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Synthesis, reactivity and properties of versatile *gem*-bis[(trifluoromethyl)sulfonyl] functionalized organic molecules†

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Incorporation of fluorinated functionalities is a valuable strategy to improve both chemical and biological properties of organic compounds. In this context, much attention is being focused on the trifluoromethanesulfonyl (triflyl) group (SO_2CF_3), due to its potent electron-withdrawing effect and mild lipophilicity. Consequently, different protocols have been developed over the years to prepare triflones, which are organic molecules bearing the triflyl functionality. The electron-withdrawing effect of the triflyl group also makes compounds bearing *gem*-bis(triflyl)methyl group (Tf_2CH) strongly acidic. Several one-pot reactions, in combination with a derivation step in some cases, merged under simple reaction conditions for the straightforward formation of divergent fluorosulfonyl-decorated cyclic scaffolds from simple starting materials, providing a convenient access to an under-explored structural space. In this way, cyclobutenes, heterocycles, and non-cyclic products have been easily prepared without the requirement for either a catalyst or an additive. This article reviews reactions between differently functionalized alkynes, alkenes and allenes with $Tf_2C{=}CH_2$ (generated *in situ* from a shelf-stable betaine) to afford cyclic and acyclic bis(triflyl)-functionalized organic molecules with novel chemical structures.

1. Introduction

In 1976, Robert Koshar and Loren Barber were working as research scientists at the Minnesota Mining and Manufacturing Company, the former name of today's big technology group 3M. During the attempts of isolate bis(triflyl)ethene molecules from a solution containing $(CF_3SO_2)_2CHCH_3$, they found that treatment of the mixture with pyridine enabled the clean precipitation of the pyridinium salt **1a** from the mother liquor. Once the pure adduct **1a** was isolated, subsequent addition of sulfuric acid successfully promoted the C–N bond dissociation, thereby recovering the pure bis(triflyl)ethene molecule. This pure compound could be then used in chemical reactions, particularly in polymer synthesis (Scheme 1).[1] Both scientists pursued long and productive careers at 3M. In particular, Koshar reported numerous patents centred on fluorine-containing advanced materials. In subsequent years, the academic community regarded the so-called Koshar zwitterion as a remarkable curiosity—a bench-stable crystalline solid that is easily prepared and handled yet encapsulates a latent bis(triflyl)ethene moiety. Nevertheless, applications in organic synthesis were almost unexplored until in the early 2010s Tokyo-based Professor Hikaru Yanai started to study Koshar-type zwitterions from a multidisciplinary perspective.

Yanai's research group carefully determined the electronic distribution, molecular conformation, X-ray structure, and an optimized synthetic method to access Koshar-type zwitterions.[2–5] They found that the multicomponent reaction of bis(triflyl)methane [triflyl = (trifluoromethyl)sulfonyl] with paraformaldehyde and pyridine in 1,2-dichloroethane (DCE) yielded the desired compounds after a simple work-up (Scheme 2a). They also identified the 2-fluoropyridine derivative **1b** as the most efficient precursor of bis(triflyl)ethene, and reported pioneering synthetic applications, including nucleophilic additions leading to carbon acids and Diels–Alder cycloadditions. Interestingly, bis(triflyl)ethene can be described as an equilibrium between the olefinic and the dipolar forms I and II, respectively. The negative charge in II is delocalized by the assistance of the two triflyl (Tf) groups, exhibiting great reactivity and a high instability (Scheme 2b). Considering these aspects, Alcaide and Almendros identified Yanai's zwitterion as

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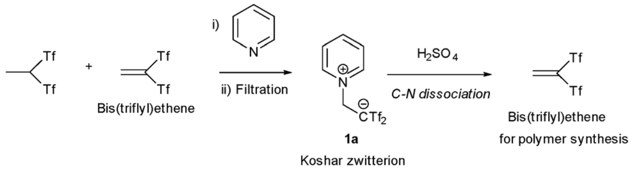
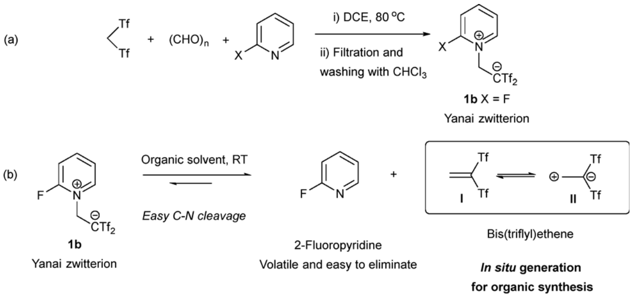
† Dedicated to Prof. José Luis Marco on the occasion of his retirement.

a promising platform for a broad range of transformations, including cycloadditions, cascade processes, and even metal-catalyzed reactions, thereby enabling exquisitely chemo-, regio-, and stereocontrolled methodologies. In addition, Koshar-type chemistry allows the incorporation of triflyl groups in final structures. The demand for diverse fluorinated heterocyclic compounds drives the development of versatile synthetic strategies, such as direct C–H fluoroalkylation, although this remains challenging.[6–8] Concerns also arise from metal-catalyzed protocols, which may leave impurities in medicinal and engineering products. The trifluoromethylsulfonyl (triflyl) group, one of the strongest electron-withdrawing substituents, imparts mild lipophilicity and enhances the acidity of compounds, making them useful in developing effective acid catalysts.[9–13]



Scheme 1 Koshar zwitterion. Preparation and use.



Scheme 2 Yanai's zwitterion. Preparation and behaviour in solution.

A substantial portion of this Feature Article is devoted to the synthetic applications, substrate development, and

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mechanistic understanding of chemical transformations involving the reagent $(CF_3SO_2)_2C{=}CH_2$. A previous review article has addressed complementary aspects of its chemistry, including the pronounced C–H acidity of the (Tf_2CH) motif arising from geminal substitution by two triflyl groups (ref. 5*c*). Other review has highlighted the distinctive ionic yet lipophilic nature of the corresponding carbanions, which enables their use as versatile "substituents" for simultaneously enhancing the aqueous solubility and lipophilicity of organic molecules (ref. 5*a*). In addition, a recent review has summarized progress in the field of stable fluorinated sulfonyl carbanions, encompassing their preparation methods, bonding characteristics, coordination chemistry, and emerging synthetic applications (ref. 5*b*).

This article reviews the synthetic applications of Koshar-type zwitterions reported over the past two decades, organized according to the target structures obtained. The synthesis of challenging four-membered rings and their subsequent synthetic transformations are discussed first. Subsequently, the generation of five- and six-membered cyclic frameworks will be presented, encompassing the synthesis of naturally occurring motifs such as triazoles, flavones, aurones, isocoumarins, and pyrans, among others. The biological evaluations of the synthesized compounds will also be discussed. Finally, the preparation of non-cyclic systems derived from readily accessible starting materials—including bis(triflyl)enones, bis(triflyl)enals, and heteroatom-based betaines—will be described.

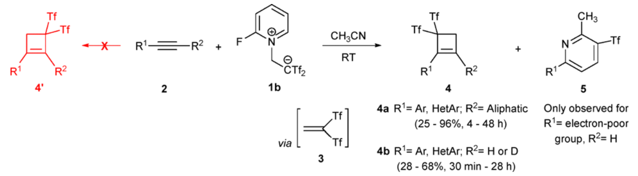
2. Four-membered rings

2.1. Synthesis of bis(triflyl)cyclobutenes

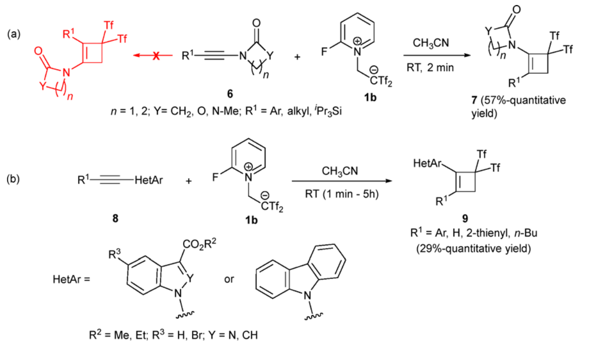
Cyclobutene derivatives serve as both target molecules and versatile building blocks for constructing complex structures, including bioactive compounds.[14–23] The traditional synthetic methods, such as [2+2] cycloaddition reactions of alkynes with unsaturated systems, often yield modest results and require harsh conditions, limiting their applicability. While recent metal-catalyzed strategies have emerged, they suffer from narrow substrate scopes and moderate selectivity, hindering their widespread use.[24–26] Due to the increasing importance of the cyclobutene motif, efforts are underway to develop innovative synthetic methodologies.[27] However, the efficient and selective introduction of functionality into the four-membered skeleton remains a difficult challenge, leading the need for novel synthetic approaches to synthesize functionalized cyclobutenes with high chemo- and regioselectivity. As mentioned above, Yanai reported that betaine **1b**, containing both a 2-fluoropyridinium cation and a stabilized carbanion moiety, quickly equilibrates in acetonitrile to form mixtures of the betaine, $(CF_3SO_2)_2C{=}CH_2$, and volatile 2-fluoropyridine. This property makes it a shelf-stable, eco-friendly, and easy-to-handle source of $(CF_3SO_2)_2C{=}CH_2$.[2–5] In this context, our research group has explored the potential of alkynes and betaine **1b** as starting materials for the synthesis of cyclobutenes *via* 1,2-dipolar cycloaddition reactions. Although this synthetic approach has been hindered by the limited availability of methods to access 1,2-dipoles, the uncatalyzed reaction employing *in situ* generated 1,1-bis(trifluoromethylsulfonyl)ethene (**3**) has delivered promising results. Building on Yanai's previous investigations into the use of betaines **1** as practical precursors of dipoles **3**, it was discovered that fluorine-substituted pyridinium salt at the 2-position (**1b**) exhibited remarkable efficiency in promoting the desired transformation under mild reaction conditions (Scheme 3).[28] Thus, a variety of aliphatic, aromatic, and heteroaromatic substituted-alkynes **2** were used in the intermolecular cyclization reaction with zwitterion **1b**. Interestingly, non-symmetrical di-substituted alkynes could be successfully transformed into cyclobutenes **4** in a regioselective way. The steric properties of the substituents in the acetylenic moiety did not significantly affect either yield or regioselectivity, while the electronic nature of the substituents did influence the reaction. In addition, disubstituted alkynes with electron-donating groups at R^1 generally resulted in better conversions compared to those with electron-withdrawing substituents and promoted the regioselective formation of isomers **4a** *versus* **4′**. (Scheme 3). Besides, less reactive terminal alkynes were also examined (R^2 = H, D). While terminal aliphatic alkynes failed to react under the normal conditions, aromatic systems smoothly underwent cycloaddition to afford the corresponding cyclobutenes **4b** in satisfactory yields. Interestingly, when R^1 is an electron-donating group a higher reactivity was observed compared to disubstitued alkynes. Noteworthy, the reaction of certain terminal alkynes exhibiting electron-poor substituents at R^1 resulted in the formation of unexpected pyridines **5** with the participation of MeCN, highlighting the importance of electronic substitution in determining the outcome of the reaction. DFT calculations supported a stepwise reaction mechanism for the formation of compounds **4** and **5**, with cyclobutene systems kinetically preferred.[28]

To increase the family of cyclobutene-based structures that can be accessed through this methodology, ynamides **6** were studied in the presence of betaine **1b** under otherwise similar reaction conditions. Interestingly, heteroatom-decorated bis(triflyl)cyclobutenes **7** were obtained, providing an easy route to aminocyclobutenes. Both aryl and alkyl substituents on the alkyne were well tolerated, delivering the desired compounds **7** with total regioselectivity and good yields (Scheme 4a). Different ynamides **8** incorporating heterocycles were also investigated, giving the expected cyclobutenes **9** with moderate to excellent yields (Scheme 4b).[29,30]

A later report explored the versatility of zwitterion **1b** in the presence of sulfur, selenium and tellurium-decorated alkynes. Despite the presumed instability of chalcogen-substituted systems, triflones **11**, **13**, **15**, **17** and **19** were obtained in high

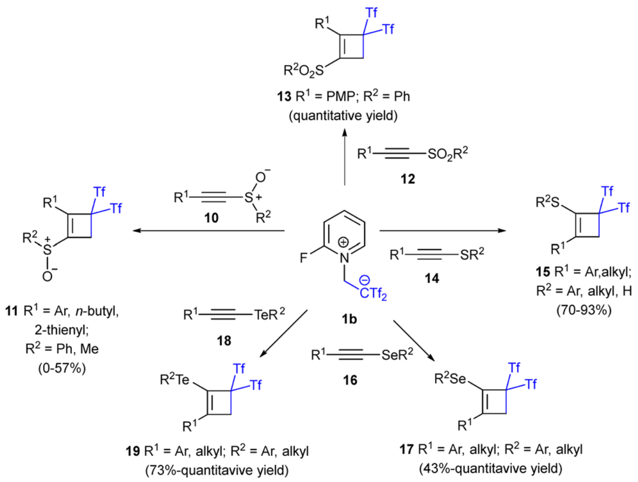


Scheme 3 Synthesis of bis(triflyl)cyclobutenes from alkynes.

