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Cobalt-Catalyzed Carbon-Carbon Bond Formation via Radicals

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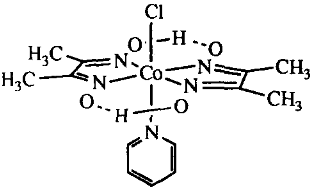
Abstract: *Catalytic amounts of cobalt complexes 2 and 3 are capable of generating alkyl radicals from the corresponding bromides under mild readion conditions, allowing the selective preparation of either saturated or unsaturated radical cyclization products.*

It is well established that alkyl cobalt(III) complexes with dimethylglyoxime, salen or salophen Schiff's base ligands are suitable for the formation of carbon-carbon and carbon-heteroatom bonds via radical cyclization or intermolecular radical cross coupling reactions. The transformations often require the use of stoichiometric amounts of cobalt salts, as the alkyl complexes are usually generated *in situ*[1] or even isolated prior to the reaction.[2] Catalytic processes using chlorocobaloxime **1** are only reported for 5-hexenyl cyclizations[3] and radical cross couplings with styrene.[4] The cyclizations proceed under moderatly basic and strongly reductive conditions (electrochemistry or $NaBH_4$) and partially yield mixtures of saturated and unsaturated cyclization products.[3d,5] During our investigations on cobalt-mediated radical reactions we recently demonstrated that the iodo cobalt(III) complexes **2** and **3** with two modified oxime ligands are suitable catalysts for the generation of alkyl radicals.[6] As the cobalt(III) complexes **2** and **3** can be easier reduced than the chlorocobaloxime **1**,[7] it is possible to use milder reductive conditions than in the cobaloxime catalyzed reactions. We now report that this benefit can be used to prepare either specifically saturated or unsaturated cyclization products.



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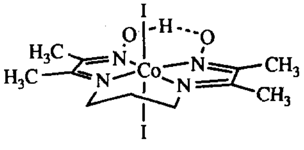

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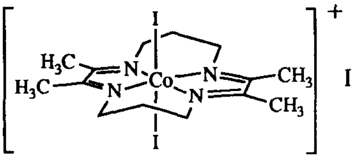

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The bromoacetals **4**, common model system for radical 5-ring cyclizations, were dissolved in DMF or acetonitrile and treated with 0.01 to 0.4 equivalents of the complex **2** using zinc or a cathode as electron source.[8] The results summarized in Table 1 show that on dependance of the reaction conditions either the unsaturated products **5** or the saturated cyclization products **6** are formed in high yields.[9] The unsaturated products **5** are mixtures of double bond isomers[10] and the saturated compounds **6** are mixtures of cis/trans isomers.[11]

The product composition is influenced by three major factors: 1) the reductant (Zn or Zn/NH_4Cl) or the reduction potential, 2) the amount of cobalt complex, and 3) additional irradiation of the reaction mixture.

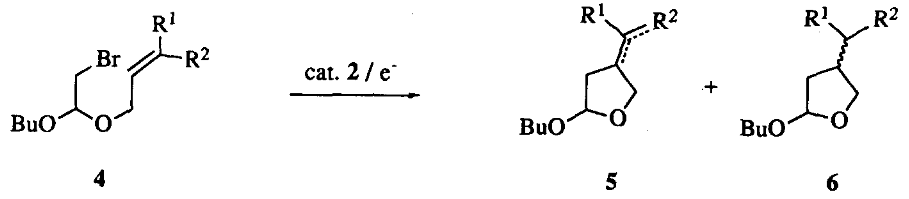
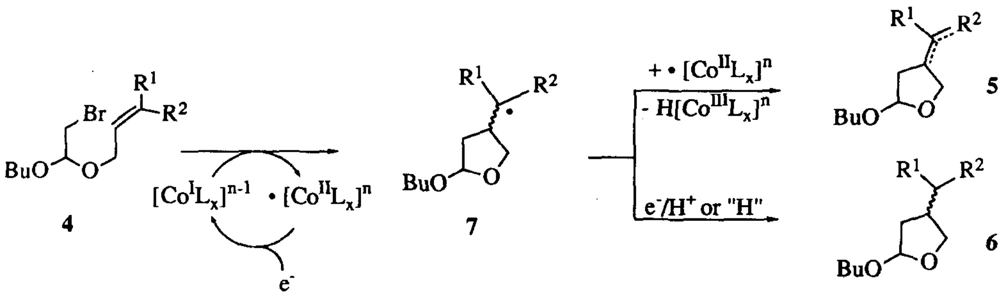


