CHEMISTRY A European Journal



Accepted Article Title: Cp2TiX Complexes for Sustainable Catalysis in Single Electron Steps Authors: Andreas Gansäuer, Ruben Benedikt Richrath, Theresa Olyschläger, Sven Hildebrandt, Daniel G Enny, Godfred D Fianu, and Robert A Flowers II This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201705707

Link to VoR: http://dx.doi.org/10.1002/chem.201705707

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Cp₂TiX Complexes for Sustainable Catalysis in Single Electron Steps

Ruben B. Richrath,^[a] Theresa Olyschläger,^[a] Sven Hildebrandt,^[a] Daniel G. Enny,^[b] Godfred D. Fianu,^[b] Robert A. Flowers II,^{*[b]} and Andreas Gansäuer^{*[a]}

Abstract: We present a combined electrochemical, kinetic, and synthetic study with a novel and easily accessible class of titanocene catalysts for catalysis in single electron steps. The tailoring of the electronic properties of our Cp_2TiX -catalysts that are prepared in situ from readily available Cp_2TiX_2 is achieved by varying the anionic ligand X. Of the complexes investigated, Cp_2TiOMs proved to be either equal or substantially superior to the best catalysts developed earlier. The kinetic and thermodynamic properties pertinent to catalysis have been determined. They allow a mechanistic understanding of the subtle interplay of properties required for an efficient oxidative addition and reduction. Therefore, our study highlights that efficient catalysts do not require the elaborate covalent modification of the cyclopentadienyl ligands.

Introduction

Chemical reactions involving carbon-centered radicals are highly attractive due to the mildness of their conditions, their high chemoselectivity, the ease of radical generation, and the ease of C-C bond formation.^[1,2] Traditionally, radical reactions are conducted as chain processes that proceed under substrate control. The alternative process of carrying out radical reactions via a transition metal catalyzed process under reagent control is less well established.^[3] However, it is highly appealing because the metal and its ligands can control radical generation, radical trapping, and radical translocation because the metal remains bound to the radical.

In order to be able to catalyze radical reactions, the metal complex must be able to shuttle between neighboring transition states efficiently. This implies that oxidative additions and reductive eliminations occur in single electron steps.^[4] The realization of this concept in titanocene(III) catalyzed reactions^[5] has been called

[a] R. B. Richrath, T. Olyschläger, S. Hildebrandt, Prof. Dr. A. Gansäuer Kekulé-Institut für Organische Chemie und Biochemie Universität Bonn Gerhard Domagk-Str. 1, D-53121 Bonn (Germany) E-mail: andreas.gansaeuer@uni-bonn.de
[b] D. G. Enny, G. D. Fianu, Prof. Dr. R. A. Flowers II Department of Chemistry Lehigh University Bethlehem, PA 18015 USA E-mail: rof2@lehigh.edu

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'catalysis in single electron steps'^[6] and 'metalloradical catalysis' in cobalt(II) catalyzed transformations.

In the latter case, Co(II) porphyrin complexes react with diazo compounds or azides to give Co(III) metalloradicals that are either carbon or nitrogen centered. These intermediates have been used in many reactions including cyclopropanations, aziridinations, and C-H bond aminations.^[7] The use of enantiomerically pure porphyrin ligands has led to highly enantioselective reactions.^[8]

With titanocene(III) complexes, epoxides were used as radical precursors in oxidative additions to generate β -titanoxy radicals.^[9] These intermediates have been used in atom-economical syntheses of polycyclic tetrahydrofurans^[3,6a,6b] and in atom-economical radical arylations^[10] via catalysis in single electron steps. In both cases, the reductive elimination is critical for catalytic turn-over (Scheme 1).



Scheme 1. Single electron reductive elimination as key-step in the titanocene catalyzed tetrahydrofuran synthesis and radical arylation.

In tetrahydrofuran synthesis, the reductive elimination can be regarded as an organometallic oxygen rebound. In the arylation, this step is composed of the 'back electron transfer' from the radical σ -complex followed by the protonation of the Ti-O bond or a proton coupled electron transfer (PCET).^[11] It is clear that for the

FULL PAPER

tetrahydrofuran synthesis and the radical arylation, the reductive elimination will be thermodynamically more favorable if the Ti(IV) is a stronger oxidant and, correspondingly, Ti(III) a weaker reductant. Quantitatively, these effects can be easily determined by measuring the redox potentials of the corresponding species by cyclic voltammetry (CV).

