



HAL
open science

Photoredox-and Piezo-Catalysed Access to Complex Trifluoromethylated Polycyclic Structures from Ynamides

Amal Lakhal, Maud Villeneuve, Laure Haberkorn, Jean-Marie Fourquez, Jeremy Forte, Geoffrey Gontard, Louis Fensterbank, Cyril Ollivier

► **To cite this version:**

Amal Lakhal, Maud Villeneuve, Laure Haberkorn, Jean-Marie Fourquez, Jeremy Forte, et al.. Photoredox-and Piezo-Catalysed Access to Complex Trifluoromethylated Polycyclic Structures from Ynamides. *Organic Chemistry Frontiers*, 2024, 11, pp.1341. 10.1039/D3QO02016A . hal-04797035

HAL Id: hal-04797035

<https://hal.science/hal-04797035v1>

Submitted on 21 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

ARTICLE

Photoredox- and Piezo-Catalysed Access to Complex Trifluoromethylated Polycyclic Structures from Ynamides[#]

Amal Lakhal^[a], Maud Villeneuve^[c], Laure Haberkorn^[c], Jean-Marie Fourquez^[c], Jeremy Forte^[a], Geoffrey Gontard^[a], Louis Fensterbank^{*[a,b]}, Cyril Ollivier^{*[a]}

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Radical cyclization cascades triggered by a trifluoromethyl radical represent a valuable tool for accessing highly complex and biologically relevant scaffolds. Herein, we introduce a strategy employing ynamides as pivotal functions for the diastereoselective synthesis of γ -lactam polycyclic compounds incorporating a trifluoromethyl group. Using photoredox conditions, this cascade featuring notably a 1,5 hydrogen atom transfer proceeds with high efficiency and diastereoselectivity. Additionally, a mechanoredox approach utilizing piezocatalysis proved to be competent in providing the same highly functionalized polycyclic products.

Introduction

Since the seminal total synthesis of (\pm)-hirsutene by Curran in 1985, radical cascades,¹ *i.e.* the combination of several inter- or intramolecular homolytic steps, have dramatically transformed the way we approach the synthesis of complex polycyclic molecules over the last three decades.² They have also demonstrated that, in some cases they were the only viable routes to the target molecules.³ A variety of reaction conditions including the use of stoichiometric mediators such as tributyltin hydride and congeners² or of single electron transfer (SET) reagents were initially mobilized.⁴ In the latter case, some versatile catalytic processes were also developed.⁵ In addition, with the advent of photoredox catalysis, which allows for very mild conditions and enjoys a broad scope of possible reactions,⁶ new synthetic horizons have emerged. Over the last two decades, many groups, including our own, have demonstrated the versatility of ynamides as radical cascade partners.^{7,8} In initial strategies of types I and II, the ynamide served as a relay function, *i.e.* each carbon atom of the triple bond was mobilized only once through radical addition, affording polycyclic structures bearing an enamide function.⁹ Initially run using stoichiometric amounts of the now undesirable Bu₃SnH/AIBN mediating system (Scheme 1A) to perform the halogen atom abstraction, Evans judiciously

upgraded this chemistry by reporting a copper photocatalyzed version of strategy I that relies on the reductive cleavage of a carbon-iodine bond to initiate the cyclization.¹⁰

While monocyclic or bicyclic products involving a radical intermediate generated through prior intermolecular addition on another acceptor of the ynamide precursor could be formed,¹¹ intermolecular radical additions onto ynamides have also been reported but those have generally provided acyclic products.¹² A noticeable exception consisted in our recently reported access to trifluoromethylated isoindolinones triggered by the addition of a trifluoromethyl radical (Scheme 1A).¹³

All these examples have so far led to flat enamide substrates lacking stereogenic centres on the polycyclic backbone. This observation motivated us to develop a second generation of cascades leading to more complex chiral structures. Thus, we aimed at γ -lactam polycyclic frameworks, that are found in a large number of plant alkaloids and have received over the past few decades considerable attention from biochemists and biologists, uncovering various interesting biological activity.¹⁴ A showcase example of this activity is Oleracein E (Scheme 1B),¹⁵ which was found to be a promising candidate for the treatment of Parkinson's disease by preventing neuronal apoptosis. In addition, γ -lactams were found to possess neuroprotective effect against NMDA-induced excitotoxicity in PC12 cells.¹⁶ Schizozygane indoline showed good antimicrobial activity against fungi and bacteria,¹⁷ while Tylophora alkaloids were found to have good hypoxia-inducible factor-1 (HIF-1) and HIV inhibitory activity.¹⁸ A tetrahydroisoquinoline derivative has been used to target AKR1C3,¹⁹ displaying good inhibitory properties for the treatment of pancreatic cancer. Considering the importance of the trifluoromethyl group in medicinal chemistry,²⁰ its introduction on the aimed γ -lactam polycyclic scaffolds could enhance their pharmacological properties.

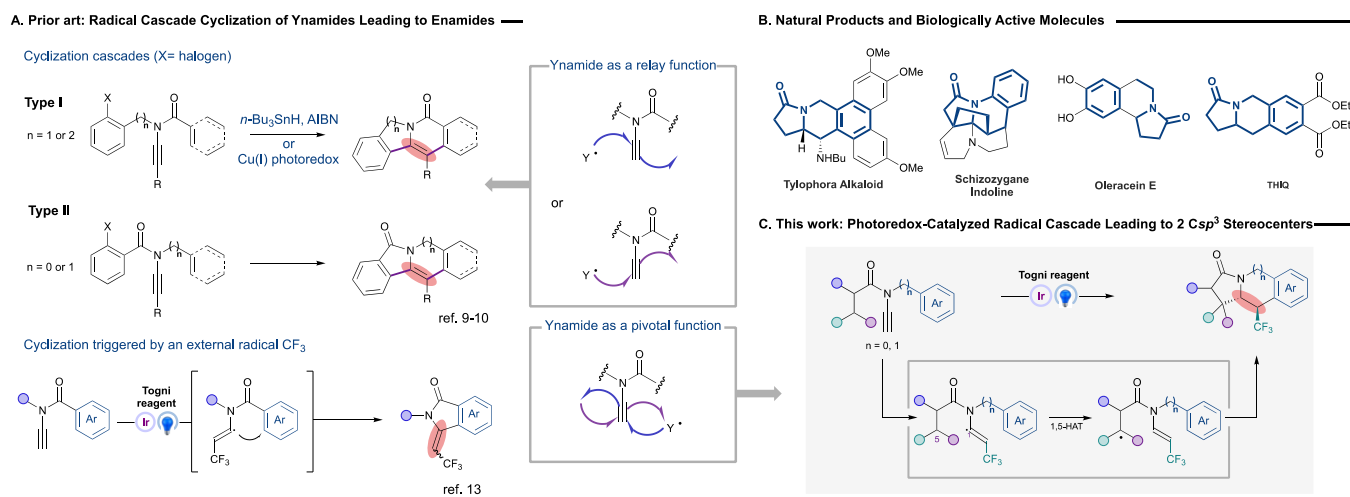
^a Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, 4 Place Jussieu, CC 229, 75252 Paris Cedex 05 France.

