Research Article

Trifluoromethanesulfonic Anhydride in Amide Activation: A Powerful Tool to Forge Heterocyclic Cores

Haoqi Zhang, Margaux Riomet, Nuno Maulide

Institute of Organic Chemistry, University of Vienna, Währinger Strasse 38, 1090 Vienna, Austria
E-mail: maulide@univie.ac.at

Abstract

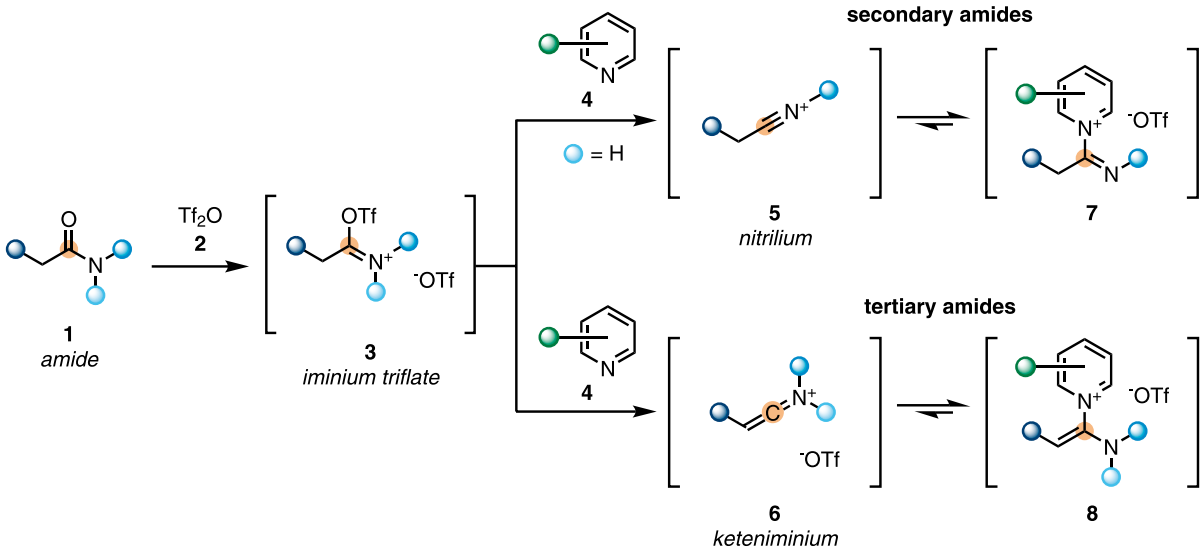
Trifluoromethanesulfonic anhydride is a powerful reagent for the activation of a wide range of functionalities. Among them, the electrophilic activation of amides is a compelling approach to access heterocycles under mild reaction conditions. Herein, we outline the most recent achievements in the construction of heterocycles *via* amide activation with trifluoromethanesulfonic anhydride.

Keywords: Trifluoromethanesulfonic anhydride, triflic anhydride, amide activation, heterocycle, Umpolung

Introduction

In recent decades, trifluoromethanesulfonic anhydride, also known as triflic anhydride, has proven to be an extraordinary reagent for a broad range of transformations. Given its high affinity towards *O*-nucleophiles, reaction with alcohols, carbonyls, sulfur-phosphorus- and iodine oxides towards formation of the corresponding triflates is strongly favoured. As one of the premier leaving groups in organic chemistry, the generated triflates then open the door to various downstream transformations, including (but not limited to) substitution reactions, cross-coupling processes, redox reactions and rearrangements.[1,2]

In this ocean of possible applications, our group has been particularly interested in the electrophilic activation of amides with triflic anhydride. Thanks to the pioneering work of Ghosez and Charette,[3,4] it is known that the reaction can proceed through different reactive intermediates, depending on the nature of the amide **1** as well as the presence (or absence) of a base (**Scheme 1**). When subjected to triflic anhydride **2**, amides are generally rapidly converted to the corresponding iminium triflates **3**. Further deprotonation, usually by a pyridine derivative can lead to formation of a highly electrophilic intermediate – a nitrilium ion **5** in case of secondary amides, or a keteniminium ion **6** for their tertiary counterparts. These ionic species participate in an equilibrium with the pyridine adducts **7** and **8**. Amide activation with triflic anhydride has yielded a literal cornucopia of novel transformations.[5–7] In particular, recent years have seen its exploitation by various groups for the generation of heterocyclic cores. Due to their pervasive presence in biological and pharmaceutically relevant structures, the preparation of heterocycles remains a focal point in organic synthesis. In this short review, we will focus on recent discoveries for the formation of heterocycles *via* amide activation with triflic anhydride.



