# Dithioallyl cation (3+2) cycloadditions under aprotic reaction conditions: rapid access to spiro-fused cyclopentane scaffolds

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We report a general method to effect all-carbon (3+2) cycloadditions that can elaborate cyclopentenes from a range of olefins. The required dithio-allyl cation reagents can be generated in a newly developed mild protocol starting from 2-allyloxypyridine precursors, thus avoiding the use of strong Brønsted acids. The novel method significantly expands the substrate scope, which now also includes acid-sensitive olefins, and thus enables the preparation of previously inaccessible spiro-fused scaffold types from simple and readily available starting materials.

## Introduction

Cyclopentanoid scaffolds are common motifs in bioactive metabolites as well as in modern drug scaffolds (Fig. 1).[1] Compared to other small carbocycles (3-, 4- and 6-membered carbocycles), synthetic methods for their rapid and stereoselective assembly are still less well developed.[2] Often, cyclopentanoids are still elaborated via multistep routes from readily available cyclopentane building blocks. More modular methods can be found in the classical Pauson-Khand,[3] and Nazarov reactions.[4] These allow the assembly of a wide variety of substituted cyclopentanes starting from simpler building blocks, often with control of stereochemistry. One particularly attractive alternative option, reminiscent of the Diels-Alder reaction for cyclohexenes, is the synthesis of cyclopentenes from a (3+2)-type annulation between allyl cations and olefins.[5] This four-electron cyclization reaction is iso-electronic to the Nazarov reaction, but is not a pericyclic cycloaddition. It rather involves a stepwise carbocationic cycloaddition, consisting of two consecutive cation olefin additions.[6,7]

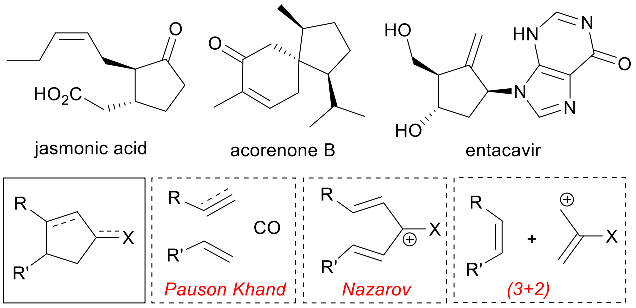
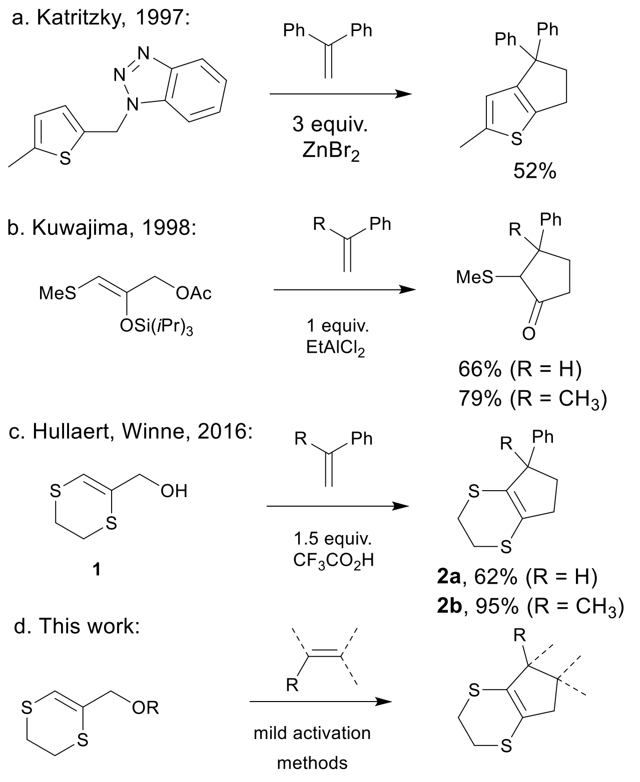


**Fig. 1** Substituted cyclopentanoid scaffolds in bioactive natural products and drugs with some common cyclopentane synthesis strategies.

Due to the stepwise nature of allyl cation (3+2) cycloadditions, control of the carbocationic reactivity can be hard to achieve, although good yields and good stereoselectivities for cyclopentane adducts can be obtained. This is especially the case when cation-stabilizing substituents are present in the olefin substrates and in the allylating reagents. Efficient reactions using stabilized (oxy)allyl cations and have been developed by Hoffman,[5e] Noyori,[8] Mayr,[9] and Wu.[10,5a] Seminal works by Katritzky,[11] Kuwajima,[12] and Harmata,[13] have shown



**Scheme 1** Modular synthesis of cyclopentanes using thio-substituted allyl cation (3+2) cycloadditions: see references 11, 12 and 14.