^b Collège de France, Chaire Activations en Chimie Moléculaire, 11 Place Marcelin Berthelot, 75005 Paris, France.

^c Unité Drug Design Small Molecules, Institut de Recherche et Développement Servier Paris-Saclay, 22 route 128, Gif-sur-Yvette, 91190, France.

^d # Dedicated to Prof. Dennis Curran at the occasion of his 70th birthday (CCDC): 2295986 (for **2a**), 2295987 (for **2g**), 2295985 (for **2d**) and 2295988 (for **2t**), 2301768 (for **2o**). Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

ARTICLE



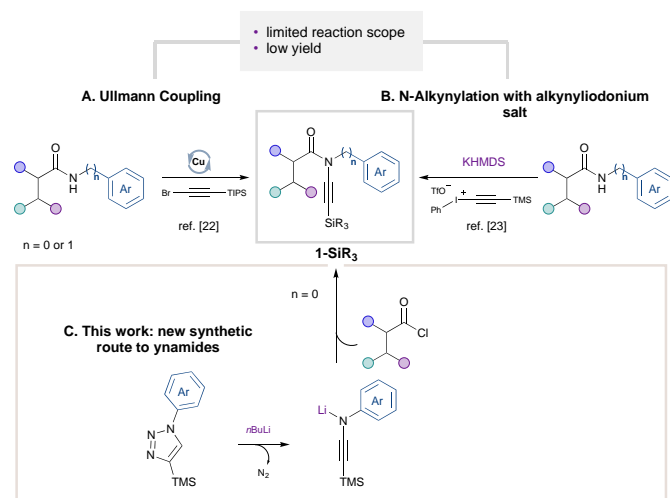
Scheme 1 a) In prior works, the processes do not fully consume the insaturations of the relay ynamides and lead to enamides; b) Natural products and biologically active molecules; c) In this work: both carbons of the pivotal ynamide plays a dual role in the cascade process leading to full consumption of the insaturations and setting two controlled stereogenic centres.

In that context, we aimed at developing new photoredox radical cascades using an ynamide as a pivotal function, *i.e.* each carbon of the triple bond was mobilized twice. In order to reach such level of complexity, we devised a sequence involving a preliminary trifluoromethyl radical addition – a 1,5-hydrogen atom transfer (HAT) from the generated vinyl radical (at the expense of cyclization on the pendant aryl ring) – a subsequent 5-exo-trig cyclization and a final cyclization on the aryl ring (Scheme 1C).

Results and discussion

Ynamides are a unique class of compounds, combining an alkyne moiety with a nitrogen atom bearing an electron-withdrawing group, which contributes greatly to their enhanced stability.²¹ Given the proposed strategy, our focus was on preparing ynamides **1** containing a N-C=O group and we initially relied on two synthetic methods for the preparation of the TMS-protected ynamides **1-TMS**. Method **A** consisted in a copper-catalysed Ullmann coupling reaction and Hsung's protocol proved to be instrumental in our case.²² Alternatively, Witulski's method **B** involving the *N*-alkynylation of amides by the use of hypervalent iodonium salts in the presence of a sterically hindered base was also used²³ (Scheme 2).

Despite the versatility of these methods, limitations remained for the preparation of some functionalized ynamide derivatives, which prompted us to explore a new synthetic route. Inspired by Hanessian's work on the synthesis of *N,N'*-



Scheme 2 Different methods for the preparation of ynamides **1-SiR₃**

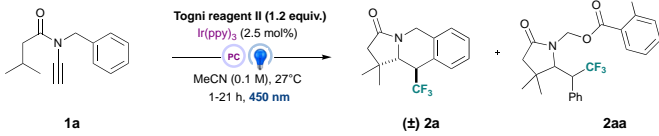
disubstituted cyanamides from tetrazoles,²⁴ we hypothesized that easily reachable *N*-aryl-4-(trimethylsilyl)-5*H*-triazoles could serve as synthons for ynamide synthesis (Scheme 2, method **C**). Conveniently, treatment of the triazole substrate with a strong base such as *n*-BuLi leads to a *N*-metalated ynamide intermediate formed through the cycloreversion of the triazole releasing dinitrogen. The latter could react *in situ* with various acid chlorides to smoothly give the desired ynamides **1-TMS**.

We initially focused on benzylic ynamide **1a** for validating our strategy as this precursor bears a dimethyl group on the acyl chain aimed to promote an efficient 1,5-HAT.²⁵ By using 2.5 mol % Ir(ppy)₃ (E(Ir(III)*/I(IV)) = -1.73 V vs. SCE in MeCN)²⁶ as photocatalyst and 1.2 equiv of Togni I reagent (-1.41 V vs. SCE in MeCN)²⁷ as the trifluoromethyl radical source in MeCN (0.1 M) (Table 1, entry 3), we were pleased to obtain the expected tricyclic product **2a** in 53% yield as single diastereomer. Of note, no product resulting from a cyclization of the vinyl radical **3**¹³ was observed (Scheme 4).

A further solvent screening (Table S1 entry 1-6) showed that the reaction proceeds well in DMSO, MeOH and to a lesser extent in DMF, DCM and EtOAc. Screening of trifluoromethyl radical sources, such as Umemoto reagents in MeCN indicated that the reaction works less efficiently compared to Togni reagents (Table S1). The best reaction conditions were found when using Togni II reagent (-0.32 V vs. SCE in MeCN)²⁷ (Table 1, entry 1), which also led to the formation of the minor carboxylate side product **2aa** in 13% yield. The formation of **2aa** would occur through an *ipso*-cyclization of the γ -CF₃ radical on the pendant benzyl group, followed by a 1,4-aryl shift,²⁸ oxidation of the resulting *N*-methylene radical followed, and addition of the iodobenzoate by-product (Scheme 4). We nevertheless decided to use Togni II for all further studies. When the reaction was conducted with other photocatalysts, lower yields of **2a** were obtained (Table S1). Control experiments supported that all reaction components were required for the reaction to proceed efficiently.

