Radical Reactions

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Cationic Titanocene(III) Complexes for Catalysis in Single-Electron Steps**

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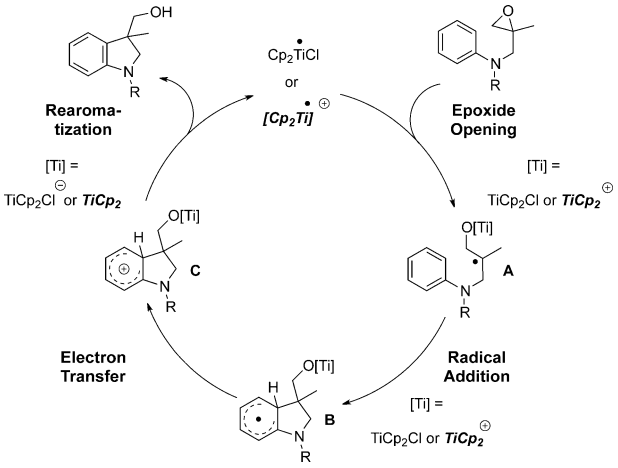
Abstract: *By exploiting solvent and anion effects, $[Cp_2Ti]^+$ complexes for atom-economical catalysis in single-electron steps were developed and applied for the first time. These complexes constitute remarkably stable and active catalysts for radical arylations. The reaction kinetics and catalyst composition were studied by cyclic voltammetry and in situ IR spectroscopy.*

Catalysis in single-electron steps[1] has recently emerged as a new concept for conducting radical reactions. It merges the attractive features of classic radical chemistry, such as high functional-group tolerance and high reactivity in C–C bond forming reactions,[2,3] with the concepts of transition-metal catalysis. As a result of its easy shuttling between the +III and +IV oxidation states, the $[(C_5H_4R)_2TiCl]/[(C_5H_4R)_2TiCl_2]$ redox couple is unique in inducing both oxidative addition and reductive elimination in single-electron steps.[4] Controlling the performance of the elemental steps through catalyst modification is essential for the success of these reactions. To date, this has been achieved by modifying the cyclopentadienyl ligands through the introduction of electron-withdrawing substituents.

Herein, we demonstrate that the use of $[Cp_2Ti]^+$ (Cp = cyclopentadienyl) is a more efficient way to modulate catalyst reactivity and stability through solvent and anion effects. The arylation of epoxide-derived radicals (Scheme 1) is an ideal reaction to validate the potential of $[Cp_2Ti]^+$ in comparison to $[Cp_2TiCl]$ and its ring-substituted derivatives.[1f,5] This is because both epoxide opening to give **A** (single-electron oxidative addition) and the oxidation of **B** to give **C** through electron transfer (the crucial step of single-electron reductive elimination) depend on the redox properties of the titanocene complexes involved. The oxidation of the radical σ-complex **B** is endothermic and rate-limiting for $[Cp_2TiCl]$. More electron-deficient derivatives of $[Cp_2TiCl]$, such as $[(C_5H_4Cl)_2TiCl]$, are therefore more efficient catalysts.[1f,5b] With the pendant cationic $[OTiCp_2]^+$ complex in **B**, the oxidation to **C** should be much more favorable than for the neutral $[OTi(C_5H_4R)_2Cl]$.



Scheme 1. Catalytic cycles for radical arylation with the cationic titanocene(III) catalyst $[Cp_2Ti^{III}]^+$ or the neutral $[Cp_2TiCl]$.

Stephan et al. have shown that from CH_3CN solutions of Zn-reduced $[Cp_2TiCl_2]$ (Zn-Cp_2TiCl_2 hereafter), $[Cp_2Ti(NCCH_3)_2]^+$ salts can be crystallized.[6] To examine the identity and properties of the Ti^{III} complex in CH_3CN, the generation of Ti^{III} from $[Cp_2TiCl_2]$ by Zn metal in CH_3CN was compared to its generation under identical conditions in THF (Figure 1) by using in situ IR spectroscopy and cyclic voltammetry (CV). Previously, we found that the C–H wag of the Cp ligand on Ti was sensitive to the oxidation state of the metal.[5b] Reduction of $[Cp_2TiCl_2]$ in THF by Zn or Mn results in a shift from 821 cm^{-1} to 798 cm^{-1}. The generation of Ti^{III} in CH_3CN gives a shift in the C–H wag to 813 cm^{-1}, which is indicative of a change in the electronic character of the metal and consistent with the formation of $[Cp_2Ti]^+$.

