Oxidative Coupling

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Powerful Fluoroalkoxy Molybdenum(V) Reagent for Selective Oxidative Arene Coupling Reaction

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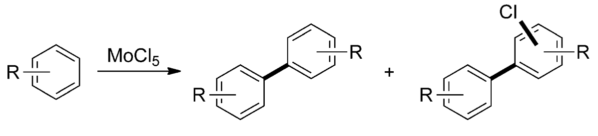
Dedicated to Professor Rudolf Zentel on the occasion of his 60th birthday

Abstract: *We introduce the novel fluoroalkoxy molybdenum(V) reagent **1** which has superior reactivity and selectivity in comparison to $MoCl_5$ or the $MoCl_5/TiCl_4$ reagent mixture in the oxidative coupling reactions of aryls. Common side reactions, such as chlorination and/or oligomer formation, are drastically diminished creating a powerful and useful reagent for oxidative coupling. Theoretical treatment of the reagent interaction with 1,2-dimethoxybenzene-type substrates indicates an inner-sphere electron transfer followed by a radical cationic reaction pathway for the oxidative-coupling process. EPR spectroscopic and electrochemical studies, X-ray analyses, computational investigations, and the experimental scope provide a highly consistent picture. The substitution of chlorido ligands by hexafluoroisopropoxido moieties seems to boost both the reactivity and selectivity of the metal center which might be applied to other reagents as well.*

Oxidative coupling reactions of aryls are twofold CH activations. Although known for a long time, this transformation is experiencing a renaissance in synthetic organic chemistry, since no leaving functionalities are required.[1] Many metal salts in high oxidation states or strong electron acceptors are capable to efficiently induce this conversion.[2] Modern applications focus on oxidants based either on salts of biocompatible metals, that is, iron or molybdenum, or metal-free systems, such as hypervalent iodine reagents.[3] Currently, the bis(trifluoroacetoxy)iodobenzene-based compounds seem to be the most versatile reagents. However, in several comparative studies, the oxidative power of this iodine(III) reagent was outperformed by $MoCl_5$.[4] Moreover, domino oxidations exclusively induced by $MoCl_5$ underline the unique reactivity.[5] $MoCl_5$ was employed in several oxidative arylation reactions (Scheme 1).[6] The unique feature of this reagent is that the coupling process is fast and clearly completed before typical side reactions, that is, protodeiodation reactions in iodoaryl substrates or cleavage of ketals can occur.[7] $MoCl_5$ was successfully applied to form five-,[8] six-,[4,9] seven-,[5,10] and eight-membered rings.[11] Yet, chlorination is a typical undesired side reaction (Scheme 1).[1,12] It can even become the dominate pathway when very electron-rich substrates are employed or the C−C coupling is rather slow.[13] Addition of Lewis acids (usually $TiCl_4$) which are assumed to bind the co-formed chloride ions has proven to be helpful in some of these cases, but the beneficial effect is not general.[14] Therefore, a novel molybdenum reagent with less chlorinating potential is highly desirable.



Scheme 1. Conversion of the organic substrate into the desired coupling product and the undesired chlorinated by-product.

We report the synthesis and properties of a next-generation molybdenum(V) reagent **1** (Figure 1, Scheme 2) and elucidate mechanistic details. The superior reactivity of **1** in comparison to $MoCl_5$ in various challenging substrate conversions (Table 1) is demonstrated.

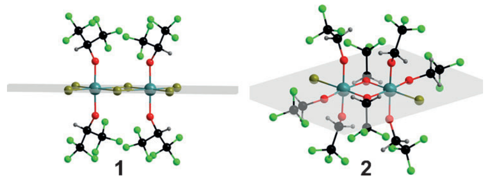


Figure 1. Molecular structures of **1** and **2** determined by single-crystal X-ray diffraction.