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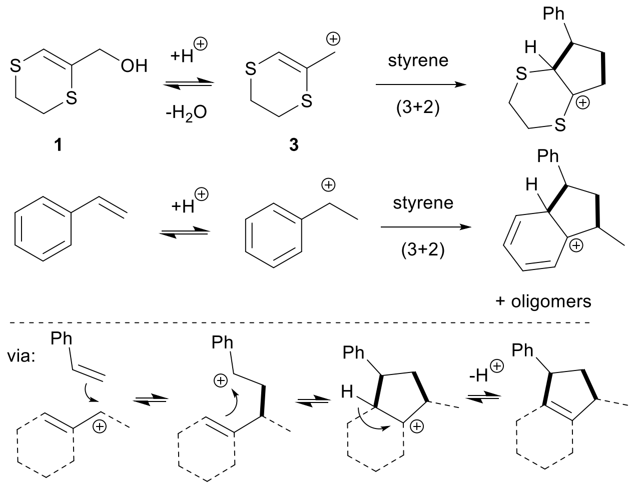
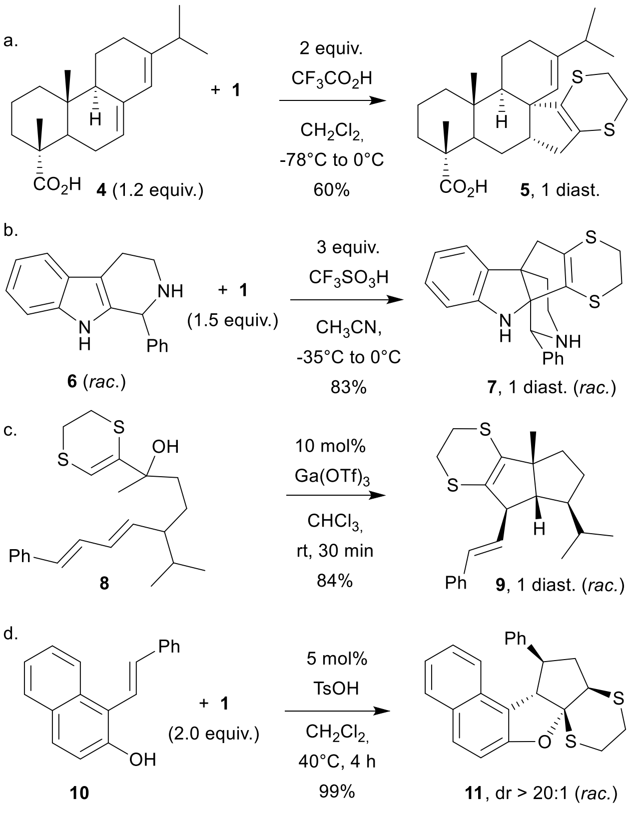
Electronic Supplementary Information (ESI) available: description of additional experiments, experimental procedures and characterization data for all compounds and copies of NMR spectra. See DOI: 10.1039/x0xx00000x that thio-substitution of allyl cations can also be an effective and complementary strategy to control the reactivity of allyl cation species (Scheme 1). Katritzky found that thiophenyl cations undergo an allylation/internal Friedel-Crafts sequence with highly activated olefins (Scheme 1a).[11a] Kuwajima found that oxyallyl cations showed a wider substrate scope in (3+2) cycloadditions when one of the termini was substituted by a thioether group (Scheme 1b).[12] In 2016, our group reported an allyl cation (3+2) cycloaddition in which the simple dithioallyl alcohol **1** serves as a versatile three-carbon synthon for cyclopentene assembly (Scheme 1c).[14] An attractive feature of this methodology is that the obtained cyclopentanoids like **2a** or **2b** can be chemoselectively transformed into a cyclopentene, via hydrodesulfurization.[15] Thus, the dithioallyl alcohol serves as a synthetic equivalent of a 'naked' allyl cation, opening up attractive options in synthesis.

One of the obvious limitations of the methodology using dithioallylalcohol **1** is that the generation of the allyl cation species requires an excess of a strong Brønsted acid, and that the reaction mechanism involves several equilibrating carbocationic species (Scheme 2). Most activated olefin substrates, like styrenes, are also prone to undergo protonation to form a stabilized carbocation, which can in turn lead to cationic polymerizations, or to the classical (3+2) cyclic styrene dimer formation.[16] Good allyl cation reagents must thus show a balanced reactivity: they should not undergo a reaction with their own precursor olefin, and they should be more electrophilic towards olefins compared to the carbocations derived from those olefins. The dithioallyl cation **3** meets those criteria for a wide range of conjugated olefin substrates, and as a result shows a wide substrate scope in (3+2) cycloadditions. An example of a borderline substrate here is styrene itself (Scheme 1c). Styrene actually very swiftly oligomerizes under cation-generating conditions, and the fact that the cyclopentannulated product **2a** is observed as the major product here is an indication of the efficiency of the stepwise cycloadditions of allyl cation **3** from dithioallyl alcohol **1**. The alpha-methylstyrene substrate affords the adduct **2b** without such side reactions, as its derived tertiairy benzyl cation is much less electrophilic.