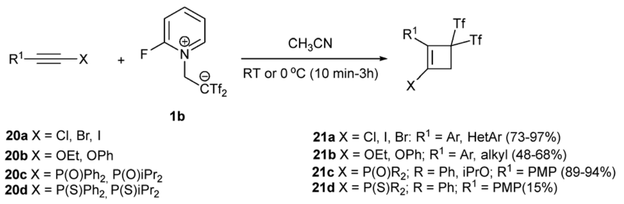


Scheme 4 Synthesis of aminocyclobutenes.

yields in most of the cases. Thus, the reactivity of sulfur-based alkynes exhibiting different oxidation states was explored, delivering the desired cyclobutenes **11**, **13** and **15** (Scheme 5, top). Interestingly, a reverse regiochemistry was observed for sulfinyl- and sulfonyl-cyclobutenes **11** and **13**, showing the exquisite selectivity of this transformation, influenced by subtle changes of the substitution pattern. Also, alkynyl precursors **16** and **18** featuring Se- and Te- respectively, formed polyfunctionalized cyclobutenes with moderate to excellent yields (Scheme 5, bottom).[30] To gain a better understanding of betaine's reactivity with differently substituted alkynes, haloalkynes **20a** and alkynyl ethers **20b** were submitted to cycloaddition reaction conditions. No remarkable electronic or steric effects were observed in the formation of chloro-, bromo-, or iodo-cyclobutenes, delivering the expected structures **21a** with very good yields in all cases (Scheme 6). The enhanced reactivity of alkynyl ethers **20b** led to complex reaction mixtures using standard conditions. Fortunately, lowering the temperature to 0 °C allowed the synthesis and isolation of the corresponding cyclic enol ethers **21b** in good yields (Scheme 6).



Scheme 5 Synthesis of chalcogen-substituted bis(triflyl)cyclobutenes.



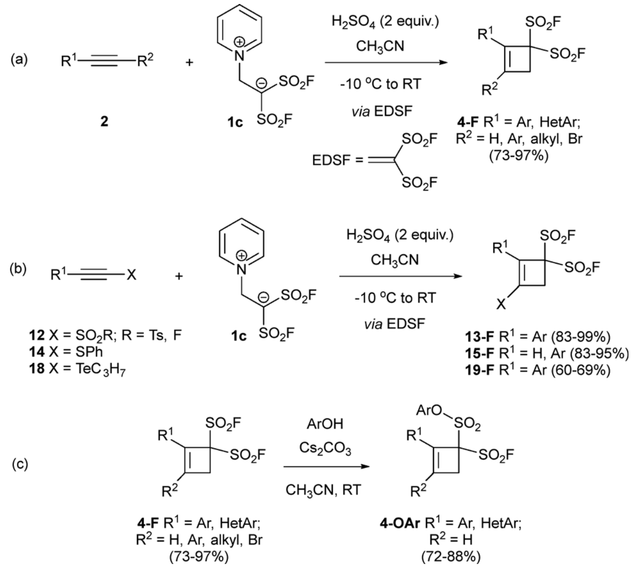
Scheme 6 Synthesis of heteroatom-substituted bis(triflyl)cyclobutenes.

Moreover, phosphorus-substituted alkynes **20c** and **20d** were examined as precursors of functionalized cyclobutenes **21c** and **21d**. In this transformation, phosphine oxides **20c** yielded phosphorylcyclobutenes **21c** in excellent yields and in a complete regioselective manner. In addition, thiophosphine oxide **20d** produced the desired cyclobutene **21d**, showing the same selectivity, although the yield was low (Scheme 6).[30,31]

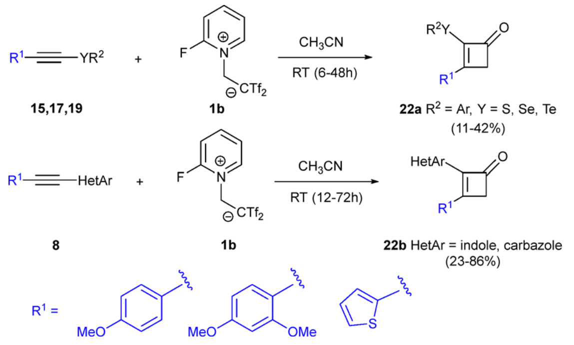
Moses and Smedley have reported an interesting addition to the zwitterion-based synthesis of cyclobutenes using compound **1c** as a source of ethene-1,1-disulfonyl difluoride (EDSF). Noteworthy, addition of sulfuric acid is needed to achieve full transformation. In these conditions, the reaction shows high efficiency in the presence of both terminal and disubstituted alkynes, and despite the presence of strong mineral acid, good group tolerance was observed (Scheme 7a).[32] In a later work, alkynes **12**, **14** and **18** bearing heteroatom-based substituents such as S or Te were also nicely transformed into the corresponding cyclobutene scaffolds **13-F**, **15-F** and **19-F** (Scheme 7b).[33] Taking advantage of the presence of SO_2F groups in final cyclic structures, sulfur-fluoride exchange reactions (SuFEx) were examined. Thus, reaction of cyclobutenes **4-F** with phenols under mild basic conditions provided substituted cyclobutenes **4-OAr** in good yields (Scheme 7c).[32,33]

2.2. Synthetic applications of bis(triflyl)cyclobutenes

The previous examples prove the versatility and efficiency of the zwitterion-based synthesis of bis(triflyl)cyclobutenes employing betaine **1b** and a wide range of alkynes. Besides the inherent reactivity of the highly strained cyclobutene system, with the



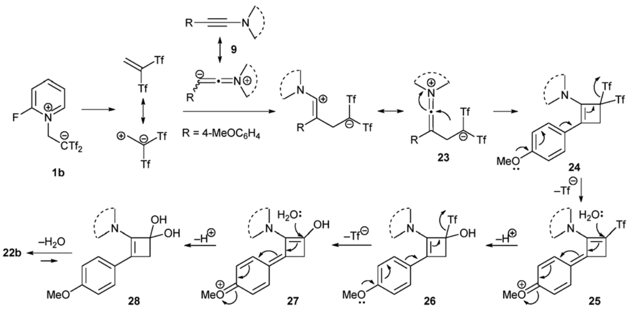
Scheme 7 Synthesis of bis(SO_2F)cyclobutenes and SuFEx transformations.



Scheme 8 Synthesis of cyclobutenones.

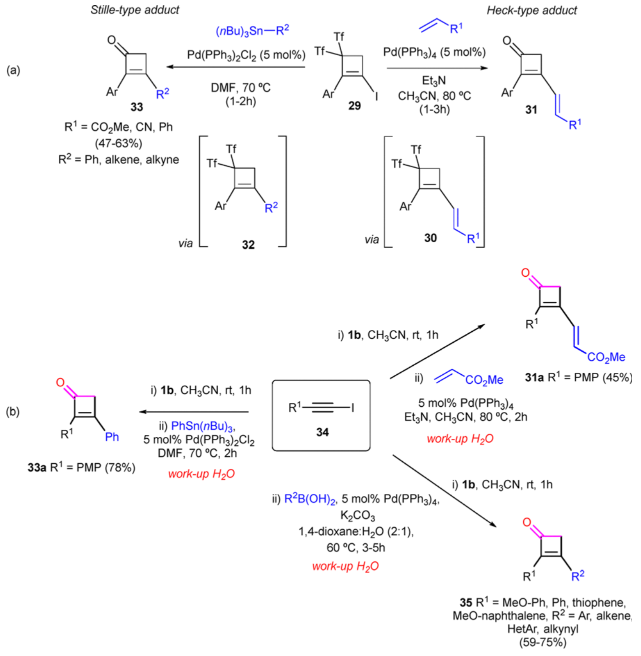
presence of a bis(triflyl) group embedded in the cyclic core, interesting chemical transformations are enabled. When the alkyne moiety is specifically activated by anisole groups (or electronically related motifs) on one side, and chalcogen- or ynamide-containing substrates on the opposite terminus, an unexpected reaction occurs under the standard conditions. Thus, reaction of alkynes **15**, **17** or **19** with zwitterion **1b** yielded cyclobutenones **22** instead of the formerly observed bis(triflyl)cyclobutenes. The formation of cyclobutenones appears to be spontaneous, but it can be facilitated by the addition of water and base during work-up (Scheme 8).[30] A plausible reaction mechanism for the formation of cyclobutenones **22b**, would involve two primary processes: the bis(triflyl)cyclobutene ring construction and an eventual hydrolysis. The proposal for the first process, builds upon previous DFT studies, with the regioselectivity now governed by the electronic effects of the heterocyclic amine, providing cyclobutenes **24** from the ring closing reaction of zwitterionic intermediates **23**. Regarding the hydrolysis process, the presence of adventitious water in the reaction medium is essential for the double trifluoro(hydrosulfonyl)methane elimination, yielding hydrates **28**. This two-fold water addition is facilitated by the resonance effect of the 4-methoxy substituent in the intermediates **25** and **27**. Dehydration eventually occurs in adducts **28**, leading to the formation of cyclobutenones **22b** (Scheme 9).[30]

Also envisioned is the use of palladium catalysis to promote both the C–C bond formation and the subsequent ketone formation by addition of water. While iodocyclobutenes **29** exhibited limited reactivity under Negishi conditions; Heck and Stille reactions proceeded effectively, leading to cyclobutenones **31** and **33** from the non-isolated bis(triflyl)cyclobutenes **30** and **32**, respectively (Scheme 10a).[34] Interestingly, the one-pot version of the Heck an Stille-type reactions was succesfully developed, starting from iodoalkynes **34** and betaine **1b**. The formal [2+2] cycloaddition toward the synthesis of the cyclobutene core tollerates the presence of the palladium salts, leading to the expected ketones **31a** and **33a** (Scheme 10b). Suzuki conditions were also examined in the cross-coupling reaction of *in situ*-generated bis(triflyl)iodocyclobutenes through a one-pot procedure. This approach allowed the direct synthesis of different functionalized 2,3-disubstituted-cyclobut-2-en-1-ones **35** in good yields from iodoalkynes **34** (Scheme 10b).[34]

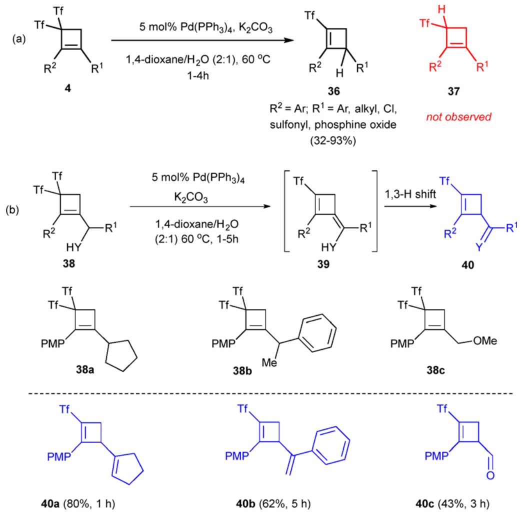


Scheme 9 Mechanism proposal for the formation of cyclobutenones **22b**.

