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# Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides

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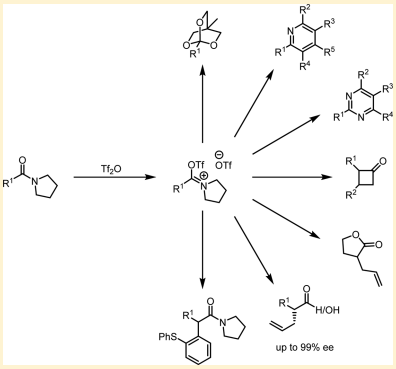
**ABSTRACT:** The electrophilic activation of amides, especially by the action of trifluoromethanesulfonic (triflic) anhydride, enables the formation of highly electrophilic and reactive intermediates, lending themselves to diverse reaction pathways. This synopsis sets out to highlight recent advances in the field of amide activation, focused on the use of triflic anhydride, and the myriad of transformations that can ensue upon addition of several classes of electrophiles to the intermittently generated high energy intermediates.




The carboxamide group is generally considered one of the least reactive carboxylic acid derivatives,[1] owing to the high degree of nitrogen lone-pair delocalization and the ensuing stabilization of the electrophilic carbonyl carbon. While this property is responsible for somewhat widespread disregard of amides as useful synthetic intermediates, the stability of the amide group has also proven to be a valuable asset in the search for novel synthetic routes and chemoselective transformations.[2a,b] Much progress concerning the activation and functionalization of amides has been made in the past 140 years. Classical examples of amide activation, such as the Vilsmeier–Haack and the Bischler–Napieralski reactions (utilizing $POCl_3$), are textbook organic transformations,[2c−e] and the Hofmann rearrangement[2f] has given rise to a myriad of related protocols.[2g,h] In addition to the aforementioned use of phosphorus reagents and halogenation, several other methods of activation have been reported, including activation with other strong electrophiles,[2i,j] transition-metal-catalyzed insertion into the C–N bond,[2k−m] exploitation of the enhanced reactivity of sterically hindered amides,[2n] and transient formation of a formamidinyl group.[2o] In particular, the treatment of amides with trifluoromethanesulfonic anhydride (triflic anhydride) has enabled the development of a considerable body of new synthetic chemistry.[3] Through interaction with this reagent, amides are converted in situ to *O*-trifluoromethanesulfonyloxyiminium trifluoromethanesulfonates (iminium triflates) which can be seen as amide equivalents of increased electrophilicity or can be employed to form highly reactive and synthetically versatile keteniminium ions.[4] Even at a glance, the progressively increased electrophilic character along this series of reagents/intermediates is readily apparent (Scheme 1).

The selectivity and versatility of triflic anhydride as an activator of carboxamides has led to our continued and unbroken interest in the studies of this mode of activation. This synopsis will focus on our work dealing with the use of amides as precursors for high energy intermediates and highlight the diverse classes of compounds that, through our work and that of others, can be targeted by this chemistry.

In depth spectroscopic studies on the reaction of secondary and tertiary amides with triflic anhydride in the presence of various pyridine bases have led to a good understanding of the underlying reaction mechanisms and equilibria (Scheme 2).[5] Following the formation of an iminium triflate **3**, often via the intermediacy of an *N*-(trifluoromethylsulfonyl)pyridinium triflate (**2**) as the active triflating agent, the reaction pathways diverge, depending on the nature of the $\alpha$-substituents (see pathways A and B, Scheme 2). Alongside Charette's pioneering work on iminium triflate (**3**) formation and the ensuing equilibria,[5a,b] pathways A and B (Scheme 2) have been studied in depth by the group of Movassaghi[5c] and our group,[5d] respectively.

The absence of $\alpha$-protons leads to the direct nucleophilic substitution of the triflate by the pyridine base, forming stabilized dicationic pyridinium intermediates **4** or **5** (in equalibrium with nitrilium ion **5′**), depending on the degree of substitution of the amide nitrogen. While Charette has shown that these structures can be directly functionalized, resulting in incorporation of the pyridine,[6a] Movassaghi reported the possibility of *N*-pyridinylation of **5**/**5′**.[6b] Additionally, intermediates such as **3**–**5** are amenable to several derivatization pathways. For instance, they can be reduced to the corresponding amines or carbonyl compounds by the action of hydride reductants, organometallic reagents, or a combination thereof.[7]

