**Oxidative Coupling**

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# Over-Oxidation as the Key Step in the Mechanism of the $MoCl_5$-Mediated Dehydrogenative Coupling of Arenes

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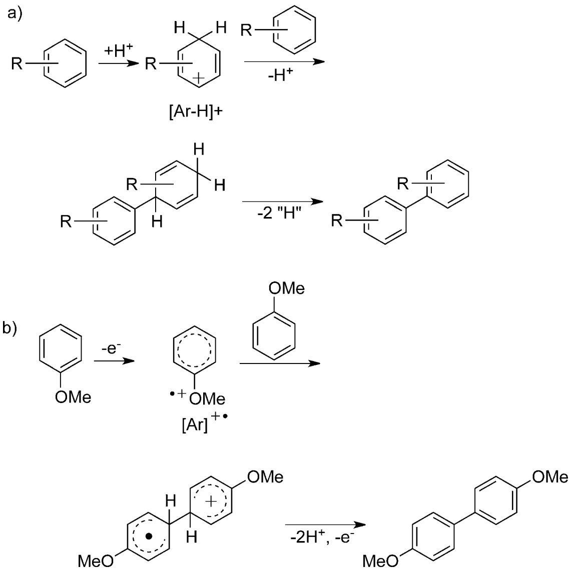
***Abstract:** Molybdenum pentachloride is an unusually powerful reagent for the dehydrogenative coupling of arenes. Owing to the high reaction rate using $MoCl_5$, several labile moieties are tolerated in this transformation. The mechanistic course of the reaction was controversially discussed although indications for a single electron transfer as the initial step were found recently. Herein, based on a combined study including synthetic investigations, electrochemical measurements, EPR spectroscopy, DFT calculations, and mass spectrometry, we deduct a highly consistent mechanistic scenario: $MoCl_5$ acts as a one-electron oxidant in the absence of $TiCl_4$ and as two-electron oxidant in the presence of $TiCl_4$, but leads to an over-oxidized intermediate in both cases, which protects it from side reactions. In the course of aqueous work-up the reagent waste ($Mo^{III/IV}$ species) acts as reducing agent generating the desired organic C−C coupling product.*

**M**olybdenum pentachloride is an unusually powerful reagent often used in the oxidative coupling reaction of arenes.[1] The reaction can be employed for constructing five- to eight-membered ring systems,[2] including carbazoles[2a] and phenanthrenes,[2b] with a huge variety of labile but synthetically useful moieties (e.g. iodo groups or ketals).[2c–j] The tolerance of sensitive moieties, such as ketals, is attributed to the high reaction rate of oxidative couplings with $MoCl_5$.[1b] Empirical studies showed that addition of Lewis acids (e.g. $TiCl_4$) can further promote the coupling process with $MoCl_5$.[1b–c] Although this reaction was already mentioned in early 1960s by Kovacic et al.,[1a,3] its mechanism is still a topic of controversy in the literature. Besides the mechanistic course, the stoichiometry of the reaction was contentious as well. As a result of the initially reported low yields and many side-reactions, $MoCl_5$ passed into oblivion until 1997 when Kumar and Manickam applied it successfully in the oxidative trimerization of veratrole.[4] Henceforth, $MoCl_5$-mediated coupling reactions have been intensively investigated. The two proposed pathways for the $MoCl_5$-mediated oxidative coupling reactions of aryl ethers are an arenium-cation $[Ar\text{-}H]^+$ mechanism and a radical-cation $[Ar]^{+\bullet}$ pathway (Scheme 1; for a detailed discussion about weaknesses of previous studies favoring one or the other of the mechanisms see Refs. [1a],[5]).



