structures were solved by direct methods and refined by full-matrix least-squares on F^2. The cyanide group in **2** is disordered over a site of symmetry 2, and the independent carbon atom is represented by $^1/_2$C + $^1/_2$N.

CCDC-184663 (**1**) and CCDC-184664 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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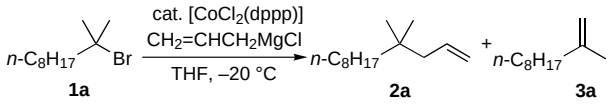
Cobalt-Catalyzed Coupling Reaction of Alkyl Halides with Allylic Grignard Reagents**

Takashi Tsuji, Hideki Yorimitsu, and Koichiro Oshima*

Nickel- and palladium-catalyzed cross-coupling reactions of organic halides with organometallic reagents is one of the most versatile carbon–carbon bond-forming reactions in organic synthesis.[1] In most cases, aryl and vinyl halides are employed as organic halides, yielding sp^2–sp, sp^2–sp^2, and sp^2–sp^3 linkages. The connection of two sp^3 carbon atoms under transition metal catalysis is also important, and a variety of retrosynthetic analyses are conceivable in which an arbitrary carbon–carbon bond in an alkyl chain is cleaved. However, coupling with alkyl halides is difficult for two main reasons: 1) Oxidative addition of alkyl halides is much slower than that of aryl and vinyl halides. 2) β-Hydride elimination of the alkylpalladium and -nickel compound is problematic. Thus, novel and efficient methods for alkyl–alkyl coupling are currently under intense investigation.[2,3]

We are interested in cobalt-catalyzed reactions[4,5] and report herein the cobalt-catalyzed cross-coupling reaction of alkyl halides with allylic Grignard reagents. Allylation of various alkyl halides proceeds smoothly, and even quaternary carbon atoms have become readily accessible by transition-metal-catalyzed coupling reactions.

Allylmagnesium chloride (1.0 M solution in THF, 1.5 mmol) was added to a solution of 2-bromo-2-methyldecane (**1a**; 0.50 mmol) in THF in the presence of [$CoCl_2$(dppp)] (0.05 mmol) at −20 °C (Scheme 1; dppp = 1,3-bis(diphenylphosphanyl)propane). Stirring for 2 h at −20 °C provided the



Scheme 1. Cobalt-catalyzed cross-coupling reaction of alkyl halide **1a** with allylmagnesium chloride.

allylated product **2a**, which contains a quaternary carbon center (90% yield), and **3a** (8%). No allylated product was obtained when the [$CoCl_2$(dppp)] catalyst was omitted. The yield of **2a** was lower when 1,4-bis(diphenylphosphanyl)butane (DPPB), 1,2-bis(diphenylphosphanyl)ethane (DPPE), and bis(diphenylphosphanyl)methane (DPPM) were employed in place of DPPP. Reaction at −40 °C led to recovery of **1a**, whereas reaction at 0 °C resulted in a lower ratio of **2a**/**3a** (82:18).

Allylation of a variety of alkyl halides proceeded smoothly, although tuning of reaction conditions was necessary for the different substrates (Table 1). Benzylic allylation of **1d** required DPPE in place of DPPP to attain a satisfactory result. Primary and secondary bromides were less reactive. Instead, use of alkyl iodides such as **1g-I** led to high yields at −40 °C. It is worth noting that halides **1h**, **1h-I**, and **1i-I**, which have alkoxy groups at the β position to the halide atom, participated in the allylation.

Other allylic Grignard reagents were available for this reaction (Scheme 2). Regioselective coupling was observed to yield methyl-branched product **5b** upon treatment of **1g-I** with crotyl Grignard reagent. Unfortunately, reaction of prenyl Grignard reagent was unsuccessful.

Substrates having proper carbon–carbon double bonds were then subjected to the cobalt-catalyzed allylation (Scheme 3). Consequently, tandem cyclization/allylation occurred, thereby affording 3-butenyl-substituted lactones after Jones oxidation of the cyclic acetals. For example, iodoacetal **7c** was converted to lactone **9c** bearing a quaternary center, and cyclization of **7d** provided the *trans* isomer **9d** exclusively.