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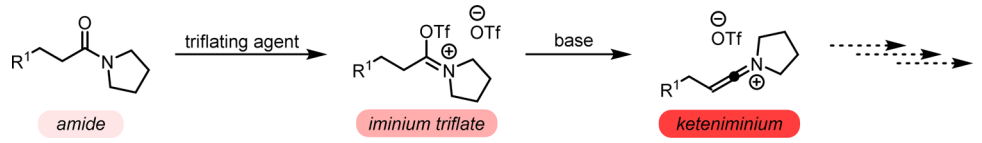
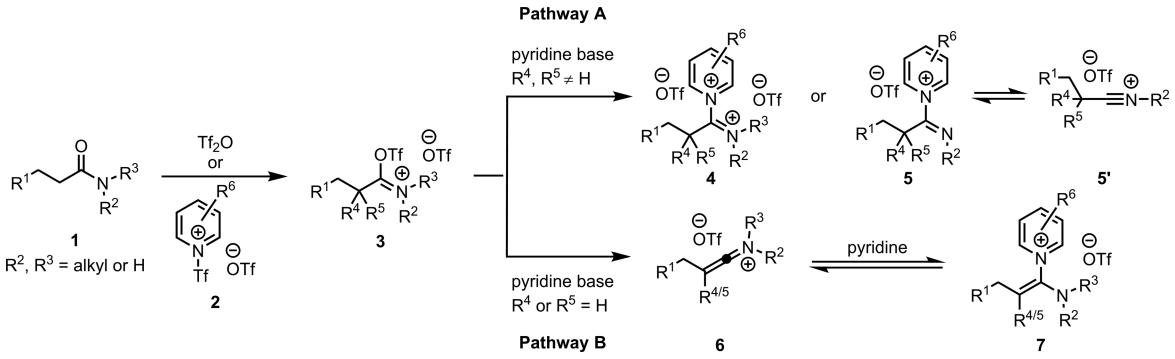
**Scheme 1. Increasing Reactivity of Various Stages of Amide Activation**




**Scheme 2. Intermediates of the Activation of Amides with Trifluoromethanesulfonic Anhydride and a Pyridine Base**



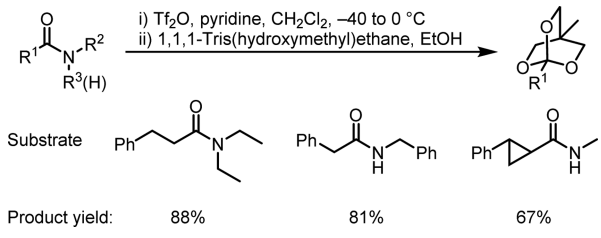

Deprotonation of the $\alpha$-carbon with formal loss of triflic acid, when possible, furnishes a keteniminium triflate **6**, provided that the geometry of the system allows for the incorporation of an sp-hybridized carbon. The keteniminium ion, in turn, can reversibly combine with the pyridine base to form ketene-aminal intermediates of type **7**. While the activation of amides with triflic anhydride can proceed in both the presence and the absence of a pyridine derivative, the keteniminium ⇆ pyridinium equilibrium is strongly influenced by the steric and electronic properties of the base. The addition of unsubstituted pyridine is de facto irreversible in the presence of moderately strong nucleophiles, while bulky pyridines (e.g., 2,4,6-collidine, 2,6-di-*tert*-butyl-4-methylpyridine) or pyridines containing an electron-withdrawing substituent in position 2 (e.g., 2-halopyridines) lead to an active equilibrium and a persistent presence of the keteniminium triflate.[5c,d,8]

## INTERCEPTION OF ACTIVATED AMIDES WITH NUCLEOPHILES

The concept of intercepting activated amides, either stabilized as the pyridinium adducts or in the keteniminium form, by the action of a nucleophile opens up numerous opportunities for the increase of molecular complexity and late-stage modification.

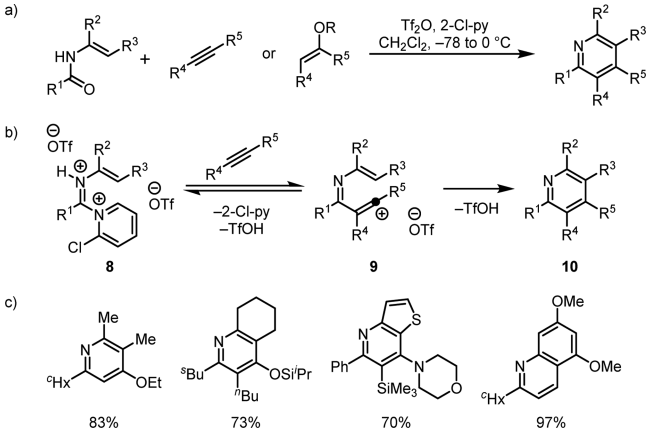
Charette's pioneering work on the synthesis of bridged orthoesters by addition of a triol to an activated amide opened up the floor for a wide array of nucleophilic additions to keteniminium ions and their stabilized equivalents (Scheme 3).[9] These transformations often hinge on the favorable entropic balance permitted by the use of bi- and tridentate nucleophiles or the energetically preferable formation of (hetero)aromatic compounds.

