Title: 1,2-Redox Transpositions of Tertiary Amides

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Abstract: Reactions capable of transposing the oxidation levels of adjacent carbon atoms in organic molecules enable rapid and fundamental alteration of a molecule’s reactivity. Herein, we report the 1,2-transposition of carbon atom oxidation level in cyclic and acyclic tertiary amides, resulting in the one-pot synthesis of 1,2- and 1,3-oxygenated tertiary amines. This oxidation level transfer was facilitated by the careful orchestration of an iridium-catalyzed reduction with the functionalization of transiently-formed enamine intermediates. Remarkably, a novel 1,2-carbonyl transposition was observed when the commercial oxidant mCPBA was selected as the coupling partner. The scope of this transformation and the breadth of this redox transposition strategy has been explored and the diverse β-functionalized amine products were shown to be multi-faceted and valuable synthetic intermediates, accessing challenging biologically-relevant motifs.

Main Text: Chemical reactions that dramatically transform the reactivity of molecules and bypass traditional sequences of functional group interconversions offer the opportunity to overturn the prevailing logic in synthetic chemistry. Forging the vanguard of such reactions, the emergent class of novel molecular skeletal editing reactions has enabled highly-coveted transformations to become a reality (1–7). A related yet comparatively under-explored avenue is the analogous approach towards redox editing of molecules. This reaction paradigm seeks to challenge the dogma of redox transformations being limited to single carbon atom oxidation level changes, instead aspiring to complementary oxidation level transfers between adjacent carbon atoms (8). Such processes reform notoriously non-strategic and lengthy sequences of redox manipulations into highly choreographed “oxidation level dances” to deliver efficiently high-value building blocks and intermediates. Such a conceptual framework has been encapsulated elegantly in a seminal report from Dong of a net redox-neutral sequence transposing ketone functionality (9) and, more recently, in an palladium-mediated oxidative rearrangement of 1,1-disubstituted alkenes to ketones, reported by Zhu (10).

Given the ubiquity of amines in medicinal chemistry, agrochemistry, and functional materials, the development of this strategy to incorporate and manipulate nitrogen-containing structural motifs would have widespread utility in chemical synthesis (11, 12). In particular, the conversion of amides to functionalized amines represents a uniquely appealing strategy given the ubiquity of the amide functional group in known chemical space, their renowned stability, and their facile synthesis. Applying this 1,2-redox transposition logic to the amide functional group leads to β-functionalized amine products which are widespread among natural product, pharmaceutical, and agrochemical molecules, highlighting the preponderance of pharmacophores featuring such motifs (Scheme 1A & 1B) (13, 14). Despite several prominent contemporary contributions to access β-functionalized amines (15–19), the predominating synthetic logic, from amides, remains the
multistep amide α-deprotonation, electrophilic functionalization, and subsequent amide reduction. Such an approach is inherently limited by the functional group tolerance of the harsh deprotonation and reduction steps, by a limited scope of viable electrophiles and is unappealing from the point of view of step and redox economy (20).

We envisioned a complete reversal of this sequence, initiated by a catalytic reduction of the tertiary amide to access a species at the enamine oxidation level (Scheme 1A). The reduction thereby simultaneously enacts both an oxidation level decrease and a transfer of oxidation level to the adjacent carbon atom. Guided by well-established principles in enamine reactivity, appropriately leveraging this enamine intermediate could enable broad access to β-functionalized amines. Such a transformation would elegantly complement the recent inspiring approaches of molecular scaffold- and redox-editing (Scheme 1C)(1–7, 9, 10).

Scheme 1. A) Redox transposition of amides and the design of an iridium-catalyzed redox transposition framework; B) The prevalence of β-functionalized amines in pharmaceuticals and natural products; C) Key literature inspiration supporting the proposed concept and its importance; D) This work, targeting β-functionalized amines. Tf, triflyl; NBE, a norbornene.

We believed that reductive iridium catalysis, namely the use of Vaska’s complex (IrCl(CO)(PPh₃)₂) in conjunction with a suitable silane reductant, would be ideally suited to such a strategy and were drawn to its under-explored potential as a means of accessing enamines. Our
group, among others, has reported extensively on the reductive functionalization of tertiary amides to α-substituted amines, via generation of transient silylated hemiaminals with exquisite chemoselectivity (21–26). The application of the same reductive framework to access analogous β-functionalized amines has remained limited to a few isolated reports on the generation of enamines (27–32). In the seminal report from Nagashima, a series of stable enamines were generated, however, the utilization of the enamine products was limited to an ex-situ cyclopropanation reaction. In related work, Adolfsson, while exploring alternative reduction conditions, reported the synthesis of a number of functionalized heterocycles and highlighted the potential for installing β-oxygenation in such sequences.

