ORGANOMETALLICS

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Organometallics, **1993**, 12 (11), 4262-4264• DOI: 10.1021/om00035a002 • Publication Date (Web): 01 May 2002

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4262 *Organometallics* **1993,** *12,* 4262–4264

An Example of the Persistent Radical Effect in Cobaloxime-Mediated Radical Alkyl–Alkenyl Cross Coupling

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Received July 19, 1993[⊗]

Summary: Photolysis of alkylcobaloximes in the presence of activated alkenes results in both β-H elimination and alkyl–alkenyl cross coupling. A proposed mechanism predicts that buildup of the persistent radical ${}^{\bullet}$Co^{II}(dmgH)$_2$py as the reactions proceed enhances β-H elimination, lowering the yield of cross coupling. Scavengers of ${}^{\bullet}$Co^{II}(dmgH)$_2$py suppress β-H elimination and enhance cross coupling, presumably by lowering the concentration of ${}^{\bullet}$Co^{II}(dmgH)$_2$py. These data provide support for the proposed reaction mechanism and illustrate how a persistent radical can control product distributions in an organometallic radical reaction.

In the past few years metal-mediated radical cross couplings, particularly cobalt-mediated alkyl–alkenyl reactions, have been developed for applications in organic synthesis.[1] One novel and synthetically useful feature of cobalt-mediated alkyl–alkenyl cross couplings is regeneration of the alkene functionality in the cross-coupled product. Scheme I shows the currently accepted reaction mechanism, illustrated for the reaction of the alkylcobaloxime R–Co^{III}(dmgH)$_2$py (dmgH = dimethylglyoxime monoanion) with α-ethoxyacrylonitrile. Given all of the plausible possible radical reactions that might occur, such as radical–radical combination and disproportionation, β-H elimination of the cobalt alkyl, or polymerization, it is noteworthy that these reactions can be so selective for cross coupling under the appropriate conditions. Fischer proposed in 1986 that the concentration of persistent radicals can exert significant control over the product distribution in radical reactions.[2] The selectivity in cobalt-mediated radical cross couplings is most likely due to a persistent radical effect of 17-electron Co^{II} complexes, such as ${}^{\bullet}$Co^{II}(dmgH)$_2$py in Scheme I, formed by reversible carbon–cobalt bond homolysis. In this paper we report results which illustrate how persistent radical effects can explain the selectivity in cobalt-mediated alkyl–alkenyl cross coupling and how these effects can be used to control reaction product distributions.

Photolysis or thermolysis of alkylcobalt complexes produces alkyl radicals and 17-electron Co^{II} radicals, but dimerization and disproportionation of the alkyl radicals are not observed.[3] Instead, β-H elimination occurs and/or radical trapping if a radical scavenger is present.[4] This phenomenon has recently been given a quantitative treatment using numerical integration kinetic modeling techniques.[5] The crux of the explanation is that a small amount of dimerization and disproportionation of alkyl radicals does indeed occur in the first few seconds of a reaction, leaving behind a sufficiently high excess of the persistent 17-electron Co^{II} radical that it effectively captures any new alkyl radicals that are produced and guides them into other reaction pathways. If persistent 17-electron Co^{II} radicals are removed using scavengers, then radical–radical combination becomes the dominant pathway.[6] Since the presence or absence of persistent 17-electron Co^{II} radicals can dramatically affect radical–radical dimerization, it seemed likely that significant effects on cross-coupling reactions might exist.

To probe the effect of the concentration of persistent 17-electron Co^{II} radicals on the product distribution in a cobalt-mediated radical cross coupling, the reaction of **1** with α-ethoxyacrylonitrile to produce the β-H elimination product **2** and the cross-coupled product **3** was studied.[7,8] Compared to other primary cobaloximes,[9] **1** was somewhat

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[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1993.