**Scheme 3. Charette's Formation of Caged Orthoesters from Activated Amides**




Diverse heterocycles, such as thiazolines,[10] triazoles,[11] and perhaps most notably, pyridines and quinolines[12] (Scheme 4), have been made accessible by the interception of activated amides with various carbon and heteroatom nucleophiles.[13]

**Scheme 4. (a) Movassaghi's Pyridine/Quinoline Synthesis. (b) Mechanistic Outline. (c) Selected Products**




For example, Movassaghi showed that the use of acyl enamines, triflic anhydride, and 1 equiv of 2-chloropyridine enables the formation of an intermediate **8**, which exhibits both electrophilic and nucleophilic properties.[12b] After the addition of a nucleophilic alkyne or enol, forming cation **9**, ring formation and aromatization take place to afford the highly substituted and functionalized pyridines **10**.

Furthermore, fully substituted pyrimidines can be prepared analogously,[8] either by the addition of hydrazides or of nitriles, respectively, to intermediates stemming from the activation of amides (Scheme 5).



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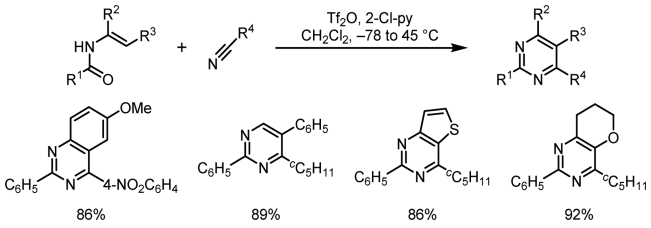
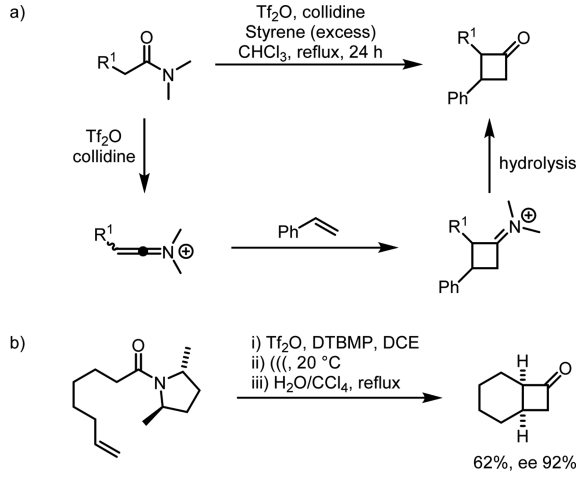
**Scheme 5. Formation of Fully Substituted Pyrimidines**




## REACTIVITY OF ACTIVATED AMIDES IN THE PRESENCE OF UNSATURATED COMPOUNDS

In 1981, Ghosez first reported of the use of amide-derived keteniminium triflates for inter- as well as intramolecular [2 + 2]-cycloadditions with alkenes (Scheme 6a).[3,14] While the general cycloaddition reactions of keteniminium ions with olefinic or acetylenic partners had been previously reported,[15] starting from $\alpha$-halo enamines, these procedures were known to perform poorly for "aldo" keteniminium salts, as the reaction with their precursor (the $\alpha$-halo enamine) outcompetes the desired cycloaddition.[3] Therefore, iminium triflates were designed as non-nucleophilic precursors for the generation of keteniminium ions, which, in turn, reacted smoothly with a variety of alkenes and alkynes to yield, after hydrolysis, diversely substituted cyclobutanones and cyclobutenones, respectively.

**Scheme 6. (a) General [2 + 2]-Cycloaddition of Keteniminium Ions with Styrene. (b) Enantioselective Intramolecular Cyclobutanone Formation**




Following this seminal work, increased academic interest led to further developments, most prominently, in the form of an auxiliary-controlled asymmetric [2 + 2]-cycloaddition (Scheme 6b).[16]

## NUCLEOPHILIC ATTACK FOLLOWED BY REARRANGEMENT

In 2010, our group serendipitously found that the use of an $\omega$-allyloxyamide in this chemistry did not furnish the expected

