

## Synthetic Methods

## Iridium-Catalyzed Reductive Deoxygenation of Esters for the Synthesis of Sterically Hindered Ethers

Yaseen A. Almeahmadi, Anna J. Passmore, Pablo Gabriel, and Darren J. Dixon\*

Dedicated to Professor Steven V. Ley CBE FMedSci FRS on the celebration of his 80th birthday

**Abstract:** The synthesis of sterically hindered  $\alpha$ -tertiary and  $\beta$ -quaternary (neopentyl) ethers has long been constrained by the limitations of traditional  $S_N2$  and related  $S_N1$  approaches, namely low or inexistent reactivity arising from severe steric hindrance or competitive elimination/rearrangement pathways diverting the reaction outcome. Herein, we describe a general solution to the synthesis of sterically hindered ethers via an iridium-catalyzed reductive deoxygenation reaction of readily available ester and lactone starting materials. Employing commercially available, bench-stable  $\text{IrCl}(\text{CO})(\text{P}[\text{OCH}(\text{CF}_3)_2]_3)_2$  as a precatalyst at 1 mol% loading with 4 equivalents of tetramethyldisiloxane (TMDS) as the terminal reductant at room temperature, this practical synthetic approach to hindered ethers features a simple, mix-and-stir, single-vessel protocol under ambient conditions and produces a diverse range of both acyclic and cyclic ether products in good to excellent yields. Control experiments demonstrated that the  $\text{IrCl}(\text{CO})(\text{P}[\text{OCH}(\text{CF}_3)_2]_3)_2$ /TMDS catalytic system could not only rapidly hydrosilylate esters to mixed silyl/alkyl hemiacetal intermediates but also catalyze the reduction of acetals directly to ethers, revealing the Lewis acidic and hydridic properties required for this deoxygenative transformation.

## Introduction

Sterically hindered ethers, such as those possessing  $\alpha$ -tertiary or  $\beta$ -quaternary (neopentyl) carbon atoms, are commonplace structural motifs found across biologically relevant molecules, such as natural products and pharmaceutical compounds (Scheme 1a).<sup>[1–3]</sup> Despite their abundance and importance, there are numerous challenges associated with the synthesis of these motifs. Textbook synthetic approaches, such as the venerable Williamson reaction or the Mitsunobu reaction, can often deliver unhindered ethers with relative ease but are rarely applicable to the synthesis of more sterically encumbered variants.<sup>[4–6]</sup> For example, attempted bimolecular union of sterically demanding alkoxide nucleophiles with secondary, tertiary, and neopentyl electrophilic coupling partners typically fails due to severe steric repulsions hindering the desired  $S_N2$  pathway. This

results in low or inexistent reactivity, or competitive elimination/rearrangement pathways dominating the reaction outcome.<sup>[7–10]</sup> An alternative approach to the synthesis of  $\alpha$ -tertiary ethers relies on weak alcohol nucleophiles intercepting tertiary carbocationic intermediates, formed via acid-mediated reactions (solvolysis) or by protonation of a suitable alkene substrate. However, acid sensitivity of some substrates, poor reactivity, and competitive rearrangement pathways limit the applicability of this approach.<sup>[11]</sup> To address these challenges, in recent years, significant efforts have been made to improve the synthetic accessibility of such hindered ethers.<sup>[3]</sup> Productive lines of enquiry have focused on single-electron reaction manifolds using both electrochemical and photochemical activation approaches, with notable contributions from the group of Baran,<sup>[12,13]</sup> Ohmiya,<sup>[14–16]</sup> Knowles,<sup>[17]</sup> Doyle,<sup>[18,19]</sup> Glorius,<sup>[20,21]</sup> as well as our own.<sup>[22,23]</sup> Despite these advances, major synthetic hurdles still remain in achieving their synthesis, especially for  $\alpha$ -tertiary or  $\beta$ -quaternary (neopentyl) ethers, underscoring the need for novel chemical methodologies to address this ongoing challenge.<sup>[3]</sup>