Analysis of the 2 mM Zn-Cp_2TiCl_2 solution in 0.2 M Bu_4NPF_6/CH_3CN solution by cyclic voltammetry (CV)[7] revealed that under these conditions, $[Cp_2Ti]^+$ is formed exclusively. The minor amount of $[Cp_2TiCl]$ observed results from chloride transfer to $[Cp_2Ti]^+$ in the diffusion layer of the electrode. The difference between the oxidation potentials of $[Cp_2TiCl]$ and $[Cp_2Ti]^+$ in CH_3CN is 0.53 V. On the reductive sweep, a wave pertaining to $[Cp_2Ti^{IV}Cl]^+$ is observed. The existence of this cationic Ti^{IV} species suggests that the pendant $[OTiCp_2]^+$ of **B** can be generated in CH_3CN.

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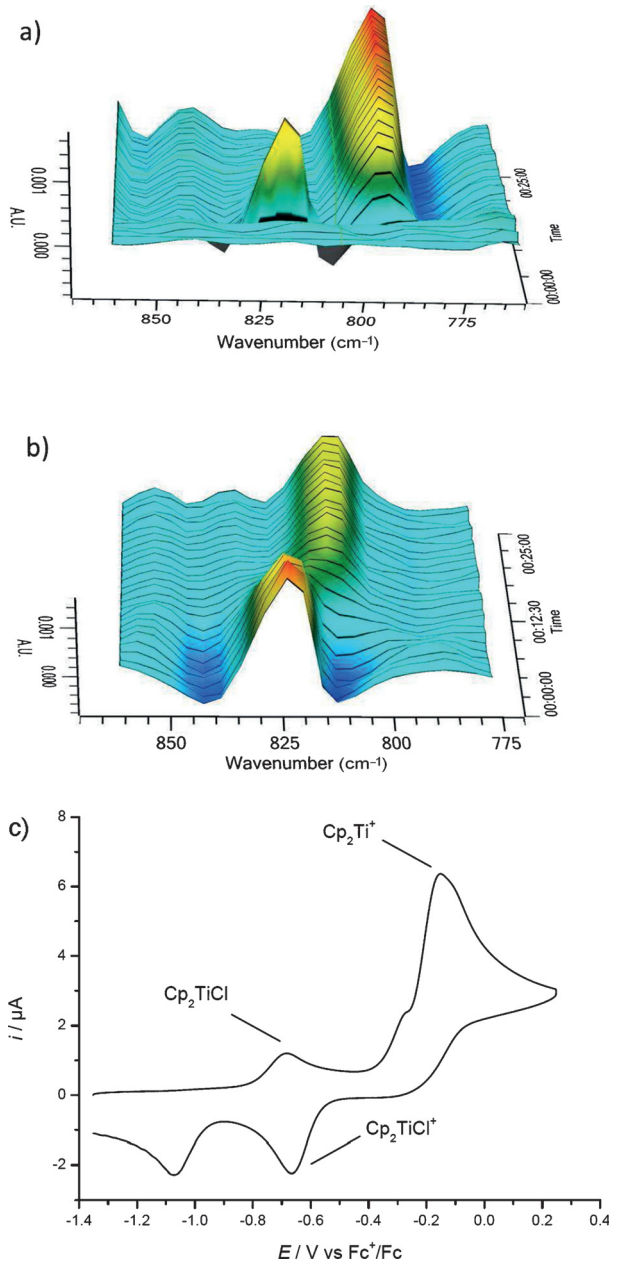
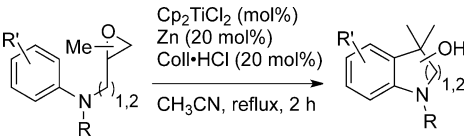
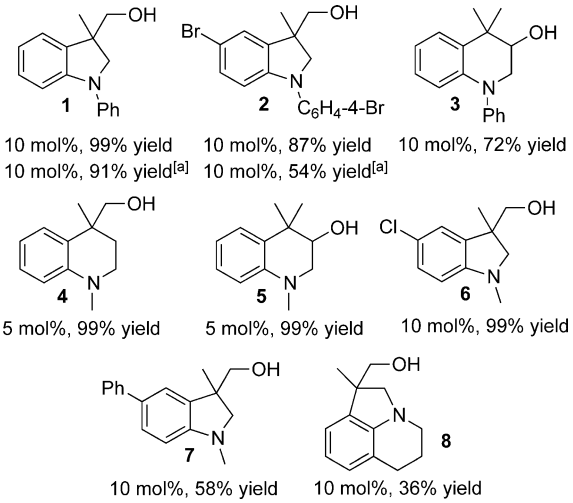