As stated, the zwitterion-alkyne methodology stands out as an efficient and straightforward tool to build bis(triflyl)-cyclobutenes. Inspired by the classic Tsuji–Trost reaction, it was envisioned that metal-catalyzed tandem process to access mono(triflyl)cyclobutenes, would lead to a wider range of synthetic applications of Yanai's betaine. Thus, the combination of 5 mol% Pd$(PPh_3)_4$ and K_2CO_3, in 1,4-dioxane facilitated the smooth conversion of bis(triflyl)cyclobutenes **4** into (triflyl)cyclobutenes **36** (Scheme 11a). This transformation exhibited tolerance towards aryl groups with diverse electronic properties, as well as heteroaryl moieties such as indole, carbazole, and indazole. Moreover, heteroatomic substituents such as chlorine, sulfone, and phosphine oxide were effectively accommodated. Notably, the allylic substitution reaction displayed complete regioselectivity, as evidenced by the absence of isomeric products **37**. Furthermore, the palladium-catalyzed hydrodetriflylation reaction of bis(triflyl)cyclobutenes **38** bearing alkyl substituents led to the formation of



Scheme 10 Pd-catalyzed synthesis of cyclobutenones from alkynes, step-wise and one pot methodologies.



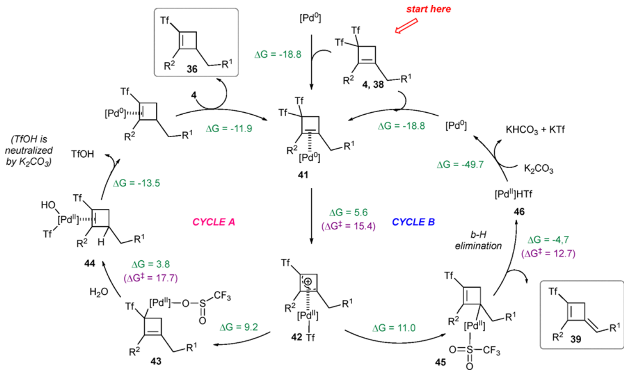
Scheme 11 Triflyl-assisted metal-catalyzed transformations.

(triflyl)cyclobutenes **40**, featuring an additional alkene functionality. This transformation resulted in the generation of 1,4-dienes **40a,b** and cyclobutenal **40c** through the evolution of 1,3-dienes **39** *via* a 1,3-H shift (Scheme 11b). Deuterium-labelling experiments and DFT calculations were conducted to elucidate the hydrodetriflylation process.[35]

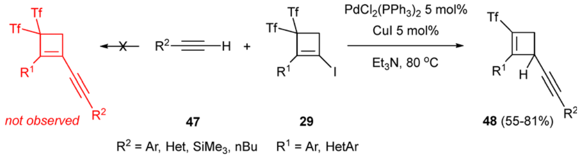
The reaction mechanism would initially start with the coordination of the Pd(0) species to the alkene moiety of bis(triflyl)cyclobutenes **4** or **38** through an exergonic process, yielding intermediate **41**. Subsequent oxidative addition would lead to the formation of π-allyl Pd(II) complex **42** with a moderate activation energy. Notably, the formation of two different σ-allyl Pd(II) complexes, **43** and **45**, from **42** could be feasible. The energetics suggested an equilibrium between those species in solution. Further investigations revealed distinct reaction pathways from each σ-allyl Pd(II) complex. Starting from **43**, water-assisted protodemetallation to yield **44** was nearly thermoneutral, facilitated by a moderately low activation energy. In contrast, β-hydride elimination from **45** to form product **39** and palladium hydride **46** was found to be exergonic with moderately low activation energy. Interestingly, water coordination along the reaction pathways would contribute to stabilize the transition states, suggesting that the calculated activation energies may represent upper limits. Additionally, an overall assessment of the reductive elimination step assisted by K_2CO_3 would indicate highly favourable energetics. Based on these findings, cycle B involving β-hydrogen elimination was identified as the preferred reaction pathway due to its lower energy barrier compared to alternative cycle A. Cycle A was postulated for (triflyl)cyclobutenes **36** where β-hydride elimination was unattainable (Scheme 12).[35]

Halocyclobutenes **29** and terminal alkynes **47** were reacted with a Pd–Cu bimetallic system under Sonogashira conditions, leading to adducts **48** through a tandem reaction involving a hydride addition with loss of triflyl group (Scheme 13).[36]

Two plausible mechanisms for the Pd-catalyzed alkynylation reaction were proposed, with experimental and computational data favouring path b (through iodopalladium intermediate **52**) over the path a (through triflylpalladium complex **50**). Further investigations using isotopic labelling experiments provided insights into the reaction mechanism, highlighting the involvement of water in the process (Scheme 14).[36]



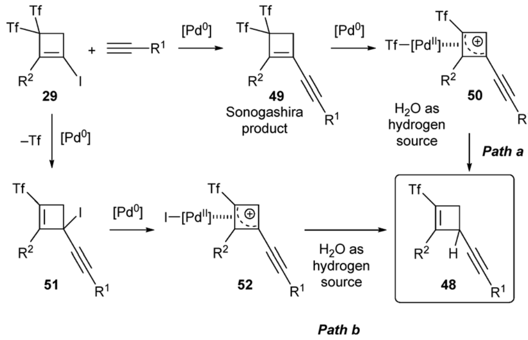
Scheme 12 Suggested catalytic reaction pathway for triflyl-assisted transformations.



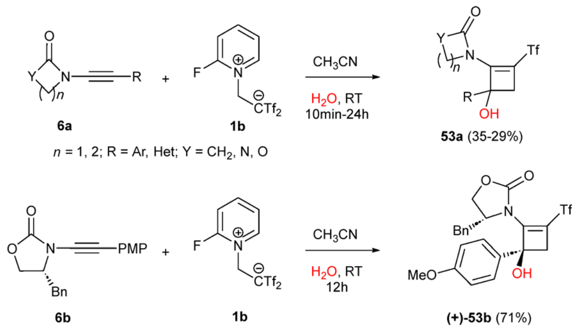
Scheme 13 Palladium-catalyzed reactions of bis(triflyl)iodocyclobutenes with terminal alkynes.

A metal-free approach to the mono(triflyl)cyclobutene skeleton was found using highly activated alkynes and zwitterion **1b** in the presence of water as nucleophile. Under those conditions, mono(triflyl)-decorated cyclobutenols have been described through a one-pot strategy. For instance, the reaction of ynamides **6a** with **1b** yielded cyclobutenols **53a** through a cyclization/hydroxylation sequence. The transformation was extended to ynamides bearing heterocycles, such as furan, thiophene, and indole, with moderately electron-rich rings showing better performance. Interestingly, enantiopure chiral ynamides **6b**, despite their steric hindrance, afforded aminocyclobutenols **53b** with full retention of chirality and good yields. Those results showcase the significant impact of the electronic properties of the starting alkyne and the versatility of the zwitterion-based cyclization methodology. Moreover, they reveal an interesting tolerance of Yanai's zwitterion to the presence of equimolecular quantities of water (Scheme 15).[29]

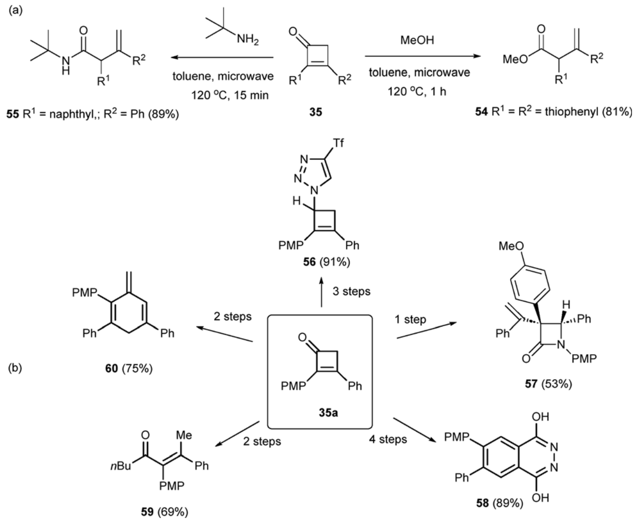
The cyclobutanone motif has emerged as a fruitful building block, giving rise to a variety of structures through different reactions. Cyclobutenones **35** were submitted to thermal ring-opening conditions in the presence of trapping reagents such as alcohols or amines. Thus, β,γ-unsaturated ester **54** and amide **55** were respectively obtained in very good yields and full regioselectivity (Scheme 16a).[34] Noteworthy, cyclobutenone **35a** has been submitted to a wide range of chemical



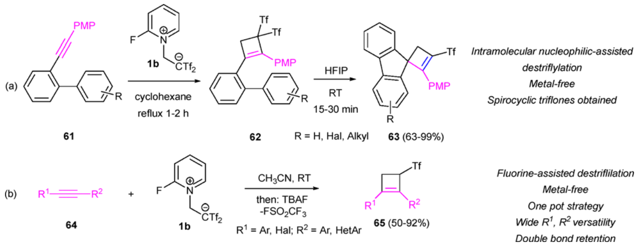
Scheme 14 Possible reaction pathways for the reaction of iodocyclobutenes with alkynes.



Scheme 15 Synthesis of 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols.



Scheme 16 Synthetic transformations of cyclobutenones.

