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Condition Screening for Sustainable Catalysis in Single-Electron Steps by Cyclic Voltammetry: Additives and Solvents

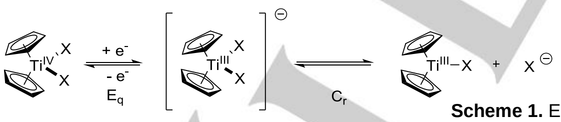
Theresa Liedtke,[+] Tobias Hilche,[+] Sven Klare,[+] and Andreas Gansäuer*

Abstract: Our cyclic voltammetry-based screening method for Cp_2TiX-catalyzed reactions is extended to the screening of other solvents for bulk electrolysis of the catalyst and radical arylation. It was found that CH_3CN is a solvent that can be used for both processes without additives. Furthermore, in THF, squaramide **L2** is more efficient than our previously best supramolecular halide binder, Schreiner's thiourea **L1**. The results extend the usefulness of our time and resource efficient screening method for the reaction design in catalysis in single-electron steps.

Introduction

Understanding the mechanism of a catalytic reaction and its key steps is an essential prerequisite for increasing product formation and developing more sustainable reaction conditions. We recently reported a cyclic voltammetry-based screening method for catalysis in single-electron steps[1,2] that enabled us to develop highly sustainable conditions for the arylation of epoxide-derived radicals by the exact knowledge and characterization of the catalytically active titanocene-species.[3] Our concept is based on the 'before' analysis of the nature and relative proportions of the catalytically active titanocene-species in solution[4] at various potential reaction conditions. The technique used to this end is cyclic voltammetry (CV).[5] Moreover, our CV analysis represents a minimum waste screening technique for the titanocene-catalyzed arylation reaction of epoxides[6] and potentially of other titanocene-catalyzed reactions.[7]

Our approach relies on the precise knowledge of the E_qC_r-mechanism[8] of the generation of the active catalyst Cp_2TiCl that is essential for a catalyst design and reaction condition screening by CV (Scheme 1).



Scheme 1. E_qC_r-Mechanism of the electrochemical reduction of titanocene complexes.

In particular, we have gained insight into the feasibility of the quasi-reversible electrochemical reduction of the titanocene complex (E_q) to the anionic $[Cp_2TiX_2]^-$ species which can undergo a reversible ligand dissociation (C_r) to form Cp_2TiX, the catalytically active species.[4] For efficient catalysis, a C_r-equilibrium shifted to Cp_2TiX is critical. In THF, this goal was achieved with the aid of thiourea-derived additives, especially Schreiner's thiourea **L1**.[9] Thioureas are well known H-bond donors and CV reveals that they act as reversible abstractors of X^- from $[Cp_2TiX_2]^-$ via H-bonding.[10] This abstraction does not only increase the concentration of Cp_2TiX. However, it also enables bulk electrolysis of precatalyst Cp_2TiX_2 in THF, presumably by preventing a deactivation of the electrode. Without additives, no bulk electrolysis of Cp_2TiX_2 in THF was possible.

Herein, we further validate the adaptability of our CV-screening method by identifying reaction conditions for an 'additive-free' electrochemical activation of Cp_2TiCl_2 in other solvents than THF and a new additive for the bulk electrolysis of Cp_2TiX_2 in THF and CH_3CN. The solutions obtained are tested in radical arylations.[6] The results on the identification of solvents will be discussed first.

Results and Discussion

Solvent Screening and Arylation after Bulk Electrolysis in CH_3CN

Solvent Screening

For the solvent screening two issues are essential. First, the solvent employed must not solvate Cl^- well enough to shift the C_r-equilibrium completely to the side of Cp_2TiCl. In this case no resting state is available to the catalyst. Second, the generation of Cp_2Ti^+ in the presence of a protic solvent, such as H_2O or CH_3OH, is to be avoided, because complexes of Cp_2Ti^+ with these solvents have been shown to be excellent hydrogen atom donors[11] that can intercept radicals and prevent the radical arylation. It should be noted that the titanocene catalyzed 5-exo cyclizations is about one order of magnitude faster than the arylation.[12]

