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ALKYL-ALKENYL CROSS COUPLING VIA ALKYL COBALOXIME RADICAL CHEMISTRY. AN ALKYL EQUIVALENT TO THE HECK REACTION COMPATIBLE WITH COMMON ORGANIC FUNCTIONAL GROUPS

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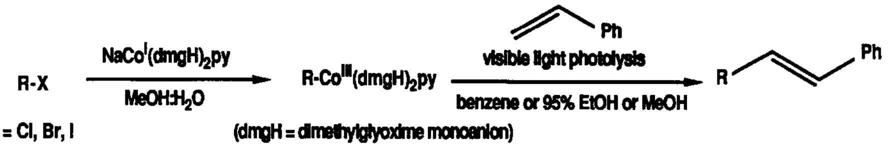
Summary: A novel cobalt-mediated radical-olefin coupling reaction is described which regenerates the olefin functionality in the final product. The regeneration of olefin functionality is unique among radical-olefin couplings using simple activated alkenes.

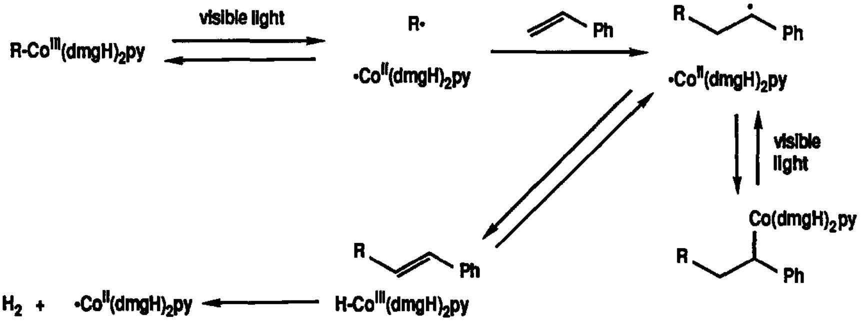
In this paper we report several examples of a new alkyl-alkenyl cross coupling reaction via alkyl cobaloxime radical chemistry.[2,3] The two-step process involves (1) conversion of an alkyl halide to the corrresponding pyridine alkyl Co^{III} cobaloxime [py(dmgH)$_2$Co-R] followed by (2) visible light photolysis of py(dmgH)$_2$Co-R in the presence of styrene. The py(dmgH)$_2$Co-R were prepared according to standard literature procedures.[4] Visible light photolyses were performed for 48 hr under an Ar atmosphere using 20 mM py(dmgH)$_2$Co-R and 400 mM (20 eq) styrene in an apparatus previously described in detail.[4] Reactions proceed in good yield for both steps using primary substrates.[5,6] For secondary substrates each reaction step proceeds in modest yield.[5,6] For all of the reactions ^{1}H NMR indicates exclusive formation of the E-isomer shown.



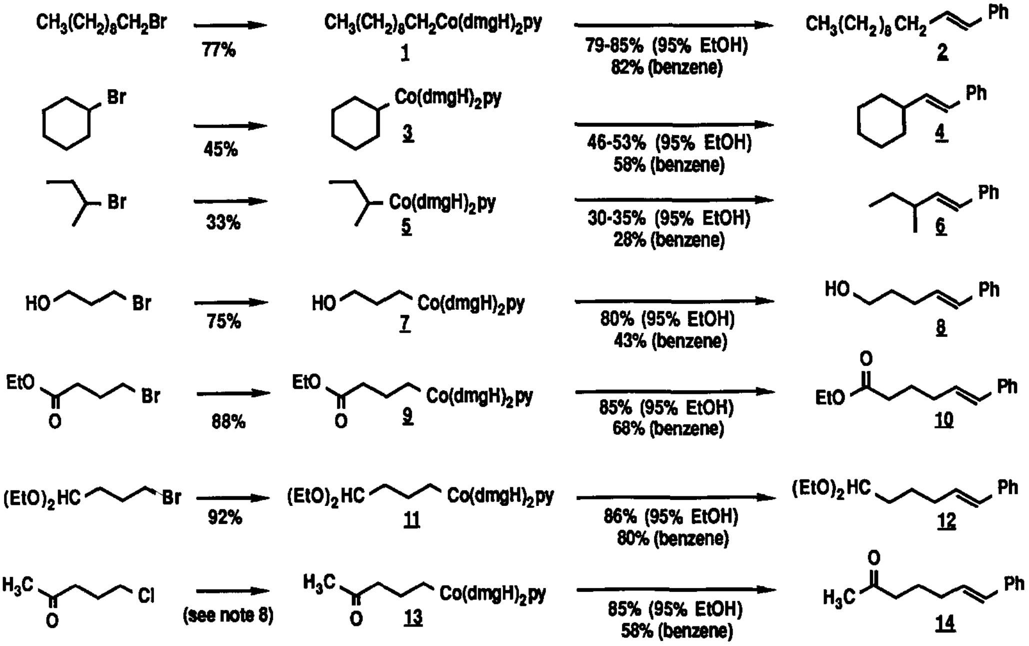
The overall transformation represents an alkyl equivalent to the synthetically important Heck reaction, Pd-catalyzed coupling of aryl, vinyl, or allyl halides with olefins.[7] The Heck reaction generally cannot be performed on alkyl halide substrates due to facile competing beta-H elimination from the transient Pd-alkyl intermediate.[7] The cobaloxime-mediated reaction is feasible with alkyl substrates because it proceeds through an entirely different set of fundamental intermediates and reaction steps than in the Heck reaction.