There are two ways of manipulating the redox properties of titanocene(III) and titanocene(IV) complexes. First, the introduction of substituents to cyclopentadienyl ligands significantly affects the redox potential of the titanocene complexes.^[12] The drawback of this powerful approach is that particular ligands have to be prepared for each complex and that the complexes require hydrochloride additives, such as Coll*HCI. Therefore, an efficient screening of a large variety of potential catalysts can be difficult. Second, the electronic properties can be altered by variation of the inorganic ligand. This approach has remained largely unexplored and has the potential advantage of using a single titanocene precursor for the preparation of a large variety of complexes. In this way, the properties of many potential catalysts can be screened in a fast and efficient manner. A first step in this direction has been the use of Cp₂TiOTf as catalyst in radical arylation reactions.^[13] The modification of the inorganic ligand from chloride to iodide or phenoxide has been shown to substantially improve the yields in titanocene catalyzed reductive umpolung reactions with nitriles as radical trap.^[5i,j]

Here, we give a full account of our investigation of the synthesis, electronic properties and catalytic performance of Cp_2TiX_2 and Cp_2TiX complexes (X = sulfonates and $O_2C_2F_3$). Thereby, we provide a toolbox for the development of efficient reaction conditions for catalysis in single electron steps. As a result, we identified new catalysts that are easily prepared and that display high activity, stability, and functional group tolerance in the absence of additives. They are therefore superior to and more sustainable than our earlier complexes.

Results and Discussion

Synthesis and Reduction of Cp₂TiX₂

For providing a general and high yielding approach to the desired Cp_2TiX_2 catalyst precursors, an efficient and flexible synthesis of these complexes from a readily available titanocene building block is important (Scheme 2).

The use of operationally simple and high yielding transformations and of easily accessible and cheap reagents is mandatory. The syntheses of Cp₂Ti(OTf)₂ highlight these issues.^[14a,b] Originally, the complex has been synthesized from Cp₂TiCl₂ and AgOTf via a chloride exchange.^[14a] This approach uses commercially available Cp₂TiCl₂ as the most attractive titanocene building block. As pointed out by Luinstra, the choice of solvent and the control of stoichiometry is critical. Therefore, the reaction of Cp₂TiMe₂ with TfOH was introduced as a more robust and simple alternative for the preparation of Cp₂Ti(OTf)₂.^[14b] Moreover, no Ag-salts have to be employed. Solutions of Cp₂TiMe₂ are commercially available or can be easily prepared from Cp₂TiCl₂ and 2 eq. of MeLi. We have synthesized complexes 2-6 by this strategy from Cp₂TiMe₂ and the corresponding acids in the indicated yields (Scheme 2). For applications in catalysis in single electron steps an easy in situ reduction of Cp₂Ti(IV)X₂ to the active Cp₂Ti(III)X is essential. Gratifyingly, complexes **4**, **5**, and **6** can be conveniently reduced at room temperature to Cp₂TiX in THF with Zn dust in less than 30 min.^[16] However, for **3**an extended time of about 90 min is required. The convenient and operationally simple Zn-reduction is inadequate for **2** because it requires more than 10h. The exact reasons for these differences remain unclear. We suggest that differences in the solubility of ZnX₂ are involved. Instead, for Cp₂Ti(OTf)₂ the reduction has to be carried out with NaBH₄.^[14b] Care has to be taken to avoid the formation of catalytically inactiveCp₂TiBH₄.

		MeLi Et ₂ O 40 min, rt	$HX = HX$ $HX = Et_2O$ $0 \ ^{\circ}C \text{ to rt}$	
	complex	нх	р <i>К</i> а (Н2О)	yield/[%]
	2 ^[14a,b]	HOTf	-20 ^[15a]	80
	3 ^[14c]	HOTs	-2.8 ^[15b]	88
	4 ^[14d]	HOMs	-1.9 ^[15c]	97
	5 ^[14e]	TFA	-0.2 ^[15d]	67
	6	CSA	2.2 ^[15e]	77

OTf = triflate, OTs = tosylate, OMs = mesylate, TFA = trifluoroacetate, CSA = camphorsulfonate.