Therefore, we have chosen the following aprotic solvents: CH_3CN ($\varepsilon = 37.5$), DMF ($\varepsilon = 37.0$), acetone ($\varepsilon = 20.7$), pyridine ($\varepsilon = 12.4$), and CH_2Cl_2 ($\varepsilon = 8.9$) ranging from 'polar' to 'unpolar'.[13] The cyclic voltammograms of the reduction of Cp_2TiCl_2 in these solvents and in THF[3] are shown in Figure 1.

As screening criterion[3] for an attractive solvent for bulk-electrolysis and for the radical arylation, we chose the presence of the oxidation waves due to $[Cp_2TiCl_2]^-$ and Cp_2TiCl. For the success of the bulk-electrolysis and the radical arylation it is important that the latter wave has a higher intensity than the former. This was found to be essential for preventing electrode deactivation and reflects an E_qC_r-mechanism with the C_r-

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equilibrium shifted towards the catalytically active Cp_2TiCl. This requirement has led to the discovery of the conditions for bulk-electrolysis in THF by adding Schreiner's thiourea **L1**.[3]

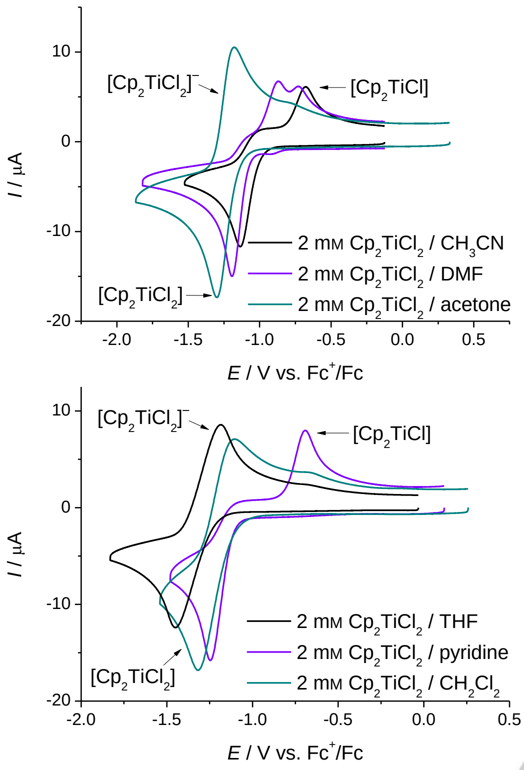


Figure 1. Cyclic Voltammograms of Cp_2TiCl_2 in different organic solvents with 0.2 M Bu_4NPF_6 at a scan rate of 2 Vs^{-1}.

Of the solvents with low permittivity ($\varepsilon < 21$) only pyridine showed a voltammogram fulfilling our criterion. In CH_2Cl_2, and acetone only minor amounts of Cp_2TiCl were detected. The situation is different for CH_3CN and DMF, the solvents with a permittivity ε of about 37.

