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Lewis Acids Promoted Formal Intramolecular [3 + 2] Parallel and Cross-Cycloadditions of Cyclopropane 1,1-Diesters with Allenes

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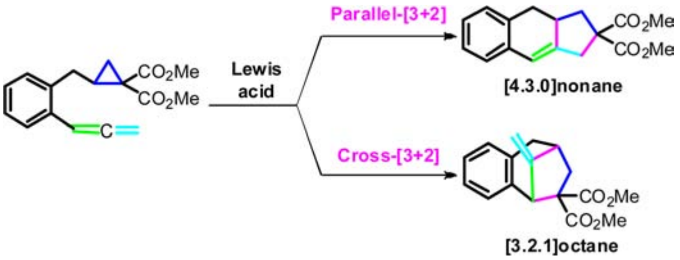
ABSTRACT



A novel Lewis acid promoted formal intramolecular [3 + 2] parallel/cross-cycloaddition of cyclopropane 1,1-diesters with allenes has been successfully developed, in which the two C═C of allenes were involved respectively. This provides a general and efficient strategy for the construction of structurally diverse [4.3.0]nonane and [3.2.1]octane skeletons.

Skeletally complex and diverse polycycles broadly exist in biologically important natural products and synthetic molecules, thus developing highly efficient and general strategies for the construction of such skeletons is and will continue to be an important and challenging task in organic synthesis. Cycloadditions (including the formal ones in the context), especially the intramolecular ones, are an important means for generating skeletal complexity and diversity. Allenes are useful building blocks in organic synthesis. [3 + *n*] and [2 + *n*] are the two major types of allenes cycloadditions in which allenes are used as 3C and 2C synthons respectively.[1] We are interested in the [2 + *n*] route, because the two C═C bonds in an allene unit can be involved in selectivity (chemoselectivity) for skeletal diversity. While the intramolecular [2 + *n*]-cycloadditions of allenes have been widely studied, their chemoselectivities closely depend on the structures of substrates. Successful examples of regulating the chemoselectivity of the same substrate by reaction conditions are quite limited. Only two such examples were reported under the catalysis of transition metals: Brummond et al.[2a] reported an intramolecular Pauson−Khand [2 + 2 + 1]-cycloaddition with Rh/Mo, and Wender et al.[2b] reported an intramolecular [4 + 2]-cycloaddition with Rh/Ni. On the other hand, cycloadditions of cyclopropanes have been proven to be

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(1) Selected reviews for construction of cyclic skeletons through cycloadditions or cyclizations of allenes: (a) Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4863. (b) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (c) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (d) Pei, C. K.; Shi, M. *Chem.—Eur. J.* **2012**, *18*, 6712. (e) López, F.; Mascarenas, J. L. *Chem.—Eur. J.* **2011**, *17*, 418. (f) Inagaki, F.; Kitagaki, S.; Mukai, C. *Synlett* **2011**, 594. (g) Gulías, M.; López, F.; Mascareñas, J. L. *Pure Appl. Chem.* **2011**, *83*, 495. (h) Chen, G.; Jiang, X.; Fu, C.; Ma, S. *Chem. Lett.* **2010**, *39*, 78. (i) Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498. (j) Pfrengle, F.; Reissig, H.-U. *Chem. Soc. Rev.* **2010**, *39*, 549. (k) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783. (l) Brasholz, M.; Reissig, H. U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (m) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (n) Pinho e Melo, T. M. *Curr. Org.Chem.* **2009**, *13*, 1406. (o) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (p) Ohno, H. *Chem. Pharm. Bull.* **2005**, *53*, 1211. (q) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2004**, 3377. (r) Reissig, H.-U.; Schade, W.; Okala Amombo, G. M.; Pulz, R.; Hausherr, A. *Pure Appl. Chem.* **2002**, *74*, 175.

(2) (a) Brummond, K. M.; Chen, H.; Fisher, K. D.; Kerekes, A. D.; Rickards, B.; Sill, P. C.; Geib, S. *Org. Lett.* **2002**, *4*, 1931. (b) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843.

