

The Mechanism of Titanium Complex-Catalyzed Reduction of Aryl Halides by Sodium Borohydride Is Strongly Solvent Dependent

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Summary: The titanium complex-catalyzed reduction of aryl halides by sodium borohydride in dimethylacetamide (DMA) or ethers proceeds by electron transfer from a reduced titanium species, yielding an intermediate aryl radical.

We recently noted reduction of aryl halides by sodium borohydride in dimethylformamide (DMF), which was catalyzed by various titanium complexes.¹ This reaction proceeded rapidly, following an induction period whose duration depended on the concentration of the added titanium species, but aryl halide reduction, itself, was not titanium complex-concentration dependent. We showed that a borohydride–DMF adduct was formed, which was the actual reducing agent, and we demonstrated that aryl halide reduction occurred by a nonradical pathway. However, the high reactivity of borohydride toward the DMF solvent, with resultant formation of extensive gaseous byproduct, prompted us to investigate other solvents for aryl halide reduction which might be, themselves, more stable toward NaBH₄. We found that the simple change of solvent from DMF to dimethylacetamide (DMA) enabled us to reduce aryl halides smoothly, with neither induction period nor significant solvent intervention, if at a slower rate. However, we were surprised to discover that both the actual reducing agent and the mechanism for aryl halide reduction changed entirely as a result of this seemingly minor solvent substitution.

Sodium borohydride (378 mg, 10.0 mmol), Cp₂TiCl₂ (125 mg, 0.5 mmol), and 4-bromochlorobenzene (195 mg, 1.02 mmol) were added to 10.0 mL of DMA under N₂. The reaction mixture was heated at 50 °C. It rapidly turned violet and then blue-violet, and catalyzed reduction of 4-bromochlorobenzene to chlorobenzene occurred with a pseudo-first order rate constant, $k_{\text{obs}} = 1.9 \times 10^{-3} \text{ s}^{-1}$. In contrast to reactions done in DMF,¹ reduction rates were dependent on both titanocene complex and NaBH₄ concentrations,² with no apparent gas evolution.³ When competitive reduction of a series of *para*-substituted bromobenzenes was examined under these conditions, reduction rates were found to be substituent dependent. No simple correlation of $\log(k_X/k_H)$ existed with σ_p ,⁴ which might have been expected if reduction of the aryl halide

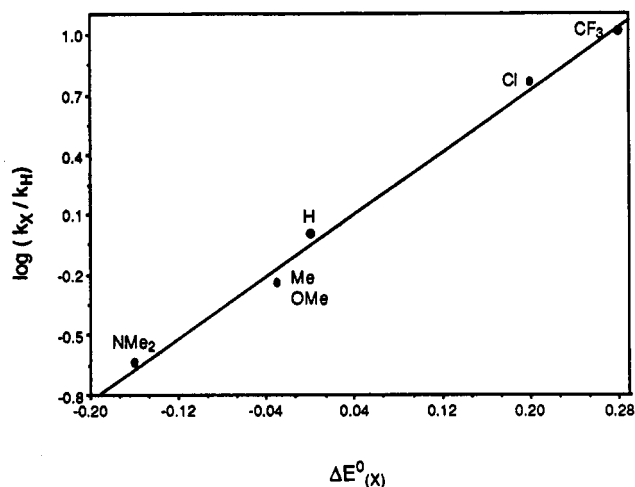


Figure 1. Good correlation exists between relative reduction rates and reduction potentials.

Table 1. Relative Reactivity of *Para*-Substituted Bromobenzenes

X	k_X/k_H	$\log(k_X/k_H)$	σ_p^4	$E_{1/2}^5$ (V)
NMe ₂	0.23	-0.64	-0.63	-1.970
OMe	0.57	-0.24	-0.28	-1.840
CH ₃	0.58	-0.24	-0.14	-1.840
H	1.00	0.00	0.00	-1.810
F	3.28	0.52	0.15	
Cl	5.80	0.76	0.24	-1.610
CF ₃	10.3	1.01	0.53	-1.530

occurred by a mechanism in which nucleophilic attack was rate determining; note in particular relative rates for reduction of *p*-CH₃- and *p*-CH₃O- analogs, which would have been predicted to be quite different, using this parameter. In contrast, an excellent correlation of $\log(k_X/k_H)$ with the reduction potential of the aryl halide was observed (Figure 1; Table 1), suggesting reduction of the aryl halide proceeds by an electron-transfer pathway.⁵

Investigations into either electrochemical reduction⁶ of aryl halides or oxidative addition⁷ of aryl halides to low-valent metal complexes *via* electron transfer indicate rapid

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(1) Liu, Y.; Schwartz, J. *J. Org. Chem.* 1993, 58, 5005.