**Scheme 2** Mechanistic outline for allyl cation (3+2) cycloadditions.

In our original report of the reactivity of dithioallyl alcohol **1**, we found that the use of an excess of a strong Brønsted acid consistently gave the best results with the widest range of olefins, including *s-trans*-locked dienes like abietic acid **4** (Scheme 3).[14a] In some cases, such as for indoles like **6**, we found that an excess of triflic acid is the most effective procedure to achieve a cyclopentannulation with allyl alcohol **1** (Scheme 3b).[17] This is related to the need for a swift generation of the allyl cation **3**, in the absence of basic or nucleophilic counter ions that can give a premature bimolecular quench of the equilibrating carbocationic species along the stepwise (3+2) cycloaddition (cf Scheme 2). Employing weaker acids, or mild Lewis acids at higher temperatures generally leads to side product formation, related to such undesired carbocation quenching events. An exception was found for intramolecular reactions, where a catalytic amount of a mild Lewis acid can also give an efficient (3+2) cycloaddition, such as in the bicyclization of the alkene-functionalized dithioallyl alcohol **8** to the diquinane **9** (Scheme 3c).[15b] Recently, He and Han reported an efficient (3+2) cycloaddition using dithio allyl alcohol **1** for the cyclopentannulation of styryl-naphthol substrates like **10** (Scheme 3d).[18] These specific substrates are indeed expected to be less prone to olefin ologimerization reactions, given their steric bulk, while they are also highly nucleophilic. These milder, catalytic procedures unfortunately do not give a good result for more generic intermolecular (3+2) olefin annulations, as they give low conversions and complex reaction mixtures.

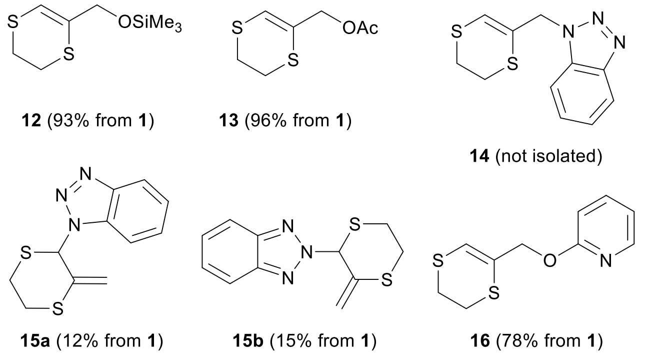


**Scheme 3** Previous results with dithioallyl alcohols (3+2) cycloadditions and the different reaction conditions: a) see ref 14a; b) see ref 17; c) see ref 15b; d) see ref 18.

In this article, we report our efforts to expand the (3+2) cycloadditions of dithioallyl cation **3**, to include substrates that are prone to undergo acid-promoted side reactions.

## Results and discussion

A clear drawback of employing a large excess of a Brønsted acid for the generation of dithioallyl cation **3** from the alcohol **1** (cf Schemes 1c, 2a and 2b), is that many olefins are prone to undergo acid-promoted side reactions under those conditions. Olefin substrates can become protonated themselves and thus engage in alternative electrophilic addition pathways. One obvious way to improve the substrate scope would therefore be to search for reaction conditions that can generate the allyl cation **3** very efficiently, without the use of a strong acid. In addition to the dithioallyl alcohol **1**, we thus decided to investigate some more activated precursors for allyl cation **3** (Fig. 4). Unfortunately, all attempts to transform the hydroxyl function in allyl alcohol **1** into a classical leaving group failed, as these activated derivatives either degraded or strongly resisted isolation in pure form. We thus turned to mildly activated derivatives, such as the silyl ether **12** or the acetate **13**, which could be obtained in good yield from dithioallyl alcohol **1** (Figure 2, also see ESI). Inspired by Katritzky's Friedel-Crafts-type cyclopent-annulation of thiophenes (cf Scheme 1a), we wanted to prepare the benzotriazole derivative **14**. Surprisingly, Mitsunobu reaction of dithioallyl alcohol **1** with benzotriazole as a protonucleophile did not afford the expected N-allylated triazole **14**. Instead, an $S_N2'$-type substitution occurred, wherein a mixture of two regioisomeric allyl triazoles **15a** and **15b** were obtained. These could be separated and isolated in low yield. As both of these compounds can still act as precursors of dithioallyl cation **3**, we decided to explore their utility in synthesis. Finally, the dithioallyl 2-pyridyl ether **16** was obtained from **1** by treatment with sodium hydride and 2-chloro-pyridine (see ESI). We anticipated that the pyridyl ether would act as a leaving group that can be activated by milder Brønsted or Lewis acids.