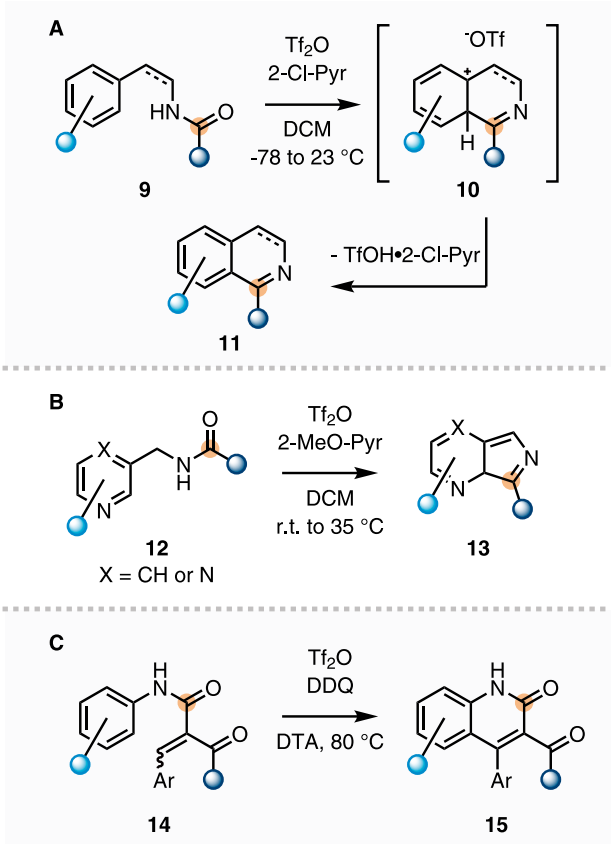
Scheme 1. Amide activation with Tf_2O and formation of different reaction intermediates.

Activation of Secondary Amides with Triflic Anhydride

Intramolecular Annulations

The susceptibility of amides for nucleophilic attacks after activation with triflic anhydride was explored for a range of cyclisation processes. Movassaghi *et. al.* showcased its utility for a Bischler-Napieralski type process (**Scheme 2A**).[8] After amide activation, the intermediate underwent intramolecular SE_{Ar} reaction; rearomatization then resulted in **isoquinolines 11** and their 3,4-dihydro derivatives. In comparison to classical Bischler-Napieralski conditions using $POCl_3$, elevated reaction temperatures could be avoided, while acid-sensitive substrates were well tolerated. As an alternative approach, Hendrickson's reagent, obtained from triphenylphosphine oxide and triflic anhydride, was employed in the same transformation to further exacerbate oxophilicity in the amide activation event.[9]

As an extension of this mild cyclodehydration reaction, the activation of *N*-(2-pyridinylmethyl)-benzamides **12** with triflic anhydride resulted in formation of bicyclic **imidazo[1,5-*a*]pyridines 13** (**Scheme 2B**). By utilising an electron richer base in form of 2-methoxy-pyridine in conjunction with mild heating, the conversion could be further increased.[10] In contrast, amide activation in presence of a conjugated C-C double bound (**14**) led to increased β-electrophilicity as showcased in the intramolecular cyclisation of *N*-aryl cinnamyl amides **15** (**Scheme 2C**).[11] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was employed as an additional oxidant to decrease the reaction time and improve selectivity towards poly-substituted **quinolin-2(1*H*)-ones 15**.

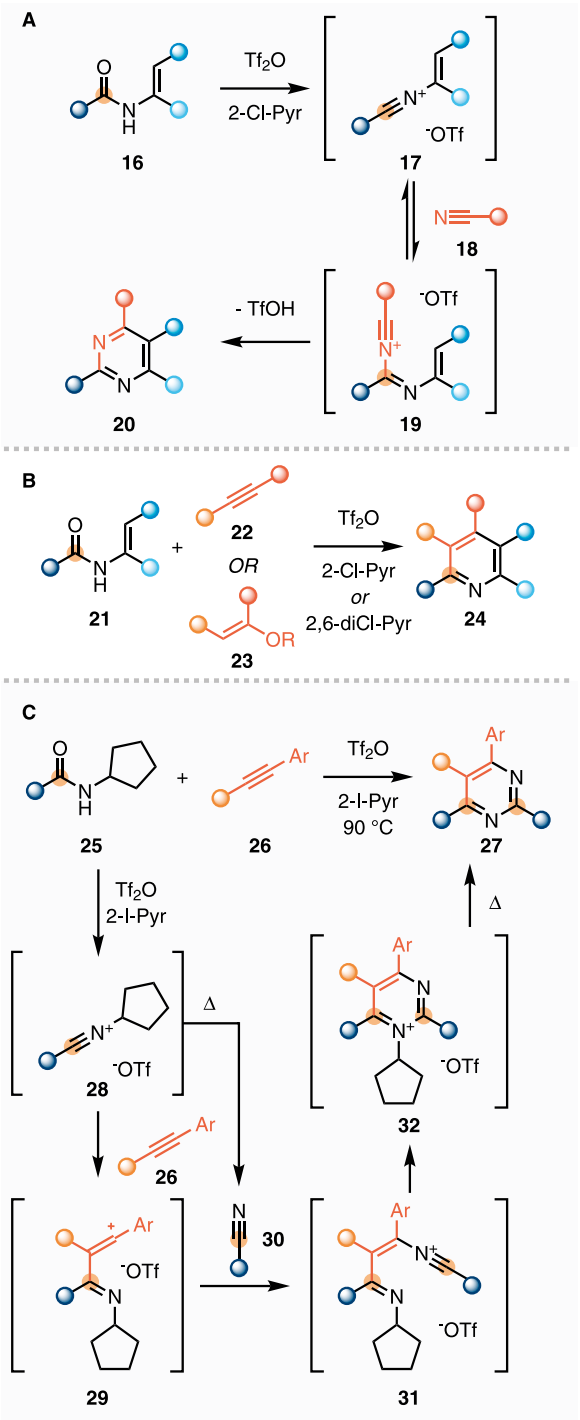


Scheme 2. Intramolecular annulations of activated secondary amides. **A**: **isoquinolines**. **B**: **imidazo[1,5-*a*]pyridines**. **C**: **quinolin-2(1*H*)-ones** (DTA = *N*,*N*-dimethyl trifluoroacetamide).