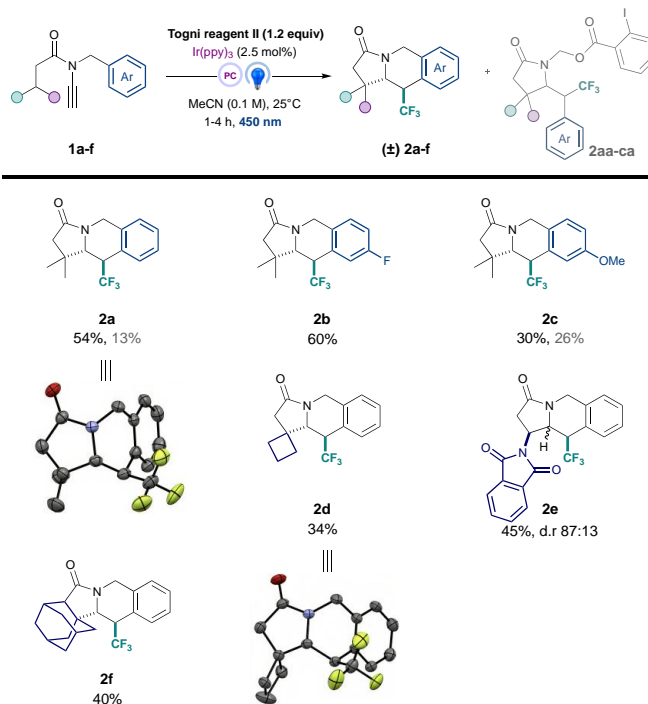
Having established the optimized reaction conditions, we surveyed the substrate scope of this cyclization cascade (Table 2). We began by testing benzylic ynamides (*n* = 1) bearing a tertiary or a secondary C-H moiety. When an electron poor aryl derivative (**1b**) was used, only **2b** was obtained in 60% yield. Conversely, when an electron rich ynamide **1c** was used, a mixture of both products was obtained in similar yield. We then turned our attention to the scope of the C-H bond that could be engaged in the 1,5-HAT. Ynamide **1d** bearing a cyclobutyl group underwent the expected cascade process, resulting in the formation of product **2d** in a moderate yield (34%). Nevertheless, this unprecedented intramolecular HAT from a cyclobutyl moiety, represents a new approach for the generation of cyclobutyl radicals complementary to the use of chloride radicals as described in literature.²⁹

Table 2 Optimization of reaction conditions^a



entry	Deviation from standard conditions	2a (%)	2aa (%)
1	none	60	13
2	MeOH as solvent	30	-
3	Togni I (1.2 equiv.) as CF ₃ radical donor	53	-
4	Umemoto (1.2 equiv.) as CF ₃ radical donor	22	-
5	[Ir(dtbbpy)(ppy) ₂][PF ₆] (2.5 mol %)	35	-

Table 1 Scope of ynamides bearing a benzyl group



^a Reactions were performed on a 0.1 mmol scale. **1** (1.0 equiv), Togni II (1.2 equiv), Ir(ppy)₃ (2.5 mol %) in MeCN (0.1 M), blue LED at rt, Yields were determined by ¹H NMR by using trimethoxybenzene as internal standard.

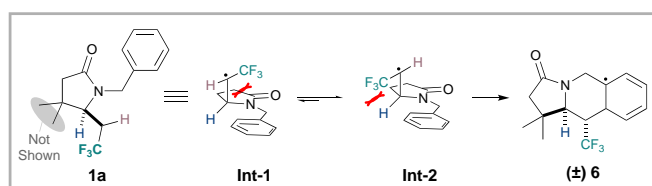
Reactions were performed on a 0.2 mmol scale. **1** (1.0 equiv), Togni II (1.2 equiv), Ir(ppy)₃ (2.5 mol %) in MeCN (0.1 M), blue LED at rt for 1-16h, isolated yields are reported.

Interestingly, the use of an ynamide flanked with a phthalimide group afforded the mixture of two diastereoisomers **2e**. Finally, substrate **2f** was generated through the C-H abstraction from adamantyl precursor **1f** in 40% yield. The X-ray diffraction (XRD) structures of both **2a** and **2d** gave insight into the relative configuration of these tricyclic products.

The observed diastereoselectivity on tricyclic derivatives **2** can be rationalized by considering the carbon-centred radical intermediate **5** (Schemes 3 and 4). Among the two possible conformations, **Int-1** is expected to possess the highest energy due to the substantial steric clash between the trifluoromethyl group and the pyrrolidinone ring. Conversely, **Int-2** would be more favourable as the trifluoromethyl group and the pyrrolidinone are oriented in opposing directions and leads to the formation of the radical intermediate **6**, where the trifluoromethyl substituent and the hydrogen atom at the cyclic junction are in a *syn* relationship.

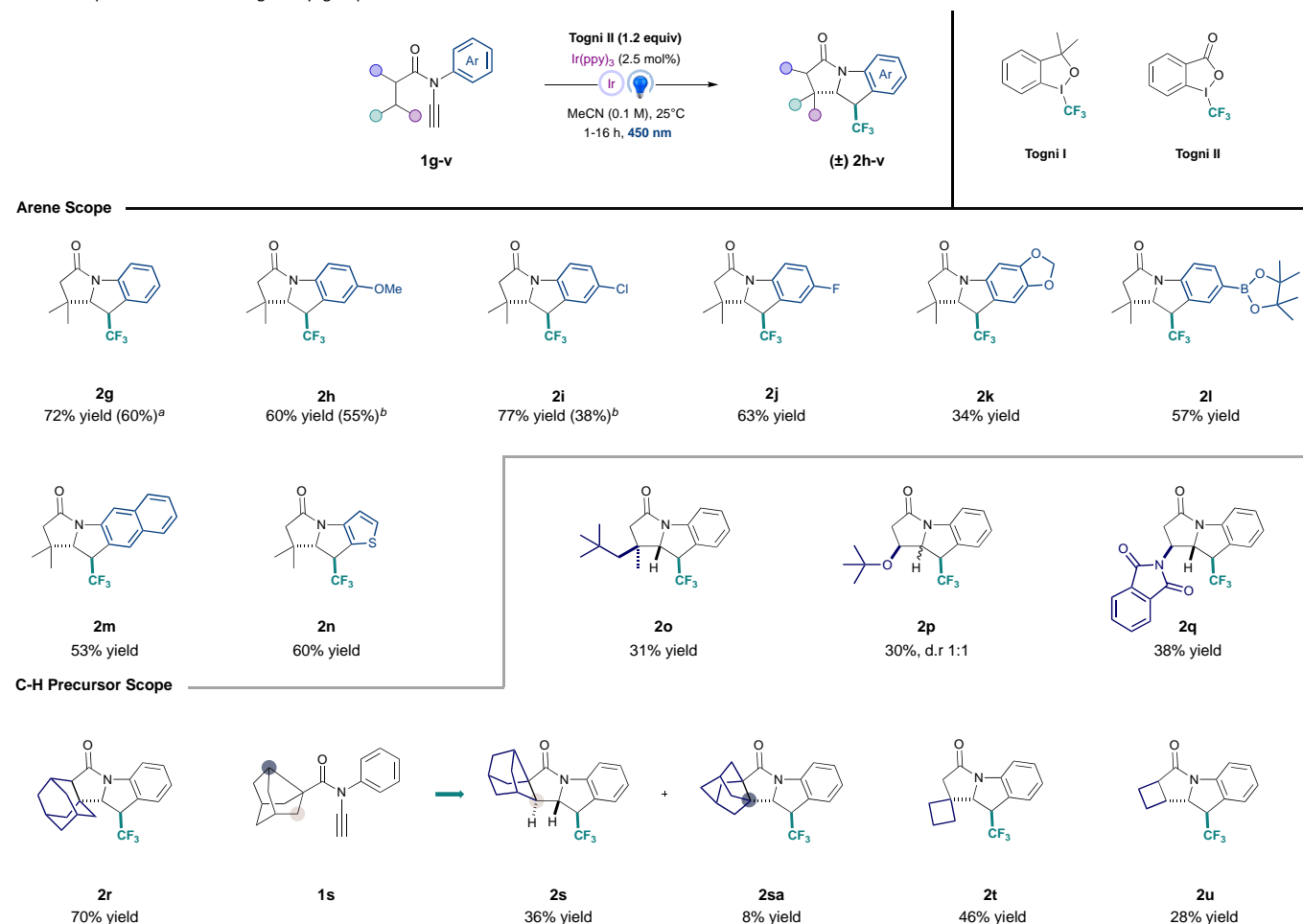
Further details on this diastereoselectivity are provided in the supporting information.