(1) Some recent references: (a) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron Lett.* **1992,** *48,* 9373. (b) Thomas, G.; Giese, B. *Helv. Chim. Acta* **1992,** *75,* 1123. (c) Giese, B.; Erdmann, P.; Gobel, T.; Springer, R. *Tetrahedron Lett.* **1992,** *33,* 4545. (d) Giese, B.; Carboni, B.; Goebel, T.; Muhn, R.; Wetterich, F. *Tetrahedron Lett.* **1992,** *33,* 2673. (e) Ali, A.; Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1992,** *33,* 2851. (f) Giese, B.; Carboni, B.; Göbel, T.; Muhn, R.; Wetterich, F. *Tetrahedron Lett.* **1992,** *33,* 2673. (g) Hu, C. M.; Qiu, Y. L. *J. Org. Chem.* **1992,** *57,* 3339. (h) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1992,** 553. (i) Branchaud, B. P.; Detlefsen, W. D. *Tetrahedron Lett.* **1991,** *32,* 6273. (j) Branchaud, B. P.; Yu, G.-X. *Tetrahedron Lett.* **1991,** *32,* 3639. (k) Branchaud, B. P.; Yu, G.-X. *Organomettalics* **1991,** *10,* 3795. (l) Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1991,** *32,* 243. (m) Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1991,** *32,* 259. (n) Giese, B.; Zehnder, M.; Neuburger, M.; Trach, F. *J. Organomet. Chem.* **1991,** *412,* 415. (o) Hartung, J.; Giese, B. *Chem. Ber.* **1991,** *124,* 387. (p) Baldwin, J. E.; Adlington, R. M.; Kang, T. W. *Tetrahedron Lett.* **1991,** *32,* 7093. (q) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1991,** *47,* 155. (r) Essig, S.; Scheffold, R. *Chimia* **1991,** *45,* 30. (s) Yamamoto, K.; Abrecht, S.; Scheffold, R. *Chimia* **1991,** *45,* 86. (t) Lee, E. R.; Lakomy, I.; Bigler, P.; Scheffold, R. *Helv. Chim. Acta* **1991,** *74,* 146. (u) Giese, B.; Thoma, G. *Helv. Chim. Acta* **1991,** *74,* 1135, 1143. (v) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990,** *46,* 7263. (w) Viet, A.; Giese, B. *Synlett* **1990,** 166. (x) Busato, S.; Tinembart, O.; Zhang, Z. D.; Scheffold, R. *Tetrahedron* **1990,** *46,* 3155. (y) Clark, A. J.; Jones, K. *Tetrahedron Lett.* **1989,** *30,* 5485.

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(7) Cobaloximes **1**, **4**, and **6** had satisfactory ^{1}H NMR and ^{13}C NMR data, and **1** and **6** had satisfactory elemental analysis data. Products **2** (1:1 mixture of *E* and *Z* diastereomers) and **3** had satisfactory ^{1}H NMR, ^{13}C NMR, MS, and exact MS data. Products **5** (1:1 mixture of *E* and *Z* diastereomers) and **7** (1:1 mixture of *E* and *Z* diastereomers) had satisfactory ^{1}H NMR, ^{13}C NMR, and exact MS data.

(8) All reactions (Tables I–IV) were run in Pyrex test tubes in 95% EtOH under argon. Visible-light photolysis was provided by a 300-W incandescent light bulb held several inches from the tube. Reactions were maintained near room temperature with a circulating cooling bath. All yields are for isolated, chromatographically purified materials (silica gel column chromatography). Yields were determined by ^{1}H NMR integration against a known quantity of Ph$_3$CH added as an internal standard to purified samples. Yields determined by this method are accurate to approximately ±5%. Each data point in Table II is from an individual run of the reaction, which was stopped at the indicated time. Each reaction in Tables I, III, and IV was allowed to proceed until no more alkylcobaloxime was visible by silica gel TLC. The reactions at 100, 200, and 400 mM **1** in Table I were very slow, did not go to completion, and were worked up when no more reaction progress was observed by TLC.

(9) Branchaud, B. P.; Choi, Y. L. *Tetrahedron Lett.* **1988,** *29,* 6037.

