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Cobaloxime-Catalyzed Radical Alkyl-Styryl Cross Couplings

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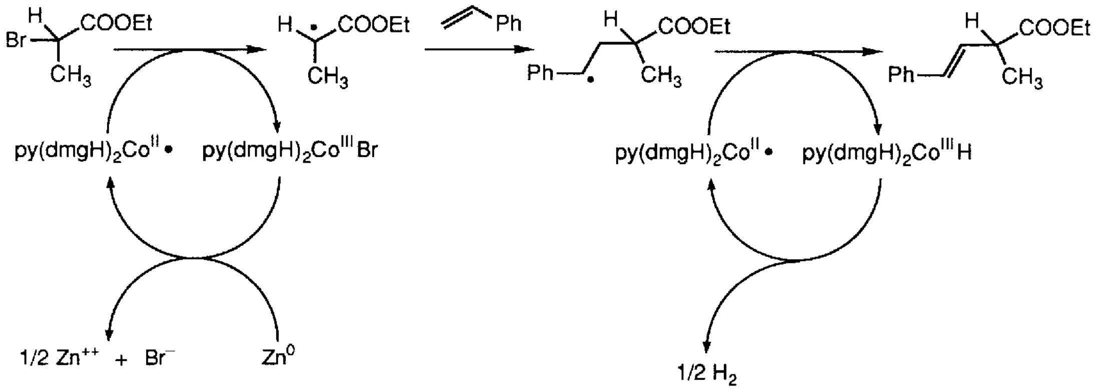
Abstract: *Cobaloxime-catalyzed radical alkyl-styryl cross couplings can be accomplished by visible light photolysis of various alkyl bromides + styrene + in-situ-generated* $Co^{II}(dmgH)_2py$ *+ Zn in refluxing* CH_3CN *or refluxing 95%EtOH.*

Alkyl-cobalt complexes have recently been used for intramolecular radical cyclizations and intermolecular radical cross couplings.[2-6] Alkyl cobaloximes, $RCo^{III}(dmgH)_2py$ (dmgH = dimethylglyoxime monoanion), can be formed and used in hydroxylic solvents, allowing applications to polar, highly-functionalized bio-molecules. For example, alkyl-alkenyl, alkyl-protonated heteroaromatic, and alkyl-nitroalkylanion cross couplings have been developed in mixed alcohol-water solvents using protected and unprotected carbohydrates.[2,4] One disadvantage of these cross couplings is that they are two-step stoichiometric processes: formation of $RCo^{III}(dmgH)_2py$ by oxidative addition of primary or secondary alkyl halides to $NaCo^{I}(dmgH)_2py$ followed by visible light photolysis of $RCo^{III}(dmgH)_2py$ with cross coupling partners. Another problem is premature β-H eliminination, in which R• and $\cdot Co^{II}(dmgH)_2py$ [formed by photolytic homolysis of $R\text{-}Co^{III}(dmgH)_2py$] react to produce an alkene and $H\text{-}Co^{III}(dmgH)_2py$ instead of leading to productive cross coupling.[2d] Catalytic amounts of a cobaloxime in the direct cross coupling of alkyl halides with cross coupling partners would avoid the isolation of $RCo^{III}(dmgH)_2py$ and should suppress premature β-H eliminination by maintaining low concentrations of $\cdot Co^{II}(dmgH)_2py$. We report herein cobaloxime-catalyzed radical alkyl-styryl cross couplings.

Cobaloxime-catalyzed intramolecular radical-alkene cyclizations have been reported using $[Co^{I}(dmgH)_2py]^-$ for reactions with "5-hexenyl" alkyl halides.[3,7] Such reactions use moderately basic and somewhat strongly reducing conditions such as electrochemistry at -1.8 V [3a] or $NaBH_4$.[7] We focused on $\cdot Co^{II}(dmgH)_2py$ since it can be prepared and used under neutral, mildly reductive conditions, compatible with base-sensitive and redox-sensitive functional groups incompatible with $[Co^{I}(dmgH)_2py]^-$ reaction conditions. We chose to focus on α-bromoesters, such as ethyl 2-bromopropionate **1**, since they are incompatible with basic $[Co^{I}(dmgH)_2py]^-$ conditions.[8a] We focused heavily on **1** since the hydrogens in the β position would allow study of the premature β-H elimination problem. A proposed mechanism for a catalytic process using $\cdot Co^{II}(dmgH)_2py$ is shown in Scheme 1 for cross coupling of **1** with styrene.