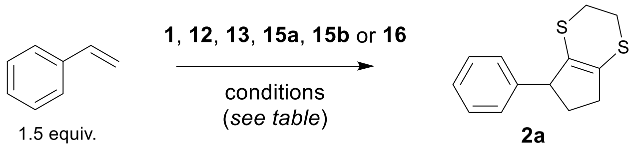


**12** (93% from **1**) **13** (96% from **1**) **14** (not isolated)

**15a** (12% from **1**) **15b** (15% from **1**) **16** (78% from **1**)

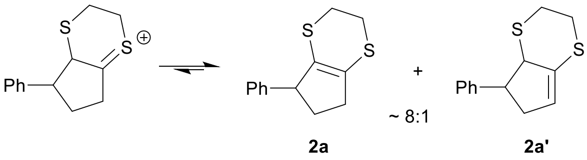
**Fig. 2** Activated derivatives of dithioallyl alcohol **1**.

We selected styrene as a simple test substrate to identify suitable aprotic reaction conditions, as this olefin was known to to react with 3 in low yield due to bimolecular quenching and proton-initiated oligomerization reactions (cf Scheme 1c). A tabular overview of our observations is given in Scheme 4 (also see ESI).



| entry | reagent | solvent | (Lewis) acid | temp. | **2a** (isol.) |
|---|---|---|---|---|---|
| 1. | **1** | $CH_2Cl_2$ | $CF_3CO_2H^a$ | -78°C - rt | 62% |
| 2. | **1** | $CH_2Cl_2$ | $Ga(OTf)_3^b$ | rt | 21% |
| 3. | **1** | $CH_2Cl_2$ | $ZnBr_2^c$ | rt | 24% |
| 4. | **12** | $CH_2Cl_2$ | $Ga(OTf)_3^b$ | rt | 33% |
| 5. | **13** | $CH_2Cl_2$ | $ZnBr_2^c$ | rt | 51% |
| 6. | **15a** | $CH_2Cl_2$ | $ZnBr_2^c$ | rt | 26% |
| 7. | **15b** | $CH_2Cl_2$ | $ZnBr_2^c$ | rt | 36% |
| 8. | **16** | $CH_2Cl_2$ | $ZnBr_2^c$ | rt | **96%** |
| 9. | **16** | HFIP | - | rt | **69%**[d] |

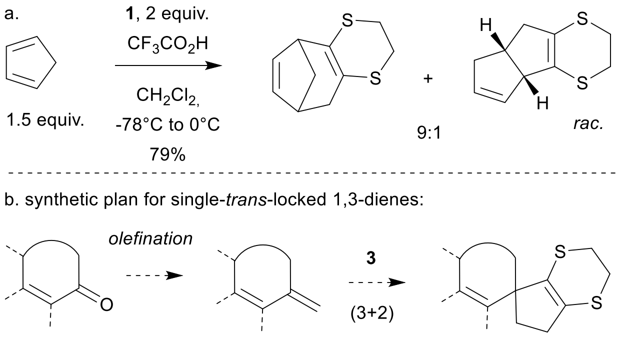
a. 2.0 equiv. of trifluoroacetic acid was used, b. 0.2 equiv. of gallium(III)triflate was used, c. 2.5 equiv. of zinc(II) bromide was used, d. for this reaction, the compound **2a** was initially co-isolated with its regioisomer **2a'**.



**Scheme 4** Screening of different reagents and reaction conditions for the cyclopentannulation of styrene with dithioallyl cation **3**. In all entries 3 equiv. of (Lewis) acid are used, except for $Ga(OTf)_3$, in which case 0.1 equiv. were used.

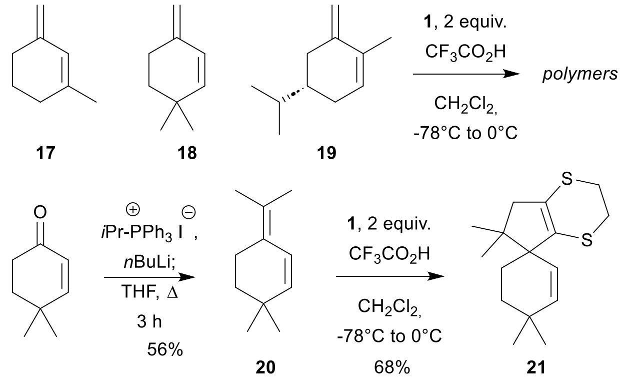
Lewis acids in combination with dithioallyl alcohol **1** generally gave poor results for the cyclopentannulation of styrene as this gave complex mixtures. The most promising reactions were those with gallium(III)triflate and zinc(II)bromide,[14,15] but these still gave low isolated yields for the expected adduct **2a** compared to the reference experiment with trifluoroacetic acid (Scheme 4, entries 1-3). The combination of the silyl ether **12** with gallium(III)triflate gave a relatively clean reaction,[15a] but the isolated yield was again low (entry 4). The allyl acetate reagent **13** gave a reasonable yield using mild $ZnBr_2$, and a relatively clean reaction mixture, but no improvement in isolated yield was obtained compared to our standard protic conditions (entry 5). Benzotriazole reagents **15a** and **15b**, inspired by Katritzky's Friedel-Crafts-type cyclopentannulation (cf. Scheme 1a) did also not give better results in terms of isolated yield (entries 6-7). A remarkable improvement was seen, however, when the 2-pyridyl ether **16** was employed. Using three equivalents of zinc(II)bromide gave a very clean conversion to the expected cyclopentene **2a**, isolated in excellent yield (entry 8). As pyridyl ethers can be activated by mild Brønsted acids, we also performed a trial with 2-pyridyl ether **16** in hexafluoroisopropanol (HFIP), a solvent which has often been investigated in the field of carbocation chemistry.[19] This gave a relatively clean reaction and also a reasonable isolated yield (entry 9). However, the reaction mixture seemed to be less clean here at first, as two positional isomers of the alkene **2a** were formed. These isomers could not be separated, but upon standing in deuteroform, the minor isomer **2a'** spontaneously and completely transformed into the more usually observed isomer **2a**. It is therefore likely that these positional alkene isomers are in fact formed in all investigated reactions, but that under sufficiently protic conditions an isomerization happens, as the alkenylsulfide ether **2a'** can be readily reprotonated and rearrange to the more conjugated isomer.