Intermolecular Annulations

The activation of amides opens the doorway to a broad range of external nucleophiles. The nucleophilic addition of a nitrile **18** to the *in-situ* formed nitrilium ion **17** led to the formation of a new nitrilium species **19** (**Scheme 3A**).[12,13] In presence of an *N*-vinyl or *N*-aryl moiety, Movassaghi showed that this reactive intermediate further underwent an electrocyclisation event, convergently yielding **pyrimidine** derivatives **20**. Similarly, the reaction with alkynes **22** or enol-ethers **23** proceeded with formation of corresponding cations followed by cyclisation and aromatization to **pyridine** and **quinoline** derivatives **24** (**Scheme 3B**).[14–16]

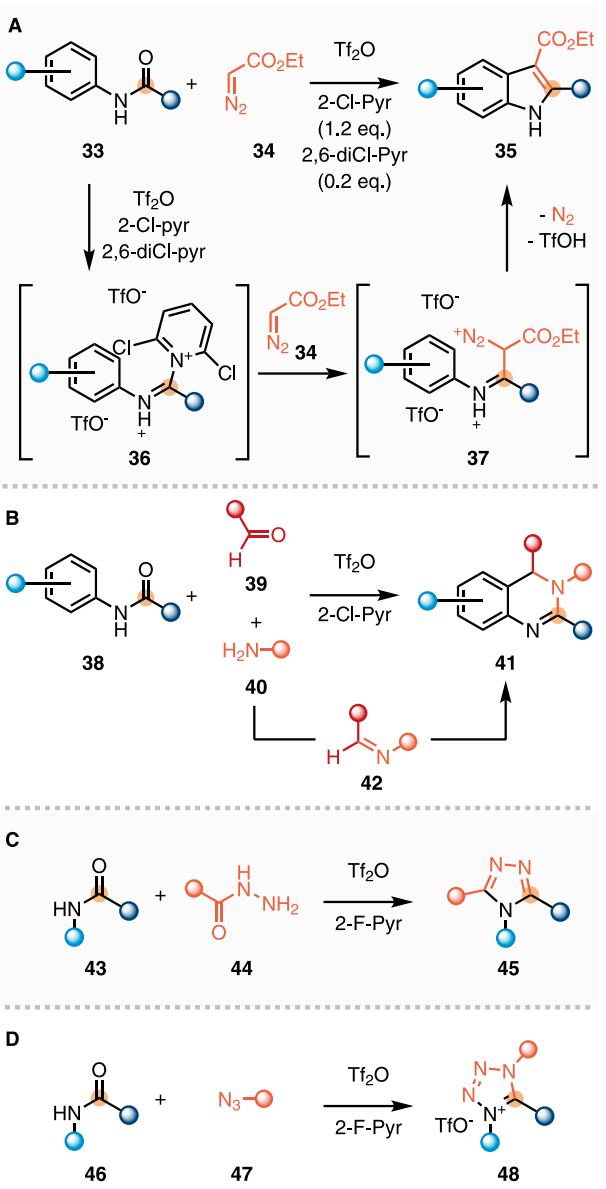
In complementary fashion, our group investigated the transformation with alkynes **26** in absence of *N*-vinyl or *N*-aryl functionality on the amide substrate **25** (**Scheme 3C**). In comparison to the former approaches, the reaction was conducted at elevated temperature and with an excess of amide starting material, resulting in poly-substituted **pyrimidine** derivatives **27**. Comparable to the previous reaction, a vinylcation intermediate **29** is formed after addition of the alkyne substrate **26**. Fuelled by the high reaction temperatures, the initial nitrilium species also partially underwent fragmentation to the corresponding nitrile **30**, which subsequently attacked the vinylcation intermediate. Ensuing cyclisation and dealkylation eventually resulted in formation of the heterocyclic core **27**.[17]



Scheme 3. Intermolecular annulations of activated secondary amides. **A**: **pyrimidines** *via* nitriles. **B**: **pyridines** and **quinolines** *via* alkynes and enols. **C**: **pyrimidines** *via* formal (2+2+2) with alkynes.

Furthermore, the use of ethyl diazoacetate **34** as nucleophile in conjunction with *N*-aryl amides **33**, Wang and coworkers achieved a concise, single step synthesis of **indoles 35** (**Scheme 4A**).[18] Of particular note was the necessity for catalytic amounts of 2,6-dichloropyridine in addition to the usual 2-chloropyridine. The authors reasoned this as the consequence of reversible formation of a highly electrophilic species **36**, which could be further intercepted by ethyl diazoacetate **34**. The resulting intermediate **37** underwent a Friedel-Crafts type cyclisation releasing nitrogen gas and producing the indole core **35** after tautomerization. Moreover, the activation of *N*-aryl amides with triflic anhydride was exploited for an one-pot Pictet-Spengler-like cyclisation (**Scheme 4B**).[19] This domino process started with the *in-situ* condensation of aldehyde **39** and amine **40** to imine **42**, followed by nucleophilic attack thereof on the activated amide, prior to electrophilic aromatic substitution to obtain **3,4-dihydroquinazolines 41**.

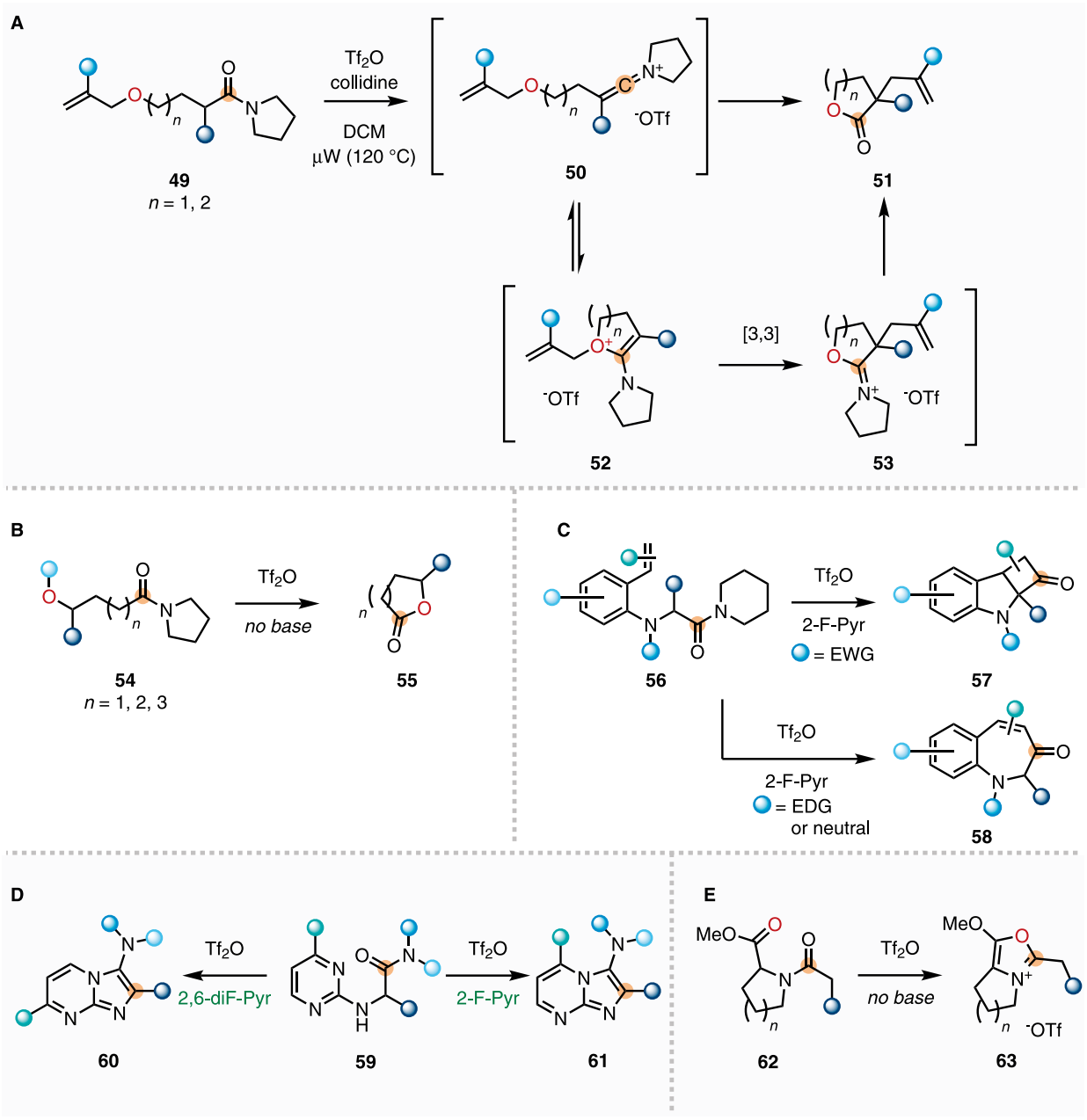
In absence of *N*-aryl or *N*-vinyl moieties, the cyclisation event can also be realized by condensation of the former amide nitrogen. This approach was employed for the synthesis of highly substituted **1,2,4-triazoles 45** (**Scheme 4C**).[20] Here, the attack of hydrazide **44** on activated amide **43** was followed by cyclodehydration to forge the heterocyclic core. In parallel, our group has realized the regioselective synthesis of **tetrazolium** scaffolds **48** through a formal [3 + 2] cyclisation (**Scheme 4D**).[21] Computational studies revealed a stepwise mechanism initiated by the nucleophilic attack of azide **47** on the nitrilium intermediate, followed by annulation to the final heterocycle.



Scheme 4. Attack of various nucleophiles on nitrilium ion and subsequent cyclisation. A: **indoles** *via* ethyldiazoacetate. **B**: **3,4-dihydroquinazolines** *via* Pictet-Spengler-like cyclisation. **C**: **1,2,4-triazoles** *via* hydrazines. **D**: **tetrazolium** ions *via* azides.

Activation of Tertiary Amides with Triflic Anhydride

Intramolecular Annulations



Scheme 5. Intramolecular cyclisations initiated by activation of tertiary amides. **A**: **lactones** by rearrangement of ethers. **B**: **lactones** by attack of alcohol derivatives. **C**: **benzazepinones** with alkenes. **D**: base dependent regio-selective formation of **pyrimidines**. **E**: **oxazolium** ions in absence of base.

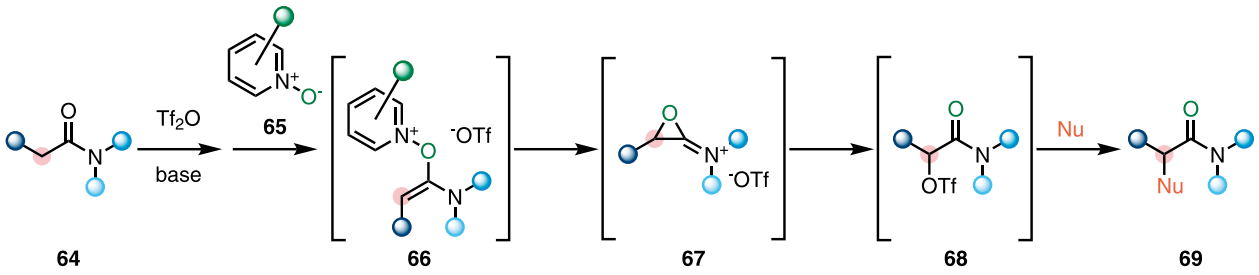
Compared to the aforementioned secondary amides, the activation of tertiary derivatives with triflic anhydride in presence of a weak nucleophilic base typically forms keteniminium ions as reactive intermediates. Our group investigated the reactivity of tertiary amides **49** carrying an inbuilt ether moiety (**Scheme 5A**).[22] After formation of intermediate **50**, the reaction favoured the nucleophilic attack of the ether oxygen and formation of oxonium ion **52**. The intermediate subsequently underwent a [3,3]-sigmatropic rearrangement, leading to intermediate **53**. Further hydrolysis resulted in functionalised 5- and 6-membered **lactones 51**. Complementary to this work, the direct use of alcohols or ether derivatives **54**, non-amenable to sigmatropic rearrangement, produced the 5-, 6- and 7-membered heterocycles **55** (**Scheme 5B**).[23] For this approach, the absence of the usual base was crucial to avoid formation of elimination products. The competition between the [2+2] cycloaddition and nucleophilic pathways with alkenes was further investigated by De Mesmaeker and coworkers with α-aminoamides **56** (**Scheme 5C**).[24] In presence of an electron-withdrawing substituent on the amino nitrogen

56, the [2+2] cyclisation was favoured. With electron-neutral or -donating substituents on **56**, amide activation promoted the nucleophilic attack of the styryl group and ultimately yielded **benzazepinones 58**.

Additionally, the susceptibility of keteniminium ions towards intramolecular capture was showcased in the synthesis of 3-amino-**thiophene** derivatives [25–27] and aminoimidazo-**pyrimidines 60** and **61** (**Scheme 5D**).[28] In the latter reaction, the nature of the base played a paramount role in the regioselectivity. The authors hypothesised that the 2-fluoropyridine-promoted reaction kinetically favoured the cyclisation to pyrimidine **60**. On the other hand, 2,6-difluoropyridine primary acted as a buffer for the *in situ* generated triflic acid and thus supported the formation of the thermodynamic product **61**. Our group further investigated the role of the pyridine base during regio- and chemoselective cyclisation of amide **62** to bicyclic alkoxy **oxazolium** ions **63** (**Scheme 5E**).[29] To our surprise, the addition of a base suppressed the reaction and only starting material was recovered. In stark contrast, the absence of base quantitatively yielded the desired heterocycle.

α-Umpolung of Amides with Triflic Anhydride

In all presented cases above, the electrophilic activation of amides yields a highly electrophilic amide carbon. Under suitable conditions, this reactivity can also be transferred to the usually nucleophilic α-carbon. This concept was recently investigated by our group in the α-Umpolung of amides (**Scheme 6**). Following activation with triflic anhydride, the keteniminium intermediate can be intercepted by a pyridine-*N*-oxide derivative **65**, forming the adduct **66**. It is noteworthy that this species possesses electrophilic character at what was formerly the α-carbon to the amide functionality in the starting amide **64**. Postulated fragmentation to the epoxide **67** allows attack at the α-carbon by triflate ion. In contrast to the starting amide **64**, the resulting reactive key intermediate **68** is now susceptible toward nucleophiles at the α-position, opening up a broad range of new transformations.

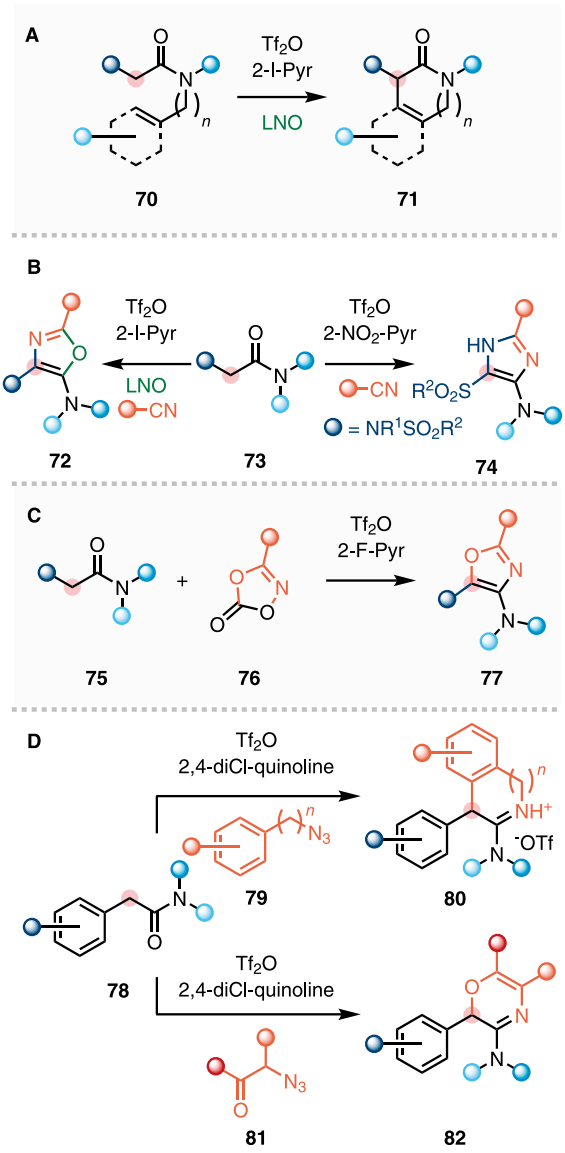


Scheme 6. Umpolung of amides with triflic anhydride and *N*-oxides

Our group utilised this electrophilic Umpolung of amides for an intramolecular, metal-free C-C coupling reaction (**Scheme 7A**).[30] As opposed to previously discussed transformations originating from a Friedel-Crafts-like cyclisation, the activation of amide **70** and subsequent Umpolung by lutidine *N*-oxide resulted in C-C coupling at the α-carbon, ultimately affording a broad range of **pyridinone** and **isoquinolinone** derivatives **71**.

Further investigation revealed that the absence of an internal nucleophile in nitrile solvents leads to a different reaction mode (**Scheme 7B**).[31] Instead of the formation of the triflate intermediate, the *in-situ* formed epoxide was attacked by the ubiquitous solvent, resulting in the annulation product **74**. By exchanging acetonitrile to alternative nitriles, a broad palette of amino **oxazoles** could be synthesised. Additionally, the employment of an *N*-sulfonyl functionality at the amide α-position resulted in a mechanistically intriguing rearrangement sequence. In absence of the competing *N*-oxide, the transformation involved migration of the sulfonyl group, consequently yielding **imidazole** derivatives **72** as the final products. In a similar fashion, using 1,4,2-dioxazol-5-ones (as both Umpolung-reagent and nucleophilic substrate), an alternative direct synthesis of amino-**oxazole** scaffolds **77** was achieved (**Scheme 7C**).[32]

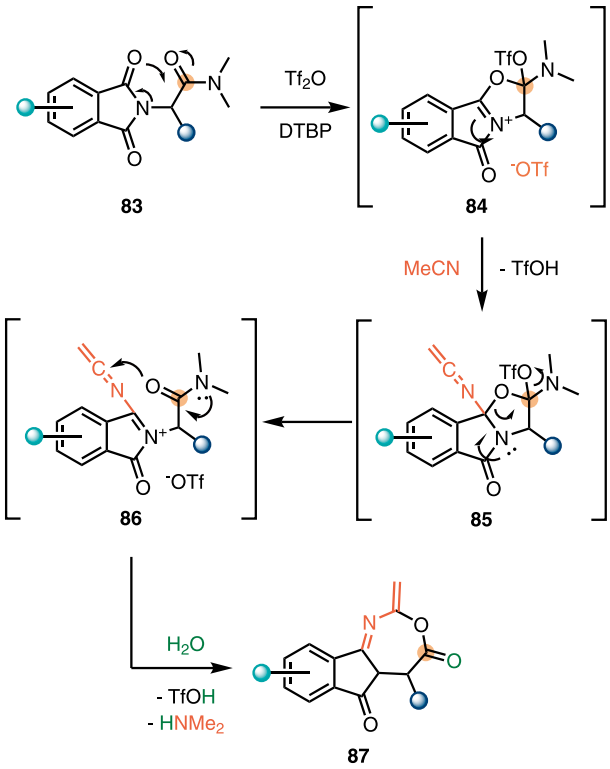
By taking this concept further, arylalkylazides **79** were investigated as Umpolung reagents and nucleophiles to forge heterocycles. In presence of a bulky, weak nucleophilic base, such as 2,4-dichloroquinoline, addition of arylalkylazide **79** resulted in a domino cyclisation event (**Scheme 7D**).[33] Depending on the chain length of the azides, 6- or 7-membered **cyclic amidiniums 80** were accessible. By interchanging the arene functionality with other nucleophiles such as ketones or esters, an efficient synthesis of functionalised **oxazines/oxazinones 82** was achieved.



Scheme 7. Heterocycle formation by Umpolung of amides. **A**: **pyridinone** and **isoquinolinone** derivatives by C-C coupling. **B**: **imidazoles** and **oxazoles** *via* nitriles. **C**: **oxazoles** with 1,4,2-dioxazol-5-ones as the Umpolung-reagent. **D**: **cyclic amidiniums** and **oxazine** derivatives with azides and cascade cyclisation.

Miscellaneous

In addition to the discussed methodologies, the mild activation of amides with triflic anhydride also allows unusual reactivity *en route* to heterocycles. In an example from our own work, the presence of a phthalimide functionality on the α-branched amide **83** led to an unexpected rearrangement reaction with acetonitrile (**Scheme 8**).[34] In contrast to the usual conditions, 2,6-di-*tert*-butylpyridine (DTBP) was used as a base. We hypothesized that this base would not add to the activated amide, thus favouring cyclisation to **84**. A nucleophilic attack followed by deprotonation of acetonitrile might then afford intermediate **85**. Subsequent ring opening to **86**, followed by 7-membered ring closure and hydrolysis resulted in novel heterocyclic scaffolds **87**.



Scheme 8. Synthesis of novel heterocycles by a cascade rearrangement reaction.

Conclusion

The electrophilic activation of amides with triflic anhydride provides a mild and sustainable approach to forge heterocyclic cores. Depending on the nature of the amides and the presence or absence of base additives, highly reactive intermediates in form of vinyl- triflates, nitrilium ions or keteniminium ions are accessible. Each of these species offers new pathways for functionalisation and annulation, leading to a wide palette of heterocycles. By using suitable reacting partners, such as *N*-oxides or azides, the α-Umpolung of amides is enabled. This in turn opens the door to an array of powerful transformations, including C-C bound formation, α-oxidation and mechanistically intriguing rearrangement reactions. The breadth of recent examples of heterocycle formation highlights the utility of triflic anhydride for electrophilic amide activation and outlines its potential for the future discovery of further, hitherto unknown transformations.

References

[1] R. D. Howells, J. D. Mc Cown, *Chem. Rev*. **1977**, *77*, 69.
[2] I. L. Baraznenok, V. G. Nenajdenko, E. S. Balenkova, *Tetrahedron* **2000**, *56*, 3077.
[3] J. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, *Angew. Chem. Int. Ed*. **1981**, *20*, 879.
[4] A. B. Charette, M. Grenon, *Can. J. Chem*. **2001**, *79*, 1694.
[5] C. Madelaine, V. Valerio, N. Maulide, *Chem. Asian J*. **2011**, *6*, 2224.
[6] D. Kaiser, N. Maulide, *J. Org. Chem*. **2016**, *81*, 4421.
[7] D. Kaiser, A. Bauer, M. Lemmerer, N. Maulide, *Chem. Soc. Rev*. **2018**, *47*, 7899.
[8] M. Movassaghi, M. D. Hill, *Org. Lett*. **2008**, *10*, 3485.
[9] M. Wu, S. Wang, *Synthesis* **2010**, 587.
[10] G. Pelletier, A. B. Charette, *Org. Lett*. **2013**, *15*, 2290.
[11] Q. Zhang, J. Yuan, M. Yu, R. Zhang, Y. Liang, P. Huang, D. Dong, *Synthesis* **2017**, *49*, 4996.
[12] M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc*. **2006**, *128*, 14254.
[13] O. K. Ahmad, M. D. Hill, M. Movassaghi, *J. Org. Chem*. **2009**, *74*, 8460.
[14] M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc*. **2007**, *129*, 10096.
[15] T. Wezeman, S. Zhong, M. Nieger, S. Bräse, *Angew. Chem. Int. Ed*. **2016**, *55*, 3823.
[16] L. H. Li, Z. J. Niu, Y. M. Liang, *Chem. Eur. J*. **2017**, *23*, 15300.
[17] T. Stopka, P. Adler, G. Hagn, H. Zhang, V. Tona, N. Maulide, *Synthesis* **2019**, *51*, 194.
[18] S. L. Cui, J. Wang, Y. G. Wang, *J. Am. Chem. Soc*. **2008**, *130*, 13526.
[19] C. L. Magyar, T. J. Wall, S. B. Davies, M. V. Campbell, H. A. Barna, S. R. Smith, C. J. Savich, R. A. Mosey, *Org. Biomol. Chem*. **2019**, *17*, 7995.
[20] W. S. Bechara, I. S. Khazhieva, E. Rodriguez, A. B. Charette, *Org. Lett*. **2015**, *17*, 1184.
[21] V. Tona, B. Maryasin, A. De La Torre, J. Sprachmann, L. González, N. Maulide, *Org. Lett*. **2017**, *19*, 2662.
[22] C. Madelaine, V. Valerio, N. Maulide, *Angew. Chem. Int. Ed*. **2010**, *49*, 1583.
[23] V. Valerio, D. Petkova, C. Madelaine, N. Maulide, *Chem. Eur. J*. **2013**, *19*, 2606.
[24] A. Kolleth, D. Dagoneau, P. Quinodoz, A. Lumbroso, M. Avanthay, S. Catak, S. Sulzer-Mossé, A. De Mesmaeker, *Helv. Chim. Acta* **2019**, *102*, e1900168.
[25] A. Lumbroso, J. Behra, A. Kolleth, P. Y. Dakas, U. Karadeniz, S. Catak, S. Sulzer-Mossé, A. De Mesmaeker, *Tetrahedron Lett*. **2015**, *56*, 6541.
[26] A. Kolleth, S. Müller, A. Lumbroso, G. Tanriver, S. Catak, S. Sulzer-Mossé, A. De Mesmaeker, *Tetrahedron Lett*. **2018**, *59*, 3242.
[27] D. Dagoneau, A. Kolleth, A. Lumbroso, G. Tanriver, S. Catak, S. Sulzer-Mossé, A. De Mesmaeker, *Helv. Chim. Acta* **2019**, *102*, e1900031.
[28] R. P. Law, S. Ukuser, D. T. Tape, E. P. A. Talbot, *Synthesis* **2017**, *49*, 3775.
[29] E. Spinozzi, A. Bauer, N. Maulide, *Eur. J. Org. Chem*. **2019**, *2019*, 5230.
[30] D. Kaiser, A. de la Torre, S. Shaaban, N. Maulide, *Angew. Chem. Int. Ed*. **2017**, *56*, 5921.
[31] G. Di Mauro, B. Maryasin, D. Kaiser, S. Shaaban, L. González, N. Maulide, *Org. Lett*. **2017**, *19*, 3815.
[32] Y. Weng, L. Min, L. Shan, H. Li, X. Wang, Y. Hu, *J. Org. Chem*. **2021**, *86*, 199.
[33] H. Zhang, M. Riomet, A. Roller, N. Maulide, *Org. Lett*. **2020**, *22*, 2376.
[34] A. Bauer, E. Borsos, N. Maulide, *Eur. J. Org. Chem*. **2020**, *2020*, 3971.

