of bromides. In this section, trialkylmagnesate (R_3MgLi)-induced halogen–magnesium exchange reactions are described. This reagent is highly effective for the preparation of polyfunctional aryl- and alkenylmagnesium compounds from the corresponding halides at low temperatures due to its higher reactivity than Grignard reagents.

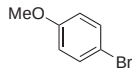
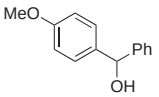
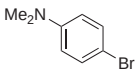
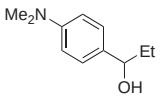
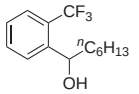
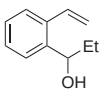
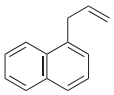
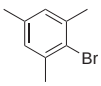
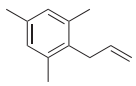
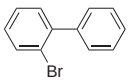
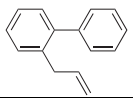
4.2.1 Iodine–Magnesium Exchange of Aryl Iodides: Iodine–magnesium exchange of aryl iodides with *n*-Bu_3MgLi, which is prepared by mixing *n*-BuMgBr and *n*-BuLi in a 1:2 ratio in THF at 0 °C, proceeded smoothly at 0 or −78 °C within 0.5 h, and the resultant arylmagnesium species were trapped by electrophiles. Examples are shown in Table 9.

Table 9. Iodine–Magnesium Exchange of Aryl Iodides with *n*-Bu_3MgLi[a)]

Entry	Substrate	Temp/°C	E^+	Product	Yield/%
1		0	$^nC_6H_{13}CHO$		80
2[b)]		−78	EtCHO		75
3		−78	$^nC_6H_{13}CHO$		94
4		−78	PhCHO		92
5[b)]		−78	CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		88
6[c)]		−78	$^nC_6H_{13}CHO$		72
7		−78			85

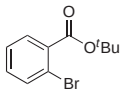
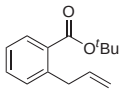
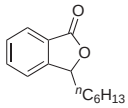
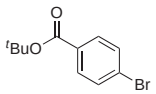
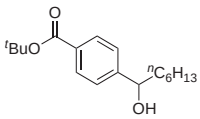
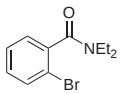
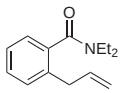
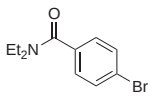
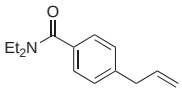
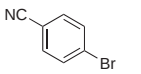
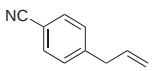
a) Substrates are treated with *n*-Bu_3MgLi (1.2 molar amount) in THF for 0.5 h. b) *n*-Bu_3MgLi (0.5 molar amount) is used for exchange. c) A solution of *n*-Bu_3MgLi is added to a THF solution of the substrate and heptanal, and the mixture is stirred for 1.5 h.

Table 10. Bromine–Magnesium Exchange of Aryl Bromides[a)]

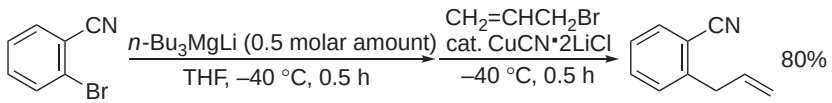
Entry	Substrate	E^+	Product	Yield /%
1[b)]		PhCHO		85
2		EtCHO		94
3		^{n}C$_6$H$_{13}$CHO		76
4[c)]		EtCHO		62
5		CH_2=$CHCH_2Br$		97
6		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		93
7		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		100

a) n-Bu_3MgLi (1.2 molar amount) is used as a reagent. All reactions are performed in THF at 0 °C for 0.5 h. b) n-Bu_3MgLi (0.5 molar amount) is used. c) n-$BuMe_2MgLi$ (1.0 molar amount) is used.

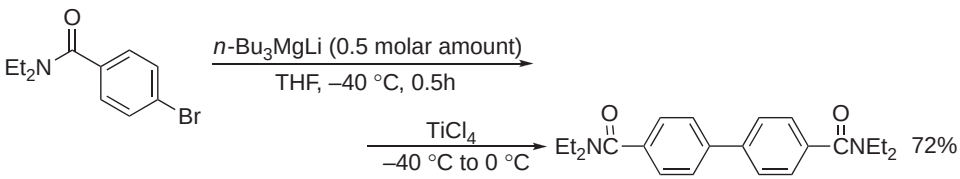
Table 11. Bromine–Magnesium Exchange of Aryl Bromides Bearing Reactive Functional Groups[a)]

Entry	Substrate	E^+	Product	Yield /%
1		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		99
2		^{n}C$_6$H$_{13}$CHO		61
3		^{n}C$_6$H$_{13}$CHO		71
4		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		80
5		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		79
6		CH_2=$CHCH_2Br$ cat. CuCN·2LiCl		87

a) i-Pr(n-Bu)$_2$MgLi (1.2 molar amount) is used as a reagent. All reactions are performed in THF at −78 °C for 1 h.



Scheme 27.



Scheme 28.

Even electron-rich aryl iodides could be converted into the corresponding arylmagnesium compounds at −78 °C (Entries 2–4). A half molar amount of the reagent was sufficient for complete exchange (Entries 2 and 5). This procedure is applicable for the preparation of polyfunctional organomagnesium compounds. Iodobenzoates were converted into the magnesium species without a loss of the ester group (Entries 5 and 6). The ester group of ethyl (2-iodophenoxy)acetate survived under the reaction conditions, and 3-coumaranone was obtained via intramolecular attack of the resultant magnesium reagent (Entry 7).