Given the prestigious history of enamines in synthetic chemistry (33, 34), the minimal exploration of the chemistry of reductively-generated enamines and, in particular, the scarcity of such reductive functionalization of lactams, we were drawn to this as a powerful and untapped reactivity space.

Taking inspiration from the Amadori and α-iminol rearrangements (35, 36), we believed that appropriate β-oxidation of the enamine to the hydroxy-iminium ion should then follow a related mechanistic course and tautomerize to the thermodynamically more stable α-aminoketone. Indeed, enamine oxidation has been demonstrated on “N-deactivated” substrate classes, e.g. N-aryl indoles and N-Boc heterocycles, and ketone-derived enamines; however, such oxidations remain limited to stable isolable enamines of limited scope and are frequently accompanied by over-oxidation. (Scheme 1C) (37–44). In our proposed one-pot strategy from the tertiary amide, this reaction would constitute an unprecedented 1,2-carbonyl shift, enabling direct conversion of widely available tertiary amides to synthetically valuable, and electronically distinct, α-aminoketones (Scheme 1D). Such a transformation, if successfully executed, would not only unlock new avenues for reductive amide functionalization but would also facilitate streamlined access to structural motifs of fundamental importance in biomedical sciences.

Critical to achieving this reactivity was establishing conditions for the clean and reliable formation of the stable enamine, in a manner amenable to both acyclic and lactam substrates. In order to investigate this goal, N-benzyl caprolactam 1a was chosen as a model substrate and studied under standard Vaska’s reductive conditions [IrCl(CO)(PPh3)2 (1.0 mol%), tetramethyldisiloxane (TMDS, 1.5 eq.), C6D6 and monitored via 1H NMR]. No silylated hemiaminal was observed in the reaction mixture (45) but instead a mixture of both the desired enamine 2a and the ring opened dimeric dienamine 2b was obtained (Scheme 2A). Furthermore, we observed that, over time, the reaction mixture would transform completely to this species 2b. This dimerization likely follows catalytic generation of the iminium ion from the enamine (See SI, Scheme S2) implying that the presence of trace Bronsted acidity could be effecting this deleterious pathway. Hence, the reaction was repeated in the presence of 1.2 eq. diisopropylethylamine (DIPEA) and, gratifyingly, a marked improvement in enamine stability was observed.

Treatment of the in situ-generated enamine with mCPBA resulted in a very rapid consumption of the enamine with only one product visible by NMR which was confirmed to be the desired aminoketone 3a, albeit in low 17% yield (entry 1, Scheme 2B). The solvent, base, temperature and stage timings of the reaction were optimized and the NMR yield was increased to 50% (entries 2-6). Running the reaction with the rigorous exclusion of air and addition of the mCPBA as a CH2Cl2 solution, to dilute the reaction mixture, enabled the product to be isolated in 63% yield. Neither
Bronsted acidic, Lewis acidic nor Lewis basic additives could further improve the yield (see SI for details).

Scheme 2. Optimization studies A) Investigation into enamine stability; B) optimization of the carbonyl transposition procedure; a reaction left for 16 hours following oxidation; b mCPBA added as a CH2Cl2 solution; c reaction conducted with rigorous exclusion of air (See SI); d commercial mCPBA used. mCPBA, meta-chloroperoxybenzoic acid; TMDS, 1,1,3,3-tetramethyldisiloxane; r.t., room temperature; Bn, benzyl; DIPEA, diisopropylethylamine; DMDO, dimethyldioxirane; yields refer to NMR yields employing 1,2,4,5-tetramethylbenzene as internal standard; isolated yields are given in brackets.