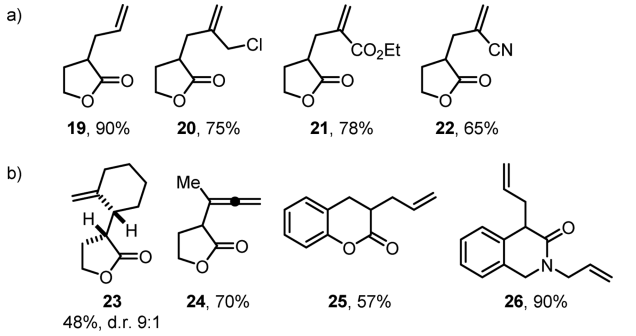
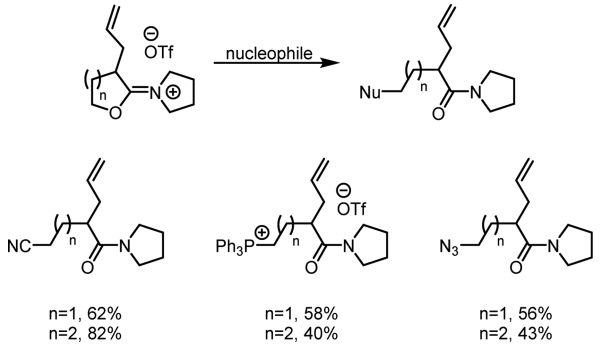
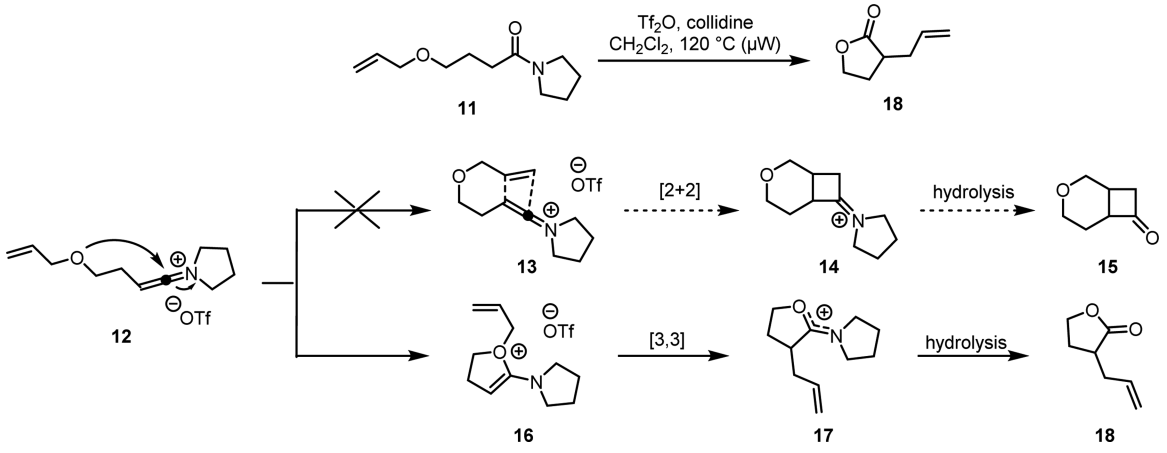



**Figure 1.** Lactones showcasing the functional group tolerance and generality of amide-activation with triflic anhydride, followed by [3,3]-sigmatropic rearrangement.

**Scheme 8. Nucleophilic Interception of Iminium Ethers: Selected Examples**




**Scheme 7. Unexpected Electrophilic Rearrangement of Activated Amides and Allyl Ethers**



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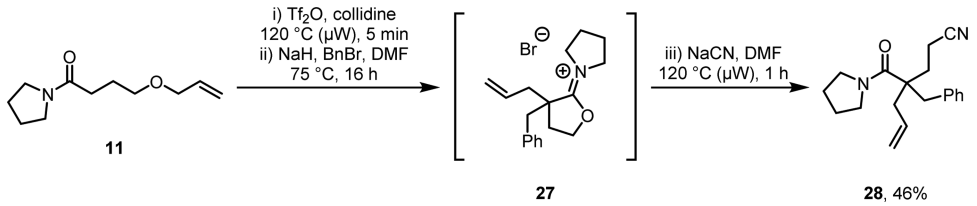
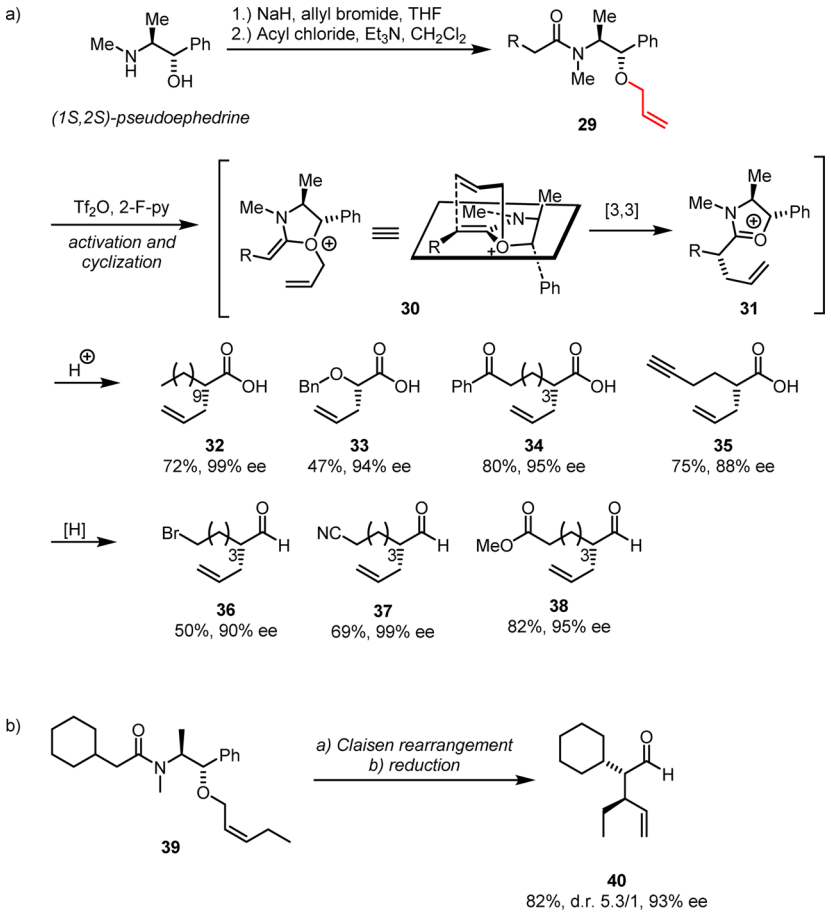
**Scheme 9. Formation of an $\alpha$-Quaternary Amide by Sequential C−C Bond Formations**




