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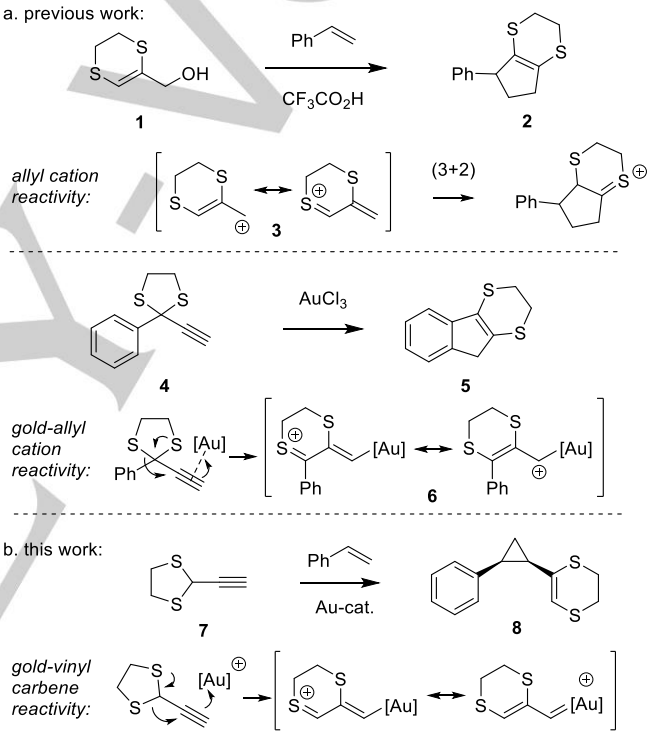
Stereoselective Gold(I)-Catalyzed Vinylcyclopropanation via Generation of a Sulfur-Substituted Vinyl Carbene Equivalent

Tengrui Yuan,[a] Bram Ryckaert, Kristof Van Hecke,[b] Jan Hullaert,[a] Johan M. Winne*[a]

Abstract: A stereoselective gold(I)-catalyzed vinylcyclopropanation of alkenes has been developed. A gold-coordinated cationic vinyl carbene species, readily generated via a rearrangement of the ethylenedithioacetal of propargyl aldehyde, reacts with a wide range of alkenes to afford thio-substituted vinylcyclopropanes. The gold-catalyzed vinyl cyclopropanation proceeds under mild conditions at room temperature and is generally selective for the formation of *cis*-substituted cyclopropanes. The reaction allows the formal introduction of a 'naked' vinyl carbene, by subsequent chemoselective hydrodesulfurisation of the ethylenedithio-bridge. The synthetic utility of the new method is demonstrated by a short, racemic formal synthesis of the alkaloid cephalotaxin, hinging on a key vinyl cyclopropane-cyclopentene rearrangement.

Allyl cation cycloadditions are unusual but useful synthetic methods for the construction of both cyclopentane and cycloheptane ring systems.[1] In previous studies, we developed an efficient (3+2) cycloaddition between conjugated alkenes and the allyl cation derived from dihydrodithiin-methanol **1**.[2] Simple treatment of **1** with a protic acid generates the ethylenedithio-bridged allyl cation **3**, which is stabilised by resonance as a vinyl thionium species, and engages a wide range of styrenes and s-*trans*-1,3-dienes in an unusually efficient (3+2) cycloaddition, readily affording cyclopentannulated derivatives like **2** (Scheme 1a). Aiming to expand this reactivity towards milder, catalytic methods to generate the key allyl cation intermediate **3**, we were intrigued by a report from Wang on the cationic rearrangement of propargyl ketone dithioacetals into indenes (*cf.* **4** → **5**).[3] This catalytic transformation is postulated to involve a Au(III)-promoted rearrangement of **4** to the vinyl thionium gold complex **6**, which can then undergo a Nazarov-type cyclisation to afford **5**. We envisioned that similar treatment of ethylenedithioacetal **7** with $AuCl_3$, could thus serve as a very mild method to generate the allyl cations of the type **3**. However, as we set out to explore this reactivity, we quickly found out that our proposed gold-coordinated reactive cationic intermediate derived from **7** behaved more like a metal carbenoid species and engaged styrenes in a swift (2+1) cycloaddition, affording *cis*-vinylcyclopropanated derivatives like **8** rather than the envisaged cyclopentenes (also see Scheme S5 in SI). As vinylcyclopropanes (VCPs) are actually quite important and versatile synthetic targets and intermediates,[4] we decided to explore the scope and utility of this intriguing and possibly quite useful method and now report our findings in this area.



Scheme 1. Background and inspiration for this work. a) Allyl cation cycloaddition developed by Hullaert and Winne (ref. [2]), and gold-catalysed allyl cation cyclisation developed by Wang and coworkers (ref. [3]); b) Vinyl carbene cycloaddition reactivity reported herein.

Metal-catalysed vinylcyclopropanations involving the catalytic generation of vinyl carbenoids from alkyne precursors have been studied and developed by Uemara,[5] and by Toste (Scheme 2).[6] While highly useful, and often very stereoselective or even enantioselective, the reactive alkyne precursors are relatively elaborate species and also typically require a quite specific substitution pattern. The same is in fact true for many other vinylcyclopropanation reactions.[7,8] More generic, less substituted vinyl carbene precursors are indeed likely to undergo self-condensations and other side reactions. The dithiosubstitution found in alkyne precursor **7** is of course also quite specific, but the dithioethylene-bridge in cycloadducts like **8** can actually be readily removed via chemoselective hydrodesulfurisation,[2] resulting in

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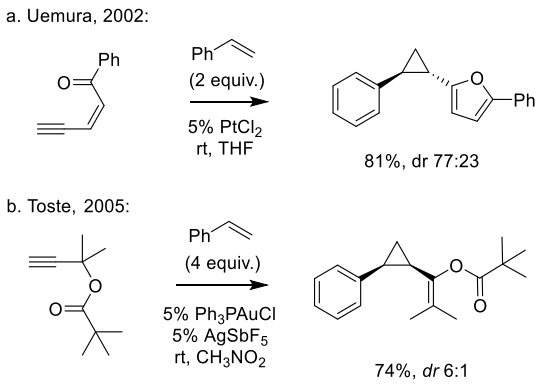
an overall vinylcyclopropanation that can introduce a 'naked' VCP moiety on olefinic substrates.



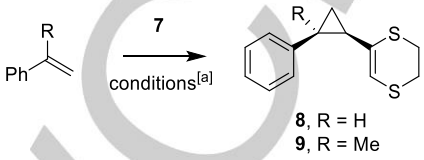
Scheme 2. Established metal-catalysed vinylcyclopropanations via rearrangement of propargylic reactants (references [5] and [6b]).

Inspired by Toste's gold-catalysed stereoselective cyclopropanations, and intrigued by the potential of a generic vinylcyclopropanation method, we thus set out to explore various reaction conditions to promote the gold-catalysed rearrangement and cycloaddition of **7**. For this screening, we used α-methyl styrene as a model substrate, as this substrate proved highly reactive and generally gave the cleanest reaction mixtures in our initial trials (Table 1). Thus, we arrived at a set of conditions that afforded very clean and swift reactions with good isolated yields of **9** and also decent dr's for this sterically unbiased substrate, namely 5% (IPr)AuCl with $AgSbF_6$ in nitromethane at room temperature. Interestingly, one catalyst, Nolan's dinuclear gold complex $[\{(IPr)Au\}_2(\mu\text{-}OH)]BF_4$,[9] also performed very well for this transformation, but actually favored the formation of the *trans* stereoisomer, demonstrating a strong ligand dependency of the stereocontrol. These observations also clearly indicate an intimate relationship between the ligand sphere and the cycloaddition transition state for these catalysts, rather than a mere generation of 'free' carbene species that would undergo a cyclopropanation.[7]

Our conditions for the rearrangement and cycloaddition of **7** were explored using 3 equivalents of the alkene substrate. In general, for similar reported metal-catalysed cyclopropanation reactions of this type, indeed large excesses of the alkene need to be employed to achieve high yields and conversions (3-10 equiv.).[5-8] Such skewed stoichiometry suppresses the self-addition reactions of the reactive carbene species with its own precursor. Thus, we were pleased to find that also good yields (85%) can still be obtained, using only 1.5 equivalents of α-methylstyrene. However, further approaching stoichiometric conditions leads to a marked decrease in isolated yield, and without resorting to syringe pump techniques, isolated yields for VCPs in the range of 55-65% are obtained for 1.05 equiv. of α-methylstyrene. We actually managed to isolate and identify one of the main self-addition products of **7**, showing a C-S bond insertion reaction of the vinyl carbene into the dithiolane of another molecule of **7** (see supporting info). As can be expected, employing an excess of the alkyne reagent **7** relative to the alkene leads to many side reactions, leading to much more complex reaction mixtures and difficult chromatographic separations.

Finally, application of the best conditions found for α-methylstyrene to the less reactive substrate styrene also gave a very good isolated yield of the expected VCP **8** and, as expected, also a good stereoselectivity, again for the *cis*-isomer.

Table 1. Screening of catalysts and reaction conditions for synthesis of **9**.



Alkene equiv.	Catalyst	Additive	Solvent, temp	Yield *(cis*:*trans)*
1.5	10% $AuCl_3$	-	toluene, 60°C	40% (1:1.7)
1.5	10% $(Ph_3P)AuCl$	-	toluene, 60°C	nd (complex)
3.0	5% $(Ph_3P)AuCl$	5% $AgSbF_6$	CH_3NO_2, rt	68% (1.5:1)
3.0	5% JohnPhosAuCl	5% $AgSbF_6$	CH_3NO_2, rt	86% (3.5:1)
3.0	5% JohnPhosAu (MeCN) SbF_6	-	CH_3NO_2, rt	93% (2.2:1)
3.0	5% IPrAuCl	5% $AgSbF_6$	CH_3NO_2, rt	98% (4.8:1)
3.0	2% $(IPrAu)_2OH.BF_4$	-	CH_3NO_2	80% (1:1.9)
3.0	2% $(IPrAu)_2OH.BF_4$	-	$Cl(CH_2)_2Cl$	92% (1:5.7)
1.5	5% IPrAuCl	5% $AgSbF_6$	CH_3NO_2, rt	83% (2.8:1)
1.0	5% IPrAuCl	5% $AgSbF_6$	CH_3NO_2, rt	62% (2.3:1)
3.0	-	5% $AgSbF_6$	CH_3NO_2, rt	no reaction
3.0[b]	5% IPrAuCl	5% $AgSbF_6$	CH_3NO_2, rt	85% (9:1)

[a] General conditions: a solution of **7** and α-methyl styrene was stirred for 6-12 h at the indicated temperature and quenched with a small amount of Et_3N when consumption of **7** was observed via TLC. The VCP **9** was then isolated in the indicated yield and diastereomeric ratio after chromatography of the concentrated reaction mixture over silica gel. [b] Styrene was used as alkene instead of α-methylstyrene, affording the VCP product **8**.

With a set of reliable standard conditions for the vinylcyclopropanation of styrene in hand, we next explored the substrate scope. For styrene substrates (see overview in Figure 1), we found a wide range of substitution patterns are tolerated on the aromatic ring, and that the preference for the cis-stereochemistry is well preserved. Electron donating groups speed up the reaction and gave high yields and high stereoselectivities (**10**-**13**), whereas electron-withdrawing ones lead to more sluggish reactions, with nitro and nitrile groups deactivating the styrenic bond for addition the cationic gold carbene species to the point where no desired product formation was observed (**15**,**16**). A basic amine also led to a shut-down of

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the reaction (*cf.* **17**), probably due to catalyst poisoning. *Ortho*-substitutions seem to be tolerated (**23**,**24**) but can lead to a significant drop in yield, as was found to be the case for an *ortho*-bromo styrene. Beta-substitution on the styrenic olefin is also tolerated (**25**-**29**), but can lead to erosions of the yield and stereoselectivity.

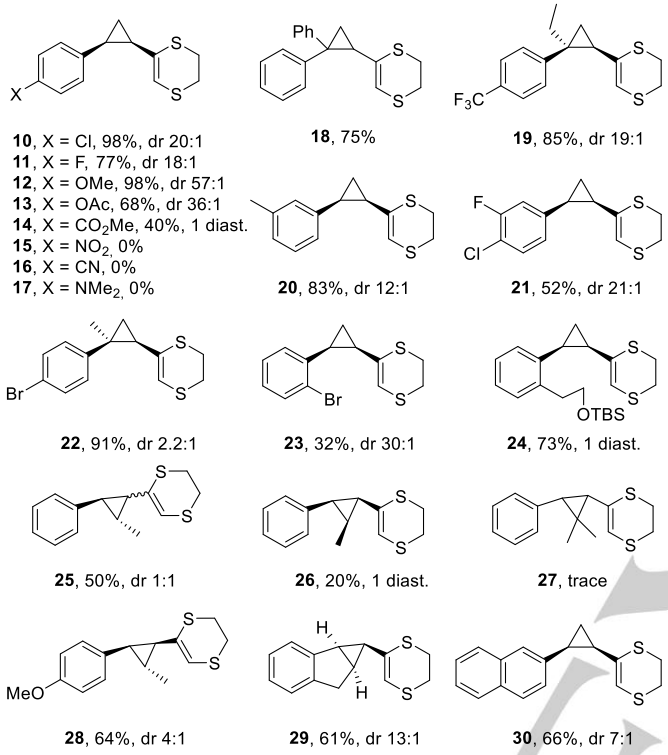

Figure 1. Vinylcyclopropanation of various substituted styrene substrates. All compounds were obtained as racemates, using the standard conditions,using 3 equiv. of the alkene.

Encouraged by the general utility of this straightforward vinylcyclopropanation reaction for styrenes, we also explored a range of unactived, non-conjugated alkenes (overview in Figure 2). In fact, many unconjugated alkenes were found to be viable substrates for this reaction under our standard conditions, with the exception of terminal, monosubstituted alkenes (**31**,**32**). Internal disubstituted olefins also generally gave low yields (**33**,**34**), but geminally dialkylsubstituted olefins afforded the cyclopropanated derivatives in good to excellent yields (**35**-**44**). Also sterically demanding fully substituted olefins even gave a reasonable yield (**39**). Chemo- and regioselectivity is also good for polyfunctional substrates (**40**-**42**). As observed for styrene substrates, basic amines proved to be incompatible with the transformation, but free hydroxyls and ketones are tolerated. Again, the overall *cis*-stereoselectivity is generally observed for substrates with a strong steric discrimination between either side of the olefinic bond, with the single exception of the selective synthesis of the *trans*-cyclopropane-fused steroid core **44**, the stereochemistry of which was unambiguously confirmed by single crystal XRD analysis, and can be rationalized by the extreme steric clash with the quaternary C13-center that shields one side of the incumbent cyclopropane (See SI, Figure S34).

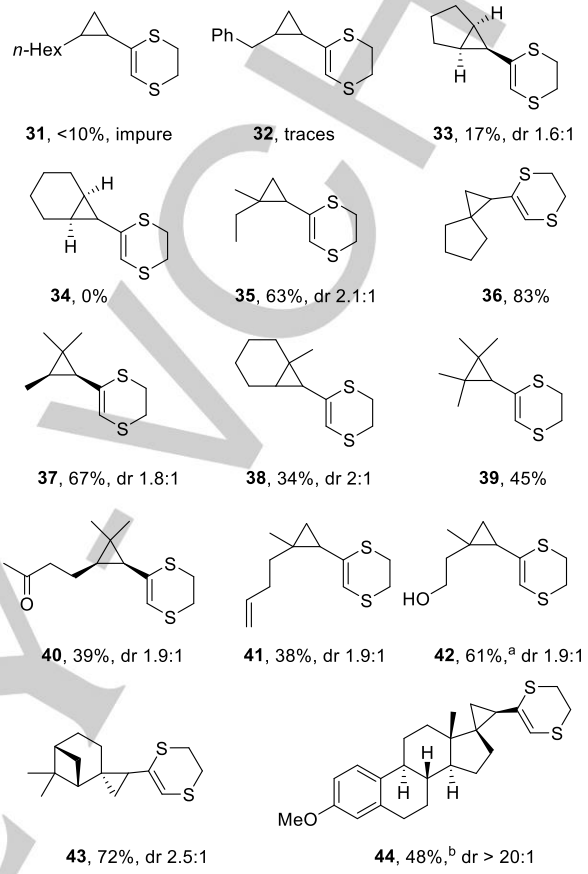

Figure 2. Vinylcyclopropanation of various unactivated alkene substrates obtained using the standard conditions using 3 equiv. of the alkene. All compounds were obtained as racemic mixtures, except for **43** and **44** which were prepared from optically pure SM and obtained as single enantiomers. a) only 1.5 equiv. of the alkene was used; b) only 1.5 equiv. of the alkene was used.

We also investigated a range of more diversely substituted olefins, focusing on terminal alkenes that might be expected to be more activated towards the cationic vinyl gold carbenoid by a specific substitution pattern (Figure 3). Indeed, in stark contrast to other terminal olefins, trimethylsilyl allylsilane and vinyl phenylthioether, gave an efficient vinylcyclopropanation to afford **45** and **46**, respectively. Normal enol ethers proved to be too sensitive substrates under these conditions, but the expected VCP adduct **47** was obtained in low yield using vinyl acetate as a substrate, albeit in good stereoselectivity. Vinyl phthalimide performed quite well and gave 60% yield of the pure cis-isomer **48**. A captodatively substituted protected dehydroalanine derivative gave an excellent yield of the vinylcyclopropane amino acid building block **49** with a quite good *dr* (9:1). Finally, 2-vinylthiophene also readily afforded the expected VCP **50** in decent yield and stereoselectivity.

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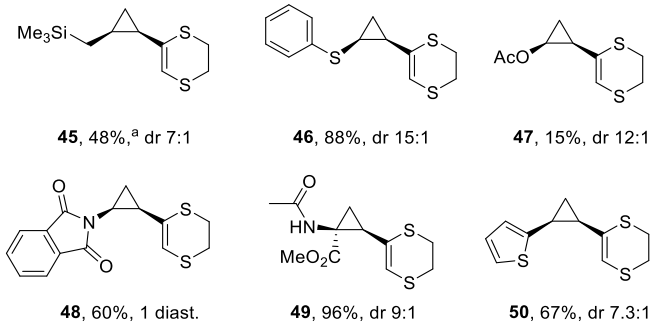


Figure 3. Vinylcyclopropanation of diversely substituted and functionalized alkene substrates. Compounds obtained as racemic mixtures according to standard procedure using 3.0 equiv. of alkene. a) only 1.5 equiv. of alkene substrate waq used.

More substituted, internal alkynes derived from **7** proved to be more troublesome substrates, prone to undergo allyl cation-type reactivity (see SI, Scheme S4). However, one of the major advantages of the vinylcyclopropanation method reported herein compared to existing similar methods (cf Scheme 2),[5-8] is its simplicity and the synthetic versatility of the vinylcarbene fragment that is introduced. For example, reductive removal of the dithioethylene bridge from the obtained vinylcyclopropane adducts should give the result of a formal cycloaddition with 'naked' vinylcarbene. The hydrodesulfurisation of the VCPs (Figure 4) actually required quite some optimisation, as hydrogenation of the vinyl group and/or ring opening of the cyclopropane ring were observed as major side reactions under several conditions. However, using W3 grade Raney nickel, together with a quick quench and fast work-up procedure, critically performed before a full conversion is reached, afforded the 'naked' vinyl cyclopropanes in useful isolated yields for many substrate types. For the styrenic substrate **24** we also observed some diastereomeric scrambling during the course of the reaction, likely related to a facile Ni-catalysed reversible ring opening.

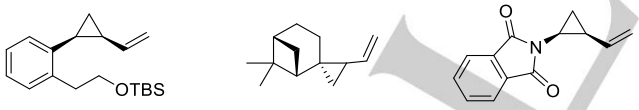
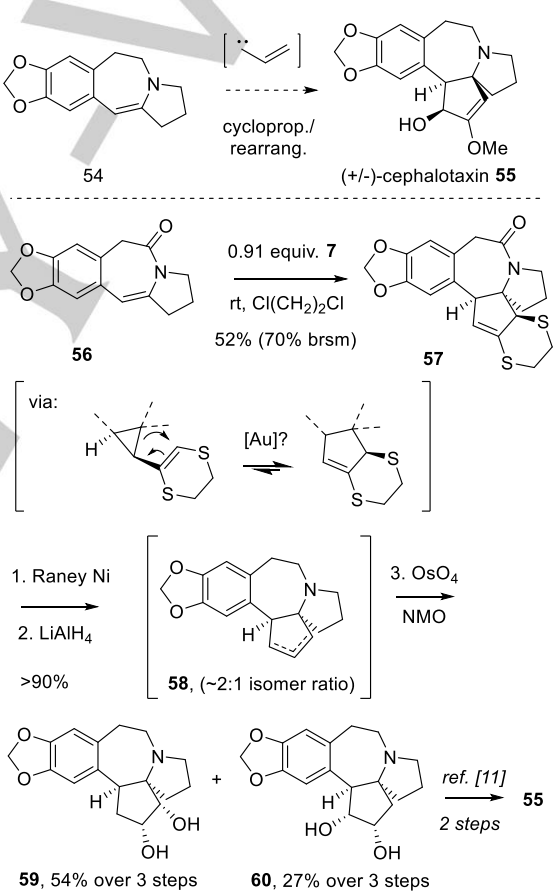


Figure 4. Chemoselective hydrodesulfurisation of dithiin-substituted cyclopropanes to 'naked' VCPs using W3 grade Raney nickel.