0276-7333/93/2312-4262$04.00/0

Scheme I

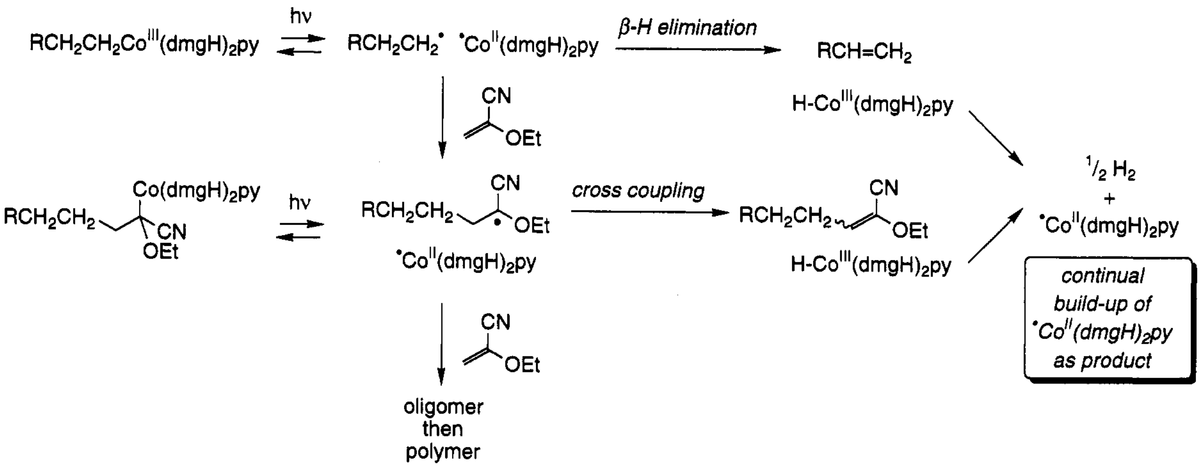


Table I. Concentration Dependence of Cross Coupling of 1 with $CH_2{=}C(OEt)CN$

concn of 1 (mM)	concn of $CH_2{=}C(OEt)CN$ (mM)	yield of 2 (%)	yield of 3 (%)	total yield 2 + 3 (%)	2/3 ratio
20	20	5	83	88	0.067
20	100	15	59	74	0.26
20	200	33	45	78	0.71
20	400	48	34	82	1.40
100	400	24	43	67	0.56
200	400	15	36	51	0.40
400	400	11	36	47	0.30

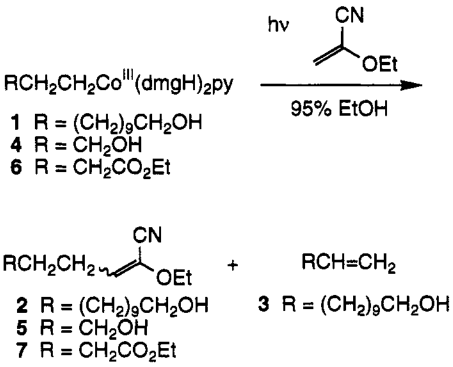
Table II. Time Course for Cross Coupling of 20 mM 1 with 400 mM $CH_2{=}C(OEt)CN$

time (min)	yield of 2 (%)	yield of 3 (%)	total yield 2 + 3 (%)	2/3 ratio
10	15	4	19	3.7
60	22	8	30	2.7
180	39	16	55	2.4
600	48	34	82	1.4

Table III. Effect of $[BrCO^{III}(NH_3)_5]^{2+}$ $Br\text{-}Br^-$ on Cross Coupling of 20 mM 1 with 400 mM $CH_2{=}C(OEt)CN$

amt of $[BrCO^{III}(NH_3)_5]^{2+}$ $Br\text{-}Br^-$ (equiv)	yield of 2 (%)	yield of 3 (%)	total yield 2 + 3 (%)	2/3 ratio
0.0	48	34	82	1.4
0.5	58	18	76	3.3
1.0	80	10	90	8.0
1.5	78	9	87	9.0

more susceptible to β-H elimination and thus provided a good test case for thorough study.