Since the cobaloxime-mediated cross coupling reaction proceeds via radicals, it is compatible with many common organic functional groups, as the variety of functional groups examined here demonstrates. The reaction is even compatible with potentially radical-sensitive functional groups such as acetal C-H (in 11, 12, 16, 17, 19, & 20), benzylic ether C-H (in 16, 17, 19, & 20), C-H alpha to oxygen (in 7, 8, 16, 17, 19, 20, 95% EtOH solvent, & MeOH solvent), and allylic C-H in the products. These results demonstrate that cobaloxime-mediated alkyl-alkenyl cross coupling is a highly chemoselective method for the formation of carbon-carbon bonds without protection of common organic functional groups.

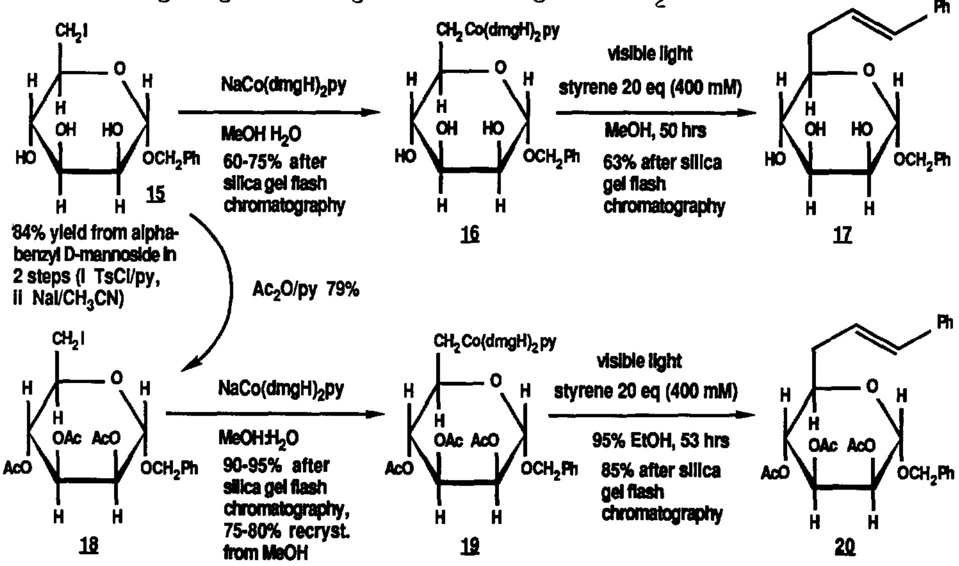
The course of the reaction can be rationalized as shown in the scheme. Photolysis of py(dmgH)$_2$Co-R results in carbon-cobalt bond homolysis, the reversibility of which makes py(dmgH)$_2$Co a photochemically unmasked "radical protecting group." At the styrene concentration employed, styrene efficiently traps the alkyl radicals in a standard radical-olefin addition reaction. The ensuing beta-H elimination reaction between the benzylic radical and py(dmgH)$_2$Co is facilitated by the phenyl group.[9] Subsequent fast ($k \sim 10^4$ $M^{-1}s^{-1}$)[10] disproportionation of py(dmgH)$_2$Co-H is essentially irreversible[9] and drives the reaction to completion.



