Radical Chemistry

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Catalytic, Atom-Economical Radical Arylation of Epoxides**

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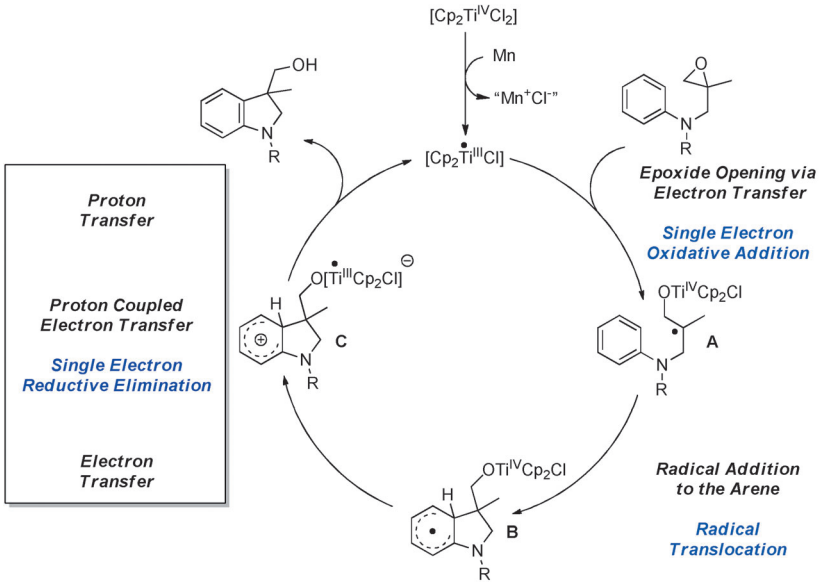
The development of efficient catalytic reactions is one of the central aspects of chemistry and arguably the most important for the invention of novel sustainable processes.[1] Radical-based transformations are among the most attractive methods for use in catalytic cycles owing to the ease of radical generation, high functional group tolerance, and selectivity in C–C bond formation.[2]

Herein we present such a process, an atom-economical titanocene-catalyzed[3] intramolecular arylation of epoxide-derived radicals. Our approach exploits the innate capability of the titanocene(III)/(IV) redox couple to undergo reversible electron-transfer reactions.[4] This allows the implementation of both oxidative additions and reductive eliminations in single-electron steps into catalytic cycles. The key step of our method is presumed to be a proton-coupled electron transfer (PCET).[5] It constitutes the pivotal single-electron reductive elimination, provides the driving force for efficient rearomatization of the radical σ-complex, and negates the need for sacrificial co-reductants or oxidants necessary in radical-based chain processes or catalytic reactions.[6] This issue is critical in Minisci reactions,[7] radical additions to electron deficient heteroarenes, which often require stoichiometric amounts of metal (Fe, Ag) salts and oxidants (H_2O_2 or organic peroxides). More recently, significant progress towards more sustainable radical arylation has been reported by Heinrich et al.[8] In these reactions, aryl diazonium salts are employed as radical precursors. Nevertheless, titanium trichloride has to be employed in stoichiometric amounts for radical generation in rather acidic media (aqueous HCl).

Our catalytic cycle is shown in Scheme 1. It is initiated by the single-electron oxidative addition of $[Cp_2TiCl]$ to the substrate generating radical intermediate **A**. Addition of the



Scheme 1. Proposed catalytic cycle. Cp = cyclopentadienyl, M = metal.

radical to the pendant arene produces the pivotal radical σ-complex **B** in the radical translocation step. The single-electron reductive elimination of $[Cp_2TiCl]$ can be accomplished by an electron transfer from the arene **B** to the titanocene to form **C**. Subsequent proton transfer to the titanocene(III)-bound alkoxy group yields product and catalyst. As a consequence, the catalytic cycle is completely atom-economical and does not require the use of stoichiometric amounts of an external acid for the protonation of a Ti–O bond, or a source (such as O_2) for the oxidation of **B** to the cationic σ complex, and in principle requires only the amount of a metal powder necessary for the initial reduction of the precatalyst $[Cp_2TiCl_2]$.[9]