(2) The rate for reduction of 4-bromochlorobenzene to chlorobenzene in DMA is not first-order dependent on borohydride or Ti concentration. At 50 °C, the half-life for reduction was 6 min when [Cp₂TiCl₂] = 0.05 M and [NaBH₄] = 1 M and 28 min when [Cp₂TiCl₂] = 0.05 M and [NaBH₄] = 0.5 M; it was 10 min when [Cp₂TiCl₂] = 0.08 M and [NaBH₄] = 1 M.

(3) The Cp₂TiCl₂-NaBH₄-DMF mixture ([Cp₂TiCl₂] = 0.01 M and [NaBH₄] = 1 M; 30 mL of DMF; 92 °C) showed a complex profile for aryl halide reduction. On initial treatment, the test substrate 1,2,4,5-tetrachlorobenzene was reduced very slowly to 1,2,4-trichlorobenzene ($k_{\text{obs}} = 3.73 \times 10^{-5} \text{ s}^{-1}$); following an induction period of ca. 60 min and concomitant with evolution of trimethylamine and bis(dimethylamino)methane,¹ reduction was very rapid ($k_{\text{obs}} = 1.41 \times 10^{-3} \text{ s}^{-1}$). For a comparable mixture in DMA ([Cp₂TiCl₂] = 0.01 M and [NaBH₄] = 1 M; 30 mL DMA; 95 °C), the rate of reduction was $k_{\text{obs}} = 2.26 \times 10^{-3} \text{ s}^{-1}$.

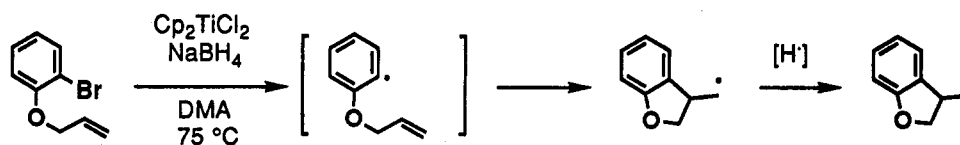
(4) March, J. *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*; John Wiley & Sons: New York, 1992; p 280.

(5) Measured in DMF vs Ag/AgBr. See: Sease, J. W.; Burton, F. G.; Nickol, S. L. *J. Am. Chem. Soc.* 1968, 90, 2595. These data measure half-wave reduction potentials, $E_{1/2}$, and not E_{redox}^* . A quantitative correlation with E_{redox}^* would be required for a definitive proof of an outersphere pathway. Obtaining E_{redox}^* for aryl halides from simple electrochemical studies can be difficult. Although $E_{1/2}$ depends on E_{redox}^* , it is also affected by variable electron-transfer rates from the electrode to the substrate and the rate of halide loss from the radical anion intermediate.⁶ These complications can be handled for our series of strongly similar substrates through analysis of $E_{1/2(X)} - E_{1/2(H)}$, the difference between $E_{1/2}$ for a substituted bromobenzene and the parent bromobenzene, assuming that electron-transfer rates from the electrode to variously *para*-substituted bromobenzenes and rates of halide loss from the radical anion intermediates are similar: $\Delta E_{1/2}^{\text{ox}} = E_{1/2(X)}^{\text{ox}} - E_{1/2(H)}^{\text{ox}} \approx E_{1/2(X)} - E_{1/2(H)}$. See: Bockris, J. O. M.; Khan, S. U. M. *Surface Electrochemistry. A Molecular Level Approach*; Plenum Press: New York, 1993; Chapter 6. The good correlation obtained between $\log(k_X/k_H)$ and $E_{1/2(X)} - E_{1/2(H)}$ suggests that an outersphere process does indeed exist.

