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

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Supporting Information Placeholder

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 5exo radical cyclization involving attack onto a vinyl chloride. We suggest that the radicals are generated by an initial electron transfer.

Tin hydrides such as Bu_3SnH 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 Bu_3SnX and any leftover Bu_3SnH are toxic and difficult to remove.¹ The few reactions that use tin catalytically rely on a strong hydride donor to reduce the Bu_3SnX back to Bu_3SnH , reducing functional-group tolerance.²

initiation

		initiator	\longrightarrow	2 init•			(1)
init•	+	Bu₃Sn–H		init–H	+	Bu₃Sn•	(2)
heavy aton	ı abs	traction					
Bu ₃ Sn•	+	R ()n X	>	Bu ₃ Sn–X	+	R _{(n}).	(3)
hydrogen a	tom i	transfer					
Bu₃Sn–ŀ	4 +	R .	\rightarrow	Bu ₃ Sn•	+ F	R ()n H	(4)
net reaction (omitting initiator)							

 $R-X + Bu_3Sn-H \longrightarrow Bu_3Sn-X + R-H$ (5)

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 radicalgenerating 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 Bu_3SnH 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.

$$R-X + [CpV(CO)_{3}H]^{-} \longrightarrow R-H + [CpV(CO)_{3}X]^{-} (6)$$

$$I$$

$$R-X + [CpV(CO)_{3}H]^{-} \longrightarrow R-H + [CpV(CO)_{3}X]^{-} (6)$$

$$I$$

$$R-X + [CpV(CO)_{3}H]^{-} \longrightarrow R-H + [CpV(CO)_{3}H]^{-} (7)$$

$$R-X + [CpV(CO)_{3}H]^{-} \longrightarrow R-H + [CpV(CO)_{3}H]^{-} (7)$$

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 twodonors electron 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), which will regenerate the hydride anion $[CpV(CO)_{3}H]^{-}(1)$ if the H₂ ligand were deprotonated. This sequence (Scheme 1) would enable the catalytic hydrodehalogenation of alkyl halides.

Scheme 1. Reactions Relevant to Catalysis Under H₂



H₂ must, however, compete with other L (including polar solvents) for the vacant coordination site of **3**. We have therefore studied the equilibrium between CpV(CO)₃L and CpV(CO)₃(H₂) (eq 10). The THF adduct of **3** (**4b**) has been generated by removal of H⁻ from **1**,¹⁵ and the MeCN adduct **4c** has been made by protonating **1** in CH₃CN.¹⁶ We have, however, found that **4c** can be made more easily by oxidizing **1** with Cp*₂Fe⁺ (eq 8).¹⁷

$$\begin{array}{c} [PPN][CpV(CO)_{3}-H] & \underbrace{[Cp^{\star}_{2}Fe][B(C_{6}F_{5})_{4}]}_{MeCN} & CpV(CO)_{3}(MeCN) & (8) \end{array}$$

Eq 10 must lie far to the left, as the ¹H NMR of $4c^{18}$ does not change under 1 atm of H₂. However, sufficiently strong base pulls **4c** through **5** to the hydride anion **1**. There is no reaction between **4c** and H₂ in the presence of Et₃N, but DBU gives **1** (by ¹H NMR) after several h (eq 9, 10). These experiments imply that the pKa of **5** lies between 18 and 25 in MeCN.

H ₂ + CpV(CO) ₃ MeCN \rightarrow (4c)	MeCN	+	CpV(CO) ₃ (H ₂) (5)	(9)
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$$DBU + CpV(CO)_{3}(H_{2}) \xrightarrow{} [DBU-H]^{+} + \begin{array}{c} [CpV(CO)_{3}-H]^{-} \\ (1) \end{array}$$
(10)

Knowing that each step in Scheme 1 was practical, we tried $\mathbf{1}^{19}$ as a catalyst for the reduction of alkyl bromides (vide infra) and alkyl iodides in the presence of DBU and H₂. For alkyl iodide substrate **6**, we observed a catalytic hydrodehalogenation²⁰ to generate **7** in MeCN, but the reaction worked better in the less-coordinating solvent THF (Table 1). A higher H₂ pressure and an increased concentration of DBU led to a quantitative yield of **7**.

