ChemPubSoc Europe

DOI: 10.1002/chem.201502579

CHEMISTRY A European Journal Communication

Asymmetric Synthesis

Formal Asymmetric (4+1) Annulation Reaction between Sulfur Ylides and 1,3-Dienes

Olivier Rousseau, Thierry Delaunay, Geoffroy Dequirez, Tran Trieu-Van, Koen Robeyns, and Raphaël Robiette*[a]

Abstract: A highly enantioselective synthesis of functionalized cyclopentanoids by a formal asymmetric (4+1) annulation strategy was developed. The methodology consists of a stereoselective cyclopropanation reaction between chiral sulfur ylides and 1,3-dienes followed by a, in situ, stereospecific MgI_2-catalyzed rearrangement of vinylcyclopropanes. This method is distinguished by a remarkable compatibility with functional groups and a high stereocontrol.

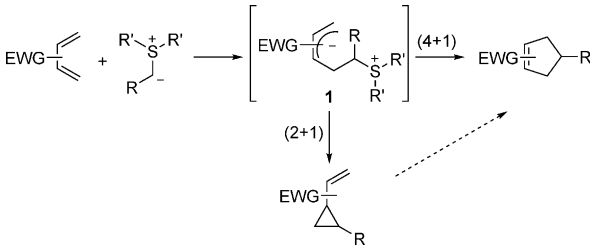
Cycloaddition reactions occupy a central role in organic chemistry as they allow the construction of complex molecular architectures in a single convergent step.[1] The usually high stereocontrol of the newly formed stereogenic centers in these transformations has also contributed to their prominence. Given the ubiquity of five-membered carbocyclic motifs in biologically active compounds,[2] several strategies have been disclosed to develop a (4+1) cycloaddition methodology.[3] Most reported (4+1) cycloaddition strategies toward five-membered carbocycles involve addition of carbenes onto 1,3-dienes or vinylketenes.[4] The high reactivity of carbenes is, however, responsible for a low functional-group tolerance. Alternatives to carbenes have thus been explored by using carbenoid reagents, such as isocyanides,[5] carbon monoxide (and transition-metal catalysis),[6] ylides,[7] α-benzotriazolyl lithium compounds[8] or palladium catalysis.[9] Other four-carbon units have also been considered, such as ω-halogeno-alkenes[10] or 2-(acetoxymethyl)-buta-2,3-dienoate.[11] Intensive efforts are thus underway in order to develop an efficient (4+1) strategy; with the main actual challenges being the chemoselectivity and the lack of asymmetric variants.[12] Herein, we report the enantioselective synthesis of functionalized cyclopentanoids by a formal asymmetric (4+1) annulation strategy using 1,3-dienes and sulfur ylides.

[a] O. Rousseau, Dr. T. Delaunay, Dr. G. Dequirez, T. Trieu-Van, Dr. K. Robeyns, Prof. R. Robiette
Institute of Condensed Matter and Nanosciences
Université catholique de Louvain
Place Louis Pasteur 1 box L4.01.02 (Belgium)
Fax: (+32) 010474168
E-mail: raphael.robiette@uclouvain.be
Homepage: http://www.uclouvain.be/raphael.robiette

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201502579.

Sulfur ylides are versatile reagents which have been reported to be efficient alternatives to (metal) carbenes in different (2+1) annulations, such as epoxydation, aziridination, and cyclopropanation reactions.[13] They have the advantage over carbenes of being easy to generate and handle, and of tolerating a wide range of functional groups. Another important aspect is that, in all these methods, the use of chiral sulfur ylides allowed the resulting products to be obtained with a high enantiocontrol.[13a–d]

We envisioned that the addition of sulfur ylides onto electron-poor 1,3-dienes would lead to zwitterionic intermediates such as **1** that could undergo a ring-closing reaction to form cyclopentenes (Scheme 1).[14] Another possibility is to ring

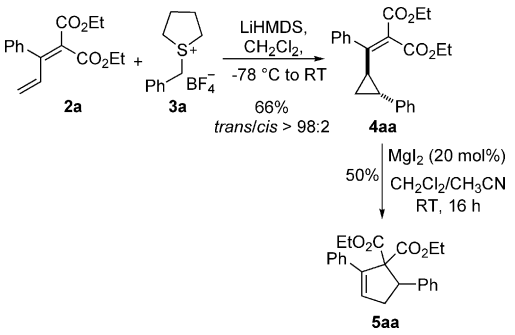


Scheme 1. Reaction of electron-poor 1,3-dienes and sulfur ylides.