Dithioallyl cation (3+2) cycloadditions have a wide substrate scope, but unactivated simple alkenes do not give synthetically useful reactions. The intermediate carbocations (cf Scheme 2) are too reactive and do not cleanly cyclize into cyclopentanes, but rather engage in multiple cationic pathways, resulting in mixtures of allylated products, with only minor amounts of cyclized products.[14a,12] The substrate scope is thus limited to activated olefins such as styrenes and conjugated dienes, as these show a more controlled carbocationic reactivity. For conjugated dienes, the substrate scope is still limited, because the dithioallyl cation **3** can also undergo a competitive (4+3) cycloaddition with such olefins (Scheme 5),[20] which is actually favored as a possible concerted cycloadditions according to Woodward-Hoffman orbital symmetry arguments (six electron transition state). The substrate scope is thus limited to 1,3-dienes that are locked into a *single-trans* conformation, as is the case for substrate **4** (Scheme 3a). Conjugated dienes that are locked into a single-*trans* conformation seem to make up a quite narrow substrate class, compared to styrenes, but one particularly attractive synthetic possibility is offered by the simple synthetic strategy outlined in Scheme 5. Cyclic α,β-unsaturated ketones (e.g. cyclohexenones) are very common motifs in natural products and in synthetic building blocks and intermediates. Their olefination rapidly affords access to a by necessity *s-trans*-locked 1,3-diene. These substrates should be amenable to a (3+2) cycloaddition with allyl cation **3**, affording a spiro-fused cyclopentene. For methylenated cyclic enones, the cationic addition should show a predictable selectivity for the exocyclic alkene bond, and thus give a rapid access to interesting spirocarbocyclic scaffolds.[21,22]



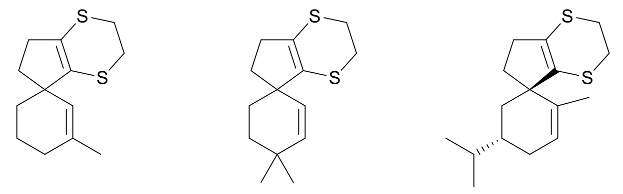
**Scheme 5** a. competitive (4+3) cycloadditions with conjugated dienes (see ref. 14a); b. synthetic strategy to rapidly access a wide variety of s-trans locked dienes that will exclusively afford cyclopentene adducts.

Our initial investigations of the two-step reaction scheme to elaborate spiro-fused cyclopentanes onto a cyclic enone (cf Scheme 5) were in fact highly unpromising (Scheme 6). None of the simple methylenated products **17**, **18** or **19** gave even a trace amount of the expected spirocycles under our standard reaction conditions. Instead, the major product in each of these cases were polymers. Treatment of a mixture of the diene and dithioallyl alcohol **1** with trifluoroacetic acid resulted in the very rapid consumption of the diene. It seems that the carbocations that result from the protonation of these dienes are rapidly formed and are also highly electrophilic towards other dienes. This rationale is confirmed by the fact that more substituted olefins did provide the expected cyloadducts, albeit mostly as complex reaction mixtures. Apart from regioselectivity issues, there was also evidence that under the applied protic conditions, the alkene bonds migrate into an endocyclic position, giving (4+3) cycloaddition products (cf Scheme 5a). A proof-of-principle synthesis of a spirocyclic scaffold was finally afforded by the very specific substrate **20** derived from 4,4-dimethyl cyclohex-2-enone (Scheme 6, bottom). Here, alkene bond migration is unfavorable, and the quaternary center also sterically encumbers the endocyclic terminus of the diene, directing the addition to the exocyclic bond against the expected electronic preferences in this case. However, no general method for the synthesis of such interesting spiro-fused scaffolds could be established using our previously developed method.



**Scheme 6** Competitive (4+3) cycloadditions with conjugated dienes and and synthetic strategy to rapidly access a wide variety of s-trans locked dienes that will exclusively afford cyclopentene adducts.

