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Catalysis of Radical Cyclizations from Alkyl Iodides Under H₂: Evidence for Electron Transfer from [CpV(CO)₃H][−]

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Abstract

Radical cyclizations are most often achieved with Bu₃SnH in the presence of a radical initiator, but environmental considerations demand that alternative reagents be developed – ones that can serve as a synthetic equivalent to the hydrogen atom. We have revisited [CpV(CO)₃H][−], a known replacement for Bu₃SnH, and found that it can be used catalytically under H₂ in the presence of a base. We have carried out the tin-free and catalytic radical cyclization of alkyl iodide substrates. The reactions are atom-efficient and the conditions are mild, with broad tolerance for functional groups. We have, for example, achieved the first 5-exoradical cyclization involving attack onto a vinyl chloride. We suggest that the radicals are generated by an initial electron transfer.

Graphical Abstract

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.

Tin hydrides such as Bu₃SnH are frequently used to reduce organic halides R-X to the corresponding hydrocarbons R-H. These reactions occur by the radical chain mechanism in eqs 1–5, and thus require stoichiometric amounts of the tin hydride. Both the resulting

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Supporting Information

The Supporting Information (synthetic procedures for the substrate/catalyst, a general procedure for the radical cyclization, characterization data (¹H- and ¹³C-NMR, tabulated IR and HRMS data) is available free of charge on the ACS Publications website.

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Bu₃SnX and any leftover Bu₃SnH are toxic and difficult to remove.¹ The few reactions that use tin catalytically rely on a strong hydride donor to reduce the Bu₃SnX back to Bu₃SnH, reducing functional-group tolerance.²

Transition-metal hydrides are also potent H• donors. Their M-H bonds are often weaker³ than the Sn-H bond of Bu₃SnH (78 kcal/mol),⁴ allowing them to transfer H• to substrates that do not react with the latter. For example, transition-metal hydrides can generate radicals by H• transfer to activated alkenes and alkynes.⁵ The resulting M• can be converted back to M-H by H₂,⁶ making these radical-generating reactions catalytic, with near-perfect atom economy.⁷ H• transfer reactions are finding synthetic applications;⁸ the Snyder group recently found that H• transfer from a metal hydride was the only practical way of hydrogenating a key enone in the synthesis of exochomine.⁹

Still needed, however, is a replacement for Bu₃SnH in the reduction of R-X. Transition-metal hydrides are known to reduce alkyl halides,¹⁰ but in general these reactions are stoichiometric, have limited functional group tolerance, or use harsh reductants to make the reaction catalytic. Hydrides that can be regenerated from H₂ are a more atom efficient approach for catalyzing the reduction of R-X.

A hydride known to generate R• stoichiometrically from R-X (eq 6) is the [CpV(CO)₃H][−] anion (**1**), reported by Kinney, Jones, and Bergman by 1978.¹¹ The loss of stereochemistry that is observed when **1** reacts with α-bromoethylbenzene (eq 7) is consistent with a radical intermediate.

A series of observations in the literature imply that **1** can be regenerated from [CpV(CO)₃Br][−] (**2**) under H₂. Dissociation of Br[−] from **2** should generate the coordinatively unsaturated CpV(CO)₃ (**3**),¹² which can be trapped by many two-electron donors to generate complexes like CpV(CO)₃(PMe)₃ (**4a**), CpV(CO)₃THF (**4b**),¹³ and CpV(CO)₃MeCN (**4c**).^{11a} Similarly, **3** should coordinate H₂ to generate the dihydrogen complex CpV(CO)₃(H₂) (**5**),¹⁴ which will regenerate the hydride anion [CpV(CO)₃H][−] (**1**) if the H₂ ligand were

and Zard have observed cyclizations promoted by Bu_3SnH result in the dechlorination of such substrates.²²

We have encountered few difficulties when cyclizing substrates containing heterocyclic moieties. Both 3-substituted and 2-substituted thiophenes (entries 7 and 8) generate the corresponding tetrahydrofuranyl thiophenes. The elimination product in entry 8 (see Table 3, footnote c) is presumably the result of its more acidic C-H bond.²³ Pyridyl- and furanyl-substituted alkenes (entries 9 and 10) generate other polycyclic products in good yield.