Scheme 2. Modular two-step synthesis of Cp_2TiX_2 (2) - (6) from Cp_2TiCl_2 (1).

For an efficient catalytic turn-over in radical arylations with Cp_2TiX_2 -derived systems, it is essential to understand the composition of the catalytic system and the redox potentials of its components. Since no information is available on our Cp_2TiX_2/Cp_2TiX redox couples, we studied their redox properties and compositions in THF by cyclic voltammetry to provide the necessary information for the efficient design of reactions catalyzed by Cp_2TiX complexes.

Cyclic Voltammetry of Cp₂TiX₂ and Zn-Cp₂TiX₂

Cyclic voltammetry is ideally suited to identify compounds in mixtures of redox-active compounds, the study of their properties, and the kinetics of their reactions.^[17] The seminal studies of Daasbjerg have demonstrated that this is also the case for titanocene halides.^[18] Therefore, we decided to examine the Cp₂TiX₂-derived systems using this technique. Our investigation is divided into two parts. First, we determined the properties of electrochemically reduced Cp₂TiX₂. In this manner, the redox properties of [Cp₂TiX₂]⁻ and Cp₂TiX can be measured and it can

FULL PAPER

be established how easily X⁻ dissociates from [Cp₂TiX₂]⁻. Second, Zn-reduced Cp₂TiX₂ (Zn-Cp₂TiX₂) was analyzed. In this fashion, it can be shown if Cp₂TiX dimerizes in solution and how easily Cp₂Ti⁺, an attractive catalyst in its own right especially for those substrates which suffer from a slow 'electron-back transfer' (Scheme 1, lower image), can be formed from Cp₂TiX in THF.

Electrochemically reduced Cp₂TiX₂

The electrochemically reduced complexes allow the investigation of the E_qC_r scheme shown in Scheme 3 as a function of X.^[19]In this way, the peak potentials of $[Cp_2TiX_2]^-$ and Cp_2TiX that are both pertinent to catalysis can be measured. Moreover, information about the position of the equilibrium can be obtained. In the case of Cp_2TiCl -based systems, this equilibrium is essential for the stability of the catalytic system by providing the anionic titanocene(III) complex as a resting state for the catalyst.^[12]



Scheme 3. E_qC_r -scheme for the electrochemical reduction of Cp_2TiX_2 , (E_q = quasi-reversible electrochemical reduction, C_r = reversible chemical reaction).

Changing the anionic ligands in our readily accessible Cp_2TiX_2 complexes 2-6 should allow a straightforward modification of the redox properties of titanocene complexes and the dissociation of the anionic ligands from the metal center.



Figure 1. Cyclic voltammograms of 2 mM Cp₂TiX₂ (legend) recorded at a glassy carbon disk electrode with ν = 0.2 V s⁻¹ in 0.2 M Bu₄NPF₆/THF.

The formation of Cp₂TiX is more favorable for the less nucleophilic tosylate than for mesylate. However, steric effects are also very important for the formation of Cp₂TiX. With the bulky camphorsulfonate the loss of the anionic ligand is even more advantageous than for OTs⁻. Interestingly, even for the bidentate trifluoroacetate that should also be the most nucleophilic anion investigated some Cp₂TiX is formed.

The relevant peak potentials of the species observable in the voltammograms are summarized in Table 1. We found that under our conditions the potentials are reproducible within a margin of 0.02 V. Curiously, the highest potential ($E_{p,c}$) for the reduction of Cp_2TiX_2 is that of $Cp_2Ti(OTs)_2$ (3) and not that of $Cp_2Ti(OTf)_2$ (2). Complex 5 is most difficult to reduce. Since 4 and 6 have essentially the same potentials, the steric demand of the ligand has no appreciable effect on the redox properties.

