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Unified Approach to the Chemoselective α-Functionalization of Amides with Heteroatom Nucleophiles

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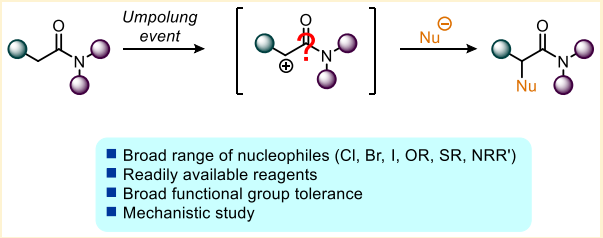
Supporting Information

ABSTRACT: Functionalization at the α-position of carbonyl compounds has classically relied on enolate chemistry. As a result, the generation of a new C−X bond, where X is more electronegative than carbon requires an oxidation event. Herein we show that, by rendering the α-position of amides electrophilic through a mild and chemoselective umpolung transformation, a broad range of widely available oxygen, nitrogen, sulfur, and halogen nucleophiles can be used to generate α-functionalized amides. More than 60 examples are presented to establish the generality of this process, and calculations of the mechanistic aspects underline a fragmentation pathway that accounts for the broadness of this methodology.



INTRODUCTION

The α-functionalization of carbonyl compounds has been classically dominated by enolate chemistry. Indeed, the recognition of the synthetic value of nucleophilic enolates, available by treatment of a carbonyl precursor with a strong base, has rendered them the reactants of choice for C−C, C−O, C−N, C−S, and C−halogen bond formation at the α-position of a carbonyl moiety for more than half a century.[1,2] Because of the inherent electronegativity of most heteroatoms listed in the preceding sentence (O, N, and halogens), their derivatives are also typically nucleophilic in nature. Introducing such a species into the α-position of a carbonyl therefore formally requires an oxidation event, either in the reaction itself[3,4] or in the generation of highly reactive electrophilic heteroatom reagents.[5−7] Although this can result in poor functional group tolerance under the reaction conditions, it more significantly means that a truly unified approach has failed to materialize, with specific reagents required for each element (Figure 1a).

The generation of enolates typically requires strong bases (usually with pK_a > 22), which can pose problems of chemoselectivity in contexts where several competing carbonyl functional groups are present. Furthermore, a common issue of classical enolate functionalization is "over-reaction" because the products are often more CH-acidic and therefore more reactive under the reaction conditions than the starting materials themselves. A common tactic to circumvent this hurdle is to prefunctionalize the α-position with a leaving group which is amenable to S_N2-type substitution (Figure 1b).[8]

As an example, the mono-α-bromination of carboxamides is frequently achieved with Br_2 or *N*-bromo succinimide (NBS). In both cases, overbromination can lead to lower yields, and the oxidative potential of those reagents means that the functional group tolerance is moderate (namely, but not only, toward unsaturations)[9,10] With these commonly used methods, the chemoselective α-bromination of amides over other carbonyl groups remains a challenging transformation.

On the other hand, carboxamides have particularly high nucleophilicity at the carbonyl oxygen. As pioneered by Ghosez, upon activation with triflic anhydride and a base, amides are

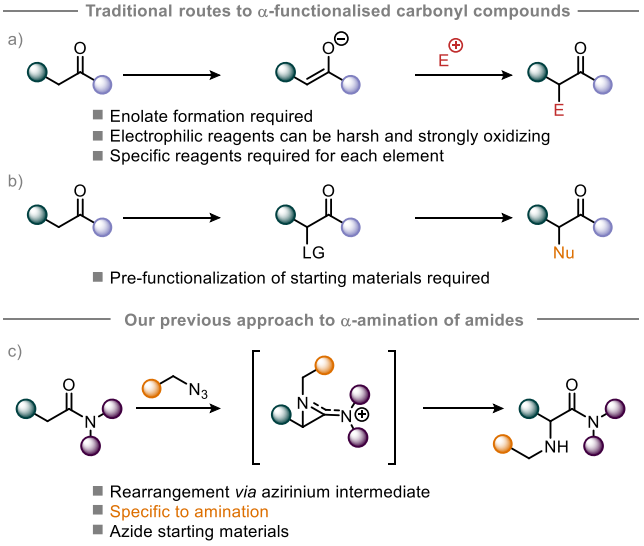


Figure 1. Approaches to α-carbonyl functionalization.