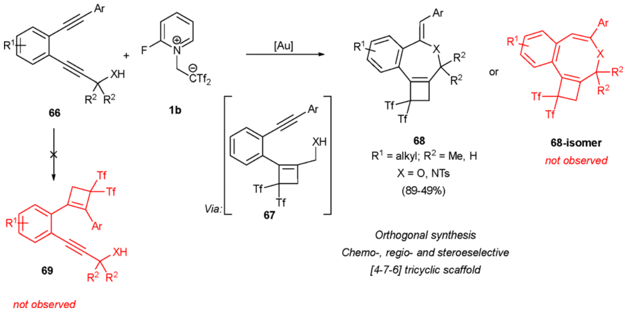


Scheme 17 Metal-free desulfonylation of bis(triflyl)cyclobutenes.

transformations. For instance, a three-step route led to triazole-decorated cyclobutene **56**, or β-lactam derivative **57** in one single reaction step. Also, phtalazine 1,4-diol **58** was obtained through after a four-step sequence. The chemical versatility of cyclobutenones **35** was illustrated with the preparation of conjugated ketones **59** or cyclohexa-2,5-dien-1-one **60** (Scheme 16b).[34]

In a recent work, Yanai's research group has presented a desulfonylation methodology of bis(triflyl)cyclobutenes promoted by HFIP and nucleophiles, leading to mono-(triflyl)cyclobutene systems.[37] Opposite to the examples shown above, Yanai's contribution allows the destriflylation step in the absence of metal species or external nucleophiles and under very mild conditions. Activated arenes are needed to promote the destriflylation reaction. Thus, starting from biaryl-alkynes **61** and 2-fluoropyridinium salt **1b**, gem-bis(triflyl)cyclobutenes **62** were obtained in yields from 87 to 96%. Subsequent desulfinative spirocyclization step mediated by HFIP allowed the preparation of spirocyclic compounds **63** (Scheme 17a). In a parallel approach, our group has reported an alternative metal-free synthesis of mono(triflyl)cyclobutenes using Yanai's salt as a synthon for $CF_3SO_2CH{=}CH_2$. Treatment of differently substituted alkynes with zwitterion **1b** under standard conditions, followed by TBAF-assisted hydrodesulfonylation allows the preparation of compounds **65** with good to excellent yields. This innovation permits the synthesis of mono(triflones) instead of the usual bis(triflyl) derivatives using a one-pot strategy, tolerant to a wide number of substituents and functionalities. Interestingly, whereas all other methods to access monotriflones from bis(triflyl)cyclobutenes involve double-bond migration leading to the conjugated triflyl motif, no isomerization was observed in adducts **65** using the TBAF-assisted methodology (Scheme 17b).[38]

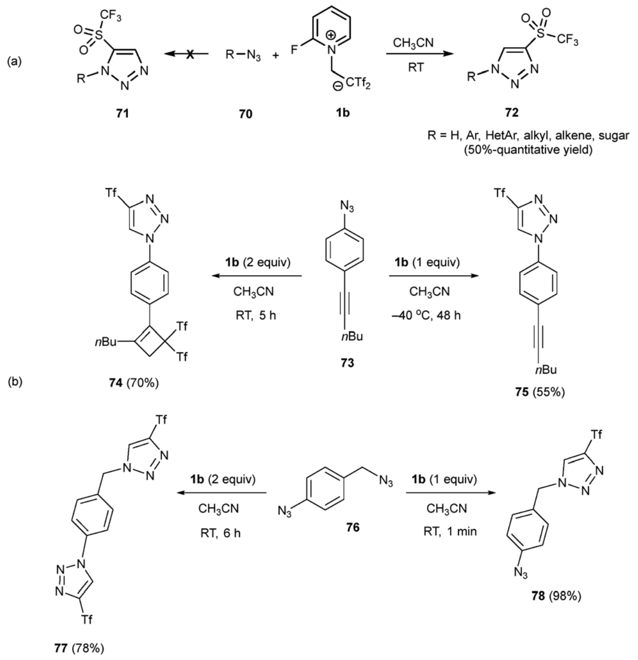
In a recent collaboration, Yanai and Almendros have described an interesting application of the bis(triflyl)-cyclobutene system towards the direct synthesis of fused [4-7-6] tricycles **68**. Readily accessible bisalkynes **66** were treated with betaine **1b** yielding monocyclobutenes **67** exhibiting complete chemo- and regioselectivity. The presence of a nucleophile in molecules **67** allowed a further 7-*exo-dig* heterocyclization reaction catalyzed by gold salts, leading to tricycles **68** as sole reaction products and in a complete stereoselective manner. The regioselectivity in the cyclobutene formation step is influenced by the aryl substituent on the lower alkyne moiety. This substituent stabilizes the carbocation formed during the attack of the alkyne on the highly polar olefin $Tf_2C{=}CH_2$, leading to the exclusive formation of cyclobutenes **67** rather than their regioisomer **69**. Importantly, the transformation allows the one pot methodology, revealing an orthogonal [2+2] formal cycloaddition/Au-catalyzed heterocyclization reaction. The compatibility observed between gold metal catalysts and betaine **1b** constitutes a promising precedent for future transformations (Scheme 18).[39]



Scheme 18 Synthesis of fused [4-7-6] tricycles through a tandem [2+2] cyclization/gold-catalyzed 7-*exo-dig* heteroannulation.

3. Synthesis of five and six-membered rings

Five- and six-membered cyclic and heterocyclic scaffolds are crucial in bioactive compounds, functional dyes, and advanced materials. Enhancing their molecular functions often involves adding new functionalities, with fluorine-containing groups particularly valued for their unique physicochemical and pharmacological properties.[40–42] Efficient organic synthesis aims to transform readily available precursors into target molecules with minimal steps, and waste. In order to explore the reaction of zwitterion **1b** with organic azides to access C-triflyl 1,2,3-triazoles *via* a mild metal-free protocol, differently substituted azides **70** were submitted to diverse reaction conditions to avoid undesired side reactions (Scheme 19a).[43] Solvent optimization was critical due to the insolubility of zwitterion **1b** in several solvents, leading to heterogeneous conditions. Acetonitrile was found to be the optimal solvent, yielding the desired C-triflyl triazoles **72** in excellent yields and at room temperature.



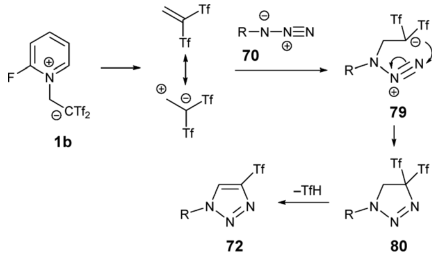
Scheme 19 Synthesis of C-triflyl 1,2,3-triazoles.

This method also showed high efficiency on a large scale, producing **72** in similar yields.

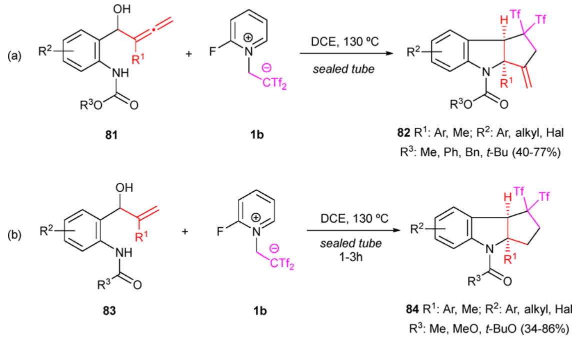
An interesting chemoselectivity was revealed regarding the reactivity of alkynyl azide **73**. Under optimized reaction conditions, cyclobutenyl triazole **74** was obtained from alkynyl azide **73** with good yields as sole reaction product when two equivalents of **1b** were employed. Nevertheless, performing the reaction at a lower temperature (−40 °C) and controlling the addition of zwitterion **1b** exclusively produced alkynyl triazole **75**, showing the higher reactivity of azides *versus* alkynes. On the other hand, the selective monofunctionalization of diazide **76**, containing both aromatic and aliphatic azide moieties, resulted in 4-triflyl triazole **78** using one equivalent of **1b**, while a two-fold reaction yielded bis(triazole) **77**. The mildness of the protocol allowed for chemocontrol and differentiation in the reactivity of the alkyl azide (faster reaction) *versus* the aryl azide in **76**. This method effectively resolved chemoselectivity issues that are typically challenging with traditional methods (Scheme 19b).[43]

The formation of 4-trifluoromethanesulfonyl 1,2,3-triazoles **72** from **1b** and organic azides **70** would likely involves the initial generation of 1,1-bis(trifluoromethylsulfonyl)ethene from zwitterion **1b**. This is followed by a stepwise [3+2] cycloaddition between azides **70** and the *in situ* generated dipole, forming the zwitterionic species **79**. Intermediate **79** would then undergo ring-closure reaction to produce the cycle **80**. This intermediate rapidly eliminates trifluoro(hydrosulfonyl)methane, yielding the final 4-triflyl 1,2,3-triazoles **72**, driven by the gain in aromaticity associated with triazole formation (Scheme 20).[43]

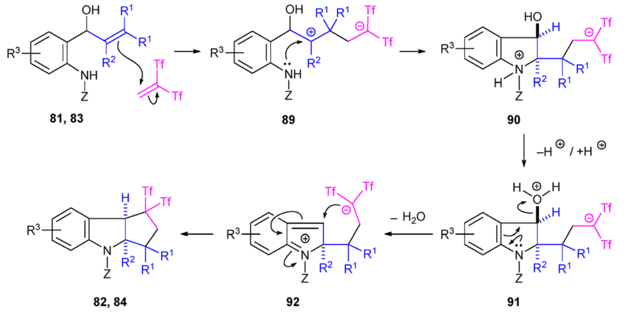
The enhanced reactivity of the allene system compared to the alkyne moiety normally leads to complex reaction mixtures upon exposure of allenes to Yanai's zwitterion **1b**. Nevertheless, some examples have been reported when the starting material is carefully designed under the appropriate reaction conditions. Thus, starting with aniline-tethered allenols **81** and zwitterion **1b**, indolines **82** have been prepared exhibiting moderate to good yields. The methodology tolerated both aromatic and aliphatic substituents at the allene moiety, and diverse functional groups were well accommodated at the aromatic ring (Scheme 21a). Indeed, allenols **81** behave as activated alkenols, with only the inner double bond of the allene participating in the reaction. With this result in hand, the scope of the transformation was successfully extended to aniline-tethered alkenols **83**. When anilide **83** with an electronically unbiased



Scheme 20 Mechanism proposal for the formation of 4-trifluoromethanesulfonyl 1,2,3-triazoles.



Scheme 21 Synthesis of bis(triflyl)-decorated tricyclic indolines.



Scheme 23 Proposed mechanism for the formation of indolines.

allylic alcohol was exposed to the standard conditions, the desired indoline **84** was obtained, showing similar functional group tolerance and yields (Scheme 21b). The structures of compounds **84** were determined unambiguously by single-crystal X-ray diffraction analysis.[44] Tricyclic indolines were submitted to further synthetic transformations, showing the applicability of the protocol. For instance, nucleophilic addition of amines and thiols to **82a** occurred in one pot, yielding functionalized derivatives **85** and **86**. Interestingly, conjugate diene **87** also served as an excellent dienophile in the Diels–Alder reaction with 2,3-dimethylbuta-1,3-diene, forming **88** stereoselectively, a compound with the tetracyclic core of indole sesquiterpene polyveoline (Scheme 22).[44]

The formation of indolines **82** and **84** would start with the nucleophilic attack of the β-carbon from the alkenol (or allenol) moiety to the $Tf_2C{=}CH_2$ unit, forming a zwitterionic intermediate **89**. This intermediate could cyclize to generate **90**, which, after protonation and dehydration, is proposed to form the 2*H*-indol-1-ium intermediate **92**. **92** then would undergo an intramolecular ionic carbocyclization, resulting in gem-bis(triflyl)indolines **82** and **84**. The proposed reaction mechanism is supported by DFT simulations, showing a low activation barrier for key steps and explaining the selective formation of *cis*-fused tricyclic indolines (Scheme 23).[44]

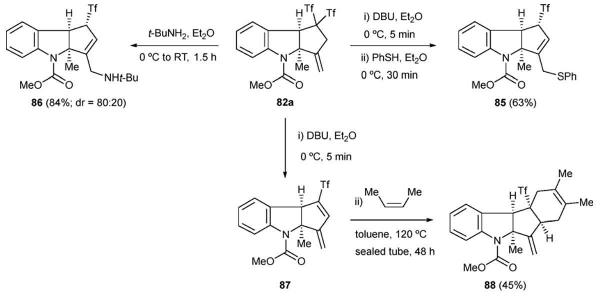
Interestingly, a divergent reactivity was observed for precursor **93** changing the substitution pattern of precursors, resulting in the formation of novel tetrahydroquinoline (THQ) structures **94** through a [4+2] reaction, instead of the indoline structure previously observed. Different substituents at both the amine and aromatic moieties were well tolerated, leading to compounds **94** with good to excellent yields in most cases. Also, diverse alkene substituents (R^2) were successfully accommodated (Scheme 24).[45]

Interestingly, allylic alcohols **95** and allenyl substrates **96** exhibited similar behaviour as **93**, yielding THQs **94** and **97** (Scheme 25a and b). However, tertiary allylic alcohol **98** significantly altered the reactivity, resulting in the exclusive formation of bis(triflyl)ethylated dihydroquinoline **99** (Scheme 25c).[45]