For Cp₂TiOTf a peak potential of -0.31 V was measured on the oxidative sweep (Figure 1, pink voltammogram) that is generally associated with the generation of Cp₂Ti⁺.^[12,13,20] Therefore, OTf can dissociate from Ti even in THF without the aid of a Lewis acid. It is noteworthy, that the cationic species Cp₂Ti⁺ is not generated during the sweep by a so called parent-child reaction since the oxidation current of Cp₂Ti⁺ does not decrease significantly upon increasing the sweep rate, which is otherwise indicative for this reaction. The other peak potentials (E_{p,a1}) corresponding to the oxidation of [Cp₂TiX₂]⁻ follow the expected trend. The least coordinating anion OTs⁻ results in the most difficult oxidation, whereas the trifluoroacetate complex with the most nucleophilic anion has the most negative potential. As for the E_{p,a1} the E_{p,c} value is, within experimental error, not affected by the steric bulk of the ligand.

Table 1. CV data for the reduction of Cp₂TiX₂ (**1–6**) in THF in terms of peak potentials for the cathodic wave (E_{p,c}) and the two anodic waves (E_{p,a1} and E_{p,a2}) recorded at a glassy carbon disk electrode in 0.2 M Bu₄NPF₆/THF at a sweep rate of 0.2 Vs⁻¹.^[a]

	complex	E _{p,c} /V	E _{p,a1} /V	E _{p,a2} /V	
	1, X = Cl	-1.37 ^[b]	-1.23 ^[b]	_[b]	
	2 , X = OTf	-1.05	-0.31	-	
	3 , X = OTs	-0.96	-0.81	-0.70	
	4 , X = OMs	-1.03	-0.92	-0.62 ^[c]	
	5 , X = TFA	-1.08	-0.98	-0.58	
	6 , X = CSA	-1.05	-0.93	-0.64	

[a] All potentials are given in units of V vs. Fc⁺/Fc and can be converted to V vs. SCE by adding 0.52 V. [b] not visible at the sweep rates used here^[12] [c] Recorded at a sweep rate of 0.5 Vs⁻¹.

The second oxidation wave ($E_{p,a2}$) pertains to the oxidation of Cp_2TiX . We did not observe the formation of any dimers (Cp_2TiX)₂. Since the decomposition of Cp_2TiCl has been suggested to occur via its dimer^[10d] our catalysts should be stable without additives. Curiously, of all measured complexes $Cp_2Ti(OTs)$ (-0.70 V) is the strongest and $Cp_2Ti(O_2C_2F_3)$ (-0.58 V) the weakest reductant. To understand this difference quantitatively, an analysis of the solvation of Cp_2TiX and Cp_2TiX^+ is necessary. This is beyond the scope of this study. From these values, it is clear that just by varying the anionic ligand the values for $E_{p,c}$, $E_{p,a1}$, and $E_{p,a2}$ (except for $E_{p,a1}$ of **2** that pertains to Cp_2TiX_2 . Thus, it can be expected that these complexes show distinctly differing

FULL PAPER

reactivity in oxidative additions and reductive eliminations in single electron steps.

Zn reduced Cp₂TiX₂ (Zn-Cp₂TiX₂):

Typically, the Cp₂TiX complexes employed in catalytic radical arylations or tetrahydrofuran synthesis are prepared by reduction of Cp_2TiX_2 with Zn powder (Zn-Cp₂TiX₂).^[16] The presence of Zn²⁺ has a profound influence on the composition of Cp2TiCl2 based systems as they are able to abstract Cl⁻ from [Cp₂TiCl₂]⁻ to generate the catalytically active Cp2TiCl. For our complexes 3 -6, Cp₂TiX and no [Cp₂TiX₂]⁻ could be detected. Their voltammograms are shown in the upper part of Figure 2. In case of 5 only one oxidation peak is observable at -0.48 V that can be assigned to the neutral Cp₂Ti(O₂C₂F₃). For 4 a second oxidation wave at -0.19 V was observed that is owing to Cp2Ti⁺. The difference of the oxidation potential pertaining to Cp2Ti⁺ derived from Cp₂Ti(OTf)₂ is due to the lower sweep rate which effects the peak potential of the wave (Table 1, entry 2). Also, the different reaction conditions for the preparation of (Zn-Cp₂Ti(OTs)₂) and the in situ electrochemical reduction of the catalyst (Cp₂Ti(OTf)₂) might have a minor effect on the peak potential. The situation is less clear-cut for 3 and 6. The second oxidation waves cannot originate from Cp2Ti⁺. We suggest that they are due to Cp₂TiX*ZnX₂ because of their potentials of -0.40 V (for 3) and -0.37 V (for 6) that demonstrate that they are less electron deficient than Cp₂Ti⁺ but more electron deficient than Cp₂TiX.



