

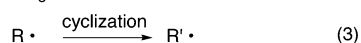
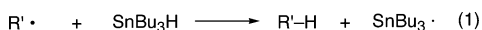
Tin-Free and Catalytic Radical Cyclizations

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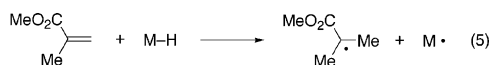
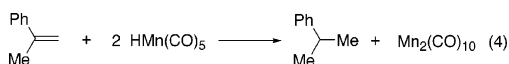
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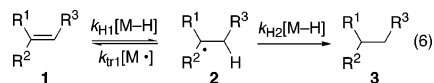
Radical cyclization (eqs 1–3), invaluable for natural product synthesis in the laboratory,¹ has not been industrially useful because of its reliance on toxic organotin reagents. Special procedures are required to handle trialkyltin hydrides and the waste they generate, and standard purification techniques often leave toxic levels of tin compounds in the product.² Methods catalytic in tin have been developed,³ along with tin hydride reagents modified to make their removal easier,⁴ but the need for alternatives to tin remains.⁵ Substitutes such as (Me₃Si)₃SiH,⁶ (Me₃Si)₃GeH,⁷ HGaCl₂,⁸ and HInCl₂⁹ contain a bond to hydrogen stronger than that in Bu₃SnH¹⁰ and are therefore likely to be less reactive at H• transfer (eq 1). Furthermore, these methods are stoichiometric in some other heavy element, typically iodine, bromine, selenium, or sulfur, which is abstracted by tin to generate the organic radical species (eq 2).



Studer has remarked that “transition metal based hydrides are promising alternatives to the tin hydrides.”¹¹ The use of Cp₂Zr-(H)Cl as a tin hydride analogue in cyclizations of halo acetals has been reported.¹² However, the difference in strength between transition metal–hydrogen bonds (typically 60 kcal/mol)¹³ and Sn–H bonds (78 kcal/mol)¹⁰ allows a different approach to generating radicals. The weaker M–H bond can transfer H• directly to olefins. The transfer in eq 4 was reported by Sweany and Halpern in 1977,¹⁴ and the transfer in eq 5 is essential in the catalysis of chain transfer during the radical polymerization of MMA.¹⁵



In order to know which radicals are accessible via H• transfer, we have looked at the reaction of various alkenes with CpCr(CO)₃H (Table 1),¹⁶ which has a Cr–H BDE of 61.5 kcal/mol.¹⁷ The extent of hydrogenation per H• transfer for each alkene measures the ratio of *k*_{H2} to *k*_{H1} (eq 6), while the observed values of *k*_{H1} measure the relative reactivity of these alkenes toward H• transfer. The data in Table 1 for compounds **1a** and **1b** show that only alkenes with a single substituent on the incipient radical center are extensively hydrogenated, implying that a secondary radical is appreciably more receptive to a second H• than a tertiary one.

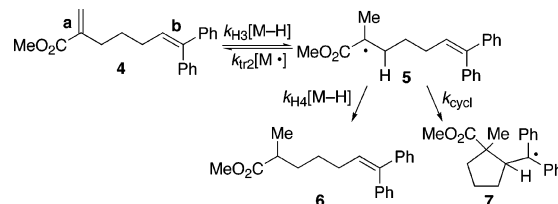


These kinetic data have enabled us to design a diene substrate **4** that can be cyclized by the H• transfer agent CpCr(CO)₃H.¹⁸ Table 1 predicts that the **a** double bond in **4** will accept H• 25 times more

Table 1. Rates of H• Transfer to Alkenes from CpCr(CO)₃H

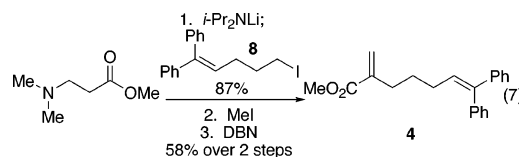
compound	<i>k</i> _{H1} (×10 ⁻³) (M ⁻¹ s ⁻¹)	observed
1a : R ¹ = R ² = Ph, R ³ = Me	0.59	1a
1b : R ¹ = Ph, R ² = R ³ = H	15.8	3b
1c : R ¹ = CO ₂ Me, R ² = Me, R ³ = H	14	1c

Scheme 1

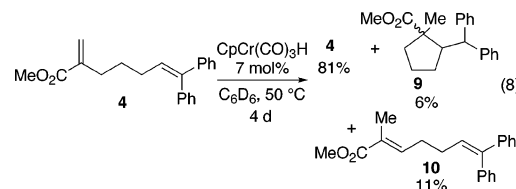


rapidly than the **b** double bond, so the principal product of H• transfer to **4** will be **5** (Scheme 1). Not only will **5** cyclize quickly (*k*_{cycl} for its carboethoxy analogue is 3.3 × 10⁵ s⁻¹ at 20 °C)¹⁹ but, because it is tertiary, it will resist the transfer of a second H• leading to **6**, that is, its *k*_{H4} will be relatively small.

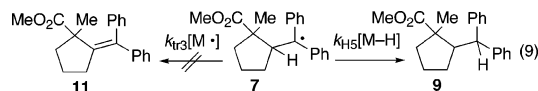
The diene **4** was synthesized from the iodoalkene **8** and commercially available methyl 3-(dimethylamino)propionate in three steps (eq 7).



