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Cobalt-Catalyzed Reductive Coupling of Saturated Alkyl Halides with Activated Alkenes

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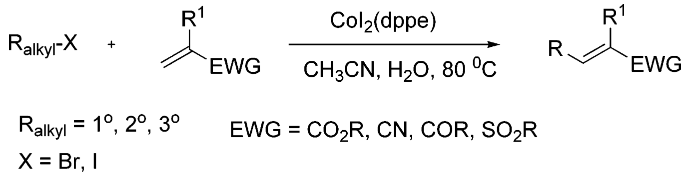
Received October 3, 2005



An efficient cobalt-catalyzed reductive coupling reaction of alkyl halides with electron-withdrawing alkenes ($CH_2{=}CR^1EWG$, EWG = electron-withdrawing group) in the presence of water and zinc powder in acetonitrile to give the corresponding Michael-type addition product (RCH_2CR^1EWG) was described. The methodology is versatile such that unactivated primary, secondary, and tertiary alkyl bromides and iodides and various conjugated alkenes including acrylates, acrylonitrile, methyl vinyl ketone, and vinyl sulfone all successfully participate in this coupling reaction. For the alkyl halides used in the reaction, the iodides generally gave better yields compared to those of the corresponding bromides. It is a unique method employing CoI_2dppe, zinc, and alkyl halides, affording conjugate addition products in high yields. Mechanistically, the reaction appears to follow an oxidative addition driven route rather than the previously reported radical route.

Introduction

Transition-metal catalysts have a well-established niche in C−C bond-forming reactions.[1] Specifically, the catalytic coupling of aryl and alkenyl halides with alkenes or nucleophiles has been extensively investigated.[2] However, the use of unactivated alkyl halides to construct $C_{sp^3}-C_{sp^3}$ bonds catalyzed by transition-metal complexes is particularly challenging[3] in view of the difficulty in overcoming β-hydrogen elimination and the low reactivity of unactivated alkyl halides toward transition-metal complexes. Broadly, there have been two main transition-metal-mediated approaches to the construction of $C_{sp^3}-C_{sp^3}$ bonds. The first one involves the catalytic reductive coupling of an alkyl halide and an alkene. Most previous accounts of related reductive couplings necessitated stoichiometric amounts of metal.[4] Although some nickel-catalyzed reductive couplings of saturated alkyl halides with electron-withdrawing alkenes were reported, they were of limited scope for saturated alkyl halides,[5a] requiring the use of stoichiometric amounts of pyridine[5b] or requiring the use of a polymer resin.[6] The second

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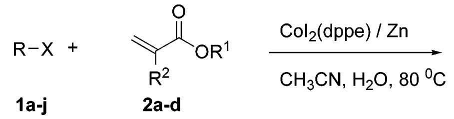
10.1021/jo052065w CCC: $33.50

SCHEME 1



2a: R^1 = Me, R^2 = H
2b: R^1 = Et, R^2 = H
2c: R^1 = *n*--Butyl, R^2 = H
2d: R^1 = Me, R^2 = Me

approach, currently much in vogue, utilizes cross-coupling[7] reactions of alkyl electrophiles (halides, sulfonates, etc.) with main group metal alkyls catalyzed by Pd, Ni, Fe, and so forth. Several cobalt-catalyzed reactions, reported by Oshima et al., that are closely related to our work are the Heck reaction of alkyl halides with styrene in the presence of a Grignard reagent,[8a] a three-component coupling of an alkyl halide, a 1,3-diene, and a silylmethylmagnesium chloride,[8b] and a cross-coupling reaction of an alkyl halide with an allylic or benzylic Grignard reagent.[8c] All of the above cobalt-catalyzed reactions required the use of a Grignard reagent and involved the addition of an alkyl radical to a C−C double bond. In addition, the method cannot be used for the coupling of an alkyl halide with an electron-withdrawing alkene as a result of the presence of the Grignard reagent, which shows high reactivity toward activated alkenes. Our interest in cobalt-catalyzed reactions[9] prompted us to explore the coupling of alkyl halides with alkenes. Herein, we describe an efficient cobalt-catalyzed C_{sp^3}−C_{sp^3} bond-forming process via the reductive coupling of primary, secondary, and tertiary alkyl halides with electron-withdrawing alkenes under mild conditions (Scheme 1). The catalytic mechanism appears to be different from that proposed previously involving the addition of an alkyl radical to a C−C double bond.[4,6−8,10]