With 10 mol% **3**, complete conversion of **1a** to **2a** was realized in refluxing THF after 30 min and was isolated in 98% yield (Scheme 2). This result clearly demonstrates that neither an external oxidant nor an acid are necessary for turnover. Manganese is only required for the generation of the active catalyst, as without $[Cp_2TiCl_2]$ no reaction takes place. However, catalyst loading is still rather high. To overcome this limitation, the influence of the reaction

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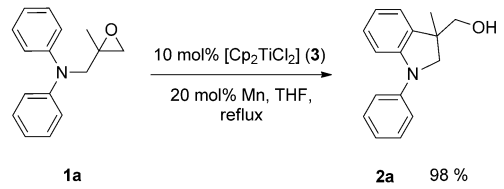
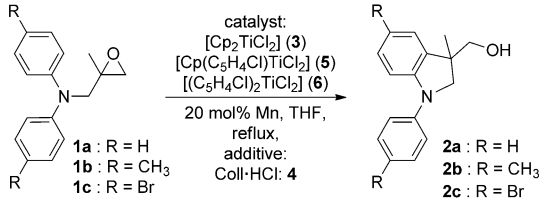


Scheme 2. Atom-economical aromatic substitution with **1a**.

conditions and additives on the performance of the catalyst was investigated, as summarized in Table 1.

Decreasing catalyst loading to 5 mol% **3** resulted in incomplete conversion. Addition of **4** has a dramatic effect on the reaction. The complete conversion of **1a** to **2a** can be

Table 1: Atom-economical catalytic radical aromatic substitution.[a]



Substr.	Mol%, cat.	Mol% **4**	*t*	**1**/**2**	Yield [%]
1a	10, **3**	–	30 min	0:100	98[b]
1a	5, **3**	–	30 min	25:75[b]	–
1a	5, **3**	10	30 min	0:100[b]	–
1a	1, **3**[c]	5	2 h	0:100	96[d]
1b	1, **3**[c]	5	2 h	0:100	91[d]
1c	10, **3**	–	30 min	87:13[e]	–
1c	5, **6**	–	30 min	40:60[e]	–
1c	5, **5**	20	2 h	0:100	92[e]
1c	5, **6**	20	2 h	0:100	93[e]

[a] Sub. = substrate, Coll·HCl = 2,4,6-Me_3Py·HCl (**4**). All concentrations refer to **1**. [b] 0.1 M. [c] 10 mol% Mn. [d] 0.5 M. [e] 0.03 M.

achieved with as little as 1 mol% **3**, 5 mol% of **4**, and 10 mol% of Mn. The yield of isolated **2a** was 96%. Thus, Mn-reduced **3** in combination with **4** constitutes a highly efficient catalytic system for the conversion of **1a** to **2a**. The same results were obtained when excess manganese powder was filtered off. The most practical way of carrying out the reaction is by the addition of substrate, precatalyst, and a slight excess manganese dust to THF and refluxing the mixture until starting material is consumed. Neither $MnCl_2$, the protic acid 2,4,6-trimethylpyridinium hydrochloride (Coll·HCl; **4**), nor Cp_2TiCl_2 initiate the reaction on their own. Therefore, a highly unlikely cationic epoxide opening can be ruled out.