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reversibly converted to an electrophilic and highly versatile keteniminium species.[11−14] We have previously shown that this intermediate can be captured by simple alkylazides, resulting in an unusual and modular α-amination reaction (Figure 1c).[15,16] Nonetheless, this was specific to amination and neatly exemplifies the situation alluded to earlier.

In more recent work, our group has used lutidine *N*-oxide as the nucleophile, enabling the formation of an electrophilic enolonium species (Figure 2a).[17−21] An analysis of this species

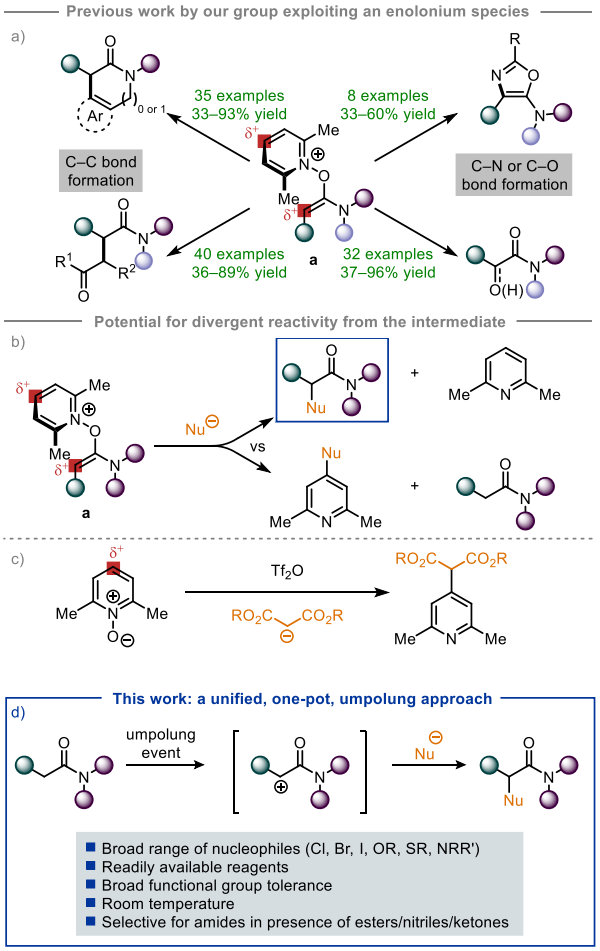

Figure 2. Previous work and reactivity of the umpoled intermediate.

allows certain considerations to be made with regard to its reactivity. While the α-position is, in principle, a "soft" electrophilic center,[16] a problem that could arise by the use of other "hard" nucleophiles, such as alkoxides, would be attack at the 4-position of the lutidine moiety (Figure 2b). This reaction manifold would lead to the formation of the starting material and a substituted lutidine product and was previously observed by us in a different context (Figure 2c).[22]

Here (Figure 2d), we report a detailed study of the reactivity of the enolonium intermediate **a** toward a broad range of heteroatom nucleophiles, including O-, N-, S- and halogen species. This study results in a unified approach to the α-functionalization of amides in a fully chemoselective fashion.

RESULTS AND DISCUSSION

At the outset, we were eager to investigate the use of halide salts as nucleophiles.[23] Pleasingly, we found that adding tetrabutylammonium halides to the preformed enolonium intermediate **a** afforded α-halogenated amides **1aa-1h** in high yields. Commercial 95%-purity NaCl can also be used to synthesize the α-chlorinated product **1aa**. Attack of the halide occurred selectively at what was originally the α-position of the amide rather than at the 4-position of the lutidine site of the intermediate in all cases investigated (chloride, bromide and iodide) giving the products **1aa-1ac** in high yields. The reaction could also be scaled up 50 times affording product **1aa** in a similar 74% yield. Besides pyrrolidine-derived amides, dimethylamine derivatives also gave products in excellent yields (**1ba-1bc**). Importantly, a carbon-chlorine bond is well tolerated in the molecule with no halogen scrambling observed (**1ca-1cc**). This α-halogenation procedure displays high chemoselectivity, with the reaction occurring solely α- to carboxamides even in the presence of other carbonyl derivatives such as esters (**1da-1dc**) or ketones (**1e**), as well as nitriles (**1f**). Amides bearing alkenes (**1g**) or alkynes (**1h**) are also well tolerated under these reaction conditions.

