New synthetic reactions catalyzed by cobalt complexes*

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Abstract: Without suffering from β-elimination, cobalt complexes allow cross-coupling reactions of alkyl halides with Grignard reagents. A combination of a cobalt complex and trimethylsilylmethyl Grignard reagent effects Mizoroki–Heck-type reaction of alkyl halide with styrene, which conventional palladium catalysts have never made possible. Cobalt exhibits intriguing catalytic activities on hydrophosphination and allylzincation of alkynes. Silylmethylcobalt reagent is a powerful tool for the synthesis of highly silylated ethenes.

Keywords: cobalt; synthesis; Grignard reagents; cross-coupling reactions; Mizoroki–Heck reactions.

INTRODUCTION

Palladium and nickel catalysts play a key role in modern organic synthesis. Cross-coupling and Mizoroki–Heck reactions are among the most important carbon–carbon bond-formation reactions. Normally, aryl and vinyl halides are 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 was performed. During the course of our study on transition-metal-catalyzed reaction [1], 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.

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 [2]. Treatment of bromo acetal **1** with phenyl Grignard reagent in the presence of [CoCl$_2$(dppe)] yielded benzyl-substituted cyclic acetal **2** in good yield (eq. 1). Cyclic acetals such as **2** are useful building blocks of a variety of tetrahydrofuran derivatives. For instance, Jones oxidation of **2** provided β-benzyl-γ-lactone **3**. Not only oxacycles, but also azacycles and carbocycles have become readily available (eq. 2). Other aromatic Grignard reagents such as 2-thienylmagnesium bromide could be employed (eq. 3). Intriguingly, DPPE

is the choice of ligand, and other bidentate ligands such as DPPM, DPPP, DPPF, and triphenylphosphine considerably diminished the yield of **2**.
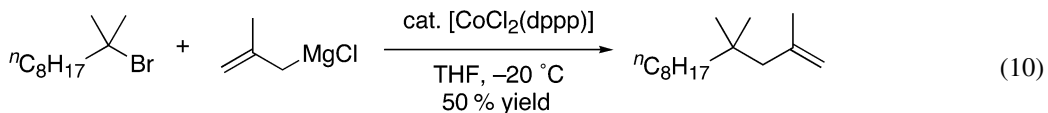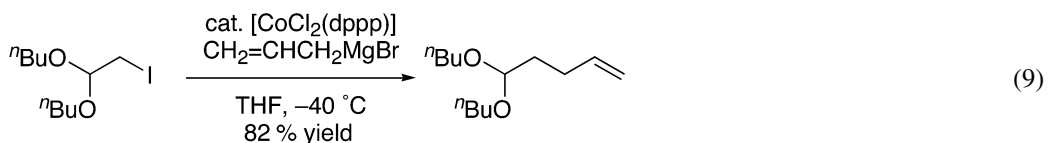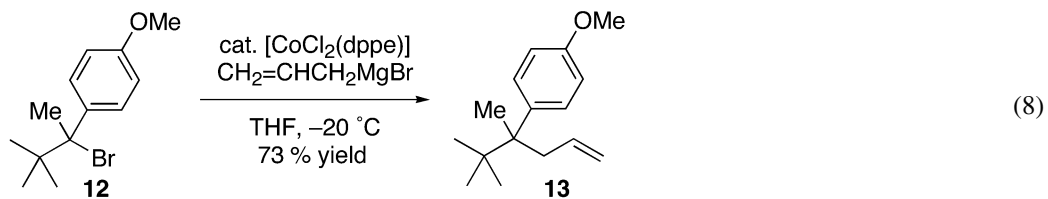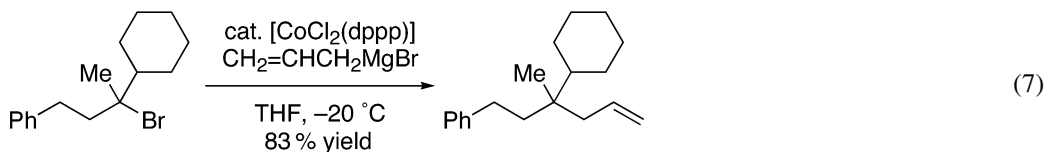

(1)