Epoxide **1b** with two *p*-methyl substituents also constitutes an excellent substrate. The yield of isolated **2b** under identical conditions as for **1a** was 91%. Substrate **1c** does not constitute a suitable substrate for **3**. Because the oxidative addition to epoxides is usually unproblematic, we reasoned that for **1c** the radical transfer to convert **B** to **C** is critical. In this case, titanocene catalysts that are better oxidants than $[Cp_2TiCl_2]$ should be superior catalysts. Such a redox tuning is straightforward to achieve by introducing electron-withdrawing substitutents to the cyclopentadienyl ligands. Indeed, the chloro-substituted complexes $[(C_5H_4Cl)CpTiCl_2]$ (**5**) and $[(C_5H_4Cl)_2TiCl_2]$ (**6**) turned out to be efficient catalysts, resulting in complete conversion of **1c** to **2c** with 5 mol% catalyst after 2 h and high yields of isolated **2c** (92% and 93%). Compared to $[Cp_2TiCl]$, the oxidation potential of $[(C_5H_4Cl)CpTiCl]$ is 120 mV more positive and the oxidation potential of $[(C_5H_4Cl)_2TiCl]$ is 290 mV more positive. Thus, the relatively small change in the redox potential of **5** is already sufficient for a significant improvement of the yield of **2c**. It is clear, however, that for even more difficult substrates the use of **6** will be highly attractive. Addition of **4** improves the performance of the reaction further and reduction of catalyst loading to 5 mol% is possible for both **5** and **6**.

To explore the mechanism and role of catalyst, reaction-progress kinetic analysis (RPKA) experiments were performed.[10,11] Ideally, the concentration of the catalyst remains constant over the course of the reaction. The deactivation of the catalyst, if any, occurring during the course of the reaction can be determined through "same excess" experiments. Runs 1 and 2 are set up so that run 2 starts with concentrations at 50% of run 1. Lack of overlay shows deactivation of catalyst under reaction conditions (Figure 1). Furthermore, an induction period owing to the reduction of **3** by manganese dust was observed. To activate the metal, **4** was added and the induction period was shortened significantly (see Supporting

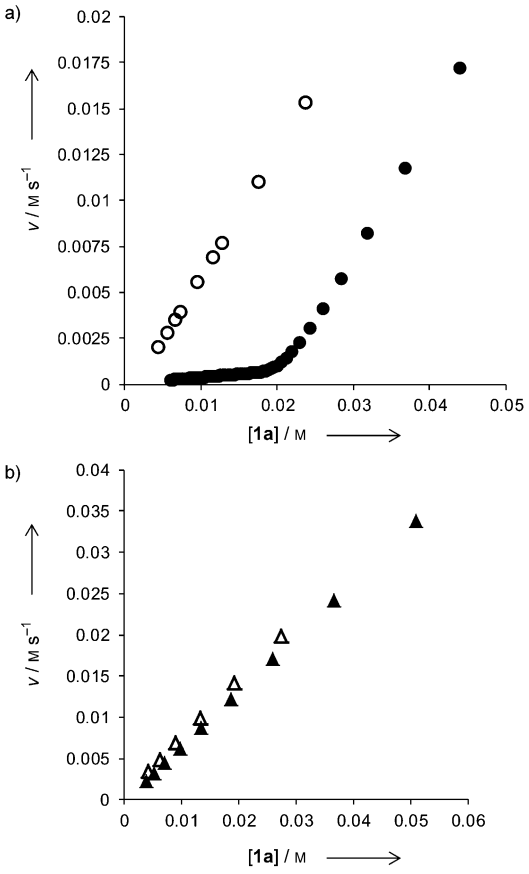


Figure 1. Rate vs. concentration of epoxide for same-excess experiments with and without Coll·HCl. a) Run 1 at 100%, no Coll·HCl (●), run 2 at 50%, no Coll·HCl (○). b) Run 3 at 100% with Coll·HCl (▼), and run 4 at 50% with Coll·HCl (△).

Information). Moreover, same excess experiments containing a twofold excess of Coll·HCl (based on $[Cp_2TiCl]$) showed that the acid also facilitated turnover. The same excess kinetic runs 3 and 4 show overlay that is consistent with constant concentration of catalyst.

