

Iridium-Catalyzed Reductive Allylation of Esters

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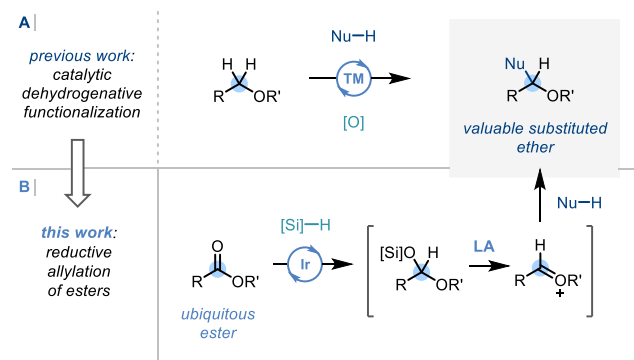
ABSTRACT: The catalytic reductive transformation of carboxylic esters into α -branched ethers is described. The procedure pivots on the chemoselective iridium-catalyzed hydrosilylation of ester and lactone functionality to afford a silyl acetal intermediate. Upon treatment with Lewis acid these hemi-labile intermediates ionize to form reactive oxocarbenium ions, which can be intercepted by allyl tributyltin nucleophiles, resulting in the formation of valuable α -branched alkyl-alkyl ether derivatives. This reductive allylation procedure was amenable to a range of carboxylic ester starting materials and good chemoselectivity for ethyl over *t*-butyl esters was demonstrated. Furthermore, downstream synthetic manipulation of α -amino acid derived products led to efficient formation of pyrrolidine, piperidine, and azepane frameworks.

The α -branched alkyl-alkyl ether motif is prevalent in many biologically active structures and industrially relevant materials. Accordingly, the development of new, effective, and practical protocols to synthesize such fragments is important.¹ Although traditional and well-established synthetic methods to substituted ethers – including Williamson ether synthesis, hydroalkoxylation of alkenes, and C-O bond cross coupling to name a few² – are still routinely used, in recent years the development of complementary, chemoselective, mild and efficient ways for their preparation has attracted substantial interest, including pioneering photocatalytic and C-H functionalization techniques.³ In particular, direct α -C-H oxidative coupling (cross-dehydrogenative coupling) of ether derivatives and nucleophiles (Scheme 1A) has become a powerful complementary approach to classical routes.⁴ From a synthetic standpoint, we recognized that the ability to access similar architectures from corresponding feedstock, commercially available, or readily synthesized carboxylic esters – using a catalytic reductive protocol – could provide a powerful alternative towards these desirable complex ether products.

Due to its relatively low electrophilicity, direct nucleophilic addition to ester functionality generally requires reactive organometallic nucleophiles (such as organomagnesium and organolithium reagents) and typically results in the formation of tertiary alcohols. Furthermore, long-standing interest concerning ester transformations has focused on the use of aluminum acetal intermediates, generated by partial reduction of esters with DIBAL. The activity of this intermediate allows the coupling with various carbon-centred nucleophiles in the presence of Lewis acids, either directly or *via* acetylated acetal intermediates, affording secondary alcohols or cyclic ethers as products.^{5,6} Conversely, the transition metal catalysed hydrosilylation of an ester to a silyl acetal under mild conditions has also been achieved.⁷ However, the use of silyl acetal intermediate for carbon-carbon bond formation has been largely overlooked,^{7m} especially towards the synthesis of α branched ether fragments.⁸

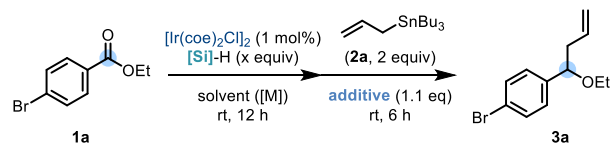
We envisaged that a selective reductive transition metal-catalyzed hydrosilylation of an ester would create the silyl acetal, which under the activation of an appropriate Lewis acid would afford the corresponding oxocarbenium ion (Scheme 1B). Interception of this reactive intermediate with a suitable carbon-centered nucleophile would then afford the α -branched ether in a two-step, one-pot procedure. Such an efficient, catalytic, chemoselective, and general approach to the reductive transformation of ubiquitous esters to high value α -branched ethers could be of importance to synthetic development programmes, and herein we wish to report our findings.