**Scheme 10. Asymmetric Claisen-Type Rearrangement, Following Amide Activation**




cyclobutanone after hydrolysis, rather resulting in the surprising formation of an $\alpha$-allylated $\gamma$-lactone (**18**, Scheme 7).[17]

This unexpected result was rationalized assuming that the treatment of amide **11** with triflic anhydride and collidine furnished keteniminium triflate **12**. Instead of following a [2 + 2]-cycloaddition pathway to yield 3-oxabicyclo[4.2.0]octan-7-one **15** (via iminium **14**), nucleophilic attack of the ether moiety presumably occurs faster to generate an allylvinyloxonium ion **16**. This system should be prone to Claisen-type [3,3]-sigmatropic rearrangement, effectively transferring the allyl moiety from oxygen to carbon and resulting in stabilized amidium salt **17**. Alkaline hydrolysis subsequently furnishes the isolated allylated lactone **18**.

Owing to the high chemoselectivity of triflic anhydride, reacting preferably with amides even in the presence of esters (**21**), a reasonable array of functional groups was tolerated in this transformation (Figure 1a). The use of internal olefins led, as expected for a [3,3]-rearrangement, to allylic inversion (**23**, Figure 1b). This, in turn, generated an additional stereogenic center in the final products, and moderate to good diastereoselectivity was observed. Notably, the use of propargyl ethers enables the formation of challenging allenyl-substituted lactones (**24**). The formation of allylated hydrocoumarin **25** exemplifies the possibility of ring-size variation as well as the use of less nucleophilic ether moieties. Moreover, diallylamines offer the opportunity to form allylated lactams **26** in high yields.[17b]

In the above examples, hydrolysis, effectively the nucleophilic attack of water onto the amidium ion which ultimately results from the [3,3]-sigmatropic rearrangement, yields the corresponding lactone (or lactam) as product. Further experimentation showed, interestingly, that the use of various carbon-centered heteroatom and hydride nucleophiles enables ring-opening, ultimately restoring the amide, now including a newly introduced $\alpha$-allyl moiety, and resulting in overall formal nucleophilic substitution of the ethereal oxygen (Scheme 8).[18] For instance, cyanide, triphenylphosphine (yielding the corresponding phosphonium triflate), and azide could all be easily introduced to the carbon formerly bearing the allyl ether.



