

Lewis Acid Catalyzed Formal Intramolecular [3+2] Cross-Cycloaddition of Cyclopropane 1,1-Diesters with Alkenes: General and Efficient Strategy for Construction of Bridged [n.2.1] Carbocyclic Skeletons**

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Developing efficient and general strategies to construct skeletally complex and diverse polycyclic skeletons is important for both synthesis of natural products and chemical biology research. The structurally complex, diverse, and interesting family of bridged [n.2.1] ($n=2,3,4$) carbocyclic skeletons, especially that of [3.2.1]octane, exists in terpenoids and alkaloids which display an important and wide range of biological activities (Figure 1).^[1] Additionally, because of

ment of a more general, efficient, and conceptually new strategy to afford such [n.2.1]carbocyclic skeletons still remains important and challenging.

A cyclopropane 1,1-diester can be easily prepared and has been proven to be a versatile building block in Lewis acid (LA) promoted intermolecular cycloadditions^[2ae] for the construction of various cyclic skeletons.^[4] Compared to its intermolecular variant, examples of LA-promoted intramolecular cycloadditions of cyclopropane 1,1-diester are limited.^[5,6] Our laboratory recently described an IMCC (intramolecular cross-cycloaddition) of functionalized cyclopropanes with carbonyl or imine groups under the catalysis of LAs and it provides a general strategy for the construction of bridged oxa- and aza-[n.2.1] or [n.3.1] skeletons. The method has been successfully applied to the total synthesis of platensimycin and bruguierol.^[7] We envisioned using the IMCC on cyclopropane 1,1-diester/alkene system to provide a general and efficient strategy for the construction of bridged [n.2.1] carbocyclic skeletons (Scheme 1).

Prior to our research, only one IMPC (intramolecular parallel cycloaddition) example of a cyclopropane 1,1-diester and an alkene was reported by Snider et al. in 1986 (Scheme 1).^[5,8] Upon analyzing the reported examples,^[5,9,10] we hypothesized that in the case of the intramolecular reaction of a cyclopropane 1,1-diester with an alkene the most important factor for regioselectivity was the stability of the generated carbenium in the first cyclization step, and thus the substitution of alkene must play an important role (Scheme 1). When the less-substituted internal carbon atom in C=C connects to C2, a more stable carbenium is generated on the more substituted external carbon atom in the C=C, and a second carbon-carbon bond is formed subsequently to afford a fused bicyclic skeleton (IMPC: Snider's case). We thus envisioned that by using a less-substituted external carbon atom in the C=C, the generated internal carbenium would be more stable and a bridged [n.2.1] skeleton would result (IMCC). Herein we describe the first LA-catalyzed intramolecular cycloaddition of cyclopropane with an alkene as a general strategy for the construction of bridged [n.2.1] carbocyclic skeletons.^[11]

Based on a preliminary intermolecular experiment between a cyclopropane 1,1-diester and styrene,^[12] the benzene-linked substrate **1a** was employed to explore the optimized reaction conditions for the intramolecular [3+2] cycloaddition. Under the catalysis of Sc(OTf)₃ (20 mol %) in 1,2-dichloroethane (DCE), we found that a [3+2] IMCC successfully afforded the desired [3.2.1]octane product **2a** in

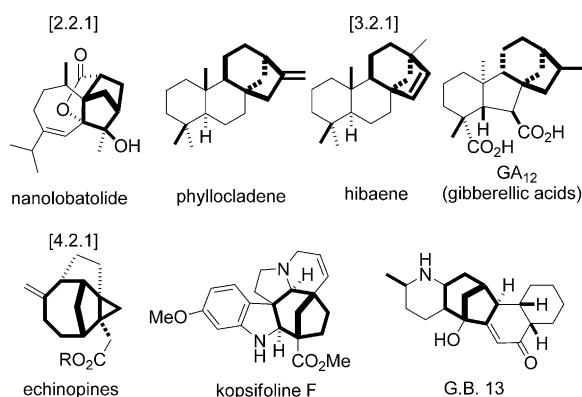


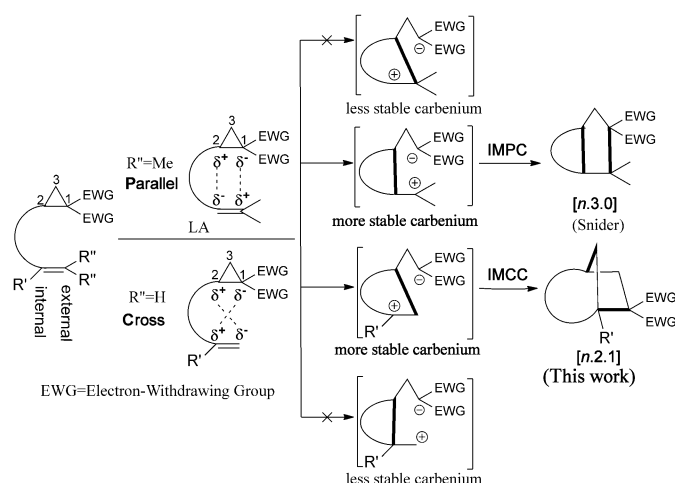
Figure 1. Representative natural products with [n.2.1] carbocyclic skeletons.