**Scheme 1.** Arenium-cation mechanism (a) and radical cation mechanism (b).

In previous work, we obtained clear evidence that the dehydrogenative arene coupling starts with an inner-sphere single-electron transfer (SET) forming a radical cation $[Ar]^{+\bullet}$ and $MoCl_5^-$. This finding alone does not confirm that the radical-cation pathway is followed, however, because the initially formed radical cation could also abstract a hydrogen atom from the solvent and, thus, enter the arenium-cation pathway.[5,6]

To gain further insight into the reaction mechanism, we performed squarewave voltammetric studies, electrospray ionization-mass spectrometry (ESI-MS), and electron paramagnetic resonance (EPR) experiments of reaction mixtures of substrates **1a**–**c** with $MoCl_5$ in dichloromethane

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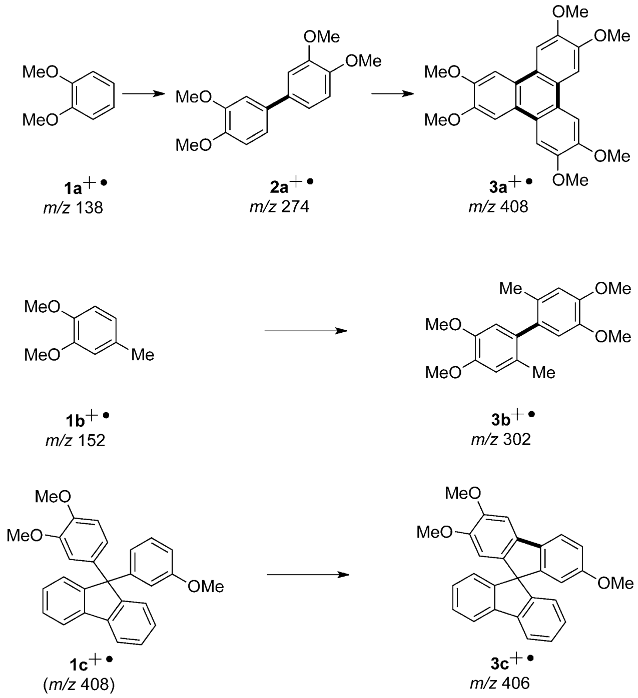


***Scheme 2.*** Reaction intermediates detected by ESI mass spectrometry and EPR spectroscopy.

(Scheme 2), as well as density functional theory (DFT) studies. The combined results clearly support that the expected products **3a**–**c** are further oxidized to their respective radical cations **3a**$^{+\cdot}$–**c**$^{+\cdot}$.[7,8] The electrochemical experiments indicate that the products **3a**–**c** are indeed more easily oxidized to the radical cations **3a**$^{+\cdot}$–**c**$^{+\cdot}$ than the respective starting arenes **1a**–**c**, as expected (Table 1). Hence, Mo$^{V}$ (or even Mo$^{IV}$) should be able to oxidize **3a**–**c** to **3a**$^{+\cdot}$–**c**$^{+\cdot}$.

***Table 1:*** First oxidation potentials of **1a**–**c**, **2a** and **3a**–**c** determined by squarewave voltammetry in $CH_2Cl_2$/[$n$Bu$_4$N][B($C_6F_5$)$_4$] versus ferrocene/ferrocenium couple.

| | **1/1**$^{+\cdot}$ [V] | **2/2**$^{+\cdot}$ [V] | **3/3**$^{+\cdot}$ [V] |
|---|---|---|---|
| **a** | 1.03 | 0.68 | 0.60 |
| **b** | 0.88 | – | 0.74 |
| **c** | 0.93 | – | 0.51 |

Interestingly, oxidation of **1c** to **1c**$^{2+}$ via **1c**$^{+\cdot}$ in the squarewave experiment (0.93 V and 1.50 V) leads to the appearance of the waves of the **3c**$^{+\cdot}$/**3c**$^{2+}$ and **3c**/**3c**$^{+\cdot}$ couples (1.23 V and 0.51 V) in the reductive scan suggesting that C–C coupling might occur by the elimination of two electrons and two protons at the electrode (see Supporting Information: 5.6).

