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DOI: 10.1039/C7CY00336F

Catalysis Science and Technology

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Efficient Carbon-Supported Heterogeneous Molybdenum-Dioxo Catalyst for Chemoselective Reductive Carbonyl Coupling

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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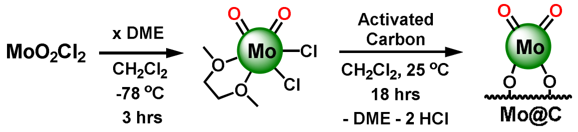
Shengsi Liu,[a] Jiaqi Li,[a] Titel Jurca,[a] Peter C. Stair,[ab] Tracy L. Lohr,[a*] Tobin J. Marks[a*]

Reductive coupling of various carbonyl compounds to the corresponding symmetric ethers with dimethylphenylsilane is reported using a carbon-supported dioxo-molybdenum catalyst. The catalyst is air- and moisture-stable and can be easily separated from the reaction mixture for recycling. In addition, the catalyst is chemoselective, thus enabling the synthesis of functionalized ethers without requiring sacrificial ligands or protecting groups.

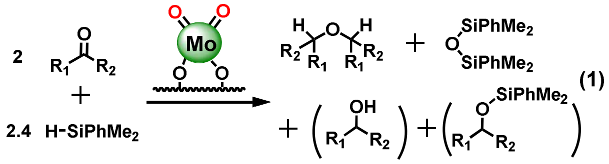
Alkyl and aryl ethers are important classes of organic compounds with wide ranging applications in bioscience, natural product synthesis, industrial polymers, and as protecting groups in organic synthesis.[1-3] The classical method of ether synthesis was reported by Williamson[4-6] more than a hundred years ago using alkyl halides and alkoxide anions. However, this process suffers from major limitations, including base-labile functional group intolerance and poor selectivity when using sterically hindered alkyl halides, where elimination is favoured over substitution. Alternatively, the Mitsunobu reaction can be used for ether synthesis, employing phosphine salts and diethyl azodicarboxylate in acidic media.[7, 8] Recent advances using transition metal catalysts or promoters to access ethers via Chan-Evans-Lam[9-11] and Buchwald-Hartwig coupling[12-15] have also found utility. A promising alternative approach for ether synthesis is the reductive coupling of carbonyl compounds using silanes.[16-22] Nevertheless, despite these advances in in synthetic methodology, many of these transformations require platinum metals, anhydrous conditions, toxic additives, strongly acidic/basic conditions, sacrificial ligands, or excess quantities of alkali salts. As such, the development of more time-efficient procedures and the use of more cost-effective reagents to improve overall reductive coupling efficiency would be highly desirable.

While many homogeneous catalysts have been used for ether synthesis,[23-32] the use of heterogeneous catalysts for this reaction has received substantially less attention. It is well accepted that heterogeneous catalysts offer several advantages over analogous homogeneous processes, such as greater thermal stability, recyclability, and ease of separation from reaction mixtures.[33-36] Recent work from this laboratory has shown that a single-site dioxo-molybdenum catalyst supported on high surface area activated carbon, **Mo@C** (Scheme 1), is a highly active and selective catalyst for alcohol oxidation[37] and transesterification.[38] Thus we envisioned that



Scheme 1. Synthesis of **Mo@C**.

Mo@C might also serve as a useful catalyst for C-O bond-forming reactions (see ref 38 for detailed catalyst characterization and discussion of the single site nature). Here we report that **Mo@C** efficiently catalyzes the reductive coupling of diverse carbonyl compounds in the presence of dimethylphenylsilane ($PhMe_2SiH$) in high conversions (eq. 1). In addition, the catalyst exhibits both *inter*- and *intra*molecular chemoselectivity for the synthesis of ethers, thus enabling routes to functionalized ethers in the presence of unsaturated and halogenated functional groups.



(1)

Our initial study focused on **Mo@C**-catalyzed reductive coupling of *n*-octanal. At 100 °C, the catalyst achieves complete conversion of the substrate in 3 h to afford di-*n*-octyl ether as the major product with only trace amounts of the corresponding silylether and octanol (Table 1, entry 1). This

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[a] Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113, United States. Email: t-marks@northwestern.edu, tracy.lohr@northwestern.edu

[b] Chemical Sciences and Engineering Division, Argonne National Laboratory, Lemont, Illinois 60439, United States.

Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/x0xx00000x

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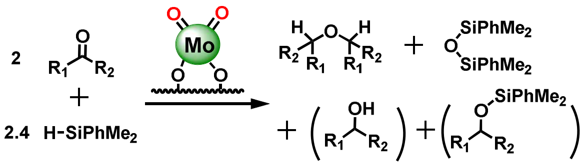
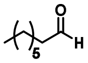
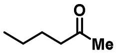
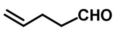
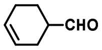
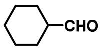
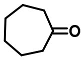
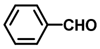
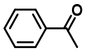
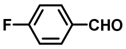
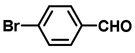
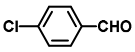
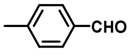
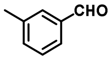
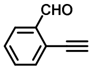
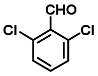
DOI: 10.1039/C7CY00336F

Table 1. Reductive carbonyl coupling substrate scope[a]



Entry	Substrate	Time (h)	Conv.	Selectivity		
				Ether	Alcohol	Silyl ether
1		3	100%	99%	<1%	<1%
2[b]		20	77%	90%	10%	<1%
3[b]		24	99%	99%	<1%	<1%
4		24	100%	94%	6%	<1%
5		6	94%	99%	<1%	<1%
6		6	99%	27%	45%	22%
7		3	100%	93% (86%)[c]	7%	<1%
8		24	89%	79%	<1%	<1%
9		3	90%	72%	10%	18%
10		6	96%	79% (71%)[c]	12%	9%
11		3	98%	65% (56%)[c]	8%	27%
12		3	74%	76% (50%)[c]	15%	9%
13		3	85%	88%	10%	2%
14		9	51%	14%	46%	15%
15		24	98%	19%	16%	65%

[a] Conditions unless otherwise specified: 6.5 mmol of substrate, 0.1 mol % of Mo (15 mg of 4.0 wt % **Mo@C**), 5 mL of anhydrous 1,1,2,2-tetreacholorethane, 500 rpm, 100 °C. Conversions and selectivity determined by ^{1}H NMR using mesitylene as internal standard; products also confirmed by ^{13}C NMR and GC-MS where appropriate but were not quantified by these methods. One equivalence of siloxane per ether product found at the end of the reaction by ^{1}H NMR. [b] Reaction at 60 °C because deoxygenation was observed at higher temperatures. [c] Isolated yield.

high product selectivity towards the ether stands in contrast to most homogeneous Mo catalysts where carbonyl hydrosilylation produces the silylether as the main product under similar conditions.[39-41] We next expanded the survey to other aliphatic, aromatic, and functionalized aldehydes and ketones (Table 1). In most cases, the catalyst achieves excellent conversion of the carbonyl substrates and exhibits high product selectivity towards the ether while the corresponding silylether and desilylated alcohol (from reaction with adsorbed water on the **Mo@C** surface, Figs. S2-S5, *vide infra*) are observed as minor side products. In general, aliphatic substrates exhibit higher ether selectivity in comparison to aromatic substrates, some of which also require longer reaction times. While no pronounced electronic effects are evident, ether selectivity is significantly reduced in the case of sterically hindered carbonyl substrates (Table 1, entries 6, 14-15). Note also that the catalyst retains excellent chemoselectivity towards carbonyl moieties in the presence of halides, alkenes, and alkynes (Table 1, entries 3-4, 9-11, and 14-15). Furthermore, intermolecular chemoselective carbonyl coupling can also be achieved with excellent product selectivity towards the ether with essentially no hydrogenation or hydrosilylation of the alkene or alkyne moiety (Table S1), in contrast to typical transition metal catalysts.[42-44]

As noted above, homogeneous analogues of **Mo@C** and other transition metal complexes are known catalysts for the hydrosilylation of carbonyl compounds under similar conditions,[45] however, silylethers and desilylated alcohols are often reported as the main products instead of ethers. This reverse shift in product selectivity observed in our system argues that these transformations are catalyzed by a heterogeneous Mo-dioxo species rather than a leached homogeneous molecular Mo species. Moreover, ICP analysis of the reaction solution revealed essentially no Mo (< 90 ppm) and the Mo loading of the used catalyst remained essentially unchanged (3.9 wt. % versus 4.0 wt. %). Additionally, the trace amounts of Mo in solution were determined to be catalytically insignificant since the reaction liquid collected from hot filtration experiments effected no substrate conversion (see SI and Figure S1 for details). Furthermore, recycling experiments show that the catalyst can be used up to 5 times with negligible decline in ether selectivity or deactivation (Figure 1A). The surface Mo on the used catalyst was next analysed by