their inherent stereochemistry such skeletons are also useful building blocks for stereoselective synthesis of natural products having other types of skeletons, for example, the *cis*-1,3-disubstituted cycloalkanes which can be accessed by cleavage of carbon-carbon bond. Because of the importance of such skeletons, it is not surprising that many efficient and novel strategies have been successfully developed. For example, cycloadditions and domino reactions.^[2,3] Develop-

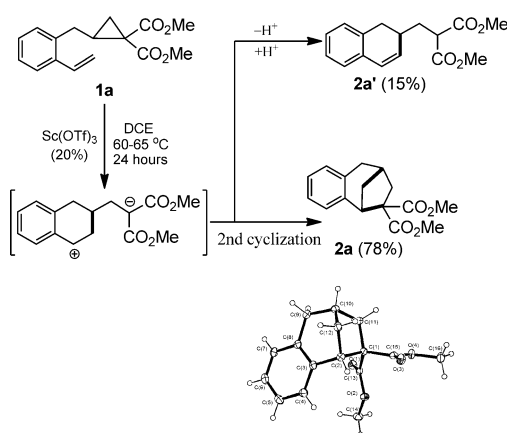
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Scheme 1. Regioselectivity of intramolecular [3+2] cycloaddition of cyclopropane 1,1-diester with alkene. EWG = electron-withdrawing group.



Scheme 2. [3+2] IMCC of **1a** and X-ray crystal structure of **2a**.

78 % yield together with **2a'** (15 %; Scheme 2). The reaction of **2a** under the same reaction conditions did not afford **2a'**. Therefore, formation of **2a'** indicated a stepwise process for the [3+2] IMCC. In this process a carbenium was generated after the first cyclization step, and gave the cycloadduct **2a** after the second cyclization step or gave the elimination product **2a'** with loss of a proton resulting from either the steric hindrance of the carbenium or the formation of a conjugated system. The structure of **2a** was unambiguously confirmed by NMR spectroscopy, HRMS, and X-ray crystal structure analysis.^[13,14] This reaction showed excellent regioselectivity and no [3+2] IMPC cycloadduct was observed. Various parameters were tested to optimize the reaction conditions (see the Supporting Information), and we selected Sc(OTf)₃/DCE for further investigation.

Under the optimized reaction conditions, a series of reactions were carried out (Table 1). Reaction of the substrate **1c** with a 1,1-disubstituted alkene also worked well with excellent regioselectivity to afford the [3+2] IMCC product **2c**. In addition to **2c** the elimination product **2c'** was also

Table 1: LA-catalyzed [3+2] IMCC of cyclopropanes **1**.^[a,b]

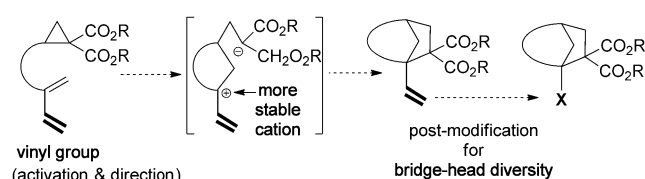
Cyclopropane 1	Product 2
	 2a (78%)
	 2b (70%)
	 2c (82%)
	 2c' (14%)
	 2d (78%)
	 2e (30%, 1.8:1)
	 2f (71%)
	 2g' (98%)
	 2h (82%)
	 2i (59%)
	 2j (18%)
	 2k' (61%)

[a] Reaction conditions: 0.4 mmol of **1**, 20 mol % of Sc(OTf)₃, 7.8 mL of DCE, 65 °C, Ar. [b] Yield of isolated product. [c] 30 mol % of catalyst was employed. [d] Reaction was run at 10–15 °C. [e] 5 mol % of catalyst was used.

obtained. The substrate **1d**, having a quaternary carbon center (C2) in the cyclopropane ring also worked well, and the substrate **1e** having a 1,2-disubstituted alkene (*Z/E* = 3.0:1) gave the [3+2] IMCC product **2e** as a mixture of two

diastereoisomers (1.8:1). The change in the ratio of the isomers was probably a result of the different facial attack of C=C on C2 of the cyclopropane. In the reaction of the enyne substrate **1f**, the IMCC product **2f** and the [3+2] IMPC product **2f'**, from the cyclopropane 1,1-diester reaction with the alkyne, was also obtained.^[6a] We also tried the reaction of the enol silyl ether **1g**, however, instead of the IMCC product, **2g'** was obtained as a result of a retro-aldol of the IMCC product, a reaction similar to that reported by Jung et al.^[6b] and its intermolecular variant reported by Tang et al. and us previously.^[8a,f,h] When the alkene moiety was not directly connected to the benzene ring (nonstyrene type), the reaction still worked well. To the best of our knowledge, this is the first LA-catalyzed cycloaddition of cyclopropane with nonactivated alkenes. Three experiments for the construction of a [2.2.1]heptane skeleton were also carried out. The substrate **1i** gave the desired cycloadduct **2i** successfully, and reaction of **1j** with a 1,2-disubstituted alkene also worked but with a lower yield. The reaction of **1k** with a 1,1-disubstituted alkene gave the elimination product **2k'**.

