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

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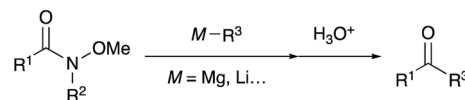
Lewis acid-assisted palladium-catalysed dealkoxylation of *N*-alkoxyamides has been developed. This reaction proceeded smoothly with a range of *N*-alkoxyamides in the absence of an external reductant, thereby establishing a convenient and reductant-free protocol. In addition, a gram-scale reaction could be achieved. Preliminary mechanistic investigations indicated that β -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.¹ 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).² This exceptional feature allows the transformation of readily available and stable *N*-alkoxyamides³ 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.⁴ While *N*-alkoxyamides are commonly used in various organic reactions, the dealkoxylation of *N*-alkoxyamides has not been explored enough yet (Scheme 1b).

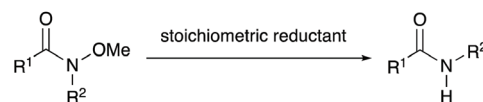
Conventional dealkoxylation of *N*-alkoxyamides requires stoichiometric metal-based reductants such as SmI_2 ,⁵ Na/Hg ⁶ and lithium powder⁷ (Scheme 2a). An organic, neutral super electron donor has been developed as a stoichiometric reductant, and it gives results comparable to those obtained using metal-based reductants.⁸ Base-mediated formal reduction of *N*-alkoxyamides has also evolved as a method for dealkoxylation.⁹ Treatment of *N*-alkoxyamides with lithium diisopropylamide,^{9a} or *tert*-butyldimethylsilyl triflate and triethylamine^{9b}

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**

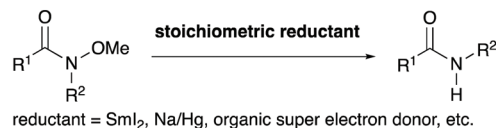


(b) Reductive N–O bond cleavage – **Less investigated**

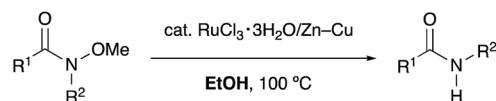


Scheme 1 Transformation of *N*-alkoxyamides: (a) nucleophilic addition of organometallic reagents and (b) dealkoxylation of *N*-alkoxyamides.

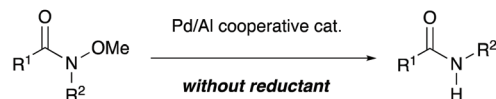
(a) Stoichiometric reaction



(b) Transition metal-catalysed reaction



(c) This work



Scheme 2 Dealkoxylation of *N*-alkoxyamides.

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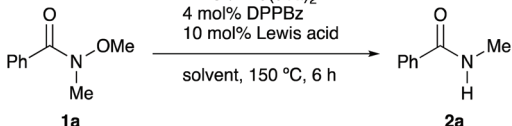


addition, these reducing reagents are sometimes expensive, difficult to handle, and hazardous. Ruthenium-catalysed dealkoxylation of *N*-alkoxyamides has been reported as an alterna-

tive protocol for avoiding the use of such stoichiometric reagents (Scheme 2b). Dealkoxylation proceeded in alcoholic solvents, which also behaved as a stoichiometric reductant.¹⁰ 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.¹¹