Figure 1. a) Shift of the C—H wag of the cyclopentadienyl ligand upon the addition of Zn to Cp_2TiCl_2 in THF. b) Shift of the C—H wag of the cyclopentadienyl ligand upon the addition of Zn to $[Cp_2TiCl_2]$ in acetonitrile. c) CV of 2 mM Zn-Cp_2TiCl_2 in 0.2 M Bu_4NPF_6/CH_3CN at $\nu = 0.2\ V\,s^{-1}$.

Table 1: Radical arylation employing Zn-Cp_2TiCl_2 in CH_3CN in the absence and presence of Coll·HCl.





10 mol%, 99% yield
10 mol%, 91% yield[a]
10 mol%, 87% yield
10 mol%, 54% yield[a]
10 mol%, 72% yield
5 mol%, 99% yield
5 mol%, 99% yield
10 mol%, 99% yield
10 mol%, 58% yield
10 mol%, 36% yield

[a] without Coll·HCl (collidine hydrochloride).

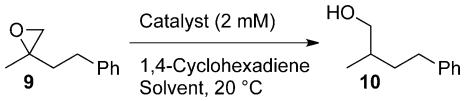
Our results for the radical arylation with Zn-Cp_2TiCl_2 in CH_3CN are summarized in Table 1. For **1**, conversion was completed with or without the addition of Coll·HCl and the yields of isolated product were excellent. $[Cp_2Ti]^+$ thus constitutes an efficient catalyst for radical arylation in CH_3CN. However, stabilization by Coll·HCl is necessary[7g] for reactions showing a slow oxidation of **B** to **C**, as for **2**. To avoid complications, 20 mol % Coll·HCl was routinely added to the reaction mixtures. The reaction leading to **2** is not efficient with Mn-Cp_2TiCl_2 in THF and requires Mn-$(C_5H_4Cl)_2TiCl_2$ instead. The use of CH_3CN for tuning the redox properties of the catalysts thus renders ligand substitution superfluous. However, for the preparation of **3**, **7**, and especially **8**, the yields were not quite satisfactory. Previously, **2**, **3**, **4**, **5**, and **8** were obtained most efficiently with Mn-$(C_5H_4Cl)_2TiCl_2$/Coll·HCl.[1f]

To understand the performance of $[Cp_2Ti]^+$ in CH_3CN, its reactions were studied by performing a kinetic analysis. Rate studies of the reaction yielding **1** with varying concentrations of catalyst and substrate show that the rate is approximately first order in both. Compared to Mn-$(C_5H_4Cl)_2TiCl$/Coll·HCl in THF, the observed rate constant k_{obs} for the arylation is lower in CH_3CN ($0.032 \pm 0.008\ min^{-1}$ at 90 °C in CH_3CN vs. $0.79 \pm 0.09\ min^{-1}$ at 60 °C in THF).

To further investigate this effect, we studied the rate of epoxide opening by employing **9** and determined the bimolecular rate constants for this process (Table 2). Rates were determined by measuring the decay of Ti^{III} at 800 nm with respect to the concentration of **9** (see the Supporting Information).[5b,7f] The reduction of **9** by Zn-Cp_2TiCl_2 in CH_3CN is approximately 600 times slower than by $[Cp_2TiCl]$ in THF and on the same order of magnitude as the arylation of **1**. Epoxide opening (the generation of **A** in Scheme 1) is thus the rate-limiting step of the arylation with Zn-Cp_2TiCl_2 in CH_3CN. This is most likely due to a strong coordination of $[Cp_2Ti]^+$ by CH_3CN that inhibits epoxide coordination and retards its opening.

