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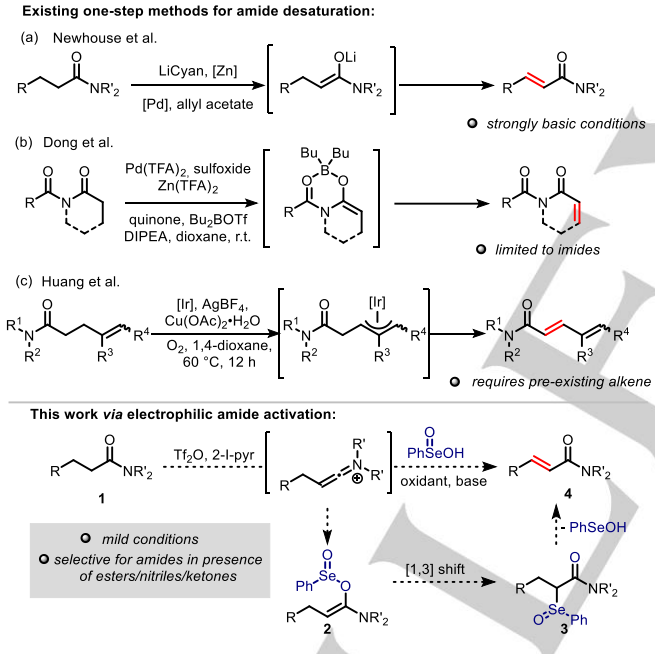
Chemoselective α,β-Dehydrogenation of Saturated Amides

Christopher J. Teskey,[a,+] Pauline Adler,[a,+] Carlos R. Gonçalves[a] and Nuno Maulide*[a]

Abstract: We report a method for the selective α,β-dehydrogenation of amides in the presence of other carbonyl moieties under mild conditions. Our strategy relies on electrophilic activation coupled to *in situ* selective selenium-mediated dehydrogenation. The α,β-unsaturated products are obtained in moderate to excellent yields and their synthetic versatility is demonstrated by a range of transformations. Mechanistic experiments suggest formation of an electrophilic Se(IV) species.

More than 130 years have passed since Arthur Michael reported his groundbreaking studies on the conjugate addition of malonate nucleophiles.[1] In the intervening time, much work has been devoted to the development of asymmetric variants of this reaction, which has become a staple transformation of the organic chemist's repertoire.[2] Given the versatility of the carbonyl functional group, the Michael addition of an enolate to an unsaturated carbonyl is one of the definitive methods for generating a 1,5-dicarbonyl relationship and, as a consequence, such transformations can be frequently found in total syntheses.[3]



Scheme 1. Approaches to amide dehydrogenation and work presented herein.

The mild conditions of conjugate addition, as the Michael reaction has come to be colloquially known, also lend this reaction well to other areas of research such as bioconjugation or dynamic combinatorial chemistry.[4]

As a result, methods to synthesize α,β-unsaturated systems are highly prized. Convenient and efficient pathways include carbonyl olefination[5] and olefin cross-metathesis,[6] although the ability to directly generate α,β-unsaturated carbonyl compounds from their corresponding saturated counterparts by dehydrogenation adds considerable flexibility to synthetic planning. Pioneering work by Kingsbury and Cram on the concerted, thermal elimination of alkyl sulfoxides[7] later inspired similar work on selenoxide elimination.[8] The Saegusa-Ito oxidation[9] is another well-known and often employed route to dehydrogenated carbonyl systems but is a two-step procedure. Despite the original use of stoichiometric palladium, notable efforts have been made to develop efficient catalytic reactions based on much greener oxidants by the groups of Stahl[10] and others.[11] Although reliable, these methods often involve two steps or are limited to (cyclic) ketones. Other important contributions include the work of Nicolaou *et. al* who reported the use of IBX to oxidise ketones to the corresponding α,β-enones.[12]