4.2.2 Bromine–Magnesium Exchange of Aryl Bromides: Bromine–magnesium exchange of aryl bromides proceeds by using n-Bu_3MgLi at 0 °C. Representative examples are shown in Table 10.

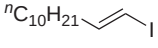
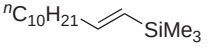
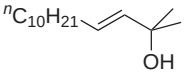
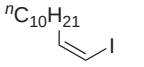
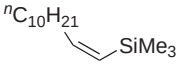
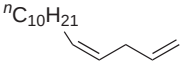
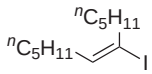
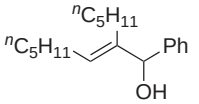
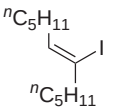
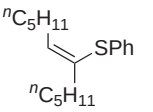
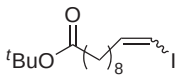
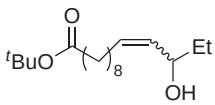
In contrast to aryl iodides, the exchange reaction of aryl bromides did not go to completion at −78 °C. Thus, the more powerful reagent i-Pr(n-Bu)$_2$MgLi, which is prepared by mixing i-PrMgBr and n-BuLi in a 1:2 ratio, was used for the preparation of polyfunctionalized arylmagnesium reagents from the corresponding bromides. Examples are shown in Table 11.

Functional groups, such as ester, amide, or cyano groups, remain during the exchange procedure. The exchange reaction also proceeded smoothly at −40 °C with a half molar amout of n-Bu_3MgLi (Scheme 27).

Treatment of the resultant functionalized arylmagnesium compounds with $TiCl_4$ afforded the corresponding biaryls in good yields (Scheme 28).

4.2.3 Halogen–Magnesium Exchange of Alkenyl Halides: Iodine–magnesium exchange of alkenyl iodides proceeded at 0 or −78 °C with complete retention of configuration of the double bond (Table 12). The presence of an ester functionality was not a problem and the alkenylmagnesium reagent formed at −78 °C (Entry 7).

Table 12. Iodine–Magnesium Exchange of Alkenyl Iodides[a)]

Entry	Substrate	E^+	Product	Yield /%
1		Me_3SiCl		95[b)]
2		CH_3COCH_3		75
3		Me_3SiCl		83[b)]
4		$CH_2=CHCH_2Br$ cat. CuCN·2LiCl		70
5		PhCHO		87
6		PhSSPh		77
7		EtCHO		80[b)]
	$E/Z = 11/89$		$E/Z = 11/89$	

a) *i*-Pr(*n*-Bu)$_2$MgLi is used. Reactions are carried out in THF at 0 °C for 1 h. b) The exchange reaction is performed at −78 °C.

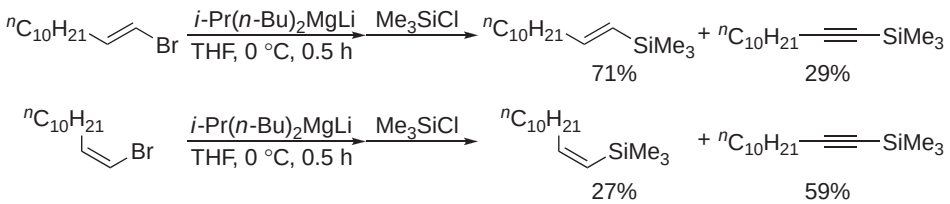
In contrast, the bromine–magnesium exchange of alkenyl bromides does not give satisfactory results (Scheme 29). Because the exchange is slow, the dehydrobromination and deprotonation affording magnesium acetylides compete with the exchange reaction.

The exchange of 1-silyl-substituted alkenyl halides proceeds in good yields with isomerization of the double bond (Table 13). The bulky silyl groups prefer the *trans* orientation to the alkyl group.

4.3 Trialkylmanganate(II)-Induced Cyclization of 2-Iodoethanal Acetal. Reactions mediated by halogen–metal exchange with trialkylmanganate or trialkylmagnesate have been described in Sections **4.1** and **4.2**. On the other hand, reactions initiated by single electron transfer from ate complexes will be described in Sections **4.3** and **4.4**.

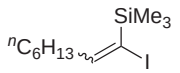
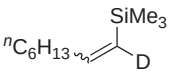
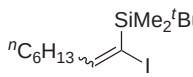
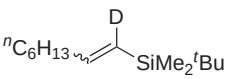
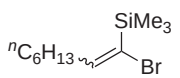
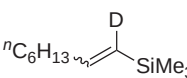
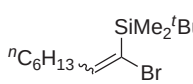
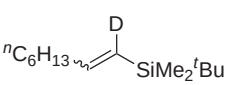
Radical cyclization reaction of unsaturated 2-iodoethanal acetals **54a** was examined. A solution of 2-iodoethanal acetal **54a** in THF was added to a solution of *n*-Bu$_3$MnLi in THF at 0 °C. The resulting mixture was stirred for 1 h at 0 °C to afford THF derivative **55a** in 82% yield (Scheme 30).

Representative results are summarized in Table 14. 2-Iodoethanal acetals **54** were prepared by reacting allylic or 2-propynyl alcohols with butyl vinyl ether or silyl enol ether in the presence of *N*-iodosuccinimide in dichloromethane.[62] Several results are worth noting: (1) The use of the iodo derivative was essential to obtain the cyclization product in high yield. Whereas 2-iodoethanal mixed acetal **54a** provided **55a** in 82% yield, the corresponding 2-bromoethanal acetal **54e** gave **55a** in only 41% yield. (2) The carbon–carbon triple bonds were as effective as olefinic linkage to trap an radical intramolecularly (Entry 6). (3) The use of tributylmanganate(II)

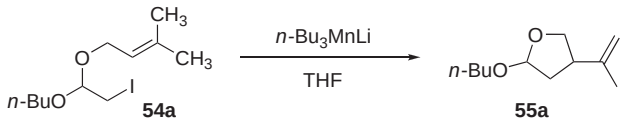


Scheme 29.

