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Cobalt-Catalyzed Trimethylsilylmethylmagnesium-Promoted Radical Alkenylation of Alkyl Halides: A Complement to the Heck Reaction

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Abstract: A cobalt complex, [$CoCl_2$(dpph)] (DPPH = [1,6-bis(diphenylphosphino)hexane]), catalyzes an intermolecular styrylation reaction of alkyl halides in the presence of Me_3SiCH_2MgCl in ether to yield β-alkylstyrenes. A variety of alkyl halides including alkyl chlorides can participate in the styrylation. A radical mechanism is strongly suggested for the styrylation reaction. The sequential isomerization/styrylation reactions of cyclopropylmethyl bromide and 6-bromo-1-hexene provide evidence of the radical mechanism. Crystallographic and spectroscopic investigations on cobalt complexes reveal that the reaction would begin with single electron transfer from an electron-rich (diphosphine)bis(trimethylsilylmethyl)cobalt(II) complex followed by reductive elimination to yield 1,2-bis(trimethylsilyl)ethane and a (diphosphine)cobalt(I) complex. The combination of [$CoCl_2$(dppb)] (DPPB = [1,4-bis(diphenylphosphino)butane]) catalyst and Me_3SiCH_2-MgCl induces intramolecular Heck-type cyclization reactions of 6-halo-1-hexenes via a radical process. On the other hand, the intramolecular cyclization of the prenyl ether of 2-iodophenol would proceed in a fashion similar to the conventional palladium-catalyzed transformation. The nonradical oxidative addition of carbon(sp^2)−halogen bonds to cobalt is separately verified by a cobalt-catalyzed cross-coupling reaction of alkenyl halides with Me_3SiCH_2MgCl with retention of configuration of the starting vinyl halides. The cobalt-catalyzed intermolecular radical styrylation reaction of alkyl halides is applied to stereoselective variants. Styrylations of 1-alkoxy-2-bromocyclopentane derivatives provide *trans*-1-alkoxy-2-styrylcyclopentane skeletons, one of which is optically pure.

Introduction

The Heck reaction is among the most powerful carbon−carbon bond formation reactions in organic synthesis.[1,2] It is applied to various fields of chemical science, ranging from syntheses of chemicals of biological interest to those of high-performance functional organic materials. The scope and limitations have been fully investigated, and considerable efforts have been made to increase the utility. Despite such devotions to the reaction during the last three decades, the major limitation unsolved so far is that one cannot use alkyl halides having hydrogen at the β position to the halide atom as substrates. The alkylpalladiums formed from such halides normally undergo β-hydride elimination more rapidly than insertion of alkenes (Scheme 1a). Although there are some reports on the palladium-catalyzed Heck reaction of alkyl halides, the reactions employ iodomethane, α-haloacetate,[3] benzyl halide,[4] and 1-bromoadamantane,[5] which have no detachable β-hydrogens. An additional difficulty stems from the much slower oxidative addition of alkyl halides due to the lack of proximal π-systems.[6]

To overcome these difficulties, Heck-type reactions of alkyl halides with alkenes mediated by transition metals other than

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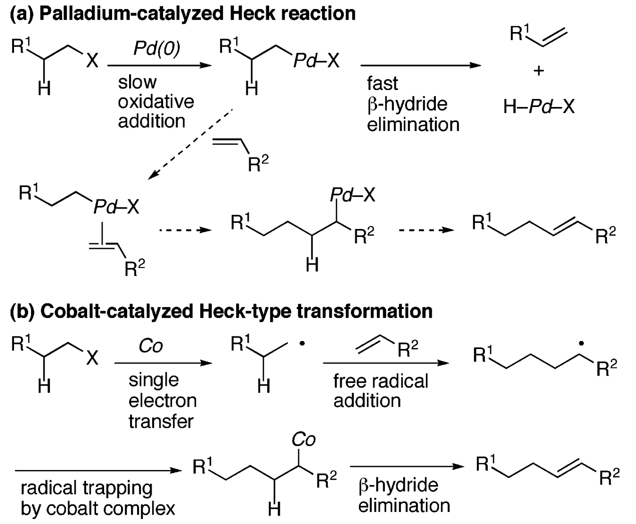
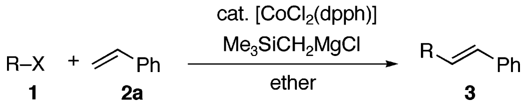
Scheme 1



palladium have been attracting increasing attention. However, most of the variants are not satisfactory with regard to yield and/or reaction conditions. Nickel-catalyzed reaction of alkyl bromides with styrene afforded the desired products in moderate yields.[7] Cobaloxime-catalyzed zinc-mediated similar transformations required photolysis and resulted in unsatisfactory yields.[8] Very recently, it was found that titanocene-catalyzed butylmagnesium bromide-promoted styrylation of alkyl bromides and some chlorides is very effective in attaining satisfactory yields.[9] We independently found that a cobalt salt catalyzes intermolecular styrylation of alkyl halides in the presence of trimethylsilylmethylmagnesium chloride.[10] Here we report the full details and application of the cobalt-catalyzed Heck-type reactions.[11]

Our approach to an alkyl version of the Heck reaction is outlined in Scheme 1b. We have been interested in the synthetic use of single electron transfer from electron-rich cobalt complexes to alkyl halides.[12] Compared with the conventional oxidative addition of alkyl halides to palladium, the cobalt-mediated single electron transfer process is reasonably rapid to generate the corresponding alkyl radical and halide anion. The radical generated does not suffer from β-hydride elimination and adds to an activated alkene, styrene, for instance, to yield a new stabilized radical. The new radical is trapped by a cobalt complex, and subsequent β-hydride elimination provides the desired Heck-type product.

Table 1. Cobalt-Catalyzed Styrylation of Alkyl Halides[a]

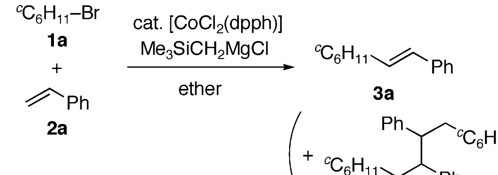


entry	R–X **1**	time/h	temp/°C	**3**	yield/%
1	$^{n}C_6H_{13}CH(CH_3)Br$	8	20	**3b**	73
2	$^{n}C_{12}H_{25}Br$	8	20	**3c**	76
3	$^{n}C_{12}H_{25}Br$	3	35	**3c**	71
4	Ad-Br[b]	8	20	**3d**	87
5	$^{t}C_4H_9Br$	8	20	**3e**	11
6	$^{t}C_4H_9Br$	3	35	**3e**	67
7	$^{n}C_{12}H_{25}I$	3	35	**3c**	57
8	$^{n}C_{12}H_{25}Cl$	3	35	**3c**	74
9	Ad-Cl[b]	3	35	**3d**	90
10	$^{c}C_6H_{11}Cl$	3	35	**3a**	84
11	CH_3I	3	35	**3f**	55[c]
12	$CH_2{=}CH(CH_2)_3Br$	3	35	**3g**	53

[a] Conditions: R−X (**1**, 1.5 mmol), styrene (**2a**, 1.0 mmol), the Grignard reagent (2.5 mmol), $CoCl_2$ (0.05 mmol), and DPPH (0.06 mmol). [b] Ad = 1-adamantyl. [c] *p*-Chlorostyrene was used instead of styrene.