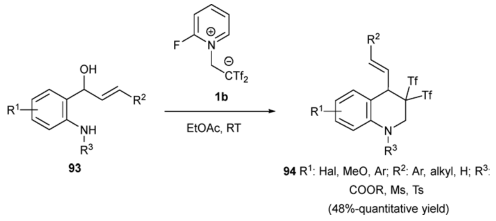
A possible pathway for the formation of bis(triflyl) tetrahydroquinolines **94** and **97** would start with the generation of aza-*ortho*-quinone methide intermediate **100** *via* a dehydration process catalyzed by bis((trifluoromethyl)sulfonyl)methane, which may be formed *in situ* from betaine **1b** in the presence of water. Subsequently, a zwitterionic intermediate **101** could be formed by the nucleophilic attack of the imine double bond in **100** to one molecule of $Tf_2C{=}CH_2$. Finally, ring process would lead to the formation of the experimentally observed THQs **94** and **97** (Scheme 26).[45]

The generation of six-membered rings using zwitterion **1b** has a smart precedent in a preliminary work from Yanai *et al.* Bis(triflyl)ethene obtained *in situ* from the dissociation in solution of betaine **1b** reacts effectively with differently substituted dienes through a [4+2] cycloaddition. Thus, bis(triflyl) cyclohexenes **102** can be prepared in good yields in a straightforward manner (Scheme 27).[3]

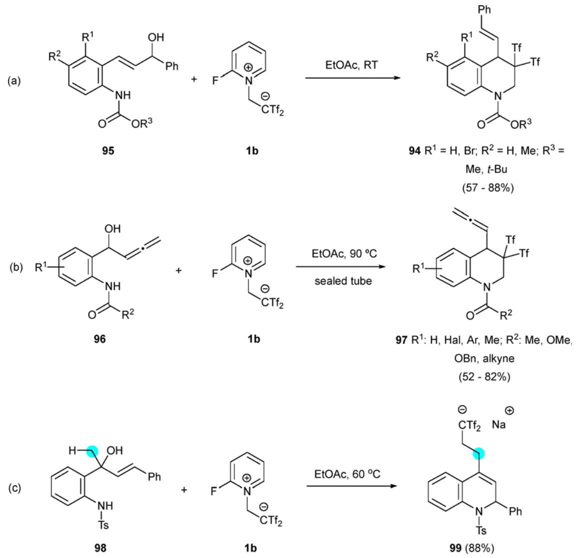
In a different approach, bis(triflyl)ethene has been employed as electrophile promoter in intramolecular carbocyclizations, leaving the bis(triflyl) moiety at an exocyclic position in the final structures. Thus, a straightforward synthesis of bis(triflyl)ethyl-linked carbazoles **104** has been described from easily available indolyl alkynols **103** under mild reaction conditions. Interestingly, the strong acidic nature of the proton



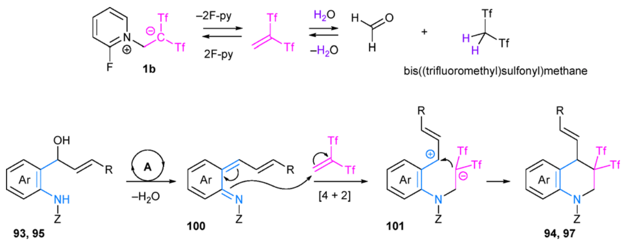
Scheme 22 Synthetic transformations of indolines.



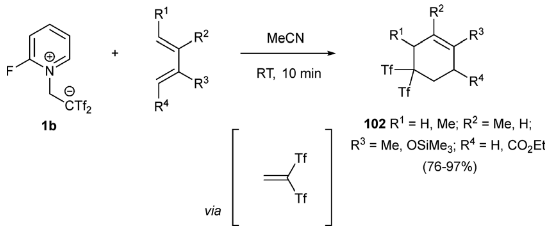
Scheme 24 Synthesis of tetrahydroquinolines.



Scheme 25 Synthesis of bis(triflyl)ated tetrahydroquinolines and dihydroquinolines.

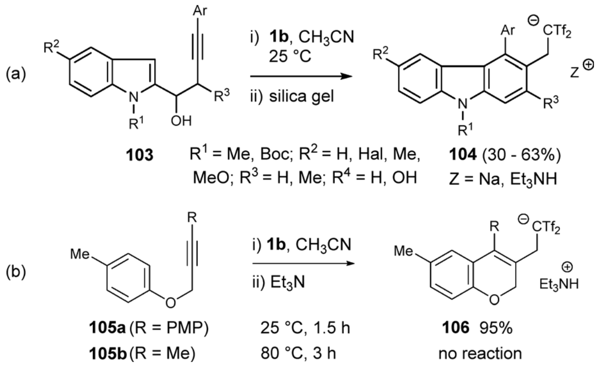


Scheme 26 Proposed reaction pathway for the formation of bis(triflyl) tetrahydroquinolines.



Scheme 27 [4+2] cycloaddition reaction of bis(triflyl)ethene and dienes.

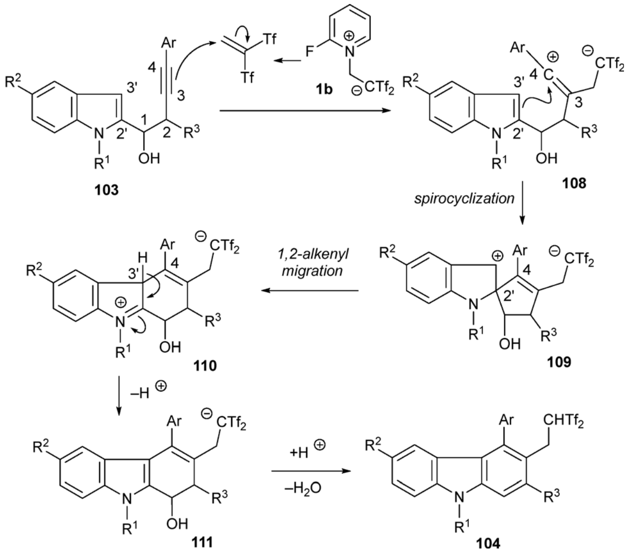
directly connected to both triflyl groups allows the isolation of carbazoles **104** as sodium or triethylammonium salts, depending on the conditions used during purification. The scope of the bis(triflyl)ethylation/benzannulation reaction was investigated, showing that substituents of different electronic nature and steric hindrance successfully yielded carbazole molecules **104** (Scheme 28a).[46] Different starting materials were investigated for alternative electrophile-mediated carbocyclization reactions, such as propargyl ether **105a**, leading to 2*H*-chromene **106** in 95% yield. However, dialkyl alkyne **105b** showed significantly lower reactivity, even under harsh reaction conditions (Scheme 28b).[46]



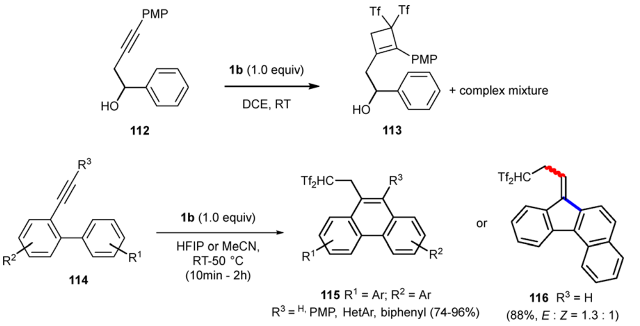
Scheme 28 Synthesis of bis(triflyl)ethylcarbazoles and related structures.

A plausible reaction pathway for the formation of carbazoles would start with the reaction of the alkyne moiety of **103** with $Tf_2C{=}CH_2$, resulting in the formation of the zwitterionic vinyl-type carbocation **108**. Then, a spirocyclization could take place yielding spirocyclic indolinium species **109**. Subsequently, fused tricyclic intermediate **110** is formed through 1,2-alkenyl migration within the spirocyclic nucleus of **109**. Further aromatization, involving deprotonation and dehydration of **111**, would lead to carbazoles **104** (Scheme 29).[46]

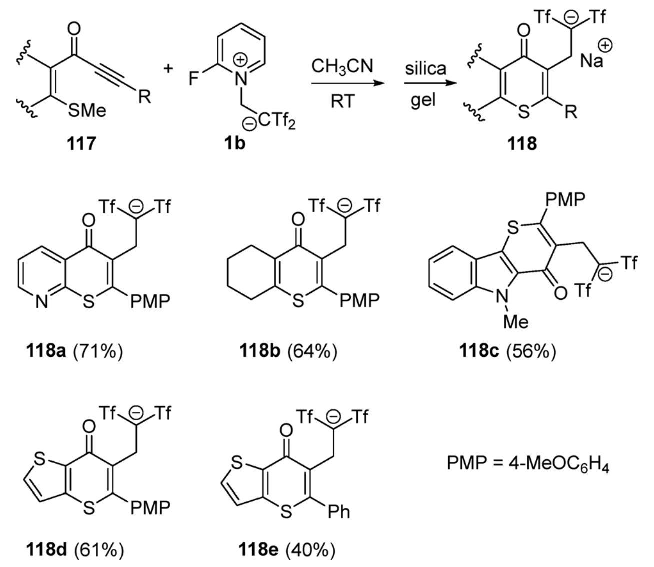
Among cyclic compounds, polycyclic aromatic hydrocarbons (PAHs), have unique photophysical and electronic properties.[47–51] Various syntheses for these compounds, including ring-closing reactions of biaryl-alkynes, have been explored. The bis(triflyl)ethene-mediated carbocyclization has also been extended to the formation of PAHs exhibiting two main advantages; milder reaction conditions with no metal catalysts needed, and the incorporation of bis(triflyl) units in the final compounds, providing good solubility in organic solvents. Despite having electronically neutral aromatic rings, substrates **112** led to cyclobutenes **113** in a complex reaction mixture.



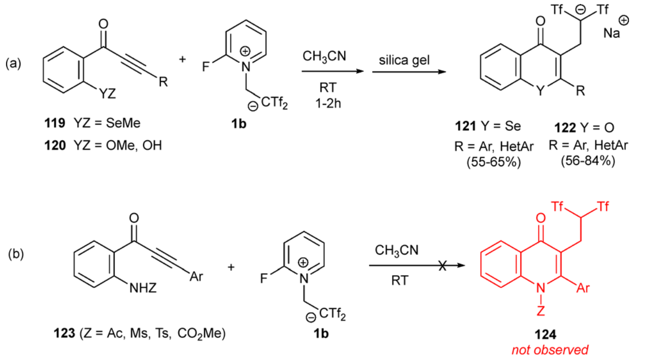
Scheme 29 Proposed reaction mechanism for the formation of carbazoles.



Scheme 30 Bis(triflyl)ethene-promoted synthesis of triflyl-decorated PAHs.



Scheme 31 Synthesis of bis(triflyl)thioflavones.



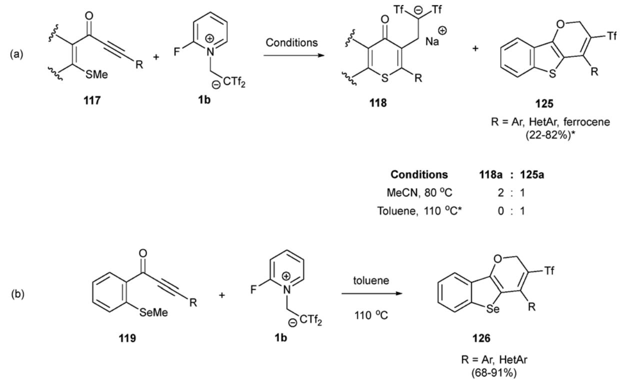
Scheme 32 Synthesis of bis(triflyl)flavones.