close **1** to a three-membered ring.[15] However, in this latter case, one could consider the, in situ, rearrangement of the formed vinylcyclopropane into its corresponding cyclopentene. Indeed, Danheiser,[4m,p] Hudilicky,[4n,o,q] Lambert,[9b] and Legault[4b] have showed that cyclopropanation of 1,3-dienes followed by a vinylcyclopropane rearrangement could constitute an efficient alternative strategy for the direct (4+1) annulation in the synthesis of cyclopentenes.[16]

We began our investigation with the model reaction of 1,3-diene **2a** (1 equiv) with the ylide formed by deprotonation of **3a** (1.1 equiv) (Scheme 2). Stirring these two reagents at −78 °C for 1 h and then at room temperature for 16 h led to vinylcyclopropane **4aa** with a total *trans* selectivity and no trace of corresponding cyclopentene.[17] All our attempts to observe direct formation of cyclopentene **5aa** by modifying the reaction conditions failed. Accordingly, we decided to find reaction conditions under which **4aa** could rearrange into the more stable cyclopentene **5aa**. In the event, we found that MgI_2 catalyzes the rearrangement of **4aa** under very mild conditions (20 mol% MgI_2, RT, 16 h) to give the desired cyclopentene **5aa** in 50% yield.[18,19]

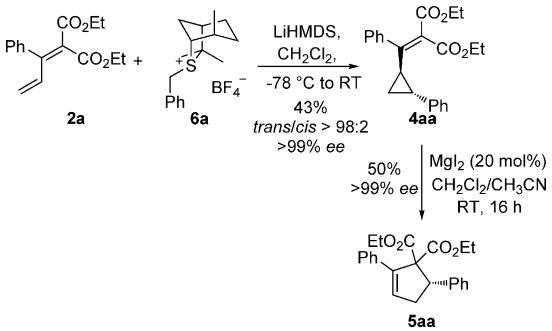
© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Investigation of the model reaction.

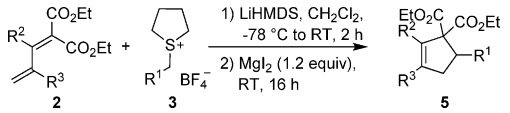
After having showed the potential of sulfur ylides in the development of a (4+1) annulation strategy, we searched for suitable reaction conditions that allowed cyclopentenes to be obtained in one synthetic step. We found that deprotonation of sulfonium salt **3a** in the presence of diene **2a**, at −78 °C, followed by addition of 1.2 equivalents of MgI_2 at room temperature allowed the synthesis of the corresponding cyclopentene **5aa** in 65% isolated yield in one synthetic step (Table 1, entry 1). The scope of the reaction was then evaluated under the optimized conditions. A variety of dienes substituted at the 2- or 3-position participated in the (4+1) annulation process to provide the desired cyclopentenes in 32–57% yields (entries 7–14).[20] The breadth of tolerated substituents was broad, allowing access to cyclopentenes with a double bond substituted by electron-rich or -poor aryl, alkyl, or additional ester groups. The nature of the ylide can also be varied: both electron-rich and -poor benzylic (or allylic) ylides react with dienes **2a** to provide the corresponding cyclopentenes in moderate yields (entries 1–6).

The success of this formal (4+1) annulation methodology encouraged us to develop an asymmetric variant of this process. 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).[21] Deprotonation of **6a** in the presence of diene **2a** allows vinylcyclopropane **4aa** to be obtained with total diastereo- and enantiocontrol, only one stereomer being observed by NMR spectroscopy and HPLC analysis (d.r. > 98:2 and *ee* > 99%; Scheme 3). Much to our surprise, the rearrangement of **4aa** in the presence of MgI_2 (20 mol%) led to corresponding cyclopentene **5aa** with no deterioration of the



Scheme 3. Development of an asymmetric version.

Table 1. Substrate scope of the formal (4+1) annulation.