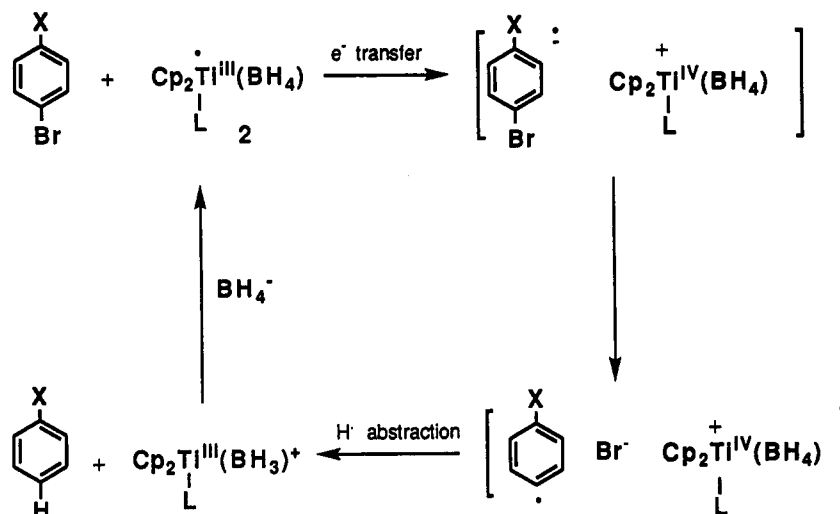
(6) Savéant, J. M. *Adv. Phys. Org. Chem.* 1990, 20, 1.

(7) Tsou, T. T. and Kochi, J. K. *J. Am. Chem. Soc.* 1979, 101, 6319.

Scheme 1. Radical "Clock" Probe



Scheme 2. Possible Catalytic Cycle for Reduction of the Aryl Halide



halide loss from an initially formed aryl halide radical anion to give the aryl radical. To probe the existence of a radical intermediate here, *o*-bromophenyl allyl ether (153 mg, 0.72 mmol) was treated with NaBH₄ (255 mg, 6.74 mmol) and Cp₂TiCl₂ (140 mg, 0.56 mmol) in 6 mL of DMA at 75 °C for 14 h. Analysis of the reaction mixture showed only 3-methyl-2,3-dihydrobenzofuran was produced; no phenyl allyl ether could be detected (Scheme 1). This diagnostic study shows that a radical is formed which is trapped with a rate $k_{\text{trap}} \leq k_{\text{cyclization}}$ ($\approx 10^9 \text{ s}^{-1}$ at 25 °C)⁸ under these concentration conditions. To determine the source of hydrogen in the product, 4-bromochlorobenzene (380 mg; 2 mmol) was treated with NaBD₄ (220 mg, 5.25 mmol) and Cp₂TiCl₂ (125 mg, 0.5 mmol) in 5 mL of DMA at 52 °C for 4 h. Both chlorobenzene (25%) and chlorobenzene-*p*-d₁ (75%) were obtained (overall yield 76%), showing that either free or Ti-coordinated borohydride is the major source of radical reduction.

Titanocene borohydride, Cp₂Ti(BH₄), **1**, is easily prepared from Cp₂TiCl₂ and NaBH₄ in various solvents;⁹ thus, **1** seemed a likely candidate to be the active agent for aryl halide reduction. Indeed, **1** smoothly reduced (bromomethyl)cyclopropane (DMA; 75 °C; 3.5 h) to a mixture of methylcyclopropane and 1-butene (67:33).¹⁰ However, the reactivity of **1** toward 4-bromochlorobenzene was quite low. For example, when a mixture of **1** (194 mg, 1.0 mmol) and 4-bromochlorobenzene (193 mg, 1.0 mmol) was heated in DMA (10 mL) at 50 °C, no reduction was observed, even after 3.5 h, but when NaBH₄ (120 mg, 3.2 mmol) in 2 mL of DMA was added, catalyzed reduction occurred readily, with a pseudo-first order rate constant, $k_{\text{obs}} = 1.2 \times 10^{-4} \text{ s}^{-1}$.² Similarly, little reaction occurred between Cp₂TiCl₂ (125 mg, 0.5 mmol), NaBH₄ (378 mg, 10.0 mmol), and 4-bromochlorobenzene (199 mg, 1.04 mmol) in diglyme (10 mL) at 50 °C after 4.5 h, but addition of DMA (1.0 mL) initiated reduction (50% reduction in 23 min). The effect of added amines on the rate of 4-bromochlorobenzene reduction was noted: Using equimolar amounts of NaBH₄ and amine, relative rates (75 °C) for reduction were pyridine (2.5; $k_{\text{obs}} = 1.63 \times 10^{-5} \text{ s}^{-1}$), 1-methylimidazole (1.8), and triethylamine (1.0). In an optimized procedure,