Clean ligand exchange at $MoCl_5$ is only successful by using a highly oxidation stable anion which has electronic properties comparable to the chlorido ligand. This is vital to conserve the unique reactivity of the Mo^V reagent. 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is a very stable solvent and has beneficial effects on the oxidative coupling

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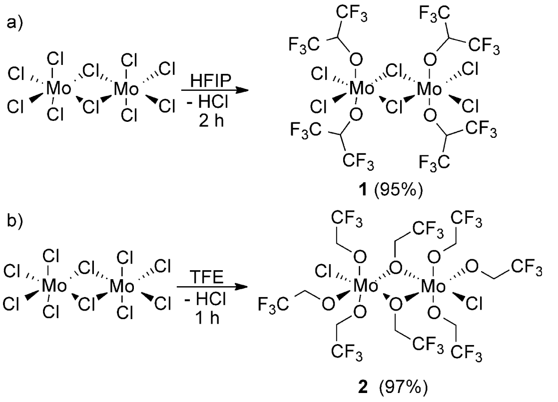
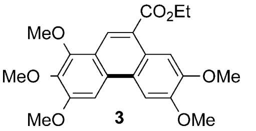
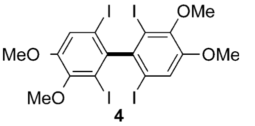
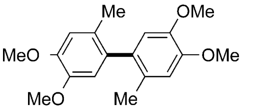
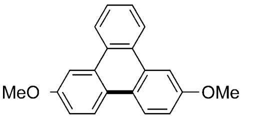
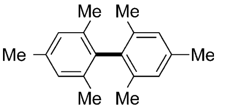


Scheme 2. Synthesis of **1** and **2** from $MoCl_5$.

Table 1: Conversions with $MoCl_5$, $MoCl_5/TiCl_4$, and **1** (formed C–C bonds are indicated in bold).

Product	Yield [%][a] $MoCl_5$	 $MoCl_5/TiCl_4$	 1
 3	26	58	71
 4	47[7a]	41	60
 5	67[20]	44	82
 6	53[4a]	40	89
 7	34[13]	< 5[b]	78

[a] Yields are of isolated products. [b] Yield determined by GC (see the Supporting Information).

of aryls.[15] The hexafluoroisopropoxy as well as the trifluoroethoxy ligands were chosen because of their good availability. Therefore, ligand substitution of chloride by 1,1,1,3,3,3-hexafluoroisopropanolate seemed to be useful and was easily achieved by heating both reaction partners (Scheme 2a). Upon evolution of hydrogen chloride a reddish-brown crystal slurry was obtained providing **1** selectively in 95% yield.

Under the same conditions the common less-fluorinated alcohol 2,2,2-trifluoroethanol (TFE) delivered **2** selectively in an isolated yield of 97% (Scheme 2b). The more electron-rich nature and smaller size of 2,2,2-trifluoroethanolate as compared to HFIP led to a further selective substitution of all but two chlorido ligands.

Both, **1** and **2**, are dinuclear complexes in the solid state (Figure 1). Similar to Mo_2Cl_{10}, the Mo^V centers are bridged by chlorido ligands in **1** while alkoxido bridges are found in **2**. The smaller alkoxido bridge necessarily leads to a much smaller Mo–Mo distance in **2** (2.832 Å) compared to **1** (3.805 Å) or Mo_2Cl_{10} (3.825 Å–3.886 Å).[16]

Dissolution of the diamagnetic dinuclear complexes Mo_2Cl_{10}, **1**, or **2** in dichloromethane leads to formation of EPR-active species in all cases. The X-band EPR spectra show characteristic resonances at g values below 2.0 with $^{95/97}Mo$ satellites ($A = 46$–51 G) clearly supporting the presence of magnetically uncoupled Mo^V (Figure 2) ($^{95/97}Mo$: $I = 5/2$ with 25% natural abundance; all other isotopes (75% natural abundance): $I = 0$). Hence, the two bridges (chlorido in Mo_2Cl_{10} and **1**; alkoxido in **2**) are at least partially disrupted and free coordination sites for substrates should be available in all cases (see the Supporting Information for possible Mo^V species and EPR spectra at 298 K including simulations).[17] Dissolved in the respective alcohols (HFIP or TFE), complexes **1** and **2** fully dissociate into mononuclear, six-coordinate species by coordination of the alcohol (**1**: $g = 1.9501$; **2**: $g_1 = 1.9480$ (80%), $g_2 = 1.9403$ (20%); **1**,**2**: $A(^{95/97}Mo) = 51.0$ G). These values are similar to those reported for $MoCl_5$ dissolved in ethanol (see the Supporting Information for EPR spectra and simulations) although this is believed to be a much more complicated reaction.[17b,18]