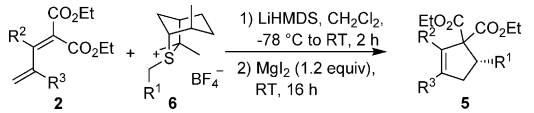
Entry	Diene (**2**)	R^1	Product	Yield [%][a]
1	**2a**	Ph	**5aa**	65
2	**2a**	*p*-FPh	**5ab**	57
3	**2a**	*p*-CO_2MePh	**5ac**	55
4	**2a**	*p*-MePh	**5ad**	50
5	**2a**	*p*-MeOPh	**5ae**	58
6	**2a**	CH=CMe_2	**5af**	57
7	**2b**	Ph	**5ba**	57
8	**2c**	Ph	**5ca**	40
9	**2d**	Ph	**5da**	55
10	**2e**	Ph	**5ea**	45
11	**2f**	Ph	**5fa**	41
12	**2g**	Ph	**5ga**	39
13	**2h**	Ph	**5ha**	32
14	**2i**	Ph	**5ia**	36[b]

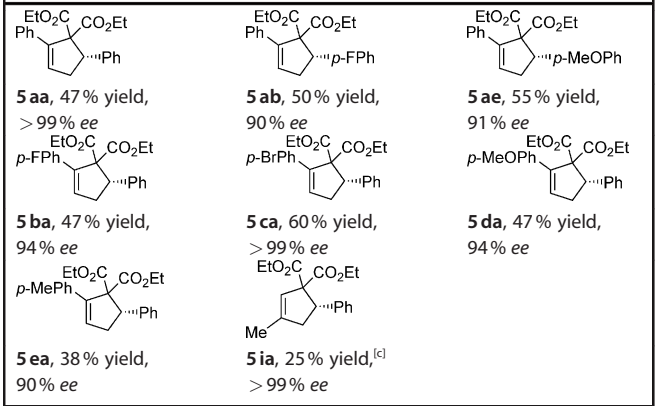
[a] Yield of pure product after purification by flash chromatography. [b] Determined on the crude by ^{1}H NMR spectroscopic analysis using an internal standard. The reaction was carried out using benzyl(diisopropyl)-sulfonium tetrafluoroborate.

enantiomeric excess, which indicated a stereospecific rearrangement (vide infra). Application of this strategy using our one-pot procedure resulted in a series of cyclopentenes in 25–60% yield and a high enantiocontrol (90–99% *ee*) (Table 2).

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

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





[a] Yield of pure product after flash chromatography. Enantiomeric excesses were determined by chiral HPLC (see the Supporting Information). [b] Absolute configuration of **5ia** was determined by single-crystal X-ray diffraction analysis (see the Supporting Information). Absolute configuration of all other products was determined by analogy. [c] Determined from the crude by ^{1}H NMR spectroscopic analysis using an internal standard.

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 (Figure 1).[21] The stereospecific character of the vinylcyclopropane rearrangement could be explained by iodide-assisted ring-opening by a S_N2 mechanism followed by intramolecular S_N2 alkylation, leading thus to an overall retention of configuration for the chiral center.[22]

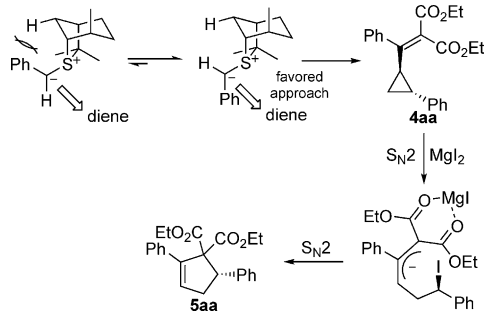
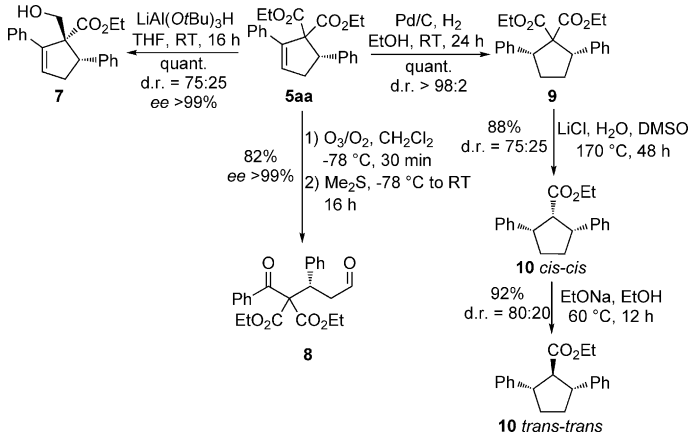


Figure 1. Model for enantiocontrol.