Interestingly, treatment of **7e** with the allyl Grignard reagent CH_2=$CHCH_2MgCl$ in the presence of [$CoCl_2$(dppp)] furnished the ring-opening product **9e** (Scheme 4). Given that intramolecular carbocobaltation proceeds to yield cyclopropylmethylcobalt species, β-carbon elimination would provide a route to **9e**. However, β-carbon elimination seems unlikely

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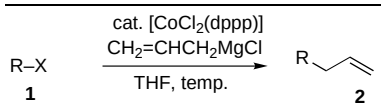
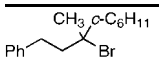
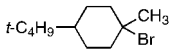
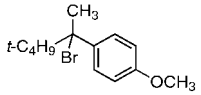
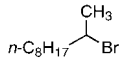
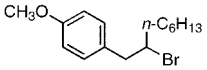
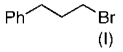
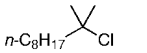
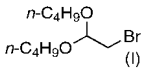
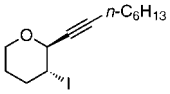
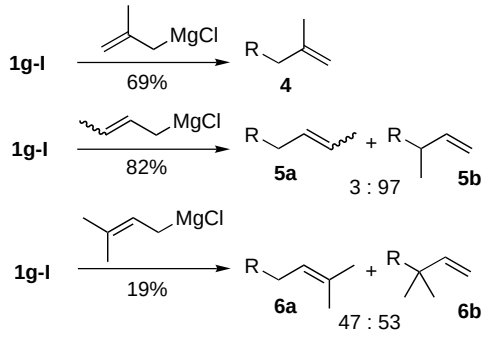
Table 1. Cobalt-catalyzed allylation of alkyl halides.

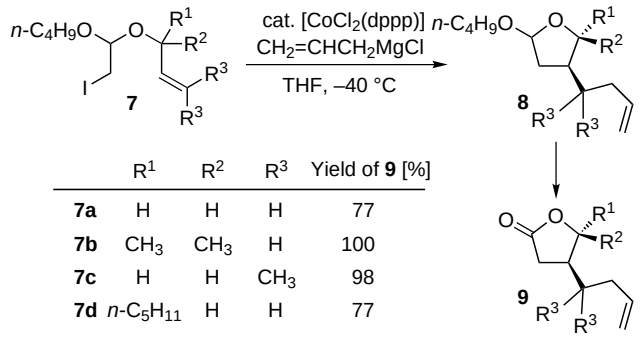


1		Temperature [°C]	Yield of **2** [%]
	**1b**	−20	83
	**1c**[a]	0	76[b]
	**1d**	−20	73[c]
	**1e**	0	57
	**1f**	−20	84
	**1g**	0	30
(I)	**1g-I**	−40	82
	**1a-Cl**	20	31
	**1h**	0	49
(I)	**1h-I**	−40	82
	**1i-I**	−40	76[d]

[a] *trans*/*cis* = 87/13. [b] *trans*/*cis* = 82/18. [c] DPPE was used. [d] *trans*/*cis* = 86/14.

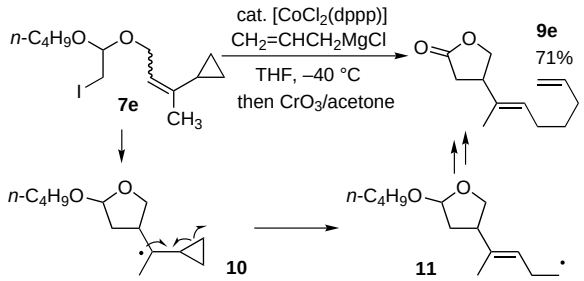


Scheme 2. R = Ph(CH$_2$)$_3$. Conditions: cat. [CoCl$_2$(dppp)], THF, −40 °C.

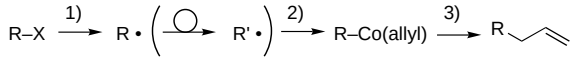


	R^1	R^2	R^3	Yield of **9** [%]
7a	H	H	H	77
7b	CH_3	CH_3	H	100
7c	H	H	CH_3	98
7d	*n*-C_5H_{11}	H	H	77

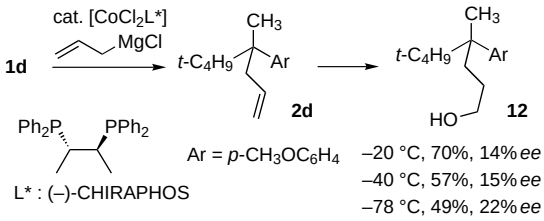
Scheme 3. Cobalt-catalyzed reaction of iodoacetals **7** to give lactones **9**.



Scheme 4. Cobalt-catalyzed reaction of **7e** with CH$_2$=CHCH$_2$MgCl to give the ring-opening product **9e**.



Scheme 5. Proposed mechanism for the catalytic reaction: 1) single-electron transfer from cobalt complex; 2) recombination of alkyl radical and cobalt complex; 3) reductive elimination.



Scheme 6. Cobalt-catalyzed asymmetric allylation of **1d**.

because β-hydride and β-alkoxy eliminations were minor processes in the reactions of **1**. Alternatively, the existence of radical intermediates **10** and **11** can account for the ring opening.[6]

Scheme 5 shows schematically a proposed mechanism for the catalytic reaction in analogy with the results of previous reports.[4] Namely, the oxidative addition proceeds via a single-electron transfer from an electron-rich allylcobalt complex to the alkyl halide. π-Allyl ligands may prevent the formation of the vacant coordination sites necessary for β-elimination, which enables allylation of tertiary and secondary alkyl halides and alkyl halides having β-alkoxy groups.