As a general and practical solution to hindered ether synthesis, we were drawn to the conceptually simple yet strategically powerful ester reductive deoxygenation approach. This would enable the direct synthesis of hindered ethers from naturally occurring or commercially available esters or lactone starting materials or, in two steps, from abundant feedstock carboxylic acids (or derivatives) and alcohols using well-established and robust esterification methods, which tolerate steric hindrance on both acyl and alkoxy sides of the ester moiety.<sup>[24]</sup> Not unsurprisingly, this reductive deoxygenative approach toward the synthesis of sterically hindered (and unhindered) ethers has been investigated previously using

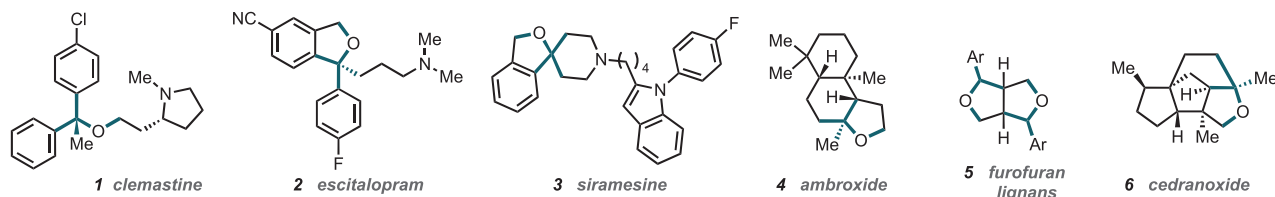
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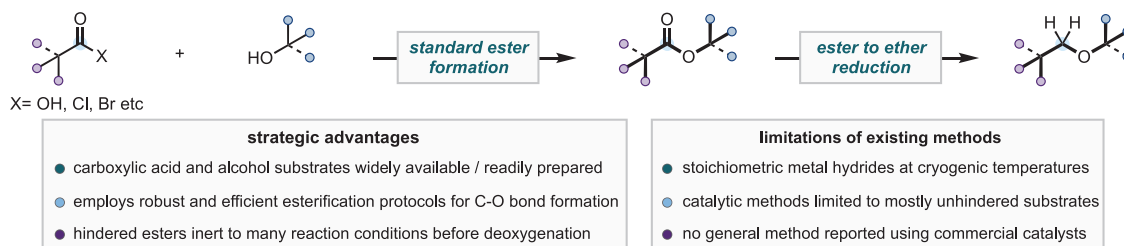
Additional supporting information can be found online in the Supporting Information section

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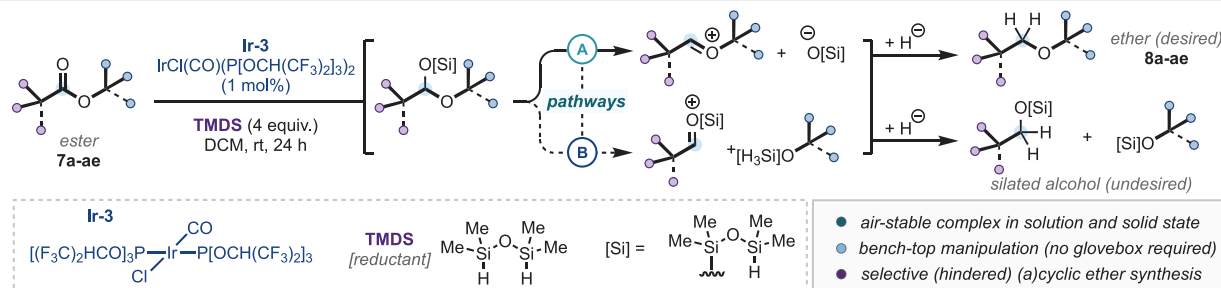
## a) | Prevalence of hindered ethers in pharmaceuticals and natural products



## b) | Advantages of the direct reductive deoxygenation approach to ethers from esters and limitations of existing methods for hindered ether synthesis



## c) | This work



**Scheme 1.** a) Prevalence of hindered ethers in pharmaceuticals and natural products; b) Direct reduction of ester to ether approach and limitations of existing methods; c) This work.