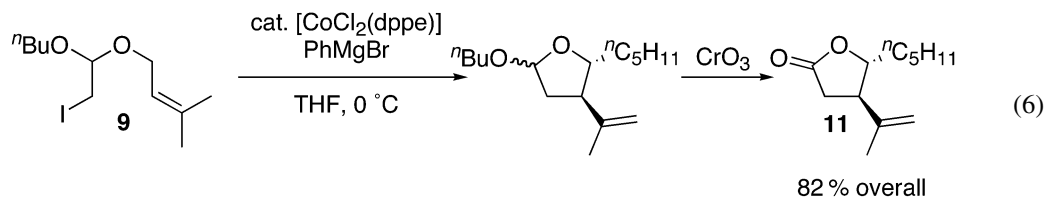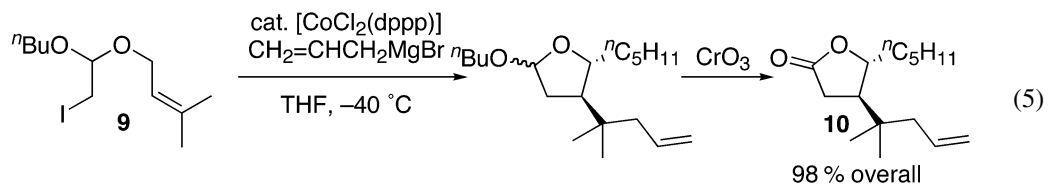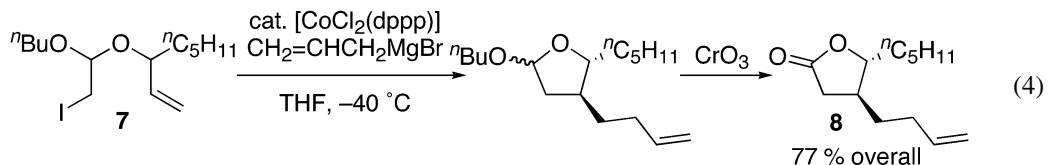X = TsN, 81 %; X = CH$_2$, 59 %

(2)

(3)
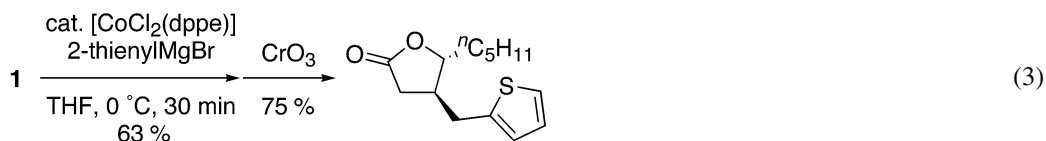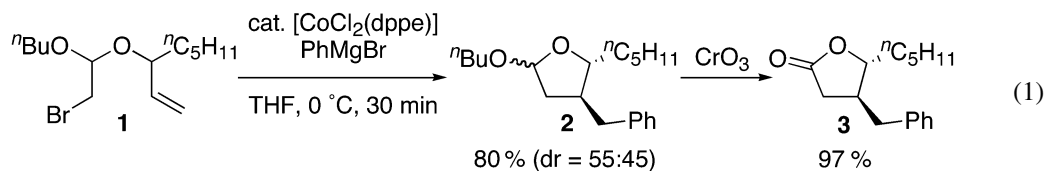
We are tempted to assume that the reaction proceeds via radical intermediates, since the stereochemical distribution of the products was quite similar to that obtained by well-established radical cyclization reactions. With some more evidence, a possible mechanism is illustrated as Scheme 1. Single electron transfer from an electron-rich low-valent cobalt complex to **1** leads to the formation of radical **4**. Radical 5-*exo-trig*-cyclization produces **5**. A cobalt complex would recombine with the carbon-centered radical **5** to form a cobalt complex **6**. Reductive elimination finalizes the catalytic cycle to yield **2**. It is fundamental knowledge that oxidative addition of organic halide to metal can proceed via a radical process. However, little attention has been paid to its application to organic synthesis. This cobalt-catalyzed reaction has provided a new methodology of a multibond-forming event 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, realizing the use of alkyl halides in cross-coupling reactions.
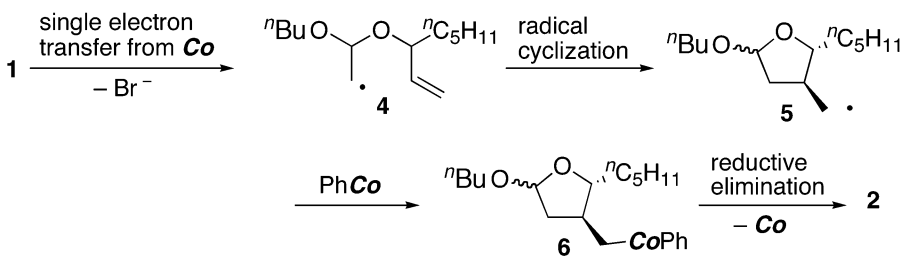
Scheme 1