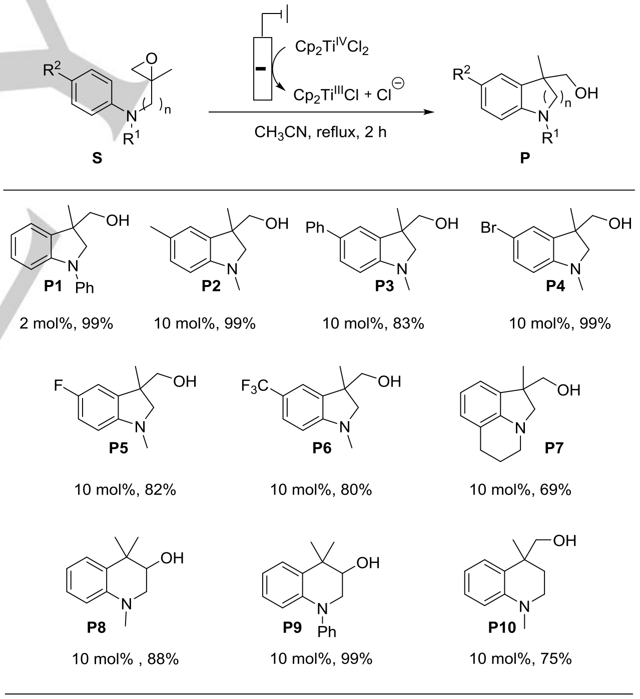
In DMF, three waves were observed that we attribute to $[Cp_2TiCl_2]^-$, $Cp_2TiCl{\bullet}DMF$, and Cp_2TiCl. The assignment of $Cp_2TiCl{\bullet}DMF$ is based on the redox-potential that lies between those of the other two species and is in agreement with an earlier study of titanocenes with a pending hemilabile amide ligand.[14] Moreover, Daasbjerg has shown that the even better donor HMPA also coordinates to Cp_2TiCl.[4c] Thus, while the catalyst's resting state and the active catalyst are formed, DMF complexes the catalyst strongly and will inhibit substrate binding.
Acetonitrile (CH_3CN), on the other hand, seems a highly attractive solvent for bulk-electrolysis and radical arylation. On the oxidative sweep, the voltammogram in CH_3CN shows two waves that are due to $[Cp_2TiCl_2]^-$ and Cp_2TiCl with the wave pertaining to Cp_2TiCl having a substantially higher intensity. This assessment was further supported by the addition of NBu_4Cl (TBAC). In this case, the wave originating from the oxidation of $[Cp_2TiCl_2]^-$ increases in intensity whereas the second wave (oxidation of Cp_2TiCl) is depleted. Thus, only the active catalyst and minor amounts of its resting state are formed during the CV experiment. This meets our criterion for the CV-screening.

Bulk-Electrolysis and Radical Arylation

The screening has identified pyridine and CH_3CN as potentially attractive solvents for the bulk-electrolysis of Cp_2TiCl_2. However, when exposed to bulk-electrolysis conditions, extensive decomposition of the Cp_2TiCl_2 derived species was observed in pyridine. It is beyond the scope of this study to provide a mechanistic interpretation of this observation. The use of CH_3CN resulted in a successful reduction. This can also be judged by the color of the solution obtained (see Supporting Information). At first glance, it may seem counterintuitive that the dipolar aprotic solvent CH_3CN is capable of solvating chloride. However, it has been reported that H_2O and CH_3CN can have similar interactions with Cl^-.[15] Therefore, the shift of the C_r-equilibrium is indeed perfectly reasonable.

Our results of the radical arylation with the electrochemically reduced solutions of Cp_2TiCl_2 in CH_3CN are summarized in Table 1.

Table 1. Catalytic radical arylation by electrochemically reduced Cp_2TiCl_2 in CH_3CN.



The reaction leads to the formation of the desired products in good to high yields. For **P1** the catalyst loading can be reduced to 2 mol%. With respect to sustainability it is worth noting that no additives for the stabilization of the catalytic system are needed.

However, it should be noted that CH_3CN is a relatively toxic solvent because it can be metabolized to HCN.

An advantage of using CH_3CN over our previously described system in THF[3] is that Cp_2TiCl_2 can be employed as catalyst precursor. It is cheaper than Cp_2TiBr_2 required for high yielding reactions in THF.

Effect of Additives on the E_qC_r-Mechanism: CV-Screening and Arylation after Bulk-Electrolysis

The results shown above demonstrate that unpolar solvents are not suitable for bulk-electrolysis of Cp_2TiX_2 (X = Cl, Br). In our initial work, we have focused on the use of ureas and thioureas to abstract chloride or bromide from $[Cp_2TiX_2]^-$ in THF to allow bulk-electrolysis and to obtain active solutions for the radical arylation at the same time. Here, we investigate, if squaramides that have been used with great success in organocatalysis[16] and in halide binding and transport[17] are also useful additives for allowing bulk-electrolysis of Cp_2TiX_2 and radical arylation in THF and how they affect the composition of the Cp_2TiX_2 solutions reduced in CH_3CN.