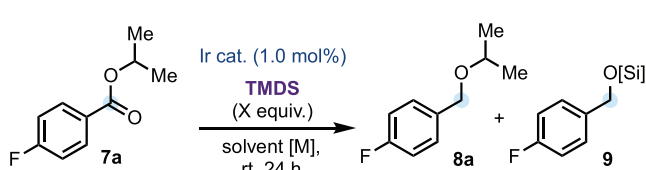
stoichiometric amounts of strong metal hydride reagents, such as lithium aluminum hydride ( $LiAlH_4$ ) or diisobutylaluminum hydride (DIBAL), followed by an in situ acylation or silylation of the metalated hemiacetal intermediate. In a subsequent step, a Lewis acidic activator, such as boron trifluoride etherate ( $BF_3 \cdot Et_2O$ ) in the presence of a silane terminal reductant, provides access to the ether product from the hemiacetal intermediate.<sup>[25–29]</sup> However, the use of stoichiometric metal hydride reagents at carefully controlled cryogenic temperatures, the two-step nature of the protocols, and the relatively harsh reaction conditions somewhat limit this approach in both academic and industrial settings.

More recently, catalytic variants of the reductive deoxygenation process for accessing ether functionality directly from relatively simple and mostly unhindered ester substrates have been reported using various catalytic systems based on organometallic complexes of Ru,<sup>[30,31]</sup> Fe,<sup>[32]</sup> Mn,<sup>[33,34]</sup> Ti,<sup>[35–37]</sup> Rh,<sup>[38]</sup> Pd,<sup>[39]</sup> Ir,<sup>[40–46]</sup> and main group metal salts such as  $GaBr_3$ ,<sup>[47]</sup>  $InBr_3$ ,<sup>[48–50]</sup> and fluorinated borate salts or boranes<sup>[51–53]</sup> in conjunction with excess silanes as the terminal reductant. However, for sterically demanding ester substrates, i.e., those possessing fully substituted carbon atoms on both sides of the carboxyl group, a general and practical catalytic reductive deoxygenation methodology to access the sterically hindered dialkyl ether products remains undeveloped.

Inspired by these pioneering studies and building on our own<sup>[54–69]</sup> and others<sup>[70–87]</sup> findings in the field of amide reductive functionalization using Vaska's complex  $IrCl(CO)(PPh_3)_2$  **Ir-1** with TMDS and the work of Brookhart on the hydrosilylation of esters to access aldehydes,<sup>[43]</sup> we reasoned that a selective catalytic reductive deoxygenation of hindered esters to hindered ethers could indeed be developed if a more powerful derivative of Vaska's complex in conjunction with a suitable silane terminal reductant could be identified. Previous work by our group had revealed that with less electron-rich anilide or hydrazide substrates, significantly enhanced carbonyl hydrosilylation reactivity could be achieved using electron-deficient triphenyl phosphite ligands in lieu of triphenyl phosphine on Vaska's complex.<sup>[59,88]</sup> Extending these observations to ester substrates, we envisioned that the necessary reactivity that we sought could indeed come from such phosphite analogues of Vaska's complex (Scheme 1c), and herein we present our findings.

## Results and Discussion

Isopropyl 4-fluorobenzoate **7a** was selected as a model ester substrate to explore the catalytic reductive deoxygenation

**Table 1:** Precatalyst screen and reaction optimization.


| Entry | Solvent           | TMDS (X equiv.) | Conc. [M] | Ir cat. | Conv. % | Ratio (%)<br>8a : 9 |
|-------|-------------------|-----------------|-----------|---------|---------|---------------------|
| 1     | toluene           | 5.0             | 0.5       | Ir-1    | 0       | 0 : 0               |
| 2     | toluene           | 5.0             | 0.5       | Ir-2    | 8       | 60 : 40             |
| 3     | toluene           | 5.0             | 0.5       | Ir-3    | 100     | 90 : 10             |
| 4     | DCM               | 5.0             | 0.5       | Ir-3    | 100     | 94 : 6              |
| 5     | Et <sub>2</sub> O | 5.0             | 0.5       | Ir-3    | 86      | 90 : 10             |
| 6     | THF               | 5.0             | 0.5       | Ir-3    | 85      | 89 : 11             |
| 7     | (TMDS)            | 5.0             | neat      | Ir-3    | 100     | >95 : 5             |
| 8     | DCM               | 5.0             | 1.0       | Ir-3    | 100     | >95 : 5             |
| 9     | DCM               | 4.0             | 1.0       | Ir-3    | 100     | >95 : 5             |
| 10    | DCM               | 3.0             | 1.0       | Ir-3    | 88      | >95 : 5             |