This reaction (catalytic cyclization by $[\text{CpV}(\text{CO})_3\text{H}]^-$) compares favorably to the corresponding reactions with Bu_3SnH . We generate only BH^+ ($[\text{DBU}\cdot\text{HI}]$) precipitates from solution, and can be removed by a filtration through a silica plug; Bu_3SnH generates an equivalent of $\text{Bu}_3\text{Sn}\cdot$ waste, which is difficult to remove. Our reaction are done at room temperature, whereas reactions with Bu_3SnH must be run at elevated temperatures to initiate a radical chain.

Table 4 shows substrates that $[\text{CpV}(\text{CO})_3\text{H}]^-$ does not process effectively. Aryl iodides (entry 1), tertiary alkyl iodides (entry 3), and alkyl bromides (entry 2) only undergo partial conversion under catalytic conditions, although these reactions work when the hydride anion is used stoichiometrically. The catalyst decomposes before the substrate can be completely converted to product.

Our observations suggest that the mechanism of the reaction between alkyl halides and $[\text{CpV}(\text{CO})_3\text{H}]^-$ should be reexamined. Kinney, Jones, and Bergman believed that the reactions occurred by a radical chain mechanism like that in eqs 1–5, and that the vanadium hydride was a better hydrogen atom donor than Bu_3SnH . However, they also considered the possibility that the reaction of R-X and **1** began by an electron transfer (eqs 11–13). Rates of electron transfer to R-X vary in the order $\text{R-I} > \text{R-Br} > \text{R-Cl}$,²⁴ and alkyl halides $>$ aryl halides. These trends match what is observed in Tables 3 and 4, suggesting that the radicals are generated by an electron transfer. A fast electron transfer enables the complete conversion of substrate before complete catalyst decomposition. Electron transfers from low valent transition metal complexes have ample precedent for generating organic radicals,²⁵ and an analogous electron transfer mechanism has been reported for the reaction of **1** with metal carbonyls.^{11c} We thus propose the overall catalytic cycle depicted in Scheme 2. The isolation of the hydrodehalogenation product in Table 2, Entry 3 suggests that the vanadium hydride may not be as effective a hydrogen atom donor as is presently believed.

There have been previous reports — some catalytic — of the initiation of radical cyclizations by electron transfer (for example with tetra(dimethylamino)ethylene,²⁶ Ni(0) with Zn,^{10a} or Fe(CO)₅ with phenanthroline,^{10d}). The present system is not only catalytic but uses no reducing agent stronger than H₂. The [CpV(CO)₃H][−] system, with H₂ as a chemical fuel, may be seen as an alternative to photo-redox catalysis²⁷ for the generation of reducing intermediates

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. In ref. 13, $\text{CpV}(\text{CO})_3(\text{THF})$ (4b) was generated by mixing $[\text{Et}_4\text{N}][\text{CpV}(\text{CO})_3\text{H}]$ with $[\text{Ph}_3\text{C}][\text{BF}_4]$ in THF, presumably via the coordinatively unsaturated $\text{CpV}(\text{CO})_3$. We tried the analogous reaction in MeCN to generate $\text{CpV}(\text{CO})_3(\text{MeCN})$ (4c) using MeOTf in place of $[\text{Ph}_3\text{C}][\text{BF}_4]$, but found that the resulting solutions decompose in a few minutes at room temperature.
16. In ref 11a, Bergman showed that $[\text{CpV}(\text{CO})_3\text{H}]^-$ (1) can be mixed with TfOH to generate $\text{CpV}(\text{CO})_3\text{MeCN}$ (4c). This presumably first generates the dihydrogen complex $\text{CpV}(\text{CO})_3(\text{H}_2)$ (5), which loses H_2 . We reacted 1 with the more mild acid $[\text{Et}_3\text{NH}][\text{BF}_4]$ to generate 4c, but observed its decomposition over a few hours at room temperature.
17. In ref 11a, Bergman reported that mixing 1 with AgCl generates the solvate complex 4c. We speculated that this occurs by an initial electron transfer, and so we tried the more mild single-electron oxidant $[\text{Cp}^*_2\text{Fe}][\text{B}(\text{C}_6\text{F}_5)_4]$.
18. It has been said that 4b and 4c are thermally unstable at room temperature (ref 13). However, we have found that solutions of $\text{CpV}(\text{CO})_4$ in MeCN undergo conversion to $\text{CpV}(\text{CO})_3\text{MeCN}$ (4c) in ambient light (31% conversion over 2977 minutes), there is no measurable decomposition of 4c at room temperature on this time scale. We suggest 4b and 4c are, in fact, stable at room temperature. Solutions of 4c generated from $[\text{Cp}^*_2\text{Fe}][\text{B}(\text{C}_6\text{F}_5)_4]$ are stable for many hours, and suitable for studying the equilibrium with H_2 .
19. During this time, we developed an improved protocol for the synthesis of $[\text{NEt}_4][\text{CpV}(\text{CO})_3\text{H}]$ (see SI). There were no differences between the reactions of the $[\text{NEt}_4]^+$ salt and the $[\text{PPN}]^+$ salt, so the tetraethylammonium salt was used subsequently.
20. The importance of green hydrodehalogenation methods is discussed further in ref 10f and 27a.
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Scheme 1. Reactions Relevant to Catalysis Under H₂