Table 13. Halogen–Magnesium Exchange of 1-Silylalkenyl Iodides[a)]

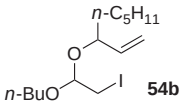
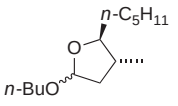
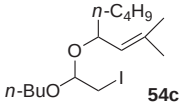
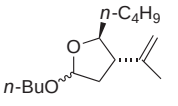
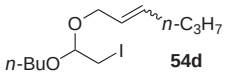
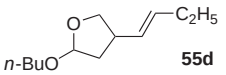
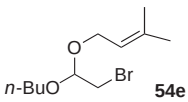
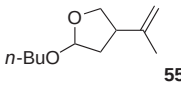
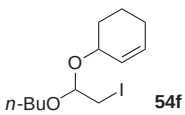
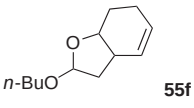
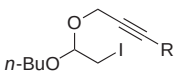
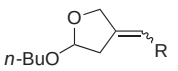
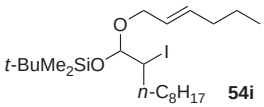
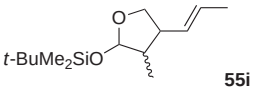
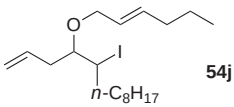
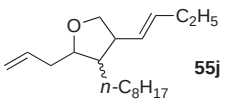
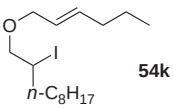
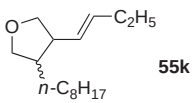
Entry	Substrate (E/Z)		Product (E/Z)		Yield/%
1		(85/15)		(32/68)	98
2		(84/16)		(96/4)	89
3		(100/0)		(93/7)	90
4		(84/16)		(93/7)	86

a) *i*-Pr(*n*-Bu)$_2$MgLi is used as a reagent. The reactions are carried out in THF at 0 °C for 1 h and quenched with D_2O.



Scheme 30.

Table 14. Radical Cyclization of Iodoacetals by Means of Tributylmanganate (n-Bu_3MnLi)

Entry	Substrate	Product	Yield /%
1	 **54b**	 **55b**	68
2	 **54c**	 **55c**	70
3	 **54d**	 **55d**	73
4	 **54e**	 **55e = 55a**	41
5	 **54f**	 **55f**	48
6	 **54g** R = $SiMe_3$ **54h** R = Ph	 **55g** **55h**	83 65
7	 **54i**	 **55i**	79
8	 **54j**	 **55j**	77
9	 **54k**	 **55k**	35

(n-$Bu_3MnMgBr$), derived from $MnCl_2$ and three molar amounts of butylmagnesium bromide, instead of n-Bu_3MnLi, gave **55a** in 42% yield. (4) 2-Iodoethanal silyl acetal **54i** derived from silyl enol ether also provided the corresponding 2-siloxytetrahydrofuran **55i** in good yield. (5) Whereas the relative stereochemistry of the anomeric carbon was not controlled, a high diastereocontrol was observed between C(4) and C(5) giving the *trans*-product in over 98% stereoselectivity.[63] Thus, treatment of **54b** or **54c** with n-Bu_3MnLi gave **55b** or **55c** as a mixture of two stereoisomers which could be converted into single isomeric *trans*-lactone **61b** or **61c** by oxidation (vide infra). The reaction of **54f** with n-Bu_3MnLi gave the cyclized product **55f** as a stereoisomeric mixture, which was contaminated by the corresponding saturated compound. However, a single stereoisomer was obtained in relation to the ring-junction. The *syn*-stereochemistry of the ring-junction of **55f** was confirmed by hydrogenation (H_2 and PtO_2) and oxidation (Jones oxidation) to the known lactone. In contrast, lactone **61i**, derived from **55i**, consisted of two stereoisomers (*cis*/*trans* = 1/1), and therefore, the relative stereochemistry between C(3) and C(4) of **55i** was *cis*/*trans* = 1/1. (6) (*E*)-Alkenes were produced selectively ($E/Z = > 95/5$) in the cyclization of 2-alkenyl ethers (**54d**, **54i**, **54j**, and **54k**) irrespective of the geometry of the starting olefins. (7) 2-Alkenyl-2-iodoalkyl ethers (**54j** and **54k**) as well as 2-iodoalkanal acetals afforded THF derivatives in good yields upon treatment with n-Bu_3MnLi. (8) Not only primary alkyl iodides but also secondary iodides (**54i**, **54j**, and **54k**) proved to cyclize effectively to give the desired products.

