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Mild, Fast, and Easy To Conduct $MoCl_5$-Mediated Dehydrogenative Coupling Reactions in Flow

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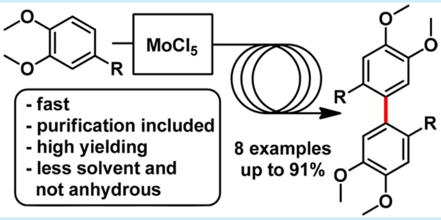
S *Supporting Information*

ABSTRACT: A convenient and straightforward approach to performing oxidative coupling reactions in flow is presented. A collection of electron-rich benzene derivatives was subjected to this protocol, and the distinct utility of molybdenum pentachloride ($MoCl_5$) is established. Using this unexplored protocol, biphenyls could be obtained in 21−91% isolated yield. This simple protocol opens a new chapter in reagent-mediated dehydrogenative coupling reactions, and yields are compared to classical approaches.



Dehydrogenative or oxidative coupling reactions have emerged as a powerful methodology to form new C−C bonds between arenes.[1] While thallium(III) reagents have been applied in the past,[2] today more environmentally friendly reagents such as iron(III) chloride,[3] molybdenum(V) chloride,[4] bis(trifluoroacetoxy) iodobenzene (PIFA),[5] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/methanesulfonic acid[6] are described in this context.[7] In particular, $MoCl_5$ exhibits high performance in establishing new C−C[4] and C−S[8] bonds, respectively. More recently, several reagent-free electrochemical protocols were investigated to efficiently provide dehydrogenative coupling products.[9] These systems operate in 1,1,1,3,3,3-hexafluoroisopropanol using an active molybdenum or BDD anode and can be considered even more environmentally friendly since no stoichiometric amounts of metal reagents are required or consumed.[10]

However, even though large amounts of oxidizers are necessary in classical dehydrogenative coupling, these reactions usually proceed rather quickly, which was recently highlighted for $MoCl_5$.[4b,8a] The high reaction rate for Mo(V) reagents is beneficial since many common side reactions occur on a slower time scale.[11] It is desirable to combine the fast reaction rate of reagent-mediated coupling reactions with the easy purification of the electrochemical protocol, which avoids an aqueous workup. A straightforward solution would be the application of flow conditions, which were reported for similar palladium-catalyzed transformations previously.[12] The solubility of $MoCl_5$ is either fairly poor in noncoordinating organic solvents or the solvents are not stable under the strongly electrophilic conditions.[13] A simple protocol that can be easily implemented into a flow chemical process is highly advantageous to generate the desired compounds in an automated fashion.

Here, we present the first example of a solid deposition of the oxidizer in a reservoir and a slow dissolution of the substrate and elution over the reagent (Figure 1). This reaction mixture could then be directly purified from remaining metal salt byproducts or impurities. Depending on the tubing length and flow rate, the reaction time can be easily adjusted and the whole process is simplified. Since often only short reaction times are necessary, no anhydrous solvents are required, which increases the simplicity and utility of this protocol. Even though oxidative coupling reactions in flow were reported to be exothermic, no self-heating of the setup or further precaution is necessary.[14] The solid bed of $MoCl_5$ is considered as single-use only. To ensure no slow decomposition of the oxidizer during storage between different runs and to avoid contamination with other substrates, each bed is freshly prepared for each reaction.

As a test and benchmark reaction, we investigated the dehydrodimerization of 4-methyl veratrole (**1**) in dichloromethane. On a 1 mmol scale, the substrate was absorbed on 100 mg silica and charged in the precolumn together with $MoCl_5$. The empty space in the PP Büchi cartridge (12 × 75 mm) could be simply filled with sand. After elution, the reaction mixture was directly purified on the silica column (cartridge: 12 × 150 mm, 8 g silica). For collection, a fraction collector was facilitated at a wavelength of 256 nm. Initially, we observed that a flow rate of 2.5 mL/min is crucial (Table 1), since a faster flow rate of 10 mL/min gave no conversion to **2**. This flow rate was kept for 15 min, to ensure that all of the substrate was dissolved and the reaction went to completion. The tubing length was about 60 cm, which corresponds to a residence time of the reaction of about 12 s. With this setup in hand, we tested different equivalents from 1.5 to 3.0 of $MoCl_5$. With 1.5 equiv a good yield of 71% was obtained (Table 1, entry 1).

