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Cobalt-Catalyzed Heck-Type Reaction of Alkyl Halides with Styrenes

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The Heck reaction is a powerful tool in organic synthesis.[1] The scope and limitations have therefore been well investigated. The major limitation is that one cannot use alkyl halides having hydrogen at the β-position to the halide atom, because such substrates suffer from the β-hydride elimination problem.[2] Although there are some examples of the palladium-catalyzed Heck reaction of alkyl halides, the reactions employ only bridgehead halides such as 1-adamantyl bromide.[3] A nickel-catalyzed reaction of alkyl bromides with styrenes was also reported.[4] However, few alkyl bromides were examined, and the yields were moderate. A similar catalytic transformation with a cobaloxime was known,[5] although photolysis was required for the successful reaction. Very recently, Kambe et al. have reported a titanocene-catalyzed alkylation reaction of styrenes, using butylmagnesium bromide as a base.[6] This protocol enables the employment of a variety of alkyl bromides and some alkyl chlorides as precursors, although yields are still not satisfactory. Functional group compatibility of this titanocene-based method remained uninvestigated.

We have been interested in radical reactions mediated by a cobalt complex.[7] Here we wish to report a complementary method to the palladium-catalyzed reaction. A cobalt−phosphine complex catalyzes a Heck-type reaction of alkyl halides with styrenes in the presence of Me_3SiCH_2MgCl.

Trimethylsilylmethylmagnesium chloride (1.0 M ether solution, 2.5 mmol) was added to a mixture of styrene (1.0 mmol) and bromocyclohexane (1.5 mmol) in ether in the presence of $CoCl_2$(dpph)[8] (0.05 mmol) at 0 °C. The reaction mixture was stirred for 8 h at 20 °C. After aqueous workup, silica gel column purification provided β-cyclohexylstyrene (**2a**) in 86% yield. Heating the reaction mixture at reflux improved the yield of **2a** up to 91%. The reaction proceeded similarly in dark conditions. Cobalt bromide, instead of cobalt chloride, worked equally well. $PhMe_2SiCH_2MgCl$ also effected the alkylation reaction (78% yield of **2a**, at 35 °C)[9] (Scheme 1).

A variety of alkyl halides were examined as shown in Table 1. Not only secondary alkyl bromides but also primary and tertiary ones participated in the alkylation reaction (entries 1−6). The reaction of lauryl bromide with styrene at 20 °C yielded β-laurylstyrene in 76% yield (entry 2). *tert*-Butyl bromide was less reactive and required heating to attain a satisfactory result (entries 5 and 6). Use of lauryl iodide resulted in a low yield of **2c** (entry 7). It is particularly noteworthy that alkyl chlorides, which are usually less reactive in transition metal-catalyzed reactions, proved to be good 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 **2c** in 74% yield under $CoCl_2$(dpph) catalysis. The reaction with iodomethane afforded β-methylstyrene **2f** in moderate yield (entry 11).

Scheme 1

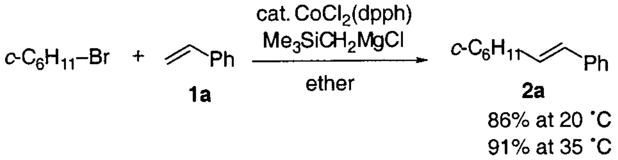
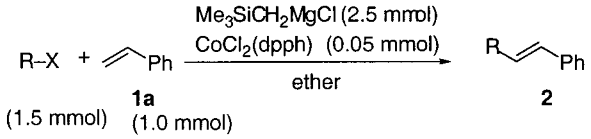


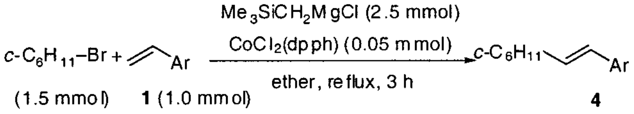
Table 1. Cobalt-Catalyzed Alkylation of Styrene



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

[a] Ad = 1-adamantyl. [b] *p*-Chlorostyrene was used instead of styrene.

Table 2. Reaction with Styrene Derivatives



entry	1	Ar	4	yield/%
1	**1b**	C_6H_4-p-Me	**4b**	87
2	**1c**	C_6H_4-p-Cl	**4c**	85
3	**1d**	C_6H_4-m-Cl	**4d**	82
4	**1e**	C_6H_4-o-Cl	**4e**	85
5	**1f**	C_6H_4-p-OMe	**4f**	82
6	**1g**	C_6H_4-p-$CON(CH_2Ph)_2$	**4g**	29
7	**1h**	C_6H_4-m-$CON(CH_2Ph)_2$	**4h**	95
8	**1i**	C_6H_4-m-COO-t-C_4H_9	**4i**	66

The reaction tolerates various functionalities (Table 2). Methoxy- and chlorostyrenes were alkylated efficiently under the standard heated conditions (entries 2−5). Disappointingly, the presence of a carbamoyl group at the para position decreased the yield of the product (entry 6). In contrast, the meta isomer **1h** underwent efficient alkylation (entry 7). A *tert*-butoxycarbonyl group survived under the reaction conditions (entry 8).