Table 1. Synthesis of unsaturated products **5** or saturated products **6** using catalytic amounts of Co-complex **2** *via* methods A-D

	R^1	R^2	Ratio **5**:**6** (Yield %)			
			A	B	C	D
a	H	H	81:19 (80)	<1:99 (80)	97:3 (78)	1:99 (65)
b	Me	H	>99:1 (90)	3:97 (88)	>99:1 (93)	1:99 (44)
c	Me	Me	>99:1 (99)	53:47 (56)	>99:1 (97)	8:92 (96)
d	Ph	H	97:3 (70)	2:98 (25)	>99:1 (68)	1:99 (42)

A: **2** (0.2 equiv.), Zn, DMF, hν; B: **2** (0.01 equiv.), Zn/NH_4Cl, DMF; C: **2** (0.4 equiv.), -0.8 V *vs.* Ag/AgCl, TBAP/acetonitrile, hν; D: **2** (0.05 equiv.), -1.6 V vs. Ag/AgCl, TBAP/acetonitrile, $C_{12}H_{25}SH$ (25 equiv.), hν.

The results obtained can be rationalized by the following mechanism: As for the cross coupling reactions of the isolated alkyl cobalt complexes, the unsaturated regioisomers **5** are formed via β-elimination from an intermediate alkyl cobalt complex. Thus, all the factors favoring the formation of the complex (high cobalt concentration, mild reducing conditions) or inducing β-elimination[12] (irradiation) lead to unsaturated products **5** (method A and C). Deuteration experiments with deuterated solvents revealed that the reduced products **6** are formed either by H-abstraction from the solvent (electrochemical pathway) or by reduction and subsequent protonation (reactions using Zn/NH_4Cl) of the cyclic radicals **7**. Therefore, decreasing the amount of cobalt complex, that can trap intermediate radical **7** in competition to hydrogen atom abstraction, and increasing the reduction potential leads to formation of reduction products **6** (method B and D).



The scope of this catalytic cobalt method is further demonstrated in the allylation of alkyl halides **8** by a radical fragmentation method.[13] This type of reaction proceeds via alkyl radical addition to the appropriately substituted alkene and subsequent β-bond cleavage of a carbon-heteroatom bond. As summarized in Table 2, treatment of primary, secondary and tertiary alkyl bromides with Zn and catalytic amounts of the cobalt complex 3 (0.05 equivalents) in the presence of allyl compounds **9** afforded the allylated products **10**.[14]

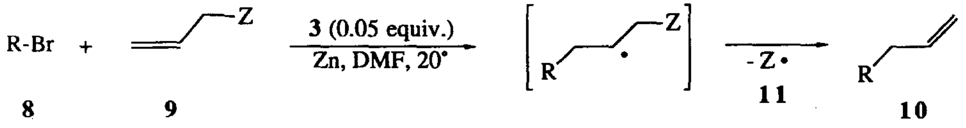
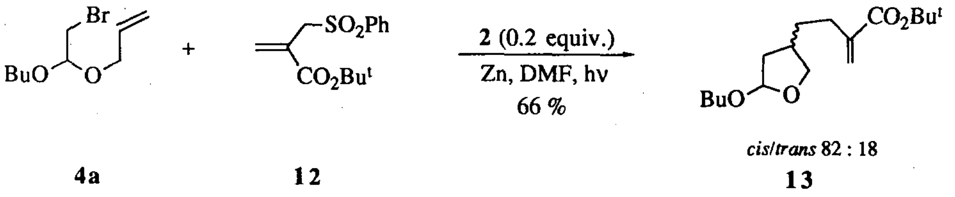