The scope of this 1,2-carbonyl transposition with respect to the amide was then investigated. N-benzyl lactams (6-, 7- and 8-membered rings) afforded the corresponding α-aminoketones in moderate to good yields (3a-c). Lactams with electron-poor N-substituents (e.g. p-cyano-benzyl), yielded low amounts of the desired product with predominant formation of the over-reduced tertiary amine observed instead. This was attributed to an increased stability of the silylated hemiaminal intermediates and decreased formation of the required enamine before oxidation; this was corroborated by NMR monitoring of the reaction course. Lengthening of both the enamine formation stage and the oxidation stage succeeded in suppressing the formation of over-reduced amine side-products and increasing the yield of the desired carbonyl transposed products (3f-g, 3i-j, 3k-l). Acyclic amides were also successfully employed and afforded the desired α-aminoketones albeit in reduced yields (3p-r), attributed to a degree of instability in the acyclic α-aminoketone products.
Scheme 3. Scope of the 1,2-carbonyl transposition (A) and reductive modification (B). Reaction conditions for the carbonyl transposition: amide (0.2 mmol), IrCl(CO)(PPh$_3$)$_2$ (1.5 mol%), TMDS (1.5 eq.), DIPEA (1.2 eq.), CH$_2$Cl$_2$ [0.083 M], r.t, 15 min then mCPBA (1.1 eq.) at −78 °C then r.t., overnight. a Reaction quenched at −78 °C with pH 5 aq. acetate buffer and stirred at r.t. for 2 hours. b Lengthened reaction times, see SI for details. Reaction conditions for the reductive transposition: as above but with addition of LiAlH$_4$ (4 eq.) following oxidation at −78 °C for 10 mins. Yields refer to isolated yields.

In order to complement this formal redox-neutral 1,2-carbonyl transposition, a synthesis of β-aminoalcohols was envisioned in which transient hydroxy-iminium ion intermediates, formed after mCPBA oxidation of the enamine, could be selectively reduced with a potent hydride reductant. This would enable alternative access to β-oxygenated amines, particularly in cases where the α-aminoketones were unstable.

Given the fast reaction rate of the oxidation, following the standard Ir-reduction/mCPBA-oxidation sequence, the reaction mixture of 1a was treated with LiAlH$_4$ (4 eq.) following 10 minutes in the presence of mCPBA at −78 °C. The resulting β-aminoalcohol 4a was afforded in good yield (60%). NaBH$_4$ in methanol could be employed in place of LiAlH$_4$ with no change in yield; however, treatment with triethylsilane and trifluoroacetic acid yielded exclusively the aminoketone 3a. Using LiAlH$_4$, this reactivity translated well across a series of lactams and amides (4a-e). Crucially, the 3-hydroxyxypiperidine motif, a fundamental building block reported over 5000 times in patent literature with varying N-substitution, could be obtained in good yield (4b). This reductive transposition was also shown to be effective in the synthesis of the highly bioactive β-
hydroxyphenethylamine motif (4d). Targeting the synthesis of the hemlock-derived alkaloid pseudoconhydrine (46), an appropriate 6-allyl 2-piperidone could be afforded in two steps from the parent imide and the reductive transposition of this lactam proceeded in high yield and moderate diastereoselectivity to yield a 3-hydroxypiperidine 4e. This was converted to the natural product (±)-pseudoconhydrine in high yield, following hydrogenation of both the alkene and the benzyl group.

To further develop the utility of this 1,2-transposition strategy and investigate the potential for C-C bond formation, we envisioned that the use of acid chlorides, and related electrophiles, could lead to stable α,β-unsaturated β-aminoketones (i.e. enamines). Such products have been highlighted as valuable intermediates in drug discovery and feature in a number of bioactive compounds (47). Acylation of transiently-generated enamines to afford enamines has been demonstrated in direct oxidative desaturation of amines (48); however, such reports have focused on the study of piperidines and typically rely on N-aryl substrates. Emboldened by this precedent and related transformations involving pre-formed enamines, the reaction of enamine 2a with benzoyl chloride was investigated in CDCl₂ and monitored by ¹H NMR. A rapid reaction was observed resulting in near quantitative conversion to enaminone 5a; however, significant decomposition was observed upon attempted isolation. An ethanolamine quench was introduced to consume any remaining acid chloride, while introduction of a coldaq. NH₄Cl work-up ensured minimal decomposition of the crude mixture upon evaporation, allowing the desired enaminone 5a to be isolated in 71% yield.