The alkyl cobaloxime mediated reaction is unique among radical-olefin coupling reactions because the olefin functionality is regenerated in the final product. Radical-olefin couplings using radicals generated via R_3SnH + alkyl halides and other functional groups,[11] $NaBH_4$ reduction of alkyl mercury compounds,[11] and Vitamin B_{12} catalyzed electrochemical reduction of alkyl halides[12] all reduce the olefin functionality. For $R_3Sn\bullet$ chemistry the use of beta-



stannyl activated olefins regenerates the olefin functionality but has the disadvantage of requiring expensive, specially prepared olefin substrates, often used in several-fold excess.[13] In the styrene reaction reported here, it is easy to envision further transformations of the olefin functionality. Ozonolysis with reductive workup would generate an aldehyde functional group and would complete an overall carbonylation of an alkyl halide under mild conditions. Ozonolysis with oxidative workup would generate a carboxylic acid functional group and would complete an overall carboxylation of alkyl halides under conditions not compatible with standard transformations using Grignard or organolithium reagents + CO_2.



The main significance of the synthetically useful styrene cross-coupling reactions reported here is as a paradigm for the development of chemoselective radical-olefin couplings with regeneration of olefin functionality. Explorations of the scope of such reactions, the use of activated olefins that incorporate synthetically useful functionality in the product, and applications to natural products synthesis are underway and will be reported in the near future.

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References and Notes

1. Fellow of the Alfred P. Sloan Foundation, 1987-1989.
2. Many of these results have been reported in preliminary form at the following conferences and meetings: 6th IUPAC International Conference on Organic Synthesis, Moscow, USSR, August 10-15, 1986, Poster D-017; 42nd Northwest Regional ACS Meeting, Bellingham, WA, June 17-19,

1987, Organic #183; 4th IUPAC Symposium on Organometallic Chemistry Directed Toward Organic Synthesis, Vancouver, BC, July 26-30, 1987, Short Talk and Poster PS1-27; 194th ACS National Meeting, New Orleans, LA, August 30 - September 4, 1987, Organic #229.

3. Similar results using alkyl cobalt^{III} complexes with saloph and salophen ligands have been independently discovered and reported very recently: V. F. Patel and G. Pattenden, J. Chem. Soc. Chem. Commun. 871 (1987).
4. B. P. Branchaud, M. S. Meier, and M. N. Malekzadeh, J. Org. Chem. 52, 212 (1987).
5. Yields for py(dmgH)$_2$-R are for isolated material purified by silica gel flash chromatography. 1, 3, 5, and 7 are known compounds. 9, 11, 13, 16, and 19 are new compounds. All py(dmgH)$_2$Co-R were moderately air-stable crystalline orange solids with the exception of 16 which was an orange glass. All py(dmgH)$_2$-R had satisfactory ^{1}H and ^{13}C NMR. 9, 11, 13, and 19 were characterized by elemental microanalysis (Desert Analytics, Tucson, Arizona); elemental microanalysis was not performed on glass 16 but all other criteria (^{1}H & ^{13}C NMR, TLC) indicated that it was of high purity. 9 Anal. Calcd for $C_{19}H_{30}N_5O_6Co$: C, 47.21; H, 6.26; N, 14.49. Found: C, 47.06; H, 6.19; N, 14.52. 11 Anal. Calcd for $C_{21}H_{36}N_5O_6Co$: C, 49.12; H, 7.07; N, 13.69. Found: C, 49.47; H, 7.18; N, 13.89. 13 Anal. Calcd for $C_{18}H_{28}N_5O_5Co$: C, 47.69; H, 6.23; N, 15.45. Found: C, 47.50; H, 6.18; N, 15.24. 19 Anal. Calcd for $C_{32}H_{42}N_5O_{12}Co$: C, 51.41; H, 5.66; N, 9.41; Co, 7.88. Found: C, 51.07; H, 5.73; N, 9.35; Co, 7.30.
6. All yields for cross-coupling products 2, 4, 6, 8, 10, 12, 14, 17, and 20 are for chromatographically purified materials. To avoid loss of product during vacuum removal of solvent residues, yields were determined by ^{1}H NMR integration vs Ph_3CH added as an internal standard to chromatographically homogeneous samples which still had traces of chromatography solvent residues. 2, 4, 6, 8, 10, and 14 are known compounds. 12, 17, and 20 are new compounds. 12 had satisfactory ^{1}H NMR, ^{13}C NMR, low-resolution MS, and exact MS data. 17, and 20 had satisfactory ^{1}H NMR, ^{13}C NMR, and elemental microanalysis data.
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8. 13 was prepared from the diethyl ketal of 5-chloro-2-pentanone in 65% yield for 2 steps by (i) reaction with 5 eq NaCo(dmgH)$_2$py/MeOH-H$_2$O for 48 hr (70%) then (ii) 10-1 THF-10% HCl (93%).
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13. G. E. Keck and D. A. Burnett, J. Org. Chem. 52, 2960 (1987) and references therein.

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