Results and Discussion

Styrylation of Alkyl Halides. A mixture of bromocyclohexane (**1a**, 1.5 mmol) and styrene (**2a**, 1.0 mmol) was treated with trimethylsilylmethylmagnesium chloride (1.0 M ethereal solution, 2.5 mmol) in ether in the presence of [$CoCl_2$(dpph)] (DPPH = 1,6-bis(diphenylphosphino)hexane). The reaction mixture was stirred for 8 h at 20 °C to afford β-cyclohexylstyrene (**3a**) in 86% yield (eq 1). Heating the reaction mixture at reflux improved the yield of **3a** up to 91% and the reaction time to 3 h. A trace amount of dimerized product **3a′** was the only detectable byproduct, which was readily separable from **3a** upon purification on silica gel.



(1)

The reaction proceeded similarly in the absence of light, which eliminates the possibility of a photoinduced reaction. Cobalt(II) bromide, instead of cobalt chloride, served as well. The amount of the Grignard reagent also affected the yield of **3a**. Use of 1.5 or 3.5 equiv of the Grignard reagent led to a decreased yield of **3a**. $PhMe_2SiCH_2MgCl$ also effected the alkylation reaction (78% yield of **3a** at 35 °C). Trialkylsilylmethyl Grignard reagents were essential to obtain the desired product. The reaction with phenyl, methyl, ethyl, and neopentyl Grignard reagents provided traces of **3a**. Cyclohexene was detected mainly. The effect of the ligand deserves discussion (vide infra).

A variety of alkyl halides were examined (Table 1). Primary and tertiary alkyl bromides as well as secondary ones underwent

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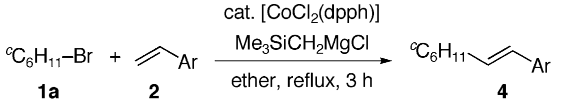
Table 2. Reaction with Styrene Derivatives[a]



entry	2	Ar	4	yield/%
1	**2b**	C_6H_4-*p*-Me	**4b**	87
2	**2c**	C_6H_4-*p*-Cl	**4c**	85
3	**2d**	C_6H_4-*m*-Cl	**4d**	82
4	**2e**	C_6H_4-*o*-Cl	**4e**	85
5	**2f**	C_6H_4-*p*-OMe	**4f**	82
6	**2g**	C_6H_4-*p*-$CON(CH_2Ph)_2$	**4g**	29
7	**2h**	C_6H_4-*m*-$CON(CH_2Ph)_2$	**4h**	95
8	**2i**	C_6H_4-*m*-$COO^tC_4H_9$	**4i**	66

[a] Conditions: **1a** (1.5 mmol), **2** (1.0 mmol), the Grignard reagent (2.5 mmol), $CoCl_2$ (0.05 mmol), and DPPH (0.06 mmol).

Table 3. Optimization of Ligand[a]

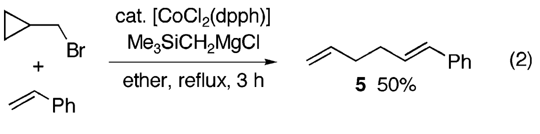
entry	ligand	yield of **3a**/%
1	$Ph_2PCH_2PPh_2$ (DPPM)	<20
2	$Ph_2P(CH_2)_2PPh_2$ (DPPE)	<10
3	$Ph_2P(CH_2)_3PPh_2$ (DPPP)	<20
4	$Ph_2P(CH_2)_4PPh_2$ (DPPB)	52
5	$Ph_2P(CH_2)_5PPh_2$ (DPPPEN)	70
6	$Ph_2P(CH_2)_6PPh_2$ (DPPH)	86
7	$Ph_2P(CH_2)_8PPh_2$ (DPPO)	75
8	Ph_3P (2 equiv to Co)	60
9	$EtPh_2P$ (2 equiv to Co)	58
10	$Ph_2PCH_2C_6H_4CH_2PPh_2$ (DPPX)	33

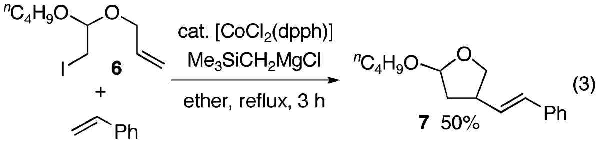
[a] Conditions: $CoCl_2$ (0.05 mmol), ligand (0.06 mmol), **1a** (1.5 mmol), **2a** (1.0 mmol), and Me_3SiCH_2MgCl (2.5 mmol) were used. The reactions were performed at 20 °C for 8 h.

the styrylation reaction (entries 1−6). The reaction of *tert*-butyl bromide required a higher temperature to attain an acceptable result (entries 5 and 6). Compared to the use of lauryl bromide, the use of lauryl iodide resulted in a low yield of **3c** (entry 7). It is worth noting that alkyl chlorides, which are often unreactive in transition metal-catalyzed reactions, proved to be excellent alkyl sources in this reaction (entries 8−10). For instance, treatment of a mixture of lauryl chloride and styrene with Me_3SiCH_2MgCl in ether at reflux furnished **3c** in 74% yield under the $[CoCl_2(dpph)]$ catalysis. The reaction with iodomethane afforded the corresponding product **3f** in moderate yield (entry 11). Because the Grignard reagent was used, functional groups such as ester, phthalimide, and hydroxy groups were not compatible. A terminal alkenyl moiety survived under the reaction conditions (entry 12).

The reaction tolerates seemingly labile functionalities (Table 2). Methoxy- and chlorostyrenes were alkylated efficiently in refluxing ether (entries 2−5). Unfortunately, the para substitution with a carbamoyl group decreased the yield of the product since the phenylogous acrylamide **2g** is so reactive that uncatalyzed side reactions took place (entry 6). The meta substituted **2h** underwent alkylation efficiently (entry 7). A *tert*-butoxycarbonyl group also was left untouched under the reaction conditions (entry 8). Unfortunately, the reactions with 1-octene and butyl vinyl ether resulted in failure. An attempted alkylation of methyl acrylate resulted in the formation of a complex mixture.