Encouraged by the efficiency of these transformations, we became intrigued by the possible incorporation of oxygen and sulfur nucleophiles. Sodium alkoxides and thiolates were competent nucleophiles on the umpoled amide. Benzylic (**2a** and **3a**) and allylic (**2b**, **3b**, and **2c**) alkoxy and thiolate nucleophiles gave the α-functionalized products in high yields. The use of *p*-nitrophenol led to product **2d**. In contrast to malonates,[16] the β-ketoester ethyl 2-oxocyclohexane-1-carboxylate reacted exclusively at the oxygen center rather than the carbon (**2e**). In the case of thiolates, even bulky *t*-butylmercaptan was tolerated (**3c**). Thioacetate attacked selectively through the sulfur (**3d**) and a ketone-bearing substrate proved unproblematic under these reaction conditions (**3e**). Significantly, during the course of our studies, we observed that the nucleophile can be added without deprotonation for some sulfur nucleophiles such as 2-(methylthio)pyrimidine (**3f**) and ethyl 2-(methylthio)acetate (**3g**), albeit with somewhat reduced efficiency (0−20% drop in yield, depending on the substrate).

Next, we sought to examine the functional group tolerance with these strongly nucleophilic alkoxy and thiolate nucleophiles with various amides. We were pleased to see that carbonyl groups such as esters (**2f** and **3h**) and ketones (**2g** and **3i**) as well as related nitriles (**2h** and **3j**) remained untouched under these conditions. Even a primary chloride was not displaced by the nucleophile (**2i** and **3k**). Terminal alkenes (**2j** and **3l**) or alkynes (**2k** and **3m**) were merely bystanders, as expected. Starting from a dimethyl amide, products **2l** and **3n** were formed with equal efficiency.

Amination in the α-position of amides is an especially interesting transformation because the products are amino acid derivatives. We started our investigations with sulfonamide sodium salts. The transformation was efficient for tosylamides carrying a plethora of substituents on the nitrogen atom. Primary (**4a**) and secondary (**4b**) alkyl as well as aromatic (**4c** and **4d**) and benzylic (**4e**) residues were tolerated and gave the α-aminated products in good yields. Concerning the sulfonyl moiety, a range of aromatic groups could be used. Indeed, Ns-protected methylamine gave product **4f** in good yield. Moreover, the alkyl substituent on the nitrogen atom is not mandatory (**4g**, *vide infra*). Shifting the nitro group to the ortho position resulted in a similar yield (**4h**). Heterocycles (**4i**) and bulky aromatics (**4j**) also yielded the expected products efficiently. In addition, indoles could be attached in good yield (**4k**), while as before