Treatment of **7** with allyl Grignard reagent under [CoCl$_2$(dppp)] catalysis, followed by oxidation, afforded cross-coupling product **8** as well (eq. 4) [3]. Interestingly, allyl Grignard reagent proved to promote radical cyclization/cross-coupling reaction of **9** having a prenyl moiety, which creates a quaternary carbon (eq. 5). An attempted phenylation of **9** with phenyl Grignard reagent resulted in failure, instead providing **11** (eq. 6). Having observed the construction of the quaternary carbon center, we

devoted ourselves to cross-coupling reaction of tertiary alkyl halides with allylic Grignard reagents (eqs. 7–9). 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 suffer from β-alkoxy elimination (eq. 9). It is assumed that π-allyl ligands may prevent the formation of vacant coordination sites necessary for β-elimination. Benzyl, methallyl, and crotyl Grignard reagents can all couple with alkyl halides (eqs. 10–12).

$$(4)$$

$$(5)$$

$$(6)$$

$$(7)$$

$$(8)$$

$$(9)$$

$$(10)$$

$$\text{Ph}\diagup\diagdown\diagup\text{I} + \diagup\diagdown\text{MgCl} \xrightarrow[\substack{\text{THF, }-40\ ^\circ\text{C} \\ 93\ \%\ \text{yield}}]{\text{cat. [CoCl}_2\text{(dppp)]}} \text{Ph}\diagup\diagdown\diagup\diagdown\diagup \quad (11)$$

$$\diagdown\diagup\diagup_{\text{Br}} + \text{Ph}\diagdown\text{MgCl} \xrightarrow[\substack{\text{THF, }0\ ^\circ\text{C} \\ 70\ \%\ \text{yield}}]{\text{cat. [CoCl}_2\text{(dppp)]}} \diagdown\diagup\diagdown\diagup\text{Ph} \quad (12)$$
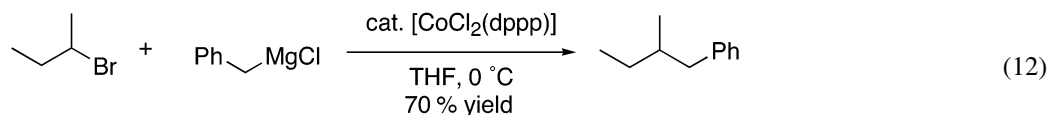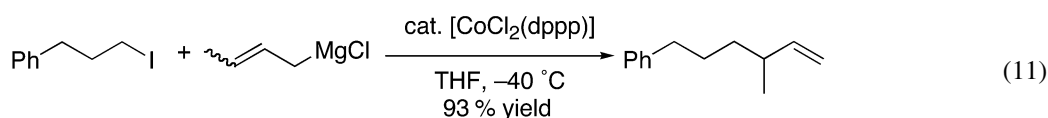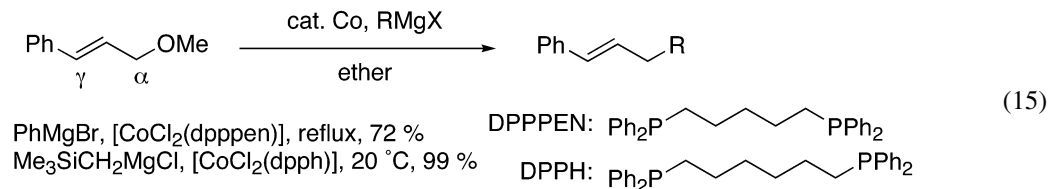
The intermediacy of a carbon-centered radical means loss of the original stereochemistry of the parent alkyl halides. The cobalt-catalyzed cross-coupling reaction may thus make possible asymmetric cross-coupling reaction using racemic alkyl halides by way of a planar carbon center. Treatment of racemic **12** with allylmagnesium chloride in the presence of [CoCl$_2$\{(–)-chiraphos\}] at –78 °C afforded **13** (eq. 13). Hydroboration/oxidation of **13** furnished **14** with 22 % enantiomeric excess (ee). Despite the miserable ee, the cobalt-catalyzed asymmetric allylation represents a new aspect of transition-metal-based radical reactions.