To further illustrate the generality of the strategy and better elucidate its potential application to the synthesis of polycyclic natural products (especially those containing a [3.2.1]octane, Figure 1), several core skeletons in related natural products have been constructed (Table 2). However, different from the benzofused substrates, the first example (**3a**) was unsuccessful. Another example (**3g**) worked but with a lower yield. Considering of the importance of the stability of the generated carbenium as mentioned above (Scheme 1), we thought that introduction of a suitable functional group (as an activating group) which would stabilize the generated carbenium might be crucial. Additionally, such a functional group should also affect the regioselectivity (directing group) and provide a means for post-modification to meet the structural diversity of bridge-head substituents in natural products (e.g. hydrogen in phyllocladene, methyl in hibaene, ester in kopsifoline, and hydroxy in G. B. 13; Figure 1). A geminal vinyl group was the suitable selection (Scheme 3). Reactions of several diene substrates were



Scheme 3.

implemented and the results were positive (**3b–f**, Table 2). Under the catalysis of Sc(OTf)₃ (20 mol %) the reaction of **3b** successfully underwent the reaction to give **4b** in 66 % yield. When SnCl₄ (20 mol %) was used as the catalyst, the yield was increased to 77 %. It should be noted that compared to the failure of the construction of [4.2.1]nonane from a non-vinyl-substituted substrate, the vinyl-substituted example **4c** was successful, albeit in a lower yield. Synthesis of the cyclopentane-based tricyclic product **4d** and the cyclohexane-

Table 2: LA-catalyzed [3+2] IMCC of cyclopropanes **3**.^[a,b]

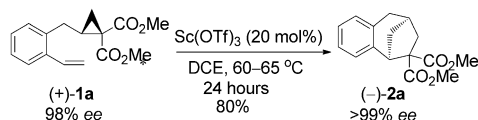
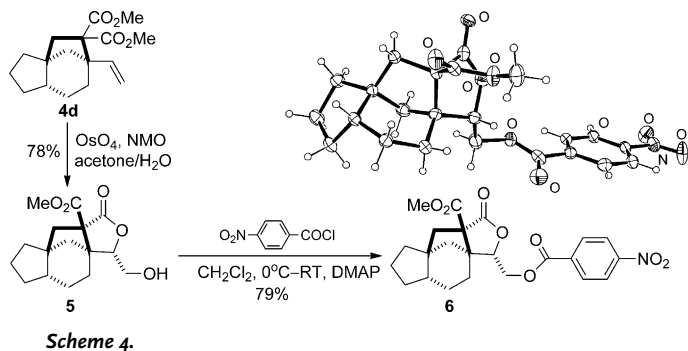
Cyclopropane 3	Product 4

[a] Reaction conditions: 0.02 mmol of **3**, 20 mol % of SnCl₄, 60–65 °C, 4.0 mL of DCE, Ar. [b] Yield of isolated product. [c] 20 mol % of Sc(OTf)₃ was used. [d] Reaction still proceeded at 50 °C with a similar yield.

based tricyclic products **4e** and **4f** were also successful. Stereoselectivities of these examples were excellent. We believe that these examples will be valuable to the synthesis of structurally complex and diverse polycyclic terpenoids and alkaloids (Figure 1). A single-crystal X-ray structure of **6** was obtained to confirm the stereochemistry of the products (Scheme 4).

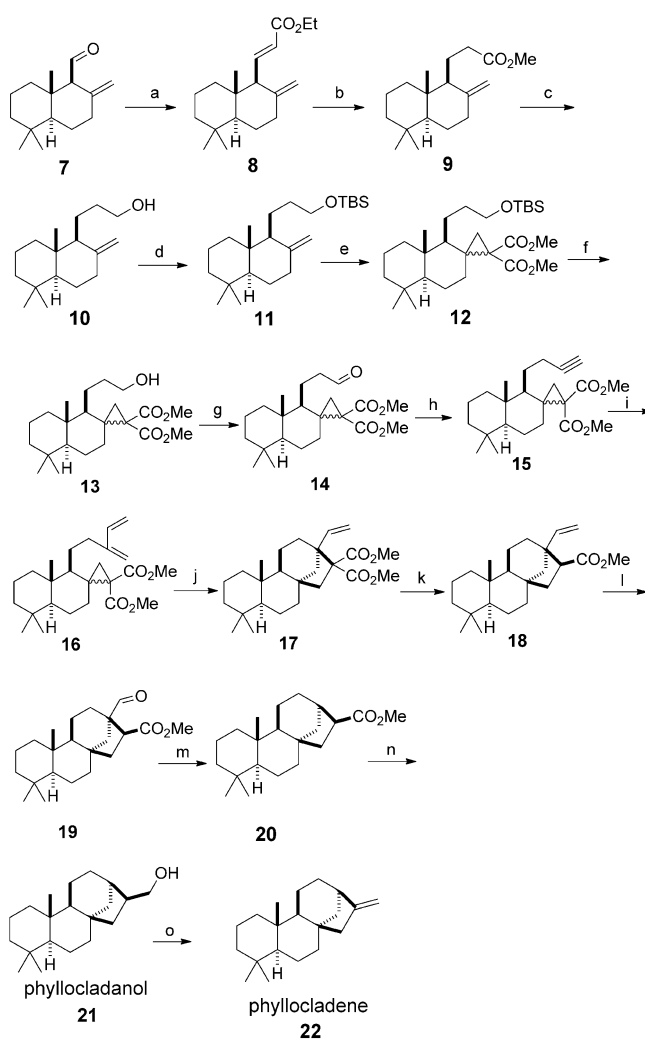
An asymmetric experiment has been carried out to further elucidate the potential application of this IMCC strategy to the synthesis of natural products. Under the catalysis of Sc(OTf)₃ (20 mol %), the [3+2] IMCC of the chiral substrate (+)-**1a** successfully afforded (–)-**2a** (> 99 % *ee*) in 80 % yield (Scheme 5). This result indicated that there was no racemization of the stereogenic carbon center in the cyclopropane ring.

