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Lewis acid-assisted palladium-catalysed dealkylation of *N*-alkoxyamides has been developed. This reaction proceeded smoothly with a range of *N*-alkoxyamides in the absence of an external reductant, thereby establishing a convenient and reductant-free protocol. In addition, a gram-scale reaction could be achieved. Preliminary mechanistic investigations indicated that  $\beta$ -hydrogen elimination from a palladium alkoxide intermediate generated an intramolecular hydride source.

*N*-Alkoxyamides are an important class of synthetic intermediates for a range of organic transformations.<sup>1</sup> In particular, *N*-methoxy-*N*-methylamides, which are known as Weinreb amides, have unique properties as acylating reagents that suppress the overalkylation of reaction products by forming remarkably stable five-membered cyclic intermediates (Scheme 1a).<sup>2</sup> This exceptional feature allows the transformation of readily available and stable *N*-alkoxyamides<sup>3</sup> into useful aldehydes and ketones in a single step. Recently, *N*-alkoxyamides have emerged as versatile directing groups for C–H bond functionalisation, and various transformations employing *N*-alkoxyamides are currently available.<sup>4</sup> While *N*-alkoxyamides are commonly used in various organic reactions, the dealkylation of *N*-alkoxyamides has not been explored enough yet (Scheme 1b).

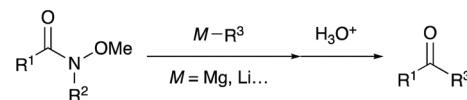
Conventional dealkylation of *N*-alkoxyamides requires stoichiometric metal-based reductants such as  $\text{SmI}_2$ ,<sup>5</sup>  $\text{Na}/\text{Hg}$ <sup>6</sup> and lithium powder<sup>7</sup> (Scheme 2a). An organic, neutral super electron donor has been developed as a stoichiometric reductant, and it gives results comparable to those obtained using metal-based reductants.<sup>8</sup> Base-mediated formal reduction of *N*-alkoxyamides has also evolved as a method for dealkylation.<sup>9</sup> Treatment of *N*-alkoxyamides with lithium diisopropylamide,<sup>9a</sup> or *tert*-butyldimethylsilyl triflate and triethylamine<sup>9b</sup>

## Dealkylation of *N*-alkoxyamides without an external reductant driven by Pd/Al cooperative catalysis†

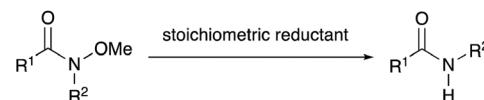
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† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for new compounds. See DOI: 10.1039/d0ob01815e

resulted in the formal reduction of the amides, along with the formation of formaldehyde. Although these reductants and bases allow facile cleavage of the alkoxy groups from *N*-alkoxyamides under very mild conditions, excess amounts of reductants or bases are required for these reactions. In

(a) Used as acylating reagent – **Well investigated**

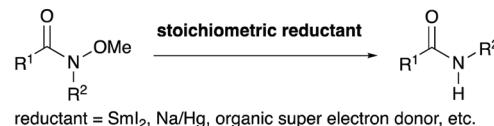


(b) Reductive N–O bond cleavage – **Less investigated**

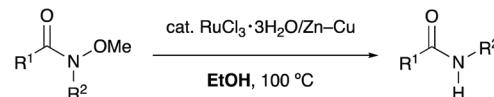


**Scheme 1** Transformation of *N*-alkoxyamides: (a) nucleophilic addition of organometallic reagents and (b) dealkylation of *N*-alkoxyamides.

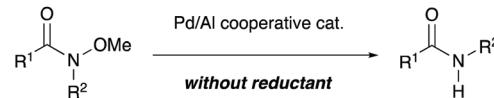
(a) Stoichiometric reaction



(b) Transition metal-catalysed reaction



(c) This work



**Scheme 2** Dealkylation of *N*-alkoxyamides.



addition, these reducing reagents are sometimes expensive, difficult to handle, and hazardous. Ruthenium-catalysed dealkoxylation of *N*-alkoxyamides has been reported as an alterna-

tive protocol for avoiding the use of such stoichiometric reagents (Scheme 2b). Dealkoxylation proceeded in alcoholic solvents, which also behaved as a stoichiometric reductant.<sup>10</sup> Although the catalytic reactions require only green and cheap alcohols as stoichiometric reductants, it is necessary to add a substoichiometric amount of Zn–Cu for activating the ruthenium catalyst. Herein, we report the palladium-catalysed dealkoxylation of *N*-alkoxyamides in the absence of an external reductant as a convenient and reductant-free protocol for dealkoxylation (Scheme 2c). To the best of our knowledge, this is the first report on the catalytic dealkoxylation of *N*-alkoxyamides without any external reductants.<sup>11</sup>