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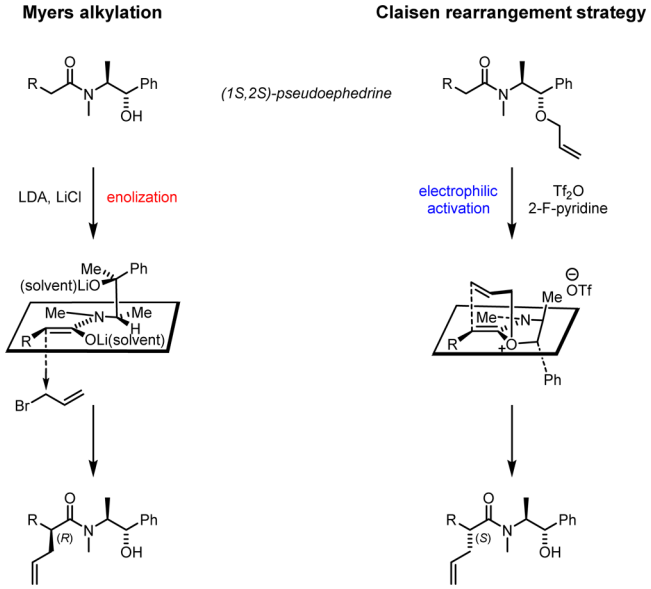
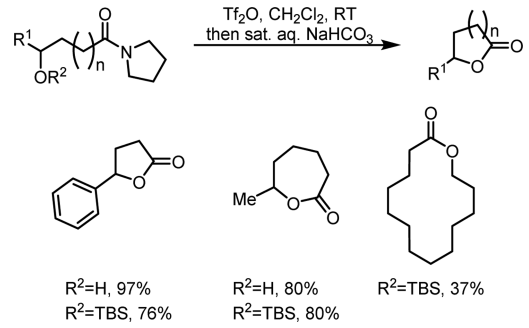
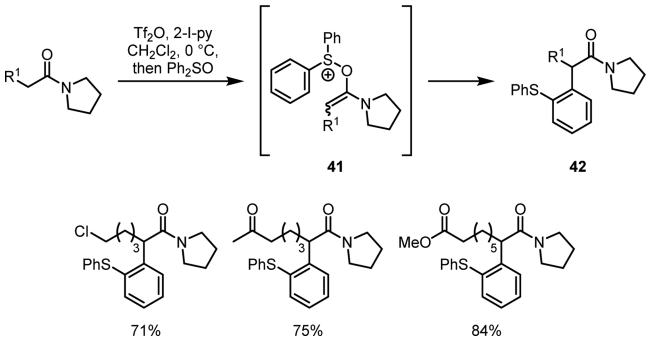
**Scheme 11. Stereochemical Comparison of the Myers Alkylation and Our Claisen Rearrangement Strategy**




**Scheme 12. Direct, Room-Temperature Lactonization of Activated Amides**




**Scheme 13. α-Arylation of Amides and Selected Examples**




It is worth mentioning in this context that, starting from linear, minimally functionalized substrate **11**, α-quaternary amide **28** could be obtained in moderate overall yield following a one-pot procedure (Scheme 9). This procedure showcases three distinct, sequential carbon−carbon bond-forming reactions (Claisen rearrangement, nucleophilic benzylation, and electrophilic cyanation), triggered by the initial activation of the linear amide.

From the outset, we were intrigued by the development of an asymmetric variant of this chemistry. Following substrate redesign, we found that tethering the allyloxy moiety to a chiral amide would be an interesting approach. In the event, choosing a readily available chiral amino alcohol such as pseudoephedrine-derived **29** allowed this endeavor to be accomplished in a surprisingly simple manner (Scheme 10a). As shown, allyloxyamides can thus be ultimately converted to α-allylated carboxylic acids (**32**−**35**) or aldehydes (**36**−**38**) in good yields and generally very good to excellent levels of enantioselectivity.[19]

The use of pseudoephedrine as the chiral auxiliary enabled the crucial formation of an alkylidene−isoxazolidine derivative **30**. The tightly organized stereochemical environment of **30** is likely the source of the high degree of stereocontrol observed upon sigmatropic rearrangement, as indicated in Scheme 10a. The resulting, comparatively stable, isoxazolinium ion **31** could then be cleaved with concomitant removal of the chiral auxiliary. Notably, this did not lead to substantial erosion of chiral information (possible through a hypothetical deleterious isoxazolinium ⇆ alkylidene isoxazolidine equilibrium).

The use of internal olefins once again enabled the preparation of branched allylated products in moderate to good diastereoselectivities (Scheme 10b). This is noteworthy, given that very few methods exist that allow the preparation of such arrays of adjacent stereocenters as contained in aldehyde **40**.

More importantly, and due to the chemoselective nature of triflic anhydride already alluded to before, this transformation is capable of tolerating a wide range of base-sensitive functional groups (Scheme 10a), including alkyl halides, nitriles, terminal alkynes, and even other carbonyls (esters and ketones). Therefore, this methodology offers a convenient complementary method to the highly efficient, now-textbook alkylation chemistry employing similar pseudoephedrine amides (Myers alkylation[20]), which generally requires use of strong bases and relies on amide enolate intermediates.

It was shown that this complementarity between the two protocols extends beyond the obvious similarity of starting materials, going all the way to the stereochemical outcome. As depicted in Scheme 11, in the sigmatropic rearrangement strategy that we developed, *internal* delivery of the allyl moiety by the oxygen substituent results in precisely the opposite absolute configuration to the intermolecular alkylation chemistry of Myers. In a curious twist, the lithium alkoxide which serves as a stereocontrol element in the Myers alkylation ultimately becomes the electrophile-delivering moiety in the protocol that we developed.