Haoqi Zhang

B.Sc., M.Sc.

Institute of Organic Chemistry, University of Vienna

Haoqi Zhang is a Ph.D. student in the group of Professor Nuno Maulide at the University of Vienna, where he received his MSc degree in 2020 working on electrophilic Umpolung of amides for the construction of cyclic amidines and oxazines. For his Ph.D. thesis, he remained at the Maulide Group and his current interest lies in natural product synthesis and drug design.

Margaux Riomet

Dipl.-Ing. Dr., M.Sc.

Institute of Organic Chemistry, University of Vienna

Margaux Riomet currently occupies a postodoctoral position in the research group of Professor Nuno Maulide at the University of Vienna. She studied chemistry at Ecole Nationale Supérieure de Chimie de Paris where she completed her Engineering Degree and Msc degree in 2015 in partnership with Université Pierre et Marie Curie. In 2018, she obtained her PhD degree under the supervision of Dr. Frédéric Taran at CEA Saclay. Her Ph. D. work was dedicated to the chemistry of iminosydnones and their applications in biology. Her current research interests combine the development of new methodologies for synthesis and the design of molecular objects for live cell imaging.

Nuno Maulide

Professor, Ph.D.

Institute of Organic Chemistry, University of Vienna

Nuno Maulide is a Full Professor and Chair of Organic Synthesis at the University of Vienna. He obtained a Ph.D. in 2007 at the Université catholique de Louvain under the supervision of Prof. István E. Markó. Subsequently, he joined the group of Prof. Barry M. Trost at Stanford University for a post-doctoral stay in 2007-2008. In 2009, he started his independent career as a Max-Planck-Research Group Leader at the Max-Planck Institut für Kohlenforschung. In 2013, he moved to his current position as a Full Professor at the University of Vienna. Since 2018, he is an Adjunct PI at CeMM. He is a member of the Board of Editors for Organic Synthesis (2018) as well as an Associate Editor of Organic Letters (2018) and JACS AU (2020). For his research, he received numerous awards, including the recent Tetrahedron Young Investigator Award (2020), Springer Heterocyclic Chemistry Award (2018) and 3 ERC Grants. Nuno Maulide was named Scientist of the Year in Austria (2019) and is an elected Corresponding Member of the Austrian Academy of Sciences (2018).

Related Products

Trifluoromethanesulfonic Anhydride (Tf_2O)	10g	25g	250g	T1100
2-Chloropyridine (2-Cl-Pyr)	25g	100g	500g	C0279
2-Methoxypyridine (2-MeO-Pyr)			25mL	M0788
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)		25g	250g	D1070
N,*N*-dimethyl trifluoroacetamide (DTA)		5g	25g	T3262
2-Fluoropyridine (2-F-Pyr)		25g	100g	F0217
2,6-Dichloropyridine (2,6-diCl-Pyr)		25g	500g	D0410
2-Iodopyridine (2-I-Pyr)		5g	25g	I0533
2,4-Dichloroquinoline (2,4-diCl-quinoline)		5g	25g	D4452
2,6-Di-*tert*-butylpyridine (DTBP)		5g	25g	D1804