Encouraged by these results, we investigated the generality of the trifluoromethylation cyclization cascade on *N*-aryl



Scheme 1 Observed transition states leading to the formation of **6**

ARTICLE

Table 3 Scope of Ynamides bearing an aryl group

Reactions were performed on a 0.2 mmol scale. **1** (1.0 equiv), Togni II (1.2 equiv), Ir(ppy)₃ (2.5 mol %) in MeCN (0.1 M), Blue LED at rt for 1-16h, isolated yields are reported. ^a on a 0.5 mmol scale. ^b Reaction was performed with Togni I reagent (1.2 equiv). unless otherwise specified, d.r is superior to 95:5.

ynamides, aiming to suppress the formation of the corresponding carboxylate side and thus the competitive ipso-cyclization. Phenyl analogue **1g** was initially tested under the same reaction conditions (Table 3). 72% as a single diastereomer and as expected with no side product. Modification of the arene core on the ynamide was first evaluated.

Para-substituted arenes underwent reaction to deliver trifluoromethylated products in excellent yields (**2h-2j**, 60–77% yield). Product **2k** with a dioxolo group was obtained in a moderate 34% yield. The cyclization cascade was also effective with arenes bearing a boronic ester (**2l**, 57% yield), providing a platform for further functionalization of these pyrroloindolinone products through metal coupling reactions. Naphthyl ynamide **1m** delivered the desired product **2m** as a

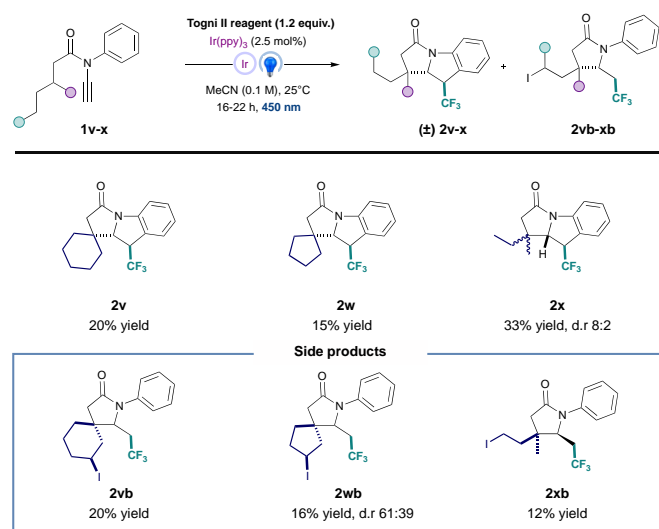
single regioisomer in satisfactory yield. The cyclization also tolerated heteroarenes like thiophene giving the product **2n** in good yield (60%).

A range of alkyl substituted ynamides were also tested in the cascade. Gratifyingly, derivatives **2o** and **2q** featuring three contiguous stereogenic centres were isolated as single diastereomers. However, cyclization with a secondary C-H centre bearing an ether resulted in a significant drop in diastereoselectivity (**2p**, d.r 1:1 in 30% yield). Adamantyl ynamide **1r** gave the expected product **2r** in excellent yield 70%.

Ynamides with fused cycloalkyl groups such as noradamantyl worked well, resulting in two regioisomers (**2s** and **2sa**) due to the HAT competition between a secondary and a tertiary C-H

on the noradamantyl moiety. Excellent diastereocontrol over all three contiguous stereogenic centres of **2s** was observed.

Table 4 Competitive pathways with some alkyl precursors



Reactions were performed on a 0.2 mmol scale. **1** (1.0 equiv), Togni II (1.2 equiv), Ir(ppy)₃ (2.5 mol %) in MeCN (0.1 M), Blue LED at rt for 1-16h, isolated yields are reported.

Cyclobutyl-containing product **2t** was obtained in 46% yield, while the highly strained tricyclic derivative **2u** could even be formed in 28% yield.

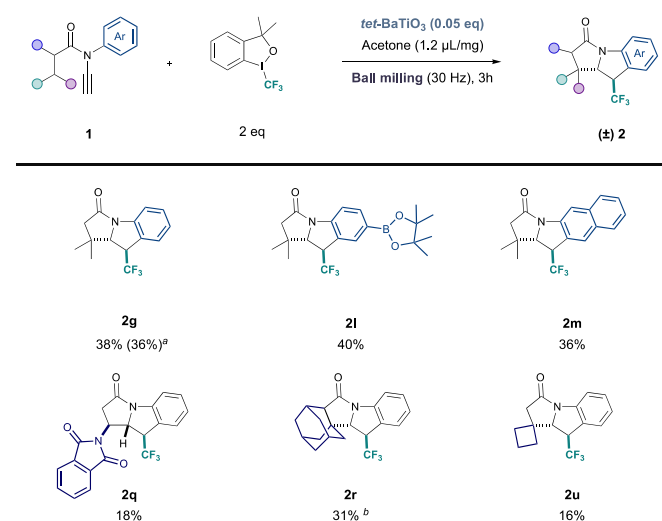
Intriguingly, when cyclohexyl and cyclopentyl ynamides **1v** and **1w** were tested, both gave a mixture of the desired product (**2v** and **2w**) and iodinated products (**2vb** and **2wb**) in comparable yields (Table 4). The same reactivity was observed with an ethyl chain (**2x** and **2xb**) and it is rationalized in the mechanistic discussion (Scheme 4). Additional side reactivity and limitations of this cascade are also reported in the SI (Fig. S4).