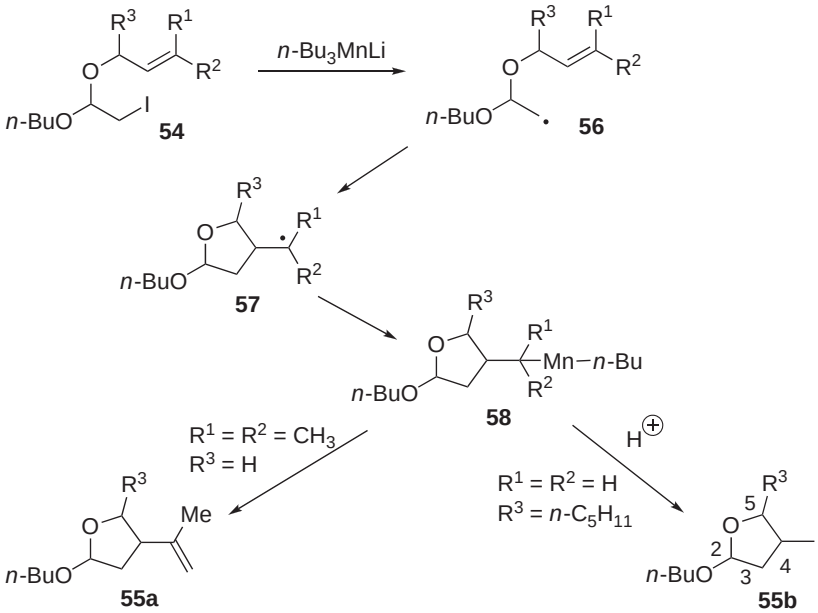
We assumed the following reaction mechanism for the stoichiometric reaction.[64] Single electron transfer from tributylmanganate(II) to the 2-iodoethanal acetal **54** would give a 2,2-dialkoxyethyl radical **56** after departure of iodide anion. 5-*exo*-Mode cyclization would afford carbon radical **57**, which recombines with n-BuMn to give alkylmanganese compound **58**. Protonation or dehydromanganation of **58** would provide the final product **55b** or **55a** (Scheme 31).

The intermediary manganese species could be trapped by various electrophiles. For instance, the addition of tributylmanganate(II) to **54b**, followed by treatment with allyl bromide, gave an allylated product **59** in 38% yield. Quenching the reaction mixture, derived from **54h** and n-Bu_3MnLi, with CH_3COOD gave a deuterated product **60** (**55h**-*d* 85%D) (Scheme 32).

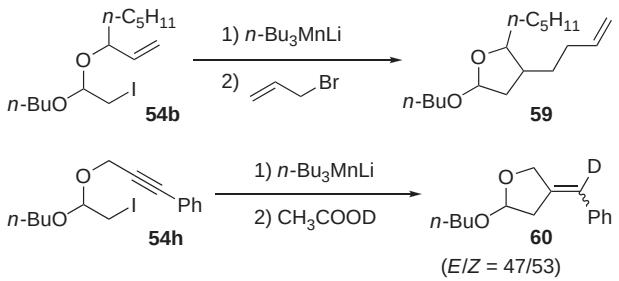
The cyclized products were easily transformed into γ-butyrolactones. For instance, treatment of **55b** or **55i** with *m*CPBA/$BF_3 \cdot Et_2O$[65] or $CrO_3 \cdot H_2SO_4$[66] provided lactone **61b** or **61i** (*cis*/*trans* = 1/1) in 70% or 99% yield, respectively (Scheme 33).

The catalytic reaction (0.1 molar amount of $MnCl_2$) using n-BuMgBr could also be applied to iodo acetal **54** to give **55**; however, the presence of oxygen was not necessary in contrast to the catalytic reaction of 3-methyl-2-butenyl ether of *o*-iodophenol, in which the presence of oxygen was essential.[67] The catalytic reaction of **54** was complete in 3 h at 0 °C under argon atmosphere in a sealed system. For instance, treatment of **54a** or **54d** (1.0 mmol) with n-BuMgBr (2.0 mmol) in the presence of $MnCl_2$ (0.1 mmol) at 0 °C for 3 h afforded **55a** or **55d** in 80% or 78% yield, respectively. Thus, the mechanism for the catalytic reaction might be as follows. A reaction between **54a** and tributylmanganate, derived from n-BuMgBr and $MnCl_2$, would provide **55a** and n-BuMn–H, which decomposes to Mn^0. Then, single electron transfer from this zero-valent manganese to **54a** would afford alkyl radical **56a** and manganese(I) species. Radical cyclization of **56a** into **57a** followed by recombination with manganese(I) would give **58a** (Scheme 34).

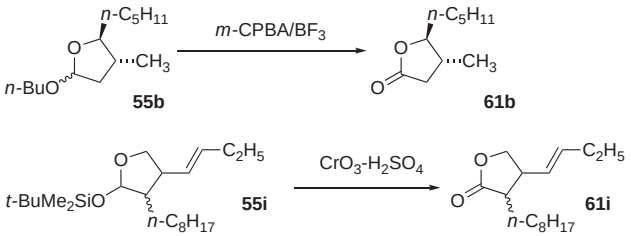
4.4 New Synthetic Reactions Catalyzed by Cobalt Complexes. Palladium and nickel catalysts play a key role in modern organic synthesis. Cross-coupling reaction and Mizoroki–Heck reaction are among the most important carbon–carbon bond formation reactions. Normally aryl and vinyl halides are



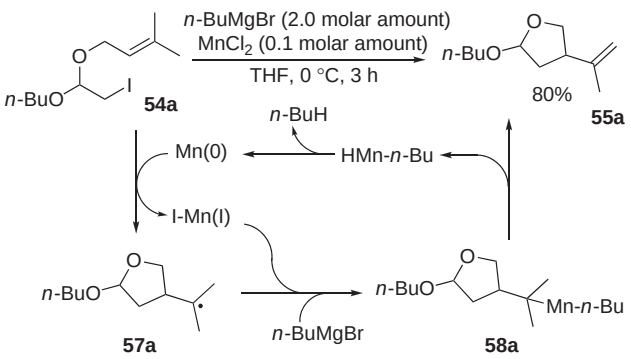
Scheme 31.



Scheme 32.



Scheme 33.