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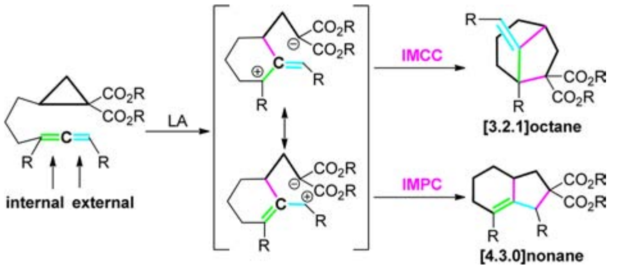
useful for the construction of cyclic skeletons. Several transition-metal-catalyzed cycloadditions of vinylcyclopropanes or methylenecyclopropanes with allenes have been reported; however, the chemoselectivities of these examples were all substrate-dependent.[3]

Scheme 1. Proposed [3 + 2]-IMCC and IMPC of Cyclopropane 1,1-Diesters with Allenes



Following our recently developed intramolecular cross-cycloaddition (IMCC) strategy of donor–acceptor cyclopropanes for the construction of bridge [*n*.2.1] and [*n*.3.1] skeletons,[4] we wondered whether the two C═C of allenes can be selectively involved in the intramolecular [3 + 2]-cycloadditions with cyclopropane 1,1-diesters,[5] in which [3 + 2]-IMCC and IMPC (Intramolecular Parallel Cycloaddition) will proceed (Scheme 1). A [3.2.1]octane or [4.3.0]nonane skeleton will be constructed respectively. The [3.2.1]octane and [4.3.0]nonane skeletons broadly exist in biologically important natrual products and are served as key intermediates for the construction of various structurally diverse cyclic/acyclic skeletons (Figure 1). The endeavor to construct such skeletons has received a great deal of attention from the synthetic community in recent years.[6,7] Thus, from the same class of starting material, a general strategy will be developed for the selective construction of [3.2.1]octane and [4.3.0]nonane skeletons. Prior to our research, only one related example was reported by Yadav et al.[8] Herein we report the first Lewis acid (LA)-*catalyzed* cycloaddition of cyclopropanes with allenes.

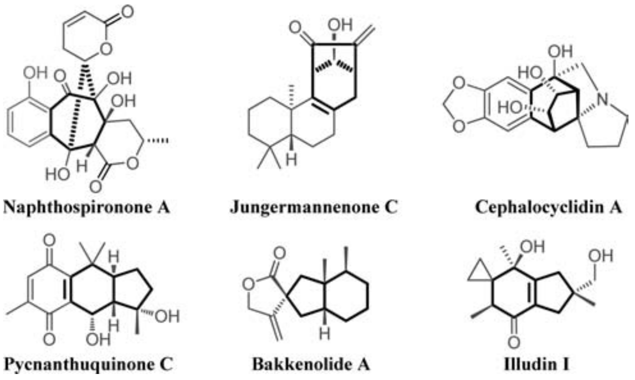


Figure 1. Representative natural products with [3.2.1]octane and [4.3.0]nonane skeletons.

We prepared **1a** (Table 1) as the first substrate to start verifying the above hypothesis. Various LAs and solvents were screened under different reaction temperatures.[9] It was found that both LAs and temperature affected the IMCC/IMPC chemoselectivity. When **1a** was catalyzed by $Sc(OTf)_3$ (0.2 equiv) in DCE, a mixture of IMPC product (**2a**) and IMCC product (**3a**: see the structure in Table 2) was formed. The ratio of **2a** to **3a** increased with the increase in temperature, and **2a** was obtained with excellent selectivity at reflux. Several other substrates with a broad substituent diversity on the allene moiety were then prepared and employed for the subsequent $Sc(OTf)_3$-catalyzed [3 + 2]-cycloadditions. Most of the substrates gave the [3 + 2]-IMPC products (**2b–e**, **2g**, and **2h**) solely and in excellent yields. In these examples, the steric hindrance of substituents on the external carbons of allenes had less influence on both chemoselectivities and yields. As an exception, **1f** gave a mixture of **2f** and **3f** (see the structure

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(3) Only limited examples were reported. For intramolecular cycloadditions: (a) Jiao, L.; Lin, M.; Yu, Z. X. *Chem. Commun.* **2010**, *46*, 1059. (b) Trillo, B.; Gulias, M.; Lopez, F.; Castedo, L.; Mascarenas, J. L. *Adv. Synth. Catal.* **2006**, *348*, 2381. (c) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348. For intermolecular cycloadditions: (d) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 2378. (e) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530. (f) Binger, P.; Schuchardt, U. *Chem. Ber.* **1980**, *113*, 1063.