In order to explore the synthetic potential of the attractive transformation we developed herein, we wanted to apply the method in the synthesis of a complex natural product target. In an essay written in 2000,[4c] Hudlicky and Reed discussed the rich history of the VCP-cyclopentene rearrangement, also pointing out an elegant idea for the total synthesis of cephalotaxin **55**, that was reportedly proposed during an oral candidacy exam of one of the authors back in 1976, but was never put into practice. The proposed synthesis entailed a VCP-rearrangement strategy which would readily elaborate the complete tetracyclic framework from a simple the tricyclic heterocyclic core (Scheme 3, top). This overall idea seemed like a very fertile testing ground for our new methodology, as the required precursor **56** can be prepared in three steps from prolinol.[10] To our considerable surprise, the reaction of the enamide **56** afforded exclusively the cyclopentannulated product **57**, isolated as a single diastereomer. This result is either caused by a spontaneous or perhaps metal-catalyzed VCP-cyclopropane rearrangement, or due to a diverging overall reaction pathway for the cationic vinyl gold species more akin to that originally intended at the outset of these investigations (cf Scheme 1, also see SI, Scheme S5).[14c] As nitromethane is not the most convenient solvent for preparative purposes, gram-scale reactions were performed in dichloroethane, yielding 52% of the hexacycle **57**, using 0.91 equiv. of the propargyl reagent, together with some recovery of unreacted starting material. The unambiguous structural assignment of this crystalline compound was afforded by single crystal XRD analysis, and revealed the formation of the complete cephalotaxin ring system (see SI, Figure S34).



Scheme 3. Formal total synthesis of cephalotaxin through a VCP-cyclopentene rearrangement approach.

Simple dehydrosulfurisation of the cyclopentannulated intermediate **57** would actually readily complete a short formal racemic synthesis of cephalotaxin **55**, as the corresponding cyclopentene (*cf.* **58)** is a known precursor in Mori's cephalotaxine synthesis.[11] However, isomeric scrambling of the alkene proved to be unavoidable for this substrate during desulfurization

conditions, with the unfortunate preference for the undesired positional isomer. We thus performed the reported dihydroxylation step on the mixture of positional alkene isomers, which allowed us to isolate Mori's known diol precursor **60**, completing the formal synthesis.[11] Interestingly, the diol **60** also has been previously proposed,[12] but recently revised,[13] as the structure of the related natural product cephalezomine G, whose erroneous structural assignment is again confirmed by this work.

In conclusion, we have developed a conceptually attractive and straightforward synthesis of vinylcyclopropanes. The reaction tolerates a wide range of olefinic substrates and functionality, and is generally stereoselective. Its synthetic utility is demonstrated by a short racemic synthesis of cephalotaxin.[15] Further investigations into its synthetic utility, including asymmetric alternatives, seem to be promising avenues for further research.

Acknowledgements

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Keywords: cyclopropanation • vinyl carbene • gold catalysis • sulfur chemistry • natural product synthesis

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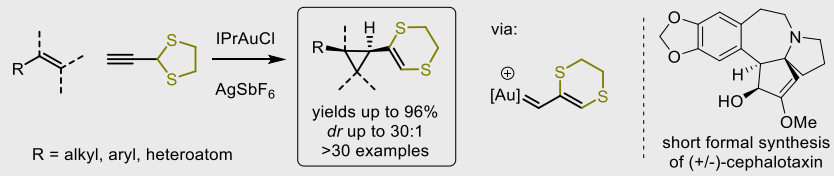

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Stereoselective Gold(I)-Catalyzed Vinylcyclopropanation via Generation of a Sulfur-Substituted Vinyl Carbene Equivalent

A cationic gold(I)-coordinated vinylcarbene species can be generated from simple propargylaldehyde ethylenedithioacetal, and engages a wide range of alkenes in a catalytic stereoselective cyclopropanation. The method was used as a key step to elaborate the polycyclic framework of cephalotaxus alkaloids.