The role of Coll·HCl for catalyst stability cannot be solely tied to proton transfer as it is employed in substoichiometric amounts. To further explore the role of Coll·HCl, cyclic voltammetry (CV) was employed. The cyclic voltammogram of Mn-reduced **3** exhibited peaks corresponding to the $[(Cp_2TiCl)_2]/[Cp_2TiCl]$ couple and $[Cp_2Ti]^+$ that is formed in a follow-up reaction during the sweep.[12] Upon addition of **4**, a new oxidation wave at −1.25 V appears that is due to $[Cp_2TiCl_2]^-$, a species that is well-known to be incapable of opening epoxides.[12] Additionally, the generation of $[Cp_2Ti]^+$ is completely suppressed. Thus, the addition of **4** to Mn-reduced **3** results in an equilibrium between $[(Cp_2TiCl)_2]$, $[Cp_2TiCl]$, and $[Cp_2TiCl_2]^-$. Usually, addition of chloride salts to solutions of Cp_2TiCl results in the exclusive formation of $[Cp_2TiCl_2]^-$ (Figure 2).

To further examine the role of **4**, DFT calculations were carried out using Gausian 03.[13] Geometry optimization of all structures were performed employing a B3LYP[14,15] functional and the def2-TZVP basis set.[16] Interestingly, the calculations revealed formation of a complex between the hydrochloride salt and the Ti^{III} center that is 9.8 kcal mol^{-1} more stable than the individual components after the zero-point vibrational energy corrections (see the Supporting Information). Taken together, CV and calculations suggest that **4** stabilizes the catalyst through a unique hydrogen bonding interaction.

At first sight, it seems paradoxical that a reduction of the concentration of the active catalyst results in more efficient reactions. However, our data clearly show that the decomposition of $[(Cp_2TiCl)_2]/[Cp_2TiCl]$ at elevated temperatures is prevented by the accessibility of the $[Cp_2TiCl_2]^-$ resting state of the catalyst.[17] As a consequence, the use of **4** as additive provides an attractive opportunity for lowering catalyst loading.

To further examine the scope of the reaction, examples of the aromatic substitution catalyzed by **4** are summarized in Table 2. Five- and six-membered, and even strained ring systems (entries 2 and 6) can be readily prepared in high yields and short reaction times. The control of diastereoselectivity (entry 7) was excellent. Moreover, a number of functional groups can be incorporated. It is especially noteworthy that with catalyst **6**, even electron-withdrawing esters

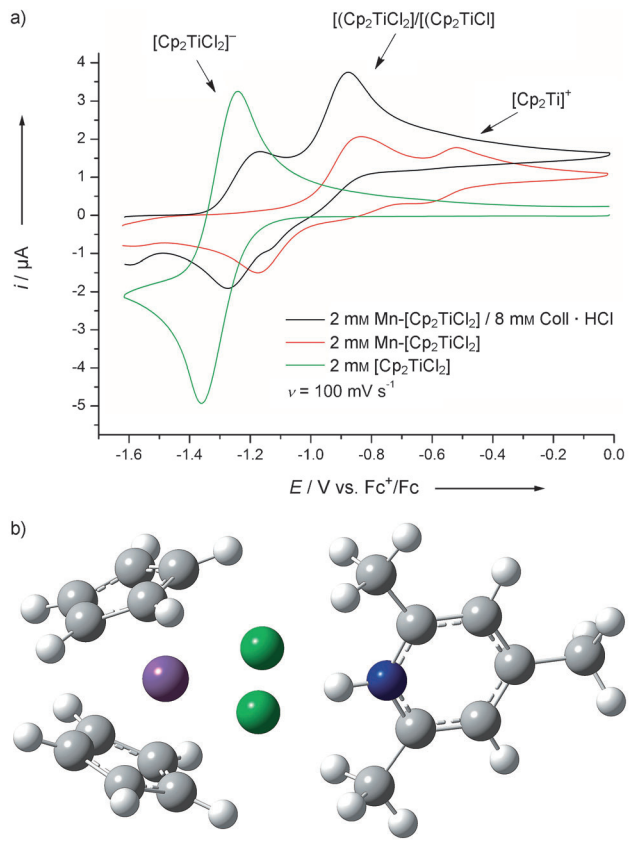
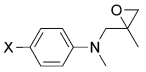
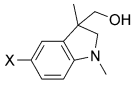
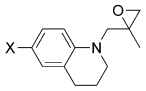
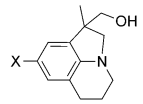
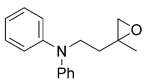
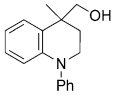
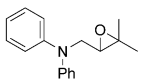
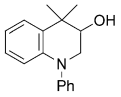
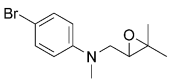
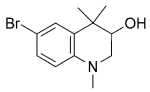
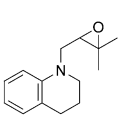
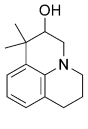
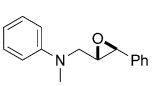
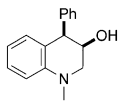