$$\quad (13)$$

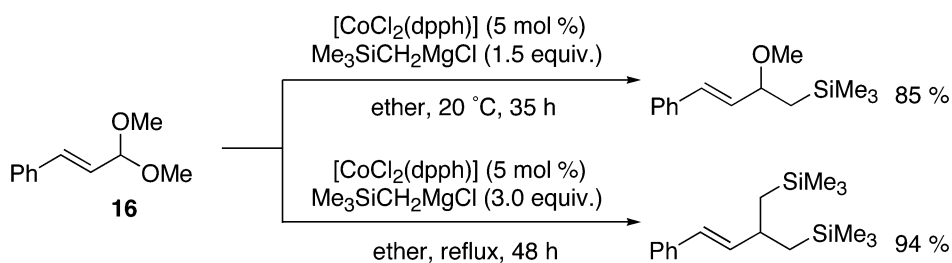L* : (–)-CHIRAPHOS

49 % overall, 22 % ee
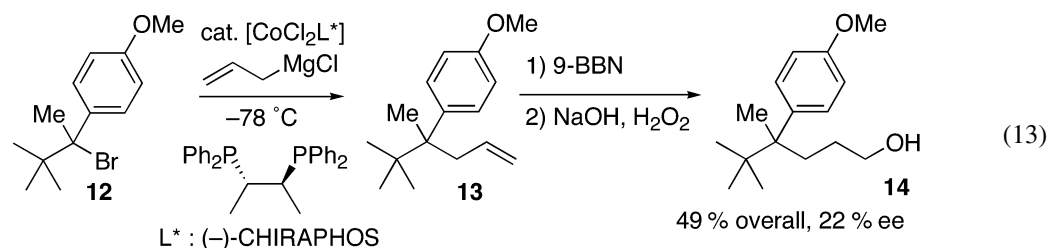
As depicted in eq. 14, chloropyridine derivative **15** also underwent cross-coupling reaction, wherein no cyclization took place [4]. A different mechanism would operate in this reaction.

$$\quad (14)$$

15
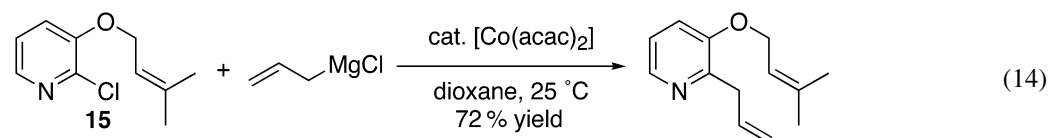
Cobalt-catalyzed allylic substitution allowed the use of hard nucleophile such as Grignard reagents (eq. 15, Scheme 2) [5]. α-Selective substitution of cinnamyl methyl ether proceeded to yield the corresponding linear products. Cinnamaldehyde dimethyl acetal (**16**) underwent sequential allylic substitution under cobalt catalysis. By changing the reaction temperature and the amount of the Grignard reagent, selective monosubstitution was performed.

$$\text{Ph}\diagup\diagdown\diagup\text{OMe} \xrightarrow[\text{ether}]{\text{cat. Co, RMgX}} \text{Ph}\diagup\diagdown\diagup\text{R} \quad (15)$$

γ   α

PhMgBr, [CoCl$_2$(dpppen)], reflux, 72 %
Me$_3$SiCH$_2$MgCl, [CoCl$_2$(dpph)], 20 °C, 99 %
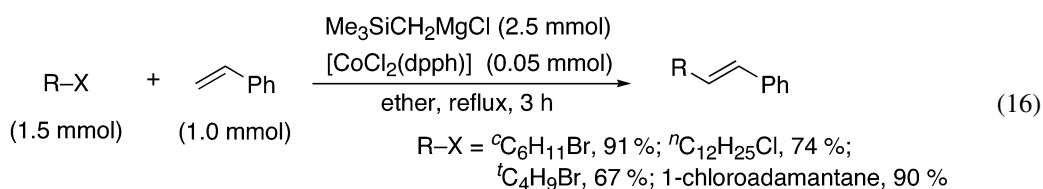
DPPPEN: Ph$_2$P⌣⌣⌣PPh$_2$

DPPH: Ph$_2$P⌣⌣⌣⌣PPh$_2$

Scheme 2

COBALT-CATALYZED MIZOROKI–HECK-TYPE REACTION OF ALKYL HALIDES 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 hydrogen 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 accomplished an alkyl version of Mizoroki–Heck reaction [6].