(4) (a) Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 2032. (b) Bai, Y.; Tao, W.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 4112. (c) Xing, S.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 12605. (d) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215. (e) Hu, B.; Xing, S.; Ren, J.; Wang, Z. *Tetrahedron* **2010**, *66*, 5671.

(5) Selected reviews: (a) Wang, Z. *Synlett* **2012**, *23*, 2311. (b) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969. (c) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293. (d) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (f) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (g) Agrawal, D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471. (h) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (i) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (j) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (k) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (l) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

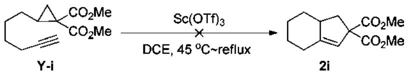
(6) (a) Presset, M.; Coquerel, Y.; Rodriguez, J. *Chem. Rev.* **2013**, *113*, 525. (b) Zhao, W. *Chem. Rev.* **2010**, *110*, 1706. (c) Filippini, M. H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27.

(7) (a) Tanasova, M.; Sturla, S. J. *Chem. Rev.* **2012**, *112*, 3578. (b) Siengalewicz, P.; Mulzer, J.; Rinner, U. *Eur. J. Org. Chem.* **2011**, 7041. (c) Silva, L. F. *Synthesis* **2001**, 671. (d) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.

(8) (a) Yadav et al. reported an *intermolecular* [3 + 2]-cycloaddition of silyl-activated cyclopropane ketones with silyl-activated allenes under promotion of more than 1 equiv of $TiCl_4$ or Et_2AlCl: Yadav, V. K.; Sriramurthy, V. *Org. Lett.* **2004**, *6*, 4495. Two other related studies: (b) Li, W.; Shi, M. *Org. Biomol. Chem.* **2009**, *7*, 1775. (c) Yu, Q.; Ma, S. *Chem. Commun.* **2012**, *48*, 11784.

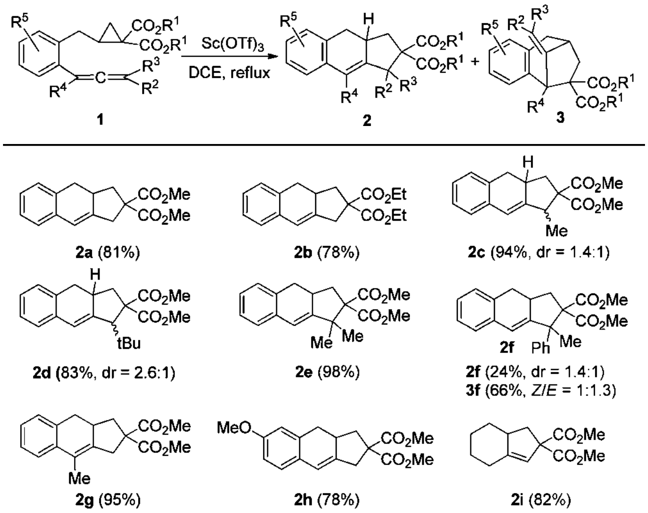
(9) See Supporting Information for details.

(10) In order to exclude the possibility of the [3 + 2]-IMPC with alkyne which might derive from the isomerization of allene, substrate **Y-i** was prepared (ref 4a) and submitted to the LA-promoted reaction. Unlike the results reported by Liang (ref 11) and our group (ref 4a), the reaction did not give the desired product **2i**.



in Table 2) with the IMCC product **3f** as the major one (**2f**/**3f** = 1:2.7) probably because of the steric hindrance. Substrate **1i** with an alkyl-chain linker also worked successfully and gave product **2i** after a double bond transfer process.[10]