reaction. Initially, we reconfirmed many previous observations that subjecting ester **7a** to standard hydrosilylation reaction conditions using Vaska's complex **Ir-1** (1.0 mol%) and 2.0 equivalents of 1,1,3,3-tetramethyldisiloxane (TMDS)<sup>[89]</sup> as the hydride source in toluene (0.1 M) at room temperature resulted in zero reactivity. Increasing the amount of TMDS to 5 equivalents, the concentration to 0.5 M in toluene, and the reaction time to 24 h also resulted in no conversion and full recovery of the starting material (Table 1, entry 1). We then turned our attention to investigating the performance of derivatives of Vaska's complex **Ir-2** and **Ir-3**, possessing triphenyl phosphite and tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite P[OCH(CF<sub>3</sub>)<sub>2</sub>]<sub>3</sub> ligands, respectively.<sup>[59,77]</sup>

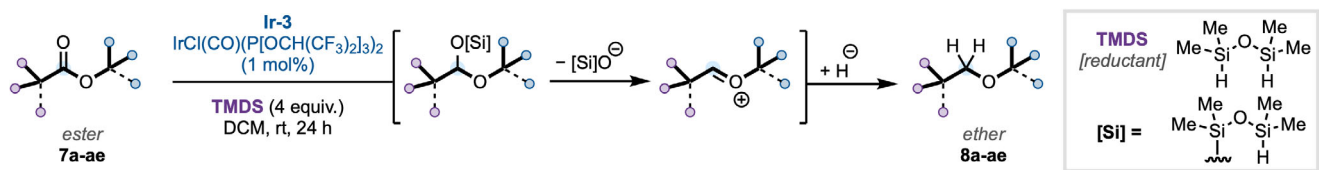
Encouragingly, use of IrCl(CO)(P[OPh]<sub>3</sub>)<sub>2</sub> **Ir-2** resulted in an 8% conversion of ester **7a** to the desired isopropyl ether **8a** and the undesired silylated alcohol **9a** in a 60:40 ratio, respectively (Table 1, entry 2). However, IrCl(CO)(P[OCH(CF<sub>3</sub>)<sub>2</sub>]<sub>3</sub>)<sub>2</sub> **Ir-3**, an air-stable, bright yellow crystalline solid,<sup>[77,90]</sup> under the same reaction conditions (Table 1, entry 3), resulted impressively in complete conversion of ester (**7a**) to the corresponding ether **8a** and silylated alcohol **9** in a 90:10 ratio, respectively. This brief precatalyst investigation identified that **Ir-3** complex was ideally suited for this reductive deoxygenative transformation, providing the necessary hydrosilylation reactivity and the Lewis acidity to form the putative oxocarbenium ion from the mixed silyl acetal intermediate prior to terminal hydride addition. Upon examining different reaction solvents such as dichloromethane (DCM), diethyl ether (Et<sub>2</sub>O), and tetrahydrofuran (THF), DCM was identified as the most suitable solvent for this reaction, increasing the ratio of **8a**:**9** to 94:6, respectively (Table 1, entries 4–6). Further optimization of the concentration of the reaction and the equivalents of TMDS (Table 1, entries 7–10) led to the optimized reaction

conditions (1.0 M in DCM, 4 equivalents of TMDS), which provided the desired isopropyl ether **8a** in 95% yield and in excellent (>95:5) product selectivity (Table 1, entry 9).

