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Chromium-Catalyzed Radical Cyclization of Bromo and Chloro Acetals

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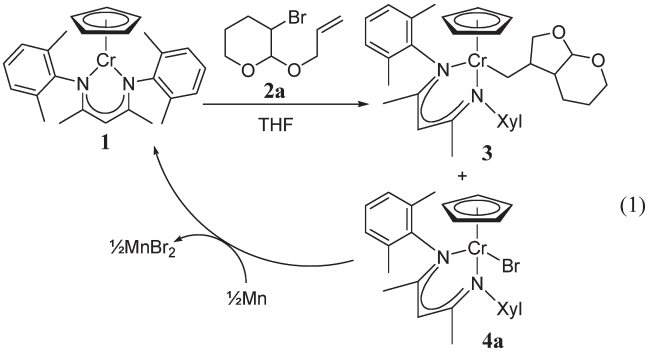
Summary: Cyclopentadienyl chromium β-diketiminate catalysts are used for the radical cyclization of bromo and chloro acetals. Mn powder activated with $PbBr_2$ or $PbCl_2$ is the stoichiometric reductant, and γ-terpinene is the hydrogen atom donor. Although the primary cyclized product can be isolated and structurally characterized as the Cr(III) complex, this substrate can also be reduced catalytically under mild photolysis conditions.

The reversible generation of organic radicals has been proposed as a key feature in several new carbon−carbon bond-forming reactions catalyzed by first-row transition metals.[1] The same reactivity mode is the foundation for transition-metal-mediated controlled radical polymerization.[2] We previously reported that the radical polymerization of vinyl acetate could be initiated and controlled using a well-defined Cr(III) alkyl complex[3] and investigated how the rate of Cr−R homolysis could be modified through steric interactions.[4] We would now like to report the use of the same CpCr[$(XylNCMe)_2CH$] system for the intramolecular radical cyclization of bromo and chloro acetals.

For decades, the biological chemistry of vitamin B_{12} has guided the study of reversible metal−alkyl bond homolysis. Organocobalt complexes with simple, readily modified Schiff base ligands exhibit the critical Co(III)−alkyl and Co(III)−hydride homolysis reactivity.[5] Once the mechanism had been established,[6] these synthetic complexes could be applied in the controlled radical polymerization and oligomerization of activated olefins,[7] as catalysts for H_2 production,[8] and as reagents for organic synthesis.[9] In each case, the key Co−R bond dissociation energy can be controlled by changing the ancillary ligands.[10] Although Cr(III) lacks the extensive biochemistry of organocobalt complexes,[11] we wish to explore the M−R homolysis reactivity of well-defined chromium complexes.

The radical cyclization of halo acetals (Ueno−Stork reaction)[12] has been used to explore new radical-based methodology.[13] The reaction products are useful precursors for synthesis, and the starting materials are readily prepared from the appropriate enol ether, allyl alcohol, and *N*-halosuccinimide. Transition-metal-mediated reactions typically employ the iodo acetals or the more stable bromo acetals.[14] Oshima and coworkers have reported radical cyclization reactions with zirconocene-based reagents that are catalytic for bromo acetals and stoichiometric for chloro acetals.[15]



(1)

Chromium(III) alkyl complexes are readily generated by the single-electron oxidative addition of Cr(II) with organic

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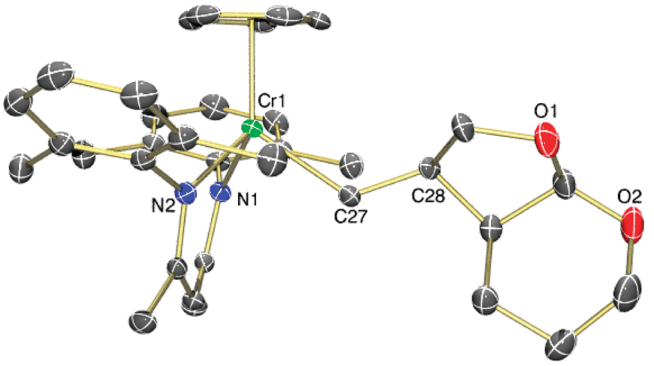


Figure 1. Thermal ellipsoid diagram (50%) of **3**. Only one isomer of the alkyl ligand is shown, and all H atoms are omitted for clarity.

halides.[16] We recently prepared CpCr[(XylNCMe)$_2$CH](CH$_2$SiMe$_3$) in high yield from the oxidative addition of Me$_3$SiCH$_2$I with CpCr[(XylNCMe)$_2$CH] (**1**) using an excess of Mn powder to selectively convert the Cr(III) halide product back to the reactive Cr(II) complex.[4] A similar reaction of **1** and bromo acetal **2a** resulted in the Cr(III) alkyl complex **3** (eq 1). Single crystals of **3** contain a cocrystallized mixture of one of the diastereomeric pairs of the cyclized product: the X-ray crystal structure of **3** is shown in Figure 1.