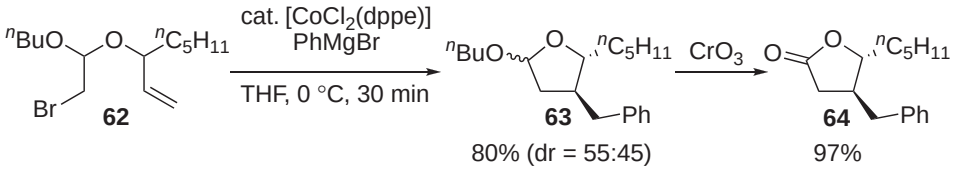


Scheme 34.

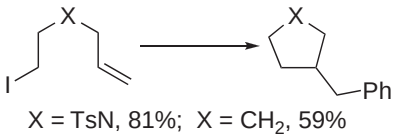
the choice of the substrates, since the use of alkyl halides having hydrogen at the β-position to the halide atom suffers from β-hydride elimination unless intensive screening of reaction conditions is performed. During the course of our study on transition-metal-catalyzed reaction,[68] readily available cobalt complexes were found to act as catalysts complementary to palladium and nickel in cross-coupling and Mizoroki–Heck reactions. The cobalt-catalyzed reactions probably proceed via carbon-centered radicals as key intermediates that are generated by single electron transfer from electron-rich cobalt complexes to alkyl halides. The radicals enable fascinating transformations that conventional palladium and nickel cannot catalyze.

4.4.1 Cobalt-Catalyzed Cross-Coupling Reaction: Cross-coupling reactions of phenyl Grignard reagent with alkyl halides are rare. In 2000, a cobalt complex was found to catalyze cross-coupling reaction of 6-halo-1-hexene derivatives with phenyl Grignard reagent, wherein radical cyclization is involved prior to the cross-coupling.[69] Treatment of bromo acetal **62** with phenyl Grignard reagent in the presence of [$CoCl_2$(dppe)] yielded benzyl-substituted cyclic acetal **63** in good yield (Scheme 35). Cyclic acetals, such as **63**, are useful building blocks of a variety of tetrahydrofuran derivatives. For instance, Jones oxidation of **63** provided β-benzyl-γ-lactone **64**. Not only oxacycle but also azacycle and carbocycle have become readily available (Scheme 36). Other aromatic Grignard reagents, such as 2-thienylmagnesium bromide, could be employed (Scheme 37). Intriguingly, DPPE is the choice of ligand, and other bidentate ligands, such as DPPM, DPPP, DPPF, and triphenylphosphine, considerably decreased the yield of **63**.

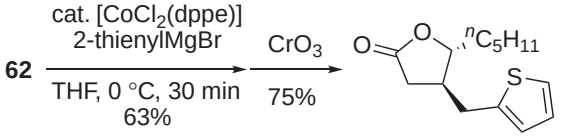
We think that the reaction proceeds via radical intermediates, since the stereochemical distribution of the products is quite similar to that obtained by well-established radical cyclization reactions. With some more evidence, a possible mechanism is illustrated in Scheme 38. Single electron transfer from an electron-rich low-valent cobalt complex to **62** leads to the formation of radical **65**. Radical 5-*exo-trig* cyclization pro-



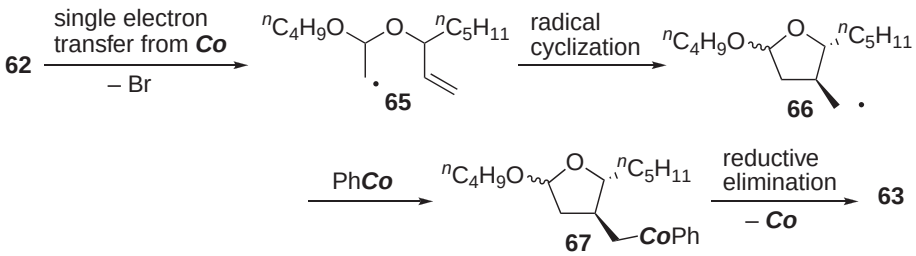
Scheme 35.



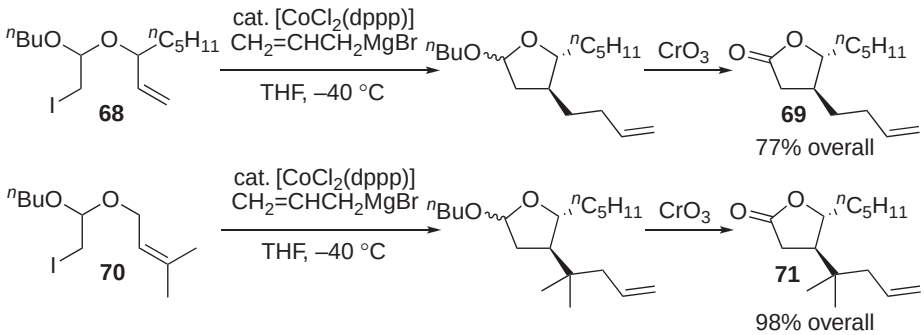
Scheme 36.



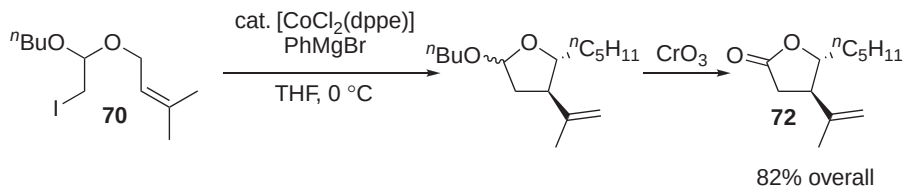
Scheme 37.