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 (eq. 16). Primary, secondary, and tertiary alkyl halides all participated in the reaction. It is worth noting that alkyl chlorides, which are usually less reactive in transition-metal-catalyzed reactions, are good alkyl sources. The reaction allows various functionalities, including ester and amide moieties, to survive during the reaction (eq. 17). Use of trimethylsilylmethyl Grignard reagent is the key for the successful reaction. Other Grignard reagents such as neopentyl, butyl, and phenyl Grignard reagents did not promote the reaction at all.

$$R{-}X = {}^{c}C_6H_{11}Br, 91\%; {}^{n}C_{12}H_{25}Cl, 74\%;$$
$${}^{t}C_4H_9Br, 67\%; 1\text{-chloroadamantane}, 90\%$$

(16)

$$Ar = C_6H_4\text{-}o\text{-Cl}, 85\%; C_6H_4\text{-}m\text{-CON(CH}_2Ph)_2, 95\%;$$
$$C_6H_4\text{-}m\text{-COO-}t\text{-}C_4H_9, 66\%$$

(17)
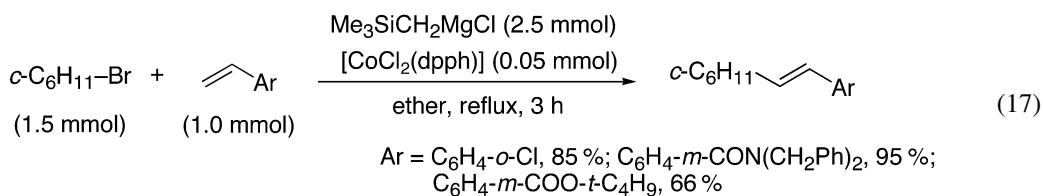
The reaction with cyclopropylmethyl bromide provided a ring-opening product **17** (eq. 18). In addition, tetrahydrofuran derivative **19** was obtained when iodo acetal **18** was employed (eq. 19). Ring-opening of a cyclopropylmethyl radical and ring-closure of a 5-hexenyl radical are well-known processes. Generation of an alkyl radical from an alkyl halide is consequently suggested. Mechanistic studies are now under way through collaboration with Profs. Mizuta and Miyoshi at Hiroshima University [7]. As a preliminary result (Scheme 3), 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 furnish benzylic radical, which is captured by a cobalt complex. The benzylic cobalt complex undergoes β-hydride elimination to afford the product.

(18)

(19)
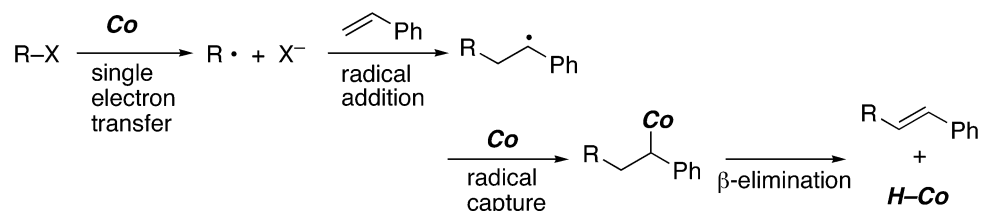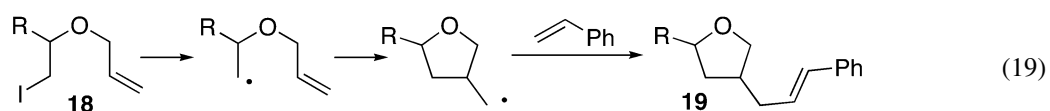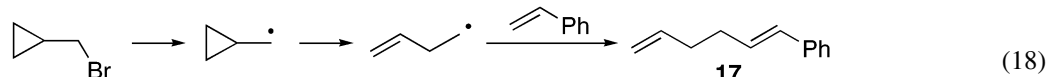
Scheme 3