We revisited the issue of spiro-annulation of cyclic enones once the mild and aprotic conditions to generate dithioallyl cation **3** were established (cf. Scheme 4). To our delight, all the olefins **17**, **18** and **19** afforded the expected spirocyclic adducts **22**, **23** and **24** after treatment with dithioallyl 2-pyridyl ether **16** and zinc(II)bromide in a mixture of acetonitrile and dichloromethane (Figure 3). The spirocycle **24** was even obtained as one main diastereoisomer.



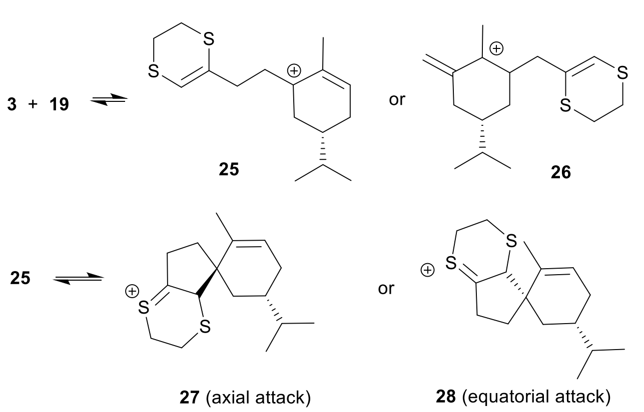
**22** (68% from **16** and **17**)

**23** (52% from **16** and **18**)

**24**, dr 95:5 (58% from **16** and **19**)

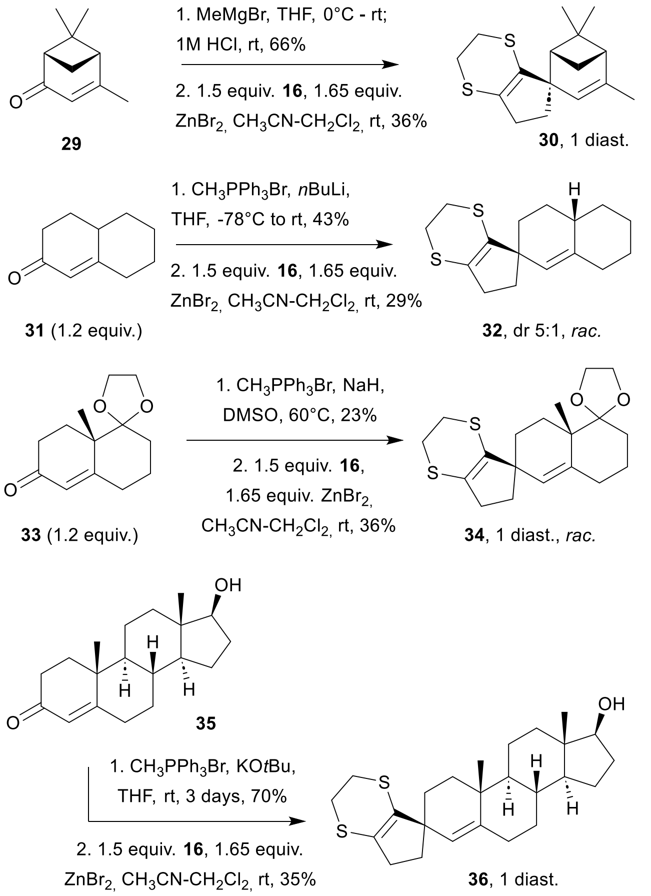
**Fig. 3** Spirocarbocyclic scaffolds obtained using 'aprotic' (3+2) dithioallyl cation cycloaddition. *Reaction conditions:* 1.5 equiv. of pyridyl ether **16**, 1.0 equiv. of diene **17**, **18** or **19**, acetonitrile and dichloromethane solvent mixture, 1.65 equiv. of zinc(II)bromide, room temperature.

Although the spirocycles shown in Figure 3 were the only isolated products derived from our s-*trans*-dienes **17**-**19**, the yield in our initial trials (3 equiv. of $ZnBr_2$ in dichloromethane) was not very reproducible, varying between 10-50%. Using substrate **17**, various reaction parameters were screened (see ESI). Acetonitrile gave the most consistent results, and also slightly higher isolated yields when a bit of dichloromethane was used as cosolvent. Using excess dithioallyl alcohol gave better results (1.5 equiv.) compared to using an excess of the diene. Stoichiometric amounts of zinc(II)bromide were essential for the success of the reaction, with 1.65 equiv. (a slight excess compared to the pyridyl ether) proved to be optimal. Thus, the substrates **22**-**24** were obtained in reasonable and reproducible yields (50-65%). The spirocycle **24** derived from methylenated dihydrocarvone **19** was obtained as one main diastereomer (dr 95:5), and no regioisomers coming from the (3+2) cycloaddition to the endocyclic alkene bond were observed in any of these cases. The regio- and stereoselectivity for the synthesis of spirocycle **24** was confirmed via analysis of 2D NMR spectra and aligns well with expectations based on a stepwise cationic cyclization pathway (Scheme 7). The cation olefin cyclization pathway should favour the formation of the more substituted allyl cation **25** over the regioisomeric **26**. Furthermore, based on stereo-electronic arguments, ring closure of the dithioalkene onto the cyclohexyl carbocation in intermediate **25** is likely to happen in an axial fashion, *i.e.* a *trans* orientation with respect to the anchoring isopropyl group.