While our approach of replacing $[(C_5H_4Cl)_2TiCl]$ by $[Cp_2Ti]^+$ proved successful in principle, the reaction conditions chosen are not satisfactory with respect to reaction rate and product yield in critical cases owing to the strong coordination of CH_3CN. As a consequence, catalyst stabilization by Coll·HCl is required.

Table 2: Rate constants for the opening of **9**.



Entry	Catalyst	Solvent	Rate constant [$M^{-1}min^{-1}$]
1	$[Cp_2Ti^{III}Cl]$[a]	THF	36 ± 6
2	$[Cp_2Ti^{III}Cl]$[b]	CH_3CN	0.06 ± 0.01
3	$[Cp_2Ti^{III}OTf]$[c]	THF	3.2 ± 0.4

[a] [**9**] = 20–50 mM, [CHD] = 80–200 mM (Reaction done in the presence of 4 mM Coll·HCl) [b] [**9**] = 40–160 mM, [CHD] = 160–640 mM [c] [**9**] = 20–80 mM, [CHD] = 80–320 mM.

Based on the findings described above, a more stable and active catalytic system based on $[Cp_2Ti]^+$ in a less coordinating solvent is required. To address this, $[Cp_2Ti(OTf)_2]$ was chosen as a precatalyst for the reduction since it is likely that the weakly coordinating triflate anions will dissociate from Ti^{III} even in less-coordinating solvents such as THF. $[Cp_2TiOTf]$ in THF was synthesized according to Luinstra by reducing $[Cp_2Ti(OTf)_2]$ with $NaBH_4$ in THF.[8] Using this approach, a sky-blue solution was formed after 2 h. Gratifyingly, in situ IR and CV of the solution indicated the exclusive presence of $[Cp_2Ti]^+$ (Figure 2). Although the C–H wag of the cyclopentadienyl ligand for the precatalyst $[Cp_2Ti(OTf)_2]$ occurs at higher energy (843 cm^{-1}), the C–H wag of $[Cp_2Ti]^+$ in THF occurs at the same energy (813 cm^{-1}) as in CH_3CN.

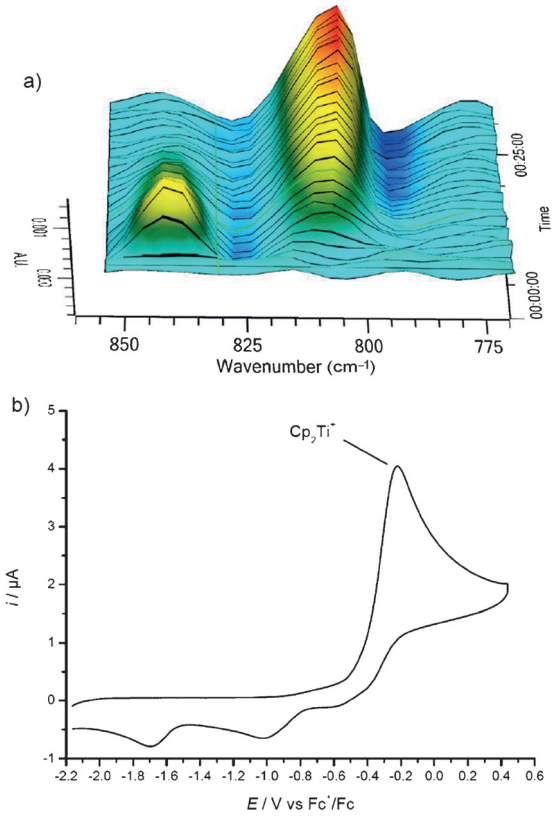
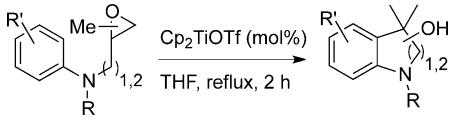
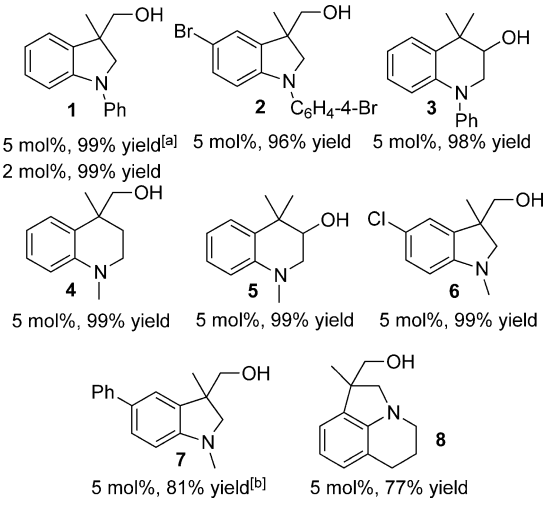