In place of styrene, the reaction with 1,3-diene was examined [8]. Unexpectedly, three-component-coupling reaction occurred to yield homoallylsilane **20** (Scheme 4). Reductive elimination would proceed faster than β-hydride elimination that forms a Mizoroki–Heck product **21**.
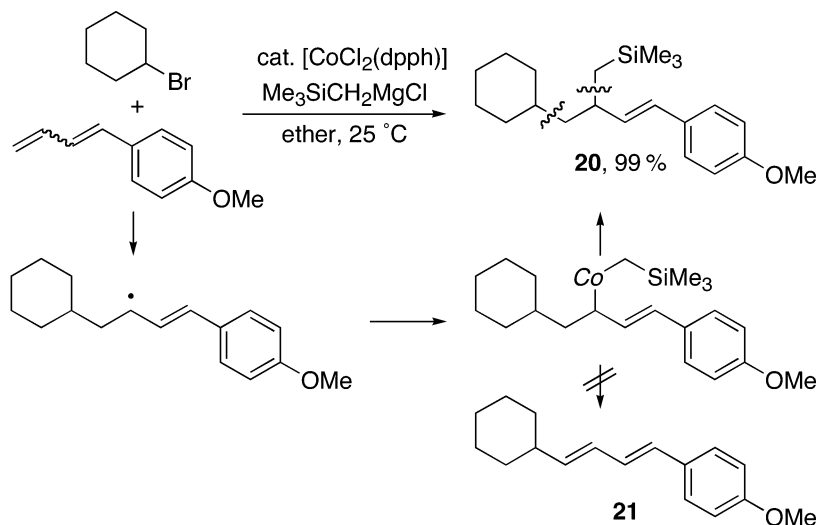

Scheme 4

Epoxide is also a substrate in the cobalt-catalyzed Mizoroki–Heck-type reaction (eq. 20) [9]. 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, not with direct single electron transfer from a cobalt complex to the epoxide.

$$(20)$$
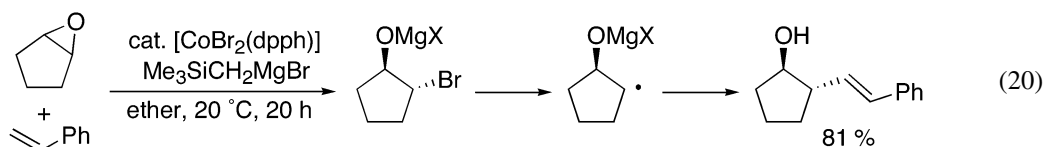
Cobalt-catalyzed intramolecular reactions of 6-halo-1-hexene derivatives produced methylene-cyclopentanes (eq. 21) [10]. A higher temperature (refluxing THF) and [CoCl$_2$(dppb)] were required to attain high yield.
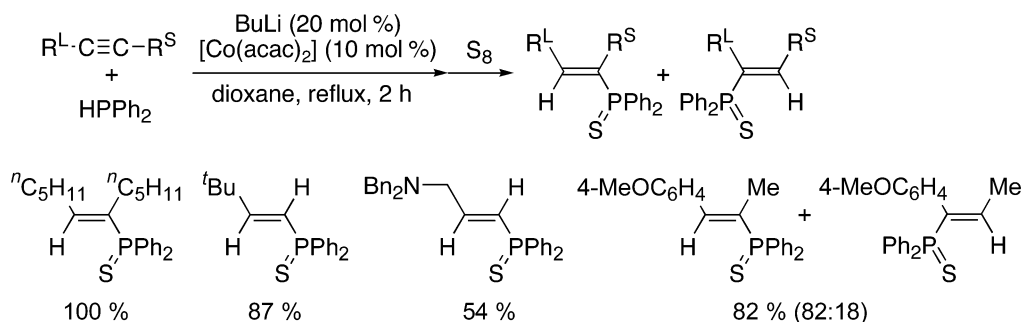

$$(21)$$
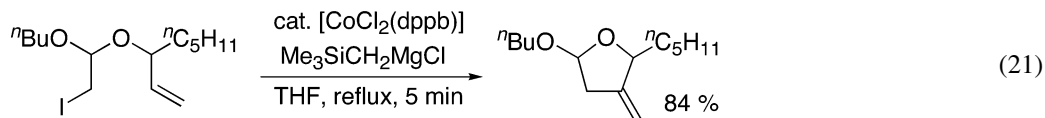
COBALT-CATALYZED REACTIONS WITH ALKYNES

Metal-catalyzed functionalization of carbon–carbon triple bonds represents an important transformation in organic chemistry. The potential of cobalt catalysts in such transformations has thus been explored.