Scheme 2.
Proposed Catalytic Cycle with $[CpV(CO)_3H]^-$

Table 1.

Brief optimization of Radical Deiodination Conditions

entry	cat. loading	H_2	DBU	Solvent ^a	SM:Pdt
1	10%	75 psig	1 eq.	MeCN	56: 44
2	10%	75 psig	1 eq.	THF	40: 60
3	10%	75 psig	1 eq.	Ether	71 : 29
4	10%	75 psig	2 eq.	THF	30: 70
5	15%	90 psig	2 eq.	THF	05: >95 ^b

All reactions run overnight at r.t.

^aConcentration: 50 mM in substrate^bisolated yield

Table 2.

Radical Cyclization Optimization

entry	cat. loading	H ₂	DBU	solvent ^a	8 : 9 : 10 : 11 ^c
1	0%	90 psig	2 eq.	THF	60 : nd : 40 : nd
2	15%	0 psig	2 eq.	THF	60 : 24 : nd : 16
3	15%	15 psig	2 eq.	THF	58 : 13 : nd : 30
4	15%	40 psig	2 eq.	THF	54 : nd : 13 : 34
5	15%	90 psig	2 eq.	THF	nd : 10 : nd : 90
6	15%	90 psig	1 eq.	THF	37 : nd : nd : 63
7	15%	90 psig	0 eq.	THF	86 : nd : nd : 14
8	15%	90 psig	2 eq.	MeCN	24 : 42 : nd : 34
9	15%	90 psig	2 eq.	THF (dil.) ^b	nd : nd : nd : 100
10	0%	0 psig	2 eq.	THF	61 : nd : 39 : nd

All reactions run overnight at r.t.

^aConcentration: 50 mM in substrate

^bConcentration: 10 mM in substrate

^cGiven as percentages; all crude yields were within 5% expected mass, ratios determined by ¹H NMR analysis

Table 3.

Radical Cyclization Substrate Scope

entry	substrate	product(s)	yield ^a	entry	substrate	product(s)	yield ^a
1			85% 59:37 cis-syn:cis-anti	6 ^b			90% 82:18 trans:cis
2			92% 84:16 trans:cis	7			73% 81:19 trans:cis
3			26%	8 ^c			51% 79:21 trans:cis
4 ^b			33%	9			67% 84:16 trans:cis
5			66% 87:13 trans:cis	10			83% 83:17 trans:cis

Reaction conditions: **1** (15 mol%), DBU (2 equiv), 90 psig H₂, 10 mM in substrate at r.t. overnight.

^aYields refer to isolated yields.

^bIn these cases, the remaining mass balance was isolated starting material.

^cAlso isolated was 41% of 2-acetylthiophene (from a background elimination reaction).

Table 4.

Substrates That Work Poorly with the Catalytic System

entry	substrate	product	yield
1			~34%
2			~15%
3			~30%

Reaction conditions as in table 3. The remaining mass balance was recovered starting material