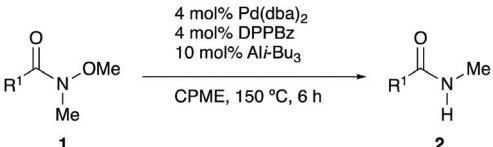
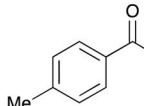
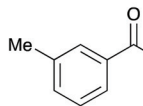
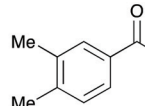
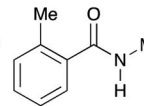
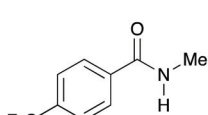
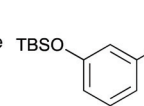
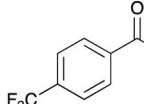
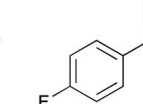
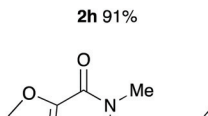
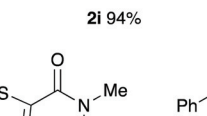
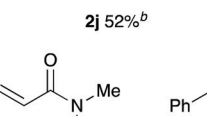
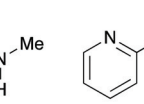
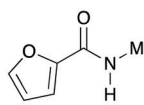
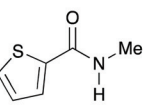
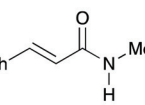
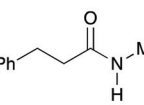
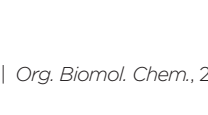
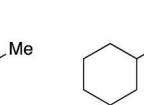
We began our investigation using *N*-methoxy-*N*-methylbenzamide (**1a**) as a model substrate, which was heated in toluene at 150 °C in the presence of the Pd(dba)₂/DPPBz catalyst (Table 1). After 6 h, the desired secondary amide **2a** was formed in a moderate yield (entry 1). We then screened aluminium Lewis acids as co-catalysts in order to activate the N–O bond.¹² The addition of aluminium(III) chloride (AlCl₃) suppressed the reaction completely (entry 2). Trialkylaluminium or trialkoxyaluminium dramatically improved the yields (entries 3–6), and the best result was obtained when triisobutylaluminium (Al*i*-Bu₃) was employed as a co-catalyst (entry 4).¹³ 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).¹⁴ In addition, this demethoxylation reaction could reach completion with reduced catalyst loadings (entry 13).

Table 1 Optimisation of reaction conditions^a

|  | | | |
|---|---------------------------------|------------------|-----------|
| Entry | Lewis acid | Solvent | Yield (%) |
| 1 | — | Toluene | 33 |
| 2 | AlCl ₃ | Toluene | NR |
| 3 | AlMe ₃ | Toluene | 87 |
| 4 | Al <i>i</i> -Bu ₃ | Toluene | 98 |
| 5 | Al(OEt) ₃ | Toluene | 83 |
| 6 | Al(O <i>i</i> -Pr) ₃ | Toluene | 94 |
| 7 | Al <i>i</i> -Bu ₃ | <i>p</i> -Xylene | 86 |
| 8 | Al <i>i</i> -Bu ₃ | 1,4-Dioxane | 86 |
| 9 | Al <i>i</i> -Bu ₃ | CPME | 99 |
| 10 | Al <i>i</i> -Bu ₃ | Diglyme | 85 |
| 11 | Al <i>i</i> -Bu ₃ | DMF | 84 |
| 12 | Al <i>i</i> -Bu ₃ | DMSO | 61 |
| 13 ^b | Al <i>i</i> -Bu ₃ | CPME | 99 |

^a Reaction conditions: **1** (0.3 mmol), Pd(dba)₂ (4 mol%), DPPBz (4 mol%) and Lewis acid (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. ^b Pd(dba)₂/DPPBz (2 mol% each) and Al*i*-Bu₃ (5 mol%) were used as catalysts. The reaction time was 20 h.

Table 2 Palladium-catalysed demethoxylation of *N*-methoxyamides^a

| | | | |
|--|---|--|---|
|  | | | |
|  |  |  |  |
| 2b 87% | 2c 93% | 2d 96% | 2e 80% ^b |
|  |  |  |  |
| 2f 90% | 2g 97% ^c | 2h 91% | 2i 94% |
|  |  |  |  |
| 2j 52% ^b | 2k 67% | 2l 80% | 2m 62% |
|  |  |  |  |
| 2n 80% | 2o 93% | 2p 70% ^b | 2q 80% ^b |
|  |  | 2r 85% ^d | 2s 79% ^b |

^a Reaction conditions: **1** (0.3 mmol), Pd(dba)₂ (4 mol%), DPPBz (4 mol%) and Al*i*-Bu₃ (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. ^b Pd(dba)₂ (8 mol%), DPPBz (8 mol%) and Al*i*-Bu₃ (20 mol%) were used (20 h). ^c The reaction time was 18 h. ^d Pd(dba)₂ (8 mol%), DPPBz (8 mol%) and Al*i*-Bu₃ (20 mol%) were used (18 h).