The reaction with cyclopropylmethyl bromide yielded a ring-opening product, β-(3-butenyl)styrene (**5**), in 50% yield (eq 2). In addition, a tetrahydrofuran derivative **7** was obtained when iodo acetal **6** was employed (eq 3). Ring opening of a cyclopropylmethyl radical and ring closure of a 5-hexenyl radical are well-known processes.[13] These observations strongly support the generation of an alkyl radical from an alkyl halide. Furthermore, as described above, the dimerization of benzylic radicals can rationalize the formation of **3a′**. The mechanism of the cobalt-catalyzed reaction is thus quite different from the palladium-catalyzed one (vide infra).





The $[CoCl_2(dpph)]/Me_3SiCH_2MgCl$ system efficiently mediates a Heck-type reaction of alkyl halides, including alkyl chlorides, with styrene derivatives. The procedure is simple, and the reaction tolerates some functionalities. The reaction represents a complementary method to the palladium-catalyzed Heck styrylation reaction.

Mechanistic Investigation: Single Electron Transfer from Cobalt Complexes. A variety of phosphine ligands were surveyed to clarify the ligand effect (Table 3). When $Ph_2P(CH_2)_nPPh_2$ ($n = 1-4$) and triphenylphosphine were employed, the yields of **3a** decreased and significant amounts of (2-cyclohexylethyl)benzene and **3a′** were obtained (entries 1−4 and 8). As the number of the methylene units between the phosphorus atoms increased, the yield was dramatically improved (entries 4−6). DPPH having a hexamethylene tether gave the highest yield. DPPO, 1,8-bis(diphenylphosphino)octane, seems to have a too long methylene chain (entry 7). The yield was fair when ethyldiphenylphosphine, electronically equivalent to DPPH, was employed (entry 9). Diphosphino-*p*-xylene also failed to afford **3a** in a satisfactory yield (entry 10). Amine ligands such as tetramethylethylenediamine afforded none of **3a**.

It is unclear whether DPPH having a long tether binds to one cobalt center intramolecularly or DPPH forms di- or multinuclear complexes with cobalt during the reaction. To explore the nature of the Co(dpph) complexes, DPPH was allowed to react with $CoCl_2$. While attempts to prepare crystals of cobalt complexes in ethereal solutions failed due to their low solubility, we could obtain blue single crystals of a macrocyclic dinuclear complex of $[CoCl_2(dpph)]_2$ from acetone (Figure 1).[14] The cobalt centers have tetrahedral geometries, wherein the P−Co−P angles are 106° and the Cl−Co−Cl angles are 111°.

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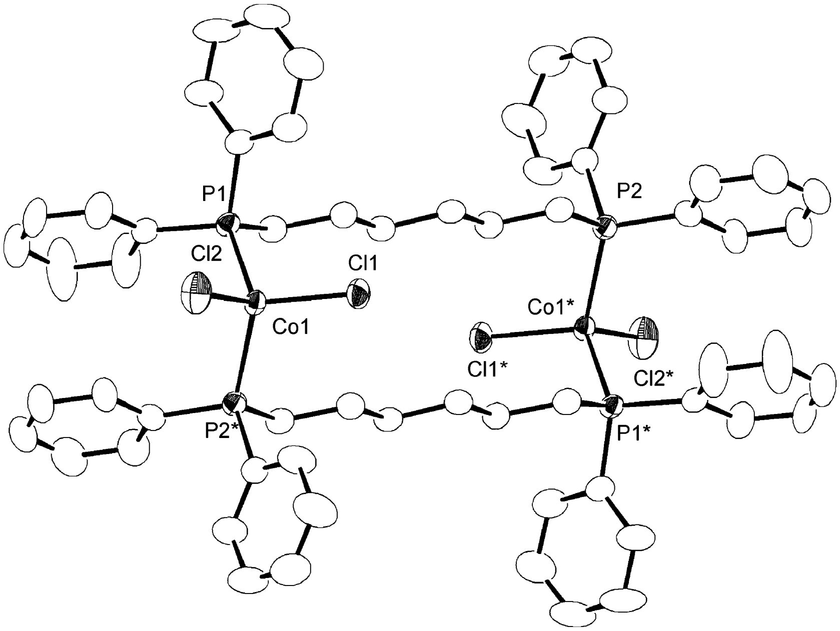
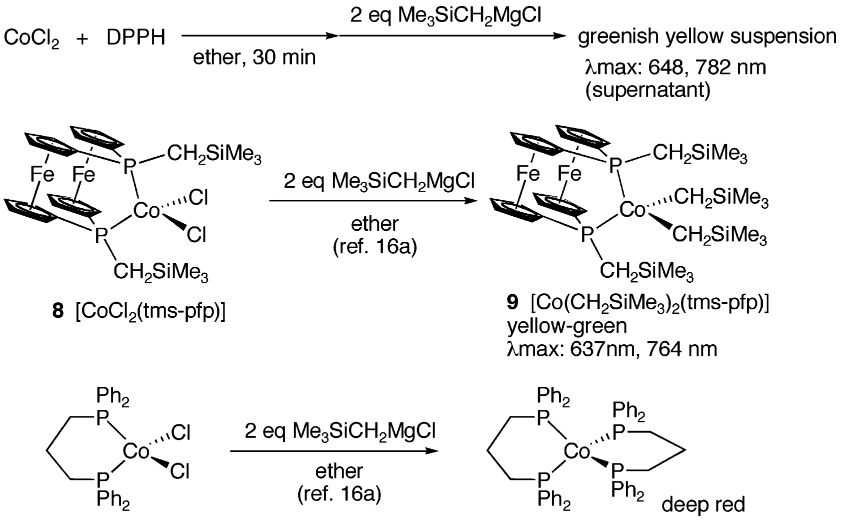


Figure 1. One of the two independent molecules of $[CoCl_2(dpph)]_2$. Displacement ellipsoids are drawn with 50% thermal ellipsoids. The selected bond distances (Å) and angles (deg) are Co1−Cl2 2.2143(10), Co1−Cl1 2.2254(9), Co1−P1 2.3595(9), Co1−P2 2.3865(10), Cl2−Co1−Cl1 111.13(4), Cl2−Co1−P1 110.97(4), Cl1−Co1−P1 108.67(4), Cl2−Co1−P2 109.45(4), Cl1−Co1−P2 110.24(4), P1−Co1−P2 106.27(3). For further details, see Supporting Information.