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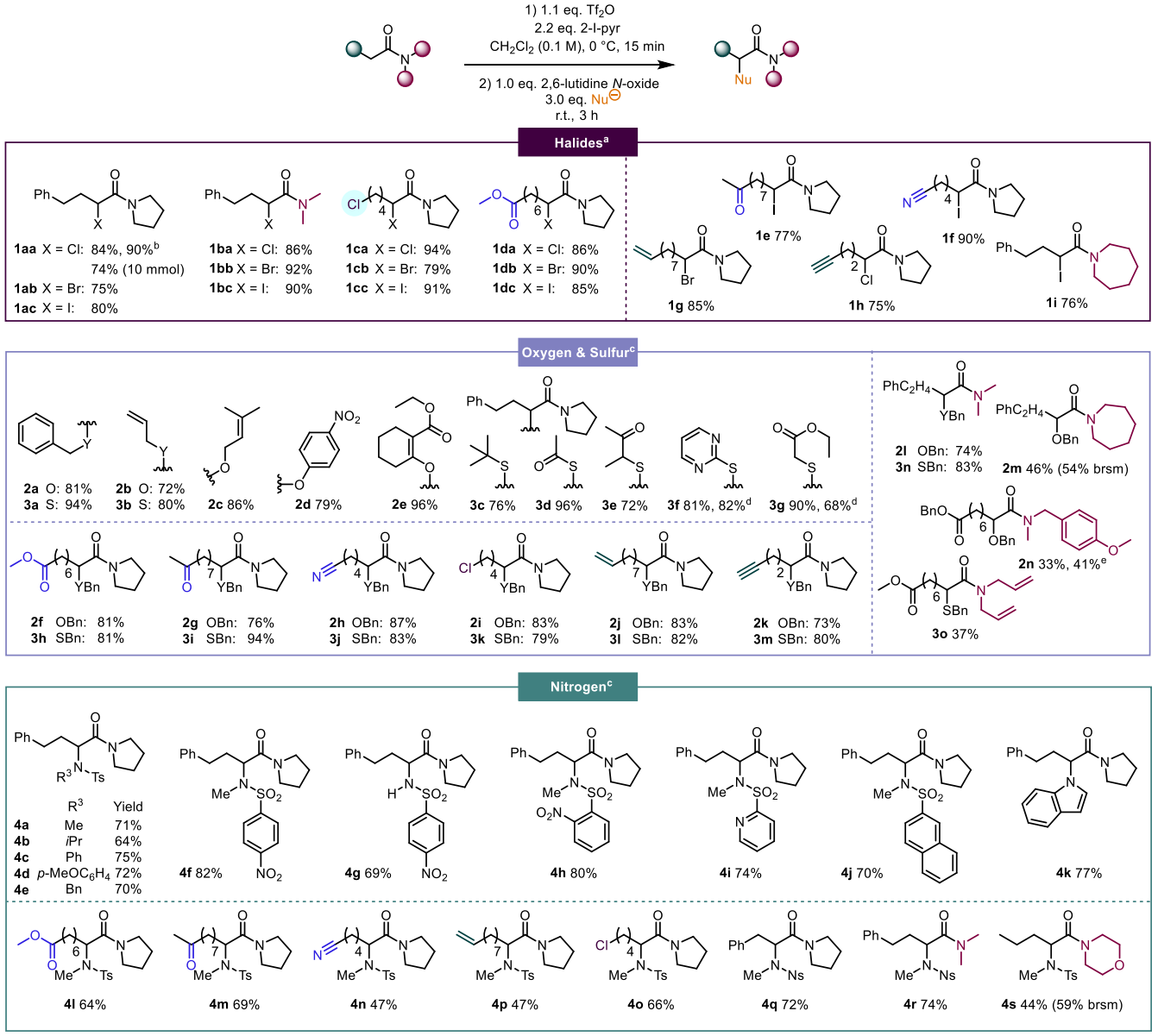
Scheme 1. Substrate Scope for the α-Functionalization of Amides[a]



[a]All reactions were run on a 0.2 mmol scale. The following labels apply to the reaction scheme. (a) After addition of 2,6-lutidine *N*-oxide, 3.0 equiv of the tetrabutylammonium halogen source was added to the reaction. (b) Commercial NaCl (95%) was used. (c) After the addition of 2,6-lutidine *N*-oxide, a solution of the deprotonated nucleophile was used (0.2 M DMF). (d) The nucleophile was added without prior deprotonation. (e) The nucleophile was added 20 s after LNO addition.

various functional groups on the amide backbone are tolerated. Esters (**4l**), ketones (**4m**), nitriles (**4n**), a primary alkyl chloride (**4o**), and a terminal alkene (**4p**) were all compatible with the reaction conditions. Unsurprisingly, small changes in the amide's carbon skeleton did not result in a significant loss of yield (**4q** and **4r**). Compared to our previously developed amination with azides,[16] the obvious advantage is the possibility to directly use amine derivatives as aminating agents in a straightforward retrosynthetic disconnection.

For all nucleophile classes, more encumbered amides were tolerated despite their lower nucleophilicity toward electrophilic activation (**1i**, **2m**, **2n**, **3o**, and **4s**).[24] In the case of possible intermolecular trapping, a shorter oxidation time after the addition of LNO was beneficial and slightly improved the yield as shown with compound **2n**.

Biorelevant nucleophiles (Scheme 2) such as amino acids (Boc protection used for threonine and cysteine, Ts protection used for glycine) were directly coupled to the amide (as the respective methyl esters) via their oxygen, sulfur, and nitrogen atoms (**5a**, **5c**, and **5d**, respectively). Protected carbohydrates are also suitable nucleophiles for this transformation, as exemplified by the formation of **5b**.