Scheme 4. Scope of the β-functionalization with carbonyl electrophiles towards enamines and related products. Reaction conditions for the synthesis of β-carbonyl derivatives: amide (0.2 mmol), IrCl(CO)(PPh₃)₂ (1.5 mol%), TMDS (1.5 eq.), DIPEA (1.2 eq.), CH₂Cl₂ [0.083 M], r.t, 15 min then DIPEA (1.0 eq.), electrophile (2.0 eq.), –20 °C to r.t., 30 min. a No additional DIPEA was added with electrophile.
Variation in both the ring size of the lactam and exchanging the amine substituent for an allyl group afforded the corresponding cyclic enaminones in good yields (5a, 5g-j). Additionally, acyclic amides could be successfully applied (5k-m). A range of benzoyle chloride were explored in this chemistry, demonstrating that the coupling proceeded efficiently with *para*-substituted benzoyle chlorides while lower yields were observed in the coupling of alkyl and *ortho*-substituted aromatic acyl chlorides (5b-f). The reactivity extended well to aryl isocyanates to afford the corresponding enaminamides (5q-u), as well as to phenyl sulfonyl chloride and the Michael acceptor dimethyl acetylenedicarboxylate (5o and 5p). Enaminone 5n could be converted in good yield to muscle relaxant tolperisone following reduction with LiAlH₄ (49).

The potential utility of these densely-functionalized N-heterocyclic products warranted detailed investigation. In order to facilitate up-scaling of the carbonyl transposition reaction, the catalyst loading could be reduced by a factor of four, to 0.38 mol%, and, accordingly, the concentration during the reduction was increased. This enabled aminoketone 3a to be isolated in unchanged yield at a 5 mmol scale. Aminoketone 3a reacted predictably under standard Grignard and Horner-Wadsworth-Emmons reaction conditions, enabling straightforward access to the corresponding β-amino tertiary alcohol (6a) and a γ-amino ester (6b) – following hydrogenation of the corresponding α,β-unsaturated ester. Furthermore, the aminoketone functionality could be employed to access a series of medicinally-relevant motifs, including: β-difluoramines (6c) via...
de-oxyfluorination, spirocyclic hydantoins (6e) via a high-yielding Bucherer-Bergs cyclisation, and 1,2-diamines (6f) via reductive amination. Additionally, a 3,4-fused azepane-quinoline tricycle (6d) could be afforded in excellent regioselectivity, following reaction under traditional Friedländer quinoline synthesis conditions.

Scheme 5. Further synthetic applications. A) Derivatization of aminoketone products; B) alternative oxidative capture of the enamine intermediates. TEPA, triethyl phosphonoacetate; TBHP, tert-butyl hydroperoxide; Thex, tert-hexyl; TMS, trimethylsilyl.

Given the successful trapping of the oxidized intermediates with a nucleophilic reductant (Scheme 3B), it was hoped that this reactivity would extend to other nucleophiles. In order to investigate this, following the standard Ir-reduction/mCPBA-oxidation sequence, the reaction mixture was treated with four equivalents of TMSCN which afforded the desired β-siloxyl-α-aminonitrile as a single diastereomer. Extending this reactivity further, Grignard and organoaluminium reagents were shown to be capable of trapping the transient iminium ion, leading to complex branched β-aminoalcohols (6i-6j). Additionally, analogous reaction with the deuterated reductant NaBD₄ resulted in selective deuterium incorporation at the α-carbon, supporting the proposed reduction of an intermediate iminium ion for the examples in Scheme 3B, rather than a conceivable tautomerization to the aminoketone and reduction of this ketone.
To demonstrate further the utility of this 1,2-redox transposition approach, the hydroboration/oxidation of model enamine 2a was investigated. Following inspiration from Singaram (28, 43), the enamine solution was treated with a freshly prepared Thex₂BH solution and, after oxidation, the desired aminoalcohol was isolated in good yield. With this successful application to hydroboration, it is hoped that this reduction/hydroboration sequence opens the door to future enantioselective β-aminoalcohol synthesis or use of this newly-introduced β-boron moiety as a versatile cross-coupling handle.

In conclusion, a new strategy for the single-step redox-editing of tertiary amides is described. Critical to this approach was the utilization of catalytically-generated enamines as redox transfer intermediates, enabling the subversion of traditional amide redox chemistry and “synthon” logic. Through judicious choice of an electrophilic coupling partner, a diverse set of 1,2- and 1,3-oxygenated amines could be afforded directly from tertiary amides. Among the reported transformations, a 1,2-carbonyl transposition has been demonstrated, accordingly, completely transforming the molecule’s reactivity profile. Following a successful scale-up of the transposition conditions, the α-aminoketone products were shown to be valuable synthetic intermediates. Furthermore, β-aminoalcohols and enamiones were also accessed by modification of the electrophilic coupling partner, enabling the synthesis of bioactive and pharmaceutically relevant molecules. It is hoped that this single step “redox-shuffling” logic may form the basis of future research towards polyfunctionalized saturated and semi-saturated N-heterocycles.

References and Notes


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**Supplementary Materials**
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Supplementary Figures and Tables
Spectral data
Supplementary References