Asymmetric Sulfur Ylide-Mediated Formal (4+1) Annulation Reaction: Scope and Mechanism

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Abstract: A formal (4+1) annulation strategy between sulfur ylides and 1,3-dienes has been developed to afford functionalized cyclopentanoids. The process consists of a stereoselective cyclopropanation reaction followed, *in situ*, by a stereospecific MgI_2-catalyzed vinylcyclopropane-cyclopentene rearrangement. The use of chiral sulfur ylides provides cyclopentanoids with an excellent enantiocontrol. A combined experimental and computational mechanistic study shows that the stereospecificity of the rearrangement can be accounted for by a double S_N2 reaction mechanism involving iodide.

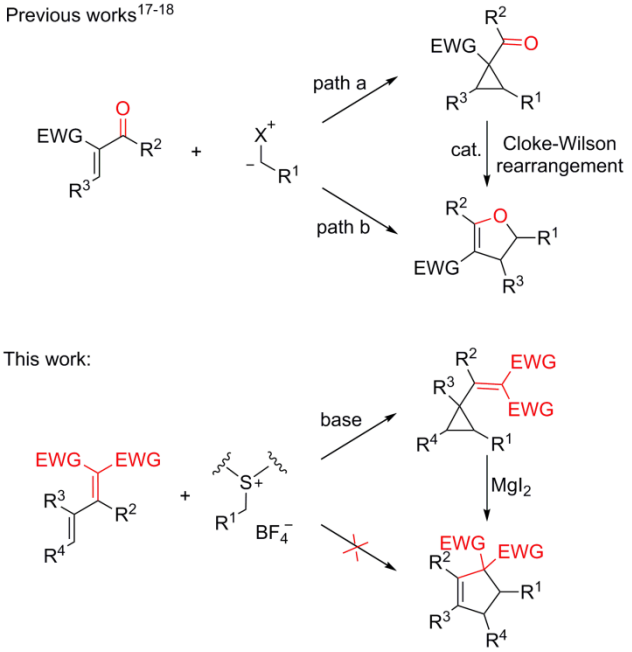
Introduction

Cyclopentanoids are central features in the structure of a number of biologically active (natural) products as well as key synthetic building blocks in the synthesis of complex targets.[1] Accordingly, a wide variety of methodologies have been elaborated for the synthesis of these carbocycles.

Among the different strategies for constructing cyclic structures, cycloaddition reactions are unrivalled in their power to rapidly build complex molecular architectures in a single convergent step from (at least) two precursors.[2] The best example of this class of reactions is the Diels-Alder reaction, which has become the most powerful strategy for forming six-membered rings; its prominence relying on the easy access to starting materials, the usually smooth reaction conditions and the observed high stereoselectivity.

In order to have an equivalent to the Diels-Alder reaction for 5-membered rings, several studies have been devoted to the development of a (4+1) cycloaddition/annulation strategy between four-atom systems and C1 sources.[3] The first reports of a (4+1) cycloaddition strategy toward five-membered carbocycles involve the use of carbenes as one-carbon synthon and 1,3-dienes as four-carbon unit.[4] The high reactivity of carbenes is however responsible for a low functional group tolerance. Accordingly, a range of carbenoids have been explored as alternatives to carbenes with a focus on isocyanides,[5] carbon monoxide (and transition metal catalysis),[6] ylides,[7] α-benzotriazolyl lithium compounds[8] or palladium catalysis.[9] Variations on the four-carbon unit have also been considered such as ω-halogeno-alkenes[10] or 2-(acetoxymethyl)-buta-2,3-dienoate.[11] However, these methodologies have been little exploited in organic synthesis thus far, probably because of their limited scope. Another challenge is the lack of asymmetric variants; only limited methods capable of imparting enantiocontrol in the (4+1) annulation have been disclosed.[12]

Onium ylides have been used for a long time for forming three-membered rings such as cyclopropane, epoxides and aziridines.[13] This last decade, it has been showed that ylides can also initiate tandem reactions allowing to go beyond the formation of three-membered rings.[14] In particular, ylides have been used in the synthesis of Donor-Acceptor cyclopropanes which can undergo subsequent (in situ) ring-opening reactions, cycloadditions and rearrangements.[15-16] One example is the synthesis of dihydrofurans via a cyclopropanation/Cloke-Wilson rearrangement strategy, resulting in a formal (4+1) heteroannulation (see path a in Scheme 1).[17-18]



Scheme 1. (4+1) annulation strategies using onium ylides.

Recently, we reported on a formal asymmetric (4+1) annulation strategy involving 1,3-dienes and sulfonium ylides[19] (see Scheme 1) which can be seen as a carbonated equivalent to the reported cyclopropanation/Cloke-Wilson rearrangement strategy in which C=O has been replaced by $C=C(EWG)_2$. Here, we explore the scope and the limitations of this methodology and investigate the mechanism of this multistep process. The versatility of the reaction is also illustrated by subjecting one of the obtained cyclopentene to a series of further transformations.

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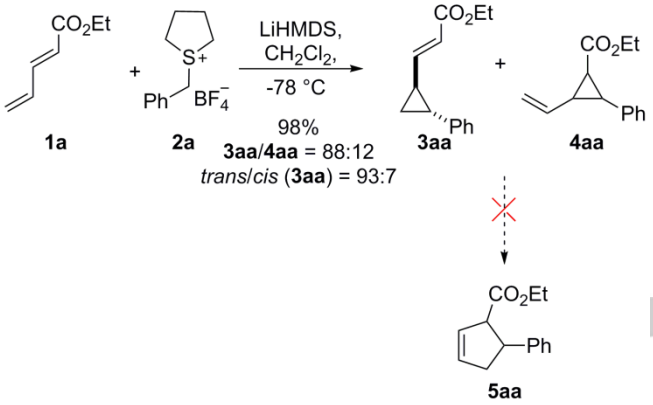
Results and Discussion

Development of the (4+1) annulation process

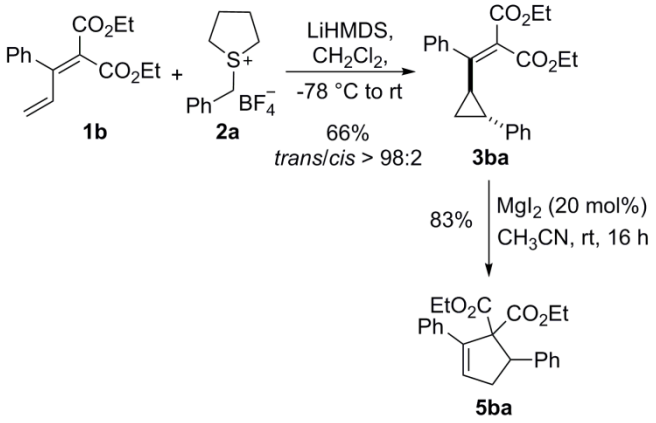
Reaction with a mono-activated 1,3-diene : Our initial investigation began with a sulfonium ylide model formed by deprotonation of **2a** and 1,3-diene **1a** (Scheme 2). Stirring these two reagents at -78°C for 1h afforded vinylcyclopropane **3aa** with a 93:7 *trans/cis* selectivity and a 88/12 regioselectivity (**3aa/4aa**).[20] All our attempts to observe direct formation of cyclopentene **5aa** by modifying reaction conditions or the nature of the ylide failed. We thus searched for reaction conditions under which **3aa** could rearrange into the more stable cyclopentene **5aa**.[21] Many Lewis acids ($BF_3{\cdot}OEt_2$, $AlCl_3$, MgI_2, $TiCl_4$, $SnCl_4$…) and reaction conditions were investigated but none of them allowed observing formation of **5aa**.