The catalytic cross coupling of **1** with styrene to produce ethyl 2-methyl-4-phenyl-3-butenoate **7** was optimized to gain insight into which factors are important for a successful catalytic process (Figure 1). Good yields and multiple catalytic turnovers were achieved. Many reactions were run with equimolar concentrations of **1** and styrene. For example, a 51% yield of **7** with 10 catalytic turnovers was obtained using 17 mM $CoCl_2$, 34 mM dimethylglyoxime, 333 mM **1**, 333 mM styrene, 161 mM pyridine, and 0.5 equiv Zn (based on **1**).[9,10] Better yields were obtained with an excess of styrene. For example, an essentially quantitative yield of **7** with 20 catalytic turnovers was obtained using 2.5 mM $CoCl_2$, 5.8 mM dimethylglyoxime, 51 mM **1**, 1000 mM styrene, 168 mM pyridine, and 3.2 equiv Zn (based on **1**).[9,10] An examination of the data in Figure 1 reveals



Scheme 1

that three factors are important in obtaining higher yields: (1) high styrene concentration to efficiently trap alkyl radicals, (2) low catalyst concentrations (pyridine + dimethylglyoxime + $CoCl_2$) to avoid premature β-H elimination, and (3) low (50-100 mM) concentrations of $CH_3CHBrCO_2CH_2CH_3$ **1**.

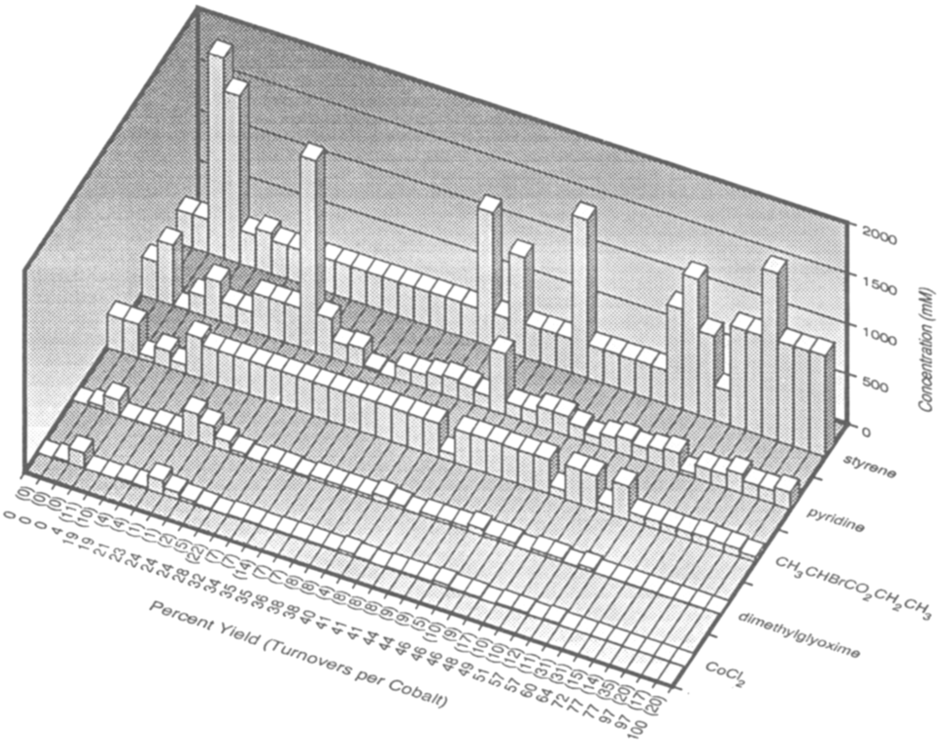
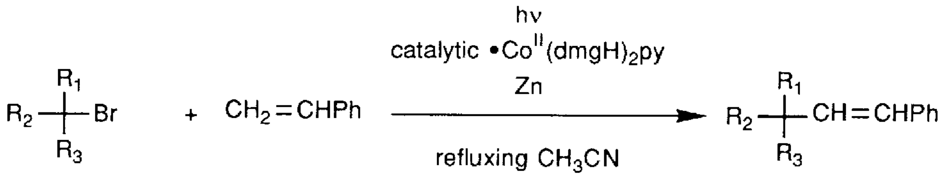


Figure 1. Plot of data for optimization of cobaloxime-catalyzed cross coupling of ethyl 2-bromopropionate (**1**) with styrene to produce ethyl 2-methyl-4-phenyl-3-butenoate (**7**).

For comparison purposes, the cross couping of **1** with styrene was performed using a two-step non-catalytic method. Reaction of **1** with 1.0 equiv of $Co^{II}(dmgH)_2py$ and excess Zn in 95% EtOH produced $py(dmgH)_2Co^{III}\ CH(CH_3)COOCH_2CH_3$ **13** in 69% isolated yield. Note that this is a special method for base-sensitive, $[Co^{I}(dmgH)_2py]^-$ incompatible alkyl halides.[8] Photolysis of 20 mM **13** and 400 mM (20 equiv) styrene in 95% EtOH produced **7** in 43% isolated yield. The overall yield for the two-step stoichiometric process was 30%. In contrast, catalytic reactions under comparable conditions of excess styrene provided nearly quantitative yields.