Allylmetallation of alkyne is one of the most powerful methods for the formation of carbon–carbon bonds. With respect to allylzincation, allylzincation across internal carbon–carbon triple bond encounters difficulty. Fortunately, it was revealed that cobalt(II) chloride catalyzes allylzincation of 1-aryl-1-alkyne with perfect regio- and stereoselectivity (eq. 22) [11]. The alkenylzinc intermediate could be trapped with several electrophiles to furnish tetrasubstituted alkenes.

$$(22)$$

$$E^+ = H_3O^+, I_2, CH_3COCl$$
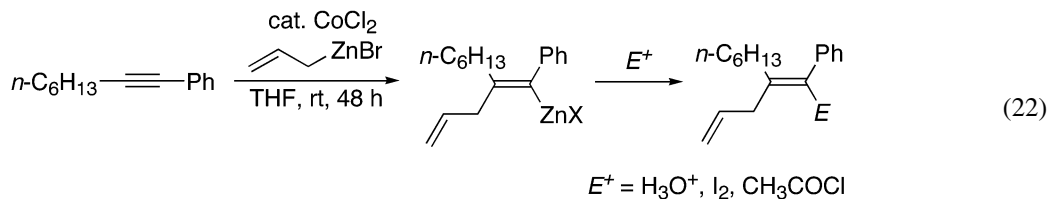
Organophosphorus compounds are indispensable heteroatom-containing molecules in organic chemistry. Hydrophosphination of alkyne is among the most useful methods to install a phosphine moiety into organic molecule. Contrary to the seeming simplicity of this reaction, there are few *syn*-hydrophosphination reactions, most of which lack generality and/or require preparation of intricate metal complexes as catalysts. Development of facile, efficient, and general methods has hence been awaited. During the course of our study on cobalt catalysis, a simple cobalt salt, cobalt(II) acetylacetonate, proved to catalyze such a hydrophosphination reaction (Scheme 5) [12]. Treatment of diphenylphosphine with 0.2 equiv of butyllithium yielded an orange mixture of lithium diphenylphosphide and diphenylphosphine. A catalytic amount of [Co(acac)$_2$], alkyne, and dioxane was added to the mixture. The resulting mixture was heated to provide the corresponding syn adduct. Various alkynes were subjected to this reaction to afford the corresponding syn adducts exclusively, irrespective of the electronic and steric factors of the alkynes used.

$$R^L \cdot C \equiv C - R^S + HPPh_2 \xrightarrow[\text{dioxane, reflux, 2 h}]{\substack{\text{BuLi (20 mol \%)} \\ [\text{Co(acac)}_2]\text{ (10 mol \%)}}} S_8$$

100 %	87 %	54 %		82 % (82:18)

Scheme 5

SYNTHESIS OF HIGHLY SILYLATED ETHENES

Multiply silylated ethenes such as 1,2-disilylethenes and 1,1,2-trisilylethenes are promising platforms for highly substituted alkenes as well as structurally interesting entities. However, there are a limited number of syntheses of multiply silylated ethenes that are both stereo- and regioselective. An ate-type trimethylsilylmethylcobalt reagent proved to react with dibromosilylmethane or dibromodisilylmethane to provide a concise synthesis of 1,2-disilylethenes or 1,1,2-trisilylethenes in a highly stereoselective and definitely regioselective manner (eq. 23) [13]. A plausible reaction mechanism includes halogen-cobalt exchange, 1,2-silylmethyl migration, and finally β-hydride elimination (Scheme 6), the reaction thus being inherently regioselective. The β-hydride elimination would favor a sterically less demanding transition state, which makes the reaction highly stereoselective.