Scheme 1. Catalytic construction of α -alkyl ethers.



We selected the reductive allylation of ethyl 4-bromobenzoate (**1a**) using allyl tributyltin (**2a**) as our model reaction. $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ was employed as catalyst and diethylsilane as the reducing agent,⁷ and initial studies using toluene as solvent delivered smooth hydrosilylation of the ester. Subsequent functionalization with **2a** (2 equiv) using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.1 equiv) as a Lewis acid additive afforded promising yields of the desired α -allylated ether product **3a** (Table 1, entry 1).

Table 1. Optimization of the iridium-catalyzed reductive allylation of esters



entry	[Si]-H (x equiv)	solvent ([M])	additive	3a ^a
1	Et ₂ SiH ₂ (2.0)	PhMe (0.2)	BF ₃ ·OEt ₂	59
2	Et ₂ SiH ₂ (2.0)	THF (0.2)	BF ₃ ·OEt ₂	74
3	Et ₂ SiH ₂ (2.0)	CHCl ₃ (0.2)	BF ₃ ·OEt ₂	44
4	Et ₂ SiH ₂ (2.0)	CH ₂ Cl ₂ (0.2)	BF ₃ ·OEt ₂	76
5	Et ₂ SiH ₂ (2.0)	CH ₂ Cl ₂ (0.1)	BF ₃ ·OEt ₂	70
6	Et ₂ SiH ₂ (2.0)	CH ₂ Cl ₂ (0.5)	BF ₃ ·OEt ₂	50
7	Et₂SiH₂ (1.5)	CH₂Cl₂ (0.2)	BF₃·OEt₂	78 (75)^b
8	Et ₂ SiH ₂ (1.2)	CH ₂ Cl ₂ (0.2)	BF ₃ ·OEt ₂	48
9	Ph ₃ SiH (1.5)	CH ₂ Cl ₂ (0.2)	BF ₃ ·OEt ₂	-
10	PhMeSiH ₂ (1.5)	CH ₂ Cl ₂ (0.2)	BF ₃ ·OEt ₂	56
11	Et ₂ SiH ₂ (1.5)	CH ₂ Cl ₂ (0.2)	BF ₃ ·THF	53
12	Et ₂ SiH ₂ (1.5)	CH ₂ Cl ₂ (0.2)	Sc(OTf) ₃	29
13	Et ₂ SiH ₂ (1.5)	CH ₂ Cl ₂ (0.2)	TMSOTf	36
14	Et ₂ SiH ₂ (1.5)	CH ₂ Cl ₂ (0.2)	PhSO ₃ H	Trace

General conditions. Step (i): ethyl 4-bromobenzoate (**1a**, 0.3 mmol), [Ir(coe)₂Cl]₂ (1 mol%), solvent [M], under an N₂ atmosphere at room temperature for 12 h. Step (ii): **2a** (0.6 mmol), additive (1.1 eq) under an N₂ atmosphere at room temperature for 6 h. ^a Formation of **3a** was calculated via ¹H NMR analysis of the crude reaction mixture against 4-dimethylaminopyridine as an internal standard. ^b Isolated yield after silica gel column chromatography.

Further experiments identified dichloromethane as the solvent of choice (entries 2–4). Pleasingly, reducing the amount of Et₂SiH₂ (from 2 – 1.5 equiv) was shown to be inconsequential to reaction proficiency, delivering α -allylated product in 75% yield (entry 7). However, further reduction in equivalents of Et₂SiH₂ to 1.2 led to decreased efficiency (entry 8). Interestingly other silane reagents – exemplified with Ph₃SiH and PhMeSiH₂ – showed substantially poorer performance in this transformation (entries 9–10). Furthermore, other Lewis acids were shown to be detrimental to reaction efficiency (including BF₃·THF, entries 11–13). Brønsted acids such as PhSO₃H (entry 14) were ineffective, and notably in this case, the amount of competitive over-reduction products was significantly increased.⁹