Results and Discussion

Treatment of (2-bromoethyl)benzene (**1a**, 1.0 mmol) with methyl acrylate (**2a**, 1.2 mmol) in the presence of CoI_2(dppe) (0.10 mmol, 10 mol %) and zinc powder (2.5 mmol) in acetonitrile (2.5 mL) at 80 °C for 12 h gave methyl 5-phenylpentanoate (**3a**) in 61% isolated yield. Surprisingly, only a trace amount of the Heck product, that is, the α,*β*-unsaturated ester, was detected in the ^1H NMR spectrum of the reaction mixture. When the amount of acrylate used was increased to 4 equiv, along with the addition of 1 equiv of water, the yield increased to 74% (Table 1, entry 1). Control experiments revealed that, in the absence of either a cobalt catalyst or zinc powder, no product was observed. Other cobalt complexes such as $CoI_2(PPh_3)_2$, $CoCl_2(PPh_3)_2$, $CoCl_2$(dppe), and CoI_2(dppm) were inferior to CoI_2(dppe), giving **3a** in 26, 41, 48, and 25% yields, respectively. Among the solvents that were tested, including THF, CH_3CN, methylene chloride, toluene, and DMF, CH_3CN gave the highest yield of product **3a**.

The CoI_2(dppe) system also catalyzes the reductive coupling of *n*-decyl bromide with ethyl acrylate (**2b**) forming **3b** in good yield (entry 3, Table 1). Similarly, phenyl 3-bromopropyl ether (**1c**) reductively coupled with **2a** to yield product **3c** (entry 4), thereby showing that an ether functionality can be tolerated under the reaction conditions. Remarkably, secondary bromide **1d** also gave the reductive Heck-type product **3d**, albeit in a lower yield. Substitutions at the α- or *β*-positions tend to make alkene insertion sluggish not only for palladium-catalyzed Heck reactions but also for cobalt-catalyzed couplings.[9a] However, in our protocol, α-substituted methacrylate **2d** reacted smoothly with **1a** to form **3e** (entry 5) in 64% yield.

The reaction appeared sluggish with alkyl chlorides while alkyl iodides were more reactive than the corresponding alkyl bromides in the present cobalt-catalyzed reaction. The reductive couplings with alkyl iodides were complete in 6 h and produced higher yields with just 5 mol % of the cobalt catalyst (entries 2 and 7−11, Table 1). Thus, 1-hexyl iodide (**1f**) reacted with *n*-butyl acrylate forming **3f** in 92% yield (entry 7). Similarly, *sec*-butyl iodide (**1g)** reacted with **2c** to afford the *γ*-substituted ester **3g** in excellent yield (entry 8). Also, the very long chain ester *n*-butyl nonadecanoate (**3h**) was formed in 91% yield (entry 9). Even *t*-butyl iodide also yielded the expected product (**3i**, entry 10) in 78% yield. Finally, treating 4-iodobutyl acetate (**1j**) with **2c** under similar conditions afforded the expected product **3m** in good yield (entry 11).

The present strategy can be further extended to other conjugated alkenes (Table 2). As depicted in Table 2, acrylonitrile reacted with (2-iodoethyl)benzene to form 5-phenylpentanenitrile (**3j**) in excellent yield (entry 1, Table 2). In the same vein, methyl vinyl ketone (entry 2) reacted with **1e** to form the reductively coupled ketone **3k**. In addition, phenyl vinyl sulfone reacted with *n*-butyl acrylate to form **3l** in good yield under similar reaction conditions (entry 3, Table 2).