The ESI-mass spectrometric analysis of solutions of $MoCl_5$ and **1a** in $CH_2Cl_2$ showed signals for the radical cations of the arene substrate **1a**$^{+\cdot}$, its dehydrodimer **2a**$^{+\cdot}$, and the final trimer coupling product **3a**$^{+\cdot}$ (Figure 1, Scheme 2, and Table S3.1). The time profiles of **2a**$^{+\cdot}$ and **3a**$^{+\cdot}$ clearly indicate that **2a**$^{+\cdot}$ undergoes a consecutive reaction to afford **3a**$^{+\cdot}$ (Figure S3.1).[9] To exclude that the observed radical cations result from anodic oxidation reactions during the ESI process,[10] we performed control experiments with the trimer coupling product **3a**. Upon positive-ion mode ESI, solutions of **3a** in $CH_2Cl_2$ afforded only very weak signals. In the presence of $MoCl_5$, however, **3a**$^{+\cdot}$ as well as chlorinated analogues were detected with high signal intensities (Figure S3.2). These results clearly demonstrate that the detected radical cations **1a**$^{+\cdot}$, **2a**$^{+\cdot}$ and **3a**$^{+\cdot}$ originated from reactions with $MoCl_5$ and not from anodic oxidations during the ESI process.

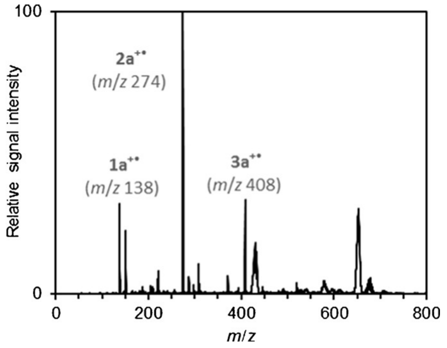


***Figure 1.*** Positive-ion mode ESI mass spectrum of a solution of $MoCl_5$ (21 mM) and **1a** (10 mM) in $CH_2Cl_2$. The signal labeled by an asterisk originated from the used solvent. The signals centered at $m/z$ 430 and 653 apparently contained Mo, but could not be assigned unambiguously.

Further ESI experiments examined mixtures of $MoCl_5$ and **1b** or **1c**, respectively. The radical cations of the coupling products, **3b**$^{+\cdot}$ and **3c**$^{+\cdot}$ (Scheme 2, Figure S3.3–S3.5, and Table S3.1) are detected. With **1b** the radical cation of the substrate (i.e., **1b**$^{+\cdot}$) is also observed initially, whereas the intramolecular coupling of **1c**$^{+\cdot}$ apparently proceeds too fast to permit its detection by ESI.[11]

The proposed radical cations **3a**$^{+\cdot}$–**c**$^{+\cdot}$ are unambiguously identified in reaction mixtures of **3a**–**c** with one equivalent $MoCl_5$ per arene on the basis of their respective characteristic hyperfine coupling patterns in their EPR resonances (see Supporting Information 4). Even more revealing are the EPR spectra of the starting materials **1a**–**c** and **2a** in the presence of one equivalent $MoCl_5$ per arene. Compound **1a** and $MoCl_5$ give the oxidized biaryl radical cation **2a**$^{+\cdot}$ without further formation of **3a**$^{+\cdot}$ under these conditions owing to the lack of sufficient Mo$^{V}$ (see Supporting Information 4.2a,b). Compound **2a** is simply oxidized to **2a**$^{+\cdot}$ without further C–C coupling (see Supporting Information 4.2c). Compound **1b** and $MoCl_5$ give the oxidized biaryl **3b**$^{+\cdot}$ (see Supporting Information 4.3). The fluorene derivative **1c** is rapidly oxidized to **1c**$^{+\cdot}$,[5a] undergoes C–C coupling and is further oxidized to the spiro compound **3c**$^{+\cdot}$ (see Supporting Information 4.4). The hyperfine coupling patterns of all individual radical cations were additionally verified by DFT calculations supporting the assignments (see Supporting Information). Hence, one further oxidation equivalent is consumed by the biaryl products **3a**–**c** giving the biaryl radical cations **3a**$^{+\cdot}$–**c**$^{+\cdot}$, respectively.