More activated systems such as compounds **114** effectively provided carbocycles **115** and **116**. Interestingly, polar solvents such as MeCN and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) improved selectivity towards the formation of bis(triflyl)-decorated PAHs, with HFIP providing best results, as it likely suppresses the carbanion nucleophilicity (Scheme 30).[52]

Bis(triflyl)ethene-mediated cyclization reactions employing zwitterion **1b** have also been described in heterocyclization tandem processes. Thus, 1-[2-(methylthio)phenyl]-3-phenylprop-2-yn-1-one **117** was treated with **1b** in acetonitrile at room temperature, obtaining bis(triflyl)thioflavone **118** as sole reaction product, with no evidence of cyclobutene formation or Friedel–Crafts-type bis(triflyl)alkylation adducts in the reaction mixture. This example constitutes a mild formation of a carbon–sulfur bond, present in many natural products and bioactive molecules. Additionally, the organofluorine substituent was incorporated in the same step under metal-free conditions *via* dual functionalization of the alkyne moiety. The scope of MeS-functionalized ynones **117** was examined to identify those susceptible to thioflavone generation. Various substituents at both the aromatic ring and the terminal alkyne were well tolerated, including heteroaromatic and ferrocene rings. Aliphatic and highly deactivating substituents at the alkyne terminus did not yield the corresponding thioflavones **118**, giving only complex reaction mixtures or unreacted starting materials (Scheme 31).[53]

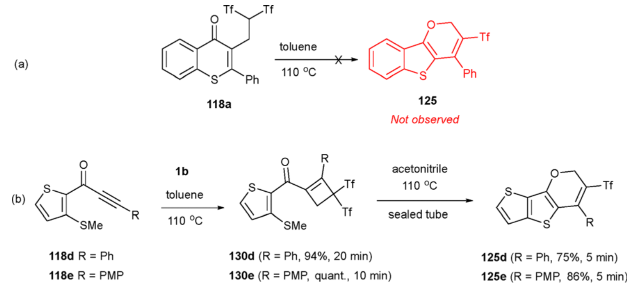
Given the rich chemistry and significant biological properties of organoselenium compounds, selenium-decorated alkynones **119** were also explored as suitable precursor of selenoflavones **121** in the presence of zwitterion **1b**. The expected heterocyclic structures **121** were obtained as sole reaction products, exhibiting complete chemo- and regioselectivity, in moderate yields (Scheme 32a).[53] The scope of heterocyclization reactions of alkynones with Yanai's reagent was extended to oxy- and aza-derivatives. Both (methoxy)-alkynones and (hydroxy)-alkynones **120** were found to be suitable cyclization precursors. The synthesis of bis(triflyl)flavones **122** was achieved with yields ranging from 56% to 84% (Scheme 32b). By contrast, compounds **123** containing amide functionalities were unreactive under the given conditions, failing to produce triflylated quinolin-4-ones **124** (Scheme 32b).[53]

The above-mentioned heteroatom-decorated alkynones exhibited an interesting dual behaviour in the presence of betaine **1b**. While room temperature experiments built the flavone skeleton through an electrophile-mediated heterocyclization, higher temperature experiments revealed a divergent reaction pattern towards unexpected structures. Thus, alkynone **117a** (R = Ph) in the presence of zwitterion **1b** in acetonitrile at 80 °C, yielded a mixture (2 : 1) of the already described bis(triflyl)thioflavone **118a** (R = Ph) and novel pyran system **125a** (R = Ph). Fortunately, adding zwitterion **1b** to a boiling solution of alkynone **117a** in toluene exclusively yielded tricycle **125a**, proving that simple changes in temperature and solvent can lead to the formation of distinct triflylated heterocyclic cores from a common precursor. Noteworthy, this domino process enables direct, metal-free access to a tricyclic framework, simultaneously forming C–S, C–O, and C–C bonds. Various MeS-alkynones **117** with different functional groups and tethers were subjected to cyclization, resulting in the selective formation of fused thieno[3,2-*b*]pyrans **125** with moderate to good yields (Scheme 33a). This transformation was successfully extended to selenyl-alkynones **119**, giving



117 **1b** **118** **125** **119** **1b** **126**

Scheme 33 Synthesis of tricyclic triflyl-benzothienopyrans.



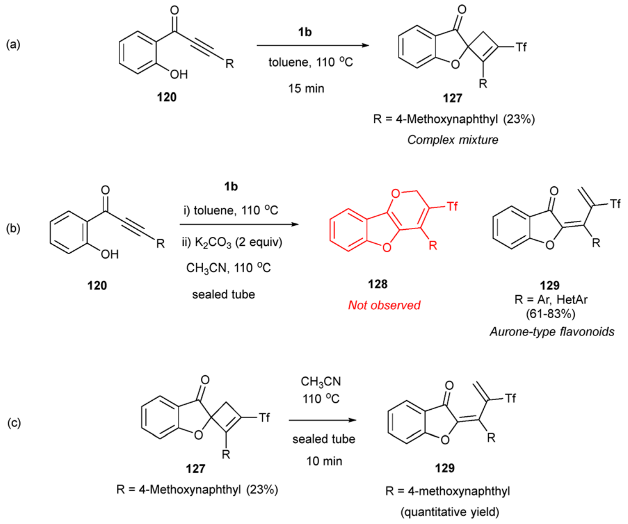
Scheme 35 Thermally-induced experiments towards a mechanistic proposal for the synthesis of tricyclic pyrans.

selenium-containing pyrans **126** with good to excellent yields (Scheme 33b).[53]

Interestingly, treating hydroxy-alkynones **120** with zwitterion **1b** in boiling toluene did not directly yield the expected tricycles due to the formation of several unstable products, with spirocyclic cyclobutenes **127** being the only isolated compounds in low yields (Scheme 34a). Nevertheless, hydroxy-alkynones **120** efficiently yielded (triflyl)vinyl aurone-type products **129** in the presence of a base, likely enhancing the nucleophilicity of the hydroxyl group (Scheme 34b). This unexpected result could tentatively be explained by considering bond lengths. The C–S and C–Se bonds are larger than the C–O bond, which may disfavor the final cyclization in this last case. An intriguing result was found when cyclobutene **127** bearing a 4-methoxynaphthyl substituent was heated in acetonitrile at 110 °C in a sealed tube, giving compound **129** in quantitative yields, and pointing to spirocyclic cyclobutene species as plausible reaction intermediates (Scheme 34c).[53]

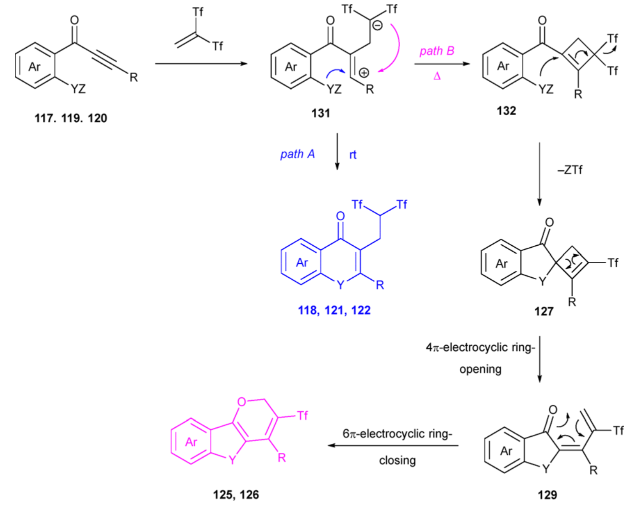
To understand the divergent formation of the tricyclic pyran skeleton *versus* bicyclic isoflavone molecules, we attempted the conversion of isoflavone **118a** into fused tricycle **125a** under thermal conditions. Nevertheless, heating a toluene solution of bicycle **118a** at 110 °C did not result in any reaction (Scheme 35a). Notwithstanding, when thioalkynones **118** were submitted to the thermal rearrangement during short reaction times, novel cyclobutenones **130** were observed instead. Interestingly, treating an acetonitrile solution of **130d** and **130e** in a sealed tube at 110 °C led to complete conversion to pyrans **125d** and **125e** (Scheme 35b). This suggests that cyclobutenes **130**, rather than bicycles **118**, are intermediates in the formation of fused pyrans **125**.

A plausible reaction mechanism which may explain those results would start with the nucleophilic attack of propynones **117**, **119** or **120** to one molecule of 1,1-bis((trifluoromethyl)sulfonyl)ethene, generating zwitterionic species **131**, which may evolve through two divergent reaction pathways. In one hand, selective intramolecular heterocyclization would form isoflavone bicycles **118**, **121** or **122** (path A). Alternatively, a different mechanistic pathway involving carbocyclization to generate cyclobutenes **132** may operate (path B). Subsequent regioselective nucleophilic addition with loss of Tf group could yield spirocyclic cyclobutenes **127**, which upon ring-opening would form dienone intermediates **129**. Finally, 6π-electrocyclic



120 **127** **120** **128** **129** **127** **129**

Scheme 34 Synthesis of triflyl-allylidenebenzofuranones and spirocyclic cyclobutene.



117, 119, 120 **131** **132** **118, 121, 122** **127** **125, 126** **129**

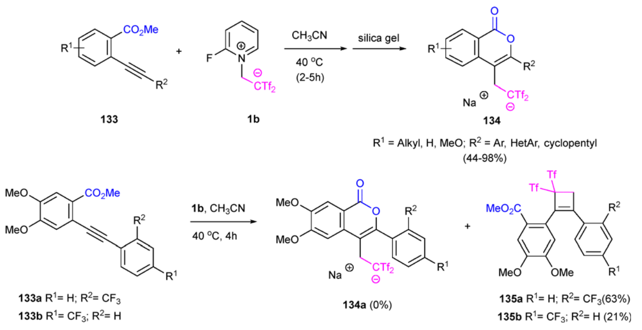
Scheme 36 Mechanistic proposal for the synthesis of the isoflavone and pyran skeletons from alkynones.

ring-closure produces tricyclic triflones **125** or **126** (Scheme 36).[53]

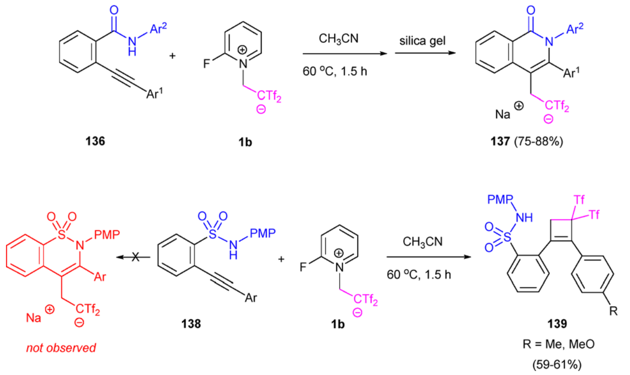
Flavone derivatives are known to be potent anticancer drugs.[54,55] Thus, structures **118, 121, 122** were tested as novel anticancer drugs. The inhibitory nature of the synthetic flavones and bioisosteric analogues against P-gp was confirmed. The rhodamine 123 accumulation assay showed a dose-dependent inhibition of P-gp by these compounds. Notably, some compounds (with R = 2-methoxynaphthalene) exhibited potent inhibitory activity, surpassing verapamil. These findings suggest that the flavone derivatives and bioisosteric analogues can be effective P-gp efflux pump inhibitors for MDR cancer treatment. Additionally, all tested compounds showed promising properties as adjuvants in cancer therapy due to their P-gp efflux pump-modulating activity.[56]