Mechanistic Considerations. To understand the nature of the present cobalt-catalyzed reaction, several experiments were carried out and the results are summarized below. First, the reaction of 6-bromo-1-hexene with *n*-butyl acrylate, under standard catalytic conditions, yielded no cyclized product (Scheme 2) but instead yielded a carbon−carbon double bond isomerized product of the reductive coupling of 6-bromo-1-hexene and the acrylate. The reaction of cyclopropylmethyl bromide with benzyl acrylate gave a complicated mixture that was difficult to characterize; there was no expected ring-opening addition product, benzyl 6-heptenoate, detected in the mixture. Second, competition reactions of *n*-propyl iodide and isopropyl iodide for benzyl acrylate under the standard catalytic conditions gave only the reductive coupling product of isopropyl iodide and the acrylate. Surprisingly, competition reactions of isopropyl iodide and *tert*-butyl iodide for benzyl acrylate again afforded chemoselectively the reductive coupling product of isopropyl

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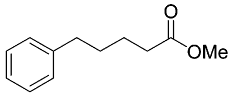
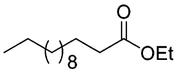
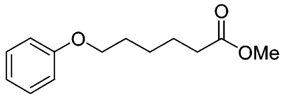
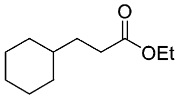
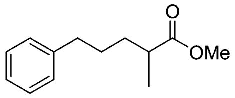
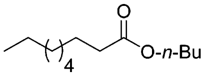
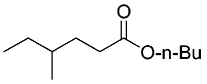
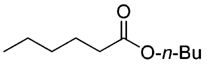
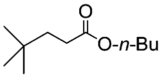
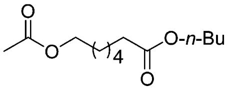
[7] For reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, P., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 12. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry Series 219; Springer-Verlag: New York, 2002. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002. For leading references, see: (a) ref 3b. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. (c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788−7789 and references therein.

[8] (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514−6515. (b) Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257−2259. (c) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem.−Eur. J.* **2004**, *10*, 5640−5648 and references therein.

[9] (a) Wang, C. C.; Lin, P. S.; Cheng, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 9696−9697. For precedents similar to the proposed mechanism, see: (b) Wang, C. C.; Lin, P. S.; Cheng, C. H. *Tetrahedron Lett.* **2004**, *45*, 6203−6206. (c) Chang, K. J.; Rayabarapu, D. K.; Cheng, C. H. *Org. Lett* **2003**, *5*, 3963−3966. (d) Chang, K. J.; Rayabarapu, D. K.; Cheng, C. H. *J. Org. Chem.* **2004**, *69*, 4781−4787 and references therein.

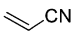
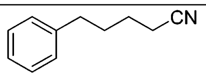
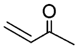
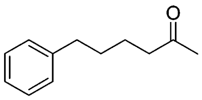
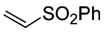
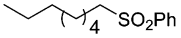
[10] Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375.

TABLE 1. Results of the Cobalt-Catalyzed Reductive Coupling of Alkyl Halides with Acrylates[a]

Entry	RX, **1**	Acrylate **2**	Product	Yield (%)[b]
1	PhCH$_2$CH$_2$Br, **1a**	**2a**		**3a** 74
2[c]	PhCH$_2$CH$_2$I, **1e**	**2a**		**3a** 85
3	CH$_3$(CH$_2$)$_9$Br, **1b**	**2b**		**3b** 71
4	PhO(CH$_2$)$_3$Br, **1c**	**2a**		**3c** 63
5	*Cyc*-C$_6$H$_{11}$Br, **1d**	**2b**		**3d** 61
6	PhCH$_2$CH$_2$Br, **1a**	**2d**		**3e** 64
7[c]	CH$_3$(CH$_2$)$_5$I, **1f**	**2c**		**3f** 92
8[c]	*sec*-BuI, **1g**	**2c**		**3g** 87
9[c]	CH$_3$(CH$_2$)$_{15}$I, **1h**	**2c**		**3h** 91
10[c]	*t*-BuI, **1i**	**2c**		**3i** 78
11[c]	MeCO$_2$(CH$_2$)$_4$I, **1j**	**2c**		**3m** 80