Table 2. Allylation of bromide **8** using catalytic amounts (0.05 equiv.) of Co-complex **3** and allyl compound **9**

8, R	**9**, Z	**10**, Yield (%)
C_6H_{13}	SO_2Ph	57
C_6H_{11}	SO_2Ph	85
adamantyl	SO_2Ph	80
C_6H_{11}	SPh	80
C_6H_{11}	SePh	74
C_6H_{11}	$OPO(OPh)_2$	52

With the cobalt mediated radical generation it is not necessary for the released heteroatom radical **11** to be a chain-transfer agent. Thus, a much broader variety of allyl systems can be used in comparison with the "classical" tin-mediated radical methods.[13]

Due to the absence of a fast hydrogen atom donor that may irreversibly trap the intermediate radicals, the "cobalt-method" is also capable of combining intra with intermolecular radical reactions.[15] Treatment of the α-bromo acetal **4a** in the presence of a two-fold excess of α-phenylsulfonyl acrylate**12** under the standard reaction conditions afforded the allylated tetrahydrofuran derivate **13**.



In conclusion, the cobalt complexes **2** and **3** can be used in catalytic amounts for intra- and intermolecular C-C bond forming reactions. In contrast to other known radical cyclizations methods specifically either unsaturated (methods A and C) or saturated products (method B and C) can be prepared and a wide variety of hetero allyl compounds can be used in allylation reactions.

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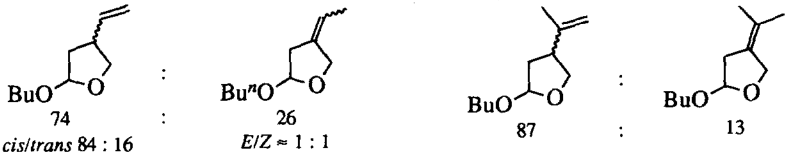
8. General reaction procedure: A: A solution of 0.3 mmol α-bromo acetal **4** and 0.2 eq. of the cobalt complex **2** in 10 ml of DMF is purged with argon for 15 min. After addition of 500 mg (7.65 mmol) zinc powder (activated by treatment with 2N HCl) the reaction mixture is vigorously stirred at room temperature (water cooling) under irridiation with a 300 W sunlight lamp. When no further product is formed (monitored by GC) 10 ml of water are added followed by extraction with 5 x 20 ml pentane. The combined organic layers are washed with 25 ml water and dried over $MgSO_4$. The residue is purified by flash chromatography. B: Reaction according A with 0.04 equiv. **2**, 500 mg (7.65 mmol) zinc powder and 150 mg NH_4Cl as reductant without additional irridiation. C and D: The reactions were carried out in a glass-frit (*G4*) divided H-type cell equipped with a three-electrode arrangement using a carbon-felt as cathode material, Pt as anode, and a Ag/AgCl reference electrode (E = -36 mV *vs.* SCE).
9. Reported yields on cyclization products were determined from the reaction mixture by GC using an internal standard and were not optimized. All products were isolated and fully characterized by ^{1}H-NMR, ^{13}C-NMR, MS, IR.
10. The double bond isomers showed a statistical distribution according to the number of β-hydrogen atoms; the *E*/*Z* isomers were formed in a 1:1 ratios (GC and ^{1}H-NMR analysis).



11. The *cis/trans* ratios for the saturated cyclization products were determined by X-ray, NMR and GC analysis: **6a** 82:18; **6b** 84:16; **6c** 63:37; **6d** 38:62.
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14. The alkyl halides were used in a ten-fold excess relative to the alkenes. The indicated equivalents of cobalt complex refer to the allyl compounds.
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