Figure 2. a) Cyclic voltammograms showing the impact of **4** on titanium-based intermediates present during redox process. Fc = ferrocene. b) Calculated gas-phase complex between **3** and **4** (Ti purple, Cl green, N blue, C gray, H white).

Table 2: Scope of the atom-economical catalytic aromatic substitution by radicals with 5 mol% of catalyst **6** and 20 mol% **4**.

Entry	Substrate	t [h]	Product [%]
1	 X= Cl (**7**); Br (**9**); CO_2Me (**11**)	2	 X= Cl (**8**), 91%; Br (**10**), 92%; CO_2Me (**12**), 77%
2	 X= H (**13**); Br (**15**); CN (**17**)	2	 X= H (**14**), 70 %; Br (**16**), 81%; CN (**18**), 72%
3	 **19**	1	 **20**, 93%
4	 **21**	1	 **22**, 94%
5	 **23**	1	 **24**, 83%
6	 **25**	2	 **26**, 84%
7	 **27**	2	 **28**, 82%

and nitriles that render the critical PCET more difficult are tolerated.

The application of homolytic aromatic substitution is experiencing a renaissance in synthetic organic chemistry because this approach provides a useful and potentially much milder alternative to classical electrophilic aromatic substitution. Recently, several groups have described the construction of biaryl compounds with the assistance of organocatalysts.[18] A recent essay presented evidence from literature precedent showing that these reactions most likely proceed through base-mediated homolytic aromatic substitution.[19] The distinguishing feature of base-mediated homolytic aromatic substitution is that the reaction proceeds through a radical chain mechanism. This inevitably necessitates the stoichiometric use of reagents for radical generation or the deprotonation of σ complexes.

The unique characteristic of the process presented herein is the catalytic role of titanium(III). Its regeneration by an intramolecular electron transfer–proton transfer mechanism negates the necessity to employ stoichiometric reagents other than the substrate. Moreover, this allows a tailoring of the reactivity of the catalyst by careful choice of the substitution pattern of the cyclopentadienyl ligands.

In summary, we have described a conceptually novel approach to conduct catalytic reactions by employing oxidative additions and reductive eliminations in single electron steps. The success of the radical aromatic substitution is critically dependent on a mechanism based approach for tuning the stability and electronic properties of the catalyst. We are currently examining intermolecular reactions and additions initiated through single electron reduction of other functional groups to fully explore the breadth and scope of the reaction. The results of these studies will be presented in due course.

Experimental Section

Epoxide **1a** (956 mg, 4 mmol, 1 equiv), catalyst **3** (10 mg, 40 μmol, 1.00 mol%), Coll·HCl (31.9 mg, 0.202 mmol, 5.1 mol%), and manganese (21.9 mg, 0.399 mmol, 0.1 equiv) were placed in an oven-dried Schlenk flask. THF (5 mL) was added, and the mixture was refluxed under an argon atmosphere for two hours. Chromatography (Alox; eluent cyclohexane/ethyl acetate/triethylamine 80:20:0.01) gave 915.5 mg (96%) of **2a**.

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