Scheme 2



The lengths of the P−Co and Cl−Co bonds are comparable to those of $[CoCl_2(dppp)]$.[15]

Motivated by the success, we tried to obtain a (trimethylsilylmethyl)(dpph)cobalt complex for X-ray crystallographic analysis. Sequential treatment of $CoCl_2$ with DPPH and with 2 equiv of trimethylsilylmethylmagnesium chloride in ether resulted in the formation of a greenish yellow solution with some precipitates of a similar color (Scheme 2). However, no crystals suitable for X-ray diffraction were available.

The UV−visible spectrum of the greenish yellow supernatant showed two absorption bands at $\lambda_{max} = 648$ and 782 nm. These absorption bands are quite similar to those of $[Co(CH_2SiMe_3)_2$-(tms-pfp)] (**9**).[16] The cobalt complex **9** showed absorptions at $\lambda_{max} = 637$ and 764 nm, in addition to absorptions at 450−550 nm arising from the ferrocenyl units. The spectra of the two cobalt complexes are significantly different from those of $[CoCl_2(dppp)]$ (λ_{max} = 584, 635, 735 nm in THF),[15] $[CoCl_2$-(dpph)$]_2$ (λ_{max} = 587, 639, 690 nm in THF), and $[CoCl_2$(tms-pfp)] (**8**, λ_{max} = 439, 605, 646, 706 nm in dichloromethane). These facts are highly suggestive of the formation of stable [Co-$(CH_2SiMe_3)_2(dpph)]_n$, where the suffix *n* means the unidentified degree of aggregation and is most likely to be 1 or 2, upon mixing cobalt chloride, DPPH, and 2 equiv of Me_3SiCH_2MgCl. The formation of $[Co(CH_2SiMe_3)_2(dpph)]_n$ is in stark contrast to the generation of homoleptic (tetraphosphine)cobalt(0), [Co-$(dppp)_2]$, upon treatment of $[CoCl_2(dppp)]$ with 2 equiv of

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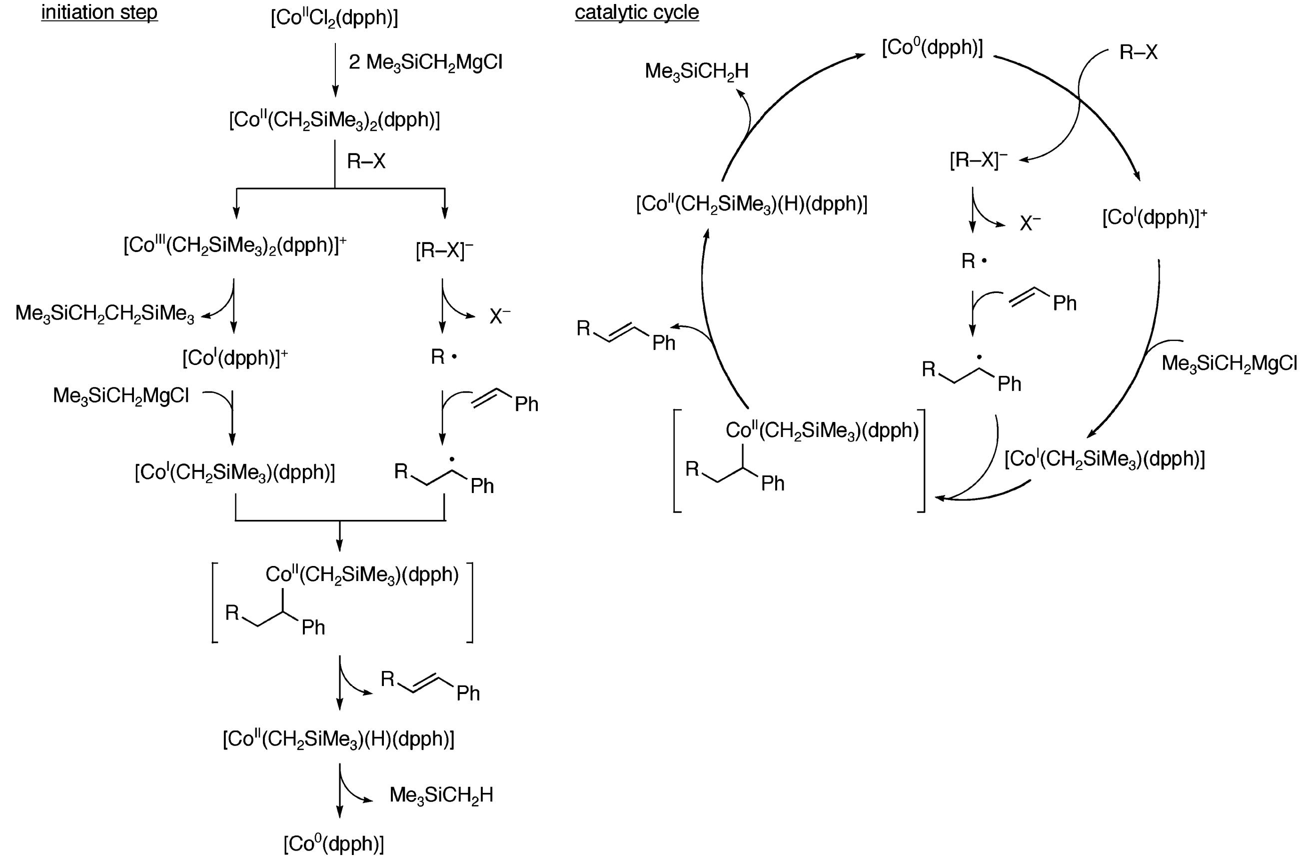
Scheme 3



trimethylsilylmethylmagnesium chloride with concomitant liberation of $Me_3SiCH_2CH_2SiMe_3$.[16a] Decomposition of $[Co(CH_2SiMe_3)_2(dpph)]_n$ that forms $Me_3SiCH_2CH_2SiMe_3$ proceeded much more slowly. It is worth noting that the deep red $[Co(dppp)_2]$ exhibited a spectrum completely different from that of $[Co(CH_2SiMe_3)_2(dpph)]_n$. Therefore, the styrylation reaction would start from $[Co(CH_2SiMe_3)_2(dpph)]_n$.