a Schlenk flask was charged with Cp₂TiCl₂ (125 mg, 0.5 mmol), NaBH₄ (454 mg, 12.0 mmol, 1.2 equiv), and 4-bromochlorobenzene (1910 mg, 10.0 mmol) under N₂. Diglyme (20 mL) and pyridine (1.00 mL, 12.4 mmol) were added, and the reaction mixture was heated at 125 °C. Catalytic reduction occurred, with a pseudo-first-order rate constant, $k_{\text{obs}} = 2.81 \times 10^{-4} \text{ s}^{-1}$. The reaction was quenched after 3.3 h (95.6% conversion to chlorobenzene; 19 turnovers).

Taken together, relative rate measurements, radical "clock" cyclization probes, and deuterium labeling studies¹¹ point to a simple scheme for aryl halide reduction by the Cp₂TiCl₂-NaBH₄-DMA system, which is based on electron transfer from a Ti complex catalyst, radical formation, and trapping (Scheme 2).¹² However, **1** is likely not the active species for aryl halide reduction under catalytic

(8) The intermolecular trapping rate, k_{trap} , is concentration dependent, since the trapping process is bimolecular. Under conditions of higher Ti complex concentration, some linear product might be produced. For studies of cyclization using this substrate, see: Johnston, L. J.; Luszyk, J.; Wayner, D. D. M.; Abeywickreya, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

(9) Noth, H.; Hartwimmer, R. *Chem. Ber.* **1960**, *93*, 2238.

(10) Similarly, (chloromethyl)cyclopropane was reduced to these same products (52:48). These (halomethyl)cyclopropanes are commonly used as mechanistic probes: The formation of 1-butene suggests an intermediate cyclopropylcarbinyl radical. For example, see: (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.

(11) Treating 4-bromochlorobenzene (194 mg, 1.01 mmol) with NaBD₄ (82 mg, 2.0 mmol) and Cp₂Ti(BH₄) (196 mg, 1.02 mmol) in DMA (5.0 mL) at 50 °C for 10 h gave chlorobenzene-*d*₀ and chlorobenzene-*d*₁ (overall yield 82%; 56:44). No deuterium incorporation was found in the reduced product when DMA-*d*₅ was used in conjunction with NaBH₄ and Cp₂Ti(BH₄).

(12) Aryl radicals photochemically generated from aryl halides react with BH₄⁻ by H-abstraction to give BH₃⁻. See: Barltorp, J. A.; Bradbury, D. J. *Am. Chem. Soc.* **1973**, *95*, 5085. Analogous H-abstraction from (Ti^{IV})BH₄ would give a (Ti^{III})BH₃ species.

(13) Preliminary ¹¹B NMR studies suggest that pyridine might react with Cp₂TiBH₄ prior to reduction of an aryl halide. When Cp₂TiBH₄ and excess pyridine were warmed at 75 °C for 5 min in THF-*d*₃ and the reaction mixture was analyzed by ¹¹B NMR, a strong signal was observed at δ -10.41 (*vs* external Et₂O-BF₃), similar to shifts noted for pyridine-BH₃ (see: Noth, H.; Wrackmeyer, B. *Nuclear Resonance Spectroscopy of Boron Compounds*. In *NMR Basic Principles and Progress*, Diehl, P., Fluck, E., Kosfeld, R., Eds.; New York: Springer-Verlag, 1978; Chapter 7, p 88, Table LXV, p 311). The active catalyst, too, might be a titanium hydride adduct of pyridine.

conditions; the active species is probably an adduct of 1, such as 2 (L = amine), in which the amine could act by coordination to the Ti or as a trap for the BH_3 liberated in the course of the reduction process¹³ or both. Investigations to determine the exact nature of the catalyst and the role of the amine are underway.

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Supplementary Material Available: Figure 1 ($\log(k_X/k_H)$ vs σ_p) and Figure 2 (Reduction of 4-Chlorobromobenzene under Catalytic Conditions) (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.