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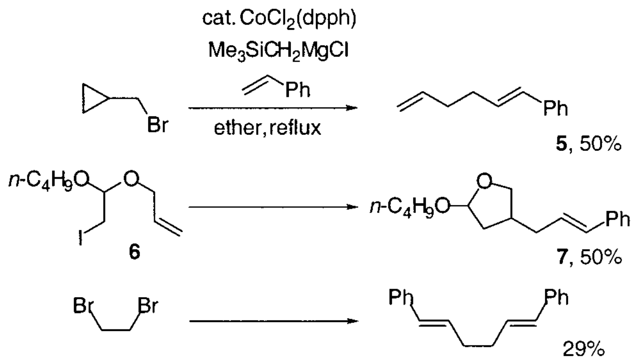
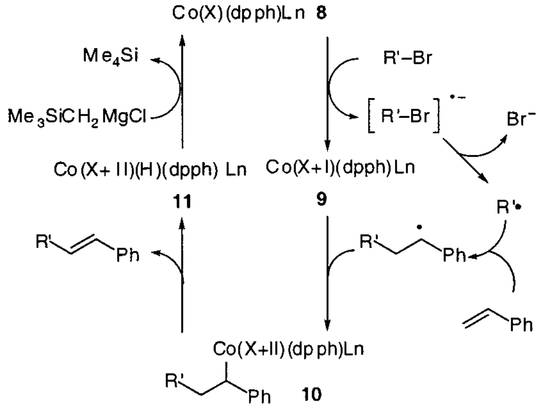
Scheme 2



Scheme 3



The reaction with cyclopropylmethyl bromide provided a ring-opening product, β-(3-butenyl)styrene (**5**), in 50% yield (Scheme 2). In addition, tetrahydrofuran derivative **7** was obtained when iodo acetal **6** was employed. Ring-opening of a cyclopropylmethyl radical and ring-closure of a 5-hexenyl radical are well-known processes.[10] Generation of an alkyl radical from an alkyl halide is consequently suggested. It is notable that bis-styrylation of 1,2-dibromoethane proceeded, albeit the yield was low. A mechanism via carbometalation of styrene is unlikely, because a 2-bromoethylmetal reagent undergoes rapid β-bromine elimination.

On the basis of these observations, we propose a draft mechanism for the catalytic reaction as shown in Scheme 3 in analogy with the previous report.[7] The reaction of $CoCl_2$(dpph) with Me_3SiCH_2MgCl gives complex **8**, which is electron-rich due to coordination of the Grignard reagent.[11] Complex **8** effects single-electron transfer to an alkyl halide to yield an anion radical of the halide and cobalt complex **9**. Immediate loss of halide from the anion radical affords an alkyl radical intermediate, which adds to styrene to yield a benzylic radical. Cobalt species **9** would then recombine with the carbon-centered radical to form cobalt species **10**. Finally, β-hydride elimination provides the product and complex **11**, which affords **8** by the action of remaining Me_3SiCH_2MgCl.

In summary, $CoCl_2$(dpph) efficiently catalyzes a Heck-type reaction of alkyl halides, including alkyl chlorides, with styrenes in the presence of Me_3SiCH_2MgCl. The procedure is simple, and the reaction tolerates a variety of functionalities because of the low reactivity of Me_3SiCH_2MgCl. The mechanism of the cobalt-catalyzed reaction is quite different from the palladium-catalyzed one. The former proceeds via a radical pathway and would consist of the following sequence: generation of an alkyl radical from an alkyl halide by single-electron transfer from a cobalt complex, an addition of the alkyl radical to styrene, formation of a benzylic carbon−cobalt bond, and β-hydride elimination.

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Supporting Information Available: Experimental details and characterization data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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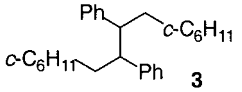
(8) dpph = 1,6-bis(diphenylphosphino)hexane. The choice of the bidentate ligand was crucial. When dppb, dppp, dppe, dppm, and triphenylphosphine were employed, (2-cyclohexylethyl)benzene and its dimer **3** were obtained significantly in addition to **2a**.



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(9) Trialkylsilylmethyl Grignard reagents were essential to obtain the desired product. The reaction of 1-bromododecane with styrene in the presence of methyl or ethyl Grignard reagents provided a trace of β-laurylstyrene. Dodecenes were obtained mainly instead.

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(11) The abbreviation Ln in Scheme 3 represents Me_3SiCH_2 groups, and the X represents valence of cobalt. The active cobalt species is unclear at this stage. A preliminary result can help understanding a mechanistic aspect: treatment of $CoCl_2$(dpph) (1.0 mmol) with Me_3SiCH_2MgCl (2.0 mmol) afforded a trace of $Me_3SiCH_2CH_2SiMe_3$. This experiment suggests that $(Me_3SiCH_2)_2Co$ species is stable and that reductive elimination providing a low-valent cobalt complex did not take place.

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