Figure 2. a) In situ IR of $NaBH_4$-$Cp_2Ti(OTf)_2$ in THF. b) CV of 2 mM $NaBH_4$-$Cp_2Ti(OTf)_2$ in 0.2 M Bu_4NPF_6/THF at $\nu = 0.2\ Vs^{-1}$.

The arylation reactions with the $NaBH_4$-$Cp_2Ti(OTf)_2$ system are summarized in Table 3. For all substrates, the $NaBH_4$-$Cp_2Ti(OTf)_2$ system for the generation of $[Cp_2Ti]^+$ in THF constitutes a very robust catalytic system that delivers

Table 3: Radical arylation with $NaBH_4$-$Cp_2Ti(OTf)_2$ in THF.





[a] 0.5 h. [b] 1 h.

the products in high to excellent yields with a catalyst loading of 5 mol%. The first example (to give **1**) suggests that the catalyst loading can be reduced even further. In the critical cases for Zn-Cp_2TiCl_2 in CH_3CN (**2**, **3**, **7**, and **8**) the yields of isolated product are noticeably superior with $[Cp_2TiOTf]$. Moreover, an additive for catalyst stabilization was not required. Therefore, the $NaBH_4$-$Cp_2Ti(OTf)_2$ system renders ligand substitution obsolete. It is substantially more efficient and robust than both Zn-Cp_2TiCl_2 in CH_3CN and Mn-$(C_5H_4Cl)_2TiCl$-Coll·HCl in THF.

The kinetic analysis of $[Cp_2Ti]^+$ in THF shows that the rate is approximately first order with respect to the catalyst and substrate. Compared to Zn-Cp_2TiCl_2 in CH_3CN, epoxide opening of **9** with $[Cp_2TiOTf]$ in THF is much faster ($3.2\pm0.4\ M^{-1}min^{-1}$ vs. $0.06\pm0.01\ M^{-1}min^{-1}$, Table 2) and the k_{obs} value for product formation is higher at lower temperature ($0.11\pm0.01\ min^{-1}$ at 60 °C vs. $0.032\pm0.008\ min^{-1}$ at 90 °C). Since epoxide opening is faster than the overall arylation, the electron back-transfe from intermediate **B** to **C** (Scheme 1) becomes rate-determining.

It is important to note that $[Cp_2Ti]^+$ could facilitate a Lewis acid initiated pathway to **1**. To examine this possibility, the substrate leading to **1** was refluxed in THF with 5 mol% $[Cp_2Ti(OTf)_2]$, which resulted in decomposition of the substrate without the formation of **1**. Additionally, performing the arylation to form **1** with stoichiometric amounts of $[Cp_2TiOTf]$ in the presence of *tert*-butyl acrylate led to isolation of the acrylate radical addition product along

with **1**.[5b] This finding confirms the mechanism proposed in Scheme 1 (see the Supporting Information).

In conclusion, we have demonstrated that $[Cp_2Ti]^+$ is a stable catalyst for radical arylation proceeding through single-electron steps. By employing solvent and anion effects, we have rendered catalyst stabilization by additives and redox tuning by ring substituted cyclopentadienyl ligands obsolete. For $[Cp_2Ti]^+$, THF is superior to the strongly coordinating CH_3CN, which inhibits epoxide binding. Solvent coordination to titanium can thus affect the overall rate of electron transfer to substrate.[9]

Keywords: cyclic voltammetry · electron transfer · homogeneous catalysis · radical reactions · titanium

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