Scheme 38.



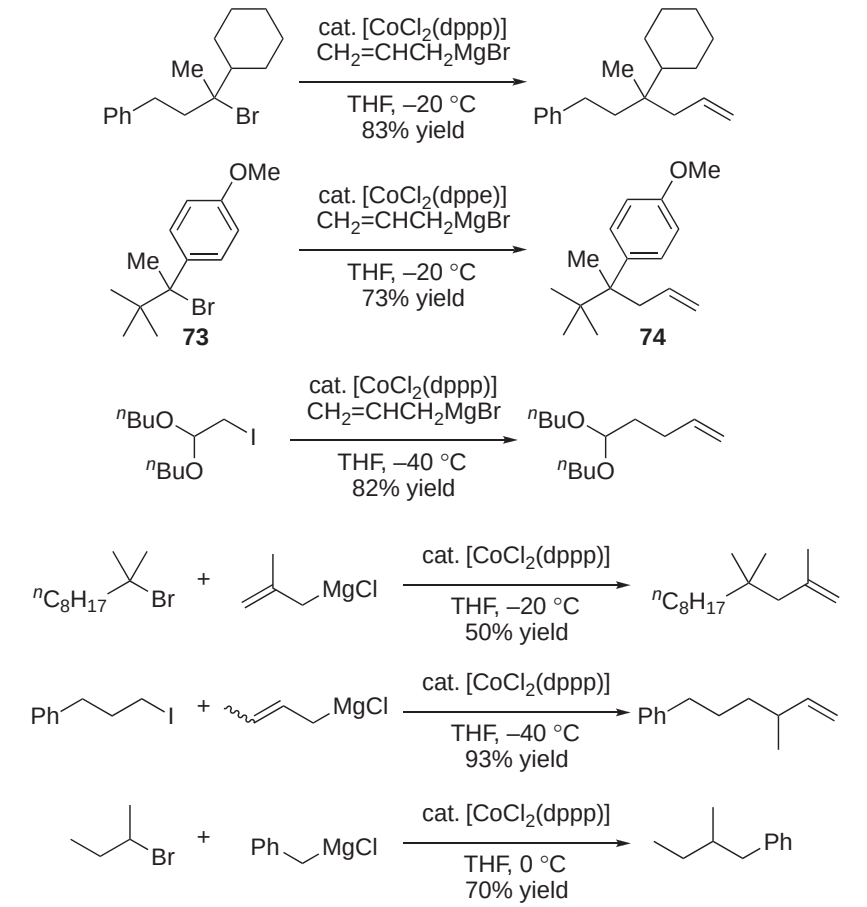
Scheme 39.



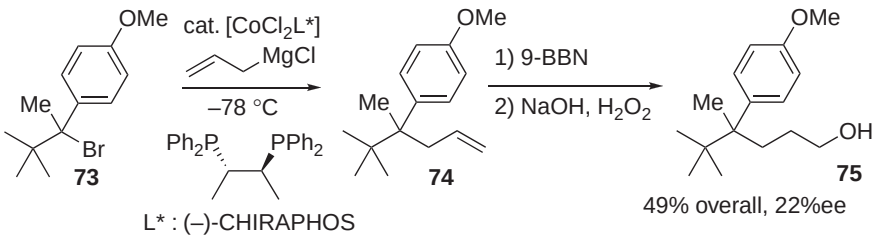
Scheme 40.

duces **66**. The cobalt complex would recombine with the carbon-centered radical **66** to form a cobalt complex **67**. Reductive elimination finalizes the catalytic cycle to yield **63**. It is fundamental knowledge that oxidative addition of organic halides to metals can proceed via a radical process. However, little attention has been paid to its application in organic synthesis. This cobalt-catalyzed reaction has provided a new methodology for multibond forming events in a single operation. More significantly, this result has shed light on the importance of radical species in cross-coupling reactions. Conventional cross-coupling reactions mostly utilize aryl or vinyl halides since oxidative addition of a C(sp^2)–X bond is generally a faster process than that of a C(sp^3)–X bond. Taking advantage of single electron transfer, the latter is more preferable, for using alkyl halides in cross-coupling reactions.

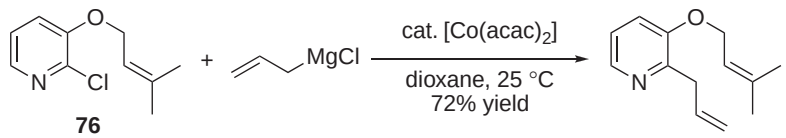
Treatment of **68** with allyl Grignard reagent under [$CoCl_2$-(dppp)] catalysis, followed by oxidation, afforded cross-coupling product **69** as well.[70] Interestingly, the allyl Grignard reagent promoted the radical cyclization/cross-coupling reaction of **70** having a 3-methyl-2-butenyl moiety, which creates a quaternary carbon (Scheme 39). Phenylation of **70** with phenyl Grignard reagent did not occur, instead **72** was produced (Scheme 40). Having observed the construction of the quaternary carbon center, we devoted ourselves to cross-coupling



Scheme 41.



Scheme 42.