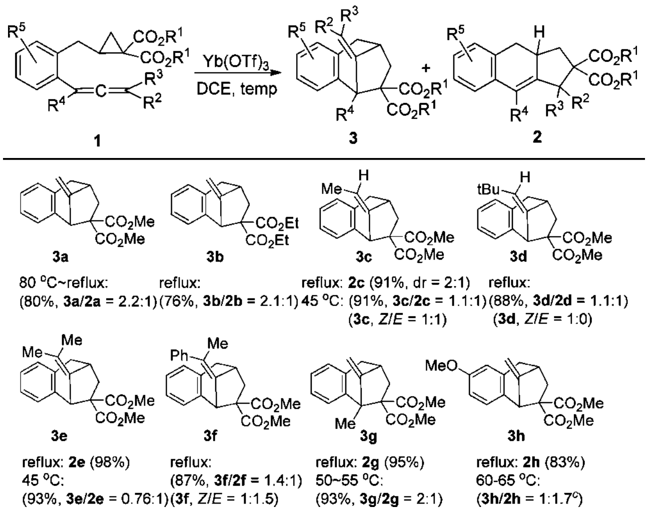
Table 1. Sc(OTf)$_3$-Catalyzed [3 + 2]-IMPC of **1**[a,b]



2a (81%)
2b (78%)
2c (94%, dr = 1.4:1)
2d (83%, dr = 2.6:1)
2e (98%)
2f (24%, dr = 1.4:1)
3f (66%, *Z*/*E* = 1:1.3)
2g (95%)
2h (78%)
2i (82%)

[a] Conditions: **1** (1.0 equiv, the diastereomer ratio was about 1:1 if existed), Sc(OTf)$_3$ (0.2 equiv), DCE, reflux, Ar. [b] Isolated yield. DCE = 1,2-dichloroethane.

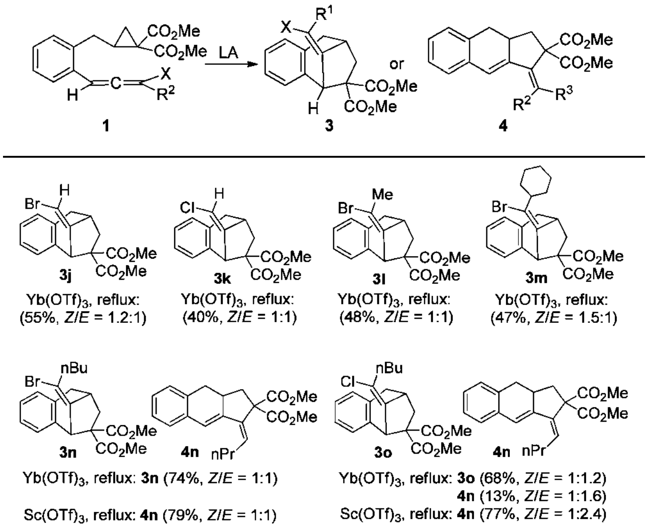
Table 2. Yb(OTf)$_3$-Promoted [3 + 2]-IMCC/IMPC of **1**[a,b]



3a 80 °C~reflux: (80%, **3a**/**2a** = 2.2:1)
3b reflux: (76%, **3b**/**2b** = 2.1:1)
3c reflux: **2c** (91%, dr = 2:1) 45 °C: (91%, **3c**/**2c** = 1.1:1) (**3c**, *Z*/*E* = 1:1)
3d reflux: (88%, **3d**/**2d** = 1.1:1) (**3d**, *Z*/*E* = 1:0)
3e reflux: **2e** (98%) 45 °C: (93%, **3e**/**2e** = 0.76:1)
3f reflux: (87%, **3f**/**2f** = 1.4:1) (**3f**, *Z*/*E* = 1:1.5)
3g reflux: **2g** (95%) 50~55 °C: (93%, **3g**/**2g** = 2:1)
3h reflux: **2h** (83%) 60-65 °C: (**3h**/**2h** = 1:1.7[c])

[a] Conditions: **1** (1.0 equiv, the diastereomer ratio was about 1:1 if existed), Yb(OTf)$_3$ (1.0 equiv), DCE, Ar. See the Supporting Information for details. [b] Isolated yield. [c] The reaction was very slow, and the product failed to be isolated.