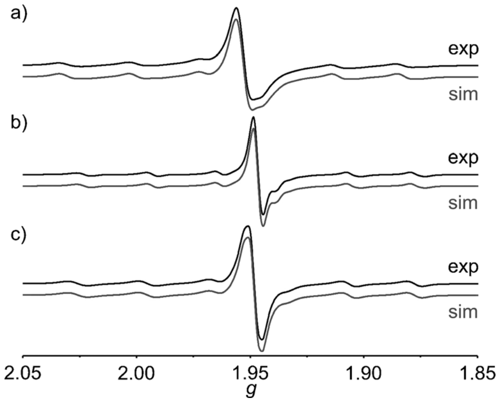


Figure 2. X-band EPR spectra (in black) and simulations (in gray) of a) Mo_2Cl_{10}, b) **1**, and c) **2** in dichloromethane at 243 K (Mo_2Cl_{10}: $g_1 = 1.9532$, $A_1 = 50.5$ G, 62%; $g_2 = 1.9472$, $A_2 = 50.0$ G, 38%; **1**: $g_1 = 1.9466$, $A_1 = 50.0$ G, 75%; $g_2 = 1.9407$, $A_2 = 46.0$ G, 25%; **2**: $g_1 = 1.9505$, $A_1 = 51.0$ G, 25%; $g_2 = 1.9473$, $A_2 = 50.5$ G, 75%).

To evaluate the oxidative power of all three compounds, their peak potentials versus ferrocene were determined in dichloromethane/$[nBu_4N][B(C_6F_5)_4]$. While Mo_2Cl_{10} and **1** show the expected high potentials ($E_p = 1.16$ V, 1.22 V), **2** has a much lower value of $E_p = 0.31$ V. Hence, **2** should be thermodynamically less competent to oxidize aromatic substrates. This view is clearly supported by DFT calculations (B3LYP, LANL2DZ, PCM CH_2Cl_2) of $MoCl_5$, $MoCl_3(OCH(CF_3)_2)_2$, and $MoCl(OCH_2CF_3)_4$, in the presence of 3,4-dimethoxytoluene (Figure 3).

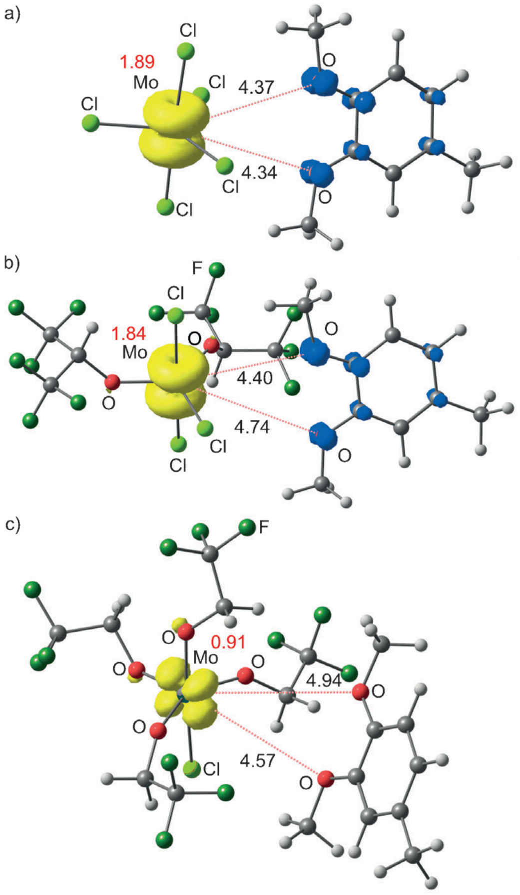


Figure 3. DFT-optimized geometries and spin densities of a) $MoCl_5$, b) $MoCl_3(OCH(CF_3)_2)_2$ with equatorial alkoxido ligands, and c) $MoCl(OCH_2CF_3)_4$ with equatorial alkoxido ligands in the presence of 3,4-dimethoxytoluene (spin multiplicity = 2; yellow/blue isosurface value 0.02 a.u.; Mulliken spin densities at Mo given in red; Mo–O distances [Å]).