(1)

Effect of Concentration of Reactants on Product Distribution (Table I). At fixed 20 mM concentrations of 1, increasing the concentration of α-ethoxyacrylonitrile from 20 to 100 to 200 to 400 mM increased cross coupling (2) and decreased β-H elimination (3). This should be expected, since higher concentrations of alkene can compete more effectively with $\bullet Co^{II}(dmgH)_2py$ for reaction with alkyl radicals. At fixed 400 mM concentrations of α-ethoxyacrylonitrile, increasing the concentration of 1 from 20 to 100 to 200 to 400 mM decreased cross coupling and increased β-H elimination. This should be expected, since increasing the concentration of 1 should lead to higher concentrations of $\bullet Co^{II}(dmgH)_2py$ as reactions proceed due to the continual buildup of $\bullet Co^{II}(dmgH)_2py$, formed by fast ($k \approx 10^4$ M^{-1} s^{-1})[10] and essentially irreversible[11] disproportionation of $HCo^{III}(dmgH)_2py$.

Production Distribution versus Time (Table II). At early times and low conversion the cross-coupled product 2 was predominant. Over the course of the reaction, the cross-coupling/β-H elimination ratio (2/3) eroded. This should be expected, due to the continual buildup of $\bullet Co^{II}(dmgH)_2py$ as the reaction proceeds to completion.

Effect of Scavengers of $\bullet Co^{II}(dmgH)_2py$ on Product Distribution. The preceding data suggest that the reaction pathway is directed by the concentration of persistent $\bullet Co^{II}(dmgH)_2py$. If this is true, then the product distribution should be controllable by intentionally adjusting the concentration of $\bullet Co^{II}(dmgH)_2py$. Some efficient scavengers of $\bullet Co^{II}(dmgH)_2L$ have been documented.[12] The bromine atom transfer, $\bullet Co^{II}(dmgH)_2OH_2 + Br\text{–}Co^{III}(NH_3)_5{}^{2+}Br\text{-}Br^- \rightarrow Br\text{–}Co^{III}(dmgH)_2OH_2 + \bullet Co^{II}(NH_3)_5{}^{2+}Br\text{-}Br^-$, with $k = 3.2 \times 10^5$ M^{-1} s^{-1} at 24.9 °C, should be fast enough to compete with the various reactions of $\bullet Co^{II}(dmgH)_2py$ shown in Scheme I.[13] The addition of $Br\text{–}Co^{III}(NH_3)_5{}^{2+}Br\text{-}Br^-$ to cross-coupling reactions of 1 with α-ethoxyacrylonitrile significantly increased cross coupling and decreased β-H elimination (Table III). Another efficient scavenger of $\bullet Co^{II}(dmgH)_2L$ is $Fe(CN)_6{}^{3-}$ ($k = 3 \times 10^7$ M^{-1} s^{-1} at 24.9 °C for reaction with $\bullet Co^{II}(dmgH)_2OH_2$).[12,14] A similar effect on product dis-

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[10] Chao, T.-H.; Espenson, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 129.

[11] (a) Ng, F. T. T.; Rempel, G. L.; Halpern, J. *J. Am. Chem. Soc.* **1982**, *104*, 621. (b) Reference 6. (c) Halpern, J.; Ng, F. T. T.; Rempel, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 7124.

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[13] The product, $\bullet Co^{II}(NH_3)_5{}^{2+}Br\text{-}Br^-$, is substitution labile and should react with 6 H_2O from solvent to form $Co^{II}(H_2O)_6{}^{2+}Br\text{-}Br^- + 5\ NH_3$. It was assumed that the cobaloxime ligand is necessary for a Co^{II} species to perform a radical β-H elimination. The results reported here are consistent with that assumption.