Treatment of $[CoCl_2(tms\text{-}pfp)]$ with 2 equiv of Me_3SiCH_2MgCl followed by an addition of 10 equiv of benzyl bromide provided 1 equiv of 1,2-diphenylethane and 1,2-bis(trimethylsilyl)ethane, along with 8 equiv of benzyl bromide recovered. No trimethyl(2-phenylethyl)silane was detected. Sequential treatment of $CoCl_2$ with 1 equiv of DPPH, 2 equiv of Me_3SiCH_2MgCl, and 10 equiv of benzyl bromide led to the same distribution of products. The formation of 1,2-diphenylethane would stem from the homo-coupling of benzyl radicals. A reductive elimination pathway can account for the production of 1,2-bis(trimethylsilyl)ethane. The absence of the cross-coupling product, trimethyl(2-phenylethyl)silane, is noteworthy. Judging from these results, the following electron-transfer process is most plausible for the initial single electron-transfer step. The complex $[Co^{II}(CH_2SiMe_3)_2(dpph)]$ (hereafter the suffix *n* is omitted for clarity) would transfer a single electron to an alkyl halide to yield $[Co^{III}(CH_2SiMe_3)_2(dpph)]^+$ and the radical anion of the alkyl halide. The cobalt complex would undergo instant reductive elimination to yield $[Co^{I}(dpph)]$ and 1,2-bis(trimethylsilyl)ethane. Meanwhile, the radical anion of the alkyl halide would fragment into the corresponding alkyl radical and halide anion.

On the basis of these observations, we are tempted to propose a mechanism for the cobalt-catalyzed reaction (Scheme 3). The mechanism comprises an initiation step and a catalytic cycle. The initiation step starts with the reaction of $[Co^{II}Cl_2(dpph)]$ with Me_3SiCH_2MgCl to yield $[Co^{II}(CH_2SiMe_3)_2(dpph)]$. Although an excess of the Grignard reagent was in the reaction mixture, the formation of conceivable cobaltate complexes is unlikely.[17] $[Co^{II}(CH_2SiMe_3)_2(dpph)]$ would undergo the single electron-transfer process to yield $[Co^{I}(dpph)]^+$ and an alkyl radical $R^\bullet$. The 12-electron cationic complex $[Co^{I}(dpph)]^+$ is so electron-deficient that the complex can react immediately with Me_3SiCH_2MgCl to furnish $[Co^{I}(CH_2SiMe_3)(dpph)]$.[18] The complex captures the benzylic radical that emerges through the addition of the alkyl radical to styrene. Productive β-elimination followed by rapid reductive elimination of tetramethylsilane would yield $[Co^{0}(dpph)]$. In the catalytic cycle, the zerovalent cobalt complex would be instead responsible for the single electron transfer. The catalytic cycle consists of reactions similar to those in the initiation step. The only difference is that reductive elimination does not occur after the single electron transfer since $[Co^{0}(dpph)]$, the electron donor, has no Me_3SiCH_2 groups. Instead of $[Co^{0}(dpph)]$, an ate complex, $[Co^{0}(CH_2SiMe_3)(dpph)]^-MgCl^+$, which is derived from $[Co^{0}(dpph)]$ and 1 equiv of the Grignard reagent, can effect the single electron transfer (not shown in Scheme 3). In the alternative case, neutral $[Co^{I}(CH_2SiMe_3)(dpph)]$ would be directly produced after the single electron transfer, capturing the benzylic radical. Also note that, even with the present mechanistic work, there still remains

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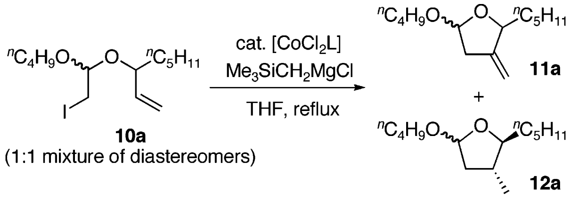
(17) See the formation of $[Co^{II}(CH_2SiMe_3)_2(tmeda)]$ in the presence of an excess of Me_3SiCH_2Li: Hay-Motherwell, R. S.; Wilkinson, G.; Hussain, B.; Hursthouse, M. B. *Polyhedron* **1990**, *9*, 931−937.

(18) The number of CH_2SiMe_3 groups on the cobalt is likely to be one, yet zero or two is possible.

Table 4. Influence of Ligand in the Cobalt-Catalyzed Intramolecular Cyclization



entry	L	11a/%	12a/%
1	DPPM	58	28
2	DPPE	8	74
3	DPPP	68	20
4	DPPB	84	9
5	DPPPEN	78	8
6	DPPH	69	8
7	DPPF	81	11

a possibility that the reaction proceeds via Co^{I} and Co^{III} as observed in vitamin B_{12}- or cobaloxime-mediated reactions.[8]

Intramolecular Heck-Type Transformation: An Implication of the Mechanistic Duality of the Oxidative Addition of Organic Halide to the Cobalt Complex. The intramolecular Heck reaction of 1-halo-1,5-hexadiene derivatives is a powerful and reliable method in constructing a diverse range of organic molecules.[19] On the other hand, palladium-catalyzed intramolecular cyclization reactions of 6-halo-1-hexene derivatives, wherein fission of the sp^3-hybridized carbon−halogen bond is required, have rarely been reported.[20] Alternatively, cobaloxime-mediated cyclization allows for the conversion of 6-halo-1-hexene derivatives into methylenecyclopentanes.[21] In most cases, a stoichiometric amount of cobaloxime and irradiation are essential. No reports of cobaloxime-catalyzed cyclization of 6-halo-1-hexenes leading to methylenecyclopentanes are known.[22] With the success of the intermolecular styrylation of alkyl halides, we next examined the cobalt-catalyzed intramolecular cyclization of 6-halo-1-hexenes into methylenecyclopentanes.[23]

The reaction of iodo acetal **10a** was first examined (Table 4). Treatment of **10a** with trimethylsilylmethylmagnesium chloride in refluxing THF under [$CoCl_2$(dppb)] catalysis provided the desired product **11a** in 84% yield, along with a saturated compound **12a** (entry 4). The intramolecular version required reaction conditions slightly different from those of the intermolecular reaction. THF was used as a solvent, and a higher temperature was essential. The reaction at ambient temperature in THF was slow and yielded a more complex crude mixture. The reaction in ether at reflux resulted in a lower yield of **11a**, incomplete consumption of **10a**, and an increased amount of **12a**. A higher temperature would facilitate the β-hydride elimination that produces **11a** as well as the single electron-transfer process. The choice of the ligand was important. Use of DPPM, DPPP, DPPPEN, DPPH, and DPPF furnished **11a** in lower yields. The reason for the advantage of DPPB over DPPH in the intramolecular cyclization is not clear. Coordination of the olefinic part to the cobalt complex upon single electron transfer[24] might occur, leading to the superiority of DPPB. Surprisingly, **12a** was obtained as a major product when DPPE was employed. Only a small amount of deuterium was incorporated at the methyl group of **12a** upon quenching the reactions with DCl/D_2O. The formation of **12a** thus supports a radical cyclization mechanism, wherein a part of the corresponding oxacyclopentylmethyl radical abstracts a hydrogen atom from THF[25] and the rest was trapped by a cobalt complex to finally produce **11a** (Scheme 4). Use of a trialkylsilylmethyl Grignard reagent was again essential for a successful reaction. For example, neopentylmagnesium bromide was inferior to the trimethylsilylmethylmagnesium reagent and afforded **11a** and **12a** in 18% and 60% yields, respectively. Other alkyl Grignard reagents such as butylmagnesium bromide also yielded **12a** as a major product. In the absence of [$CoCl_2$(dppb)], **10a** was left untouched. The corresponding bromide of **10a** was inferior to the iodide **10a** (59% of **11a** and 20% of **12a**).