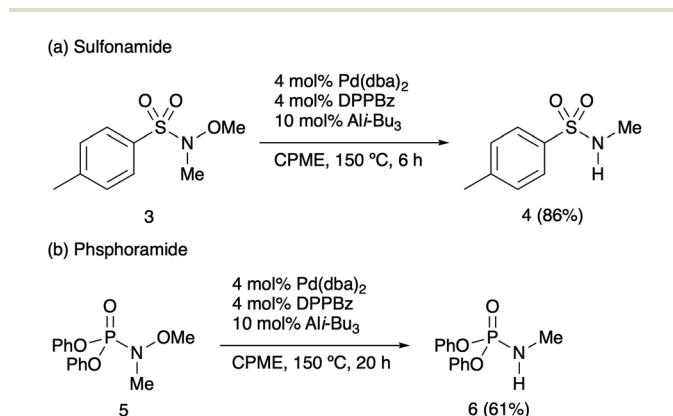
With the optimised reaction conditions in hand, we investigated the scope of demethoxylation (Table 2). Introduction of methyl groups at the *para*- and *meta*-positions of the benzene ring (**1b–d**) did not affect the efficiency of transformations. However, the reactivity decreased with *o*-methylbenzamide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

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.¹⁰ It is worth noting that the demethoxylation of enolisable *N*-methyl-*N*-methoxyamides **1q–s** proceeded smoothly, and no side reactions were observed.

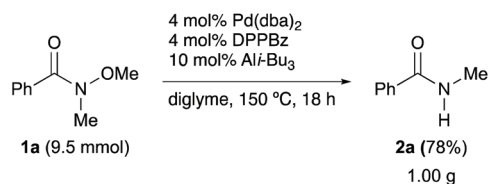
To further demonstrate the applicability of demethoxylation, other alkoxyamides were examined. Under the optimal conditions, sulfonamide **3** gave the desired secondary sulfonamide **4** in a high yield (Scheme 3a). Moreover, phosphoramidate **5** was found to be a promising substrate for the demethoxylation 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).¹⁵

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 β -hydrogen elimination from a palladium alkoxide intermediate. The results reveal that an α -hydrogen atom with respect to the oxygen atom of the alkoxy group functions as a hydride source.^{11,16}

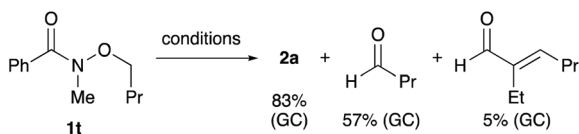
A plausible mechanism for the reductant-free demethoxylation is proposed on the basis of a previous report¹¹ and our preliminary mechanistic investigations (Scheme 6). The carbonyl oxygen of alkoxyamide **1** coordinates to the aluminium Lewis acid to form **A**, thereby weakening the N–O bond. Subsequently, oxidative addition of the N–O bond to Pd(0) generates palladium alkoxide **B**, which undergoes β -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.



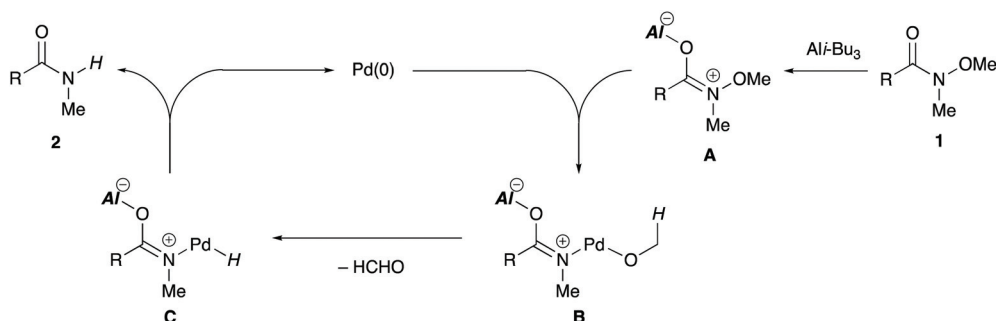
Scheme 3 Palladium-catalysed demethoxylation of sulfonamide **3** and phosphoramidate **5**.



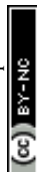
Scheme 4 A gram-scale reaction.



Scheme 5 Palladium-catalysed debutoxylation of *N*-butoxy-*N*-methylbenzamide (**1t**) (conditions: 4 mol% Pd(dba)₂, 4 mol% DPPBz, 10 mol% Al*i*-Bu₃, CPME, 150 °C, 6 h).



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 phosphoramidate 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 β -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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