With optimal conditions established, we then explored the scope of this reductive allylation methodology by submitting a range of esters to the reaction conditions.¹⁰ Variation of the alkoxy part of the ester including ethyl (**3a**, Scheme 2), isopropyl (**3b**), butyl (**3h**), and notably methyl (**3i**), previously predominately giving competitive hydrolysis products⁸ esters were demonstrated to form the corresponding allylated ether products in good yields. Esters bearing benzyl ether (**3d**), aryl ether (**3e**), secondary amine (**3f**) and carbamate (**3g**) functionalities were also amenable to the reductive allylation protocol, delivering the corresponding α -allyl substituted ethers in excellent efficiency – with a glycine derived substrate shown to perform effectively on gram-scale (**3f**). Pleasingly, free hydroxyl containing esters also proved applicable to this protocol (**3g–j**). We then looked to cyclic lactones as viable substrates, where ω -pentadecalactone (**3k**), (\pm)- δ -undecalactone (**3l**), and D-glucono lactone (**3m**) proceeded in moderate to good yields and excellent diastereoselectivities (where applicable).¹¹

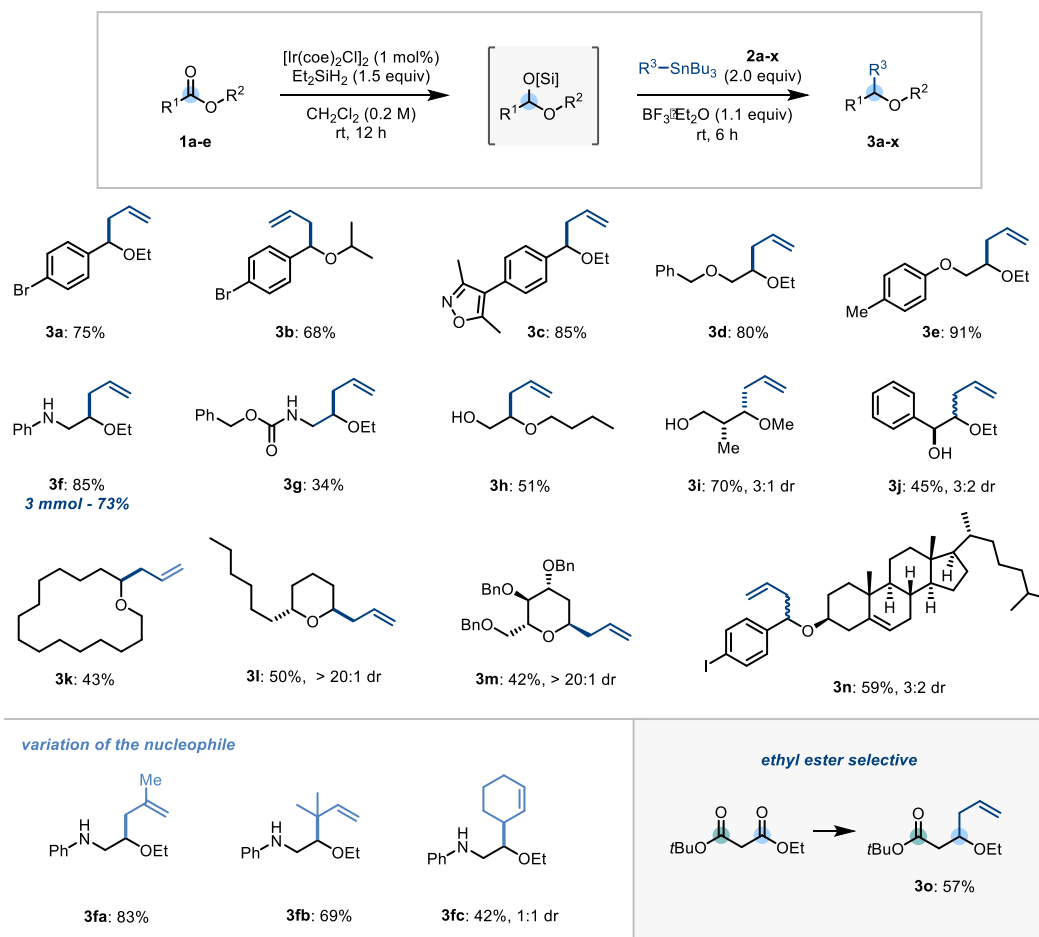
Furthermore, subsequent studies demonstrated that variation of the allyl tributyltin reagent was also tolerated, enabling the synthesis of homologous allyl substituted ethers. Thus, the