This is the minimum amount required for the transformation since an overoxidation is crucial in the reaction mechanism,[15] which can be observed when this reaction is conducted under inert batch conditions wherein **2** could be

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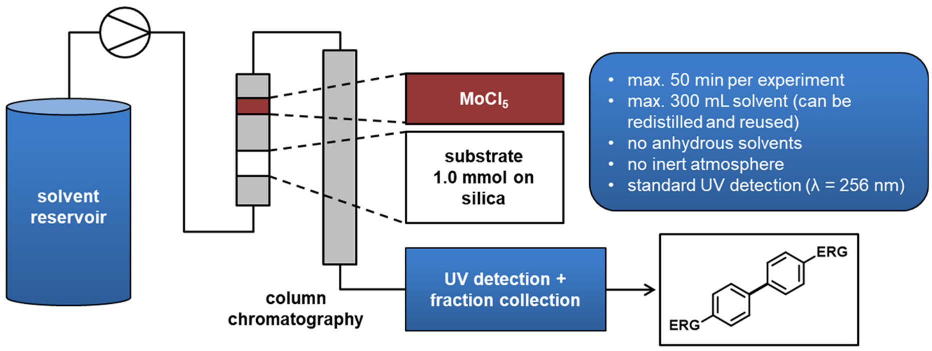
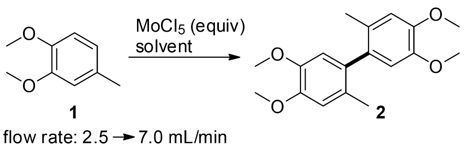


Figure 1. Schematic example of a MoCl$_5$-mediated oxidative coupling reaction under flow conditions (ERG = electron releasing group, newly formed bond in bold).

Table 1. Optimization of the Flow Conditions Using MoCl$_5$ to give 2



entry	solvent	equiv	yield[a] (%)
1	CH_2Cl_2	1.5	71 (93)[b]
2	CH_2Cl_2	2.0	84 (77)[b]
3	CH_2Cl_2	3.0	38
4	MeCN	2.0	–
5	*t*-BuOCH$_3$	2.0	26
6	THF	2.0	3
7	1,4-dioxane	2.0	–
8	toluene	2.0	7

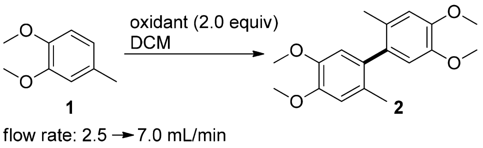
[a] Isolated yield. [b] Yield in parentheses corresponds to the same reaction under inert batch conditions, reaction time of 15 min.

isolated in 93% yield. We found that 2.0 equiv of MoCl$_5$ is required to give a high yield of 84% under flow conditions (Table 1, entry 2). The slight excess comes along with the avoidance of inert conditions and anhydrous solvents for this flow-type reaction. When the amount of reagent (3.0 equiv) is further increased, the yield drops down to 38% due to side reactions such as overoxidation or chlorination (Table 1, entry 3). Interestingly, the isolated yields of **2** are inversed for 1.5 and 2.0 equiv when comparing the classical batch reaction with the flow conditions, and only 77% yield was obtained using 2.0 equiv in batch, which could be explained by overoxidation and oligomerization. Since dichloromethane is not desirable in terms of sustainability and halogen-footprint, we tested the effect of other solvents on the yield of **2**. Strongly coordinating solvents such as acetonitrile gave no conversion of **1** (Table 1, entry 4).

Ethereal solvents were previously reported to be less stable with MoCl$_5$,[16] which was clearly confirmed by using methyl-*tert*-butyl ether (MTBE), THF, or 1,4-dioxane (Table 1, entries 5–7). Whereas MTBE gave a poor yield of 26% of **2**, in THF only traces of the product were isolated and dioxane completely suppressed the syntheses of the biphenyl derivative **2**. Less polar solvents such as toluene gave product **2** in only 7% isolated yield, which corresponds to the diminished solubility of MoCl$_5$ in such solvents (Table 1, entry 8).

Furthermore, we investigated the impact of molybdenum pentachloride on this reaction, since other oxidants such as FeCl$_3$, PIFA, and DDQ/MeSO$_3$H are often applied in similar transformations. All of the reagents were reported to provide biphenyl **2** in yields higher than 90% under batch conditions.[6c,17] Surprisingly, only MoCl$_5$ gave **2** in a sufficient yield of 84%, whereas FeCl$_3$ and PIFA gave no conversion in flow (Table 2, entries 1–3).