The formal addition of ammonia to amides is a difficult task and has been previously achieved only with highly electrophilic reagents such as *O*-(diphenylphosphinyl)-hydroxylamine.[25] Ns-protected derivative **4h**, accessible in one step, enables a subsequent deprotection with thiophenol to afford NH_2-aminoamide **6** in 93% yield.

The versatility of the sulfonamide group can be further showcased by the structural diversification of products **4f**, **4q**,

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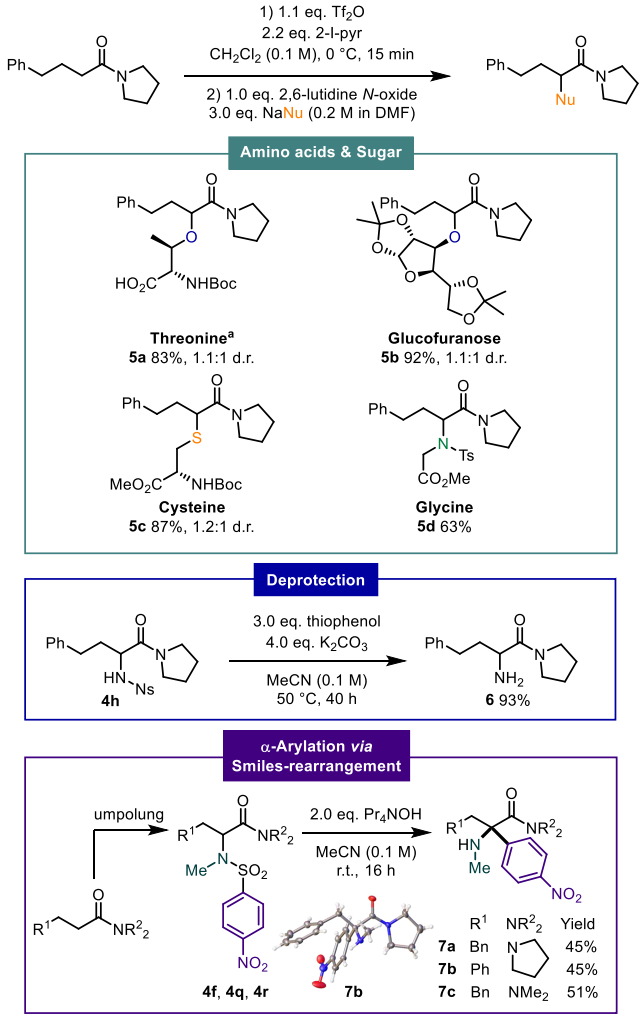
Scheme 2. α-Functionalization of Amides with Complex Nucleophiles and the Derivatization of Products



[a]From the methyl ester. See the SI for details.

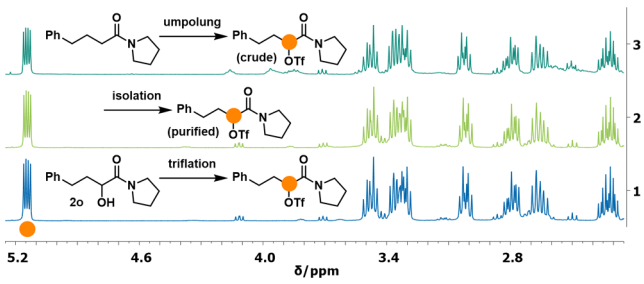


Figure 3. Formation of an α-OTf intermediate and unambiguous assignment by comparison to an authentic sample.

and **4r** via the Smiles rearrangement.[26] These sulfonamides rearranged smoothly to corresponding α-amino-α-aryl amides **7a**, **7b**, and **7c** with the concomitant loss of SO_2. Although previous reports on the Smiles rearrangement of amides derived from Ns-protected amino acids are limited, products **7a**–**7c** carrying a fully substituted carbon center were obtained in just two steps from simple starting materials.[27]

Clearly, the large scope of nucleophiles and the generality of this process surpassed even our most optimistic expectations. Our attention thus turned to investigating the mechanism of this