Table 3. LA-Regulated [3 + 2]-IMPC/IMCC of Haloallenes **1**[a,b]



3j Yb(OTf)$_3$, reflux: (55%, *Z*/*E* = 1.2:1)
3k Yb(OTf)$_3$, reflux: (40%, *Z*/*E* = 1:1)
3l Yb(OTf)$_3$, reflux: (48%, *Z*/*E* = 1:1)
3m Yb(OTf)$_3$, reflux: (47%, *Z*/*E* = 1.5:1)
3n **4n**
Yb(OTf)$_3$, reflux: **3n** (74%, *Z*/*E* = 1:1)
Sc(OTf)$_3$, reflux: **4n** (79%, *Z*/*E* = 1:1)
3o **4n**
Yb(OTf)$_3$, reflux: **3o** (68%, *Z*/*E* = 1:1.2)
4n (13%, *Z*/*E* = 1:1.6)
Sc(OTf)$_3$, reflux: **4n** (77%, *Z*/*E* = 1:2.4)

[a] Conditions: **1** (1.0 equiv, the diastereomer ratio was about 1:1), Yb(OTf)$_3$ (1.0 equiv) or Sc(OTf)$_3$ (0.2 equiv), DCE, reflux, Ar. See the Supporting Information for details. [b] The relative stereochemistries were confirmed by NOESY.

The results of reactions promoted by Yb(OTf)$_3$ (1.0 equiv) were listed in Table 2. When **1a** was run at 70 °C, the reaction preferred the formation of **3a** (**3a**/**2a** = 4:1) but with an extremely lower reaction rate (16 h, 20% yield with 70% starting material recovered). The reaction proceeded faster at 80 °C to reflux and still preferred the formation of **3a** but with a decreased ratio (**3a**/**2a** = 2.2:1). **1b**, **1d**, and **1f** gave similar results. In some examples (**1c**, **1e**, **1g**, and **1h**), when the reactions were run at lower temperature (with a prolonged reaction time), mixtures of **2** and **3** were formed with various chemoselectivities. However when these reactions were run at reflux, **2** were obtained selectively. For **1i**, although various reaction conditions were screened,[9] the IMCC product was not obtained, which was probably due to the less stable internal carbocation than that of the benzene-linked examples.

The above results implied that the relative stability of the internal and external carbocations of the resonant intermediate might play a role in the chemoselectivity. We then decided to assemble a halogen atom on the external carbon of allene moiety to get a higher selectivity for IMCC. This was assumed to reduce the stability of the external carbocation and thus relatively increase the stability of the internal one. Several haloallene substrates were prepared, and to our great delight, under the promotion of Yb(OTf)$_3$ the IMCC selectivities were all excellent (Table 3: **3j**–**3o**). It was interesting that, under the catalysis of Sc(OTf)$_3$, selectivities of the reactions of **1n** and **1o** were completely switched to IMPC and **4n** was obtained after a subsequent elimination of HBr or HCl.[12] The structures of **2a**, **3a**, *Z*-**3j**, *Z*-**3k**, and *E*-**3l** were unambiguously confirmed by NMR spectroscopy, HRMS, and X-ray crystal structure analysis.[9]

The different IMPC/IMCC chemoselectivities under various reaction conditions (LAs and temperature) imply

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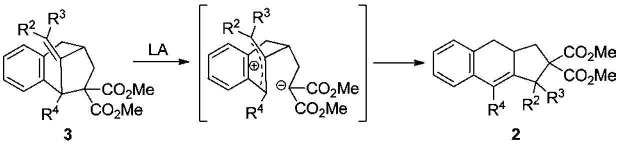
(11) Xia, X. F.; Song, X. R.; Liu, X. Y.; Liang, Y. M. *Chem.—Asian J.* **2012**, *7*, 1538.