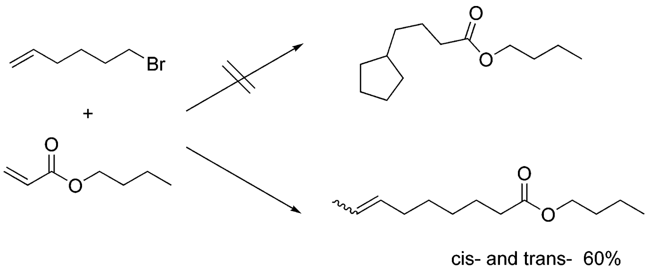
[a] Unless stated otherwise, all reactions were carried out in a sealed tube or a sidearm flask, consisting of an alkyl halide (1.0 mmol), acrylate (2−5 mmol), CoI$_2$(dppe) (0.10 mmol, 10 mol %), H$_2$O (1.0 mmol), and Zn (2.5 mmol) in CH$_3$CN (2.5 mL) at 80 °C under N$_2$ for 12 h. [b] Isolated yields. [c] Reaction time was 6 h and only 5 mol % of the Co catalyst was used.

TABLE 2. Cobalt-Catalyzed Reductive Coupling with Other Conjugated Alkenes[a]

Entry	halide	alkene	product	yield (%)[b]
1	**1e**			**3j** 83
2	**1e**			**3k** 60
3	**1f**			**3l** 75

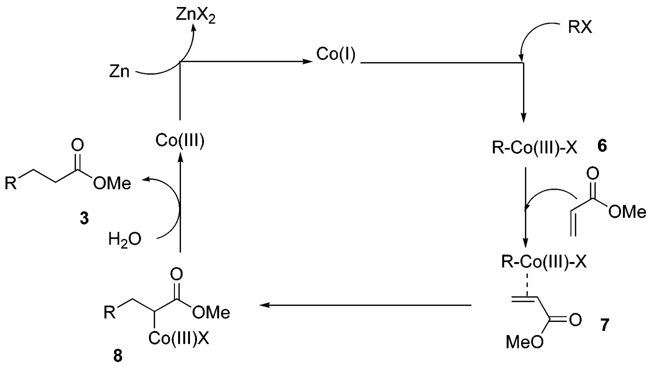
[a] Reaction conditions: similar to those in Table 1. [b] Isolated yields

SCHEME 2

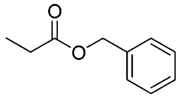


iodide and the acrylate. These competition experiments indicate that isopropyl iodide is much more reactive than *n*-propyl iodide and *t*-butyl iodide. Third, the reaction of 2-phenylethyl iodide (**1e**) with benzyl acrylate under the standard catalytic conditions and at a high 2-phenylethyl iodide/benzyl acrylate ratio (≥1:1) led to a substantial amount of the hydrogenation product of acrylate, benzyl propionate, and styrene. The observation suggests that β-hydride elimination of the phenylethyl−Co species in the catalytic cycle competes strongly with the addition of the phenylethyl group to the acrylate. The Co−H that is formed then reacts with acrylate to give the reduced product **4**. Similar reduced products of the acrylates were also observed for the different alkyl halides and acrylates used. Fourth, the

SCHEME 3



reaction of alkyl halides with acrylates under the standard catalytic conditions at low alkyl halide/acrylate ratio ($\leq$1:3) in the reaction led clearly to the observation of the corresponding reductive dimerization product of acrylate **5**. The linear reductive dimerization of acrylates was reported by us previously.[9b] Finally, the reaction of the cobalt(I) complex $CoCl(PPh_3)_3$ with 2-iodoethylbenzene (**1e**) and *n*-butyl acrylate (**2a**) stoichiometrically in acetonitrile at 80 °C afforded the reductive coupling product **3a** in 63% yield.



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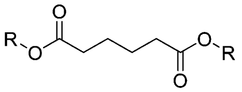

5

Although the details of the catalytic steps are not clear,[9c,d] based on the above observations, we propose the following mechanism to account for this cobalt-catalyzed reductive coupling reaction. The catalytic cycle is likely initiated by the reduction of CoI_2(dppe) to Co(I) by zinc powder followed by the oxidative addition of an alkyl halide to give an alkyl cobalt(III) intermediate (Scheme 3). Subsequent coordination of the conjugated alkene, insertion into the Co−alkyl bond, and protonation gives rise to the final reductive coupling product **3**. Reduction of the Co(III) species by zinc powder regenerates the active Co(I) catalyst.