addition of methallyltributyltin to the generated silyl hemiacetal intermediate allowed the proficient synthesis of **3fa**. Sterically demanding organostannanes – exemplified by tributyl(3-methyl-2-butenyl)tin – were also applicable, furnishing the corresponding α -branched ether **3fc** in 69% yield. Furthermore, the compatibility of tributyl(cyclohex-1-en-1-ylmethyl)tin led to the installation of cyclohexenyl functionality (**3fe**). Encouraged by the success of the scope with respect to both reaction partners, we then submitted unsymmetrical malonic acid diester substrate (**3o**) to this reductive allylation protocol. Selective reductive allylation of the ethyl ester took place with *tert*-butyl ester functionality remaining largely intact, affording ether product in 57% yield, demonstrating the steric preference in the hydrosilylation step.

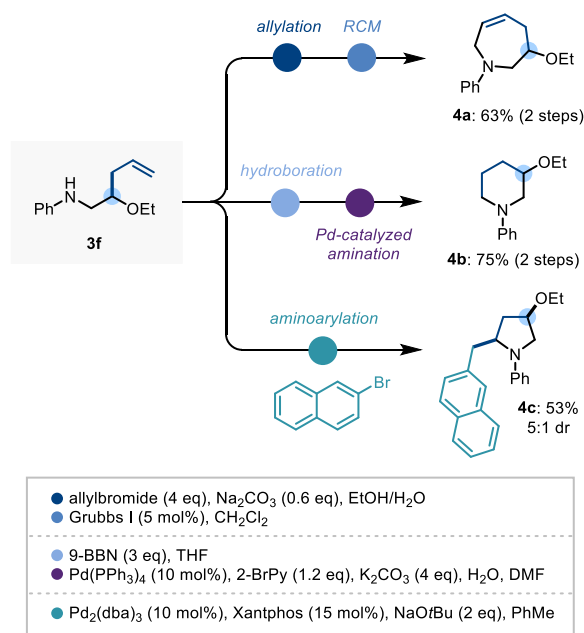
We recognized that this chemistry and the ethers they produce could provide new avenues into sp³-rich heterocycle synthesis. The products of this reductive allylation methodology could readily enable the construction of decorated 5-, 6-, and 7-membered nitrogen-containing heterocycles from simple amino acid precursors (Scheme 3). Identifying **3f** as a synthetic lynchpin, first a two-step *N*-allylation, ring closing metathesis sequence gave the unsaturated azepane (**4a**, see supporting information for full reaction details)¹². Next, a tandem hydroboration,¹³ palladium-catalyzed amination protocol gave the substituted piperidine in excellent yields for a two-step process (**4b**). Finally we envisaged that **3f** could undergo palladium-catalyzed aminoarylation to give the corresponding substituted pyrrolidine.¹⁴ Pleasingly, using 2-naphthylbromide as a coupling partner, this was indeed achieved in good yields to create the 5-membered heterocycle (**4c**).

In conclusion, an iridium-catalyzed reductive allylation of esters for the synthesis of α -branched ethers, by coupling of *in situ* generated silyl hemiacetal intermediate and allyltributyl tin derivatives, has been developed. This reaction benefits from the strategic use of stable and readily available esters as abundant and under-exploited ether precursors. The broad scope of substrates that can be tolerated under the mild reductive conditions demonstrates the practicality of this new carbon-carbon bond formation reaction. In combination with the illustrated synthetic utility by derivation of the ether products, this α -allyl substituted ether synthesis protocol will likely find use in selective syntheses of simple and complex ethers alike.

Scheme 2. Substrate scope for the reductive allylation of esters



Scheme 3. Applications in heterocycle synthesis



ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Synthetic procedures and full characterization data of compounds (PDF).

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