Scheme 2. Investigation using mono-activated 1,3-diene **1a**.

Accordingly, we decided to further activate the vinylcyclopropane toward the vinylcyclopropane-cyclopentene rearrangement by adding a second electron-withdrawing group (EWG) on the vinylcyclopropane, thus starting from a bis-activated 1,3-diene.

Reaction of 1,1-bis-activated 1,3-dienes : Deprotonation of sulfonium salt **2a** in the presence of diene **1b** at −78°C and then stirring for 16h at room temperature led to vinylcyclopropane **3ba** with a total regio- and diastereoselectivity with, again, no trace of the desired cyclopentene (Scheme 3). Next, we searched for reaction conditions to rearrange **3ba** into cyclopentene **5ba**. After a screening of different Lewis acids (see SI), we found that MgI_2 catalyzes the rearrangement of **3ba** under very mild reaction conditions (20 mol% MgI_2, rt, 16h) to give **5ba** in 83% isolated yield.[22]



Scheme 3. Reaction of 1,1-bis-activated diene **1b**

Having showed the potential of sulfur ylides in the development of a (4+1) annulation strategy, we searched for suitable reaction conditions allowing a two steps one-pot synthesis. We found that deprotonation of sulfonium salt **2a** in the presence of diene **1b**, at -78°C, followed by addition of 1.2 equivalents of MgI_2 at room temperature, allows obtaining the desired cyclopentene **5ba** in 65% isolated yield in one synthetic step (Table 1).

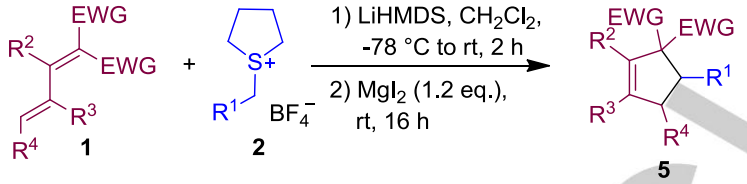
Exploring the scope of the formal (4+1) annulation

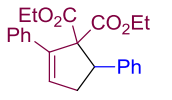
The scope of our methodology was evaluated under the optimized reaction conditions (*i.e.* 1 equiv. of LiHMDS at −78°C, then 1.2 equiv. of MgI_2 at rt). The results are collected in Table 1. Both electron-rich and -poor benzylic (or allylic) ylides react with 1,3-diene **1b** to provide corresponding cyclopentenes in moderate yields (see **5ba-bf** in Table 1). The reaction proceeds even with an ester-stabilized ylide (see **5af**), yet in a lower yield.

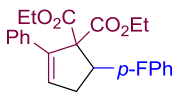
A range of 1,1-dicarbonyl ester 1,3-dienes with different substituent patterns was explored.[23] The breadth of tolerated substituents is broad (aryl, heteroaromatic, alkyl and ester groups) allowing to access variously substituted cyclopentenes (**see** Table 1). It is interesting to note that, in the case of 4-substituted 1,3-dienes, a second stereogenic centre is generated with a good to excellent diastereoselectivity (**5ma, 5na, 5oe** and **5me**). The stereochemistry of the major isomer varies however according to the substitution of the ylide: the only observed isomer for **5ma** and **5na** shows a *cis* stereochemistry as confirmed by single crystal X-ray diffraction analysis[24] whereas in the case of **5oe** and **5me** that is the *trans* isomer which is the major product. The rearrangement being stereospecific this difference is due to a change in stereoselectivity in the cyclopropanation step as shown by supplementary experiments (see SI).

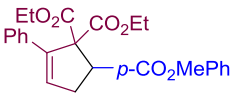
The nature of the activating electron-withdrawing groups on the diene was also varied: Replacing the two esters by two cyano groups led to **5ra, 5sa** and **5ta** in good yields (see Table 1). The rearrangement is however slower in this case and requires 1.5 equivalents of MgI_2 in acetonitrile at reflux for 48h.

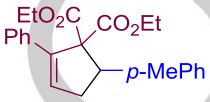
Table 1.Substrate scope of the formal (4+1) annulation reaction.[a]

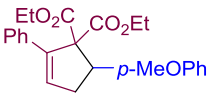


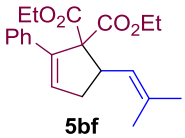

5ba
65%


5bb
57%


5bc
55%

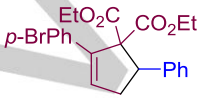

5bd
50%

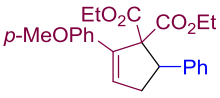

5be
58%


5bf
57%

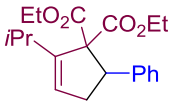

5af
32%

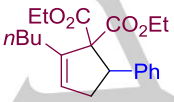

5ca
57%

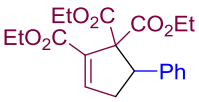

5da
40%

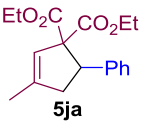

5ea
55%

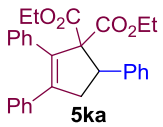

5fa
45%

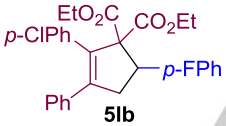

5ga
41%

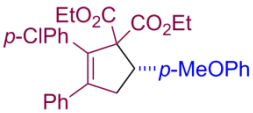

5ha
39%


5ia
32%


5ja
36%[b]

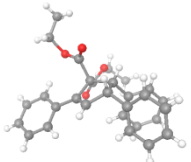

5ka
61%


5lb
52%

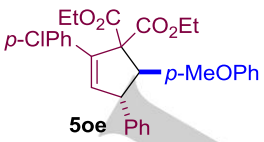

5le
48%

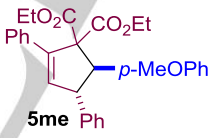

5ma
65% (dr > 95/5)

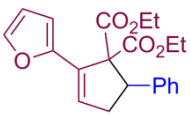
≡

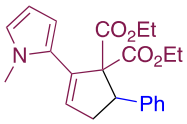

CCDC 1819344[24]