When considering the direct dehydrogenation of carbonyl compounds beyond ketones and aldehydes, a major obstacle is the significantly reduced α-acidity of esters, nitriles or particularly carboxamides. The Newhouse group has published a number of impressive reports showcasing how zinc enolates (generated by transmetallation from the corresponding lithium counterparts) can be dehydrogenated under palladium catalysis,[13] including those derived from amides (Scheme 1a).[14] Furthermore, those authors have demonstrated this methodology to be applicable in total synthesis.[15]

Dong has used a related strategy to desaturate *N*-acyllactams,[16] relying on a two-point binding activation (Scheme 1b) and, most recently, the group of Huang showed that iridium catalysis could be used for desaturation in the specific case of γ,δ-unsaturated amides (Scheme 1c).[17]

We believed there remains space for complementary methods that proceed under conditions tolerant of other carbonyl functionality and that are applicable to structurally diverse amides. We envisaged the use of electrophilic amide activation[18] for the possibilities it might afford in developing a strategy for chemoselective desaturation of amides in the presence of other carbonyl functional groups.[19] Herein we report a mild, room-temperature α,β-dehydrogenation of amides with a broad applicability and which is selective for amides, thus reaching beyond the scope of most current protocols as it does not rely on enolate formation. Our reaction design was based on the simple assumption that seleninic acid (PhSe(O)OH) might possess enough nucleophilicity to attack a keteniminium intermediate as shown in Scheme 1. This might lead to an enamine-type species such as **2** which could undergo an unusual [1,3]-sigmatropic rearrangement.[20] The resulting α-selenated species **3** should already lie at the oxidation state required for concerted elimination, ultimately affording the α,β-dehydrogenated product in a single step.

In initial efforts using amide **1a**, the desired dehydrogenated product **4a** was observed from the very first experiments, albeit in yields never surpassing 50% (Table 1, entry 1; see the SI for additional attempts). Indeed, the crude reaction mixture

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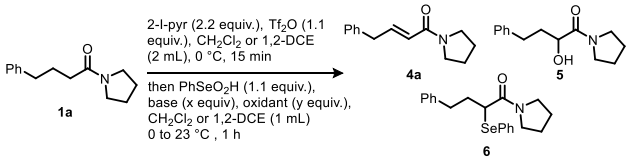
commonly contained variable amounts of both α-hydroxylated amide **5** and α-selenated amide **6**.

Table 1. Optimization of the reaction.