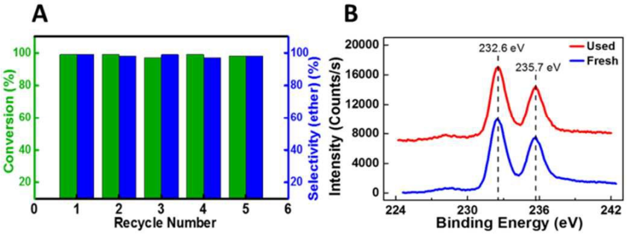


Fig. 1. A. Recycling experiments illustrating the conversion and selectivity from *n*-octanal to di-*n*-octyl ether using the recycled **Mo@C** catalyst. Reactions run for 3 hours at 100 °C at 500 rpm. **B.** Mo (3d) XPS spectra of **Mo@C** before (blue) and after (red) a catalytic run.

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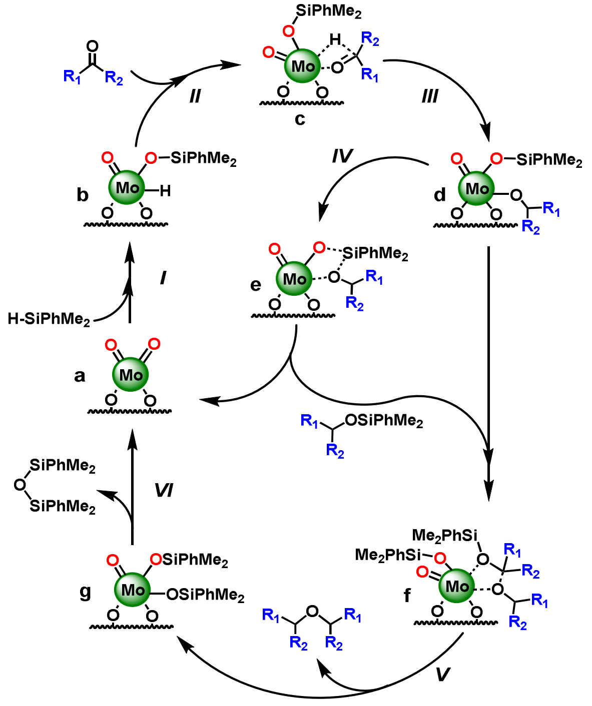
XPS (Figure 1B). The Mo 3d$_{5/2}$ peak of the used catalysts was found to be 232.6 eV with a spin orbit splitting of 3.1 eV which is in good agreement with our previous XPS data,[38] and no variation in the Mo binding energy is observed with respect to the fresh catalyst, confirming that the nature of the surface bound Mo-species (depicted in Scheme 1; see ref 38 for detailed structure determination) remains unchanged.

Based on previous studies of homogeneous dioxo-molybdenum-catalyzed transesterification[38] and reductive carbonyl coupling,[19, 23, 27, 46] we propose the reaction scenario in Scheme 2. Based on previous mechanistic investigations of high-valent Mo-dioxo mediated hydrosilylation, Si-H activation is proposed to be initiated across the Mo=O bond (Scheme 2, *I*).[40, 47-49] The metal hydride (**b**) then migrates to the incoming electrophilic carbonyl carbon atom (Scheme 2, *II*) generating an alkoxide species (Scheme 2, **d**, step *III*). Molybdenum oxohydroxoalkoxy complexes are known,[50, 51] so analogous oxosiloxyalkoxy complex **d** is reasonable to propose. The Mo-alkoxide can then proceed to eliminate the silylether, regenerating the dioxo-molybdenum active center (Scheme 2, **a**, step *IV*). However, weakly coordinating silylethers (or alcohols) can undergo nucleophilic attack by the alkoxide to yield the symmetric ether (Scheme 2, **f**, step *V*), similar intermediate structures have been previously proposed.[23, 52] DFT calculations show this step to be thermodynamically favourable,[46] so that the selectivities for the hydrosilylated product and the desilylated alcohol are low unless the carbonyl moiety is sterically encumbered, in good agreement with the present results. Subsequently, the siloxane is eliminated to regenerate the dioxo-molybdenum and complete the catalytic cycle (Scheme 2, *VI*). One equivalent of siloxane per ether product is found at the end of the reaction by ^{1}H NMR spectroscopy, further validating the proposed sequence in Scheme 2.



Scheme 2. Proposed mechanism of **Mo@C**-mediated reductive carbonyl coupling.