We began our investigation using *N*-methoxy-*N*-methylbenzamide (**1a**) as a model substrate, which was heated in toluene at 150 °C in the presence of the Pd(dba)<sub>2</sub>/DPPBz catalyst (Table 1). After 6 h, the desired secondary amide **2a** was formed in a moderate yield (entry 1). We then screened aluminium Lewis acids as co-catalysts in order to activate the N–O bond.<sup>12</sup> The addition of aluminium(III) chloride (AlCl<sub>3</sub>) suppressed the reaction completely (entry 2). Trialkylaluminium or trialkoxyaluminium dramatically improved the yields (entries 3–6), and the best result was obtained when triisobutylaluminium (Ali-Bu<sub>3</sub>) was employed as a co-catalyst (entry 4).<sup>13</sup> Solvent screening (entries 7–12) revealed that cyclopentyl methyl ether (CPME) was the optimal solvent for affording the desired product in an excellent yield (entry 9).<sup>14</sup> In addition, this demethoxylation reaction could reach completion with reduced catalyst loadings (entry 13).

Table 1 Optimisation of reaction conditions<sup>a</sup>

Entry	Lewis acid	Solvent	Yield (%)	Reaction conditions: <b>1</b> (0.3 mmol), Pd(dba) <sub>2</sub> (4 mol%), DPPBz (4 mol%) and Lewis acid (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. <sup>b</sup> Pd(dba) <sub>2</sub> /DPPBz (2 mol% each) and Ali-Bu <sub>3</sub> (5 mol%) were used as catalysts. The reaction time was 20 h.	
				4 mol% Pd(dba) <sub>2</sub>	4 mol% DPPBz
1	—	Toluene	33		10 mol% Lewis acid
2	AlCl <sub>3</sub>	Toluene	NR		
3	AlMe <sub>3</sub>	Toluene	87		
4	Ali-Bu <sub>3</sub>	Toluene	98		
5	Al(OEt) <sub>3</sub>	Toluene	83		
6	Al(Oi-Pr) <sub>3</sub>	Toluene	94		
7	Ali-Bu <sub>3</sub>	p-Xylene	86		
8	Ali-Bu <sub>3</sub>	1,4-Dioxane	86		
9	Ali-Bu <sub>3</sub>	CPME	99		
10	Ali-Bu <sub>3</sub>	Diglyme	85		
11	Ali-Bu <sub>3</sub>	DMF	84		
12	Ali-Bu <sub>3</sub>	DMSO	61		
13 <sup>b</sup>	Ali-Bu <sub>3</sub>	CPME	99		

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), Pd(dba)<sub>2</sub> (4 mol%), DPPBz (4 mol%) and Lewis acid (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. <sup>b</sup> Pd(dba)<sub>2</sub>/DPPBz (2 mol% each) and Ali-Bu<sub>3</sub> (5 mol%) were used as catalysts. The reaction time was 20 h.

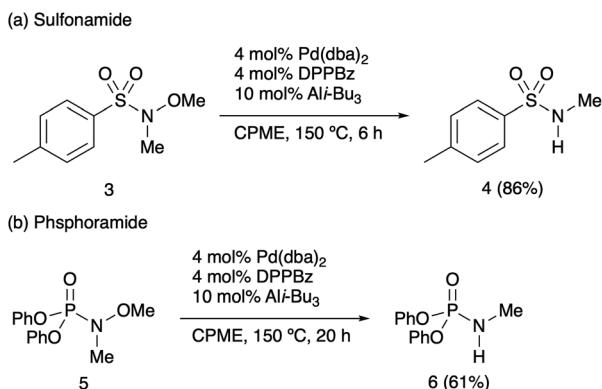
Table 2 Palladium-catalysed demethoxylation of *N*-methoxyamides<sup>a</sup>

<b>1</b>	<b>2</b>

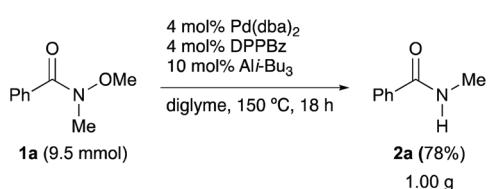
<sup>a</sup> Reaction conditions: **1** (0.3 mmol), Pd(dba)<sub>2</sub> (4 mol%), DPPBz (4 mol%) and Ali-Bu<sub>3</sub> (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. The yields represent the average yield of two reaction runs. <sup>b</sup> Pd(dba)<sub>2</sub> (8 mol%), DPPBz (8 mol%) and Ali-Bu<sub>3</sub> (20 mol%) were used (20 h). <sup>c</sup> The reaction time was 18 h. <sup>d</sup> Pd(dba)<sub>2</sub> (8 mol%), DPPBz (8 mol%) and Ali-Bu<sub>3</sub> (20 mol%) were used (18 h).