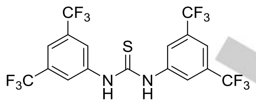
Halide Binding through Hydrogen Bonding with Squaramides

While Schreiner's thiourea **L1** serves the desired purpose very well with Cp_2TiBr_2 as precatalyst it is less efficient with Cp_2TiCl_2. Therefore, it is interesting to investigate the effect of other additives, in particular those that might lead to an improved activation of Cp_2TiCl_2. To this end, better halide binders than thioureas seemed suitable.

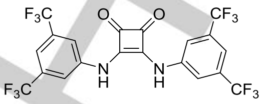
In the comparison of ureas and thioureas, we found that the efficiency of halide abstraction depended on the acidity of the additive. **L2**[18] has a pK_a value similar to **L1** (**L1**: 8.5, **L2**: 8.4) in dimethylsulfoxide (DMSO)[19] and is therefore an attractive additive for screening. Gratifyingly, **L2**'s chloride binding is higher by a factor of 16 as judged by its chloride binding constant (K_a^{Cl}, NBu_4Cl in DMSO/0.5% H_2O at 298 K) due to its more rigid coordination geometry.[17] For our purposes this allows to additionally understand the geometrical effects of complexation of Cp_2TiCl_2 and halide abstraction from $[Cp_2TiCl_2]^-$•**L2**. To study these issues, we applied our CV-screening method (Figure 2).

The voltammograms show that the effects of **L1** and **L2** are markedly different. First, the complex Cp_2TiCl_2•**L2** is more activated towards reduction than Cp_2TiCl_2•**L1** ($\Delta E_{½}$ = 160 mV for Cp_2TiCl_2 vs. Cp_2TiCl_2•**L2** compared to $\Delta E_{½}$ = 110 mV for Cp_2TiCl_2 vs. Cp_2TiCl_2•**L1**).[3] This is a clear indication of a stronger complexation of Cp_2TiCl_2. The complexation by **L2** is fully reversible because addition of TBAC results in the regeneration of Cp_2TiCl_2 (see Supporting Information). Second, in the CVs no complex between $[Cp_2TiCl_2]^-$ and **L2** can be observed whereas this is the case for **L1**. Once again, this underlines the improved chloride abstraction ability of **L2**. Finally, **L2** forms a complex with Cp_2TiCl whereas **L1** does not. Cp_2TiCl•**L2** has a lower reducing power than Cp_2TiCl ($\Delta E_{½}$ = 160 mV for Cp_2TiCl vs. Cp_2TiCl•**L2**). The complex is not caused by follow-up reactions during the CV experiment because the intensity of its oxidation wave increases with higher sweep rate.[4]

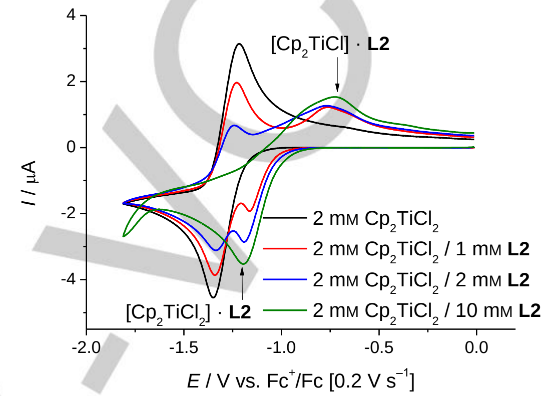
Besides revealing the important information about the different complexes formed, the CVs also suggest that a bulk-electrolysis of Cp_2TiCl_2 in the presence of **L2** should be viable and the solutions obtained should be active catalysts for the radical arylation. This is indeed the case. The bulk-electrolysis can even be carried out in the presence of 0.5 or 1 eq. of **L2** and requires a potential of -1.3 V (vs. Ag/Ag$^+$). With **L1**, at least 1 eq. of the additive and -1.4 V are required. The results of some arylation reactions are summarized in Table 2.