To further demonstrate the potential of this strategy, the [3+2] IMCC was used in the total synthesis of the natural products phyllocladanol^[15] and phyllocladene^[16] (Scheme 6). The Wittig olefination of the known aldehyde **7**^[17] afforded **8** which was additionally reduced to the alcohol **10**. Cyclopropanation of **11** gave the cyclopropane 1,1-diester **12**, and after the sequential deprotection/oxidation/alkynylation/



RCM^[18] process, the [3+2] IMCC precursor **16** was obtained. Under the catalysis of SnCl_4 , the [3+2] IMCC product **17** was successfully obtained in an 81 % yield. To our surprise, even though the precursor **16** was a mixture of two stereoisomers (1.5:1), the cycloadduct **17** was obtained as a single isomer, thus indicating a stepwise ring-opening/cyclization process. Subsequent dealkoxycarbonylation^[19] and oxidative cleavage of the double bond gave the aldehyde **19**, which was easily oxidized in air and quickly subjected to the decarbonylation^[20] step to afford **20**. The reduction of **20** afforded phyllocladanol (**21**), and phyllocladene (**22**) was finally obtained from **21** by a one-pot iodination/dehydroiodination operation.^[21] The characterization data were identical with those reported in the literature.^[16,22]

In summary, by rationally analyzing the influence of the activation and directing effects of the substituents of an alkene moiety on the regioselectivity and reactivity, we developed a novel [3+2] IMCC of cyclopropane 1,1-diester with alkenes. To the best of our knowledge, this is the first acid-catalyzed intramolecular [3+2] cycloaddition of a cyclopropane with an alkene, as well as the first acid-catalyzed [3+2] cycloaddition of cyclopropane with a non-activated alkene. This [3+2] IMCC offers an efficient and general strategy for the construction of structurally complex and diverse bridged [*n*.2.1] carbocyclic skeletons. The features of this strategy include high efficiency, excellent stereo- and regioselectivity, mild reaction conditions, and generality. The [3+2] IMCC strategy has been successfully applied to the total synthesis of the tetracyclic diterpenoids phyllocladanol and phyllocladene. Additional investigation of this [3+2] MCC strategy, including its potential application to the total synthesis of polycyclic terpenoids and alkaloids is being carried out in our laboratory.



Scheme 6. Total synthesis of (±)-phyllocladanol and (±)-phyllocladene: a) $\text{PPh}_3=\text{CH}_2\text{CO}_2\text{Et}$, ethanol, 98 %; b) Mg/MeOH , reflux, 90 %; c) LiAlH_4 , THF, 0 °C, 89 %; d) TBSCl , Imidazole, PPh_3 , CH_2Cl_2 , RT, 83 %; e) $\text{N}_2=\text{C}(\text{CO}_2\text{Me})_2$, $[\text{Rh}(\text{esp})_2]$, 32 °C, 54 %; f) 1 M HCl , THF, RT, 83 %; g) IBX , DMSO/THF , RT, 87 %; h) Bestmann reagent, K_2CO_3 , MeOH , RT, 84 %; i) Grubbs-II, ethylene, 2.5 MPa, DCM, RT, 86 %; j) SnCl_4 (20 mol %), DCE, 60–65 °C, 81 %; k) LiCl , wet DMSO , 160 °C, 86 %; l) O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1), –78 °C, 74 %; m) PPh_3RhCl , PhCN , 140–170 °C, 81 %; n) LiAlH_4 , THF, RT, 90 %; o) 1. I_2 , PPh_3 , Imidazole, CH_2Cl_2 , 0 °C–RT; 2. $t\text{BuOK}$, DMSO , RT, 66 % (two steps). DMSO = dimethylsulfoxide, IBX = *o*-iodoxybenzoic acid, $[\text{Rh}(\text{esp})_2]$ = bis[rhodium ($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)], TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