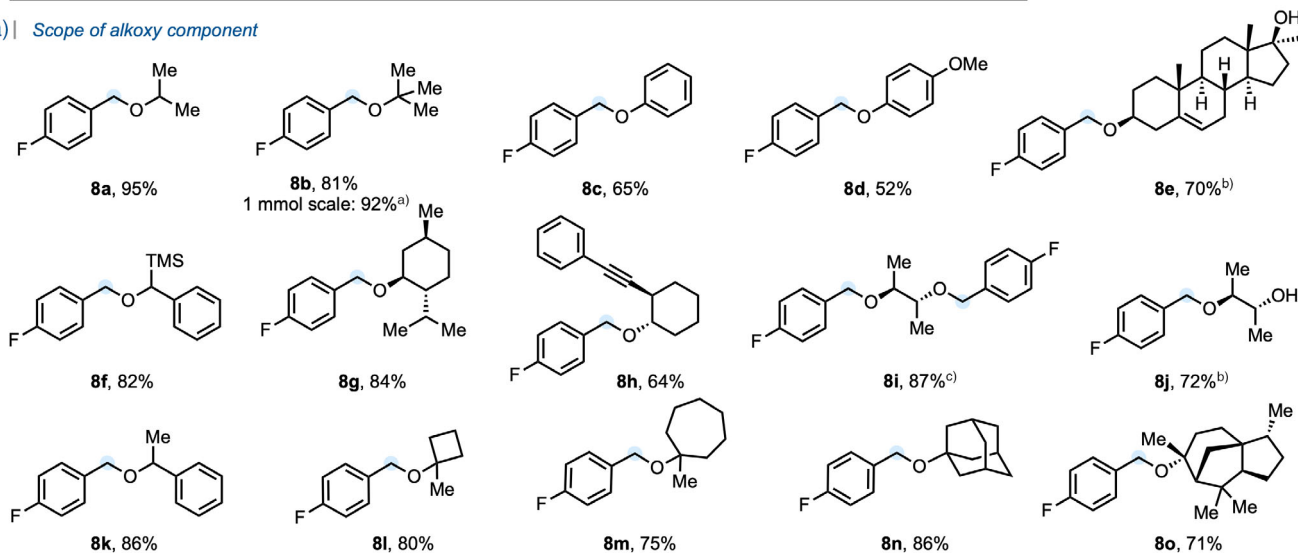
Having established a practically simple and highly efficient protocol for the reductive deoxygenation of model substrate **7a**, we then turned our attention to the scope of the reaction. Initially we explored its generality with respect to the alkoxy group of 4-fluorobenzoyl esters (Scheme 2a). Under the optimized conditions, increasing the bulk of the alkoxy component from isopropyl (**7a**) to *tert*-butyl (**7b**) gratifyingly resulted in an excellent yield of alpha *tert*-butyl ether **8b**. The 4-fluorobenzoic ester of phenol (**7c**) and *para*-methoxy phenol (**7d**) were also tolerated under our reductive protocol, providing a good yield of their respective ethers **8c–d**. Furthermore, esters derived from methandriol (**7e**), trimethylsilyl-containing alcohol (**7f**), menthol (**7g**), and alkyne-containing alcohol (**7h**) were also amenable to this methodology. Pleasingly, double reductive deoxygenation of diester **7i** proceeded in high yield (87%), as did the reductive deoxygenation of an ester carbonyl in the presence of an unprotected secondary alcohol (**7j**), although an additional equivalent of TMDS was required for transient in situ alcohol silylation. 4-Fluorobenzoyl esters of other more sterically hindered alcohols (**7k–o**) were smoothly reduced to their corresponding hindered ethers **8k–o** in good yields (71%–86%). Remarkably, the reduction of chiral esters **7e**, **7g–j**, and **7o** proceeded without observable racemization, delivering the corresponding hindered ethers **8e**, **8g–j**, and **8o** in good to excellent yields.