Scheme 4

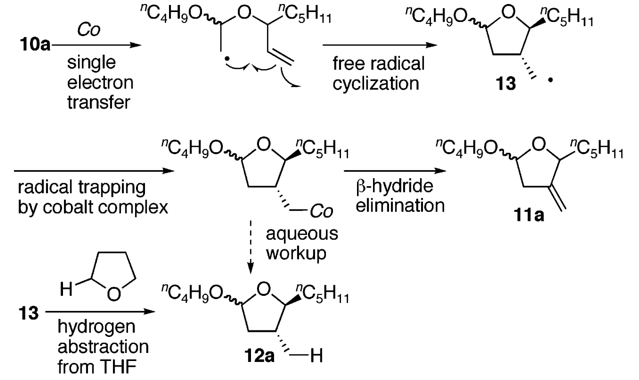


Table 5 summarizes the results of the cobalt-catalyzed intramolecular cyclization. Substrates with terminal alkenes **10b**−**10f** participated in the cyclization to yield the corresponding products in excellent yields. In addition to oxacycles, aza- and carbocycles **11e** and **11f** were also readily accessible. In each case of **11b**−**11f**, its saturated analogue was detected in less than 9% yield. Treatment of **10g** with Me_3SiCH_2MgCl under the catalysis of [$CoCl_2$(dppb)] furnished bicyclic product **11g**. Cyclization onto a trisubstituted alkene resulted in a moderate yield of the expected isopropenyl-substituted product **11h**. Use of DPPP instead of DPPB slightly increased the yield of **11h** to 66%. It is worth noting that small yet significant amounts of the saturated analogue of **11h** were obtained in both cases (13% with DPPB, 14% with DPPP).

Substrates **14** and **16**, which securely undergo usual oxidative addition to palladium, were subjected to the reaction conditions (eqs 4 and 5).[26] The prenyl ether of 2-iodophenol (**14a**) and

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(19) (a) Bräse, S.; de Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, Chapter IV.2.2. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; Chapter 31. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. Also see ref 2b.

(20) See ref 19b. However, in most cases, there are no hydrogens that are involved in β-hydride elimination. An exception was the following: Oppolzer, W.; De Vita, R. J. *J. Org. Chem.* **1991**, *56*, 6256−6257.

(21) (a) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361−382. (b) Tada, M. *Yuki Gosei Kagaku Kyokaishi* **1998**, *56*, 544−556. (c) Reference 8e.

(22) Cobaloxime-catalyzed intermolecular Heck-type reaction under irradiation was reported. See ref 8a. Vitamin B_{12}-catalyzed reaction of 6-halo-1-hexene derivatives giving vinylcyclopentanes, not methylenecyclopentanes, was reported: (a) Busato, S.; Tinembart, O.; Zhang, Z.; Scheffold, R. *Tetrahedron* **1990**, *46*, 3155−3166. (b) Busato, S.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 92−99.

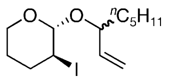
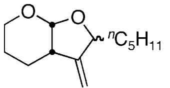
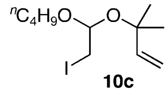
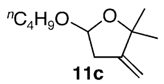
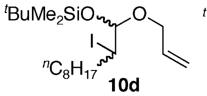
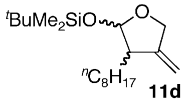
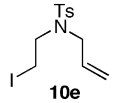
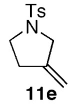
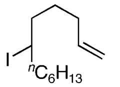
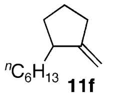
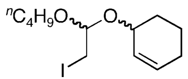
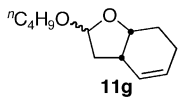
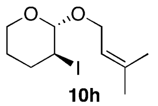
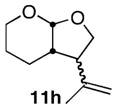
(23) A part of this section was communicated: Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257−2259.

(24) Intramolecular coordination of a tethered alkene to a metal in action often has a considerable effect on the overall transformation. For instance, see: Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342−15343.

(25) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206−214.

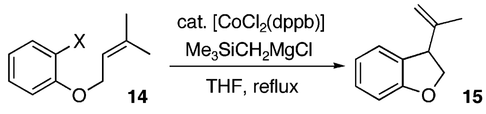
(26) For example, Larock reported a palladium-catalyzed cyclization reaction of **14** leading to isopropyl-substituted benzofuran. Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687−4690.

Table 5. Cobalt-Catalyzed Intramolecular Cyclization of 6-Halo-1-hexene Derivatives[a]

entry	substrate[b]	product	yield[c]
1	 **10b**	 **11b**	74% (67:33)
2	 **10c**	 **11c**	79%
3	 **10d**	 **11d**	94% (62:38)
4	 **10e**	 **11e**	91%
5	 **10f**	 **11f**	82%
6	 **10g**	 **11g**	82% (50:50)
7	 **10h**	 **11h**	58% with DPPB 66% with DPPP (63:37)

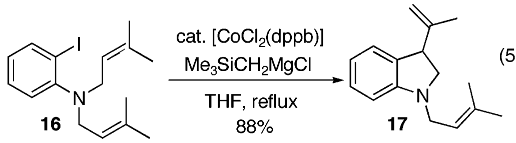
[a] Conditions: **10** (0.50 mmol), the Grignard reagent (1.5 mmol), $CoCl_2$ (0.05 mmol), DPPB (0.06 mmol), THF, reflux, 5 min. [b] Substrates having wavy bonds are 1:1 mixtures of diastereomers. [c] Diastereomeric ratios of the products are in parentheses.

N,*N*-diprenyl-2-iodoaniline (**16**) were cleanly transformed to isopropenyl-substituted heterocycles **15** and **17**, respectively.



