Cobalt-Mediated Mizoroki–Heck-Type Reaction of Epoxide with Styrene

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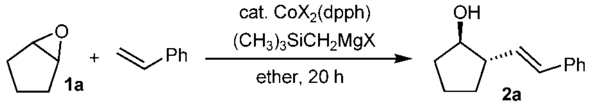
Abstract: Treatment of a mixture of epoxide and styrene with trimethylsilylmethylmagnesium bromide in the presence of a cobalt-phosphine complex afforded homocinnamyl alcohol in good yield. The reaction should begin with ring opening of the epoxide by the action of magnesium bromide which leads to the formation of a magnesium 2-bromoethoxide derivative and not with a direct single electron transfer from a cobalt complex to the epoxide.

Keywords: cobalt; epoxide ring opening; 2-hydroxyethylation; Mizoroki-Heck reaction; radical reaction

The Mizoroki–Heck arylation and vinylation reaction of alkenes is a powerful tool in organic synthesis.[1,2] Aryl or vinyl halides (or pseudohalides) are usually the precursors. On the other hand, there are only scattered examples of the palladium-catalyzed Mizoroki–Heck alkylation reaction of alkenes.[3] Recently, Mizoroki–Heck type reactions of alkyl halide with alkene mediated by transition metal catalysts other than palladium have attracted increasing attention.[4] We have also reported a cobalt-mediated alkylation reaction of styrene with alkyl halide.[5] Here we report the use of epoxide as a precursor of the alkylation reaction instead of alkyl halide. The established reaction is equivalent to the 2-hydroxyethylation of styrene, for which no successful palladium catalysts is known.

We first examined the reaction of cyclopentene oxide (**1a**) with styrene (Table 1). A mixture of **1a** (1.5 mmol) and styrene (1.0 mmol) was treated with trimethylsilylmethylmagnesium chloride (2.5 mmol) in ether in the presence of cobalt(II) chloride combined with 1,6-bis-(diphenylphosphino)hexane (DPPH) at 20 °C for 20 h. Usual work-up followed by silica gel column purification afforded 2-(2-phenylethenyl)-1-cyclopentanol (**2a**) in 62% yield (entry 1). The styrene moiety of **2a** had the *E* configuration according to ^{1}H NMR analysis. It is worth noting that the *trans* isomer was exclusively formed with respect to the hydroxy and 2-phenylethenyl groups. The *trans* stereochemistry of **2a** was verified by synthesizing an authentic sample by the copper-mediated ring opening of **1a** with (*E*)-2-phenylethenyl Grignard reagent.[6] The use of cobalt(II) bromide and trimethylsilylmethylmagnesium bromide slightly increased the yield of **2a** (entry 2). In addition, the reaction with 7 mol % of the cobalt catalyst resulted in the formation of **2a** in 81% yield (entry 3). However, neither a higher catalyst loading (10 mol %) nor higher reaction temperature (in refluxing ether) was effective (entries 4 and 5). The ligand DPPH was essential to obtain **2a** in satisfactory yields. Use of $Ph_2P(CH_2)_nPPh_2$ (n = 1–5) as a ligand decreased the yields of **2a** (12, 7, 20, 1, 60%, respectively), along with formation of significant amounts of 2-bromocyclopentanol.

Table 1. Reaction of cyclopentene oxide with styrene.[a]



Entry	X	Co catalyst [mol %]	Temp [°C]	Yield [%]
1	Cl	5	20	62
2	Br	5	20	71
3	Br	7	20	81
4	Br	10	20	78
5	Br	7	35	75

[a] Styrene (1.0 mmol), **1a** (1.5 mmol), $(CH_3)_3SiCH_2MgX$ (2.5 mmol, 1.0 M ethereal solution), and ether (1.0 mL) were used.

The reaction of cyclohexene oxide (**1b**) with styrene under the same reaction conditions furnished the corresponding alkenol **2b** in 65% yield as a mixture of the *trans* and *cis* isomers in a ratio of 77/23 (Table 2, entry 1). To improve the yield of **2b**, we further examined several reaction conditions. Gratifyingly, we found that cobalt(III) acetylacetonate [Co(acac)$_3$] was a good precursor of the active catalyst (entry 5). Co(acac)$_3$ is far less moisture-sensitive than $CoCl_2$ or $CoBr_2$ and hence much easier to handle. Moreover, toluene was the solvent of choice for this reaction. All the reactions shown in Table 2 yielded a mixture of the stereoisomers in essentially the same ratio.