In view to the above-presented results, alkynyl esters **133** were envisioned as readily available precursors of the isocoumarin skeleton, a recurring organic motif with a wide range of biological applications, bearing an extra bis(triflyl) moiety. Thus, reaction of 2-ethynylbenzoates **133** with **1b** smoothly provided the expected heterocyclic compounds **134** with moderate to excellent yields, exhibiting complete chemo- and regioselectivity. Different substitution at the arene ring was examined, showing that electron-donating groups provided better yields under milder reaction conditions. Also, steric effects were minimal and only the 6-*endo-dig* oxycyclization occurred. Interestingly, substitution at the alkyne terminus showed more dramatic influence in the reaction outcome. While activating groups at R^2 position efficiently yielded the expected isocoumarins, electron-withdrawing groups, such as deactivated arenes, quenched the oxycyclization process, giving cyclobutenes **135** as sole reaction products (Scheme 37).[57]

Given the significance of nitrogen heterocycles in natural products and pharmaceuticals, related 2-ethynylbenzamides **136** and 2-ethynylbenzenesulfonamides **138** were examined as cyclization precursors. Benzamide-derived arylethylenes **136** successfully formed isoquinolin-1(2*H*)-ones **137** through a 6-*endo-dig* azacyclization/functionalization cascade. Notwithstanding, benzenesulfonamides **138** underwent intermolecular [2+2] cyclization, producing cyclobutenes **139**, presumably due to the lower nucleophilicity of the sulfonamide group. These results underscore the unpredictable yet highly selective reactivity between betaine **1b** and functionalized alkynes (Scheme 38).[57]



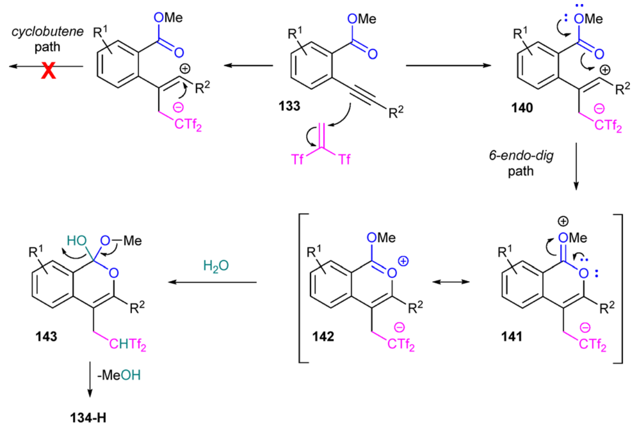
Scheme 37 Oxycyclization *versus* carbocyclization of alkynyl esters.



Scheme 38 Aza-cyclization *versus* carbocyclization of alkynyl amides.

A possible reaction mechanism would start with the nucleophilic attack of the alkyne moiety in compounds **133** to the highly polar olefin $Tf_2C{=}CH_2$, generating zwitterionic species **140.** Then, annulation across the carbonyl oxygen, facilitated by methoxy group conjugation, would yield intermediate **141**, stabilized by resonance with species **142.** Subsequent water addition at the carbonyl carbon could lead to species **143**, which may eventually evolve into 3,4-disubstituted isocoumarins **134-H** by releasing methanol. The regioselectivity towards the 6-*endo-dig* path is attributed to the preferential formation of intermediate **140**, with the positive charge closer to the more activating aromatic moiety R^2, supressing a plausible 5-*exo-dig* path (Scheme 39).

The biological potential of the isocoumarin family, particularly in neurological disorders, has been extensively studied.[58,59] Recently, 4-isochromanones with fluoroaryl groups have shown promising activity as Alzheimer's disease inhibitors by interacting with human acetylcholinesterase (hAChE).[60] It was hypothesized that compounds **134**, featuring flexible fluoroalkyl substituents, could serve as alternative hAChE inhibitors for docking studies. Molecular docking of compounds **134a** and **134b** revealed distinct binding modes



Scheme 39 Proposed reaction mechanism for the functionalization-oxycyclization reaction of alkynyl esters and Yanai's reagent.

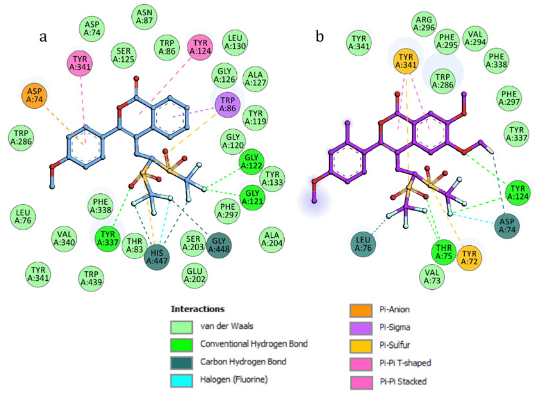
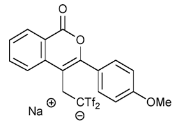
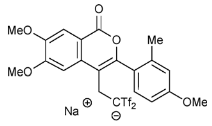


Fig. 1 Amino acids at the binding site of hAChE interact with ligand **134a** in mode I (a) and ligand **134b** (b).

within hAChE. In mode I, **134a** exhibited higher affinity for the catalytic active site (CAS) due to interactions with key amino acids, while in mode II, interaction with the peripheral anionic site (PAS) is preferred. Interestingly, the more sterically demanding **134b** adopted a conformation akin to **134a** in mode II, favoring PAS interaction over CAS. This suggests that less substituted compounds, like **134a**, may have better access to the active site (Fig. 1).[57]



134a

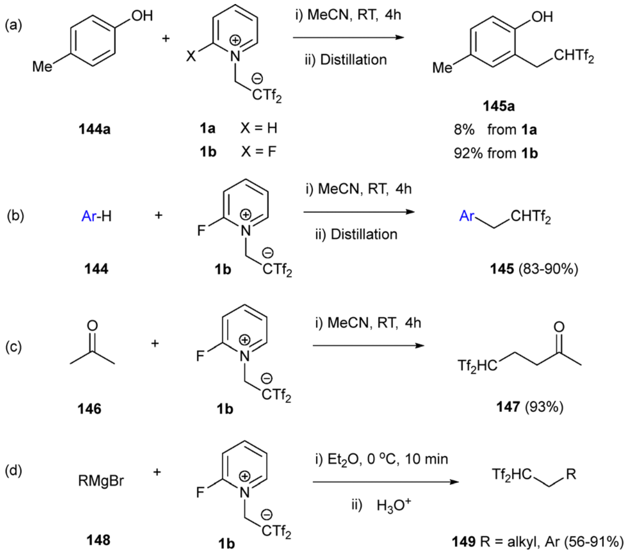


134b

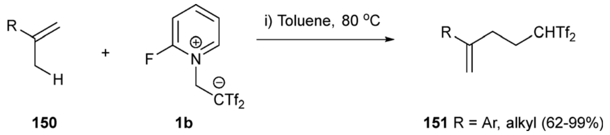
4. Non-cyclic products

The utility of zwitterion **1b** extends beyond the formation of cyclic products, as it enables the addition of the $Tf_2C{=}CH_2$ group to carbon- and heteroatom-based nucleophiles, providing access to diverse functionalization. In this context, Yanai's research group has invested great effort building the pillars of the zwitterion chemistry regarding alkyltriflylation procedures and ene reactions. Those transformations allow the synthesis of different molecular structures exhibiting the group $CHTf_2$, with a super acidic proton conferring interesting properties to final compounds. In a preliminary work, zwitterion **1b** was tested as an efficient trifluorosulfonyl-alkylating agent in the presence of *p*-cresol (**144a**) as nucleophile. A remarkable 92% yield was observed in final compound **145a**, compared to an 8% yield using X = H derivative **1a** (Scheme 40a).[61] This result encouraged the group to prepare a family of carbon acid structures from electronically activated arenes **144** (Scheme 40b), ketones **146** (Scheme 40c) or Grignard reagents **148** (Scheme 40d).[3]

The same group has reported the first example of a reaction between betaine **1b** and alkene systems **150**. Alkenes exhibiting hydrogen atoms at β-position proceed through an ene rearrangement in the presence of **1b** to yield carbon acid structures **151**. Both aromatic and aliphatic alkenes are suitable for this transformation, expanding the family of molecules showing the $CHTf_2$ group (Scheme 41).[62]



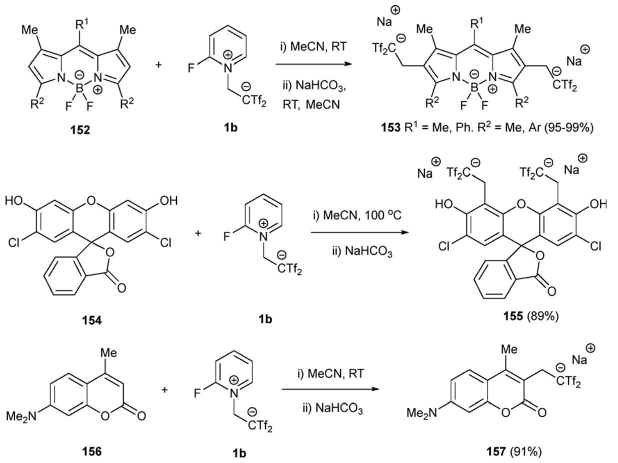
Scheme 40 Synthesis of carbon acids through nucleophilic addition reactions with zwitterion **1b**.



Scheme 41 Alkene-ene reaction with zwitterion **1b**.

The application of zwitterion chemistry towards the synthesis of carbon acids has recently expanded into polymer and materials science, where it has been employed in post-polymerization modifications to introduce bis(triflyl)methyl groups onto material surfaces, enabling the development of superacid-functionalized membranes with catalytic activity.[63] In a recent report, it has been presented an approach that utilizes a naked carbanion as counteranion in bis(trifyl)-based polybetaines and preliminarily unveiled their antifouling properties against human whole blood.[64] Boron-dipyrromethenes (BODIPYs) **152**, fluorescein **154** and aminocoumarin **156** have been successfully submitted to 2,2-bis(triflyl)ethylation reaction using betaine **1b** providing carbanionic dyes. Notably, compounds **153**, **155**, and **157** showed an unusual balance of high hydrophilicity and lipophilicity, while maintaining significant fluorescent activity (Scheme 42).[65] Moreover, Yanai and co-workers have developed structural variations of the reagent, such as 4-substituted 2-fluoropyridinium zwitterions, which not only allow efficient *in situ* generation of $Tf_2C{=}CH_2$ but also facilitate recovery of the fluoropyridine byproduct through multiple purification strategies, thus broadening its synthetic utility and operational practicality.[66]

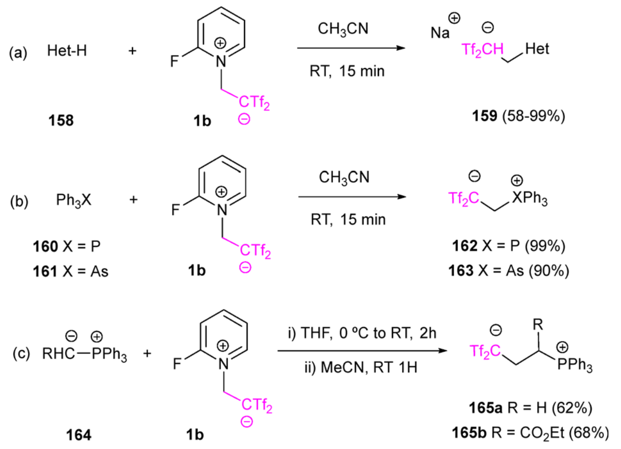
In the context of a collaboration between Yanai's and Almendros' research groups, different heterocyclic scaffolds **158** were selected to react with *in situ* generated bis(triflyl)-ethene olefin delivering bis(triflyl)-decorated molecules **159** with moderate to excellent yield and high selectivity



Scheme 42 Bis(triflyl)ethylation of organic dyes.