(4)

a (X = I) : 90% **b** (X = Br) : 77% **c** (X = Cl) : 26%

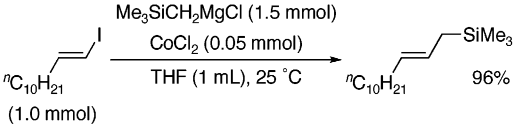


(5)

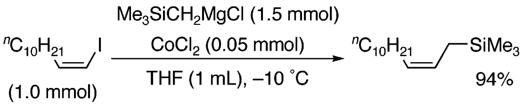
Bromide **14b** and chloride **14c** were less reactive. In the reaction of **14c**, 42% of **14c** was recovered, and chlorophenol was obtained in 20% yield.

In the reaction of **14** and **16**, no traces of isopropyl-substituted products were detected, which is intriguingly different from the reaction of **10** having an sp^3-C-X bond. If the relevant aryl radical was generated, the subsequent radical cyclization would form a tertiary alkyl radical. It is unlikely that the tertiary alkyl radical would be completely trapped by a cobalt complex, judging from the product distribution of the reactions of halo acetals **10**. Alternatively, it is quite reasonable that aryl halides **14** and **16** undergo oxidative addition to form aryl−cobalt bonds in a fashion similar to the conventional oxidative addition of aryl halide to palladium, instead of the generation of the corresponding aryl radical via a single electron-transfer process. The behavior of the cobalt complex depends on the organic halides, which will be confirmed in the next section.

Stereospecific Cross-Coupling Reaction of Alkenyl Halides with Silylmethyl Grignard Reagents: Evidence of Substrate-Dependent Oxidative Addition. The generation of an alkenyl radical from an alkenyl halide would lead to the loss of the original stereochemistry of the starting halide through a very rapid isomerization of the alkenyl radical.[27] Hence, a stereospecific cross-coupling reaction of alkenyl halides with trimethylsilylmethylmagnesium chloride would be a suitable probe to verify the nonradical oxidative addition mechanism of an sp^2-hybridized carbon−halogen bond to cobalt (eqs 6 and 7).



(6)



(7)

Treatment of (*E*)-1-iodo-1-dodecene with trimethylsilylmethylmagnesium chloride in the presence of a catalytic amount of anhydrous cobalt(II) chloride in THF at 25 °C afforded (*E*)-1-trimethylsilyl-2-tridecene exclusively. On the other hand, (*Z*)-

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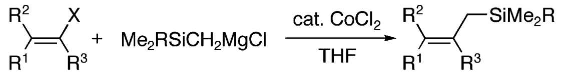
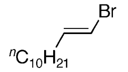
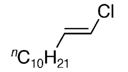
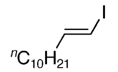
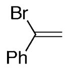
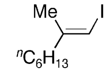
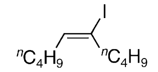
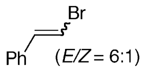
(27) (a) Fessenden, R. W.; Shuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147−2195. (b) Wedegaertner, D. K.; Kopchik, R. M.; Kampmeier, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6890−6895.

Table 6. Preparation of Allylsilanes[a]

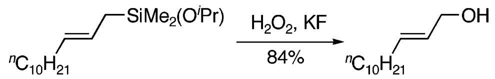


entry	alkenyl halide	R	temp /°C	time /h	yield /%
1		Me	25	8	85
2		Me	35	5	81
3		O^iPr	25	1	100
4		Me	25	14	77
5		Me	35	7	74
6		Me	35	8	25[b]
7		Me	25	12	83 (E/Z = 6:1)

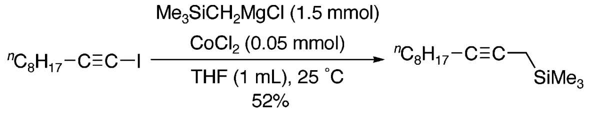
[a] Alkenyl halide (1.0 mmol), Me_2RSiCH_2MgCl (1.5 mmol), and $CoCl_2$ (0.05 mmol) were employed. [b] Starting material (46%) was recovered.

1-iodo-1-dodecene solely afforded the corresponding (*Z*)-allylsilane at −10 °C. The reaction of (*Z*)-1-iodo-1-dodecene at 25 °C gave rise to contamination of (*Z*)-isomer with (*E*)-isomer (∼10%). Use of ligands such as DPPH and triphenylphosphine decreased the efficiency of the reaction, albeit with no effects on the stereospecificity.

In light of the importance of allylsilanes in organic synthesis,[28] a cobalt-catalyzed cross-coupling reaction of alkenyl halides with trimethylsilylmethylmagnesium halide was investigated (Table 6). It is worth noting that ligandless cobalt(II) chloride is much cheaper than palladium and nickel complexes.[29,30] Not only alkenyl iodides but also alkenyl bromides and chlorides reacted effectively to give the corresponding allylsilanes in good to excellent yields (entries 1 and 2). Isopropoxydimethylsilylmethylmagnesium chloride reacted as well as $TMSCH_2MgCl$ (entry 3). The product enjoyed Tamao−Fleming oxidation[31] to furnish the corresponding allyl alcohol (eq 8). Trisubstituted alkenyl iodide, (*E*)-1-iodo-2-methyl-1-octene, provided (*E*)-1-trimethylsilyl-3-methyl-2-nonene in 74% yield upon treatment with $TMSCH_2MgCl$ (entry 5). Unfortunately, the transformation of (*E*)-5-iodo-5-decene resulted in a low yield (entry 6). However, the reaction proceeded with a retention of configuration. The retention of the stereochemistry was also observed in the reaction of a stereoisomeric mixture of β-bromostyrene (entry 7). It is worth noting that similar reactions in the presence of styrene resulted in no significant changes. The anticipated Heck transformation was not observed. A propargylic silane was also prepared in a similar fashion (eq 9).



(8)



$$^nC_8H_{17}-C{\equiv}C-I \xrightarrow[\text{THF (1 mL), 25 °C; 52\%}]{Me_3SiCH_2MgCl\ (1.5\ mmol),\ CoCl_2\ (0.05\ mmol)} {}^nC_8H_{17}-C{\equiv}C-CH_2SiMe_3 \quad (9)$$

Diastereoselectivity in the Styrylation Reaction of 1-Alkoxy-2-bromocycloalkane Derivatives. The present intermolecular cobalt-catalyzed Heck-type reaction allows us to use alkyl halides having hydrogen or heteroatom at the β position to the halide atom. We thus examined the use of alkyl bromides having stereocenters next to the brominated carbons in the intermolecular styrylation reaction. The reaction inherently posed interesting questions about the diastereoselectivity of the intermolecular Heck-type reaction. The selectivity would originate from the steric reasons, i.e., styrene would approach preferentially trans to the shielding substituent of the radical.[32]

We chose 1-alkoxy-2-bromocycloalkane derivatives as substrates because of their ready availability through bromoetheri-

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(30) Cobalt-catalyzed alkenylation with organometallic reagents in THF/NMP: (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159−6162. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163−6166. Cobalt-catalyzed monocoupling reaction of 1,2-dihaloethylenes with silylmethylmagnesium reagents in THF/NMP to yield (*E*)-3-halo-2-propenylsilanes was reported: (c) Kamachi, T.; Kuno, A.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 4677−4679. Cobalt-catalyzed cross-coupling reaction of aryl halides with organometallic reagents. (d) Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2947−2951. (e) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892−1894.