The synthesis and stability of bicyclic alkyl complex **3** is consistent with our previous mechanistic proposals for this system. Although the trapping of carbon-based radicals with Cr(II) is typically rapid and irreversible, Cr(III)−alkyl bond homolysis can be induced through adverse steric interactions.[4,17] The steric discrimination displayed by the CpCr[(XylNCMe)$_2$CH] system is remarkably subtle, as demonstrated by the dramatic difference in homolysis rates observed between the Cr(III) neopentyl and isobutyl complexes (Figure 2A).[4] Similarly, the decrease in the rate of chain growth in the controlled radical polymerization of vinyl acetate initiated by CpCr[(XylNCMe)$_2$CH](CH$_2$CMe$_3$) was attributed to the diminished propensity of homolysis of the primary alkyl radical resulting from 2,1-insertion (Figure 2B).[3] Bromine atom abstraction from bromo acetal **2a** generates a secondary alkyl radical: intermolecular trapping of this radical by Cr(II) does not compete with the rapid intermolecular cyclization reaction. However, the primary alkyl radical of the cyclized product is unhindered enough to form thermally stable Cr(III) alkyl complex **3** (Figure 2C).

The Cr(III)−alkyl bond strength in the cyclized product may be attenuated through increased steric hindrance. Reaction of 3,4-dihydro-2*H*-pyran with NBS and substituted allyl alcohols provides the bromo acetal substrates **5a**−**7a**, shown in eq 2. The Cr(III) bromo complex **4a** was prepared by single-electron oxidation of **1** with PbBr$_2$,[18] as previously reported for the corresponding 2,6-i$Pr_2C_6H_3$-substituted derivative.[19] The cyclization

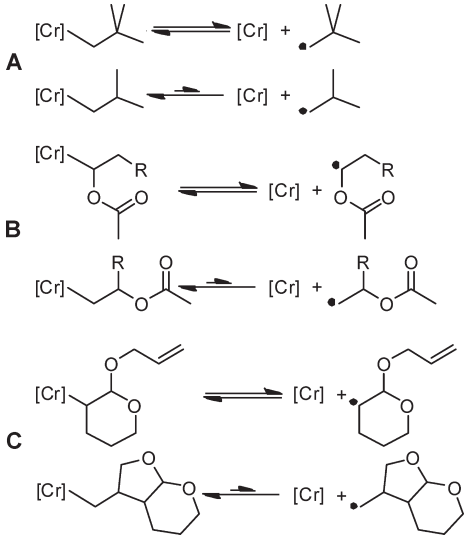
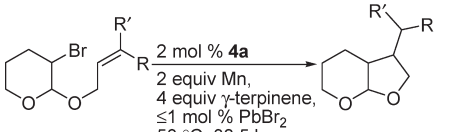


Figure 2. Steric hindrance and Cr−R homolysis in Cr(III) alkyl complexes: [Cr] = CpCr[(XylNCMe)$_2$CH].

and reduction of the bromo acetals was achieved using Mn powder,[16a] γ-terpinene as hydrogen atom donor,[20] PbBr$_2$,[21] and 2 mol % bromo complex **4a** at 50 °C in THF, as shown in eq 2. No product was obtained in the absence of chromium catalyst **4a**, consistent with the expected low activity of Mn powder toward alkyl bromides.[22]



(2)

The reduced bicyclic products **10** and **11** were obtained in good yields, with observed diastereomeric ratios consistent with those previously reported for these radical cyclizations (Table 1, entries 2 and 3). The lower yield of **12** (Table 1, entry 4) is attributed to the electronic stabilization of the radical formed upon cyclization of **7a**. The less reactive secondary benzylic radical is not as efficiently trapped by the H-atom donor γ-terpinene, leading to unwanted side reactions.[9b,20a] Bromo acetal **8a**, prepared from a substituted propargyl alcohol, is also successfully cyclized and reduced to **13** under the catalytic reaction conditions (Table 1, entry 5).