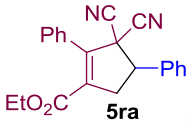

5na
46% (dr > 95/5)


5oe
64% (dr 80/20)


5me
56% (dr > 95/5)


5pa
48%


5qa
67%


5ra
71%[c]


5sa
48%[c]


5ta
73%[c]

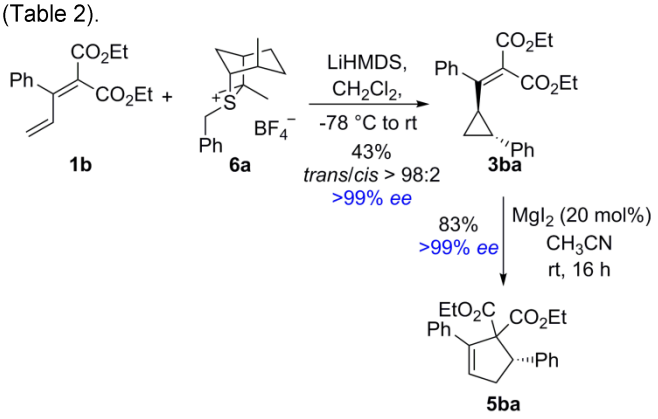
[a] Yield in pure product after purification by flash chromatography. Diastereoisomeric ratios were determined by ^{1}H NMR on the crude mixture. [b] Determined on the crude by ^{1}H NMR analysis using an internal standard. The reaction was carried out using benzyl(diisopropyl)sulfonium tetrafluoroborate. [c] Rearrangement was carried out with MgI_2 (1.5 eq.) for 48h at reflux of acetonitrile.

Development of an enantioselective version

We next focused our attention on the development of an enantioselective version of our methodology. Aggarwal *et al.* have shown that high enantiocontrol in cyclopropanation reactions could be obtained using sulfonium salt **6a** (which is readily available optically pure in two steps from sulfur and limonene).[25] Accordingly, we prepared **6a** and investigated the reaction of the corresponding ylide with diene **1b**. Deprotonation of **6a** in the presence of diene **1b** allows obtaining vinylcyclopropane **3ba** with a total diastereo- and enantiocontrol,

only one stereoisomer being observed by NMR and chiral HPLC analysis (*dr* > 98/2 and *ee* > 99%; Scheme 4).

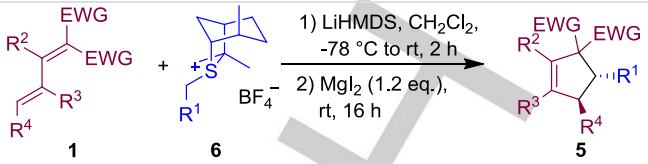
Much to our surprise, the rearrangement of **3ba** in the presence of MgI_2 (20 mol%) led to corresponding cyclopentene **5ba** with no deterioration of the enantiomeric excess; indicating a totally stereospecific rearrangement. Application of this strategy using our one-pot procedure resulted in a series of cyclopentenes with a very high enantiocontrol (81-99 % *ee*) (Table 2).

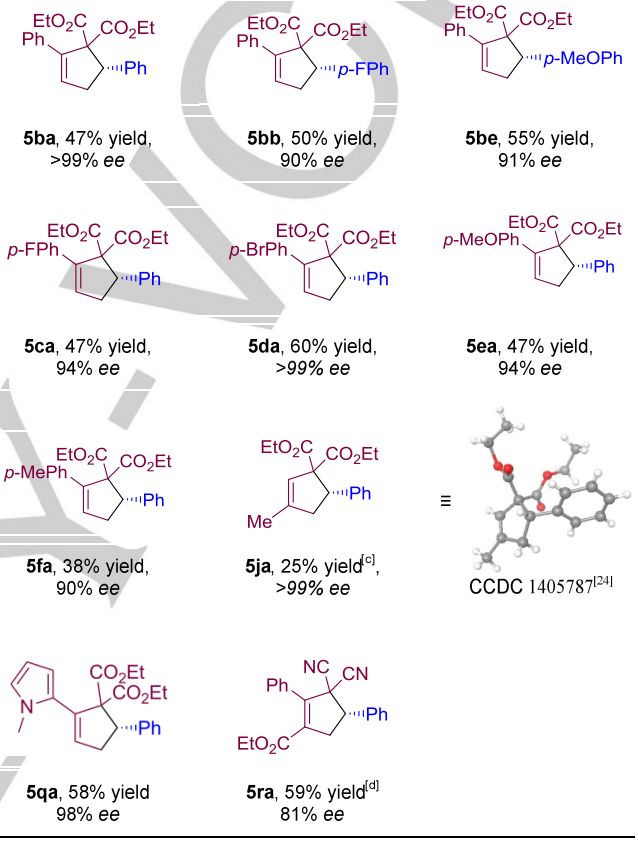


Scheme 4. Development of an enantioselective version using a chiral sulfonium ylide.

The absolute configuration of the stereogenic centre of cyclopentene **5ja** could be determined by single-crystal X-ray diffraction analysis (see Table 2).[24] Absolute configuration of all other products was determined by analogy.

Table 2. Enantioselective (4+1) annulation reaction.[a,b]



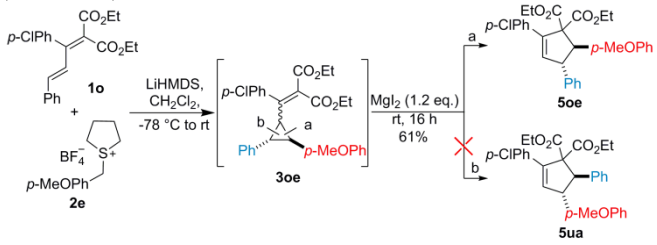


[a] Yield in pure product after flash chromatography. Enantiomeric excesses were determined by chiral HPLC (see SI). [b] Absolute configuration of **5ja** was determined by single crystal X-ray diffraction analysis (see SI). Absolute configuration of all other products was determined by analogy. [c] Determined on the crude by ^1H NMR analysis using an internal standard. [d] Rearrangement was carried with MgI_2 (1.5 eq.) for 48h at 80°C in acetonitrile.