Table 1. Optimization of Radical Deiodination Conditions

\bigcirc	Ph 	cat. [NEt ₄ H ₂ , DE	.][CpV(3U, Sol	CO) ₃ –H] → vent	H	Ph
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. ^a Concentration: 50 mM in substrate ^b isolated yield

Since the hydrodehalogenation reactions of **1** proceed by radical intermediates, appropriate organic substrates should undergo radical cyclization reactions. Indeed, **1** catalyzes the cyclization of **8** with DBU under H₂ (Table 2). There is no catalysis if the **1** (entry 1), H₂ (entry 2), or base (entry 7) is omitted. A background elimination reaction between **8** and DBU results in **9** or its hydrolysis product **10** (entry 10). Optimizing reaction conditions has allowed us to obtain a quantitative yield of the cyclized product **11** (entry 9).

With the optimized conditions from Table 2, we examined substrate scope (Table 3). The first three entries involve substrates for which radical cyclizations have previously been reported; catalysis by **1** with DBU/H₂ generates the products with similar yields and selectivity. The yield is lower in the 6-exo case in entry 3, presumably because the cyclization is slow enough that the H• transfer is competitive. The functional group tolerance is quite good: the free alcohol in entry 4 is not a problem. Polyhalogenated substrates react selectively at the iodide (for example, the aryl bromide in entry 5 remains unchanged). Entry 6 is the first 5-exo cyclization of an alkyl radical²¹ onto a chlorinated double bond; Sharp and Zard have observed cyclizations promoted by Bu₃SnH result in the dechlorination of such substrates.²²

Table 2. Radical Cyclization Optimization

Ph、		P	'n	Ph	Ph	Ph
N N N N N	cat. [NEt ₄][H_2 , DBU Solvent	1]	N Ts 8	N N Ts 9	HN Ts 10	N Ts 11
Entry	cat. loading	H ₂	DBU	solvent ^a	8:9	: 10 : 11 ^c
1	0%	90 psig	2 eq.	THF	60:-	- :40 :
2	15%	0 psig	2 eq.	THF	60 : 2	4 : : 16
3	15%	15 psig	2 eq.	THF	58 : 1	3::30
4	15%	40 psig	2 eq.	THF	54:-	- :13 : 34
5	15%	90 psig	2 eq.	THF	:1	0::90
6	15%	90 psig	1 eq.	THF	37:-	- : : 63
7	15%	90 psig	0 eq.	THF	86:-	- : : 14
8	15%	90 psig	2 eq.	MeCN	24:4	2::34
9	15%	90 psig	2 eq.	THF (dil.)	^b : -	- : :100
10	0%	0 psig	2 eq.	THF	61:-	-:39:

All reactions run overnight at r.t. ^a Concentration: 50 mM in substrate ^b Concentration: 10 mM in substrate ^c Given as percentages; all crude yields were within 5% expected mass, ratios determined by ¹H NMR analysis.

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 $[CpV(CO)_3H]^-$) compares favorably to the corresponding reactions with Bu_3SnH . We generate only BH^+ ([DBU•HI] precipitates from solution, and can be removed by a filtration through a silica plug); Bu_3SnH generates an equivalent of $Bu_3Sn•$ 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 $[CpV(CO)_3H]^-$ 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 [CpV(CO)₃H]⁻ 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 Bu₃SnH. 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 R-I > R-Br > R-Cl²⁴ 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 Table 3. Radical Cyclization Substrate Scope

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.



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



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Reaction conditions as in Table 3. The remaining mass balance was recovered starting material electron transfer

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R–X	+	[CpV(CO) ₃ −H] [−]	\rightarrow	[R– <mark>X]</mark> [⊷]	+	CpV(CO) ₃ –H	(11)
		18 e ⁻				17 e ⁻	
radica	al anio	on fragmentation					
		[R–X]*-	>	R•	+	X-	(12)
hydro	gen a	atom transfer					
R•	+	CpV(CO) ₃ –H	►	R–H	+	CpV(CO) ₃	(13)
		17 e ⁻				16 e⁻	(15)

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 H₂The [CpV(CO)₃H]⁻ system, with H₂ as a chemical fuel, may be seen as an alternative to photoredox catalysis²⁷ for the generation of reducing intermediates

Scheme 2. Proposed Catalytic Cycle with [CpV(CO)₃H]⁻



ASSOCIATED CONTENT

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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Notes

The authors declare no competing financial interests.

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H-H + B: -

→ e⁻ + H• + [B-H] ⁺ Bu₃Sn-H -

waste

used in

radical cyclization

stable for many hours, and suitable for studying the equilibrium with

19. During this time, we developed an improved protocol for the synthesis of [NEt₄][CpV(CO)₃H] (see SI). There were no differences between the reactions of the $[NEt_4]^+$ salt and the $[PPN]^+$ salt, so the tetraethylammonium salt was used subsequently.

20. The importantance of green hydrodehalogenation methods is discussed further in ref 10f and 27a.

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→ H• + Bu₂Sn=

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radical cyclization