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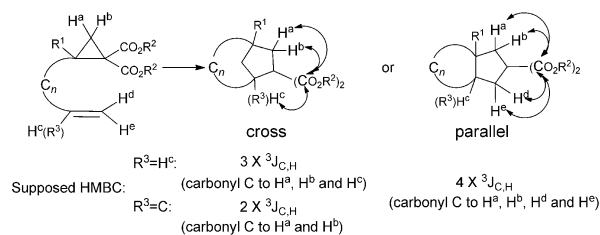
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- [1] a) H. Sun, S. Li, *Diterpenoid Chemistry*, Chemical Industry Press, Beijing, 2011; b) F. Wang, Q. Chen, X. Liu, *Nat. Prod. Rep.* **2010**, 27, 529; c) M. Dong, B. Cong, S.-H. Yu, F. Sauriol, C.-H. Huo, Q.-W. Shi, Y.-C. Gu, L. O. Zamir, H. Kiyota, *Org. Lett.* **2008**, 10, 701;

- d) Y. P. Shi, *Mono and Sesquiterpenoid Chemistry*, Chemical Industry Press, Beijing, **2008**; e) F. P. Wang, *Alkaloid Chemistry*, Chemical Industry Press, Beijing, **2008**; f) H. Sun, S. Huang, Q. Han, *Nat. Prod. Rep.* **2006**, *23*, 673; g) E. Breitmaier, *Terpenes*, Wiley-VCH, Weinheim, **2006**; h) L. N. Mander, *Nat. Prod. Rep.* **2003**, *20*, 49; i) L. N. Mander, *Chem. Rev.* **1992**, *92*, 573; j) J. R. Hanson, *Nat. Prod. Rep.* **1988**, *3*, 211.
- [2] Selected reviews: a) M. Presset, Y. Coquerel, J. Rodriguez, *Chem. Rev.* **2013**, DOI: 10.1021/cr200364p; b) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812; c) M. Ruiz, P. Lopez-Alvarado, G. Giorgi, J. C. Menendez, *Chem. Soc. Rev.* **2011**, *40*, 3445; d) W. Zhao, *Chem. Rev.* **2010**, *110*, 1706; e) M. Harmata, *Chem. Commun.* **2010**, 46, 8886; f) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.* **2009**, 5676; g) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; h) M. Harmata, P. Rashatasakhon, *Tetrahedron* **2003**, *59*, 2371; i) F. Fringuelli, A. Taticchi, *The Diels–Alder Reaction: Selected Practical Methods*, Wiley, New York, **2002**; j) M. Toyota, M. Ihara, *Synlett* **2002**, 1211; k) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; l) J. H. Rigby, *Tetrahedron* **1999**, *55*, 4521; m) M. H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27; n) E. M. M. Toyota, M. Ihara, *Tetrahedron* **1999**, *55*, 5641; o) J. H. Rigby, F. C. Pigge, *Org. React.* **1997**, *51*, 351; p) M. Harmata, *Tetrahedron* **1997**, *53*, 6235; q) V. Singh, B. Thomas, *Tetrahedron* **1998**, *54*, 3647; G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671; r) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339; s) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; t) E. Negishi, C. Coperet, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365; u) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; v) H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203; w) J. H. Rigby, *Acc. Chem. Res.* **1993**, *26*, 579; x) P. Dowd, W. Zhang, *Chem. Rev.* **1993**, *93*, 2091; y) L. E. Overman, M. M. Abelman, D. J. Kucera, V. D. Tran, D. J. Ricca, *Pure Appl. Chem.* **1992**, *64*, 1813; z) J. Casanova, G. Koukoua, B. Waegell, *Bull. Soc. Chim. Fr.* **1990**, *127*, 528; aa) J. Mann, *Tetrahedron* **1986**, *42*, 4611; ab) H. M. R. Hoffmann, *Angew. Chem.* **1984**, *96*, 29; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1; ac) L. Mander, *Acc. Chem. Res.* **1983**, *16*, 48; ad) R. Noyori, *Acc. Chem. Res.* **1979**, *12*, 61. ae) Generally, cycloadditions of cyclopropanes mentioned in this context should be called formal cycloadditions or annulations.
- [3] Some strategies reported for construction of [n.2.1] carbocyclic skeletons in recent years: a) C. W. Plummer, A. Soheili, J. L. Leighton, *Org. Lett.* **2012**, *14*, 2462; b) J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros, M. Tomas, *Angew. Chem.* **2011**, *123*, 2155; *Angew. Chem. Int. Ed.* **2011**, *50*, 2107; c) J. M. Winne, S. Catak, M. Waroquier, V. Van Speybroeck, *Angew. Chem.* **2011**, *123*, 12196; *Angew. Chem. Int. Ed.* **2011**, *50*, 11990; d) T. Achard, A. Leprier, Y. Gimbert, H. Clavier, L. Giordano, A. Tenaglia, G. Buono, *Angew. Chem.* **2011**, *123*, 3614; *Angew. Chem. Int. Ed.* **2011**, *50*, 3552; e) J. C. Green, T. R. R. Pettus, *J. Am. Chem. Soc.* **2011**, *133*, 1603; f) S. Levin, R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 774; g) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, A. E. Kaplun, I. V. Trushkov, M. Ya. Melnikov, *Adv. Synth. Catal.* **2011**, *353*, 1125; h) M. Yoshida, C. Sugimura, K. Shishido, *Org. Lett.* **2011**, *13*, 3482; i) V. M. Marx, R. L. Stoddard, G. S. Heverly-Coulson, D. J. Burnell, *Chem. Eur. J.* **2011**, *17*, 8098; j) B. B. Liau, M. D. Shair, *J. Am. Chem. Soc.* **2010**, *132*, 9594; k) T. Jin, M. Himuro, Y. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5590; l) T. Jin, M. Himuro, Y. Yamamoto, *Angew. Chem.* **2009**, *121*, 6007; *Angew. Chem. Int. Ed.* **2009**, *48*, 5893; m) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem.* **2009**, *121*, 3754; *Angew. Chem. Int. Ed.* **2009**, *48*, 3699; n) C. M. Orac, S. C. Bergmeier, *Tetrahedron Lett.* **2009**, *50*, 1261; o) J. M. Schomaker, F. D. Toste, R. G. Bergman, *Org. Lett.* **2009**, *11*, 3698; p) S. Bhunia, R.-S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16488; q) C.-C. Lin, T.-M. Teng, C.-C. Tsai, H.-Y. Liao, R.-S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16417; r) M. Movassaghi, B. Chen, *Angew. Chem.* **2007**, *119*, 571; *Angew. Chem. Int. Ed.* **2007**, *46*, 565; s) N. T. McDougal, S. E. Schaus, *Angew. Chem.* **2006**, *118*, 3189; *Angew. Chem. Int. Ed.* **2006**, *45*, 3117; t) A. Goeke, D. Mertl, G. Brunner, *Angew. Chem.* **2005**, *117*, 101; *Angew. Chem. Int. Ed.* **2005**, *44*, 99; u) K. C. Nicolaou, G. E. A. Carenzi, V. Jeso, *Angew. Chem.* **2005**, *117*, 3963; *Angew. Chem. Int. Ed.* **2005**, *44*, 3895; v) S. Katayama, M. Yamauchi, *Chem. Pharm. Bull.* **2005**, *53*, 666; w) H. M. L. Davies, X. Dai, *J. Am. Chem. Soc.* **2004**, *126*, 2692; x) L. N. Mander, M. M. McLachlan, *J. Am. Chem. Soc.* **2003**, *125*, 2400; y) G. Bélanger, P. Deslongchamps, *Org. Lett.* **2000**, *2*, 285; z) M. E. Fox, C. Li, J. P. Marino, Jr., L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 5467.
- [4] Selected reviews: a) M. J. Campbell, J. S. Johnson, A. T. Parsons, P. D. Pohlhaus, S. D. Sanders, *J. Org. Chem.* **2010**, *75*, 6317; b) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051; c) F. De Simone, J. Waser, *Synthesis* **2009**, 3353; d) D. Agrawal, V. K. Yadav, *Chem. Commun.* **2008**, 6471; e) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321; f) H.-U. Reißig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; g) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165; h) E. Wenkert, *Acc. Chem. Res.* **1980**, *13*, 27; i) S. Danishefsky, *Acc. Chem. Res.* **1979**, *12*, 66.
- [5] R. B. Beal, M. A. Dombroski, B. B. Snider, *J. Org. Chem.* **1986**, *51*, 4391.
- [6] For intramolecular [3+2] cycloadditions: a) X. Xia, X. Song, X. Liu, Y. Liang, *Chem. Asian J.* **2012**, *7*, 1538; b) M. E. Jung, J. J. Chang, *Org. Lett.* **2010**, *12*, 2962; c) T. P. Lebold, M. A. Kerr, *Org. Lett.* **2009**, *11*, 4354; d) S. K. Jackson, A. Karadeolian, A. B. Driega, M. A. Kerr, *J. Am. Chem. Soc.* **2008**, *130*, 4196; e) C. A. Carson, M. A. Kerr, *Org. Lett.* **2009**, *11*, 777; f) A. B. Leduc, M. A. Kerr, *Angew. Chem.* **2008**, *120*, 8063; *Angew. Chem. Int. Ed.* **2008**, *47*, 7945. For intramolecular [3+3] cycloaddition: g) D. A. Dias, M. A. Kerr, *Org. Lett.* **2009**, *11*, 3694.
- [7] a) Z. Wang, *Synlett* **2012**, 2311; b) Y. Bai, W. Tao, J. Ren, Z. Wang, *Angew. Chem.* **2012**, *124*, 4188; *Angew. Chem. Int. Ed.* **2012**, *51*, 4112; c) S. Xing, Y. Li, Z. Li, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2011**, *123*, 12813; *Angew. Chem. Int. Ed.* **2011**, *50*, 12605; d) S. Xing, W. Pan, C. Liu, J. Ren, Z. Wang, *Angew. Chem.* **2010**, *122*, 3283; *Angew. Chem. Int. Ed.* **2010**, *49*, 3215; e) B. Hu, S. Xing, J. Ren, Z. Wang, *Tetrahedron* **2010**, *66*, 5671.
- [8] For [3+2] cycloadditions of donor and/or acceptor-activated cyclopropanes with C=C: a) J. Qu, Y. Liang, H. Xu, X. Sun, Z. Yu, Y. Tang, *Chem. Eur. J.* **2012**, *18*, 2196; b) F. de Nanteuil, J. Waser, *Angew. Chem.* **2011**, *123*, 12281; *Angew. Chem. Int. Ed.* **2011**, *50*, 12075; c) B. M. Trost, P. J. Morris, *Angew. Chem.* **2011**, *123*, 6291; *Angew. Chem. Int. Ed.* **2011**, *50*, 6167; d) A. F. G. Goldberg, B. M. Stoltz, *Org. Lett.* **2011**, *13*, 4474; e) A. O. Chagarovskiy, O. A. Ivanova, E. M. Budynina, I. V. Trushkov, M. Y. Melnikov, *Tetrahedron Lett.* **2011**, *52*, 4421; f) J. P. Qu, C. Deng, J. Zhou, X. L. Sun, Y. Tang, *J. Org. Chem.* **2009**, *74*, 7684; g) A. O. Chagarovskiy, E. M. Budynina, O. A. Ivanova, Y. K. Grishin, I. V. Trushkov, P. V. Verteletskii, *Tetrahedron* **2009**, *65*, 5385; h) J. Fang, J. Ren, Z. W. Wang, *Tetrahedron Lett.* **2008**, *49*, 6659; i) B. Bajtos, M. Yu, H. Zhao, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2007**, *129*, 9631; j) C. Venkatesh, P. P. Singh, H. Ila, H. Junjappa, *Eur. J. Org. Chem.* **2006**, 5378; k) K. Takasu, S. Nagao, M. Ihara, *Adv. Synth. Catal.* **2006**, *348*, 2376; l) O. Kitagawa, Y. Yamada, H. Fujiwara, T. Taguchi, *J. Org. Chem.* **2002**, *67*, 922; m) D. B. England, T. D. O. Kuss, R. G. Keddy, M. A. Kerr, *J. Org. Chem.* **2001**, *66*, 4704; n) Y. Sugita, S. Yamadoi, H. Hosoya, I. Yokoe, *Chem. Pharm. Bull.* **2001**, *49*, 657; o) Y. Sugita, C. Kimura, H. Hosoya, S. Yamadoi, I. Yokoe, *Tetrahedron Lett.* **2001**, *42*, 1095; p) M. A. Kerr, R. G. Keddy, *Tetrahedron Lett.* **1999**, *40*, 5671; q) Y. Sugita, K. Kawai, H. Hosoya, I. Yokoe, *Heterocycles* **1999**, *51*, 2029; r) Y. Horiguchi, I. Suehiro, A. Sasaki, I. Kuwajima, *Tetrahedron Lett.* **1993**, *34*,

- 6077; s) J. W. Herndon, S. U. Tumer, *J. Org. Chem.* **1991**, *56*, 286; t) M. Komatsu, I. Suehiro, Y. Horiguchi, I. Kuwajima, *Synlett* **1991**, 771; u) K. Saigo, S. Shimada, T. Shibasaki, M. Hasegawa, *Chem. Lett.* **1990**, 1093; v) J. P. Marino, C. Silveira, J. Comasseto, N. Petragani, *J. Org. Chem.* **1987**, *52*, 4139; w) J. P. Marino, E. Laborde, *J. Am. Chem. Soc.* **1985**, *107*, 734. Radical [3+2] cycloadditions of vinylcyclopropanes: x) K. S. Feldman, H. M. Berven, P. H. Weinreb, *J. Am. Chem. Soc.* **1993**, *115*, 11364; y) K. S. Feldman, A. L. Romanelli, R. E. Ruckle, Jr., G. Jean, *J. Org. Chem.* **1992**, *57*, 100; z) C.-P. Chuang, S.-S. Hou, R.-R. Wu, *Synth. Commun.* **1992**, *22*, 467; aa) K. S. Feldman, A. L. Romanelli, R. E. Ruckle, Jr., R. F. Miller, *J. Am. Chem. Soc.* **1988**, *110*, 3300; ab) K. Miura, K. Fugami, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 5135. Iron-catalyzed [3+2] cycloaddition of 1,1-diactivated vinylcyclopropane with electron-deficient alkenes: ac) A. P. Dieskau, M. S. Holzwarth, B. Plietker, *J. Am. Chem. Soc.* **2012**, *134*, 5048. Radical [3+2] cycloadditions of aminocyclopropanes: ad) S. Maity, M. Zhu, R. S. Shinabery, N. Zheng, *Angew. Chem.* **2012**, *124*, 226; *Angew. Chem. Int. Ed.* **2012**, *51*, 222. Lewis acid catalyzed or radical [3+2] cycloadditions of methylenecyclopropane 1,1-diester: ae) D. Fujino, H. Yorimitsu, Koichiro Oshima, *J. Am. Chem. Soc.* **2011**, *133*, 9682; af) C. C. Huval, D. A. Singleton, *J. Org. Chem.* **1994**, *59*, 2020; ag) D. A. Singleton, C. C. Huval, K. M. Church, E. S. Priestley, *Tetrahedron Lett.* **1991**, *32*, 5765.
- [9] SnCl_4 - or electrophile-promoted intramolecular [3+2] cycloaddition of cyclopropyl ketones with alkenes: a) P. A. Grieco, R. S. Finkelhor, *Tetrahedron Lett.* **1974**, *15*, 527; b) E. J. Corey, R. D. Balanson, *Tetrahedron Lett.* **1973**, *14*, 3153; c) G. Stork, P. A. Grieco, *J. Am. Chem. Soc.* **1969**, *91*, 2407. Photo or Lewis acid promoted radical [3+2] IMPC of cyclopropyl ketones with alkenes: d) Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162. Radical-promoted [3+2] IMPC of functionalized cyclopropanes with alkenes: e) M. E. Jung, H. L. Rayle, *J. Org. Chem.* **1997**, *62*, 4601; f) K. S. Feldman, H. M. Berven, A. L. Romanelli, *J. Org. Chem.* **1993**, *58*, 6851.
- [10] a) G. Stork, M. Marx, *J. Am. Chem. Soc.* **1969**, *91*, 2371; b) G. Stork, P. A. Grieco, *Tetrahedron Lett.* **1971**, *12*, 1807.
- [11] A radical-promoted IMCC was reported for 1,1-diactivated vinylcyclopropanes: M. P. Bertrand, R. Nouguier, A. Archavlis, A. Carriere, *Synlett* **1994**, 736.
- [12] Prior to exploring the intramolecular cycloaddition, we carried out an intermolecular reaction between the cyclopropane 1,1-diester and styrene, as no examples for mono- or benzyl-substituted alkenes were given.^[5] We found that under the catalysis of $\text{Sc}(\text{OTf})_3$ (20 mol %) the [3+2] cycloaddition proceeded in DCE and the cycloadduct was obtained (57%) as a mixture of two diastereoisomers (see the Supporting Information).
- [13] CCDC 760981 (**2a**), 905293 (**2c**), 905292 (**2d**), 905294 (**2e**) and 859955 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [14] To confirm the structures of the products as cross-cycloadducts instead of the parallel ones, as well as their stereochemistry, in addition to the single-crystal X-ray (Ref. [13]), several 1D/2D NMR experiments (e.g. DEPT, COSY, HSQC, HMBC and nOe) were carried out (see the Supporting Information). Given the HMBC spectra, it is unambiguous as to whether the cycloadditions proceeded through a cross-cycloaddition:



In the case of monosubstituted alkenes ($R^3 = H^c$), the supposed HMBC spectra should show three ${}^3J_{C,H}$ values for the cross-product (carbonyl carbon atom to H^a , H^b and H^c) and four ${}^3J_{C,H}$ values for the parallel product (carbonyl carbon atom to H^a , H^b , H^d and H^e). In these cases (**2d**, **2h**, **2i**, **2j**, and **4g**), three ${}^3J_{C,H}$ values were observed and the cross-cycloaddition was thus confirmed. In the case of geminally disubstituted alkenes ($R^3 = C$), the supposed HMBC spectra should have two ${}^3J_{C,H}$ values (carbonyl carbon atom to H^a and H^b) for the cross-product and four ${}^3J_{C,H}$ values (carbonyl carbon atom to H^a , H^b , H^d and H^e) for the parallel product. In these cases (**2c**, **4b**, **4c**, **4e**, and **4f**), two ${}^3J_{C,H}$ values were observed and the cross-cycloaddition was thus confirmed. The stereochemistries of some products could be confirmed by single-crystal X-ray analysis (**6**: a derivative of **4d**) and nOe experiments (**4e** and **2j**).

- [15] A. J. McAlees, R. McCrindle, *Can. J. Chem.* **1973**, *51*, 4103.
- [16] a) A. S. Kende, P. J. Sanfilippo, *Synth. Commun.* **1983**, *13*, 715; b) D. Duc, M. Fetizon, S. Lazare, *J. Chem. Soc.* **1975**, 282; c) A. Tahara, M. Shimagaki, S. Ohara, T. Nakata, *Tetrahedron Lett.* **1973**, *14*, 1701; d) R. B. Turner, K. H. Ganshirt, P. E. Shaw, J. D. Tauber, *J. Am. Chem. Soc.* **1966**, *88*, 1776; e) L. H. Briggs, F. Cain, R. C. Cambie, B. R. Davis, *J. Chem. Soc.* **1962**, 1840.
- [17] a) N. Maezawa, N. Furuichi, S. Katsumura, *Tetrahedron Lett.* **2007**, *48*, 4865; b) D. H. Hua, X. Huang, *J. Org. Chem.* **2004**, *69*, 6065.
- [18] L. Cleary, H. Yoo, K. J. Shea, *Org. Lett.* **2011**, *13*, 1781.
- [19] Ref. [7e].
- [20] T. Ueyhara, J. Yamada, T. Furuta, T. Kato, Y. Yamamoto, *Tetrahedron* **1987**, *43*, 5605.
- [21] A. Nickel, T. Maruyama, J. L. Wood, *J. Am. Chem. Soc.* **2004**, *126*, 16300.
- [22] a) D. K. M. Duc, M. Fetizon, S. Lazare, P. K. Grant, M. J. Nicholls, H. T. L. Liao, M. J. Francis, J. Poisson, J. Bernassau, N. F. Roque, P. M. Wovkulich, E. Wenkert, *Tetrahedron* **1981**, *37*, 2371; b) R. M. Carman, M. D. Sutherland, *Aust. J. Chem.* **1979**, *32*, 1131.