$$\text{54 \%, 94 \% selectivity} \tag{23}$$
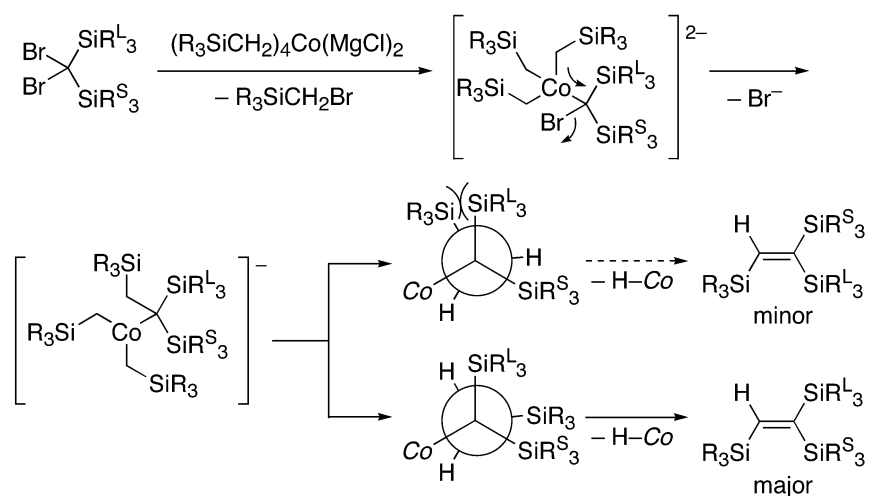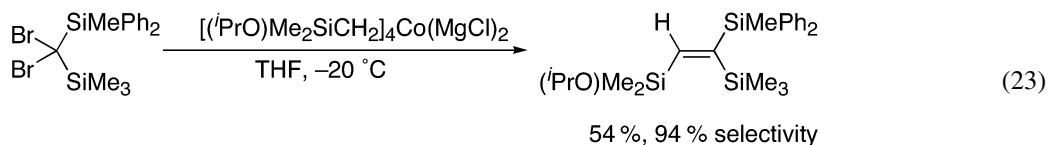
Scheme 6

CONCLUSION

Simple cobalt salts such as $CoCl_2$ and $[Co(acac)_2]$, often combined with proper ligands, serve as unique catalysts for unprecedented chemical transformations. Compared to palladium and nickel, cobalt catalysts had fallen behind in the field of organic synthesis. Cobalt will create the next generation of organic synthesis [14]. To this end, before using nickel and palladium, cobalt is the first choice.

ACKNOWLEDGMENTS

REFERENCES

1. H. Shinokubo and K. Oshima. *Eur. J. Org. Chem.* 2081–2091 (2004).
2. (a) K. Wakabayashi, H. Yorimitsu, K. Oshima. *J. Am. Chem. Soc.* **123**, 5374–5375 (2001); (b) H. Ohmiya, K. Wakabayashi, H. Yorimitsu, K. Oshima. *Tetrahedron* **62** (2006). In press.
3. (a) T. Tsuji, H. Yorimitsu, K. Oshima. *Angew. Chem., Int. Ed.* **41**, 4137–4139 (2002); (b) H. Ohmiya, T. Tsuji, H. Yorimitsu, K. Oshima. *Chem. Eur. J.* **10**, 5640–5648 (2004).
4. H. Ohmiya, H. Yorimitsu, K. Oshima. *Chem. Lett.* **33**, 1240–1241 (2004).
5. (a) K. Mizutani, H. Yorimitsu, K. Oshima. *Chem. Lett.* **33**, 832–833 (2004); (b) H. Yasui, K. Mizutani, H. Yorimitsu, K. Oshima. *Tetrahedron* **62**, 1410–1415 (2006).
6. Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima. *J. Am. Chem. Soc.* **124**, 6514–6515 (2002).
7. (a) T. Mizuta, Y. Imamura, K. Miyoshi, H. Yorimitsu, K. Oshima. *Organometallics* **24**, 990–996 (2005); (b) Y. Imamura, T. Mizuta, K. Miyoshi, H. Yorimitsu, K. Oshima. *Chem. Lett.* **35** (2006). In press.
8. K. Mizutani, H. Shinokubo, K. Oshima. *Org. Lett.* **5**, 3959–3961 (2003).
9. Y. Ikeda, H. Yorimitsu, H. Shinokubo, K. Oshima. *Adv. Synth. Catal.* **346**, 1631–1634 (2004).
10. T. Fujioka, T. Nakamura, H. Yorimitsu, K. Oshima. *Org. Lett.* **4**, 2257–2259 (2002).
11. T. Nishikawa, H. Yorimitsu, K. Oshima. *Synlett* 1573–1574 (2004).
12. H. Ohmiya, H. Yorimitsu, K. Oshima. *Angew. Chem., Int. Ed.* **44**, 2368–2370 (2005).
13. H. Ohmiya, H. Yorimitsu, K. Oshima. *Angew. Chem., Int. Ed.* **44**, 3488–3490 (2005).
14. H. Ohmiya, H. Yorimitsu, K. Oshima. *J. Am. Chem. Soc.* **128** (2006). In press.