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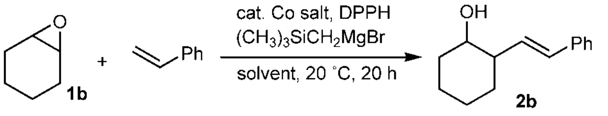
Table 2. Cobalt-mediated reaction of cyclohexene oxide with styrene.[a]

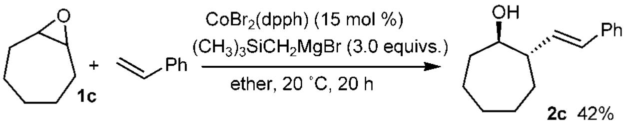


Entry	Co salt	Solvent	Yield [%]	*trans/cis*[b]
1	$CoBr_2$	ether	65	77/23
2	$CoBr_2$	hexane	53	77/23
3	$CoBr_2$	toluene	70	76/24
4	$Co(acac)_2$	toluene	72	74/26
5	$Co(acac)_3$	toluene	74	74/26

[a] Styrene (1.0 mmol), **1b** (1.5 mmol), $(CH_3)_3SiCH_2MgBr$ (2.5 mmol, 1.0 M ethereal solution), cobalt salt (7 mol %), DPPH (8.5 mol %), and solvent (1.0 mL) were used.

[b] With respect to the hydroxy and 2-phenylethenyl groups.

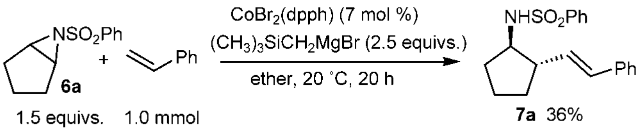
Cycloheptene oxide (**1c**) was less reactive. Homocinnamyl alcohol **2c** was obtained in 42% yield by using 15 mol % of $CoBr_2$(dpph) and 3.0 molar equivalents of $(CH_3)_3SiCH_2MgBr$ in ether [Eq. (1)]. 1,2-*trans*-Alcohol **2c** was obtained as the sole isomer and no 1,2-*cis*-isomer was observed. Unfortunately, use of cyclooctene oxide (**1d**) and cyclododecene oxide (**1e**) resulted in recovery of the starting epoxides under the various reaction conditions we tested.



(1)

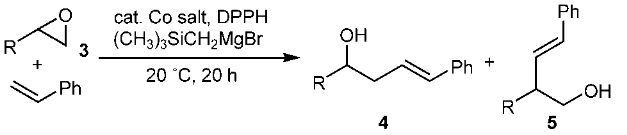
We next examined the reaction of epoxides prepared from acyclic 1-alkenes (Table 3). The yields were fair and the products were obtained as a mixture of regioisomers **4** and **5**, except for the reactions of **3e** and **3f**. The reaction of epoxides with 1-octene failed to afford the corresponding products.

The 2-aminoethylation of styrene was also successful [Eqs. (2) and (3)]. Treatment of aziridines **6a** and **6b** with $(CH_3)_3SiCH_2MgBr$ in the presence of styrene and the cobalt catalyst afforded the corresponding homocinnamylamines.



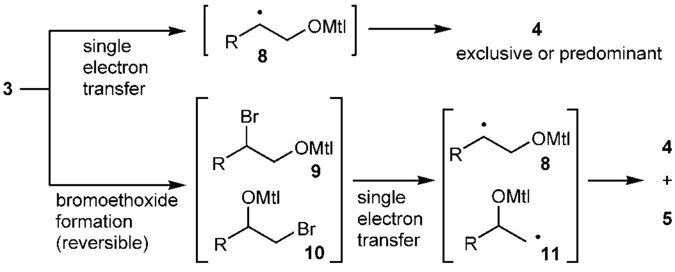
(2)

Table 3. Reaction of 1-alkene oxides with styrene.