Going further on the theme of low reactivity of amides, we wondered whether this diminutive electrophilicity of the carboxamide group could potentially warrant its use as a *protecting group*, masking a more reactive carboxylic acid derivative. The treatment of this "protecting group" with triflic anhydride at a desired synthetic stage then leads to selective activation, resulting in overall deprotection. In 2013, our group disclosed that the treatment of an amide, containing a remote ether or free alcohol functionality, with triflic anhydride in the absence of a pyridine base leads to the formation of the corresponding lactone (Scheme 12).[21]

Proceeding under very mild conditions and omitting separate, wasteful deprotection steps to furnish the free alcohol and carboxylic acid moieties, this methodology offers a convenient alternative to the classical methods for (macro)-lactonization. Owing to the mild conditions, sensitive functional groups, including benzyl ethers, sulfonamides, esters, thioethers, and even 2-iodothiophene, were well tolerated.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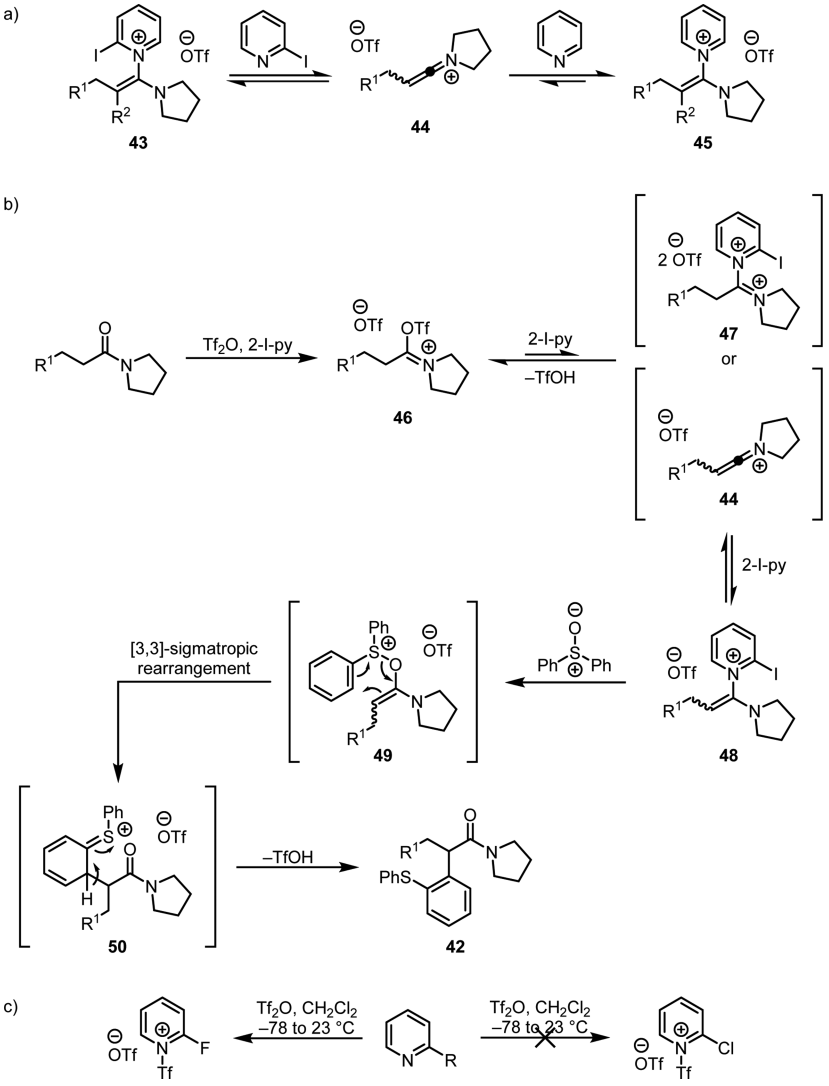
**Scheme 14. (a) Equilibria between Keteniminium Ion 44 and Pyridine Bases. (b) Proposed Mechanistic Pathway of the α-Arylation of Amides. (c) Example of the Steric and Electronic Effects of Substituents on the Electrophilicty of 2-Substituted Pyridines**




Strikingly, the addition of an excess of water exhibits a beneficial effect on the overall process. Generally speaking, the addition of an external nucleophile to a reaction mixture containing triflic anhydride seems counterintuitive. However, it could be shown that water actually serves as a scavenger for *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf),[21] which is formed during the reaction of TBS-protected ethers (the most effective substrates). Being a strong Lewis acid, TBSOTf is itself capable of catalyzing the lactonization event but also promotes the formation of an undesired elimination byproduct, the suppression of which was the major challenge of the development of this transformation. While the use of molecular sieves caused a complete shut-down of the desired reaction (thus revealing in no uncertain terms the beneficial effect of water), added water enabled the "mopping" of deleterious TBSOTf (forming TBSOTBS) and resulted in overall improved yield and selectivity for the targeted lactones.