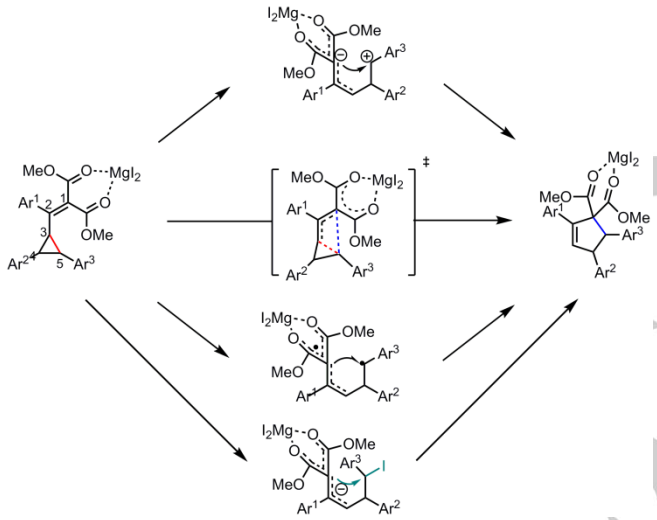
Mechanistic studies

Observations made during the development of our (4+1) annulation methodology raise a series of questions concerning the mechanism of this process: why does reaction of ylides with dienes lead exclusively to vinylcyclopropanes with no direct cyclopentene formation? Why is MgI_2 so efficient at catalyzing the rearrangement whereas the use of other, including stronger, Lewis Acids leads to no reaction or lower yields? What is the exact mechanism of this rearrangement and what is the origin of its total stereospecificity? In order to answer these questions a mechanistic study combining experimental and computational methods was set up.

Experimental study: First, we probed electronic effects of substituents in the vinylcyclopropane-cyclopentene rearrangement by analyzing the reaction of **1o** with **2e**. The exclusive formation of **5oe** from **3oe** shows that ring-opening is favored in α position of electron-rich aryls (pathway a in Scheme 5).[26] This could be explained either by a mechanism involving a heterolytic C-C bond cleavage to form a zwitterion, a concerted mechanism or an iodide-mediated ring-opening pathway (Scheme 6).[22]



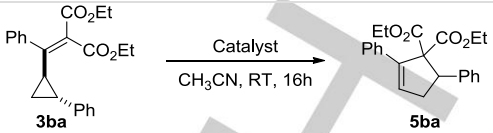
Scheme 5. Rearrangement of **3ne**.



Scheme 6. Potential mechanisms for the rearrangement step.

Next, we investigated the role of MgI_2 by probing the importance of the Lewis acid feature of magnesium(II) and of the nucleophilic character of iodide. We attempted the rearrangement of cyclopropane **3ba** in the presence of a magnesium(II) salt with a less nucleophilic counter-ion (ClO_4^- or Cl^-) as well as in the absence of magnesium but the presence of iodide, using KI (Table 3). These experiments revealed the crucial role of both magnesium(II) and iodide ions, removal of one of them leading to no reaction. These observations could be explained by an iodide-mediated ring-opening/ring-closing mechanism but hardly by a heterolytic cleavage of the C-C bond to form a zwitterion or a concerted mechanism.

Table 3. Investigation of the role of magnesium and iodide ions.



Catalyst	Yield (%)[a]
MgI_2 (0.5 eq.)	quant.[b]
MgI_2 (0.2 eq.)	quant.(83)
$Mg(ClO_4)_2$ (0.5 eq.)	0
$MgCl_2$ (0.5 eq.)	0
KI (0.5 eq.)	0
$Mg(ClO_4)_2$ (0.5 eq.) + KI (0.5 eq.)	97[b]

[a] Yield was determined by ^{1}H NMR using an internal standard. Isolated yield in brackets. [b] Reaction time is 7h.

In order to confirm further the role of iodide in the mechanism of the rearrangement, we have explored its influence on the stereospecificity of the process. In our search for best reaction conditions for the rearrangement of **3ba** into **5ba**, we have observed that other Lewis acids, such as $SnCl_4$ and BF_3.OEt, allows also observing formation of **5ba**, yet in a lower yield (see SI). Interestingly, catalysis of the rearrangement of enantiomerically pure **3ba** with these Lewis acids shows a drastic loss of stereospecificity for the process (Table 4). This suggests a change in the mechanism between the MgI_2-catalyzed and the $SnCl_4$- or BF_3-catalyzed rearrangement: In the case of MgI_2, a stereospecific double S_N2 mechanism would be favored, whereas in the case of $SnCl_4$ and $BF_3.OEt_2$ such a mechanism being disfavored (due to the lower nucleophilicity of chloride or fluoride) the process would take place via another –less stereospecific– pathway.

Table 4. Stereospecificity of the rearrangement.

Catalyst	Yield(%)[a]	*ee* of **5ba**
MgI_2	Quant.	> 99%
$BF_3.OEt_2$	Quant.	0%
$SnCl_4$	Quant.	28%

[a] Yield was determined on the crude mixture by ^{1}H NMR using an internal standard.

Computational study: In order to identify the mechanism and the key factors controlling the reactivity and stereoselectivity in our formal (4+1) annulation, we have investigated the free

energy profile of the reaction between ylide **6** and diene **1va**. Calculations were carried out at the B3LYP-D3/6-311+G(d,p)//B3LYP-D3/6-31+G(d) level of theory including a continuum description of dichloromethane as solvent.[27]

The sulfur ylide-mediated cyclopropanation reaction has been well studied and its mechanism clearly established.[28] Our calculations on ylide **6** and diene **1va** are in good agreement with reported mechanistic sequence which involves two steps. The first is addition of the sulfonium ylide onto the terminal carbon of **1va** to form a betaine intermediate (**7**) (Figure 1). This betaine can then undergo ring-closure, with concomitant expulsion of the sulfide, to give the corresponding cyclopropane (**3va**).

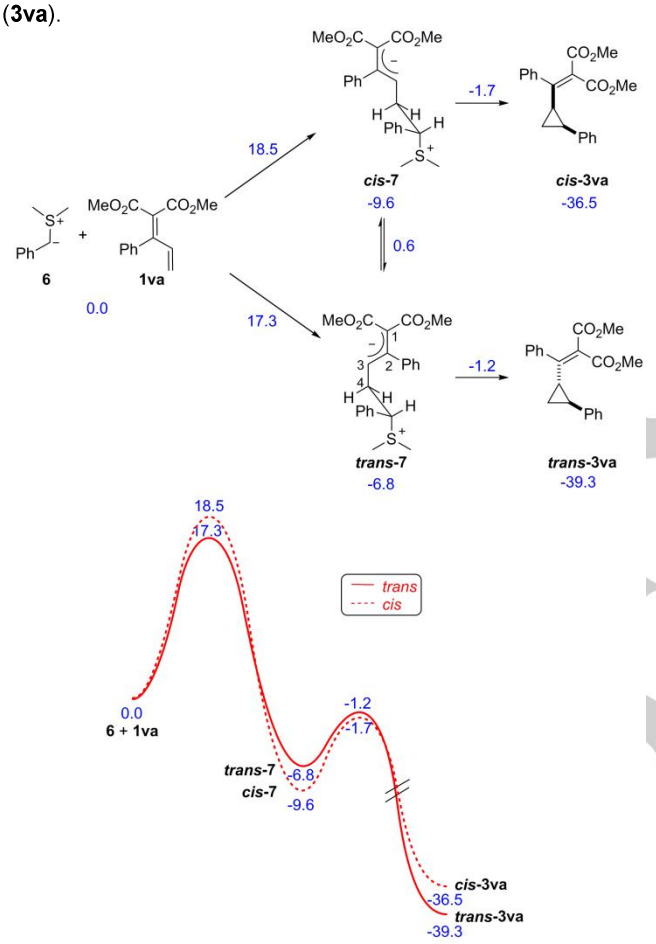
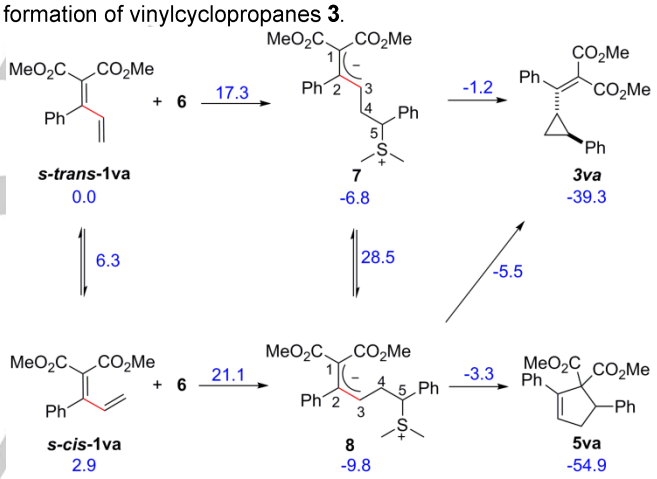