Table 4. LA-Regulated Formal 1,3-Rearrangement of **3** to **2**[a]



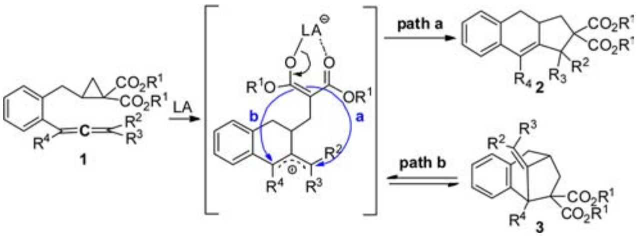
entry	SM	LA	time	product	yield[b]	dr[c]
1	**3a**	Sc(OTf)$_3$	12 h	**2a**	quant	–
2	**3a**	Yb(OTf)$_3$	12 h	**2a**	NR	–
3	***Z*-3c**	Yb(OTf)$_3$	12 h	**2c**	quant	1:0
4	***Z*-3d**	Sc(OTf)$_3$	24 h	**2d**	86%	1.1:1
5	***Z*-3d**	Yb(OTf)$_3$	12 h	**2d**	NR	–
6	**3e**	Yb(OTf)$_3$	12 h	**2e**	quant	–
7	**3g**	Yb(OTf)$_3$	12 h	**2g**	quant	–

[a] Conditions: **3** (1.0 equiv), Sc(OTf)$_3$ (0.2 equiv) or Yb(OTf)$_3$ (1.0 equiv), DCE, reflux, Ar. [b] Isolated yield. [c] The ratios were determined by ^{1}H NMR. NR = no reaction.

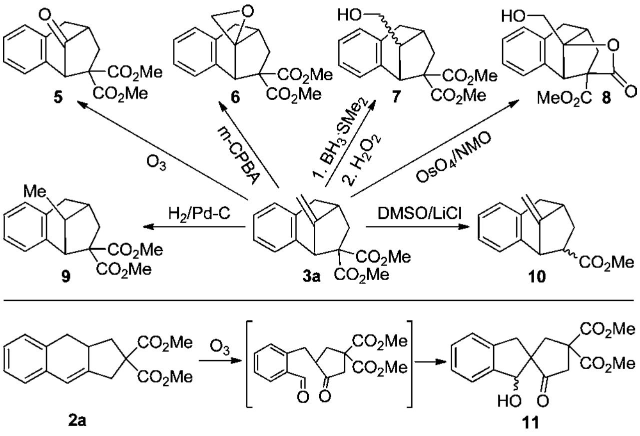
a potential relationship between the IMPC products **2** and IMCC products **3**, which is important to understand the mechanism. Several experiments were performed for the mutual conversion between **2** and **3**. Under catalysis of Sc(OTf)$_3$ or Yb(OTf)$_3$, **2a** was quite stable and no **3a** was detected. However **3a** was converted to **2a** quantitatively under the catalysis of Sc(OTf)$_3$ (Table 4, entry 1). Such conversion was also observed for some other examples (**3c**–**e** and **3g**). It should be noticed that the single isomer *Z*-**3d** was converted to **2d** as a mixture of two diastereomers (Table 4, entry 4). This result implied a stepwise process: **3d** was first converted to an allylic cation intermediate and then followed the IMPC pathway to give the thermodynamically stable product **2d**. This process can be thought of as a formal 1,3-rearrangement.

A possible mechanism is illustrated in Scheme 2. Under the promotion of LA, the reaction was initiated by an S$_N$2-like nucleophilic ring opening of the cyclopropane ring with the central carbon of the allene moiety. The resulted resonant allylic cation could proceed in two possible pathways (a and b) kinetically for the subsequent cyclization. While, in pathway a, the external carbocation gave the IMPC product, the internal carbocation was involved in pathway b and gave the IMCC product. The stability of the two carbocations in the resonant intermediate might play an important role in the pathway selection. Under stronger conditions, pathway b includes thermodynamic equilibrium and provides the thermodynamically more stable product **2** via the resonant intermediate (a formal 1,3-rearrangement).

Scheme 2. A possible mechanism for the cycloaddtions



Scheme 3



To further demonstrate the potential application of the developed method, several functional transformations of **3a** and **2a** were performed (Scheme 3).[9]

In summary, we have successfully developed a novel LA-promoted [3 + 2]-IMPC and IMCC of cyclopropane 1,1-diesters with allenes. This is the first LA-catalyzed cycloaddition of cyclopropanes with allenes and provides a general and efficient strategy for the construction of structurally diverse [4.3.0]nonane and [3.2.1]octane skeletons.

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Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.