Next, keeping the isopropoxy group as the model alcohol component, the scope with respect to the acyl group was then investigated (Scheme 2b). Pleasingly, switching the 4-fluorobenzoyl group to 3,4-methylenedioxybenzoyl, 4-methoxybenzoyl, 3-methoxybenzoyl, 2-methoxybenzoyl, and 2-methylbenzoyl gave acceptable yields of the desired ether products, **8p–t**, respectively. Importantly, isopropyl esters derived from linear aliphatic carboxylic acids such as **7u**, **7v**, and **7w**, featuring an unprotected indole, were excellent substrates and resulted in the formation of their respective ethers **8u–w** in good to excellent yields. Similarly, isopropyl cyclohexyl carboxylate **7x**, when also subjected to the optimal reaction conditions, resulted in the formation of ether **8x** in good yield. Furthermore, isopropyl  $\alpha$ -tertiary carboxylates **7y–ad** were successfully reduced to the corresponding ethers **8y–ad**; however, in the cases of such sterically hindered  $\alpha$ -tertiary alkyl esters, solvent-free conditions and 2 mol % of **Ir-3** for the initial hydrosilylation step, followed by direct addition of TMSOTf (1 equiv.) as a Lewis acid to promote ionization of the mixed silyl hemiacetals prior to hydride addition, were required.

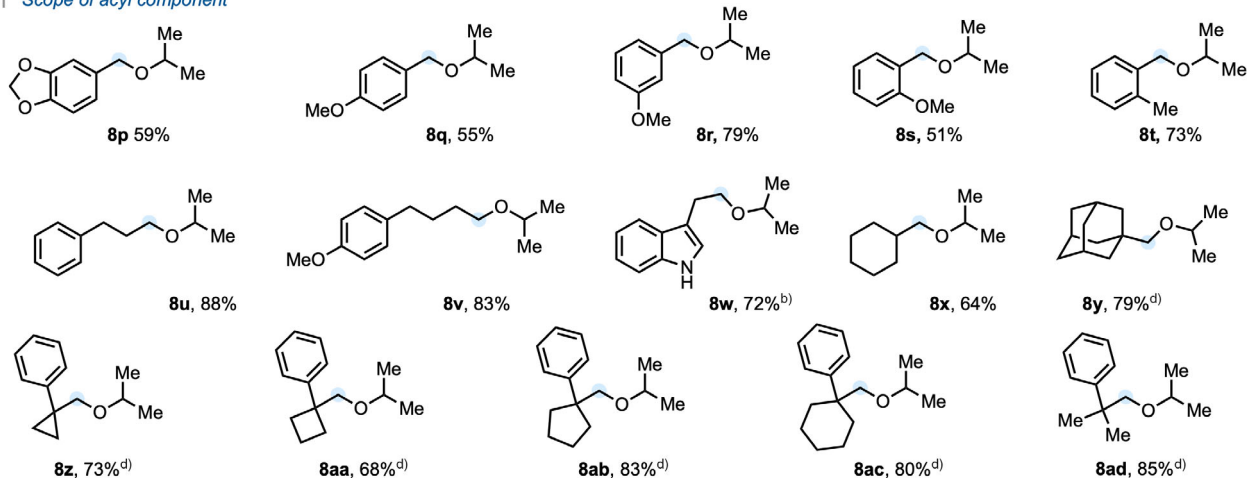
Other synthetically relevant examples are shown in Scheme 2c. *tert*-Butyl 2-phenylacetate **7ae** was reduced in excellent yield to the corresponding ether **8ae** under the standard conditions. This example is particularly noteworthy owing to the lack of feasibility of accessing such a compound using an S<sub>N</sub>2 approach with *tert*-butoxide as the nucleophile. 1-Adamantyl adamantane-1-carboxylate **7af** was successfully reduced to the corresponding ether **8af** in acceptable 67% yield using the protocol described above for other  $\alpha$ -tertiary