For $MoCl_5$ and **1**, electron transfer from 3,4-dimethoxytoluene to the Mo center has clearly occurred with Mulliken spin densities at Mo of 1.89 ($MoCl_5$ + 3,4-dimethoxytoluene) and 1.84 ($MoCl_3(OCH(CF_3)_2)_2$ + 3,4-dimethoxytoluene) confirming the presence of d^2 Mo^{IV} and negative spin density at the 3,4-dimethoxytoluene substrate (Figure 3a and b). This result clearly indicates the formation of an organic radical cation which enters the oxidative pathway. For the mononuclear species $MoCl(OCH_2CF_3)_4$ derived from **2** no such electron transfer from 3,4-dimethoxytoluene can be discerned (Mulliken spin density at Mo: 0.91) confirming the presence of d^1 Mo^V (Figure 3c).

In addition to the thermodynamic arguments presented, we were able to calculate stationary structures with 3,4-dimethoxytoluene κO- and κOκO′-coordinated to $MoCl_5$ and $MoCl_3(OCH(CF_3)_2)_2$ leading to six- and seven-coordinate complexes, respectively (see the Supporting Information). Coordination of the substrate to Mo proved to be impossible for $MoCl(OCH_2CF_3)_4$ according to DFT calculations. Hence, the steric protection by four alkoxido ligands per Mo center in **2** hinders substrate coordination and poses an additional kinetic barrier to the already unfavorable electron transfer to **2**.

The abovementioned undesired chlorination reactions during the oxidative coupling can be significantly reduced by the use of **1**. The major reasons are the lower chlorine content of the novel reagent and the lower nucleophilicity of the HFIP ligands compared to chloride.[15a,19] In addition, the use of **1** decreases the amount of undesired oligomeric materials. This observation might be explained by the higher oxidation potential of **1** in comparison to molybdenum pentachloride which possibly leads to a higher reaction rate of the substrate and subsequent conversions resulting in smaller amounts of by-products. Table 1 depicts the selection of substrates which were subjected to the oxidative coupling reaction and which had been problematic in terms of yield and selectivity using $MoCl_5$.

Reagent **1** considerably increases the yield of the desired product in all cases in our study (Table 1) whereas reagent **2** was unsuitable. The oxidative transformation of the extraordinarily sensitive substrate α-aryl cinnamate using **1** delivered phenanthrene derivative **3** isolated in 71% yield and only 18% of an undesired chlorinated by-product (Table 1, see the Supporting Information).[21] Comparative experiments with $MoCl_5$ gave **3** in a yield of only 26% but the chlorinated product was isolated in 63% yield. The use of $MoCl_5/TiCl_4$, as a reagent mixture can reduce the chlorination reaction to some extent but the total yield for phenanthrene products is significantly lower. The oxidative coupling of 1,5-diiodo-2,3-dimethoxybenzene by **1** allowed **4** to be isolated in 60% yield. Previous investigations with $MoCl_5$ of this particular conversion allowed isolation in only 47% yield. It is noteworthy, that $MoCl_5$ had to be added in small portions to reduce the yield of proto-deiodinated by-products.[7] The use of the $MoCl_5/TiCl_4$ mixture strongly promoted the proto-deiodination process. The reaction of 3,4-dimethoxytoluene with **1** to the corresponding biaryl yielded 82% of **5** ($MoCl_5$: 67%; Table 1).[16] Using **1** the formation of chlorinated by-products can even be completely suppressed in this case. The oxidation of 3,3′′-dimethoxy-*o*-terphenyl with **1** gave 2,7-dimethoxytriphenylene (**6**), isolated in 89% yield. King and co-workers report an isolation in 53% yield using a similar method with $MoCl_5$.[4a] The $MoCl_5/TiCl_4$ mixture provided no amelioration. The yield is inferior (40%) and oligomeric materials seem to be formed. The oxidative coupling of 1,3,5-trimethylbenzene using **1** gave **7,** isolated in 78% yield. Kovacic et al. reported isolation in 34% yield with $MoCl_5$. Furthermore, they report several chlorinated and oligomeric by-products that are made responsible for the low yield.[16] The use of $TiCl_4$ did not improve the situation and the desired compound is only traced by GC methods, hence HFIP ligand is clearly preferred.

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