(Scheme 43a).[67] In a later contribution, triphenylphosphine and triphenylarsine have been studied as nucleophiles in the presence of zwitterion **1b**. Thus, treatment of **1b** with Ph_3P and Ph_3As yielded the heteroatom-alkylated betaines **162** and **163**, respectively, in excellent yields under mild conditions (Scheme 43b). In addition, reactions of salt **1b** with phosphorus ylides allowed the access to 1,4-carbabetaines. For instance, treatment of both unstabilized and substituted ylides **164** with fluoropiridinium salt **1b** afforded compounds **165a** and **165b** in good yields (Scheme 43c). Spectroscopic and computational analyses confirmed that these compounds exhibit pronounced carbabetaine character, opening pathways for their application in organocatalysis and beyond.[68]

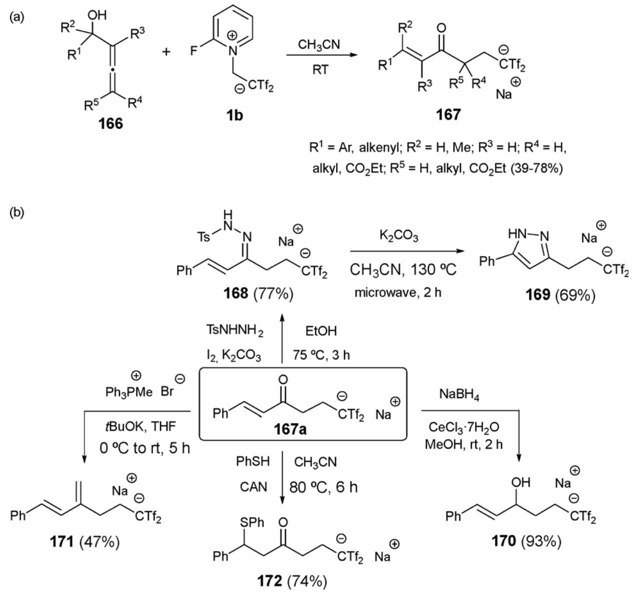
In a different transformation, the reaction of α-allenols **166** with reagent **1b** in acetonitrile at room temperature resulted in the unexpected formation of (*E*)-α,β-unsaturated ketones **167**, with no cyclization observed. This outcome likely arises from the electrophilic attack of $Tf_2C{=}CH_2$ on the terminal sp^2-hybridized carbon of the starting allene. Interestingly, the (*Z*)-isomer was detected as a minor isomer only in some cases. Due to the acidic nature of the hydrogen in the Tf_2CH group, products **167** were isolated as sodium salts after purification by column chromatography. The scope of the reaction was explored with differently substituted allenols at R^1 and R^2 positions. Allenols with both aromatic and aliphatic substituents were effectively converted into bis(triflyl)enones **167** in good yields. However, allenols tethered to heterocycles, such as indole and oxindole, yielded complex mixtures due to side reactions between the arene moiety and $Tf_2C{=}CH_2$. Remarkably, allenols with quaternary carbinolic centers also performed well, delivering stereoselective (*E*)-isomers of bis(triflyl)enones in most cases (Scheme 44a).[69]



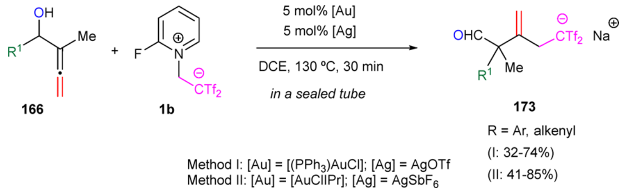
Scheme 43 Synthesis of 1,3- and 1,4-carbabetaines.

Functionalized enones **167**, containing versatile groups, provide an excellent platform for further derivatization. For example, α,β-unsaturated ketone **167a** was transformed into bis(triflyl)propyl-decorated pyrazole **169** *via* *N*-tosylhydrazone intermediate **168** in a two-step process. The chemoselective reduction of the carbonyl group in **167a** afforded bis(triflyl)allylic alcohol **170**, while Wittig olefination provided the bis(triflyl)ated 1,3-diene **171**. Additionally, a radical 1,4-addition of benzenethiol to enone **167a** produced thioether **172**, among other chemical transformations (Scheme 44b).[69]

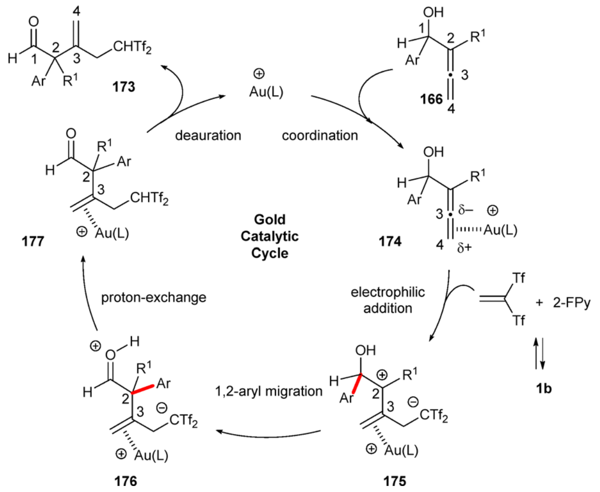
As previously noted, zwitterion **1a** and the *in situ* generated bis(triflyl)ethene exhibit chemical compatibility with gold salts, suggesting their potential in tandem transformations. Moreover, a separate transformation involving allenols **166**, betaine **1b**, and gold catalysts unveiled an unexpected reaction pathway, affording sterically encumbered β-methylene-δ,δ-bis(triflyl)pentanals **173**. Different allenols **166** exhibiting diverse substitution patterns were examined. Electron-donating groups like methoxy or methyl on the aromatic ring were well tolerated, as were halogens (Br and Cl). However, steric effects were evident, as *ortho*-substituted allenols showed slightly lower yields compared to its *meta*- and *para*-substituted counterparts. Additional studies with other electron-deficient



Scheme 44 Synthesis of bis(triflyl)-functionalized enones and synthetic transformations.



Scheme 45 Synthesis of bis(triflyl)enals.



Scheme 46 Proposed mechanism for the formation of β-methylene-δ,δ-bis(triflyl)pentanals.

alkenes, such as ethenesulfonyl fluoride and (ethene-1,1-diyldisulfonyl)dibenzene, resulted in messy reactions, highlighting the necessity of both Tf groups in betaines **1b** for successful reactivity (Scheme 45).[70]

The proposed mechanism for the formation of bis[(trifluoromethyl)sulfonyl]ethylated enals **173** from allenols **166** under gold catalysis is shown in Scheme 46. Initially, allenols form π-activated complexes **174** in the presence of gold salts. Addition of the proximal allenol double bond to the electrophile **1b** generates zwitterionic intermediates **175**, which undergo a 1,2-aryl migration to form species **176**. These intermediates would then experience deprotonation of the aldehyde moiety followed by protonation of the resulting carbanion, leading to neutral gold complexes **177**. The final products **173** are obtained after deaurative elimination, with regeneration of the gold catalyst. This pathway, where Au(I) acts as a π-Lewis base, involves an unusual allene activation, strongly supported by DFT calculations (Scheme 46).[70]

5. Conclusions

Pyridinium-based zwitterions **1** constitute a shelf-stable and efficient source of highly reactive bis(triflyl)ethene molecules. Beyond their industrial utility in polymer synthesis and the earliest theoretical studies, betaines **1** have increasingly featured in a wide range of synthetic applications. Specifically, 2-fluoropyridine derivative **1b** has shown the greatest efficiency promoting diverse reaction pathways from different starting materials.

Highly strained cyclobutenes are easily synthesize from readily available alkyne systems through a stepwise [2+2] cycloaddition. Opposite to recurring cyclobutene synthesis, the transformation proceeds in one reaction step, under mild conditions and in the absence of metal catalysts. Fluorine atoms have been incorporated not only into the design of new pharmaceuticals aimed at improving human health, but also into the construction of innovative molecular frameworks that broaden chemical space. In this context, the combination of strained carbocyclic motifs with fluorosulfonyl substituents constitutes an attractive approach for the diversification of biologically relevant scaffolds, which may provide access to unprecedented pharmacophores and distinctive privileged architectures.

Also, formal [3+2] cycloaddition between **1b** and azides allows the preparation of the triazole scaffold. Besides formal cycloadditions, Koshar-type zwitterions can promote intramolecular nucleophilic addition with incorporation of a bis(triflyl) unit. Thus, different molecular motifs, including flavones, isocoumarins, and pyrans, as well as open-chain systems, have been accessed. Remarkably, an intriguing chemo-, regio- and stereoselectivity is normally observed. In addition, first examples of orthogonal tandem reactions in the presence of metal catalysts reveal a promising chemical compatibility of zwitterion **1b** with metallic salts, giving light to complex reaction mechanisms.

Despite the significant advances described above, many chemical avenues remain largely unexplored. In contrast to the established alkyne chemistry, the application of various carbon-nucleophiles—such as allenes, allenamides, or activated alkenes—is currently understudied. The judicious design of these starting materials, along with the proper selection of substituents, will be crucial for achieving novel reaction outcomes and discovering new reaction mechanisms.

Furthermore, the initial reports of tandem methodologies employing gold catalysis point toward the development of sophisticated new transformations that combine metal catalysis, zwitterions **1**, and suitable substrates. Since concerted [2+2] processes are thermally forbidden, zwitterions **1** are known to undergo stepwise cycloaddition mechanisms. Therefore, the engagement of Koshar-type zwitterions in photochemical reactions would open a new, exciting avenue for methodologies proceeding through previously undescribed pathways.[71] It is also expected that flow synthesis integrated with informatics-driven optimization platforms can be employed in a near future to accelerate reaction development in the synthesis of *gem*-bis[(trifluoromethyl)sulfonyl] functionalized organic molecules.

Recent advances in synthetic methodologies have enabled the isolation of a broad range of fluorinated sulfonyl carbanion-containing salts, thereby allowing detailed investigations into their chemical bonding features and providing deeper insight into their stabilization modes and coordination properties. On the basis of these fundamental studies, stable bis(Tf)-based carbanions have progressively evolved from purely academic curiosities into versatile functional motifs with broad utility in molecular engineering and materials science. In the near future, these frameworks may emerge as valuable platforms not only for anionic species but also for radical-based systems. Although the currently reported examples have not yet exploited the (Tf_2C) fragment as a chiral scaffold or as a ligand framework for transition-metal coordination, continuous progress in synthetic methodologies is expected to considerably broaden its applicability as a modular substituent. The stability of organic compounds incorporating the (Tf_2C) moiety is highly dependent on the stereoelectronic characteristics of the neighboring substituents. Accordingly, expanding the structural diversity of stable bis(triflyl)-substituted organic compounds and elucidating their intrinsic properties through molecular-level theoretical studies remain highly desirable goals.

Moreover, the recent successful incorporation of the bis[(trifluoromethyl)sulfonyl]methyl unit into polymers through straightforward post-polymerization modification strategies, together with the preparation of polybetaines derived from (Tf_2C)-based carbanions, is expected to significantly broaden the scope of polymer chemistry and open new opportunities for advanced material applications involving polybetaines. Future developments may ultimately enable the preparation of organic membranes bearing strongly acidic carbon-centered functionalities, thus paving the way toward innovative applications, including ion-exchange membranes and highly efficient immobilized organocatalysts.

Finally, the reactions presented herein, combined with these promising perspectives, establish a solid pillar for zwitterion-based chemistry and anticipate the near future arrival of even more exciting results in this field.

Author contributions

Daniel Diez-Iriepa: visualization, investigation and writing – original draft, review; José Miguel Alonso: visualization, supervision, investigation and writing – original draft, review; and Pedro Almendros: conceptualization, supervision, writing – original draft, review.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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