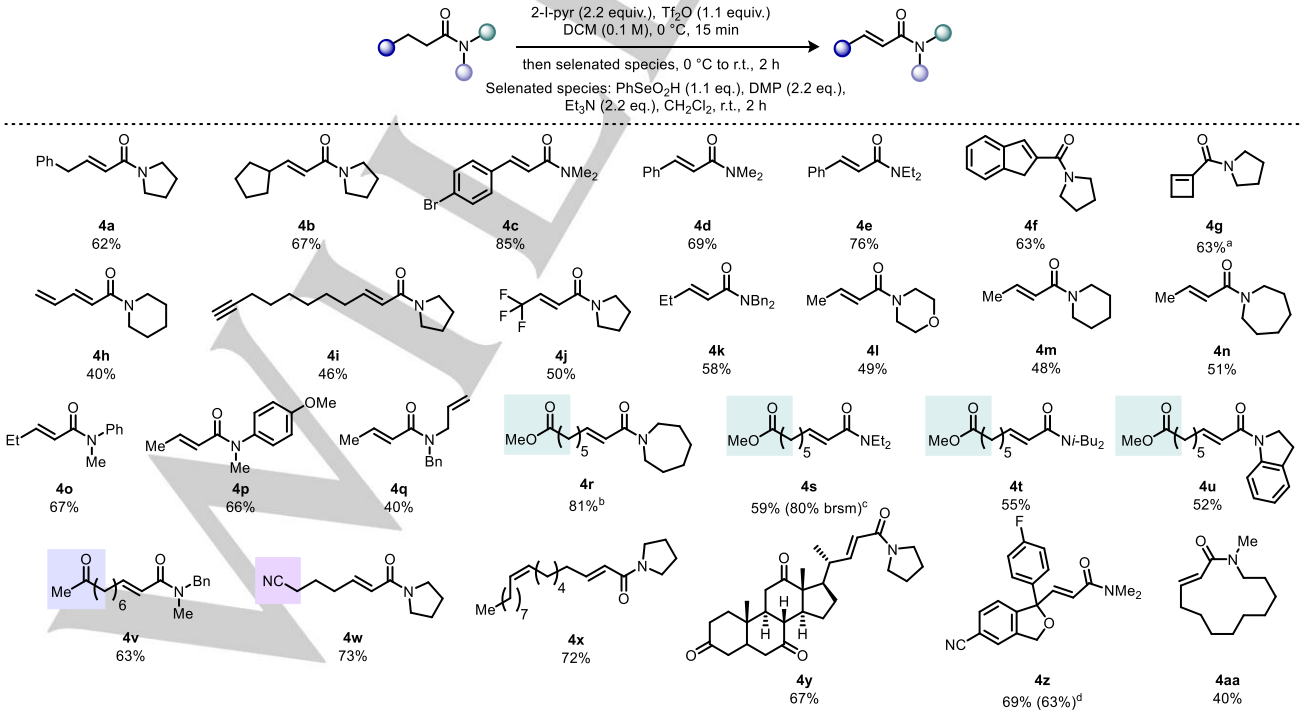
Entry	[Se]	Base	Oxidant	**4a**[a]	**5**[a]	**6**[a]	**1a**[a]
1	$PhSeO_2H$ (1 eq.)	Ag_2CO_3 (1.1 eq.)	-	48	20	-	41
2	$PhSeO_2H$ (1 eq.)	Et_3N (1.1 eq.)	-	-	24	50	14
3	$PhSeO_2H$ (1 eq.)	Et_3N (2.2 eq.)	PIDA (2.2 eq.)	22	12	-	25
4	$PhSeO_2H$ (1 eq.)	Et_3N (2.2 eq.)	IBX (2.2 eq.)	29	45	-	21
5	**$PhSeO_2H$ (1 eq.)**	**Et_3N (2.2 eq.)**	**DMP (2.2 eq.)**	**73**	**-**	**-**	**10**
6	-	Et_3N (2.2 eq.)	DMP (2.2 eq.)	8	2	-	50

[a] NMR yields (in %) determined with the use of bromoform as an internal reference

In subsequent experiments, we noted that the use of triethylamine as a base (Table 1, entry 2) yielded none of the desaturated product (**4a**) and 50% of the α-selenated amide (**6**) instead. This prompted us to try the same reaction with the addition of oxidants [see SI for more details], with hypervalent iodine species affording the most promising results (Table 1, entries 3-6). With 2.2 equivalents of Dess-Martin periodinane (DMP), the α,β-dehydrogenated product was reproducibly formed in 73% NMR yield. This procedure avoided the formation of several other products, thus simplifying the purification process although isolated yields were, in most cases, lower than those measured by NMR due to difficulties in separating the residual starting materials of nearly identical polarity.

With the optimized conditions in hand, our attention next turned to exploring the scope of the reaction (Scheme 2). Pleasingly, a broad range of tertiary amides were tolerated by this desaturation protocol. β-Substitution with a cyclopentyl chain allowed the formation of **4b**. Different cinnamyl amides could be prepared by this method (**4c**-**d**-**e**). Notably, α-substituted amides could also be dehydrogenated with the indene **4f** and cyclobutene amide **4g** isolated in good yield. The 1,3-diene **4h** was also prepared in moderate yield. The conditions of the reaction tolerated the use of alkynes (**4i**) and trifluoromethyl groups (**4j**). Tertiary amides with other *N*-substituents led efficiently to the corresponding desaturated amides, including removable dibenzyl groups **4k**, morpholine **4l**, piperidine **4m** or azepine **4n**. Aniline-derived amides also were well tolerated, delivering the products in good yields (**4o**-**4p**).