The reaction of **4** with a catalytic quantity of CpCr(CO)₃H was disappointing, showing low turnover and only a small amount of the carbocycle **9** along with the isomerization product **10** (eq 8).

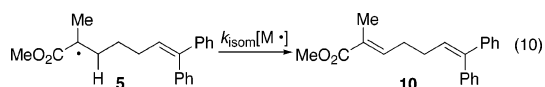


The fact that **9** is reduced indicates that the cyclized radical **7** has accepted a H• from CpCr(CO)₃H rather than donating a H• to CpCr(CO)₃• to afford the exocyclic alkene **11** (eq 9). Presumably, the tertiary C–H bond in **7** is too hindered to permit approach of the metalloradical and H• transfer (*k*_{H3}).



The formation of the isomerization product **10** in eq 8 suggested that significant CpCr(CO)₃• (which can abstract H• as in eq 10)

was present. $\text{CpCr}(\text{CO})_3\bullet$ is formed as a byproduct of any hydrogenation, such as that of **7**, and is unavoidably present as an impurity in $\text{CpCr}(\text{CO})_3\text{H}$.²⁰



As H_2 is known to regenerate $\text{CpCr}(\text{CO})_3\text{H}$ from $\text{CpCr}(\text{CO})_3\bullet$,²¹ we carried out the reaction between $\text{CpCr}(\text{CO})_3\text{H}$ and **4** under 30 psi of H_2 at 22 °C (eq 11, Table 2). Filtration of the reaction mixture through silica gel gave the cyclization products **9** and the hydrogenation product **6**, along with a small amount of the isomerization product **10**. Both diastereomers of **9** are formed, with the major product reflecting the preference of the methyl substituent for an equatorial position in a chair transition state (eq 12).²² Increasing the concentrations of $\text{CpCr}(\text{CO})_3\text{H}$ and **4**, or heating the reaction to 50 °C, shortened the reaction time but increased the extent of hydrogenation (Table 2).

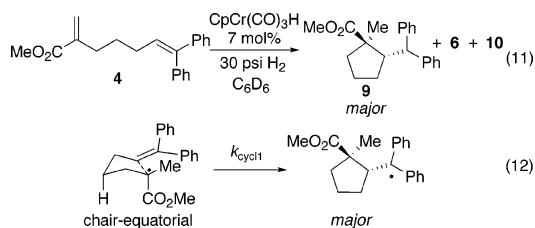
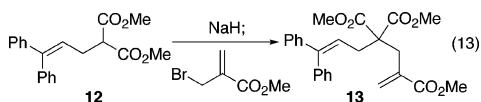


Table 2. Cyclization of **4** with $\text{CpCr}(\text{CO})_3\text{H}$

temp (°C)	[4] (M)	days	9:6:10 ^a
22	0.13	10	72:21:7
22	0.30	4	63:29:8
50	0.13	4	62:26:11
50	0.06	10	62:23:15

^a As determined by ¹H NMR analysis of the products relative to an internal standard. All conversions >95%.

Consideration of the Thorpe–Ingold effect²³ suggested construction of the substrate **13**, with geminal substituents on the carbon chain. The diene **13** was made from the alkene **12** in one step (eq 13).



Treatment of diene **13** with $\text{CpCr}(\text{CO})_3\text{H}$ at 50 °C for 10 days afforded the cyclization product **14** exclusively (eq 14, Table 3); higher concentrations of **13** and $\text{CpCr}(\text{CO})_3\text{H}$ led to clean cyclization after 1.5 days. The substituents may not only increase the rate of cyclization (k_{cycl}) but also decrease the rates of the competing hydrogenation (k_{H4}) and isomerization (k_{isom}) reactions, although they make the initial $\text{H}\bullet$ transfer slower.

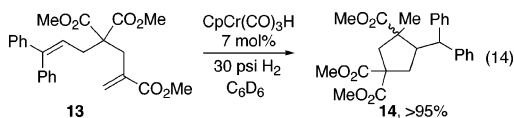


Table 3. Cyclization of **13** with $\text{CpCr}(\text{CO})_3\text{H}$

temp (°C)	[13] (M)	days
22	0.13	NR
50	0.13	10
50	0.30	1.5

Reactions 11 and 14 illustrate an approach to radical cyclizations that is both *tin-free* and *catalytic*, with the stoichiometric reductant being hydrogen gas. These results suggest a mechanism involving $\text{H}\bullet$ transfer for the cyclizations recently reported by van der Donk and co-workers, with Ti(III) citrate as a reducing agent and vitamin B_{12} as a catalyst.²⁴

Acknowledgment. We are grateful to G. Abramo, E. Papish, M. Arribas-Layton, and S. Cummings for preliminary work, to the Sames group for use of their HPLC, to DOE Grant DE-FG02-97ER14807 for financial support, and to L. Tang, J. Choi, James Franz (PNNL), and Marc Greenberg (Johns Hopkins) for helpful discussions.

Note Added after ASAP Publication. A correction was made in the last paragraph and published ASAP on January 16, 2007.

Supporting Information Available: Experimental procedures, spectroscopic data for all compounds, and spectra of cyclization substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0673276