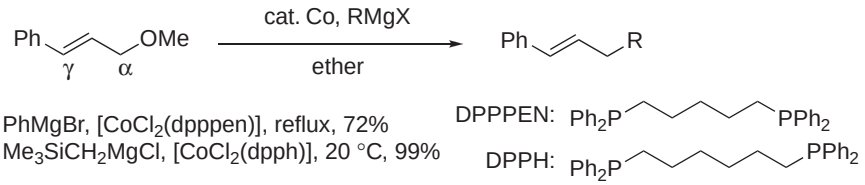


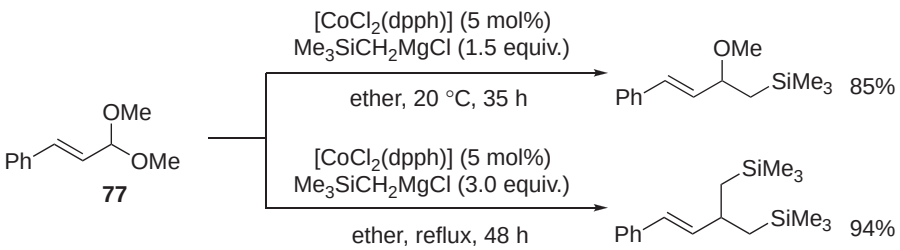
Scheme 43.

reaction of tertiary alkyl halides with allylic Grignard reagents (Scheme 41). A wide range of tertiary alkyl halides as well as primary and secondary alkyl halides participated in the cross-coupling reaction. Use of DPPE or DPPP is crucial for the successful allylation, suppressing the generation of undesirable alkenes via β-hydride elimination. It is worth noting that iodoacetaldehyde dibutyl acetal did not undergo β-alkoxy elimination. It is thought that π-allyl ligands may prevent the formation of vacant coordination sites necessary for β-elimination. Benzyl, methallyl, and 2-butenyl Grignard reagents can all couple with alkyl halides.

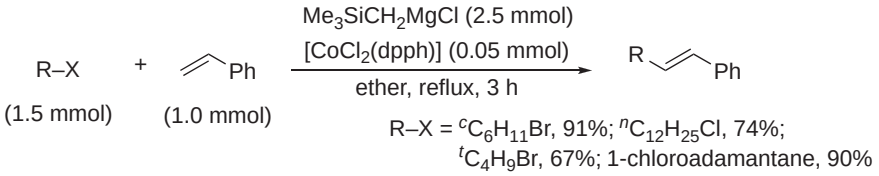
The intermediacy of a carbon-centered radical means loss of the original stereochemistry of the parent alkyl halides. The cobalt-catalyzed cross-coupling reaction may thus make possible asymmetric cross-coupling reaction using racemic alkyl halides by way of a planar carbon center. Treatment of racemic **73** with allylmagnesium chloride in the presence of [$CoCl_2$-{(−)-chiraphos}] at −78 °C afforded **74** (Scheme 42). Hydroboration/oxidation of **74** gave **75** with 22% ee. Despite the low ee, cobalt-catalyzed asymmetric allylation represents a new aspect in transition-metal-based radical reactions.

As depicted in Scheme 43, chloropyridine derivative **76**

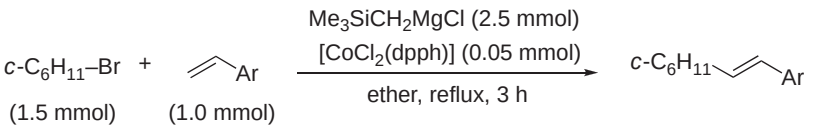




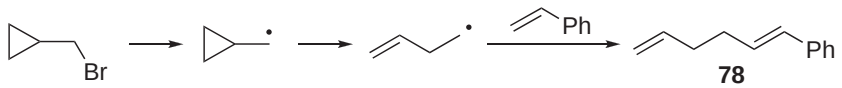
Scheme 44.



Scheme 45.



Scheme 46.



Scheme 47.

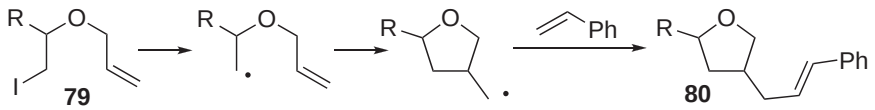
also underwent cross-coupling reaction; however, no cyclization took place.[71] A different mechanism must operate in this reaction.

Cobalt-catalyzed allylic substitution allowed the use of hard nucleophile such as Grignard reagents (Scheme 44).[72] α-Selective substitution of cinnamyl methyl ether proceeded to yield the corresponding linear products. Cinnamaldehyde dimethyl acetal **77** underwent sequential allylic substitution under cobalt catalysis. By changing the reaction temperature and the amount of the Grignard reagent, selective monosubstitution occurred.

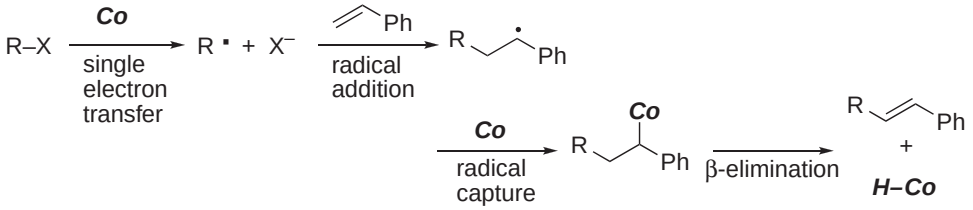
4.4.2 Cobalt-Catalyzed Mizoroki–Heck-Type Reaction of Alkyl Halide with Styrenes: Mizoroki–Heck reaction mostly employs aryl or vinyl halides as organic halides. Whereas iodomethane and 1-haloadamantane can be used for the reaction, other alkyl halides that have a hydrogen atom at the β-position to the halide atom are by no means suitable substrates. Instead of conventional palladium/base systems, a combination of a cobalt(II) complex and trimethylsilylmethylmagnesium reagent could be used to perform an alkyl version of the Mizoroki–Heck reaction.[73]

Trimethylsilylmethylmagnesium chloride was added to a mixture of styrene and bromocyclohexane in ether in the presence of [$CoCl_2$(dpph)] (DPPH = 1,6-bis(diphenylphosphino)-hexane). The reaction mixture was heated at reflux to provide β-cyclohexylstyrene in 91% yield (Scheme 45). Primary, secondary, and tertiary alkyl halides all could be used in the reaction. It is worth noting that alkyl chlorides, which are usually less reactive in transition-metal-catalyzed reactions, are good alkyl sources. Various functional groups, including ester and amide moieties, survive during the reaction (Scheme 46). Use of trimethylsilylmethyl Grignard reagent is the key for the reaction. Other Grignard reagents, such as neopentyl, butyl, and phenyl Grignard reagents, did not promote the reaction at all.