A preliminary investigation of the empirical rate law for **Mo@C**-catalyzed reductive carbonyl coupling was conducted by ^{1}H NMR monitoring with mesitylene as the internal standard (see SI for details). Because of the highly porous nature of the activated carbon support, and the carbonyl substrates competitively adsorb to the catalyst surface,[37] an accurate rate law for this system is challenging to deduce. Nevertheless, the observed rate is found to be negative mixed order in [Carbonyl], and half order in [PhMe$_2$SiH] (Figure S2). While detailed assessment and interpretation of such reaction orders are not straightforward in heterogeneous systems where reaction occurs at the liquid-solid interface,[53] these results are in accord with a complex reaction network such as the one proposed here. More comprehensive kinetic and computational studies are currently underway.

Because activated carbon is known to contain surface Lewis acid sites, control experiments using the bare activated carbon were performed under the same conditions with *n*-octanal, and less than 2% conversion is achieved, arguing that the support's surface acid sites do not significantly contribute to product formation. Alternatively, it is possible that the reaction proceeds through sequential hydrosilylation, hydrolysis, and dehydration to afford the ether. However, no ether formation is observed when either silylether or alcohol is used as the reactant under the same conditions, indicating that the dehydration mechanism is not competitive (Scheme S1). Instead, it was observed that alcohol formation proceeds through **Mo@C** catalyzed hydrolysis of the silylether with water present in the system (Figures S3-S5). Additional control experiments to probe the role of the silylether and alcohol were also performed to corroborate the proposed reaction mechanism (see SI for full details).

Conclusions

We have demonstrated that **Mo@C** is a highly stable, active, selective, and recyclable catalyst for ether synthesis through reductive carbonyl coupling under mild conditions. The product selectivity towards the ether scales inversely with the steric encumbrance of the carbonyl group. We show that the catalyst exhibits both *intra-* and *inter*molecular chemoselectivity over functional groups such as halides, alkenes, and alkynes which would otherwise be cleaved or hydrogenated using conventional protocols under reductive conditions. This robust catalytic system should be an attractive methodology for the synthesis of functionalized ethers.

Acknowledgements

This work is supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences under Award Number DOE DE-FG02-03ER154757. This work also made use of instruments at the IMSERC Center at Northwestern University which were supported by the National Science Foundation under NSF CHE-9871268 (1998), NSF CHE-1048773 and NSF DMR-0521267 (2005). This work made use of the Keck-II facility of the NUANCE Center at Northwestern University, which has received support from the Soft and Hybrid Nanotechnology Experimental (SHyNE) Resource (NSF

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DOI: 10.1039/C7CY00336F

NNCI-1542205); the MRSEC program (NSF DMR-1121262) at the Northwestern Materials Research Center; the International Institute for Nanotechnology (IIN); the Keck Foundation; and the State of Illinois, through the IIN.

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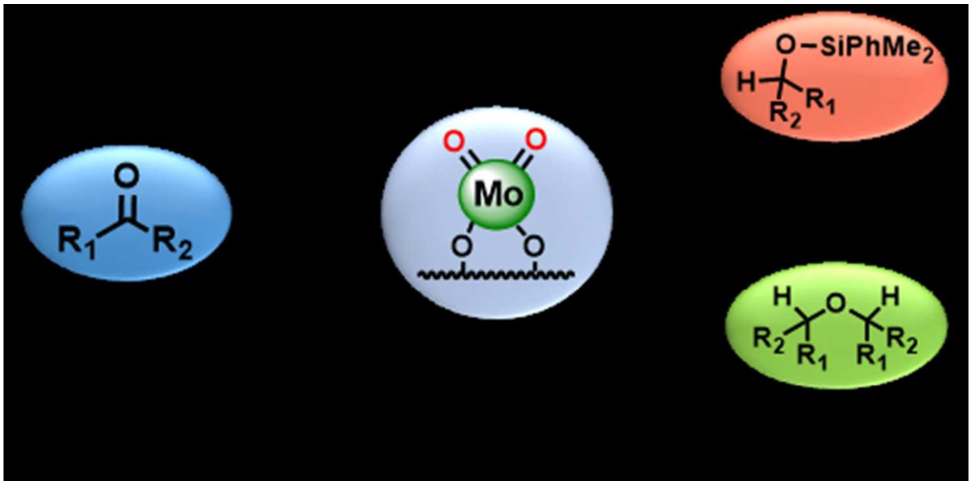

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