As an illustration of the versatility of this method, cyclopentene **5aa** was subjected to a series of transformations (Scheme 4): Upon addition of a sterically hindered aluminum hydride reagent, a diastereoselective reduction of one of the ester groups could be obtained, thus generating a chiral all-carbon quaternary stereocenter (**7**).[23] Ozonolysis of the double bond was also performed, leading to acyclic compound **8** without alteration of the enantiomeric excess. The double bond can be reduced as well to introduce a new stereocenter and produce *meso*-compound **9** with an excellent diastereoselectivity. Subsequent decarboxylation allows formation of **10** with a *cis–cis* relative configuration.[24] Interestingly, the more stable *trans–trans* isomer can be obtained by epimerization under basic conditions.



Scheme 4. Transformations of **5aa**.

In summary, we have developed a formal asymmetric (4+1) annulation methodology that provides facile access to functionalized cyclopentenes. The strategy consists of stereoselective cyclopropanation reaction between chiral sulfur ylides and 1,3-dienes followed by, in situ, stereospecific MgI_2-catalyzed rearrangement of vinylcyclopropanes. The reaction proceeds under mild reaction conditions with high functional-group tolerance and stereocontrol. Further efforts are in progress to expand the scope of this methodology and elucidate the exact mechanism and factors controlling stereoselectivity.

Acknowledgements

The authors thank C. Le Duff and L. Collard for their technical assistance in NMR and HPLC, respectively. This work was supported by the Fonds de la Recherche Scientifique-FNRS (F.R.S-FNRS), the FRIA (fellowship to O.R.) and the FSR (fellowship to T.D. and G.D.). R.R. is a Chercheur qualifié of the F.R.S.-FNRS.

Keywords: annulation · asymmetric synthesis · cyclopentenes · vinylcyclopropanes · ylides

[1] a) *Cycloaddition Reactions in Organic Synthesis* (Eds: S. Kobayashi, K. A. Jorgensen), WILEY-VCH, 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), Wiley, Hoboken, **2014**.

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

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

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[4] a) M. Déry, L.-P. Lefebvre, K. Aissa, C. Spino, *Org. Lett.* **2013**, *15*, 5456 – 5459; b) F. Beaumier, M. Dupuis, C. Spino, C. Y. Legault, *J. Am. Chem. Soc.* **2012**, *134*, 5938 – 5953; c) L. Boisvert, F. Beaumier, C. Spino, *Org. Lett.* **2007**, *9*, 5361 – 5363; d) F. Aznar, M. Fañanás-Mastral, J. Alonso, F. J. Fañanás, *Chem. Eur. J.* **2008**, *14*, 325 – 332; e) W. H. Moser, L. A. Feltes, L. Sun, M. W. Giese, R. W. Farrell, *J. Org. Chem.* **2006**, *71*, 6542 – 6546; f) C. Spino, H. Rezaei, K. Dupont-Gaudet, F. Bélanger, *J. Am. Chem. Soc.* **2004**, *126*, 9926 – 9927; g) J. H. Rigby, Z. Wang, *Org. Lett.* **2003**, *5*, 263 – 264; h) J. Barluenga, S. López, J. Flórez, *Angew. Chem.* **2003**, *115*, 141 – 143; *Angew. Chem. Int. Ed.* **2003**, *42*, 231 – 233; *Angew. Chem.* **2003**, *115*, 241 – 243; i) A. M. Dalton, Y. Zhang, C. P. Davie, R. L. Danheiser, *Org. Lett.* **2002**, *4*, 2465 – 2468; j) J. Pfeiffer, M. Nieger, K. H. Dötz, *Eur. J. Org. Chem.* **1998**, 1011 – 1022; k) J. H. Rigby, A. Cavezza, G. Ahmed, *J. Am. Chem. Soc.* **1996**, *118*, 12848 – 12849; l) M. A. Sierra, B. Soderberg, P. A. Lander, L. S. Hegedus, *Organometallics* **1993**, *12*, 3769 – 3771; m) R. L. Danheiser, J. J. Bronson, K. Okano, *J. Am. Chem. Soc.* **1985**, *107*, 4579 – 4581; n) T. Hudlicky, F. Koszyk, D. M. Dochwat, G. L. Cantrell, *J. Org. Chem.* **1981**, *46*, 2911 – 2915; o) R. P. Short, J.-M. Revol, B. C. Ranu, T. Hudlicky, *J. Org. Chem.* **1983**, *48*, 4453 – 4461; p) R. L. Danheiser, C. Martinez-Davila, R. J. Auchus, J. T. Kadonaga, *J. Am. Chem. Soc.* **1981**, *103*, 2443 – 2446; q) 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. V. Gagnier, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 4804 – 4807; b) M. Murakami, K. Itami, Y. Ito, *J. Am. Chem. Soc.* **1997**, *119*, 2950 – 2951; c) M. Murakami, K. Itami, Y. Ito, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2691 – 2694; *Angew. Chem.* **1995**, *107*, 2943 – 2946; d) M. Franck-Neumann, J.-M. Vernier, *Tetrahedron Lett.* **1992**, *33*, 7365 – 7368; e) M. Franck-Neumann, E. L. Michelotti, R. Simler, J.-M. Vernier, *Tetrahedron Lett.* **1992**, *33*, 7361 – 7364; f) B. E. Eaton, B. Rollman, *J. Am. Chem. Soc.* **1992**, *114*, 6245 – 6246.