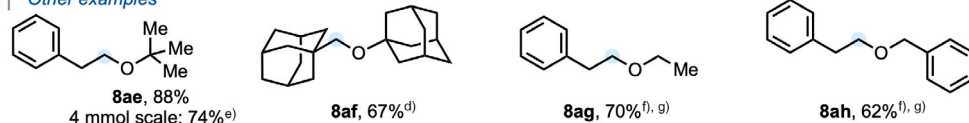
## a) | Scope of alkoxy component



## b) | Scope of acyl component



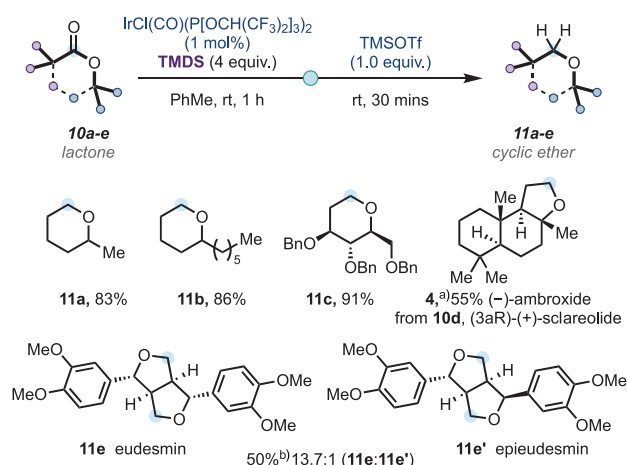
## c) | Other examples



**Scheme 2.** Substrate scope of the reduction of (hindered) acyclic esters to ethers; all yields are isolated yields. <sup>a)</sup> 0.5 mol% of **Ir-3** was used in neat TMDS. <sup>b)</sup> 5.0 equivalents of TMDS were used. <sup>c)</sup> 2 mol% of **Ir-3** and 8.0 equivalents of TMDS were used. <sup>d)</sup> 2 mol% of **Ir-3** was used in neat TMDS (4.0 equiv.), and TMSOTf (1.0 equiv.) was added at rt after 24 h. <sup>e)</sup> 0.25 mol% of **Ir-3** was used in neat TMDS. <sup>f)</sup> The reaction was carried out in 0.1 M in toluene, and the reduction was complete within 1 h at rt instead of 24 h. <sup>g)</sup> TMSOTf (1.0 equiv.) was added at rt after 1 h.

alkyl esters. Gaining access to such hindered neopentyl ether products using alternative synthetic approaches would be otherwise difficult. Pleasingly, a slight adjustment of the reaction conditions also enabled the reduction of less hindered esters **7ag** and **7ah** to the corresponding ethers **8ag** and **8ah** in 70% and 62% yield, respectively. Although the main scope was routinely carried out on 0.2 mmol scale, we

successfully demonstrated that it could be carried out on a 1 mmol (**7b**) and 4 mmol scale (**7ae**) using 0.5 mol% and 0.25 mol% loading of **Ir-3**, respectively, while maintaining reaction efficiency (see [Supporting Information](#)). Using **7ae** as a model substrate, a Glorius robustness screen<sup>[9]</sup> was carried out to test the procedure's compatibility with different additives (see [Supporting Information](#)). The reaction tolerated aryl

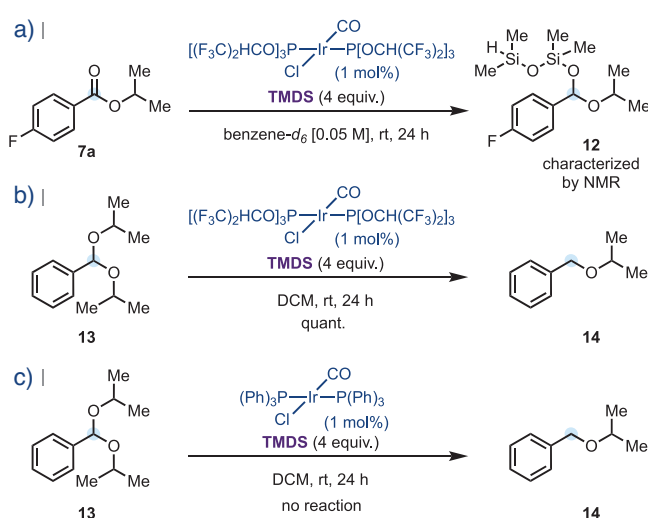


**Scheme 3.** Reductive deoxygenation of lactones to cyclic ethers: scope and application in natural product synthesis; all yields are isolated yields. <sup>a</sup>) 20 mol% of TMSOTf was used. <sup>b</sup>) TMSOTf was added at  $-20^{\circ}\text{C}$ .

bromides, chlorides, and iodides, and terminal alkenes with no reduction in yield or conversion of the additive. Conversely, nitrile and nitro groups were found to be incompatible, resulting in a decreased yield and consumption of the additive. Interestingly, with pyridine and secondary carbamate additives, the reactivity was strongly diminished, albeit with no loss of the additive, suggesting these functionalities were poisoning the active catalyst.