Figure 1. Mechanism and free energy profile of the cyclopropanation (Relative free energies in kcal.mol^{-1}).

Addition can occur through a *cis* or a *trans* approach between the two reactants, leading to betaines ***cis*-7** and ***trans*-7**, respectively.[29] These two betaines can interconvert by a simple rotation around the C3-C4 carbon-carbon bond. This conformational equilibrium involves however a barrier which is higher than those toward cyclization and elimination. ***Cis*-7** will thus lead to *cis* cyclopropane whereas ***trans*-7** will yield *trans* cyclopropane.

Barrier to formation of ***trans*-7** is computed to be lower (by 1.4 kcal.mol^{-1}) than to formation of ***cis*-7**. Addition being predicted to be non-reversible, it results that a high *trans* selectivity is computed, in good agreement with the observed total *trans* selectivity (see Scheme 3).

The exclusive formation of vinylcyclopropane and the non-observation of cyclopentene can be explained by the geometrical impossibility for carbon atom C1 to get close to electrophilic C5 in betaines **7**. In order to allow ring-closure via C1, *i.e.* toward cyclopentene **5va**, betaines **7** would first need to undergo rotation around C2-C3 to yield **8** (Scheme 7). The latter could also be directly formed by addition of **6** onto diene **3va** in its *s-cis* conformation. However, isomerization of **7** into **8** involves a very high barrier and the free energy barrier of addition onto ***s-cis*-3va** is much higher than the one onto ***s-trans*-3va**. Exclusive formation of **3** with no trace of direct (4+1) annulation to form **5** can thus be accounted for by selective reaction of 1,3-dienes in their *s-trans* conformation to form a betaine intermediate (**7**) which, for geometrical reasons, cannot ring-close to cyclopentene and therefore leads to exclusive formation of vinylcyclopropanes **3**.



Scheme 7. Rationale for the non-observation of a direct (4+1) annulation (Relative free energies in kcal.mol^{-1}).

Next, we investigated the second key-step of the process, the rearrangement. We explored different mechanisms, involving a hetero-(or homo-)lytic C3-C5 bond cleavage to form a zwitterion (or a diradical), a concerted migration of C5 (from C3 to C1) or two iodide-mediated S_N2 reactions (see Scheme 6). Every attempt to optimize a zwitterionic (or diradical) intermediate failed, leading to a cyclopropane structure. On the other hand, a transition state connecting **3va-MgI$_2$** to **5va-MgI$_2$** could be obtained, with a free energy barrier of 17.1 kcal.mol^{-1} (Figure 2). We found however that the pathway involving a cyclopropane ring-opening by iodide to form **9** followed by a ring-closure to cyclopentene and expulsion of the iodide is the most favored pathway (overall barrier at 12.7 kcal.mol^{-1}), in good agreement with our observations concerning the crucial role of iodide in the rearrangement (see Tables 3 and 4).[30]

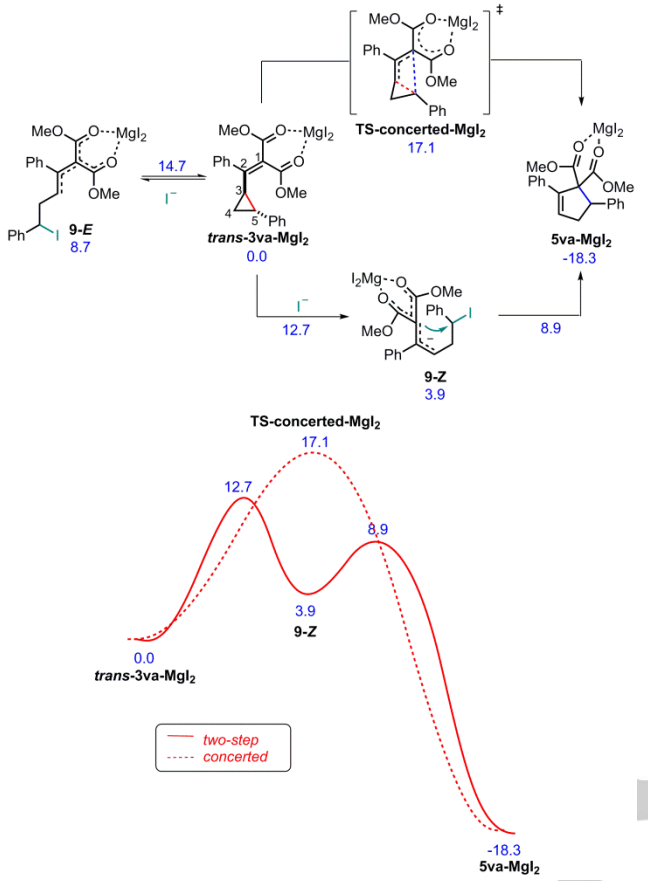
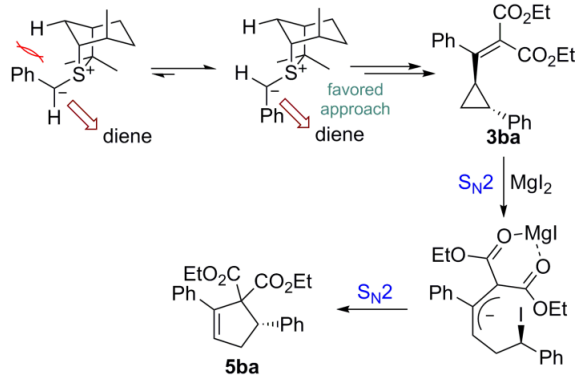


Figure 2. Mechanism and free energy profile of the rearrangement (Relative free energies in kcal.mol^{-1})

The stereospecificity of the vinylcyclopropane-cyclopentene rearrangement can thus be explained by the fact that the C4 stereogenic centre undergoes two successive S_N2 reactions, *i.e.* two stereochemical inversions, the outcome being an overall retention of configuration.