[7] a) J. Tian, H. Sun, R. Zhou, Z. He, *Chin. J. Chem.* **2013**, *31*, 1348 – 1351; b) C. R. Reddy, P. Kumaraswamy, M. D. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 9052 – 9057; c) 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) R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6950 – 6952; *Angew. Chem.* **2009**, *121*, 7084 – 7086; b) 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**,*126*, 5749 – 5753; 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 some 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), Thieme, Stuttgart, **2004**, pp. 21 – 105; e) J. E. Clark, *Nitrogen, Oxygen and Sulfur Ylide 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] Danheiser et al. have already reported a (4+1) annulation based on the reaction of (trialkylsilyl)vinylketenes with nonstabilized suflur ylides. See ref. [7c].

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

[16] For reviews on the rearrangement of vinylcyclopropanes into cyclopentenes, see: a) T. Hudlicky, J. W. Reed, *Angew. Chem. Int. Ed.* **2010**, *49*, 4864 – 4876; *Angew. Chem.* **2010**, *122*, 4982 – 4994; b) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197 – 1202.

[17] Exclusive formation of cyclopropane by addition of sulfur ylides onto 1,3-dienes was previously observed. See ref. [15].

[18] For some previous examples of cyclopropane ring opening by MgI_2, see ref. [9b] and a) A. T. Parsons, A. G. Smith, A. J. Neel, J. S. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 9688 – 9692; b) M. E. Scott, M. Lautens, *Org. Lett.* **2005**, *7*, 3045 – 3047; c) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 11505 – 11515; d) M. Lautens, W. Han, *J. Am. Chem. Soc.* **2002**, *124*, 6312 – 6316.

[19] It is worth mentioning that vinylcyclopropanes derived from monoactivated 1,3-diene methyl 2,4-pentadienoate (see ref. [15]) do not rearrange under these reaction conditions.

[20] All our attempts using 1,1-dicarbonyl ester 1,3-dienes substituted at the 4-position of the diene moiety led to no reaction or the 1,4-adduct.

[21] 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.

[22] Our hypothesis is supported by experimental results, see ref. [18c,d]. A similar mechanism was proposed by Lambert et al., see ref. [9b]. Mechanistic studies of this rearrangement are ongoing in our laboratory.

[23] Absolute configuration of the quaternary chiral center was attributed assuming that the less hindered ester group undergoes reduction faster.

[24] Stereochemistry was attributed assuming that the more stable diastereomer was obtained after epimerization. The higher stability of the *trans–trans* isomer is supported by DFT calculations (see the Supporting Information).

Received: July 2, 2015
Published online on July 31, 2015

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim