

Direct Generation of Oxygen-Stabilized Radicals by H• Transfer from Transition Metal Hydrides

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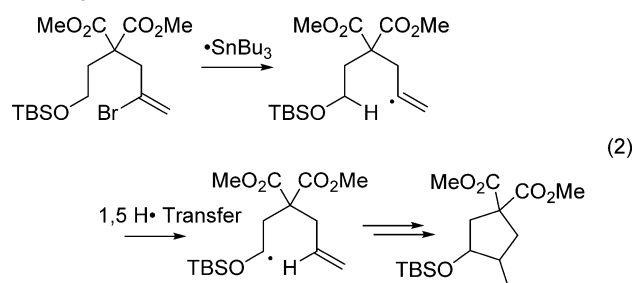
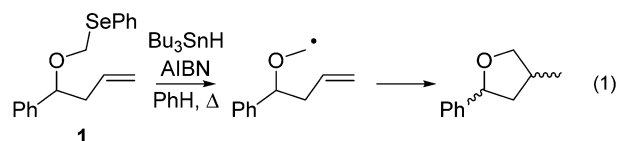
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S Supporting Information

ABSTRACT: Transition-metal hydrides generate α -alkoxy radicals by H• transfer to enol ethers. We have measured the rate constant for transfer from CpCr(CO)₃H to *n*-butyl vinyl ether and have examined the chemistry of radicals generated by such transfers. Radicals from appropriate substrates undergo 5-exo cyclization, with higher diastereoselectivity than the analogous all-carbon radicals. From such radicals it is straightforward to make substituted tetrahydrofurans.

The stabilizing effect of π -donor substituents on carbon radicals is well established. Recent theoretical work shows that a methoxy substituent stabilizes a methyl radical by 7.43 kcal/mol, more than a carbomethoxy substituent (4.88 kcal/mol).¹ α -Alkoxy substituents also increase the nucleophilicities of carbon-centered radicals. Such substituents have been shown to theoretically accelerate the addition of radicals to olefins with electron-withdrawing substituents and should thus increase the rate of appropriate radical cyclizations.² Furthermore, replacing carbons with oxygens in the precursors can accelerate radical cyclizations by 2–3 orders of magnitude.^{3,4}

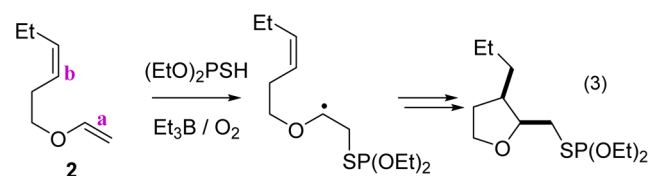
However, the literature contains few α -alkoxy radicals, presumably because of the challenges associated with their generation. For example, it is difficult to abstract a halogen atom from an α -haloether because of competitive ionization.⁵ As a result, only poor leaving groups are suitable for generating α -alkoxy radicals by abstraction. Indeed, Rawal and co-workers have shown that an α -alkoxy radical can only be generated from an alkoxy selenide such as **1** (eq 1).⁶



α -Alkoxy radicals are primarily generated by indirect methods.⁷ Curran, for example, has generated the radical in eq 2 by a 1,5 H• transfer.⁸ Reiser has achieved a similar result by a 1,6 H• transfer.⁹ Sammis and co-workers have used oxygen-centered radicals to accelerate both of these reactions, as part of relay cyclizations.¹⁰

It is easier to generate α -alkoxy radicals with special stabilization. For example, anomeric radicals have been reported by Giese and Rychnovsky.¹¹ α -Alkoxy radicals can be captodatively stabilized by an electron-accepting substituent (such as CO₂R);¹² however the additional stabilization tempers their nucleophilicity.^{2,12}

Parsons and co-workers¹³ have produced α -alkoxy radicals by the addition of thiophosphonyl radicals to enol ethers, which are increasingly available as synthetic intermediates (eq 3).¹⁴



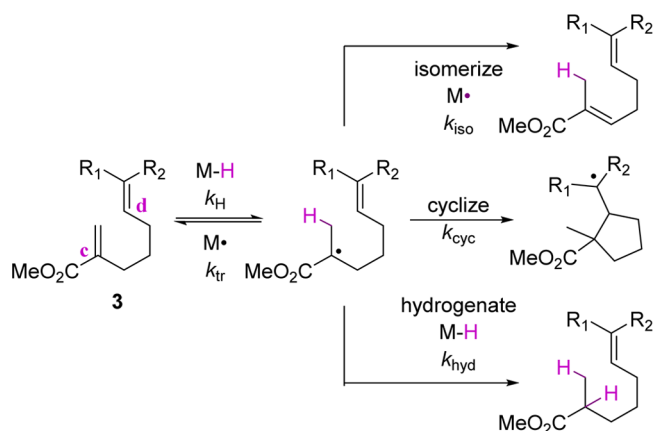
However, this reaction requires several equiv of a phosphorus hydride and obliges the introduction of a phosphonothioate ester into the product.¹³ An alternative route to such radicals involves the transfer of H• from a transition-metal hydride (M–H). Such transfers are known to generate radicals from alkenes¹⁵ and alkynes.¹⁶

We have shown that transfer of H• to α -substituted acrylate esters can initiate radical cyclizations.¹⁷ The resulting radicals can, in addition to cyclization, (1) transfer the H• back to M• to regenerate **3**, (2) transfer a different H• to M• to achieve an isomerization, or (3) accept a second H• to achieve hydrogenation; these possibilities are shown in Scheme 1. The rates of H• transfer to phenyl-, alkyl-, and carbomethoxy-substituted olefins have been studied in detail for CpCr(CO)₃H.^{15g} Generally, such rates are affected by the stability of the radical formed, though substituents on the carbon receiving the H• retard the rate by several orders of magnitude. Transfer to the *c* double bond in the acrylate substrate **3** has been shown to compete successfully with transfer to the *d* double bond. Cyclization of an enol ether such as **2** requires analogous relative rates; i.e., transfer to **a** must be faster than to **b**.

Received: November 19, 2014

Published: January 8, 2015

Scheme 1. Pathways for Radical Cyclization by M-H's



We thus needed a value for k_H , the rate constant for transfer of $H\bullet$ from $CpCr(CO)_3H$ to an enol ether. We selected *n*-butyl vinyl ether (4) as a model substrate. When 4 is mixed with an excess of $CpCr(CO)_3H$ in benzene at 50 °C, we do not observe any hydrogenation. This suggests that the reverse reaction, with rate constant k_{tr} , is considerably faster than the hydrogenation reaction, with rate constant k_{hyd} .

In the presence of $CpCr(CO)_3D$, excess 4 readily undergoes exchange. Terminal vinyl signals appear in the 2D NMR, and the hydride signal from $CpCr(CO)_3H$ grows in the 1H NMR. By monitoring these changes over time we obtain the pseudo-first-order rate constant k_{obs} for H/D exchange.^{15g}

As is shown in Figure 1, k_{obs} is linear in [4], confirming that exchange is second order overall. The slope of this line reflects

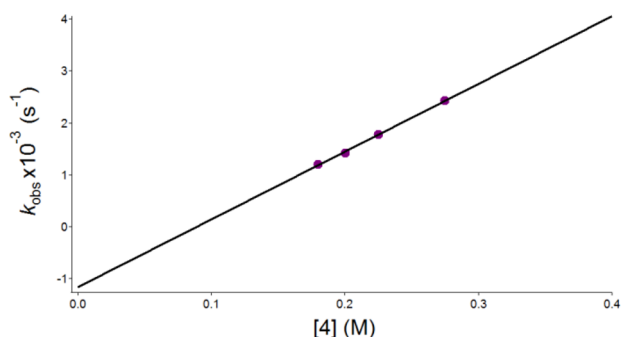
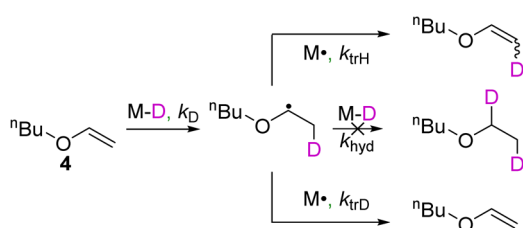


Figure 1. Pseudo-first-order kinetics, plot of k_{obs} vs [4], for $H\bullet$ transfer at 323 K in C_6D_6 .

only those cases in which a $D\bullet$ is transferred and an $H\bullet$ is abstracted. Thus, it must be corrected for $D\bullet$ reabstraction (see Scheme 2).^{15g,18} The result is k_D , the rate constant for the transfer of 2D to butyl vinyl ether. Correction by the established k_H/k_D ¹⁹ suggests that k_H is $6.84 \times 10^{-3} M^{-1} s^{-1}$, roughly half the

Scheme 2. Pathways for the Reaction of 4 with M-D



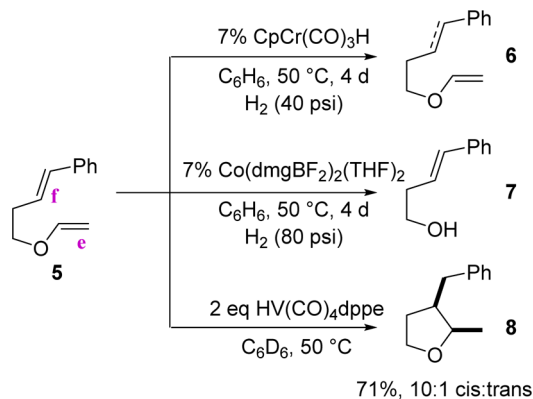
k_H for HAT to methyl methacrylate (details on the kinetic corrections and isotope effects can be found in the Supporting Information).¹⁸ The rate constant for HAT suggests that enol ethers can be used as we have previously used acrylates, as acceptors for $H\bullet$.

We thus prepared enol ether 5 and treated it with the metal hydrides our group has used in radical cyclizations: catalytic $CpCr(CO)_3H$ ^{16,17,20} or $Co(dmgBF_2)_2(THF)_2$ ²¹ under H_2 , or stoichiometric $HV(CO)_4(dppe)$.^{15e} We were surprised to find that each system produced a different product from 5. The cobaloxime system removed the vinyl substituent to give the alcohol 7, the chromium system gave almost entirely recovered starting material, but the vanadium reagent afforded the cyclized product 8 in 71% yield (Scheme 2).

We have shown elsewhere that $Co(dmgBF_2)_2(THF)_2$ generates an acidic species under H_2 ,²² and that species presumably catalyzes hydrolysis of 5 to form 7. The recovery only of starting material with $CpCr(CO)_3H$ is less easily explained, given that $HV(CO)_4dppe$ cyclizes 5 to 8; $CpCr(CO)_3H$ is generally an effective stoichiometric and catalytic cyclization reagent.

Treating an excess of 5 with $CpCr(CO)_3H$ (7 mol %) at elevated temperatures left most of the substrate unchanged after several days, although we observed some hydrogenation of the f double bond (see Scheme 3); we did not observe any

Scheme 3. Reaction of 5 with Metal-Hydride Systems



hydrogenation of the e double bond. These results were surprising because $H\bullet$ transfer to olefins is generally slowed when there are substituents on both carbons.^{15g} (Alkyl substituents on the carbon that receives the $H\bullet$ generally reduce the rate constant for transfer by 3 orders of magnitude.) Indeed, a crude measurement of the rate constant for $H\bullet$ transfer to *trans*- β -methylstyrene (a model for the f double bond in 5) is only about a tenth of our rate constant for $H\bullet$ transfer to *n*-butyl vinyl ether (a model for the e double bond in 5).²³ The rate constants for transfer to e and f double bonds can be compared directly by treating a substrate such as 5 with $CpCr(CO)_3D$. Replacing the Ph substituent with a naphthyl substituent provided better resolution in the 1H NMR. After 9 was treated with 2 equiv of $CpCr(CO)_3D$ at 60 °C for 3 days, both 1H and 2D NMR indicated almost three times more D incorporation into the g double bond than into the h double bond (Figure 2).

In combination, these observations show that $CpCr(CO)_3H$ is not effective in the cyclization of 5 because of a fast reverse reaction, not an inability to transfer $H\bullet$ (Scheme 4). HAT from $CpCr(CO)_3H$ to the f double bond of 5 (giving 5B) is slow but leads mostly to hydrogenation of that bond, yielding 6. The

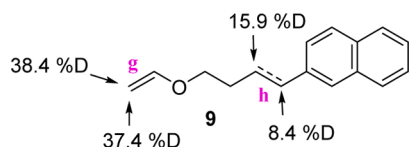
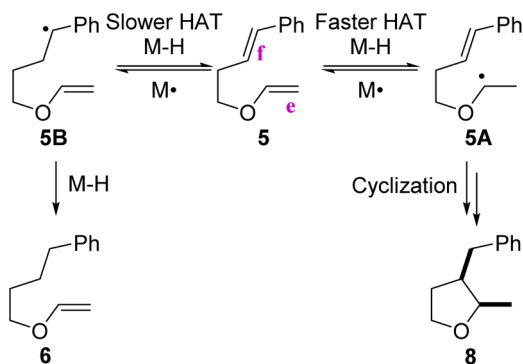


Figure 2. Percentage deuterium incorporation after reaction with 2 equiv of $\text{CpCr}(\text{CO})_3\text{D}$ (measured by ^1H NMR).

effectiveness of $\text{HV}(\text{CO})_4(\text{dppe})$ lies in the weakness of its V–H bond (57.5 kcal/mol).^{15e} The equilibrium for the initial $\text{H}\bullet$ transfer (to **5A**) is more favorable for cyclization (a slower reaction from **5A** back to **5**).²⁴ Thus, the rate of $\text{H}\bullet$ reabstraction, which we have previously neglected, does matter.²⁵

Scheme 4. Reaction Pathways for **5** and M-H ($\text{M} = \text{CpCr}(\text{CO})_3$ or $\text{V}(\text{CO})_4\text{dppe}$)



To investigate the generality of our approach we treated other enol ethers with $\text{HV}(\text{CO})_4\text{dppe}$. After 3 days at 50 °C we obtained the tetrahydrofuran derivatives (and a 2,3-dihydrofuran) in Table 1 in good yields. As in our previous reports,²⁶ the rate constant for hydrogenation, k_{hyd} , can be considered constant, so the yields reflect the values of k_{cyc} for the various cyclizations.²⁶ Electron-rich aromatic substituents on C6 (e.g., 2,5-dimethoxyphenyl, entry 3) give lower yields, an observation consistent with the idea that alkoxy-substituted radicals are nucleophilic.

Entries 1–5 in Table 1 cyclize with high diastereoselectivity. Similar results have been observed by both Parsons (eq 3)¹³ and Sammis¹⁰ in similar cyclizations. The preference for a cis product can be explained via the transition state proposed by Beckwith and Houk (Scheme 5).²⁷ The conformer with the methyl group pseudoequatorial prevails, resulting in the cis product. An oxygen in the backbone shortens the bond lengths (C–O bonds are about 0.15 Å shorter than C–C bonds), further improving the selectivity over what we obtained with acrylate substrates, presumably due to enhanced 1,3-diaxial-type interactions.²⁸ The 2,3-dihydrofuran prepared from a phenolic enol ether (Table 1, entry 6) displays reduced diastereoselectivity, presumably because the rigid backbone restricts access to the transition state.

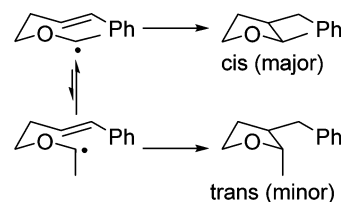
Thus, enol ethers are an effective starting point for generating α -alkoxy radicals, which carry out radical cyclizations with high diastereoselectivity. However, the necessary $\text{H}\bullet$ transfers are readily reversible, so such cyclizations are best done with hydrides (such as $\text{HV}(\text{CO})_4(\text{dppe})$) that contain weak M–H bonds.

Table 1. Substrate Scope of Enol Ether Cyclization^a

Entry	Substrate	Product
1		 75% 9:1
2		 70% 10:1
3		 58% 7:1
4		 69% 10:1
5		 91% 12:1
6		 47% 3:2

^aYields are isolated yields upon treatment with 2.1 equiv of $\text{HV}(\text{CO})_4\text{dppe}$ at 50 °C for 3 days. Ratio refers to cis:trans diastereoselectivities.

Scheme 5. Conformers of the α -Alkoxy Radical from **5**



■ ASSOCIATED CONTENT

Supporting Information

Synthetic details, compound characterization, kinetic traces, kinetic analysis, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. CHE-1401049 (IUPAC Novel Molecular and Supramolecular Theory and Synthesis Approaches for Sustainable Catalysis). J.L.K. acknowledges the National Science Foundation Graduate Research Fellowship Program. The authors are grateful to Scott A. Snyder, Deven P. Estes, and Gang Li for helpful discussions. Kevin D. Vo is acknowledged for the synthesis of starting materials.

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