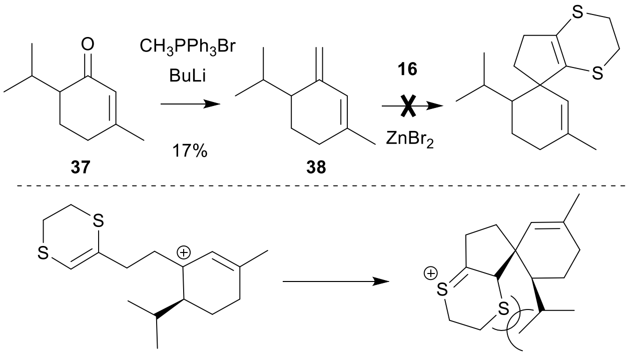
**Scheme 7** Mechanistic outline for allyl cation (3+2) cycloadditions.

We also investigated some more elaborate polycyclic enone substrates. The synthesis of the *exo*-methylidene cyclohexenes from enones **29**, **31**, **33** and **35** all followed literature procedures (Scheme 8), but did not proceed without problems. Isolation of the dienes required considerable care, as all of these dienes quite quickly degraded, compared to previously made substrates. Chromatography had to be conducted over basic alumina. These problems could in part be attributed to swift alkene isomerization reactions leading to endocyclic diene isomers. This indicated that these substrates are particularly sensitive to carbocationic isomerization and other side reactions. Nevertheless, all of the spiro-cyclopentannulated compounds **30**, **32**, **34** and **36** could be obtained in good to excellent regio- and stereoselectivity in acceptable yields using the previously established reaction conditions without modification. The stereochemical identity of the resulting spirocycles could not be unambiguously confirmed in these cases, but a tentatve assignment was made based on analogy with the stereoselectivity seen for the related substrate **24**, where an assignment was possible based on analysis of 2D NMR correlations.



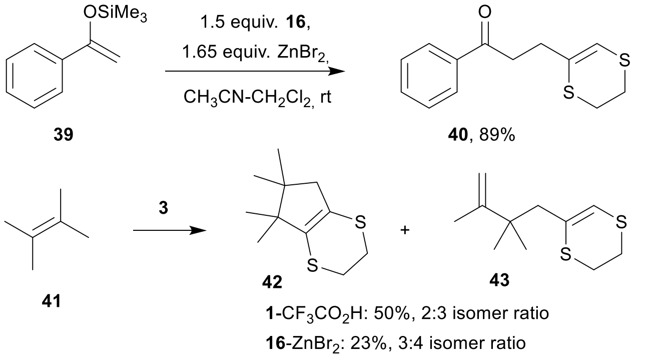
**Scheme 8** Application of the spiro-cyclopentannulation sequence to more elaborate cyclic enone substrates. The stereochemical assignment of the main observed diastereomer could not be made on the basis of NMR analysis, but is tentatively assigned in accordance with that observed for **24**. Compound **34** showed some minor impurities which could not be assigned to a diastereomer.

A substrate that defied our newly developed cyclopentannulation sequence was piperetone **37**. Problems already arose in the olefination, as the diene **38** proved quite sensitive. We surmized that this substrate can quite readily undergo a spontaneous and likely irreversible isomerization of the exocyclic disubstituted alkene into an endocyclic, tetrasubstituted alkene. Moreover, the isopropyl group here likely hinders the preferentially axial attack from the normally preferred ring side, as this ring side is hindered by the equatorially oriented *iso*propyl group.



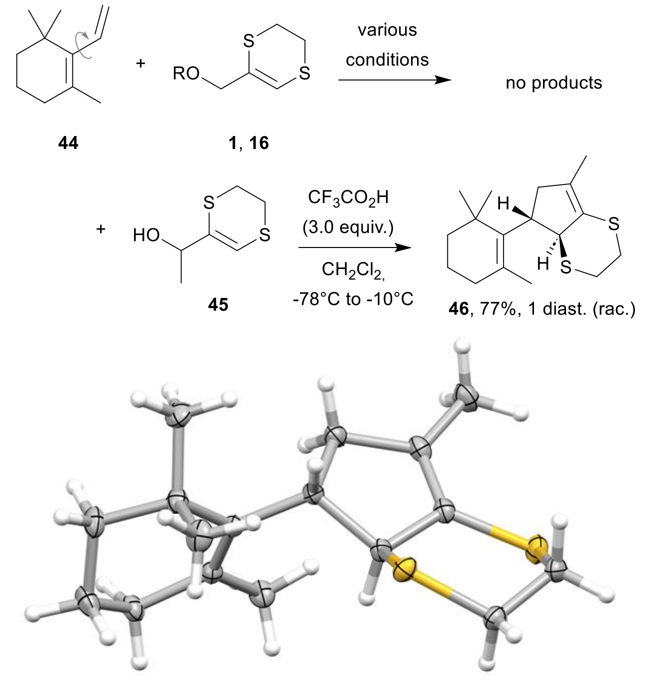
**Scheme 9** Mechanistic outline for allyl cation (3+2) cycloadditions.