A unique feature of this α,β-dehydrogenation reaction is its high chemoselectivity. Amides can be selectively desaturated even in the presence of commonly more reactive carbonyl functional groups such as esters and ketones in moderate to good yields. To the best of our knowledge, no method exists that allows this type of selectivity. Methyl esters were effectively spectators in the α,β-dehydrogenation of different tertiary amides **4r**-**4s**-**4t**-**4u**. Furthermore, the presence of a ketone **4v** or a nitrile **4w** functional group did not divert the reaction away from the amide moiety. Amides derived from natural product feedstocks such as oleic acid (**4x**) or dehydrocholic acid (**4y**) could also be selectively desaturated in good isolated yield. An amide analogue of the blockbuster drug Citalopram was also successfully dehydrogenated to afford product **4z**. Finally, we subjected a 13-membered lactam to our procedure and pleasingly obtained the desaturated product **4aa** in moderate yield.



Scheme 2. Scope of amide dehydrogenation. [a]1 mmol scale. [b]Reaction carried out at -20 °C. [c]Reaction carried out at -10 °C. [d]4.2 mmol scale.

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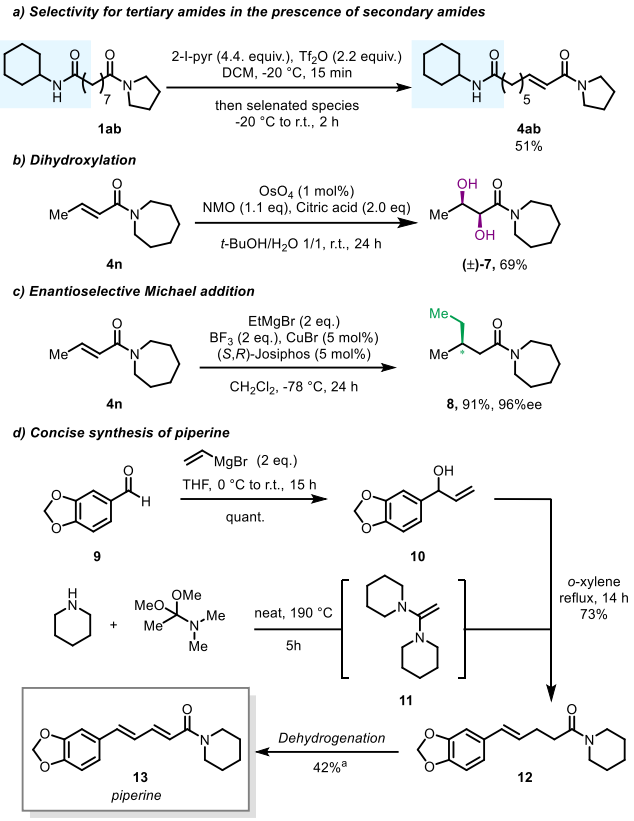
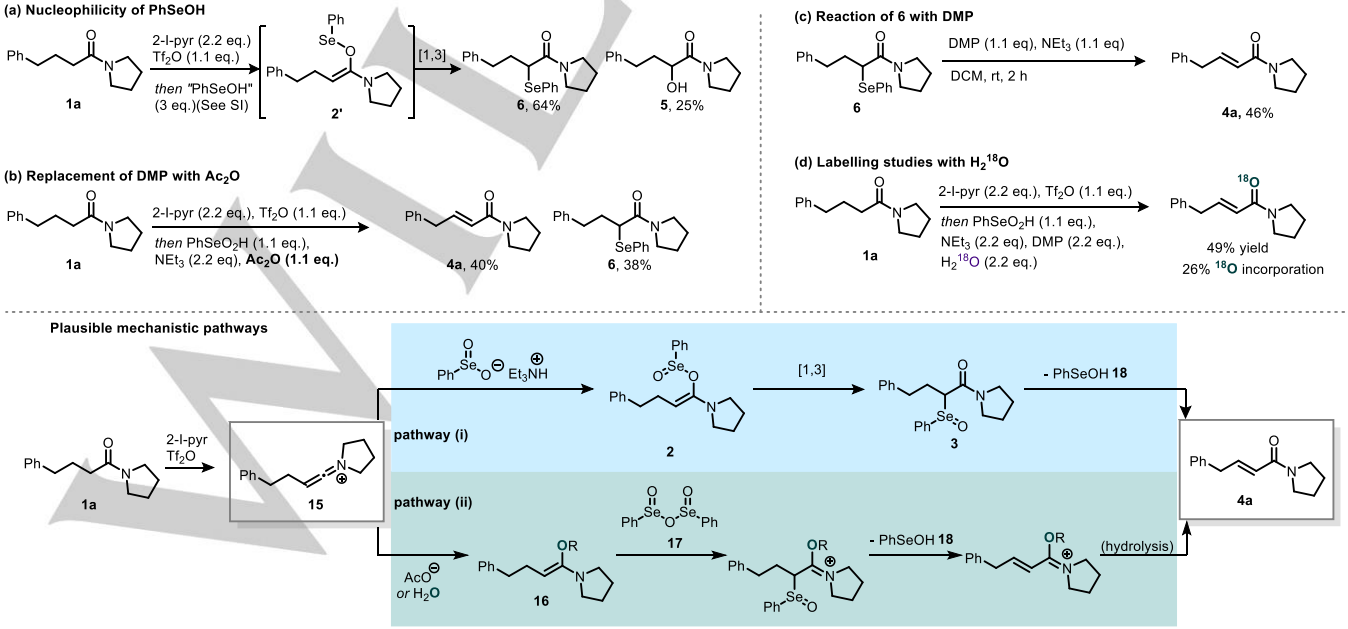