Table 2. Comparison of the Efficiency of Different Oxidizers in the Transformation of 4-Methylveratrole (1) into Compound 2 under Flow Conditions



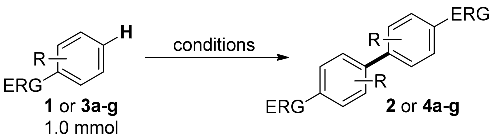
entry	oxidant	yield[a] (%)
1	MoCl$_5$	84
2	FeCl$_3$	–
3	PIFA	–
4	DDQ/MeSO$_3$H	57[b]

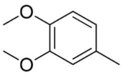
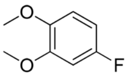
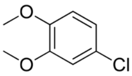
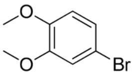
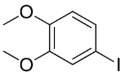
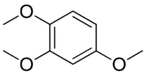
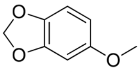
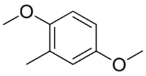
[a] Isolated yield. [b] A second chromatography step (eluent: cyclohexane/ethyl acetate) was required to remove DDQ/DDQH$_2$.

Nevertheless, the mixture of DDQ and MeSO$_3$H provided product **2** in a good yield of 57%, but a second chromatography purification step with different solvents (cyclohexane and ethyl acetate) was required since DDQ and the respective hydroquinone eluted together with the product in CH$_2$Cl$_2$ (Table 2, entry 4). This superior reactivity and characteristics of MoCl$_5$ compared to other oxidizers have not been described before, which is surprising since all other oxidizers were reported to proceed with short reaction times.[6d,17] Likewise, the performance of MoCl$_5$ can be rationalized by a distinct redox play under these particular conditions. During the reaction, an overoxidized radical-cationic intermediate is formed,[15] which is subsequently reduced to the product by Mo(III) and Mo(IV) oxo-complexes.[18] These reducing agents are generated by water impurities within the silica gel, which was not dried prior to use. In addition, silica acts as a trapping agent for HCl formed during the reaction, which will otherwise decrease the reactivity of the Mo(V) reagent.[19] By these means, MoCl$_5$ outperforms other common oxidizers under these flow conditions.

To prove the utility of this new approach to conduct MoCl$_5$-mediated oxidative coupling reactions, we subjected a collection of electron-rich benzene derivatives **3** to this protocol. In addition, these results of the formed biphenyls **4** were compared with classical batch reactions, whereas some of them were reported previously,[11a,20] along with the electrochemical approach we reported recently.[9a] Using our novel flow conditions product **2** could be isolated in a yield of 84% (Table 3). This result can easily compete with the high yields of 93% and 67%, which were reported using batch and electrochemical conditions.[9a,15] Similar observations were found for the halogenated veratrole derivatives **3a**−**c** (F, Cl, Br), and all of them gave significantly higher yields in flow compared to the other two batch-type approaches. Hence, almost quantitative yields of up to 91% were accessible. Only 4-iodoveratrole (**3d**) gave a lower yield of only 25%, which is most likely due to solubility issues of the newly formed biphenyl on the silica column. More activated benzene derivatives **3e** and **3f** gave surprisingly lower yields in flow, compared to batch and Mo-anode mediated conversions. Due to a high local $MoCl_5$ concentration and the low oxidation potential of the substrates, these could oligomerize and thereby suppress the yields down to 21% and 45%, respectively.

Table 3. Scope of Intermolecular Oxidative Aromatic Coupling for Electron-Rich Benzene Derivatives Using $MoCl_5$ under Flow Conditions[a]



substrate	$yield_{flow}$ (%)	$yield_{batch}$ (%)	$yield_{anode}$ (%)
 **1**	84	93[13]	67[9a]
 **3a**	84	58[17a]	12[9a]
 **3b**	80	53	73
 **3c**	91	63[17a]	75[9a]
 **3d**	25	81[17b]	69[9a]
 **3e**	45	98[17a]	87[9a]
 **3f**	21	84	62[9a]
 **3g**	73	64	54[9a]

[a] Flow conditions: $MoCl_5$ (2.0 equiv), CH_2Cl_2, 20 °C. Flow rate: 2.5 mL/min (15 min) → 7.0 mL/min (30−50 min). ERG: electron-releasing group.

The para-dimethoxy derivative **3g** again gave an improved conversion in flow and provided the respective biphenyl in 73% yield.

We hereby developed an easy to perform molybdenum pentachloride-mediated dehydrogenative coupling reaction using flow conditions. Compared to batch reactions, no anhydrous solvent is required, and products can be directly isolated after column chromatography in high yields and purity. The solvent can be redistilled and recycled, and the applied amount can thereby be decreased and no additional solvent change for chromatography is necessary. This protocol not only provides biphenyls in good to excellent yields but also exceeds other commonly applied oxidants such as $FeCl_3$, PIFA, or DDQ under flow conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01664.

General experimental procedures, synthetic details, and characterization, including NMR and MS spectra for all products and intermediate compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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