Not all resonance activated olefins are applicable to the dithioallyl cation (3+2) cycloaddition (Scheme 10).[14a] Enol ethers such as **39** evidently get protonated and hydrolyzed under protic reaction conditions (TFA) and thus do not engage the allyl cation **3** at all. Using the improved aprotic zinc(II)bromide promoted method with pyridyl ether **16**, the major reaction product was actually the α-allylated ketone **40**, which was cleanly obtained in good yield. The additional resonance of the silyl ether oxygen is likely slowing down the cyclization step (cf Scheme 2). Premature elimination and hydrolysis upon work-up then yields the ketone **40**. The required resonance activation of olefins can thus seemingly also prevent the cyclopentannulation if the olefin is 'too activated'. At the other side of the spectrum we find isolated olefins, which usually do not engage dithioallyl cations, giving low conversions and also mixtures of cyclized and non-cyclized adducts.[14a] A good example is 2,3-dimethylbutene **41**, which gives the most reactive isolated alkene using our standard protic conditions, giving the two isomers **42** and **43**. As expected, our milder Lewis acid promoted conditions with pyridyl ether **16** gave an even lower conversion of olefin **41**, although the isomer ratio here was slightly skewed towards the cyclized product **42**.



**Scheme 10** Reactions of more and less activated olefin substrates with dithio allyl cations, and XRD structure of **46**.

In the context of olefin substrate activation, the 1,3-diene **44** derived from β-cyclocitral showed noteworthy reactivity trends (Scheme 11). The substrate **44** cannot adopt a relaxed single-*cis* or single-*trans* conformation, as the two alkenes cannot be fully coplanar. Thus, resonance stabilization here is not as pronounced as in other conjugated substrates (styrenes or dienes). Using our standard protic reaction conditions, diene **44** undergoes a swift polymerization and not a trace of the expected (3+2) or (4+3) cycloaddition products is observed (see ESI). Using our aprotic zinc(II)bromide promoted conditions with pyridyl ether **16** we noticed that this substrate reacted extremely slowly, with most of the diene recovered after the reaction, indicating that this is indeed a highly unreactive 'conjugated' diene towards dithioallyl cations, and the dithioallyl pyridyl ether **16** is likely more reactive towards its own allyl cation. Remarkably, we noted that diene **44** does undergo a very clean and quite selective reaction with the more substituted dithioallyl alcohol **45**. The dithioallyl cation is here generated at a lower reaction temperature, as it gives a more stabilized allyl cation (compared to **3**). Moreover, the secondary dithioallyl cation seems to be more reactive towards the less nucleophilic diene **44**. The cyclopentannulated product **46** was isolated as a single diastereomer in good yield, with the alkene bond located outside of the 1,4-dithiane ring. Its structural and stereochemical identity was fully confirmed by single crystal XRD analysis. This result again indicates that these reactions can balance on delicate differences in substitution patterns of both reactants, as well as on the nature of the reaction conditions or allyl cation activation mode. Nevertheless, when the (3+2) cycloaddition pathway is operating, either by small changes to the reaction conditions or the reactant, it generally shows a good efficiency and great diastereoselectivity compared to more generic non-enzymic carbacationic cascade cyclizations.



**Scheme 11** Reactions of a ‘non-coplanar’ conjugated diene **44**, and XRD structure of the cyclopentannulated derivative **46**. CCDC 2287211 contains the supplementary crystallographic data for this paper

## Conclusions

In summary, we were able to identify improved and mild Lewis acid promoted conditions for dithioallyl cation (3+2) cycloadditions. The methodology was applied in the rapid assembly of a range of interesting spirocyclic scaffolds in just two synthetic operations starting from quite common cyclic enone building blocks. This work also sheds further light on mechanistic aspects of the intruiging cyclopentannulation reaction, which shows some pronounced substituent effects that can be readily related to the stabilization of carbacationic intermediates. We expect this methodology can find good use in synthesis, and that it can be further developed as an attractive strategy to elaborate highly functionalized and substituted cyclopentanoid scaffolds.

## Author Contributions

JMW wrote the draft manuscript, which was reviewed by all authors. JMW and JH conceptualized most of the study. FD and JMW were involved in the acquisition of funding for the experimental synthetic work. FD developed the main methodological aspects of the study, and also performed most of the experiments. BC and JH supervized some of the experimental work. BD performed some initial experimental studies on the synthesis of spirocarbocyclic scaffolds. BR and JH performed the initial studies on pyridyl ether **16**. KVH performed and acquired funding for the single crystal XRD analysis of compound **46**.

## Conflicts of interest

There are no conflicts to declare.

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