Table IV. Effect of $K_3Fe(CN)_6$ on Cross Coupling of 1 with $CH_2{=}C(OEt)CN$

concn of $K_3Fe(CN)_6$	concn of **1** (mM)	concn of $CH_2{=}C(OEt)CN$ (mM)	yield of **2** (%)	yield of **3** (%)	total yield **2** + **3** (%)	**2**/**3** ratio
0.0	20	400	48	34	82	1.4
0.5	20	400	68	11	79	6.2
1.0	20	400	60	9	69	6.5
1.5	20	400	63	11	74	5.7
0.0	20	20	5	83	88	0.067
0.5	20	20	19	57	76	0.33
1.0	20	20	34	28	62	1.2
1.5	20	20	28	10	38	2.8
0.0	50	50	10	48	58	0.22
0.5	50	50	30	24	54	1.3
1.0	50	50	24	12	36	2.0
1.5	50	50	21	10	31	2.1

tribution was found using $K_3Fe(CN)_6$ (Table IV). It is unclear why the total yield (mass balance) drops with increasing concentrations of $K_3Fe(CN)_6$, especially at low concentrations of α-ethoxyacrylonitrile. One plausible explanation is that $Fe(CN)_6^{3-}$ is not completely chemoselective for $\cdot Co^{II}(dmgH)_2py$ and that reaction of $Fe(CN)_6^{3-}$ with alkyl radicals may be important. Alternatively, $Fe(CN)_6^{3-}$ may be such an efficient scavenger of $\cdot Co^{II}(dmgH)_2py$ that the $\cdot Co^{II}(dmgH)_2py$ concentration becomes too low and polymerization becomes more important. Similar results were obtained in stoichiometric cross couplings of 20, 50, or 100 mM **4** or **6** with α-ethoxyacrylonitrile—using $K_3Fe(CN)_6$ as a $\cdot Co^{II}(dmgH)_2py$ scavenger led to a significant improvement in cross coupling vs β-H elimination but the yields of cross coupling products **5** and **7** were low, 10–20% at best. Thus, although $\cdot Co^{II}(dmgH)_2py$ scavenging uniformly leads to a significant diversion of the reaction pathway away from β-H elimination and into cross coupling, it is not useful for stoichiometric cross couplings due to low mass balance but is very beneficial for cross couplings using an excess of radical-trapping alkene where the mass balance is high.

These results illustrate the importance of persistent $\cdot Co^{II}(dmgH)_2py$ radicals. The key point is that there is an optimum concentration of the persistent radical which will favor one particular product. High concentrations of $\cdot Co^{II}(dmgH)_2py$ favor β-H elimination, intermediate concentrations of $\cdot Co^{II}(dmgH)_2py$ favor cross coupling, and low concentrations of $\cdot Co^{II}(dmgH)_2py$ favor polymerization.[15] Other types of free-radical reactions involving persistent radicals may have different sets of fundamental steps and possible products, but the same basic principle should hold—concentrations of persistent radicals should be important in determining major reaction pathways.

Acknowledgment. This work was supported by the Alfred P. Sloan Foundation and the NSF (Grant No. CHE 8806805). The GE QE-300 NMR used in this work was purchased with funds from the NIH (Grant No. RR 02336) and NSF (Grant No. CHE 8411177). The VG ZAB-2FHF MS and VG 12/253 Quad MS used in this work were purchased with funds from the NIH (Grant No. RR 03001), NSF (Grant No. DMB 8414627), and the M. J. Murdoch Charitable Trust.

Supplementary Material Available: Text giving details of the syntheses of compounds noted in this paper and characterization data (5 pages). Ordering information is given on any current masthead page.

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(14) $Br{-}Co^{III}(NH_3)_5^{2+}Br^-Br^-$ can be prepared according to the procedure described in: Diehl, H.; Clark, H.; Willard, H. H. *Inorg. Synth.* 1939, *1*, 186. $K_3Fe(CN)_6$ is commercially available and inexpensive and may be more useful for synthetic purposes.

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