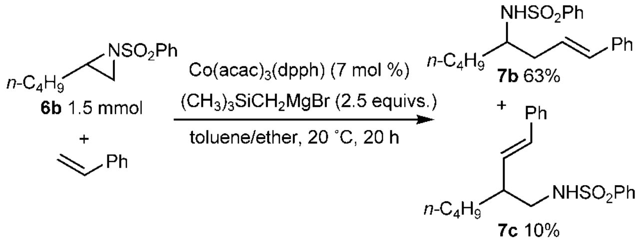


Entry	R	3	Conditions[a]	Yield [%]	4/5
1	CH_3	**3a**	A	57	79/21
2	n-C_4H_9	**3b**	A	58	57/43
3	n-$C_{12}H_{25}$	**3c**	A	46	46/54
4	c-C_6H_{11}	**3d**	B	48	63/37
5	t-C_4H_9	**3e**	A	26	>99/1
6	CH_3OCH_2	**3f**	A	50	>99/1

[a] Conditions A: the conditions of entry 5 in Table 1. Conditions B: the conditions of entry 5 in Table 2.



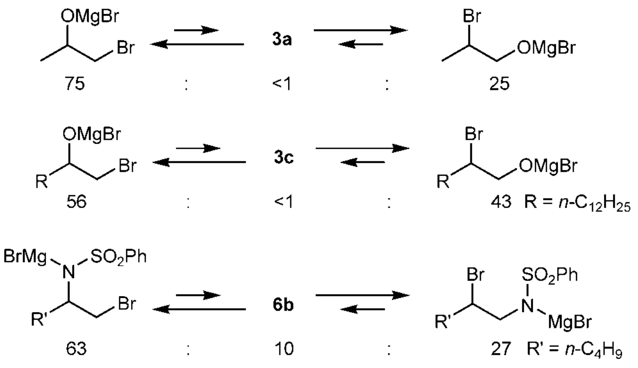
Scheme 1.



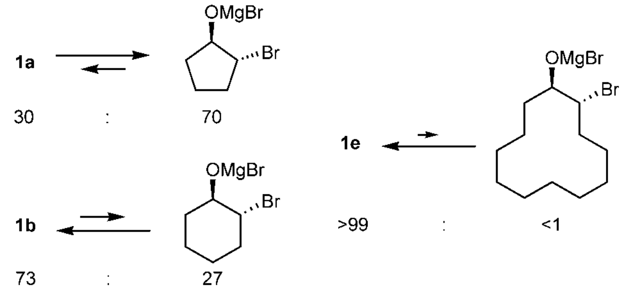
(3)

The generation of radicals from epoxides by metal reductants is well known[7] and that by titanocene chloride Cp_2TiCl has been extensively studied.[8] Direct electron transfer to an epoxide is quite likely to generate the more substituted radical **8** and finally **4** predominantly (Scheme 1). The results in Table 3 and Eq. (3) are highly suggestive of a stepwise single electron transfer pathway. Namely, 2-bromoethoxide formation followed by single electron transfer to the bromide **9** and **10** would form **8** and **11**, respectively. Magnesium bromide formed *via* the Schlenk equilibrium would effect ring opening.

The equilibria between epoxides and the corresponding 2-bromoethoxides under the reaction conditions are the key for the present reaction. We thus tried to obtain further information on the equilibria. Three-membered rings **3a**, **3c**, and **6b** were subjected to the trimethylsilylmethylmagnesium bromide-mediated ring opening re-



Scheme 2.



Scheme 3.

action (Scheme 2). For example, treatment of **3c** with the Grignard reagent in ether for 2 h followed by hydrolysis afforded 1-bromo-2-tetradecanol and 2-bromo-1-tetradecanol in a ratio of 56/43. This fact suggests that two magnesium 2-bromoethoxide derivatives exist in the reaction mixture. Treatment of 1-bromo-2-tetradecanol and 2-bromo-1-tetradecanol with the Grignard reagent also resulted in formation of the two alkoxides in the same ratio. The ratio of **4c**/**5c** was *ca.* 1/1 as shown in Table 3 and reflects the equilibrium distribution.