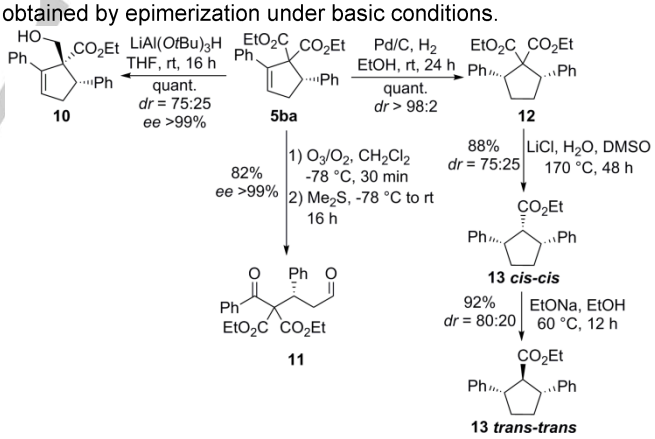
Model for enantiocontrol: The observed high enantioselectivity during cyclopropanation is consistent with the model proposed by Aggarwal for enantiocontrol in epoxidation in which ylide conformation and face selectivity are controlled through nonbonded interactions (Scheme 8).[25] Then, the vinylcyclopropane-cyclopentene rearrangement being totally stereospecific (*vide supra*), the observed enantioselectivity for **3** is transferred to **5**.



Scheme 8. Model for enantiocontrol.

Derivatization

In order to illustrate the versatility of this methodology, cyclopentene **5ba** was subjected to a series of transformations (Scheme 9): Reaction of **5ba** with a sterically hindered aluminium hydride reagent allows observing a diastereoselective reduction of one of the ester groups, thus generating an asymmetric all-carbon quaternary stereocenter (**10**).[31] Further ozonolysis of the double bond led to acyclic compound **11** without alteration of the enantiomeric excess. The double bond was reduced as well to introduce a new stereocenter and produce *meso* compound **12** with an excellent diastereoselectivity. Subsequent decarboxylation allowed formation of **13** with a *cis-cis* relative configuration.[32] Interestingly, the more stable *trans-trans* isomer could be obtained by epimerization under basic conditions.



Scheme 9. Transformations of **5ba**.

Conclusions

We have developed a new highly diastereo- and enantioselective formal (4+1) annulation methodology. We have shown that sulfur ylides react with 1,1-bis-activated 1,3-dienes to lead to vinylcyclopropanes. Upon MgI_2 catalysis, the latter undergo a rearrangement affording cyclopentenes. A one-pot

procedure of this methodology could be developed allowing the direct access to a series of functionalized cyclopentenes in one synthetic step from sulfur ylides and 1,3-dienes.

Interestingly, high enantioselectivities could be achieved using chiral sulfur ylides prepared from simple reagents, limonene, elemental sulfur and γ-terpinene.

The scope of the methodology was explored with respect to both the sulfur ylide and the 1,3-diene. The reaction proceeds under mild reaction conditions and shows a high functional group tolerance.

In order to get a fundamental understanding of factors controlling stereoselectivity in this formal (4+1) annulation process, we have investigated its mechanism by experimental and computational means. Control experiments revealed the crucial role of both the magnesium(II) and the iodide ions in the vinylcyclopropane-cyclopentene rearrangement. Iodide was shown to be determinant for the stereospecificity of the rearrangement, and hence the enantioselectivity of the overall process. Indeed experimental results supported by computational data indicate that the stereospecificity of the rearrangement can be accounted for by a mechanism involving a cyclopropane ring-opening by iodide followed by a ring-closure to cyclopentene and expulsion of the iodide, *i.e.* a double S_N2 mechanism. Based on this, a rationale for the high enantiocontrol could be devised.

Finally, the versatility of this formal (4+1) annulation process was illustrated by subjecting **5ba** to a series of subsequent transformations. Further investigations to apply this methodology in synthesis of pharmaceutically interesting compounds are currently underway.

Experimental Section

General procedure for the formal (4+1) annulation reaction

In a dried round bottomed flask, under inert atmosphere, diene **1** (100 mg, 1.0 eq.) and sulfonium salt **2** (1.1 eq.) were dissolved in 4 mL of CH_2Cl_2. LiHMDS (1.0 M solution in THF, 1.1 eq.) was then added, dropwise, at −78 °C. The reaction mixture was stirred for 1h at −78 °C and then for another hour at room temperature. A solution of MgI_2 (1.2 eq.) in CH_3CN (1 mL) was added at room temperature and the solution was stirred for 16h. The reaction mixture was diluted with CH_2Cl_2 (2 mL), water (2 mL) and an aqueous 1M HCl solution (1 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with an aqueous NaOH solution (10 wt%, 5 mL), water (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with the appropriate mixture of EtOAc/cyclohexane to give the desired product (**5**).

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Keywords: Annulation • Asymmetric synthesis • Cyclopentenes • Vinylcyclopropanes • Ylides

[1] See for example: a) V. B. Kurteva, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 6809−6857 and references therein; b) S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.* **2007**, *107*, 3286−3337.

[2] a) *Cycloaddition Reactions in Organic Synthesis* (Eds: S. Kobayashi, K. A. Jorgensen), WILEY-VCH Verlag GmbH, Weinheim, **2002**; b) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, **1990**; c) *Methods and Applications of Cycloaddition Reactions in Organic Syntheses* (Ed. N. Nishiwaki), John Wiley & Sons, New York, **2014**.

[3] For a review, see: J.-R. Chen, X.-Q.Hu, L.-Q.Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301−5365.

[4] a) K. Fuchibe, T. Aono, J. Hu, J. Ichikawa *Org. Lett.* **2016** *18*, 4502–4505; b) Y. Wang, M. E. Muratore, Z. Rong, A. M. Echavarren *Angew. Chem. Int. Ed.* **2014**, *53*, 14022–14026; *Angew. Chem.* **2014**, *126*, 14246–14250; c) M. Déry, L.-P. Lefebvre, K. Aissa, C. Spino, *Org. Lett.* **2013**, *15*, 5456–5459; d) F. Beaumier, M. Dupuis, C. Spino, C. Y. Legault, J. *Am. Chem. Soc.* **2012**, *134*, 5938–5953; e) L. Boisvert, F. Beaumier, C. Spino, *Org. Lett.* **2007**, *9*, 5361–5363; f) F. Aznar, M. Fañanás-Mastral, J. Alonso, F. J. Fañanás, *Chem. Eur. J.* **2008**, *14*, 325–332; g) W. H. Moser, L. A. Feltes, L. Sun, M. W. Giese, R. W. Farrell, *J. Org. Chem.* **2006**, *71*, 6542–6546; h) C. Spino, H. Rezaei, K. Dupont-Gaudet, F. Bélanger, *J. Am. Chem. Soc.* **2004**, *126*, 9926–9927; i) J. H. Rigby, Z. Wang, *Org. Lett.* **2003**, *5*, 263–264; j) J. Barluenga, S. López, J. Flórez, *Angew. Chem. Int. Ed.* **2003**, *42*, 231–233; *Angew. Chem.* **2003**, *115*, 141–143; k) A. M. Dalton, Y. Zhang, C. P. Davie, R. L. Danheiser, *Org. Lett.* **2002**, *4*, 2465–2468; l) J. Pfeiffer, M. Nieger, K. H. Dötz, *Eur. J. Org. Chem.* **1998**, 1011–1022; m) J. H. Rigby, A. Cavezza, G. Ahmed, *J. Am. Chem. Soc.* **1996**, *118*, 12848–12849; n) M. A. Sierra, B. Soderberg, P. A. Lander, L. S. Hegedus, *Organometallics* **1993**, *12*, 3769–3771; o) R. L. Danheiser, J. J. Bronson, K. Okano, *J. Am. Chem. Soc.* **1985**, *107*, 4579–4581; p) T. Hudlicky, F. Koszyk, D. M. Dochwat, G. L. Cantrell, *J. Org. Chem.* **1981**, *46*, 2911−2915; q) R. P. Short, J.-M. Revol, B. C. Ranu, T. Hudlicky, *J. Org. Chem.* **1983**, *48*, 4453−4461; r) R. L. Danheiser, C. Martinez-Davila, R. J. Auchus, J. T. Kadonaga, *J. Am. Chem. Soc.* **1981**, *103*, 2443–2446; s) T. Hudlicky, F. J. Koszyk, T. M. Kutchan, J. P. Sheth, *J. Org. Chem.* **1980**, *45*, 5020–5027.

[5] Z. Li, W. H. Moser, R. Deng, L. Sun, *J. Org. Chem.* **2007**, *72*, 10254–10257.

[6] a) S. Mazumder, D. W. Crandell, R. L. Lord, M.-H. Baik *J. Am. Chem. Soc.* **2014**, *136*, 9414–9423; b) S. V. Gagnier, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 4804–4807; c) M. Murakami, K. Itami, Y. Ito, *J. Am. Chem. Soc.* **1997**, *119*, 2950–2951; d) M. Murakami, K. Itami, Y. Ito, *Angew.Chem. Int. Ed. Engl.* **1995**, *34*, 2691–2694; *Angew. Chem.* **1995**, *107*, 2943–2946; e) M. Franck-Neumann, J.-M.Vernier, *Tet.Lett.* **1992**, *33*, 7365–7368; f) M. Franck-Neumann, E. L. Michelotti, R. Simler, J.-M. Vernier, *Tet. Lett.* **1992**, *33*, 7361–7364; g) B. E. Eaton, B. Rollman, *J. Am. Chem. Soc.* **1992**, *114*, 6245–6246.

[7] a) X.-Z. Zhang, Y.-H. Deng, K.-J. Gan, X. Yan, K.-Y. Yu, F.-X. Wang, C.-A. Fan *Org. Lett.* **2017**, *19*, 1752–1755; b) J. Tian, H. Sun, R. Zhou, Z. He, *Chin. J. Chem.* **2013**, *31*, 1348–1351; c) C. R. Reddy, P. Kumaraswamy, M. D. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 9052–

9057; d) J. L. Loebach, D. M. Bennett, R. L. Danheiser, *J. Am. Chem. Soc.* **1998**, *120*, 9690–9691.

[8] C. P. Davie, R. L. Danheiser, *Angew. Chem. Int. Ed.* **2005**, *44*, 5867–5870; *Angew. Chem.* **2005**, *117*, 6017–6020.

[9] a) B. Suchand, G. Satyanarayana *J. Org. Chem.* **2017**, *82*, 372–381; b) R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6950–6952; *Angew. Chem.* **2009**, *121*, 7084–7086; c) R. W. Coscia, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 2496–2498.

[10] a) D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; *Angew. Chem.* **2008**, *120*, 7649–7653; b) B. M. Kiat Tong, H. Chen, S. Y. Chong, Y. L. Heng, S. Chiba, *Org. Lett.* **2013**, *15*, 6111–6112.

[11] a) D. T. Ziegler, L. Riesgo, T. Ikeda, Y. Fujiwara, G. C. Fu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13183–13187; *Angew. Chem.* **2014**, *126*, 13399–13403; b) X. Han, W. Yao, T. Wang, Y. R. Tan, Z. Yan, J. Kwiatkowski, Y. Lu, *Angew. Chem. Int. Ed.* **2014**, *53*, 5643–5647; *Angew. Chem.* **2014**, *56*, 5749; c) Q. Zhang, L. Yang, X. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550–2551.

[12] To the best of our knowledge, only a few examples of asymmetric (4+1) annulation have been reported so far. See ref. 6b, 10a and 11a-b.

[13] For reviews, see: a) J.-F. Briere, P. Metzner, in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**; pp 179–208; b) V. K. Aggarwal, E. McGarrigle, in *Handbook of Organocatalysis*, (Ed: P. Dalko), Wiley-VCH, Weinheim, **2007**, pp 357–390; c) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107*, 5841–5883; d) V. K. Aggarwal, J. Richardson, in *Science of Synthesis* (Eds: A. Padwa, D. Bellus), George ThiemeVerlag, **2004**, *27*, pp. 21–105; e) J. E. Clark, *Nitrogen, Oxygen and SulfurYlide Chemistry: A Practical Approach in Chemistry*, Oxford University Press, Oxford, **2002**; f) A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.***1997**, *97*, 2341–2372.

[14] a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao *Chem. Rev.* **2015**, *115*, 5301–5365 ; b) C. Zhu, Y. Ding, L.-W. Ye *Org. Biomol. Chem.* **2015**, *13*, 2530–2536; c) X.-Li Sun, Y. Tang *Acc. Chem. Res.* **2008**, *41*, 937–948.