Recently, there has been a surge in studies on mechanochemical organic transformations, among which is the development of mechanoredox catalysis by Ito.³⁰ This catalytic system relies on the use of piezoelectric materials such as BaTiO₃, which upon mechanical activation undergoes polarization and acts as an electron transfer agent.³¹ In 2020, Ito reported the generation of trifluoromethyl radical enabled by mechanoredox.³² We wondered whether this seven-step radical cascade could be performed under such conditions, a type of process never accomplished before. We thus tested the reaction using Ito's conditions with compound **1g**. Traces of the tricyclic product **2g** were observed, showcasing the feasibility of this cascade in solid state. Subsequently, the optimization of the reaction was studied (Table S2).

Since both starting ynamide **1g** and tricyclic product **2g** proved to be unstable under the initially used ball milling settings, the optimal conditions required the use of catalytic quantities of BaTiO₃ and a reduced reaction time. This helped in mitigating the effect of this degradation on the reaction yield. The scope of the cascade was next investigated (Table 5). While the tricyclic products were obtained in what appears to be moderate yields (up to 40%), it has to be considered that

seven elementary steps are involved in the cascade process so that each step works with a yield of 77% for **2u** and 88% for **2i**. Also, the reaction could be amenable to diverse arene groups (**2g**, **2l**, **2m**) as well as C-H alkyl precursors (**2q**, **2r**, **2u**).

Table 5 Mechanoredox: an alternative to access trifluoromethylated tricyclic products



Yields were determined by ¹⁹F NMR with 4,4'-difluorobenzophenone as internal standard. ^a Isolated yield. ^b Grinding at 10 Hz for 13h. For experimental details, see the Supporting Information 8.2.

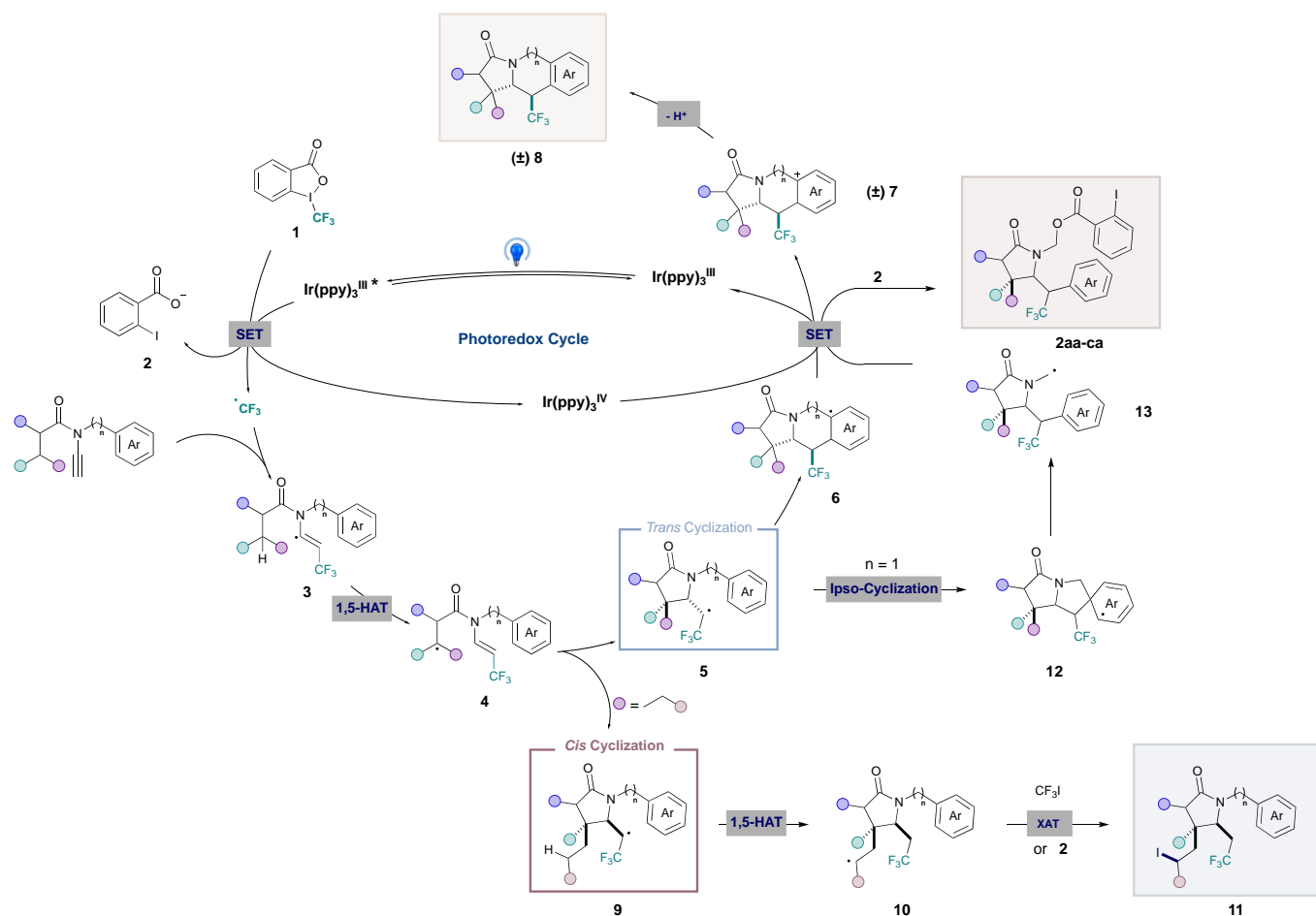
Based on the results described above, we propose the following mechanism for these transformations (Scheme 4). After generation of the trifluoromethyl radical through the photoredox cycle,³³ the latter adds regioselectively on the ynamide moiety. The resulting vinyl radical intermediate **3** undergoes a 1,5-HAT at the expense of a cyclization on the aromatic ring. The resulting C(sp³) radical **4** then cyclizes on the alkene via a 5-*exo-trig* cyclization giving the two diastereomeric intermediates **5** and **9**.³⁴ The *trans* cyclization product **5** cyclizes on the arene to give **6**.