L1



L2



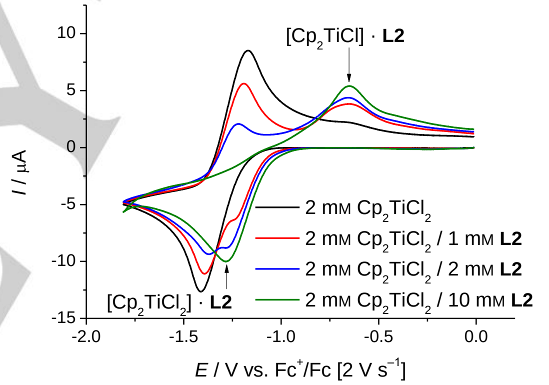
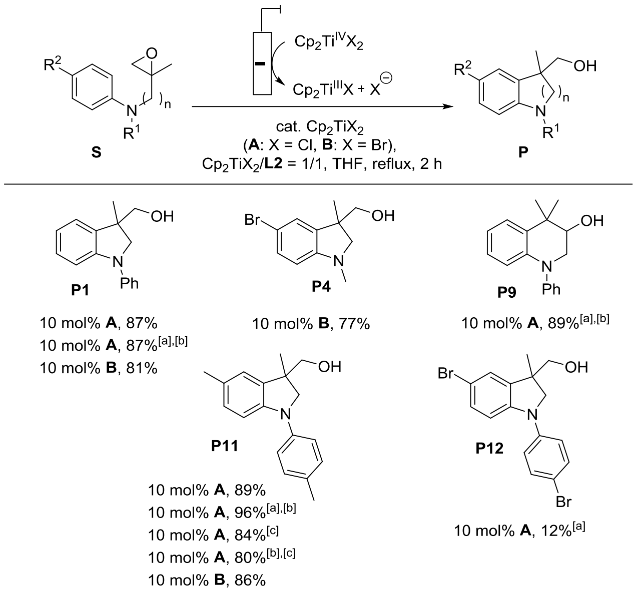


Figure 2. Cyclic Voltammograms of Cp_2TiCl_2 in THF in the presence of **L2** with 0.2 M Bu_4NPF_6 at a scan rate of 0.2 and 2 Vs^{-1}.

The arylation reactions with the Cp_2TiCl_2 solutions reduced in the presence of **L2** give higher yields than those generated in the presence of **L1**. With Cp_2TiBr_2, **L2** is slightly inferior to **L1**, however. This is in line with the better halide binding ability of **L2**. The use of **L2** results in a higher concentration of the active catalyst Cp_2TiCl. At the same time, a sufficiently high amount of the resting state is present and, so, a stable and active catalytic system is formed to avoid catalyst deactivation. In the presence of **L1** the concentration of Cp_2TiCl is too low. With Cp_2TiBr_2, as precatalyst, the situation is reversed. With **L1** the optimal balance of Cp_2TiBr and $[Cp_2TiBr_2]^-$•**L1** is obtained. With **L2**, the concentration of $[Cp_2TiBr_2]^-$ is too low to allow for a stable catalyst. From the perspective of practicability and sustainability, **L2** is therefore the superior additive because it allows the use of the cheaper and more readily accessible catalyst Cp_2TiCl_2. The use of the more expensive Cp_2TiBr_2 is not necessary.

Table 2: Catalytic radical arylation by electrochemically reduced Cp_2TiCl_2 and Cp_2TiBr_2 in THF in the presence of **L2**.