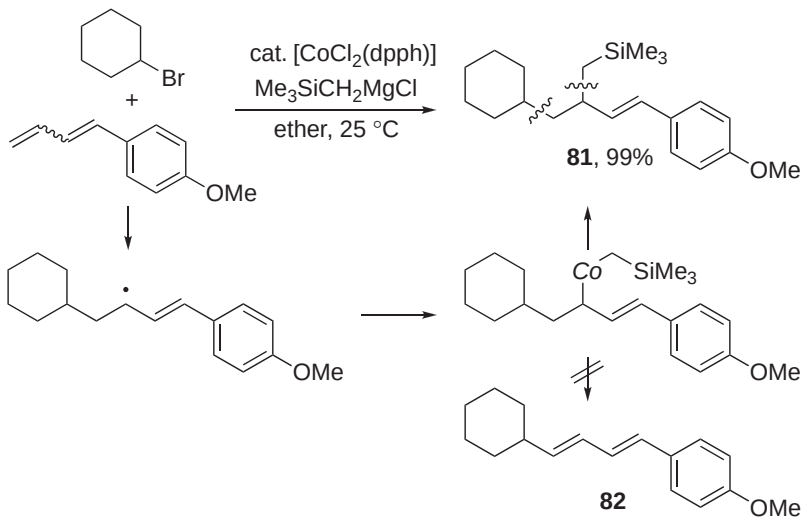
The reaction with cyclopropylmethyl bromide gave ring-opening product **78** (Scheme 47). In addition, tetrahydrofuran derivative **80** was obtained when iodo acetal **79** was employed (Scheme 48). Ring opening of a cyclopropylmethyl radical



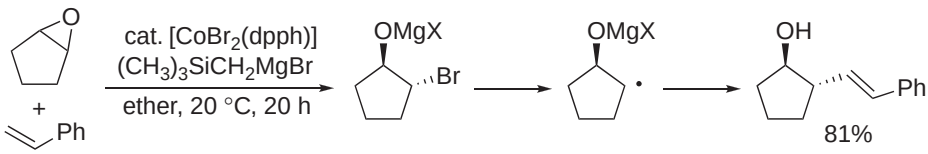
Scheme 48.



Scheme 49.



Scheme 50.

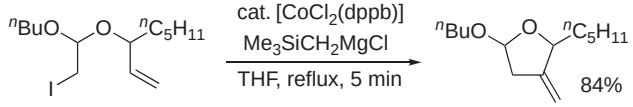


Scheme 51.

and ring closure of a 5-hexenyl radical are well-known processes. Generation of an alkyl radical from an alkyl halide is thus suggested. Mechanistic studies were done through collaboration with Profs. Mizuta and Miyoshi at Hiroshima University.[74] As a preliminary result (Scheme 49), the reaction begins with single electron transfer from an electron-rich 17-electron cobalt complex to an alkyl halide, which generates the corresponding alkyl radical. The radical adds to styrene to afford benzylic radical, which is captured by a cobalt complex. The benzylic cobalt complex undergoes β-hydride elimination to afford the product.

In place of styrene, the reaction with 1,3-diene was examined.[75] Unexpectedly, a three-component-coupling reaction occurred to yield homoallylsilane **81** (Scheme 50). Reductive elimination should proceed faster than β-hydride elimination that forms a Mizoroki–Heck product **82**.

Epoxide can also be used as a substrate in the cobalt-catalyzed Mizoroki–Heck-type reaction (Scheme 51).[76] Treatment of a mixture of epoxide and styrene with trimethylsilylmethylmagnesium bromide in the presence of [$CoBr_2$(dpph)] afforded homocinnamyl alcohol in good yield. The reaction would begin with the ring opening of epoxide to form magnesium 2-bromoalkoxide, and not with direct single electron transfer from a cobalt complex to the epoxide.



Scheme 52.

Cobalt-catalyzed intramolecular reactions of 6-halo-1-hexene derivatives produced methylenecyclopentanes (Scheme 52).[77] A higher temperature (refluxing THF) and [$CoCl_2$(dppb)] were required to obtain high yield.

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Koichiro Oshima was born in Hyogo, Japan, in 1947. He received his B.S. and Ph.D. degrees from Kyoto University in 1970 and 1975, respectively, under the guidance of Professor Hitosi Nozaki. He spent two and a half years as a postdoctoral fellow with Professor Barry Sharpless at MIT from 1975 to 1977 and became an Assistant Professor at Kyoto University in 1977. He was promoted to Lecturer in 1984, Associate Professor in 1986, and Professor in 1993. He has been involved in the development of new synthetic organic reactions by using organometallic reagents and radical species and received the Award for Young Chemists of the Society of Synthetic Organic Chemistry, Japan in 1983, the Japan Synthetic Organic Chemistry Award in 2004, and the Chemical Society of Japan Award for 2006.