In the case of benzyl ynamides, intermediate **5** as previously discussed undergoes an *ipso*-cyclization (**12**) followed by a 1,4-aryl shift to give products **2aa-ca**. The *cis* pyrrolidinone radical **9** would perform a second 1,5-HAT on the alkyl moiety to give **10**.³⁵ The iodo compound **11** could originate either from XAT (halogen atom transfer) of CF₃I generated *in-situ* or through the mesolytic cleavage of the phenyl-iodine bond.³⁶

Conclusions

To summarize, a series benzyl- and arylynamides were prepared, relying notably on a novel approach from readily available triazoles as starting materials. These precursors were engaged in a radical cyclization cascade, triggered by the addition of a trifluoromethyl radical and featuring a 1,5-HAT and two cyclizations to deliver complex γ -lactam polycyclic derivatives featuring up to three contiguous controlled stereogenic centers. Furthermore, we performed the reaction in solid state, which shows the potential of mechanoredox as a sustainable alternative for accessing these compounds. We are

confident that the photocatalysis methodology is a viable access to highly functionalized polycyclic derivatives and prompt further discovery of new bioactive compounds.



Scheme 2 Proposed Mechanism

Author Contributions

AL and MV did the experimental work. JF and GG did the XRD analyses. JMF, LH, CO and LF designed the experiments. AL, CO and LF wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Sorbonne Université, CNRS, Collège de France, IUF, Institut de Recherche et Développement Servier Paris-Saclay for financial support. Technical support from the Fédération de Chimie Moléculaire is also acknowledged.

Notes and references

- 1 D. P. Curran, D. M. Rackiewicz, Tandem radical approach to linear condensed cyclopentanoids. Total synthesis of (.-.-)-hirsutene, *J. Am. Chem. Soc.*, 1985, **107**, 1448-1449.
- 2 (a) M. Malacria, Selective Preparation of Complex Polycyclic Molecules from Acyclic Precursors via Radical Mediated- or Transition Metal-Catalyzed Cascade Reactions, *Chem. Rev.*, 1996, **96**, 289-306; (b) K. Hung, X. Hu, T. J. Maimone, Total synthesis of complex terpenoids employing radical cascade processes, *Nat. Prod. Rep.*, 2018, **35**, 174-202; (c) K. J. Romero, M. S. Galliher, D. A. Pratt, C. R. J. Stephenson, Radicals in natural product synthesis, *Chem. Soc. Rev.*, 2018, **47**, 7851-7866.
- 3 (a) X.-Y. Liu, Y. Qin, Indole Alkaloid Synthesis Facilitated by Photoredox Catalytic Radical Cascade Reactions, *Acc. Chem. Res.*, 2019, **52**, 1877-1891; (b) R. Ardkhean, D. F. J. Caputo, S. M. Morrow, H. Shi, Y. Xiong, E. A. Anderson, Cascade polycyclizations in natural product synthesis, *Chem. Soc. Rev.*, 2016, **45**, 1557-1569.