The proposed oxidative addition of alkyl halides with Co(I) species in the mechanism gains strong support as M(I) (M = Co, Rh, and Ir) reacts readily with various unactivated alkyl halides to give M(III) oxidative addition products.[11,12] Particularly, Co(I) complexes are known to be supernucleophiles, reacting with an alkyl halide via an S_N2 mechanism.[13] Furthermore, as indicated in the foregoing experiment, the involvement of Co(I) in the present catalytic cycle is evidenced by the fact that $CoCl(PPh_3)_3$ [14] reacts with **1e** and acrylate **2a** stoichiometrically to give the reductive coupling product **3a**. Indirect evidence for the presence of the alkyl−Co species was shown by the observation of a substantial amount of the hydrogenation product of the acrylate at high alkyl iodide/acrylate ratios. The proposed protonation step is supported by the fact that the addition of 1 equiv of water increases the product yield.

An alternative mechanism involving the addition of the alkyl radical to acrylate cannot be entirely excluded. In the recent reports of transition-metal-catalyzed additions of unactivated alkyl halides to C−C double bonds, an addition of the alkyl radical generated from the reaction of the alkyl halide with the low-valent transition-metal complex to the C−C double bond, was proposed by several authors.[4,6−8,10] A mechanism similar to that proposed by Oshima et al., involving an electron transfer from the Co(I) complex to an alkyl halide to generate an alkyl radical, followed by the addition of the radical to acrylate and then trapping by the cobalt species to give a Co(III) intermediate, as shown in Scheme 2, can also account for the observed reductive coupling reaction, but it is more difficult to explain the observed hydrogenation product of acrylate at a high alkyl halide/acrylate ratio. It should be noted that in the mechanism proposed by Oshima et al., a Co(0) anion was used for the electron transfer to the alkyl halide.

Conclusion

We have reported an effective utilization of a cobalt catalyst for the reductive coupling of primary, secondary, and tertiary alkyl bromides and iodides with a wide variety of conjugated alkenes such as acrylates, acrylonitrile, vinyl ketone, vinyl sulfone, and so forth, in good to excellent yields. To accomplish these cobalt-catalyzed reactions, mild conditions were employed. Also, our protocol involves the use of an easily prepared cobalt complex, namely, CoI_2(dppe). Furthermore, the reaction appears to undergo an oxidative addition driven route rather than the expected radical route.

Experimental Section

General Procedure for the Reductive Coupling of Unactivated Alkyl Halides (1) with Electron-Withdrawing Alkenes (2). Synthesis of Methyl 5-Phenylpentanoate (3a). A sealed tube (20 mL) containing CoI_2(dppe) (0.10 mmol) and zinc powder (2.5 mmol) was evacuated and purged with nitrogen three times. Freshly distilled CH_3CN (2.5 mL), (2-bromoethyl)benzene **1a** (1.0 mmol), methyl acrylate **2a** (4.0 mmol), and H_2O (1.0 mmol) were added to the sealed tube via syringes. The reaction mixture was heated with stirring at 80 °C for 12 h and was then cooled, diluted with dichloromethane, and stirred in an air atmosphere for 10 min. The mixture was filtered through a Celite and silica gel pad and washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silica gel column using hexanes−ethyl acetate as eluent to afford the desired product **3a** as a colorless liquid in 74% isolated yield.

Products **3b−m** were prepared according to similar procedures, except when the iodo compounds were used, the reaction time was reduced to 6 h and only 5 mol % of CoI_2(dppe) and 2 to 3 equiv of acrylate (2.0−3.0 mmol) were employed.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC 93-2113-M-007-033) for the support of this research.

Supporting Information Available: General experimental procedures, spectral data, and ^{1}H and ^{13}C NMR spectra for compounds **3a−m**. This material is available free of charge via the Internet at http://pubs.acs.org

JO052065W

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