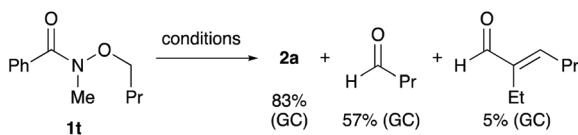
With the optimised reaction conditions in hand, we investigated the scope of demethoxylation (Table 2). Introduction of methyl groups at the *para*- and *meta*-positions of the benzene ring (**1b-d**) did not affect the efficiency of transformations. However, the reactivity decreased with *o*-methylbenzamide **1e**, and increased catalyst loadings were required to obtain a reasonable yield of the desired secondary amide. Benzamides



**Scheme 3** Palladium-catalysed demethoxylation of sulfonamide **3** and phosphoramidate **5**.



**Scheme 4** A gram-scale reaction.



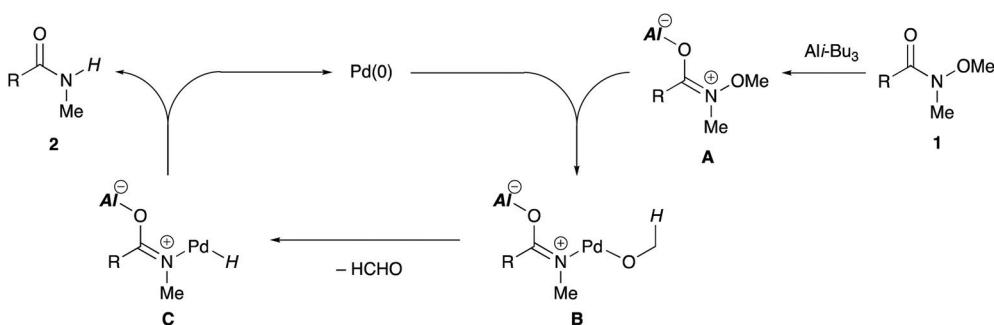
**Scheme 5** Palladium-catalysed debutoxylation of *N*-butoxy-*N*-methylbenzamide (**1t**) (conditions: 4 mol% Pd(dba)<sub>2</sub>, 4 mol% DPPBz, 10 mol% Al-i-Bu<sub>3</sub>, CPME, 150 °C, 6 h).

bearing electron-donating and electron-withdrawing groups **1f-j** were well tolerated under the optimal conditions. Heteroaryl-substituted substrates **1k-o** were also converted into the desired secondary amides with high efficiency. Cinnamamide **1p** afforded the corresponding product without the reduction of the olefin moiety.<sup>10</sup> It is worth noting that the demethoxylation of enolisable *N*-methyl-*N*-methoxyamides **1q-s** proceeded smoothly, and no side reactions were observed.

To further demonstrate the applicability of demethoxylation, other alkoxyamides were examined. Under the optimal conditions, sulfonamide **3** gave the desired secondary sulfonamide **4** in a high yield (Scheme 3a). Moreover, phosphoramidate **5** was found to be a promising substrate for the demethoxylation to afford the corresponding product in a good yield (Scheme 3b). In both cases, an N-O bond was selectively cleaved, while the other heteroatom–heteroatom bonds remained intact. In contrast to previous studies, reductant-free demethoxylation was applicable to a wide range of *N*-methoxy-*N*-methylamides, without the occurrence of any side reactions or over-reactions. Furthermore, a gram-scale reaction was performed with **1a** in diglyme, and the desired product **2a** was obtained in 78% yield (Scheme 4).<sup>15</sup>

To gain insight into the reaction mechanism, a control experiment was conducted (Scheme 5). When *N*-butoxy-*N*-methylbenzamide (**1t**) was subjected to the standard reaction conditions, butanal and its aldol condensation product were produced along with the desired secondary amide **2a**. These byproducts may have been generated *via* the  $\beta$ -hydrogen elimination from a palladium alkoxide intermediate. The results reveal that an  $\alpha$ -hydrogen atom with respect to the oxygen atom of the alkoxy group functions as a hydride source.<sup>11,16</sup>

A plausible mechanism for the reductant-free demethoxylation is proposed on the basis of a previous report<sup>11</sup> and our preliminary mechanistic investigations (Scheme 6). The carbonyl oxygen of alkoxyamide **1** coordinates to the aluminium Lewis acid to form **A**, thereby weakening the N-O bond. Subsequently, oxidative addition of the N-O bond to Pd(0) generates palladium alkoxide **B**, which undergoes  $\beta$ -hydrogen elimination to generate palladium hydride intermediate **C** and formaldehyde. Finally, reductive elimination from the intermediate **C** affords secondary amide **2** and simultaneously regenerates the catalytically active Pd(0) species.



**Scheme 6** The plausible reaction mechanism for reductant-free demethoxylation.



## Conclusions

In summary, we achieved the demethoxylation of *N*-alkoxyamides in the presence of a Pd/Al cooperative catalytic system. The reaction proceeded with various *N*-alkoxyamides including a sulfonamide and a phosphoramido in the absence of an external reductant. The N–O bond was selectively reduced, and there were no side reactions or over-reactions. Preliminary mechanistic investigations revealed that  $\beta$ -hydrogen elimination of a palladium alkoxide intermediate generated an intramolecular hydride source. Further studies on palladium-catalysed reductant-free demethoxylation are ongoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

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