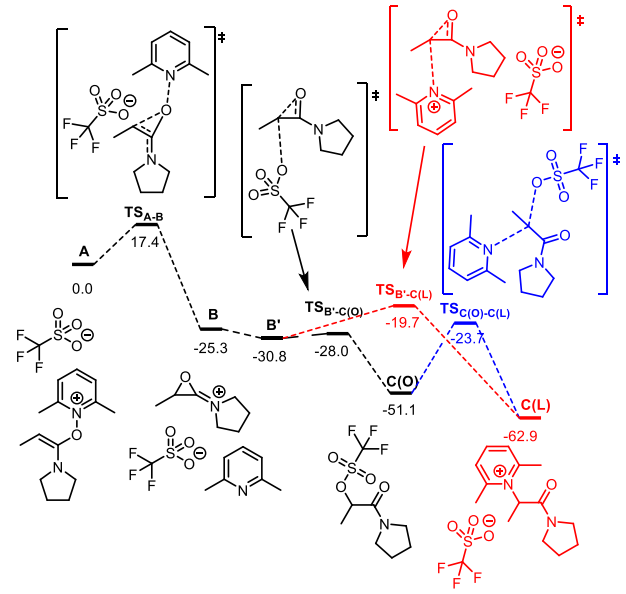


Figure 4. Computed reaction profile (DLPNO-CCSD(T)//DFT, $\Delta G_{298,DCM}$) for the formation of intermediate **C(O)** or **C(L)**. The energy of intermediate **A** is taken as a reference (0.0 kcal mol^{-1}). See the SI for computational details.

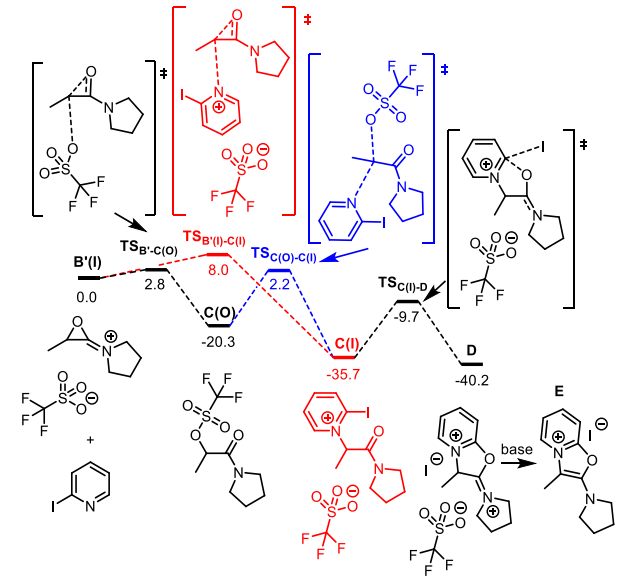


Figure 5. Computed reaction profile (DLPNO-CCSD(T)//DFT, $\Delta G_{298,DCM}$) for the formation of intermediate **C(I)**. The energy of intermediate **B′** is taken as a reference (0.0 kcal mol^{-1}).

reaction. We unexpectedly discovered that, in the absence of a suitable nucleophile, it was possible to isolate the α-OTf amide following careful purification.[21] Unambiguous assignment of this labile intermediate was possible by comparison with an authentic sample prepared by the triflation of α-hydroxyamide **2o** (Figure 3). Given the well-documented weak nucleophilicity of the triflate anion and the other possible competing nucleophiles in the reaction mixture (lutidine and 2-iodopyridine), we decided to undertake a computational study of the mechanism of this process.

We commenced by assuming the formation of enolonium intermediate **A** (cf. Figure 4). Taking this as the starting point, quantum chemical calculations suggest a possible mechanism for