The equilibria between **1** and their open forms are related to the reactivity of **1** toward the present reaction and the yield of **2** (Scheme 3). The equilibrium was shifted toward the open form in the case of **1a**, and hence **2a** was obtained in good yield. The poor conversion of **1e** would stem from the equilibrium where **1e** predominates over its open form.

In conclusion, we have developed a cobalt-mediated synthesis of homocinnamyl alcohols from epoxides and styrene. The reaction is equivalent to the 2-hydroxyethylation of styrene. The reaction proceeds *via* ring opening of epoxides by means of magnesium bromide to yield 2-bromoethoxides and generation of radicals by single electron transfer from an electron-rich cobalt complex to the 2-bromoethoxides. The mechanism is completely different from the reductive addition of epoxide with alkene reported in the literature although these reactions produce similar radical intermediates.[7,8] The reaction is applicable to the synthesis of homocinnamylamines starting from aziridines.

Experimental Section

Synthesis of *trans*-2-[(*E*)-2-Phenylethenyl]cyclopentanol (2a)

Anhydrous cobalt(II) bromide (15.3 mg, 0.070 mmol) was placed in a 20-mL two-necked flask and was heated with a hair dryer under vacuum for 3 min. 1,6-Bis(diphenylphosphino)hexane (38.6 mg, 0.085 mmol) and anhydrous ether (1 mL) were sequentially added under argon. After the mixture was stirred for 30 min to obtain a blue suspension, cyclopentene oxide (**1a**, 0.13 g, 1.5 mmol), styrene (0.10 g, 1.0 mmol), and trimethylsilylmethylmagnesium bromide (1.0 M ethereal solution, 2.5 mL, 2.5 mmol) were successively added dropwise to the reaction mixture at 0 °C. After being stirred for 20 h at 20 °C, the reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated. Purification on a silica gel column (hexane/ethyl acetate = 5/1) of the crude product provided *trans*-2-[(*E*)-2-Phenylethenyl]cyclopentanol (**2a**) as a colorless oil; yield: 0.15 g (0.81 mmol, 81%); IR (neat): $\nu = 3358, 3026, 2957, 1649, 1599, 1497, 1448, 1072, 964, 908, 841, 746, 692\ \mathrm{cm}^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.47-1.81$ (m, 5H), 1.95–2.11 (m, 2H), 2.44–2.55 (m, 1H), 3.97 (dt, $J = 6.9$, 6.9 Hz, 1H), 6.14 (dd, $J = 15.9$, 8.4 Hz, 1H), 6.48 (d, $J = 15.9$ Hz, 1H), 7.18–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 21.31$, 30.09, 33.60, 52.26, 78.54, 125.90, 126.95, 128.35, 130.23, 132.13, 137.19; anal. found: C 82.92, H 8.71%; calcd. for $C_{13}H_{16}O$: C 82.94, H 8.57%.

Synthesis of 2-(2-Phenylethenyl)cyclohexanol (2b)

Anhydrous cobalt(III) acetylacetonate (24.9 mg, 0.070 mmol) and DPPH (38.6 mg, 0.085 mmol) were placed in a 20-mL reaction flask. Anhydrous toluene was then added under argon. The mixture was stirred for 15 min. A dark green solution was obtained. Cyclohexene oxide (**1b**, 0.15 g, 1.5 mmol), styrene (0.10 g, 1.0 mmol), and trimethylsilylmethylmagnesium bromide (1.0 M ethereal solution, 2.5 mL, 2.5 mmol) were successively added to the reaction mixture at 0 °C. After stirring for 20 h at 20 °C, work-up and purification on silica gel by the aforementioned procedure provided **2b** as a mixture of stereoisomers (*trans*/*cis* = 74/26); yield: 0.15 g (0.74 mmol, 74%).

Ring Opening of 3c with Trimethylsilylmethylmagnesium Bromide

1-Tetradecene oxide (0.11 g, 0.50 mmol) and ether (1 mL) were placed in a 20-mL flask. Trimethylsilylmethylmagnesium bromide (1.0 M ethereal solution, 1.0 mL, 1.0 mmol) was added dropwise at 0 °C. After being stirred for 2 h at 20 °C, the reaction mixture was quenched with ammonium chloride solution. Silica gel column purification provided the corresponding bromohydrins (primary alcohol/secondary alcohol = 43/56).

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