Figure 2. [a] CVs of Zn-2 to Zn-6 recorded at a sweep rate of 0.2 Vs⁻¹ in 0.2 M Bu_4NPF_6/THF (upper image) and [b] segments of the oxidation wave of Zn-3 at sweep rates of 0.2, 1.0 and 2.0 Vs⁻¹.

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In the lower images of Figure 2, three segments of the oxidation wave of Zn-3 at sweep rates of 0.2, 1.0, and 2.0 Vs⁻¹ are shown. At the lowest sweep rate of 0.2 Vs⁻¹ no Cp_2Ti^+ was observed. At the higher sweep rates of 1.0 and 2.0 Vs⁻¹ the oxidation wave of Cp₂Ti⁺ at -0.19 V is detectable. Its intensity increases with higher sweep rate. Moreover, the oxidation wave pertinent to Cp₂TiOTs*Zn(OTs)₂ is present in all voltammograms but loses intensity at higher sweep rates. Based on the fact, that cyclic voltammetry is a dynamic technique, at low sweep rates the component that is easier to oxidize is detected with an oxidation wave of higher intensity. In our case, the relevant equilibrium for Zn-3 is that between Cp₂TiOTs*Zn(OTs)₂ and Cp₂Ti⁺ together with the solvent separated anion [Zn(OTs)₃]⁻. At higher sweep rates, the complexation is outrun and the detection of Cp2Ti+ becomes possible. The precise composition of the solution content could be determined if sufficiently high sweep rates are employed to decrease the time scale of the experiment and hence to outrun follow-up reactions. Unfortunately, this is not possible with the ordinary microelectrodes used here.

Kinetic Investigation of Zn-2 - Zn-6

Table 2. Rate constant for epoxide opening with Cp_2TiX_2 .

	•Ph 7 (20-50 mM)	Cp ₂ TiX ₂ Zn,THF 20 °C		Ph
Entry	Cp ₂ TiX ₂		Rate Constant, M ⁻¹ s ⁻¹	Epoxide order
1	1 ^[a] , X = Cl		1.1 ± 0.1	1.0 ± 0.1
2	$2^{[b]}, X = OTf$		0.0035 ± 0.0003	1.1 ± 0.1
3	3 , X = OTs		0.022 ± 0.005	1.1 ± 0.2
4	4 , X = OMs		0.013 ± 0.003	1.3 ± 0.2
5	5 , X = TFA		0.019 ± 0.005	0.9 ± 0.2
6	6 , X = CSA		0.019 ± 0.005	1.0 ± 0.3

 $[Cp_2TiX_2] = 2 \text{ mM}; [Zn] = 16 \text{ mM}; \text{THF} = 3 \text{ mL}; \lambda_{max} \text{ for } [Ti(III)] \text{ is } 675 \text{ nm}; [Ti(III)] \text{ solutions were filtered before commencing runs;}^{[a]} 4 \text{ mM Coll}^{+}\text{HCl added}; [Mn] = 8 \text{ mM}; \lambda_{max} \text{ for } [Ti(III)] \text{ is } 800 \text{ nm} {}^{[b]} [NaBH_4] = 2 \text{ mM}; 4-10 \text{ mM CHD added}; \lambda_{max} \text{ for } [Ti(III)] \text{ is } 800 \text{ nm}.$

The impact of ligands on the activity of titanocene(III) complexes was further investigated by measuring the rate constants for opening epoxide 7 (Table 2). The epoxide opening experiment was performed under pseudo-first order conditions and the rate constants were obtained by monitoring the decay of the active titanocene(III) band via UV-vis spectroscopy (See Supporting Information for details). The order for epoxide 7 was also determined to ensure the mechanism for the epoxide opening reactions with the different titanocene(III) complexes were similar. All experiments were repeated twice to ensure reproducibility of results. The rate constant for opening 7 was highest with the traditional Cp₂TiCl, which had to be performed in the presence of Coll*HCI to obtain a stable catalyst. Conversely, the rate constant for opening 7 was the lowest with Cp2TiOTf, the most Lewis acidic and least reducing titanocene(III) complex in this study (Table 1, entry 2).

FULL PAPER



Figure 3. Time-adjusted decay plots for 100% and 50% runs with $Zn-Cp_2TiX_2$ as catalyst. Reaction conditions: **100% Runs**; [Epoxide] = 56 mM; [Cp_2TiX_2] = 5.5 mM; [Zn] = 11 mM; THF = 15 mL; T = 60 °C; **50% Runs**; [Epoxide] = 28 mM; [Cp_2TiX_2] = 5.5 mM; [Zn] = 11 mM; THF = 15 mL; T = 60 °C.

With the newly generated titanocene(III) complexes (3 - 6), the reactions were done in the absence of salt additives and the rate constants for opening **7** where within the same order of magnitude. The rate constant for opening **7** with Zn-**3** as the catalyst was slightly higher, followed by Zn-**5** and Zn-**6**, whose rate constants were identical. Zn-**4** recorded the lowest rate constant for the newly synthesized titanocene complexes. It could however be argued that the rate constants for opening epoxide **7** are within error uncertainty for the newly generated titanocene complexes. Moreover, these titanocene catalysts are faster than Cp₂TiOTf at opening **7**.

To demonstrate the stability of the newly generated catalysts (Zn-3 to Zn-6) in the absence of a salt additive predicted by CV we studied the unimolecular arylation of 8S to 8P (Figure 3). To this end, two separate reactions were carried out with the same catalyst under identical conditions, with the only difference being that one reaction starts with 50% of the reactant concentration. The principle behind this technique is that if the stoichiometry of the reactants during the reaction is known and there is no substrate or product inhibition, the catalyst concentration should remain constant throughout the reaction. Under ideal conditions, 8S is consumed, 8P is formed and [titanocene] is constant. A second reaction that was started under conditions that correspond to 50% conversion of the first reaction should follow the reaction profile of the first reaction as long as [titanocene] is constant. In other words, a graphical overlay will be observed for a time-resolved plot of the reactant decay over time for both experiments if the catalyst is stable.^[21] The titanocene(III) complexes 3-6 efficiently catalyzed the radical arylation of 8S to 8P, and were stable without a salt additive as shown in the results obtained from the catalyst stability tests (Figure 3). The reaction progress was monitored via in situ IR spectroscopy. Thus, catalyst generation by mixing of Cp₂TiX₂ and Zn is both straightforward to carry out and more sustainable than for the earlier systems.

Performance of Zn-2 – Zn-6 in Catalysis in Single Electron Steps

Radical arylation of epoxides

We have previously shown that in the arylation of epoxide derived radicals, the 'back-electron transfer' or the proton coupled electron transfer and, therefore, the reductive elimination is the turn-over limiting step.^[10d] It is crucial to employ a catalyst with electronic properties facilitating the electron transfer from the arene to the Ti(IV)-center in order to regenerate the active catalyst and furnish the desired product (Scheme 1). If the catalyst's electronic properties are not adequately adjusted, this may lead to catalyst decomposition and even to the failure of the arylation. The reactions of **9S** highlight this point (Scheme 4).

Br 9S C ₆ H,	$\frac{Cp_2TiX_2}{Zn, 2 h}$	Br	N С ₆ H ₄ Br
	mol% catalyst	yield / [%]	
	10% 1 , X = CI	13 ^[a]	
	5% 3 , X = OTs	87	
	5% 4 , X = OMs	90	
	5% 5 , X = TFA	96	
	5% 6 , X = CSA	77	
	[a] Mn-red	uced	

Scheme 4. Performance of $Zn-Cp_2TiX_2$ in the radical arylation of 9S.

The two electron-withdrawing substituents render the 'backelectron transfer' too unfavorable to allow good results with Cp_2TiCl_2 as precatalyst. Our catalysts **3** – **6** give very good results with 7S when the Zn-reduction and arylation are carried out in refluxing THF for 2 h. Complexes 4 and 6 give similar yields than our 'best' catalysts (C₅H₄Cl)₂TiCl₂and **2**.^[10a,10d] However, our new catalysts are easier to prepare by Zn-reduction and do not require an additive (Coll*HCl for (C5H4Cl)2TiCl2).To check if shorter reaction times are possible, we investigated the reactions of8Sthat is a very good substrate for the radical arylation next (Scheme 5). Only with 5 we obtained a very good yield (90%) of 8P. Complex 4 was less active but still gave a good yield of 77%. However, 3 and 6 gave only a low conversion to the product. Because of their satisfying performance in the reactions of 7S and 8S, we decided to use 4 and 5 for a set of substrates to define their scope (Scheme 6).

FULL PAPER



Scheme 5. Performance of Zn-Cp₂TiX₂ in the radical arylation of 8S.

For the indolines and tetrahydroquinoline products 10P-13P yields in the range of 90% were obtained with both 4 and 5. For these substrates 2 gave similar yields and, therefore, our new catalysts 4 and 5 are at least as active and stable as the formerly best catalyst.

Compared to 8P and 10P-13P, the pyrrole 14P was obtained in a lower yield of 71% with 4. Presumably, this is due to the sensitivity of 14S to Lewis-acids. However, 4 is superior to 2 that resulted in a 67% yield of 14P.^[22]



Scheme 6. Performance of Zn-Cp₂Ti(OMs)₂ 4 and Zn-Cp₂Ti(TFA)₂ 5 in the radical arylation with various substrates. Conditions: THF, reflux, 2 h - 5 h.

Epoxides **15S** and **16S** are substrates that are more critical. The tricyclic core of **15P** is fairly strained and therefore an efficient back electron transfer is mandatory to a high yield of **15P**. Moreover, **15P** is somewhat sensitive to Lewis-acids and, therefore, a too Lewis-acidic catalyst will result in product decomposition. Complex **4** is the best compromise between both requirements and results in higher yields of **15P** than **2** (77%) or $(C_5H_4Cl)_2TiCl_2$ (70%).^[10a,10d]

The issue of the Lewis-acidity of the catalyst is even more important for carbamate substrates. The FMOC-protected **16S** is not suitable for reactions with $Cp_2Ti(OTf)_2$ (**2**) because of Lewis-acid induced intramolecular epoxide opening reactions by the carbamate. However, **4** gave a satisfactory yield of **16P** with 10 or 20 mol% of the catalyst. The higher loading can be rationalized

by a strong binding of the catalyst to the polar carbamate that inhibits binding of the epoxide and, therefore, leads to a slower epoxide opening.



Scheme 7. Performance of Zn-Cp₂TiX₂ in the radical arylation of 15S and 16S.

Thus, Zn-Cp₂Ti(OMs)₂ (Zn-4) is to date the best catalytic system for the radical arylation of epoxides. It is as active as the Cp₂Ti(OTf)₂-derived systems but does not lead to Lewis-acid induced side reactions and is more active than Zn-(C₅H₄Cl)₂TiCl₂ without inducing undesired side-reactions.

Synthesis of polycyclic tetrahydrofurans

The titanocene catalyzed synthesis of polycyclic tetrahydrofurans is another reaction that proceeds via catalysis in single electron steps.^[3]As in the radical arylation, the reductive elimination (Scheme 1) that proceeds via a homolytic substitution is the critical step of the catalytic cycle. The reductive elimination that may be regarded as an organometallic oxygen rebound will be favored when using more electron deficient titanocenes. We have previously shown that Zn-(C₅H₄CO₂Et)CpTiCl₂ is higher yielding catalytic system than Zn-Cp₂TiCl₂ (1) because the reductive elimination proceeds more efficiently with a catalyst containing the electron withdrawing ester substituted cyclopentadienyl

10.1002/chem.201705707

FULL PAPER

ligand.^[3]It should be noted that $(C_5H_4CO_2Et)CpTiCl_2$ has to be synthesized from the somewhat sensitive precursor $CpTiCl_3$ and the ester substituted cyclopentadiene.

Our Cp₂TiX₂derived systems are ideally suited for probing the influence of the electronic properties of the catalyst on the reductive elimination and on the overall performance of the reaction. The investigations with **17S** and the catalysts **2** – **6** are summarized in Scheme 8.



[a] Mn, 0.5 eq. Coll*HCl, [b] NaBH₄-reduced

Scheme 8. Zn-Cp₂TiX₂catalyzed tetrahydrofuran synthesis from 17S.

Of the catalyst, Zn-**3** gave the lowest yield of **17P** whereas NaBH₄reduced **2**, Zn-**5**, and Zn-**6** resulted in a similar outcome of the reaction (71%-75%). However, the use of **2** is practically disadvantageous because it leads in the formation of THF polymers that are difficult to remove. By far the best result was obtained with Zn-**4**. A high yield of 87% of **17P** was obtained. No side-products were detected and the catalyst did not initiate THF polymerization. Thus, Zn-**4** is also the most efficient catalyst for the formation of **17P**.

Finally, we studied the performance of our catalysts with **18S**. This reaction is challenging for two reasons. First, the reductive elimination is significantly more difficult because a stabilized benzylic radical is consumed in tetrahydrofuran formation rather than an alkyl radical as for **17S**.^[3,6b] Second, **18P** is sensitive to acidic conditions because a stabilized benzylic cation is formed after acid-induced ring opening.

As shown in Scheme 9, only Zn-4 and Zn-6 lead to reasonable conversion and to good yields of **18P**. The reaction had to be carried out at room temperature to avoid decomposition of **18P**. NaBH₄-2 and Zn-3lead to extensive decomposition presumably because of their Lewis-acidity. Zn-5 resulted in a low conversion to about 40% of **18P**. Zn-1 (17% **18P**)^[6b] and the currently best catalyst for tetrahydrofuran synthesis Zn-(C₅H₄CO₂Et)CpTiCl₂ (40% **18P**)^[3] give distinctly inferior results and require Coll*HCl (50 mol%) as additive.



Scheme 9. Performance of $Zn-Cp_2TiX_2$ in the synthesis of the benzylic tetrahydrofuran synthesis 18P.

Conclusions

In summary, with Zn-Cp₂Ti(OMs)₂ (Zn-4)we have discovered a highly active and stable catalytic system with a high functional group tolerance for the atom-economical arylation of epoxidederived radicals and for the atom-economical synthesis of polycyclic tetrahydrofurans. The straightforward synthesis of Cp₂Ti(OMs)₂from Cp₂TiCl₂ in two steps and the easy generation of Zn-4that requires no additives add to the sustainability of the catalytic reactions. By our approach of tailoring the electronic properties of titanocene complexes Cp₂TiX₂ by varying the anionic ligand X renders the more tedious method of covalently modifying the cyclopentadienyl ligands superfluous.

Catalyst discovery was accomplished by a combined electrochemical, kinetic and synthetic study that delineates the critical properties of an active and stable catalyst. The combination of these complementary methods is unique in providing a mechanism-based platform for efficient catalyst design that will also be useful in other systems of catalysis in single electron steps.

Experimental Section

Representative procedure: Substrate **9S** (199 mg, 0.5 mmol, 1 eq.), **5** (10.1 mg, 0.025 mmol, 5.0 mol%), and Zn (6.5 mg, 0.1 mmol, 0.2 eq.) were placed in an oven-dried Schlenk flask. THF (5 mL) was added, and the mixture was refluxed under an Ar atmosphere for two hours. The mixture was cooled to room temperature and filtered through a short pad of SiO₂with ethyl acetate (75 ml). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (SiO₂; cyclohexane/ethyl acetate 80:20) to give 193 mg (97%) of **9P**.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SFB 813 ,Chemistry at Spin Centers' and Ga 619/12-1), the Konrad-Adenauer-Stiftung (R. B. R.), the Evangelisches Studienwerk

FULL PAPER

Villigst (T. O.), the Jürgen Manchot Stiftung (S. H.) and the National Science Foundation (CHE-1123815 and CHE-1565741) for support of this work.

Keywords:arylation • catalysis • cyclic voltammetry • epoxides • kinetics • radicals

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FULL PAPER

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It's the inorganic ligand! With the aid of cyclic voltammetry and kinetic investigations Cp_2TiX_2 complexes with sulfonate ligands were identified as attractive catalysts in radical arylations and tetrahydrofuran synthesis. They do not require additives for catalyst stabilization and render the covalent modification of the cyclopentadienyl ligands for the tailoring of their performance in catalysis in single electron steps superfluous.



R. B. Richrath, T Olyschläger, S. Hildebrandt, D. G. Enny, G. D. Fianu, R.A. Flowers II,* A. Gansäuer*

Page No. – Page No.

Cp₂TiX Complexes for Sustainable Catalysis in Single Electron Steps