Scheme 3. Derivatisation of products and application of the method. [a]NMR yield.

In order to further probe the selectivity of the reaction, we subjected a substrate containing both secondary and tertiary amides to the reaction conditions. Pleasingly, product **4ab** resulting from desaturation adjacent to the tertiary amide, was exclusively obtained (Scheme 3a). We next sought to showcase the utility of these Michael acceptor products. Dihydroxylation proceeded smoothly to give product **7** in 69% (Scheme 3b).[21] Asymmetric conjugate addition to unsaturated amides, as recently described by Harutyunyan and co-workers,[22] was realized on unsaturated amide **4n** with EtMgBr, resulting in product **8** in 91% yield and 96% ee (Scheme 3c). Cognizant of the pervasiveness of amides in nature,[23] we were keen to apply our methodology to synthesis of a natural product. We selected piperine **13** (Scheme 3d), a polyunsaturated amide responsible for the pungency of pepper. Piperine possesses antioxidant, anti-inflammatory and antidepressant properties and has been synthesized previously using a variety of strategies.[24] Here, we propose an alternative 3-step synthesis starting from the commercially available aldehyde **9** (Scheme 3c). After quantitative transformation of **9** into the allylic alcohol **10**, this compound is treated with the *in situ* prepared 1,1-diamino alkene **11** in refluxing xylene to yield the γ,δ-unsaturated amide **12** in a very good 73% yield by a modified Claisen-Eschenmoser rearrangement.[25] Further dehydrogenation of **12** delivered piperine **13** in moderate 42% yield.