- 4 M. P. Plesniak, H.-M. Huang, D. J. Procter, Radical cascade reactions triggered by single electron transfer, *Nat. Rev. Chem.*, 2017, **1**, 0077.
- 5 (a) A. Gansäuer, H. Bluhm, Reagent-Controlled Transition-Metal-Catalyzed Radical Reactions, *Chem. Rev.*, 2000, **100**, 2771–2788; (b) S. Mondal, F. Dumur, D. Gignes, M. P. Sibi, M. P. Bertrand, M. Nechab, Enantioselective Radical Reactions Using Chiral Catalysts, *Chem. Rev.*, 2022, **122**, 5842–5976.
- 6 (a) M. H. Shaw, J. Twilton, D. W. C. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.*, 2016, **81**, 6898–6926; (b) J.-P. Goddard, C. Ollivier, L. Fensterbank, Photoredox Catalysis for the Generation of Carbon Centered Radicals, *Acc. Chem. Res.*, 2016, **49**, 1924–1936; (c) L. Marzo, S. K. Pagire, O. Reiser, B. König, Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis?, *Angew. Chem. Int. Ed.*, 2018, **57**, 10034–10072; (d) D. Staveness, I. Bosque, C. R. J. Stephenson, Free Radical Chemistry Enabled by Visible Light-Induced Electron Transfer, *Acc. Chem. Res.*, 2016, **49**, 2295–2306; (e) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, Exploration of Visible-Light Photocatalysis in Heterocycle Synthesis and Functionalization: Reaction Design and Beyond, *Acc. Chem. Res.*, 2016, **49**, 1911–1923.
- 7 (a) T.-D. Tan, Z.-S. Wang, P.-C. Qian, L.-W. Ye, Radical Reactions of Ynamides, *Small Methods* 2021, **5**, 2000673; (b) C. Mahe, K. Cariou, Ynamides in Free Radical Reactions, *Adv. Synth. Catal.*, 2020, **18**, 4820–4832; (c) Z.-S. Wang, Y.-B. Chen, K. Wang, Z. Xu, L.-W. Ye, One-pot synthesis of 2-hydroxymethylindoles via photoredox-catalyzed ketyl-ynamide coupling/1,3-allylic alcohol transposition, *Green Chem.*, 2020, **22**, 4483–4488.
- 8 For representative examples of cascades with alkynes: (a) S. Bogen, M. Gulea, L. Fensterbank, M. Malacria, 5-Endo-Trig Radical Cyclizations of Bromomethyl dimethylsilyl Diisopropylpropargylic Ethers. A Highly Diastereoselective Access to Functionalized Cyclopentanes, *J. Org. Chem.*, 1999, **64**, 4920–4925; (b) U. Wille, Radical Cascades Initiated by Intermolecular Radical Addition to Alkynes and Related Triple Bond Systems, *Chem. Rev.*, 2013, **113**, 813–853; (c) S. Le, J. Li, J. Feng, Z. Zhang, Y. Bai, Z. Yuan and G. Zhu, [3+2] Cycloaddition of alkyl aldehydes and alkynes enabled by photoinduced hydrogen atom transfer, *Nat. Commun.*, 2022, **13**, 4734; (d) L. Li, J.-Z. Li, Y.-B. Sun, C.-M. Luo, H. Qiu, K. Tang, H. Liu and W.-T. Wei, Visible-Light-Catalyzed Tandem Radical Addition/1,5-Hydrogen Atom Transfer/Cyclization of 2-Alkynylarylethers with Sulfonyl Chlorides, *Org. Lett.*, 2022, **24**, 4704–4709; (e) J. Qiu, S. Le, J. Su, Y. Liu, Y. Zhou, H. Zheng, Y. Bai and G. Zhu, A diastereoselective synthesis of cyclopentanones via photocatalytic reductive alkyltrifluoromethylation of ynones, *Org. Chem. Front.*, 2022, **9**, 5523–5529; (f) Y. Yang, C. G. Daniliuc and A. Studer, 1,1,2-Trifunctionalization of Terminal Alkynes by Radical Addition–Translocation–Cyclization–Trapping for the Construction of Highly Substituted Cyclopentanes, *Angew. Chem. Int. Ed.*, 2021, **60**, 2145–2148.
- 9 (a) F. Marion, C. Courillon, M. Malacria, Radical Cyclization Cascade Involving Ynamides: An Original Access to Nitrogen-Containing Heterocycles, *Org. Lett.*, 2003, **5**, 5095–5097; (b) F. Marion, J. Coulomb, A. Servais, C. Courillon, L. Fensterbank, M. Malacria, Radical cascade cyclizations and platinum(II)-catalyzed cycloisomerizations of ynamides, *Tetrahedron*, 2006, **62**, 3856–3871; (c) S. Balieu, K. Toutah, L. Carro, L.-M. Chamoreau, H. Rousselière, C. Courillon, Radical cyclization of ynamides into six- or eight-membered rings. Application to the synthesis of a protoberberine analog, *Tetrahedron Lett.*, 2011, **52**, 2876–2880.
- 10 (a) H. Bagaia, C. Deldaele, E. Romero, B. Michelet, G. Evano, Copper-Catalyzed Photoinduced Radical Domino Cyclization of Ynamides and Cyanamides: A Unified Entry to Rosettacin, Luotonin A, and Deoxyvasicinone, *Synthesis*, 2018, **50**, 3022–3030; for more recent examples : (b) C. Jacob, H. Bagaia, A. Dubart, S. Oger, P. Thilmany, J. Beaudelot, C. Deldaele, S. Peruško, Y. Landrain, B. Michelet, S. Neale, E. Romero, C. Moucheron, V. Van Speybroeck, C. Theunissen, G. Evano, A general synthesis of azetidines by copper-catalysed photoinduced anti-Baldwin radical cyclization of ynamides, *Nat. Commun.*, 2022, **13**, 560.
- 11 (a) S. Dutta, R. K. Mallick, R. Prasad, V. Gandon, A. K. Sahoo, Alkyne Versus Ynamide Reactivity: Regioselective Radical Cyclization of Yne-Ynamides, *Angew. Chem. Int. Ed.*, 2019, **58**, 2289–2294; (b) S. Dutta, B. Prabagar, R. Vanjari, V. Gandon, A. K. Sahoo, An unconventional sulfur-to-selenium-to-carbon radical transfer: chemo- and regioselective cyclization of yne-ynamides, *Green Chem.*, 2020, **22**, 1113–1118; (c) F. Chemla, F. Dulong, F. Ferreira, M. P. Nüllen, A. Pérez-Luna, Radical Zinc Atom-Transfer Based Multicomponent Approaches to 3-Alkylidene Tetrahydrofurans, *Synthesis*, 2011, **9**, 1347–1360; (d) S. Li, Y. Wang, Z. Wu, W. Shi, Y. Lei, P. W. Davies, W. Shu, A Radical-Initiated Fragmentary Rearrangement Cascade of Ene-Ynamides to [1,2]-Annulated Indoles via Site-Selective Cyclization, *Org. Lett.*, 2021, **23**, 7209–7214.
- 12 (a) A. Sato, H. Yorimitsu, K. Oshima, Regio- and Stereoselective Radical Additions of Thiols to Ynamides, *Synlett*, 2009, **1**, 28–31; (b) B. Banerjee, D. N. Litvinov, J. Kang, J. D. Bettale, S. L. Castle, Stereoselective Additions of Thiyl Radicals to Terminal Ynamides, *Org. Lett.*, 2010, **12**, 2650–2652; (c) E. Romain, C. Fopp, F. Chemla, F. Ferreira, O. Jackowski, M. Oestreich, A. Perez-Luna, Trans-Selective Radical Silylzincation of Ynamides, *Angew. Chem. Int. Ed.*, 2014, **53**, 11333–11337; (d) N. Dwadnia, H. Lingua, D. Mouysset, L. Mimoun, D. Siri, M. P. Bertrand, L. Feray, Intermolecular Addition of Carbon-Centered Radicals to Ynamides. A Regio- and Stereoselective Route to Persubstituted α -Iodo-enamides, *J. Org. Chem.*, 2020, **85**, 4114–4121; (e) A. Galibert-Guijarro, D. Mouysset, L. Mimoun, M. P. Bertrand, L. Feray, Ynamides in Radical Reactions: A Route to Original Persubstituted 2-Aminofurans, *J. Org. Chem.*, 2023, **88**, 2464–2473.
- 13 M. Cassé, C. Nisole, H. Dossmann, Y. Gimbert, J.-M. Fourquez, L. Haberkorn, C. Ollivier, L. Fensterbank, Trifluoromethyl radical triggered radical cyclization of N-benzoyl ynamides leading to isoindolinones, *Sci. China Chem.*, 2019, **62**, 1542–1546.
- 14 J. Caruano, G. G. Muccioli, R. Robiette, Biologically active γ -lactams: synthesis and natural sources, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156.
- 15 H. Sun, X. He, C. Liu, L. Li, R. Zhou, T. Jin, S. Yue, D. Feng, J. Gong, J. Sun, J. Ji, L. Xiang, Effect of Oleracein E, a Neuroprotective Tetrahydroisoquinoline, on Rotenone-Induced Parkinson's Disease Cell and Animal Models, *ACS Chem. Neurosci.*, 2017, **8**, 155–164.
- 16 L. Yang, Q. Yang, E. Wang, J. Yang, Q. Li, J. Cao, L. Wang, X. Liao, Y. Yang, X. Yang, Synthesis of novel 1-phenylbenzopyrrolizidin-3-one derivatives and evaluation of their cytoprotective effects against NMDA-induced injury in PC12 cells, *Bioorg. Med. Chem.*, 2022, **59**, 116675.
- 17 R. M. Kariba, P. J. Houghton, A. Yenesew, Antimicrobial Activities of a New Schizozygane Indoline Alkaloid from *Schizozygia coffaeoides* and the Revised Structure of Isoschizogaline, *J. Nat. Prod.*, 2002, **65**, 566–569.
- 18 (a) Z. Wang, M. Wang, L. Wang, X. Yao, Y. Li, J. Tan, W. Qiao, Y. Geng, Y. Liu, Q. Wang, Discovery and Nanosized Preparations of (S,R)-Tylophorine Malate as Novel anti-SARS-CoV-2 Agents, *Lett. Drug Des. Discov.*, 2015, **12**, 277–283; (b) C.-Y. Chen, G.-Y. Zhu, J.-R. Wang, Z.-H. Jiang,