Additionally, the analytical and theoretical results are supported by a product yield optimization study with substrate **1b** in the absence and presence of $TiCl_4$ (Table 2 and Table 3).

***Table 2:*** Stoichiometric study for conversion of **1b** by $MoCl_5$ in the absence of $TiCl_4$.

$$1\ \text{Ar-H} + 1.5\ MoCl_5 \longrightarrow 0.5\ [\text{Ar-Ar}]^{+\bullet}Cl^{-} + 1\ HCl + 1.5\ \text{"}MoCl_4\text{"}$$

| Ratio $MoCl_5$/**1b** | Yield **3b** [%] |
|---|---|
| 0.8 | 54 |
| 1.0 | 73 |
| 1.2 | 92 |
| 1.4 | 93 |
| 1.6 | 93 |

***Table 3:*** Stoichiometric study for conversion of **1b** by $MoCl_5$ in the presence of $TiCl_4$.

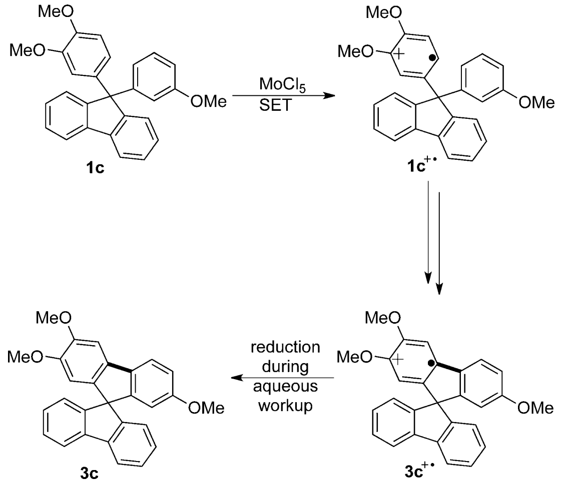
$$1\ \text{Ar-H} + 0.75\ MoCl_5 \longrightarrow 0.5\ [\text{Ar-Ar}]^{+\bullet}Cl^{-} + 1\ HCl + 0.75\ \text{"}MoCl_3\text{"}$$

| Ratio $MoCl_5$/**1b** | Ratio $TiCl_4$/**1b** | Yield **3b** [%] |
|---|---|---|
| 0.0 | 1.0 | 0 |
| 0.5 | 0.5 | 59 |
| 0.6 | 0.6 | 75 |
| 0.7 | 0.7 | 87 |
| 0.8 | 0.8 | 100 |

In previous product studies, we as well as other groups, reported $MoCl_5$ to be a one-electron oxidant.[1] Taking into account the additional over-oxidation of products **3a–c**, our present results can only be explained by $MoCl_5$ acting as a one-electron oxidant in the absence of $TiCl_4$ and acting as a two-electron oxidant in the presence of $TiCl_4$ (Tables 2 and 3). For a full conversion via the over-oxidized product, 1.6 equivalents (1.5 equiv from a theoretical standpoint) of $MoCl_5$ are required in the absence of $TiCl_4$ and 0.8 equivalents (0.75 equiv from a theoretical standpoint) of $MoCl_5$ are sufficient in the presence of $TiCl_4$. These equivalents refer to the coupling components applied (Ar-H). These findings explain why in previous debates enough arguments were found for both stoichiometric versions.

The possible effect of $TiCl_4$ addition on the oxidation of the product **3b** to $\mathbf{3b}^{+\bullet}$ by $MoCl_4$ has been probed by DFT calculations (see Supporting Information 6.7 and 6.8). Indeed, in the absence of $TiCl_4$, $MoCl_4$ simply coordinates to a 1,2-dimethoxy arene unit of **3b** in a κO,κO′ fashion but fails to oxidize **3b** to $\mathbf{3b}^{+\bullet}$. Attaching the Lewis acid $TiCl_4$ to the coordinated $MoCl_4$ moiety via two chlorido bridges results in a charge shift from the non-coordinated arene unit to the molybdenum center and hence in the formation of $\mathbf{3b}^{+\bullet}$ (see Supporting Information 6.7 and 6.8 for spin density maps of the molybdenum and mixed metal complexes). These DFT calculations suggest that the Lewis acidic $TiCl_4$ increases the oxidative power of $MoCl_4$, so that in summary, $MoCl_5$ acts as two-electron oxidant in the presence of $TiCl_4$ instead of just a one-electron oxidant in the absence of $TiCl_4$ (Tables 2 and 3). For a clarifying scheme about the decisive role of $TiCl_4$ or other Lewis acids in the $MoCl_5$-mediated oxidative coupling reaction see Figure S2.1.[1c]

The necessary reduction of the over-oxidized products $\mathbf{3a}^{+\bullet}$–$\mathbf{c}^{+\bullet}$ to the finally isolated neutral species is carried out during the aqueous workup by the molybdates formed (most likely by the remaining $Mo^{III/IV}$ species).[12,13] Considering all the analytical, theoretical, and experimental results we propose an extended mechanism for the oxidative coupling of arenes with $MoCl_5$ (Scheme 3).



***Scheme 3.*** Extended mechanism for the oxidative coupling reaction of **1c** mediated by $MoCl_5$. Intermediates $\mathbf{1c}^{+\bullet}$ and $\mathbf{3c}^{+\bullet}$ are unambiguously identified by EPR and ESI-MS experiments.[5a]

The tolerance of several labile moieties at the aromatic components can be easily attributed to the cationic intermediates $\mathbf{3a}^{+\bullet}$–$\mathbf{c}^{+\bullet}$ which are formed, and accumulated in the course of reaction. The cationic nature prevents further attack by electrophilic species, such as protons or arenium cations. This might be the reason why oligomeric species are not the dominant products. If 2,2-substituted benzo-1,3-dioxole moieties are present, a fast ring opening and ring closure can be envisioned giving rise to the isomerization and stereoselective formation of triphenylene ketals.[14] In addition, it provides a rationale for the potential chlorination reaction which can occur with several substrates. Such cationic species are prone to nucleophilic attack by chloride. For the electrochemical synthesis of **3a**, the over-oxidation to the radical cation $\mathbf{3a}^{+\bullet}$ is known and usually limits the synthetic utility. It turned out that reduction during workup is difficult giving a low yield which is due to decomposition reactions.[15] If **3a** and related compounds are insoluble in the media applied, the potentials shift and over-oxidation is avoided creating a viable synthetic route.[16] The extended mechanism (Scheme 3) including the over-oxidized product as a radical cation shows similarities to the radical cation pool method and aminations of aryls via Zincke intermediates developed by Yoshida and co-workers.[17] In both approaches, the key to success is using a cationic intermediate for the selective transformation. Furthermore, our results are fully in line with the reports of Rathore and co-workers on the 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) system in the oxidative aryl–aryl coupling reaction.[8]

In conclusion, by a combined study employing EPR spectroscopy, electrochemistry, and ESI mass spectrometry together with DFT calculations and systematic synthetic experiments we could unravel a further important part of the mechanism of the $MoCl_5$-mediated dehydrogenative arene coupling. In addition, the ongoing debate about the number of electrons being transferred to the molybdenum reagent could be solved. $MoCl_5$ is a two-electron acceptor in electrophilic media but the reaction proceeds to the over-oxidized species. Therefore, for dehydrogenative bond formation a minimum of 0.75 equivalents of $MoCl_5$ per arene is required. The current study provides a highly consistent picture and is in line with previous observations. The selective formation of suitable over-oxidized products could serve in the future as starting point for a subsequent selective cross-coupling sequence. The over-oxidized species can be considered as a cation pool opening up completely new synthetic opportunities.

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