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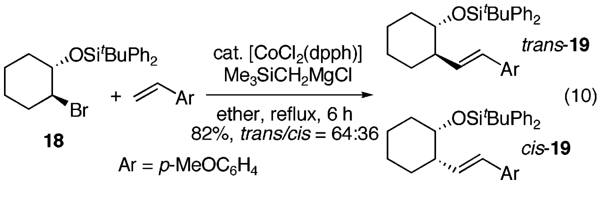
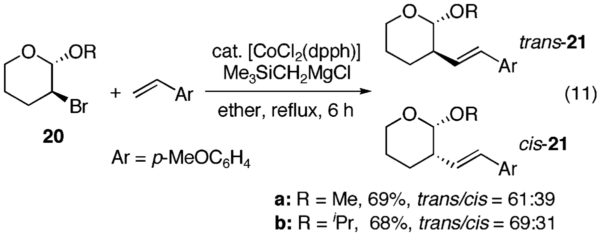
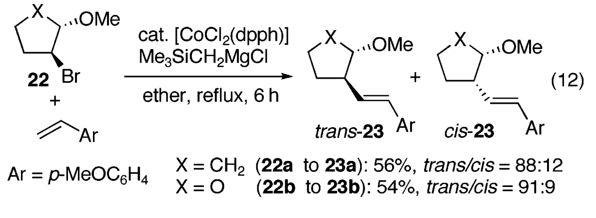
fication of cycloalkenes with alcohols and conformational restriction arising from their cyclic structures. The reaction of *trans*-2-(*tert*-butyldiphenylsiloxy)-1-bromocyclohexane (**18**) with *p*-methoxystyrene provided a mixture of diastereomers, *trans*-**19** and *cis*-**19**, in a ratio of 64:36 (eq 10, Ar means *p*-methoxyphenyl group hereafter). We thought that the low selectivity would result from the exclusive existence of the large siloxy group at the equatorial position of the cyclohexane ring. To resolve this problem, we considered the anomeric effect of cyclic acetals **20**, which permit an alkoxy substituent on the acetal carbon to locate predominantly at the axial position and hence would give rise to better diastereoselectivities (Scheme 5). To this end, bromo acetals **20a** and **20b** were exposed to the cobalt-catalyzed styrylation reaction (eq 11). The reaction of the isopropyl acetal gave the highest trans/cis ratio, which is unfortunately 69:31. These unsatisfactory selectivities would be attributable to the rather flexible nature of six-membered rings.

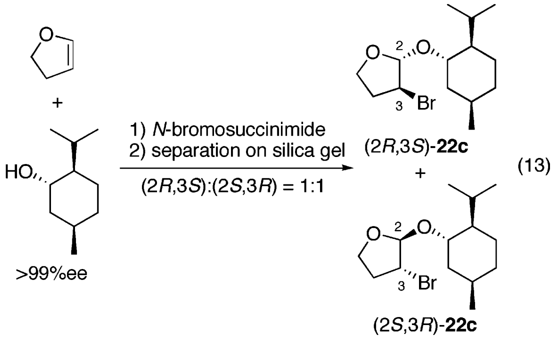


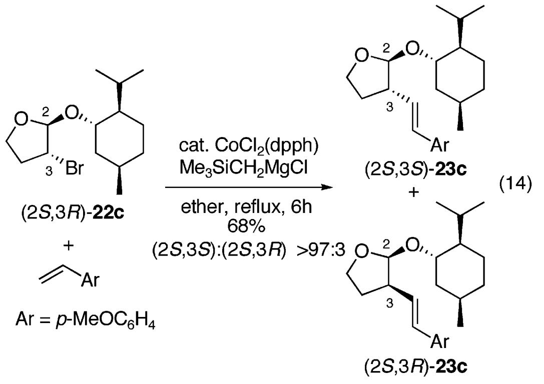


Since excellent stereocontrol is usually observed in a five-membered ring system,[32a,33] we thus turned our attention to the reactions of **22** (eq 12). To our delight, excellent diastereoselectivity was observed. An anomeric effect operated in the reaction of **22b** to improve the selectivity compared to the case of **22a**.



Bromoetherification of 2,3-dihydrofuran with enantiomerically pure (+)-isomenthol provided *trans*-bromo acetals (2*S*,3*R*)-**22c** and (2*R*,3*S*)-**22c** in a ratio of 1:1. Subsequent chromatographic separation of these diastereomers yielded both isomers in enantiomerically pure forms. Use of other chiral alcohols such as (−)-menthol and *trans*-2-phenyl-1-cyclohexanol resulted in more inefficient separation. Enantiomerically pure (2*S*,3*R*)-**22c** was subjected to the cobalt-mediated Heck styrylation reaction.





Gratifyingly, the reaction gave the *trans*-adduct **23c** exclusively (trans/cis > 97:3). The acetal **23c** would undergo a variety of transformations to yield tetrahydrofuran derivatives.[12i]

Scheme 5

Conclusion

The cobalt-catalyzed Heck-type reactions have a high potential of eliminating the possibility of β-elimination, allowing us to employ alkyl halides as coupling partners. In light of the importance of the Heck reaction, the alkyl version of the Heck reaction under the cobalt catalysis would make significant progress in organic synthesis. Its stereoselective variant is also available, in which the formation of a radical intermediate is the key for the stereoselectivity. Mechanistic investigations have revealed that single electron transfer from the cobalt complexes [Co^{II}(CH$_2$SiMe$_3$)$_2$(dpph)] and [Co^0(dpph)] to alkyl halides induces the generation of the corresponding radical intermediates. The generation of radical intermediates is limited in case alkyl halides were used. Alkenyl and aryl halides undergo nonradical oxidative addition.

Noteworthy is the generation of a new carbon−cobalt bond by the capture of a carbon-centered radical that is newly formed after a certain radical transformation. As demonstrated in the cobalt-catalyzed reaction, transition-metal-catalyzed radical

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reactions can offer novel transformation, by taking advantage of both a radical reaction and transition metal catalysis.[34]

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Supporting Information Available: Experimental details, characterization data for new compounds, and UV−visible spectra of cobalt complexes (PDF), and crystallographic data of $[CoCl_2(dpph)]_2$ (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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