The catalytic process was tested on several other substrates, as summarized in Equation 1.[10,11] It is premature to speculate too much on the mechanistic significance of the results in Equation 1 since the mechanism in Scheme 1 is only a reasonable working hypothesis at this point. However, if the mechanism in Scheme 1 is correct, the successful cross coupling of "unactivated" halides such as **4**, **5**, and **6** is surprising since the S_H2 halogen atom abstraction step proposed in Scheme 1 should be very slow for such substrates. Alternate mechanisms for C-X bond activation might be operative. Perhaps more reactive $[Co^{I}(dmgH)_2py]^-$ could be formed for reaction with R-Br to form $R\text{-}Co^{III}(dmgH)_2py$ which could then homolyze to produce R• and $\bullet Co^{II}(dmgH)_2py$. Perhaps a photoexcited state of $Co^{II}(dmgH)_2py$ is a stronger reductant or atom abstractor to perform the S_H2 step proposed in Scheme 1 (or an equivalent electron transfer followed by radical anion homolysis). Further synthetic and mechanistic studies are underway to extend the scope of the reaction and to address some of these mechanistic questions.[12,13]



$$R_2\!-\!\overset{R_1}{\underset{R_3}{+}}\!-\!Br \;+\; CH_2{=}CHPh \xrightarrow[\text{refluxing } CH_3CN]{h\nu,\ \text{catalytic } \bullet Co^{II}(dmgH)_2py,\ Zn} R_2\!-\!\overset{R_1}{\underset{R_3}{+}}\!-\!CH{=}CHPh \qquad (1)$$

1-6 **7-12**

				% Yield
1	R_1=H, R_2=CH_3, R_3=COOEt	**7**	R_1=H, R_2=CH_3, R_3=COOEt	60
2	R_1=R_2=H, R_3=COOEt	**8**	R_1=R_2=H, R_3=COOEt	20
3	R_1=R_2=CH_3, R_3=COOEt	**9**	R_1=R_2=CH_3, R_3=COOEt	0
4	R_1=R_2=H, R_3=CH_2COOEt	**10**	R_1=R_2=H, R_3=CH_2COOEt	45
5	R_1=R_2=H, R_3=$(CH_2)_2COOEt$	**11**	R_1=R_2=H, R_3=$(CH_2)_2COOEt$	37
6	R_1=R_2=H, R_3=$(CH_2)_8CH_3$	**12**	R_1=R_2=H, R_3=$(CH_2)_8CH_3$	42

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9. All reactions for the optimization of cross coupling of **1** with styrene to produce **7** were run in 95% EtOH with anaerobic reflux for 22 h with concomitant visible light photolysis through Pyrex.
10. Yields on cross coupled products were determined by ^{1}H NMR on partially purified organic mixtures (after silica gel chromatographic separation from inorganic complexes and salts) by comparison of key peak integrations to a Ph_3CH internal standard, which was added just prior to performing the NMR analysis. Yields obtained by this method are probably accurate to ±5%. Turnovers per cobalt shown in Figure 1 were calculated as mmol product **7** obtained/mmol of $CoCl_2$ used. All products reported here are known compounds. Products were isolated and chromatographically purified for full characterization by ^{1}H NMR, ^{13}C NMR, FTIR, MS, and HRMS. In all cases these results agreed satisfactorily with theoretical and literature values.
11. Reaction conditions for the results in Equation 1 for substrates **1-6** were slightly different from the optimum conditions for **1**. The reactions in Equation 1 were done in refluxing, anaerobic CH_3CN with visible light photolysis through Pyrex (300 W incandescent bulb 3 cm from round-bottom flask). Reactant concentrations were $Co(dmgH)_2py$ [8mM], RBr [80 mM], styrene [400mM], pyridine [132mM], and Zn (1.0 molar equiv, 2 electron equiv, relative to RBr).
12. Recent studies of cross coupling of **6** with styrene indicate that there is one major side reaction, S_N2 reaction of pyridine with **6** to produce decyl pyridinium bromide, identified by comparision with an authentic sample. Desired cross coupling plus the S_N2 side reaction provide a nearly complete mass balance. The higher yields in cross couplings using **1** are presumably due to the greater ease of radical formation compared to possible ionic side reactions.
13. These studies have focused on a limited number of substrates to allow an examination of the important features that contribute to successful cross coupling. The optimization of the cross coupling of **1** to produce **7**, shown in Figure 1, provided valuable insights. Future studies will further develop and test the scope of the reaction from a firm foundation of mechanistic understanding.

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