The chemistry presented above leaves little doubt that keteniminium ions are particularly reactive electrophiles, inviting the discovery of new transformations by design of mechanistically suitable nucleophilic reagents. Given our prior experience on the use of sulfur-based arylation strategies,[19,22] we put forward the somewhat provocative hypothesis that the keteniminium ion formed upon this mode of amide activation might be intercepted by a *sulfoxide oxygen*, an unusual class of nucleophiles.[23]

As shown in Scheme 13, we postulated that aryl sulfoxides would engage an activated amide through nucleophilic attack by the electronegative oxygen, transiently generating the structurally unusual oxasulfonium intermediate **41**. This, in turn, would undergo charge-accelerated [3,3]-sigmatropic rearrangement[24] followed by rearomatization to provide the corresponding α-arylated amides **42**. In practice, this strategy required adaptation of the reaction conditions to the presence of a competitor for triflic anhydride, the nucleophilic sulfoxide oxygen. Incorporating a 15 min low temperature preactivation of the amide (rendered possible by the use of 2-iodopyridine, stabilizing the keteniminium ion, *vide supra)* prior to addition of the aryl sulfoxide was sufficient to overtake this hurdle and efficiently (thio)arylate a range of amides in good to excellent yields. Here, the high chemoselectivity of triflic anhydride for amides manifests itself in a telling manner. For the first time,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direct amide $\alpha$-arylation can be achieved in the presence of esters or even methyl ketones; that, in contrast to standard $\alpha$-arylation chemistry, no strong base-promoted enolization is at stake, ensures that those functional groups behave as bystanders.[5d]

Mechanistic studies, including in situ NMR and IR experiments, provided insight into the reaction pathway and elucidated the pivotal role of the employed pyridine base. In good accordance with the results reported by Charette,[5a] enamine-like cations **43** and **45** could be detected by IR spectroscopy after the addition of triflic anhydride to a mixture of the amide and a pyridine base (Scheme 14a). It could be shown that, while less nucleophilic 2-iodopyridine cleanly affords the desired product (Scheme 14b), pyridine-derived intermediate **45** displayed no such reactivity. A profound influence of the pyridine base was also studied in Movassaghi's 2015 report on the activation of $\alpha,\alpha$-disubstituted lactams.[5c] The combined influence of steric and electronic effects of the pyridine base could be illustrated with 2-chloropyridine, being the only investigated pyridine derivative to not form *N*-sulfonylpyridinium ions (**2**) capable of acting as triflating agents themselves (Scheme 14c).

## CONCLUSIONS

Throughout this Synopsis, we have retraced and placed in context the development of several methodologies that hinge on electrophilic activation of the amide bond. The interception of highly reactive species such as iminium triflates and keteniminium ions opens up entirely different vistas for the chemistry of this group, otherwise displaying low reactivity. In particular, much of our involvement with this chemistry results from the design of nucleophiles that can transiently generate intermediates well-suited for subsequent, complexity-increasing rearrangements. The resulting overall transformations benefit from the fact that, in this chemistry, it is not $\alpha$ C−H acidity or intrinsic carbonyl electrophilicity that dominates but Lewis basicity of the carbonyl oxygen, and that is something that amides have aplenty, ensuring that several additional developments can be expected from this growing field of research.

## AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

### Biographies

Daniel Kaiser obtained his M.Sc. from the University of Vienna in 2013. In 2014 he joined Prof. N. Maulide's group as a graduate student. He is a recipient of the Austrian Academy of Science's DOC-fellowship and focuses his research in electrophilic activation of amides and alkynes.

Nuno Maulide graduated in Chemistry from the Instituto Superior Técnico in 2003 and obtained a Master's degree at the Ecole Polytechnique in 2004 and a Ph.D. from the Université catholique de Louvain in 2007. Following a Postdoctoral stay at Stanford University, he began his independent research career as a Max-Planck Group Leader at the Max-Planck-Institut für Kohlenforschung (Germany) before resuming his current position as Full Professor for Organic Synthesis at the University of Vienna (Austria). He is the recipient of several awards, including the Bayer Early Excellence Award (Chemistry) in 2012, the Heinz Maier-Leibnitz Prize in 2013, and the EurJOC Young Researcher Award in 2015 and has also received an ERC StG in 2011 and a ERC CoG in 2016. His research interests are broadly defined around the area of highly reactive intermediates and rearrangements.

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