We then turned our attention to the mechanism of the reaction. Preliminary work had demonstrated the formation of the α-selenated amide **6** in 64% yield by addition of selenenic acid, PhSeOH, onto a keteniminium ion (Scheme 4a). We hypothesized that this occurred *via* a [1,3] sigmatropic rearrangement from intermediate **2'**. During this reaction, 25% of α-hydroxylated product **5** was also formed, possibly by nucleophilic attack of the PhSeOH on the α position of the intermediate **2'** followed by hydrolysis. These results led us to postulate *pathway (i)* (Scheme 4) for the dehydrogenation mechanism by simple analogy, the only difference being the oxidation state of the selenium atom. However, during the reaction discovery process it was observed that, in the absence of an oxidant, the α-selenated amide **6** remains the major product (Table 1, entry 2). Given that *pathway (i)* generates PhSeOH **18** we believe it possible that DMP could play two distinct roles: (1) trapping of **18**, which is likely more nucleophilic than seleninic acid, and (2) oxidation of any **6** that is produced. In support of this hypothesis, we observed that DMP was able to oxidise α-selenated amide **6** to desaturated amide **4a** in moderate yield (Scheme 4c).

Alternatively, because it has been demonstrated that iodyl benzoic acid can be used as an oxidant to generate benzene seleninic anhydride (BSA) *in situ* from diphenyl diselenide (PhSeSePh)[26], we believe that we may also be generating BSA (**17**) under our reaction conditions.[27]



Scheme 4. Mechanistic experiments.

From the labelling studies we undertook with $H_2{}^{18}O$ (Scheme 4d), we established that keteniminium species **15** is likely attacked by either water or acetate released by the DMP, to give the enamine/enol (acetate) hybrid **16**.[28] Conceivably, reaction of **16** with **17** would generate an intermediate that leads to the product **4a** (Scheme 4, *pathway (i)*). Upon replacing DMP with acetic anhydride (Scheme 4b) we generated a mixture of **6** and **4a**. This further suggests that an electrophilic, oxidized selenium species (likely the mixed anhydride) plays some role in the reaction but also emphasizes that DMP is important, either to oxidise **6** to **4a,** or trap and re-oxidise species **18** and lower oxidation state selenium species.[29] We speculate that the modest efficiency of reaction 4(c) indicates the major role of the DMP to be as a secondary oxidant of species **18** which avoids side reactions of the keteniminium intermediate **15** with lower oxidation state selenium species.

In conclusion, we report a novel procedure for the synthesis of α,β-unsaturated amides from the corresponding saturated amide starting materials. The reaction proceeds by electrophilic activation followed by a unique selenium-mediated dehydrogenation. This process conveys good functional group tolerance and, significantly, enables the desaturation of amides in the presence of esters, ketones and nitriles. We have applied this method to the synthesis of natural product piperine. Current experiments allude to a mechanism which involves attack onto an electrophilic Se(IV) species however further investigations on this are underway in our laboratory and will be reported in due course.

Acknowledgements

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Keywords: dehydrogenation • amide activation • hypervalent iodine • seleninic acid • triflic anhydride

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[27] Formation of PhSeSePh was observed by NMR upon addition of NEt_3 but this NMR signal gradually disappears over time if DMP is present in the solution. In addition, we observed a peak in ^{77}Se NMR (CD_2Cl_2) at 1276 ppm when mixing PhSe(O)OH, NEt_3 and DMP together which we tentatively assign to BSA. For literature ^{77}Se NMR values, see: D. H. R. Barton, T. Okano, S. I. Parekh, *Tetrahedron* **1991**, *47*, 1823–1836.

[28] Replacement of PhSe(O)OH with BSA gave the product cleanly, albeit it in lower yield (see SI for details).

[29] ^{77}Se NMR (CD_2Cl_2) of a mixture of PhSe(O)OH, NEt_3 and Ac_2O showed peaks at 461 ppm and 1215 ppm which we postulate to be PhSeSePh and PhSe(O)OAc, respectively.

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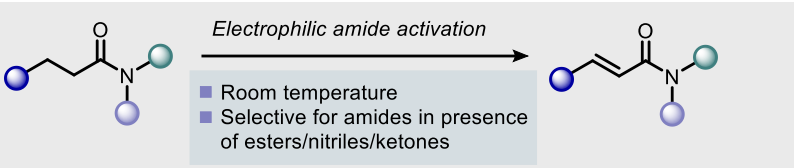

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Page No. – Page No.
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