Having successfully explored the scope of the reductive deoxygenation reaction for acyclic (hindered) esters to (hindered) ethers, we then turned our attention to cyclic systems (Scheme 3). Six-membered lactones **10a–c** were accommodated in good-to-excellent yields to access cyclic ethers **11a–c**, although TMSOTf (1.0 equiv.) was necessary to trigger the second stage of the reductive deoxygenation reaction. Lowering the amount of TMSOTf to 20 mol% was also successfully demonstrated in the case of natural product (3aR)-(+)-sclareolide **10d**, which was successfully reduced to (-)-ambroxide **4** in a good yield in a single vessel. Furthermore, natural product eudesmin **11e** was synthesized from the corresponding bicyclic bislactone **10e** in good yield and excellent diastereoselectivity; in this particular example, TMSOTf was added at  $-20^{\circ}\text{C}$  to avoid possible epimerization.<sup>[92]</sup>

To probe the proposed two-stage mechanistic course of the reaction, the standard reduction conditions were applied to model substrate **7a**; however, with higher dilution in deuterated benzene for NMR monitoring purposes (Scheme 4a). Pleasingly, after 24 h at room temperature,  $^1\text{H}$  NMR analysis revealed the presence of silylated mixed acetal **12**, the direct product of hydrosilylation of **7a**. Furthermore, as full deoxygenation was occurring without added TMSOTf in the cases of benzoate ester substrates, **7a–7o**, as well as aroyl esters **8p–t** and linear aliphatic carboxylates **7u–w**, **7x**, and **7ae**, this indicated that in the presence of TMDS, **Ir-3** acts not only as a strong hydrosilylating agent but also as a competent Lewis acid. To probe this hypothesis experimentally, hindered diisopropyl benzyl acetal **13** was synthesized and subjected to the optimized reaction conditions using **Ir-3** (1 mol%) and



**Scheme 4.** Mechanistic studies into carbonyl hydrosilylation and for acetal activation by the **Ir-3**/TMDS precatalyst system; all yields are isolated yields.

TMDS (4 eq). As shown in Scheme 4b, after 24 h acetal **13** was indeed smoothly converted to the corresponding ether **14**, which was subsequently isolated in excellent yield, whereas the analogous reaction using Vaska's complex **Ir-1** resulted in no reaction (Scheme 4c). These data are consistent with the hypothesis that in conjunction with TMDS, **Ir-3** forms catalytic intermediates sufficiently Lewis acidic to generate putative oxo-carbenium ions that are subsequently reduced by hydridic species present in the medium.

## Conclusion

In conclusion, an efficient and broad-in-scope iridium(I)-catalyzed reductive deoxygenation of hindered esters to ethers has been successfully developed. The practically simple, mix-and-stir, single-vessel, ambient-temperature reaction protocol relies on the enhanced carbonyl reducing power of bench-stable and commercially available<sup>[90]</sup> iridium complex  $\text{IrCl}(\text{CO})(\text{P}[\text{OCH}(\text{CF}_3)_2]_3)_2$  **Ir-3**, relative to that of Vaska's complex. Control experiments revealed that complex **Ir-3** in the presence of TMDS engenders Lewis acidity, which, with the more activated substrates or bulky alkoxy esters derived from linear aliphatic carboxylic acids, enables overall deoxygenation without assistance from added Lewis acids. Experiments to further explore and apply the reactivity of **Ir-3** and related complexes are actively under investigation in our group, and the results will be reported in due course.

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### Conflict of Interests

D.J.D. is a co-founder, director, and major shareholder of Cortex Organics Ltd.

### Data Availability Statement

The data that support the findings of this study are available in the [Supporting Information](#) of this article.

**Keywords:** Ester reduction • Ethers • Hindered ether synthesis • Iridium catalysis • Silanes

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