P1: 10 mol% **A**, 87%; 10 mol% **A**, 87%[a],[b]; 10 mol% **B**, 81%

P4: 10 mol% **B**, 77%

P9: 10 mol% **A**, 89%[a],[b]

P11: 10 mol% **A**, 89%; 10 mol% **A**, 96%[a],[b]; 10 mol% **A**, 84%[c]; 10 mol% **A**, 80%[b],[c]; 10 mol% **B**, 86%

P12: 10 mol% **A**, 12%[a]

Reaction conditions: Catalyst **A** or **B**, additive **L2**, cat/additive = 1/1, 10 mM in THF, isolated yields. [a] Cp_2TiX_2/**LX** = 2/1; [b] T = 25 °C, t = 16 h; [c] Cp_2TiX_2/**LX** = 1/2

Finally, we investigated the influence of **L1** and **L2** on the reduction of Cp_2TiCl_2 in CH_3CN. In these cases, the interesting problem arises how the additive will affect the already favorable C_r-equilibrium. The CVs of investigations with both ligands are shown in Figure 3.

Compared to the situation in CH_3CN without additives (Figure 1), the CVs show a third oxidation wave at higher potential than Cp_2TiCl that is assigned to the oxidation of Cp_2Ti^+.[18] With 1 eq. of **L1** and **L2**, the intensity of this wave is reduced at higher sweep rate (2 Vs^{-1}). This indicates the formation of the cation in a follow-up reaction during the CV experiment (parent-child reaction).[4] With 3 eq. of **L2**, the ratio of intensities remains almost constant indicating that Cp_2Ti^+ may indeed be an original component of the solution. This change should not affect the bulk-electrolysis and, indeed, it could be carried out without problems. However, the solutions in the presence of 1 or 3 eq. of the ligands have a distinctly different appearance. With 3 eq. the solution is dark blue which indicates the formation of Cp_2Ti^+.[19] This was verified by a CV-analysis of the solutions obtained by bulk-electrolysis (Figure 4). It is clear that with 3 eq. of **L1** or **L2** the cation is formed almost exclusively, whereas in the presence of 1 eq. of the ligands a mixture of Cp_2TiCl and Cp_2Ti^+ is obtained.

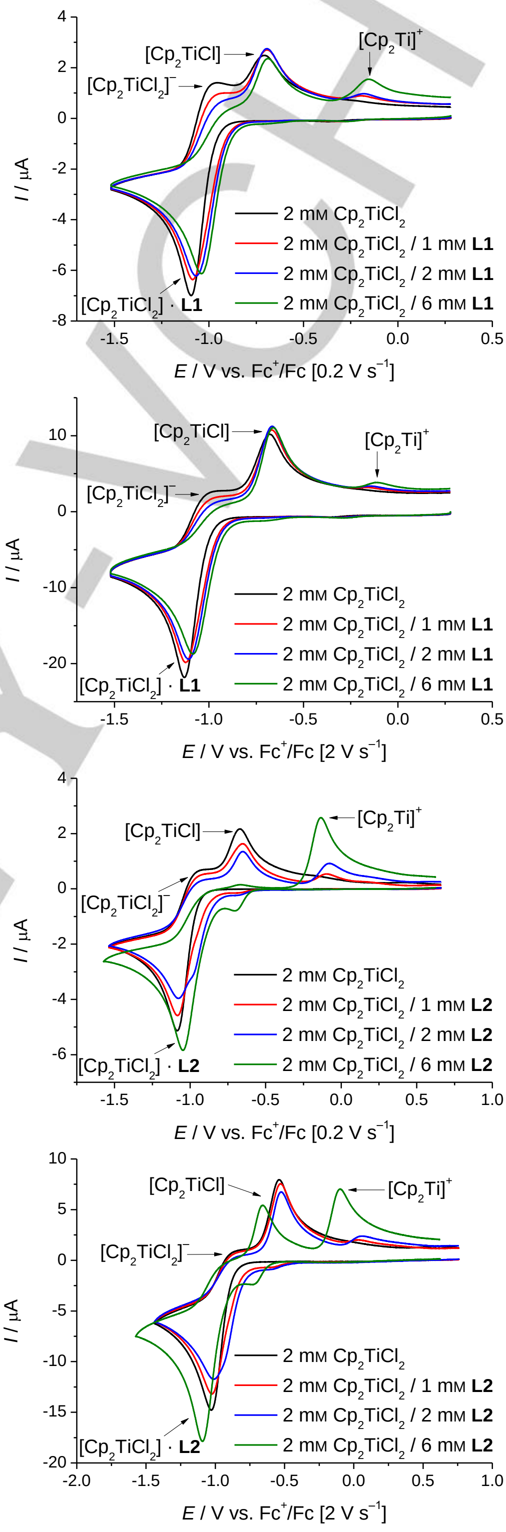


Figure 3. Cyclic Voltammograms of Cp_2TiCl_2 in CH_3CN in the presence of **L1** and **L2** with 0.2 M Bu_4NPF_6 at a scan rate of 0.2 and 2 Vs^{-1}.

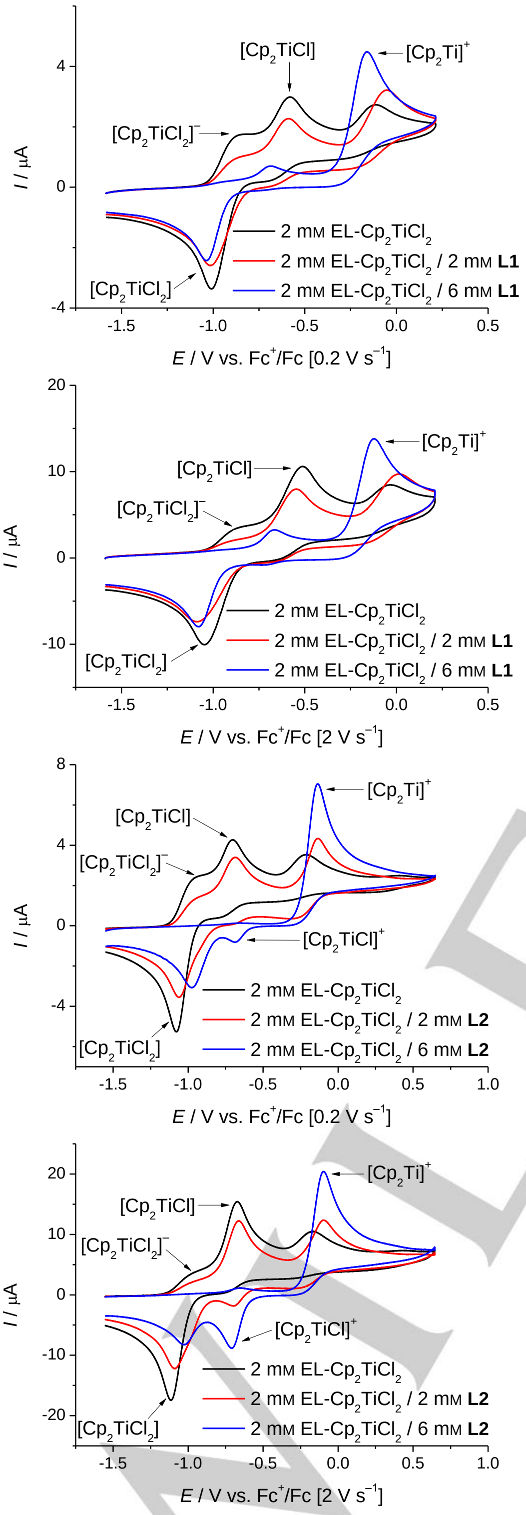
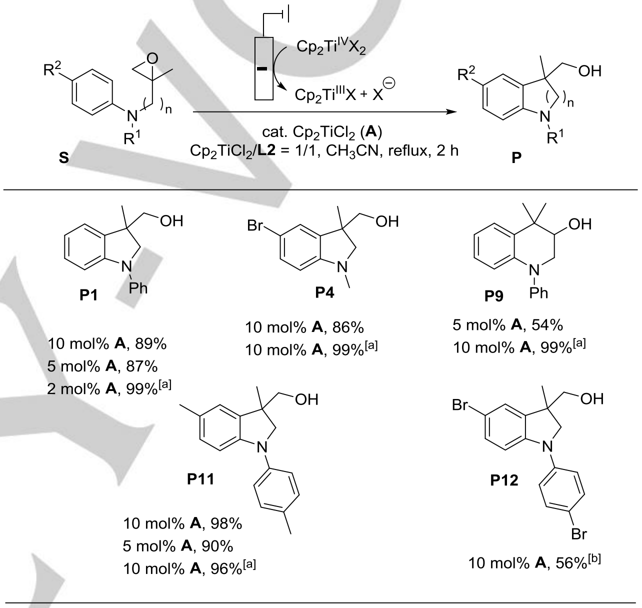


Figure 4: Cyclic Voltammograms of the solutions of Cp_2TiCl_2 in CH_3CN in the presence of **L1** and **L2** prepared by bulk-electrolysis with 0.2 M Bu_4NPF_6 at a scan rate of 0.2 and 2 Vs^{-1}.

Previous studies have shown that Cp_2Ti^+ in CH_3CN is a less active catalyst than Cp_2TiCl based systems.[6d] This is because epoxide opening is slower for more electron deficient catalysts.

In CH_3CN this step is even further slowed down by the complexation of Cp_2Ti^+ by CH_3CN[20,6d] that efficiently competes with the epoxide substrates. However, Cp_2Ti^+ is an attractive catalyst for reactions with epoxides containing electron deficient arenes. The electrochemically reduced solutions of Cp_2TiCl_2 in CH_3CN with and without **L2** react accordingly (Table 3).

Table 3: Comparison of catalytic radical arylation by electrochemically reduced Cp_2TiCl_2 in CH_3CN with and without **L2**.



Reaction conditions: Catalyst **A** or **B**, additive **L2**, cat/additive = 1/1, 10 mM in CH_3CN, isolated yields. [a] without **L2**; [b] Cp_2TiCl_2/**L2** = 1/3

The reactivity of the catalytic systems with added **L2** are reduced compared to the system without additives. However, **P3** that requires Cp_2Ti^+ for its formation can be obtained in the presence of **L2** albeit the yield is low.

Conclusions

In summary, we have demonstrated that our CV-screening method for the identification of conditions for the bulk-electrolysis have been successfully extended to other solvents and supramolecular chloride binders. CH_3CN is a suitable solvent for bulk-electrolysis of Cp_2TiX_2 and radical arylation. Moreover, squaramide **L2** is a better ligand for chloride and bromide abstraction than our previously best ligand Schreiner's thioureas **L1**. In the presence of **L2** even Cp_2TiCl_2 is an excellent and highly sustainable catalyst for the arylation.

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Keywords: arylation • cyclic voltammetry • epoxide • squaramide • titanium

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FULL PAPER

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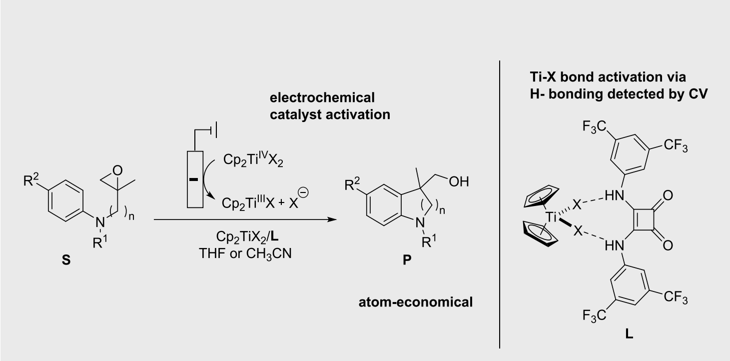
Condition Screening for Sustainable Catalysis in Single-Electron Steps by Cyclic Voltammetry: Additives and Solvents



Catalysis predicted by screening with of solvents and additves with cyclic voltammetry! Ti-X bond activation in CH3CN or in THF with squaramide **L** enables bulk electrolysis of Cp_2TiCl_2 and sustainable catalysis.