The development of reactive yet selective catalysts to activate the strong C−Cl bonds of organic chlorides has been an ongoing challenge for organometallic chemists.[14h,15,23] Gratifyingly, our catalytic conditions proved capable of also reducing chloro

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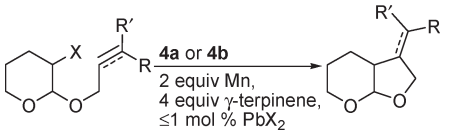
Table 1. Chromium-Catalyzed Radical Cyclization of Bromo and Chloro Acetals[a]



Entry	Substrate	Product	Yield (%)[c]
1	**2a**	**9**	*d*
2	**5a**	**10**	93 % (82/18)
3	**6a**	**11**	85 % (65/35)[e]
4	**7a**	**12**	28 % (79/21)[f]
5	**8a**	**13**	77 % (E/Z = 42/58)[g]
6	**5b**	**10**	56 % (93/7)
7	**6b**	**11**	57 % (61/39)[f]
8	**7b**	**12**	29 % (83/17)
9	**8b**	**13**	47 % (E/Z = 43/57)
10	**5b**	**10**	70 % (80/20)[h]
11	**2a**	**9**	48 % (83/17)[i]

[a] Substrate (1 mmol). [b] When X = Br: **4a** (2 mol %), $PbBr_2$ (≤1 mol %), 38.5 h at 50 °C; X = Cl: **4b** (20 mol %), $PbCl_2$ (≤1 mol %), 88 h at 70 °C. [c] Isolated yields. Diastereomeric ratios are in parentheses. [d] Isolated 73% of unreacted starting material **2a**. [e] Mn (5 equiv) and γ-terpinene (5 equiv) were used. [f] Mn (4 equiv) was used. [g] γ-Terpinene (8 equiv) was used. [h] Ten-day reaction time. [i] Performed with a 23 W compact fluorescent light bulb 10 cm from the reaction vessel.

acetals **5b**−**8b**, albeit with higher catalyst loading (20 mol %) of CpCr[(XylNCMe)$_2$CH]Cl (**4b**)[3] and lower yields (Table 1, entries 6−9). The standard reaction time used for comparing substrates was 88 h, affording yields of 29−57%. With an increased reaction time of 10 days the yield of **10** from **5b** improved to 70% (Table 1, entry 10). To the best of our knowledge, this is the first *catalytic* Ueno−Stork reaction of chloro acetals.[24]

When the homolysis reactions shown in Figure 2A were investigated, previously unappreciated *photolytic* Cr(III)−R homolysis reactivity became evident.[4] We were interested in using photolysis to induce catalytic turnovers for cyclized products that lacked signficant steric bulk. Reaction of **2a** under the standard catalytic conditions in the absence of light was unsuccessful, with 73% unreacted starting material isolated after 38.5 h. When the catalytic reaction of **2a** was performed under the light of a 23 W household compact fluorescent bulb, the cyclized product **9** was obtained in 48% yield (Table 1, entry 11).

Modulating M−R bond homolysis is critical in metal-mediated radical chemistry for both synthetic organic and controlled radical poymerization applications. This is particularly evident when extending radical reactivity to more challenging substrates. The reactivity features that made CpCr[(XylNCMe)$_2$CH](R) complexes suitable for vinyl acetate polymerization (efficient trapping of alkyl radicals by Cr(II), absence of β-hydrogen elimination, sensitivity of Cr(III)−R homolysis to steric interactions) translate smoothly to the Ueno−Stork reaction. Tin-free reduction of substituted bromo or chloro acetals can be performed with low catalyst loadings of Cr(III) halide complex **4a** or **4b**. The thermal catalytic reaction with the unsubstituted allyl substrate **2a** is unsuccessful, presumably due to the Cr(III)−R bond strength in **3**. However, the process can be rendered catalytic with mild photolysis. The lower yields with the chloro acetal substrates may be attributable to the slower reaction of Cr(II) with the stronger C−Cl bond. We are currently developing CpCr(LX) complexes with enhanced single-electron oxidative addition reactivity to address this issue.

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Supporting Information Available: Crystallographic data for **3**, complete experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) For the radical cyclization of the prenyl ether of 2-chlorophenol with a cobalt catalyst, see ref 14e.