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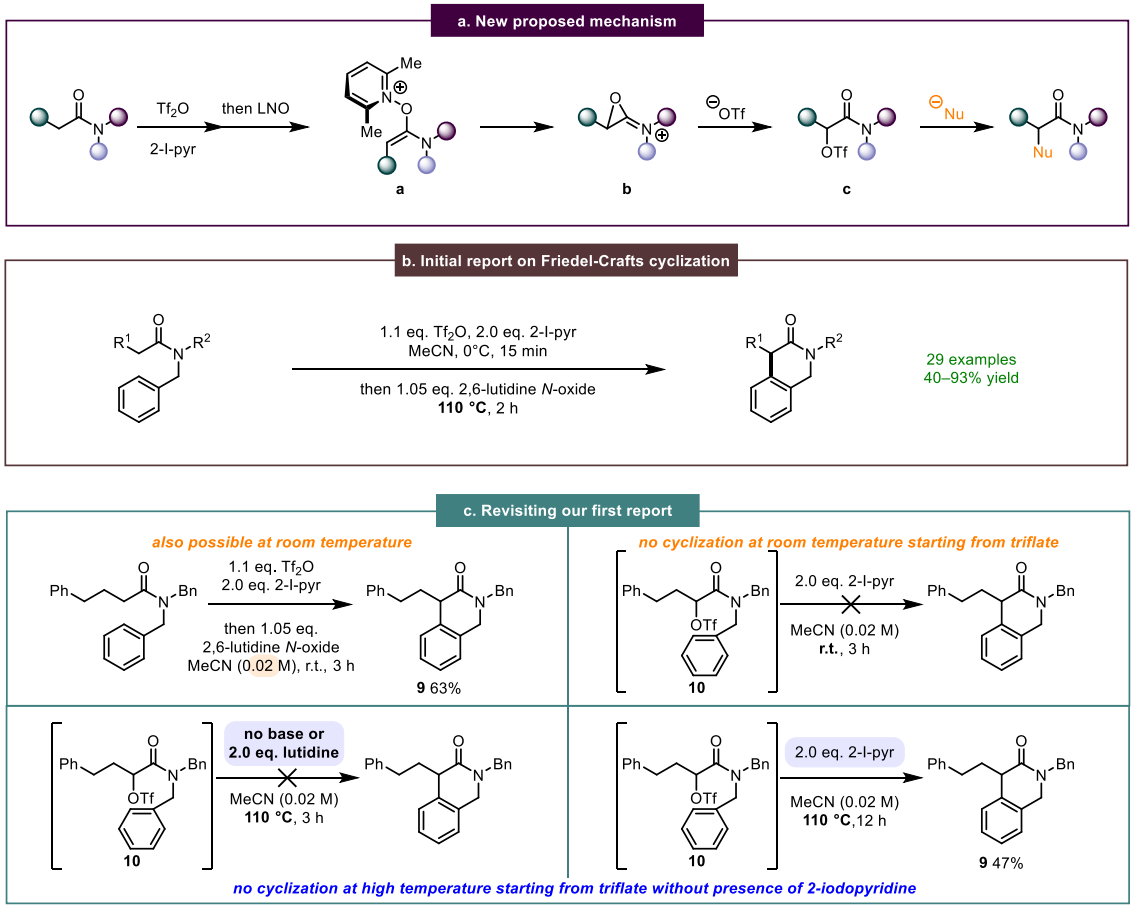
Scheme 3. Revised Mechanism and Mechanistic Insight into Our Previously Reported Transformations



the fragmentation of this intermediate to experimentally observed α-OTf amide product **C(O)**, and the computed energy profile for this process is outlined in Figure 4. (See the SI for computational details.)

In the first stage, the N−O bond is broken, leading to a concerted fragmentation of enolonium **A** via transition state $\mathbf{TS_{A\text{-}B'}}$, expelling a molecule of lutidine and epoxide intermediate **B** (**B** is the product complex consisting of the epoxide, triflate anion, and lutidine components, whereas for **B′** the energy of lutidine is added separately). This event is computed to be highly exergonic ($\Delta G(\mathbf{A} \rightarrow \mathbf{B'}) = -30.8$ kcal mol^{-1}) and kinetically allowed at room temperature (the barrier is 17.4 kcal mol^{-1}). It is noteworthy that this step can be seen as a 2π-electrocyclization, analogous to the situation previously reported for alkylazides.[16] The second step is also exergonic ($\Delta G(\mathbf{B'} \rightarrow \mathbf{C(O)}) = -20.3$ kcal mol^{-1}) and kinetically favorable ($\Delta G^{\ddagger} = 2.8$ kcal mol^{-1} via $\mathbf{TS_{B'\text{-}C(O)}}$). This process involves backside S_N2-type attack of the triflate anion on epoxide intermediate **B′** leading to product **C(O)**.