[15] a) R. A. Novikov, A. V. Tarasova, D. A. Denisov, D. D. Borisov, V. A. Korolev, V. P. Timofeev, Y. V. Tomilov *J. Org. Chem.* **2017**, *82*, 2724–2738; b) V. Ganesh, S. Chandrasekaran *Synthesis* **2016**, *48*, 4347–4380; c) R. A. Novikov, A. V. Tarasova, V. A. Korolev, E. V. Shulishov, V. P. Timofeev, Y. V. Tomilov *J. Org. Chem.* **2015**, *80*, 8225–8235; d) R. A. Novikov, A. V. Tarasova, V. A. Korolev, V. P. Timofeev, Y. V. Tomilov *Angew. Chem. Int. Ed.* **2014**, *53*, 3187–3191; *Angew. Chem.* **2014**, *126*, 3251; e) Y. A. Volkova, E. M. Budynina, A. E. Kaplun, O. A. Ivanova, A. O. Chagarovskiy, D. A. Skvortsov, V. B. Rybakov, I. V. Trushkov, M. Y. Melnikov *Chem. Eur. J.* **2013**, *19*, 6586-6590.

[16] For reviews on Donor-Acceptor cyclopropanes, see: a) M. A. Cavitt, L. H. Phun, S. France *Chem. Soc. Rev.* **2014**, *43*, 804–8018; b) T. F. Schneider, J. Kaschel, D. B. Werz Angew. Chem. Int. Ed. 2014, 53, 5504–5523; c) H.-U. Reissig, R. Zimmer *Chem. Rev.* **2003**, *103*, 1151–1196.

[17] a) T. F. Schneider, D. B. Werz *Org. Lett.* **2011**, *13*, 1848–1854; b) T. F. Schneider, J. Kaschel, S. I. Awan, B. Dittrich, D. B. Werz *Chem. Eur. J.* **2010**, *16*, 11276–11288; c) C. Brand, G. Rauch, M. Zanoni, B. Dittrich, D. B. Werz *J. Org. Chem.* **2009**, *74*, 8779–8786; d) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci, M. Spiga *Org. Lett.* **2005**, *7*, 4565–4568.

[18] See ref. 14a-b and a) P. Gouthami, L. N. Chavan, R. Chegondi, S. Chandrasekhar *J. Org. Chem.* **2018**, *83*, 3325–3332; b) D. Worgull, L. Öhler, J. P. Strache, T. Friedrichs, P. Ullrich *Eur. J. Org. Chem.* **2017**, 6077–6080; c) A. O. Chagarovsky, E. M. Budynina, O. A. Ivanova, E. V. Villemson, V. B. Rybakov, I. V. Trushkov, M. Z. Melnikov *Org. Lett.* **2014**, *16*, 2830–2833; d) J.-C. Zheng, C.-Y. Zhu, X.-L. Sun, Y. Tang, L.-X. Dai *J. Org. Chem.* **2008**, *73*, 6909–6912.

[19] O. Rousseau, T. Delaunay, G. Dequirez, T. Trieu-Van, K. Robeyns, R. Robiette, R., *Chem. Eur. J.* **2015**, *21*, 12899-12902.

[20] R. Robiette, J. Marchand-Brynaert, *Synlett* **2008**, 517–520.

[21] For reviews on the rearrangement of vinylcyclopropanes into cyclopentenes, see: a) T. Hudlicky, J. W. Reed, *Angew. Chem. Int. Ed.* **2010**, *49*, 4864–5876; *Angew. Chem.* **2010**, *122*, 4982–4994; b) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1202.

[22] For some previous examples of cyclopropane ring opening by MgI2, see a) L. K. B. Garve, A. Kreft, P. G. Jones, D. B. Werz *J. Org. Chem.* **2017**, *82*, 9235–9242; b) A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 9688–9692; c) R. W. Coscia, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 2496–2498. d) M. E. Scott, M. Lautens, *Org. Lett.* **2005**, *7*, 3045–3047; e) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515; f) M. Lautens, W. Han, *J. Am. Chem. Soc.* **2002**, *124*, 6312–6316.

[23] For the synthesis of 1,1-dicarbonyl ester 1,3-dienes, see O. Rousseau, T. Delaunay, R. Robiette, R. *Synlett* **2014**, *25*, 519–522.

[24] CCDC 1819344 (**5ma**) and CCDC 1405787 (**5ja**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

[25] a) O. Illa, M. Namutebi, C. Saha, M. Ostovar, C. C. Chen, M. F. Haddow, S. Nocquet-Thibault, M. Lusi, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 11951–119566; b) O. Illa, M. Archad, A. Ros, E. M. McGarrigle, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 1832–1830.

[26] This was also confirmed by competition experiments (see SI).

[27] Calculations were carried out at the B3LYP-D3/6-311+G**//B3LYP-D3/6-31+G* level of theory, including a continuum description of dichloromethane solvent using Jaguar 8.5 program package (Jaguar 8.5, Schrodinger, Inc., New York, NY, 2014). See SI for full computational details.

[28] a) S. L. Riches, C. Saha, N. Fontán-Filgueira, E. Grange, E. M. McGarrigle, V. K. Aggarwal *J. Am. Chem. Soc.* **2010**, *132*, 7626-7630; b) V. K. Aggarwal; H. W. Smith; G. Hynd; R. V. H. Jones; R. Fieldhouse; S. E. Spey *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267-3276; c) V. K. Aggarwal, E. Grange, *Chem. Eur. J.* **2006**, *12*, 568-575.

[29] 1,4-Addition is also conceivable but this latter is computed to involve a much higher barrier, in good agreement with experiment.

[30] A similar mechanism was proposed by Lambert *et al.*, see ref. 22c.

[31] Absolute configuration of the quaternary asymmetric centre was attributed assuming that the less hindered ester group undergoes reduction faster.

[32] Stereochemistry was attributed assuming that the more stable diastereoisomer was obtained after epimerization. The higher stability of the *trans-trans* isomer is supported by DFT calculations (see SI).

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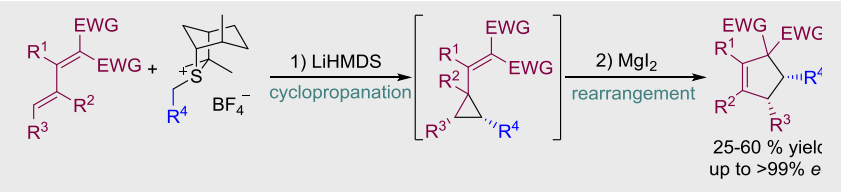

Give me five: A new formal (4+1) annulation between sulfur ylides and 1,1-bis-activated 1,3-dienes affording functionalized cyclopentenes has been developed. The reaction shows a good functional group tolerance and a high diastereo- and enantiocontrol can be achieved using chiral sulfur ylides. A combined experimental and computational study allows for a detailed understanding of the mechanism and origin of stereoselectivity.

*S. Clergue, Dr. O. Rousseau, Dr. T. Delaunay, Dr. G. Dequirez, T.-V. Tran, S. El Aakchioui, Dr. G. Barozzino-Consiglio and Prof. Dr. R. Robiette**

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Asymmetric Sulfur Ylide-Mediated Formal (4+1) Annulation Reaction: Scope and Mechanism