- Phenanthroindolizidine alkaloids from *Tylophora atrofolliculata* with hypoxia-inducible factor-1 (HIF-1) inhibitory activity, *RSC Adv.*, 2016, **6**, 79958–79967.
- 19 A. R. N. Santos, H. M. Sheldrake, A. I. M. Ibrahim, C. C. Danta, D. Bonanni, M. Daga, S. Oliaro-Bosso, D. Boschi, M. L. Lolli, K. Pors, Exploration of [2 + 2 + 2] cyclootrimerisation methodology to prepare tetrahydroisoquinoline-based compounds with potential aldo–keto reductase 1C3 target affinity, *MedChemComm*, 2019, **10**, 1476–1480.
 - 20 (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432–2506.
 - 21 (a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, Ynamides: A Modern Functional Group for the New Millennium, *Chem. Rev.*, 2010, **110**, 5064–5106; (b) G. Evano, A. Coste, K. Jouvin, Ynamides: Versatile Tools in Organic Synthesis, *Angew. Chem. Int. Ed.*, 2010, **49**, 2840–2859.
 - 22 Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, Copper Sulfate-Pentahydrate-1,10-Phenanthroline Catalyzed Amidations of Alkynyl Bromides. Synthesis of Heteroaromatic Amine Substituted Ynamides, *Org. Lett.*, 2004, **6**, 1151–1154.
 - 23 B. Witulski, T. Stengel, N-Functionalized 1-Alkynylamides: New Building Blocks for Transition Metal Mediated Inter- and Intramolecular [2+2+1] Cycloadditions, *Angew. Chem. Int. Ed.*, 1998, **37**, 489–492.
 - 24 E. Duchamp, S. Hanessian, Cyanide-Free Synthesis of Air Stable N-Substituted Li and K Cyanamide Salts from Tetrazoles. Applications toward the Synthesis of Primary and Secondary Cyanamides as Precursors to Amidines, *Org. Lett.*, 2020, **22**, 8487–8491.
 - 25 (a) D. P. Curran, W. Shen, Radical translocation reactions of vinyl radicals: substituent effects on 1,5-hydrogen-transfer reactions, *J. Am. Chem. Soc.*, 1993, **115**, 6051–6059; (b) S. Sarkar, K. P. S. Cheung and V. Gevorgyan, C–H functionalization reactions enabled by hydrogen atom transfer to carbon-centered radicals, *Chem. Sci.*, 2020, **11**, 12974.
 - 26 L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura, F. Barigelletti, in *Photochemistry and Photophysics of Coordination Compounds II*, eds. V. Balzani and S. Campagna, Springer, Berlin, Heidelberg, 2007, pp. 143–203.
 - 27 Y. Jiang, H. Yu, Y. Fu, L. Liu, Redox potentials of trifluoromethyl-containing compounds, *Sci. China Chem.*, 2015, **58**, 673–683.
 - 28 N. Fuentes, W. Kong, L. Fernández-Sánchez, E. Merino, C. Nevado, Cyclization Cascades via N-Amidyl Radicals toward Highly Functionalized Heterocyclic Scaffolds, *J. Am. Chem. Soc.*, 2015, **137**, 964–973.
 - 29 (a) A. J. Sedlacek, C. A. Wight, Free radical chain reactions of chlorine with cyclobutane in the solid state: Evidence for radical migration via H atom transfer, *J. Chem. Phys.*, 1988, **88**, 2847–2848; (b) D. F. McMillen, D. M. Golden, S. W. Benson, The rate of the gas phase iodination of cyclobutane. The heat of formation of the cyclobutyl radical, *Int. J. Chem. Kinet.*, 1972, **4**, 487–495; (c) P. Wessig, O. Muhling, Photochemical Synthesis of Highly Functionalized Cyclopropyl Ketones, *Helv. Chim. Acta*, 2003, **86**, 865–893.
 - 30 (a) T. Friščić, C. Mottillo, H. M. Titi, Mechanochemistry for Synthesis, *Angew. Chem. Int. Ed.*, 2020, **59**, 1018–1029; (b) J. L. Howard, Q. Cao, D. L. Browne, Mechanochemistry as an emerging tool for molecular synthesis: what can it offer?, *Chem. Sci.*, 2018, **9**, 3080–3094; (c) K. Kubota, Y. Pang, A. Miura, H. Ito, Redox reactions of small organic molecules using ball milling and piezoelectric materials, *Science*, 2019, **366**, 1500–1504.
 - 31 J. A. Leitch, D. L. Browne, *Chem. – Eur. J.*, Mechanochemical Chemistry as an Emerging Strategy in Synthesis, 2021, **27**, 9721–9726.
 - 32 Y. Pang, J. W. Lee, K. Kubota, H. Ito, Solid-State Radical C–H Trifluoromethylation Reactions Using Ball Milling and Piezoelectric Materials, *Angew. Chem. Int. Ed.*, 2020, **59**, 22570–22576.
 - 33 K. Guo, C. Gu, Y. Li, X. Xie, H. Zhang, K. Chen, Y. Zhu, Photoredox Catalyzed Trifluoromethyl Radical-Triggered Trifunctionalization of 5-Hexenenitriles via Cyano Migration, *Adv. Synth. Catal.*, 2022, **364**, 1388–1393.
 - 34 P. Renaud, Addition of sulfinylated and sulfonylated carbon centered radicals to alkenes and enoethers, *Tetrahedron Lett.*, 1990, **31**, 4601–4604.
 - 35 (a) D. C. Spellmeyer, K. N. Houk, Force-field model for intramolecular radical additions, *J. Org. Chem.*, 1987, **52**, 959–974; (b) A. Gross, L. Fensterbank, S. Bogen, R. Thouvenot, M. Malacria, Design of a radical translocation step through 1, n (n = 5, 6, 7) hydrogen transfers for incorporation into new radical cascades, *Tetrahedron*, 1997, **53**, 13797–13810.
 - 36 (a) R. Beniazza, M. Douarre, D. Lastécouères, J.-M. Vincent, Metal-free and light-promoted radical iodotrifluoromethylation of alkenes with Togni reagent as the source of CF₃ and iodine, *Chem. Commun.*, 2017, **53**, 3547–3550; (b) D. Dolenc, B. Plesničar, Evidence for Divalent Iodine (9-I-2) Radical Intermediates in the Thermolysis of (tert-Butylperoxy)iodanes. An Unusually Efficient Deiodination of o-Iodocumyl Alcohols by Cyclohexyl Radicals, *J. Am. Chem. Soc.*, 1997, **119**, 2628–2632; (c) D. Dolenc, B. Plesničar, Abstraction of Iodine from Aromatic Iodides by Alkyl Radicals: Steric and Electronic Effects, *J. Org. Chem.*, 2006, **71**, 8028–8036.