Given the aforementioned presence of other nucleophiles in solution, we then wished to compare this pathway with a possible alternative: the reaction of epoxide **B′** with lutidine via transition state $\mathbf{TS_{B'\text{-}C(L)}}$. (Figure 4, red color). This reaction is substantially (8.3 kcal mol^{-1}) less favorable kinetically than the formation of product **C(O)**. Alternatively, we considered the hypothetical S_N2 interconversion between systems **C(O)** and **C(L)** (Figure 4, blue color) as a reaction **C(O)** → **C(L)** via transition state $\mathbf{TS_{C(O)\text{-}C(L)}}$. However, this reaction is computed to be the kinetically least favorable of all depicted in Figure 4, having a barrier of 27.4 kcal mol^{-1}.

Another possible nucleophile in solution that could conceivably open epoxide **B** is 2-iodopyridine. This reaction is computed to have a barrier of 8.0 kcal mol^{-1} via transition state $\mathbf{TS_{B'(I)\text{-}C(I)}}$ (Figure 5, red color). Alternatively, product **C(I)** can be formed from intermediate **C(O)** via transition state $\mathbf{TS_{C(O)\text{-}C(I)}}$ (Figure 5, blue color). This event is an analogue of the **C(O)** → **C(L)** S_N2 interconversion (*vide supra*) and has also a high kinetic barrier of 22.5 kcal mol^{-1}. Product **C(I)** can further evolve through intramolecular annulation, leading to biscationic species **D** which can subsequently be deprotonated to form system **E**. This computational result is in line with the experimental detection of products such as **E** by high-resolution mass spectrometry.

The computational study provides strong evidence for the key intermediate common to these reactions being epoxide **B**. This intermediate can be attacked by different nucleophiles, and the probability of the corresponding reactions can be estimated by the height of the free-energy barriers. The calculations suggest that the productive pathway in the cases outlined in this article proceeds via the α-triflated amide (Scheme 3a). Further case-specific computations, estimating kinetic and thermodynamic factors for the reactions of intermediates **C(O)**, **C(L)**, and **C(I)**, would reveal with higher certainty which of these precedes the attack of the nucleophiles incorporated into the final products.

These findings prompted us to revisit our first publication in this area[17] (Scheme 3b), where the nucleophile is an aromatic group tethered via the nitrogen of the amide, which enables an

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intramolecular Friedel−Crafts-type reaction. In our initial studies, significant amounts of cyclized products were found at low temperatures (cf. Scheme 3c; the higher temperature involved in the reported protocol allowed for optimal yields).

To probe the possible intermediacy of α-OTf amide **10** in this process, we prepared it independently from the corresponding alcohol. (See the SI for details.) As shown in Scheme 3c, this compound was not capable of undergoing cyclization at room temperature, in contrast with the observations made before. Similarly, heating triflate **10** under reaction conditions akin to our original report but in the absence of base did not deliver any product. Under these conditions, a significant amount of cyclized product could be isolated only when 2-iodopyridine was present. This suggested that the product might be formed by the displacement of the α-OTf group first by 2-iodopyridine to form a pyridinium intermediate (a transformation made possible at high temperature, cf., the high barriers calculated by DFT and Figure 5), which then undergoes Friedel−Crafts cyclization. *In situ* triflated α-hydroxy amide **2o** underwent rapid substitution with external nucleophiles tetrabutylammonium iodide and sodium Ts-methylamide to afford amides **1ac** and **4a**, respectively (See the SI for details).

Taken together, these findings appear to paint a picture where, in the case of an intramolecular nucleophile, no direct C−C bond formation can occur without the formation of a reactive intermediate; these experimental results are in complete accordance with the proposed theoretical calculations. In the case of intermolecular nucleophiles, the remarkable broadness of species successfully employed (ranging from fluoride/halides to alkoxides, amines and amides, and thiols and enolates) suggests that, at least for some of these nucleophiles, the formation of an α-OTf species is the pivotal event.

CONCLUSIONS

We have shown that the *in situ* umpolung of amides enables a truly general platform for their α-functionalization under mild conditions. Readily available nucleophilic reagents can thus be used for the α-halogenation, -thiolation, -oxygenation, and -amination of amides. We have demonstrated the unique broadness and applicability of this method, and quantum chemical calculations confirmed experimental evidence for an unexpected pathway wherein the α-OTf amide is an intermediate. This helps rationalize the vast range of different nucleophiles that are effective in this methodology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06956.

Experimental procedures and characterization data for all new compounds and computational details (PDF)

2-(Methylamino)-2-(4-nitrophenyl)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (CIF)

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Notes

The authors declare no competing financial interest.

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