Finally, asymmetric allylation was investigated (Scheme 6).[7,8] Treatment of **1d** with allylmagnesium chloride in the presence of [CoCl$_2${(−)-chiraphos}] at −20 °C afforded **2d**. Hydroboration of **2d** followed by usual oxidation provided **12** in 70% yield and 14% *ee*. When the reaction was carried out at a lower temperature (−78 °C), the enantiomeric excess increased to 22%. The cobalt-catalyzed asymmetric allylation provides a novel utility of transition-metal-catalyzed radical reactions.

In summary, [CoCl$_2$(dppp)] effectively catalyzes the cross-coupling reaction of alkyl halides with allylic Grignard reagents. Not only primary alkyl halides but also secondary and tertiary alkyl halides undergo allylation, in the latter case to give quaternary carbon centers.

Experimental Section

Anhydrous cobalt(II) chloride (7.0 mg, 0.050 mmol) was placed in a 20 mL flask and was heated with a hair dryer in vacuo for 2 min. After the color of

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the cobalt salt became blue, DPPP (25 mg, 0.060 mmol) and anhydrous THF (1.0 mL) were sequentially added under argon. The mixture was stirred for 10 min at room temperature. 2-Bromo-2-methyldecane (**1a**, 0.12 g, 0.50 mmol) and allylmagnesium chloride (1.0 M solution in THF, 1.5 mL, 1.5 mmol) were successively added dropwise to the reaction mixture at −20 °C. While the Grignard reagent was being added, the mixture turned reddish-brown. After being stirred for 2 h at −20 °C, the reaction mixture was poured into saturated NH_4Cl solution, and the products were extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude oil by silica gel column chromatography (hexane) provided 4,4-dimethyl-1-dodecene (**2a**) and 2-methyl-1-decene (**3a**) (94 mg, 90% and 8% yields, respectively, as determined by ^1H NMR spectroscopy).

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Distal Cu Ion Protects Synthetic Heme/Cu Analogues of Cytochrome Oxidase against Inhibition by CO and Cyanide**

James P. Collman,* Roman Boulatov, Irina M. Shiryaeva, and Christopher J. Sunderland

Cytochrome c oxidase (C*c*O) is the enzyme that makes aerobic metabolism possible by catalyzing the final step in the respiratory electron-transfer chain—a four-electron (4e), four-proton ($4H^+$) reduction of O_2 to water.[1,2] Catalysis proceeds at the heterobimetallic heme/Cu_B site (Figure 1).[3] The Fe center is the site of O_2 binding, and reduction of O_2 is coupled to oxidation of Cu_B^I, at least under single-turnover conditions.[4,5] One of the poorly understood questions regarding the structure–activity relationship at the heme/Cu_B site is how the heme reactivity is affected by the closely positioned, positively charged Cu_B center. Such effects are expected to manifest themselves in an attenuated affinity of the Fe center for small molecules. Among these, CO and the ions CN^- and N_3^-, are of particular interest, because the cytotoxicity of the CN^- and N_3^- ions arises from the inhibition of C*c*O and resultant respiratory shutdown,[7] and CO is an endogenous inhibitor of ferrohemes. The mode of CN^- ion binding to the heme/Cu_B site and the effect(s) of Cu_B on such binding remain controversial.[8] Likewise, contradictory results have been reported for differences in the CO affinities of the wild-type and Cu_B-free mutants of terminal oxidases.[9,10]

Previously, we demonstrated that the biomimetic complexes shown in Figure 1b quantitatively reproduce the key reactivity of the heme/Cu_B site[6,11] and thus allow the study of questions that are not easily addressed by working with the enzyme itself. Herein we report that the steady-state reduc-

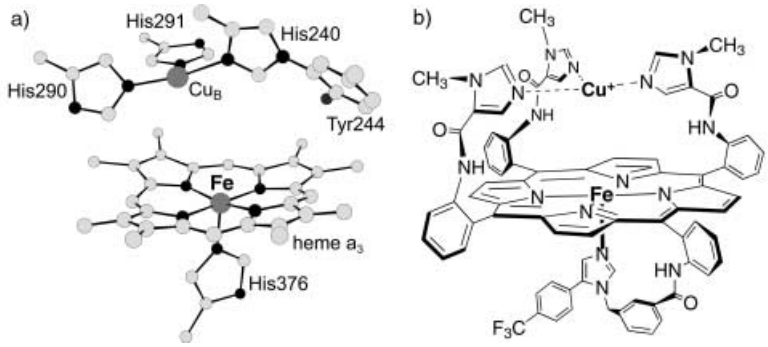

Figure 1. a) The heme/Cu_B site of bovine cytochrome oxidase;[3] the C atoms are light gray and the N and O atoms are black, b) a synthetic heme/Cu_B analogue in the reduced form; exogenous ligands and counterion are omitted.[6]

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