EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402160

Acid-Catalyzed Domino Meinwald Rearrangement of Epoxides/Intramolecular [3+2] Cross-Cycloaddition of Cyclopropane-1,1-dicarboxylates

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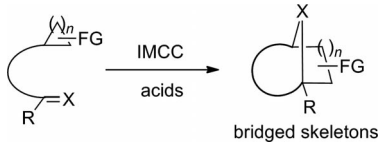
Keywords: Rearrangement / Cycloaddition / Domino reactions / Small ring systems / Epoxides

An acid-catalyzed domino Meinwald rearrangement of epoxides/intramolecular [3+2] cross-cycloaddition of cyclopropane 1,1-diesters was developed. This supplied a method for the construction of bridged oxa-[*n*.2.1] (*n* = 3, 4) skeletons.

Introduction

Bridged oxa-[*n*.2.1] skeletons exist in many biologically important natural products and are also useful building blocks in organic synthesis.[1,2] We recently developed a general and efficient strategy for the construction of bridged skeletons through intramolecular cross-cycloaddition (IMCC) of functionalized cyclopropanes with carbonyls, imines, alkenes, and allenes (Scheme 1).[3] In our previous study of the [3+2] IMCC of cyclopropane 1,1-diesters[4] with carbonyls,[3e] we found that in comparison to the benzaldehyde [Scheme 2, Equation (1)] and phenylacetone substrates [Scheme 2, Equation (2)], the phenylacetaldehyde substrate was difficult to prepare to give the desired bridged oxa-[3.2.1] skeleton owing to its instability during the isolation process. In our recent research, we found that the phenylacetaldehyde derivative could be in situ generated through a Meinwald (Pinacol) rearrangement[5] of the epoxide and that it took part in the subsequent [3+2] IMCC of cyclopropane with the carbonyl group. This novel domino reaction further expanded the scope of the IMCC strategy for the construction of bridged skeletons [Scheme 2, Equation (3)]. Herein, we report these results.



Scheme 1. IMCC strategy of functionalized cyclopropanes for the construction of bridged skeletons.

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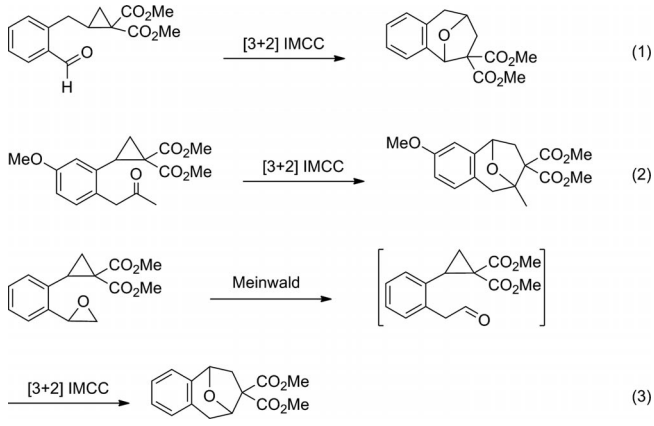
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402160.



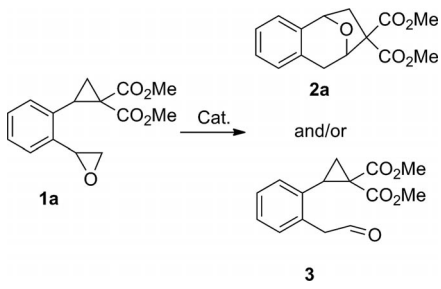
Scheme 2.

Results and Discussion

Cyclopropane epoxide **1a** was prepared as a mixture of two diastereoisomers to start the investigation. Under catalysis of scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$, 0.03 equiv.] and upon performing this reaction at –10 °C for 0.5 h, a Meinwald rearrangement of the epoxide afforded phenylacetaldehyde **3** in 65% yield (Table 1, entry 1). If the reaction was run for an additional 2 h at 60 °C, cycloaddition product **2a** was obtained in 89% yield (Table 1, entry 2). The two diastereoisomers of **1a** were then separated, and the reaction of each under catalysis of $Sc(OTf)_3$ at 60 °C for 2 h gave almost the same result (86 and 89% yield, respectively).[6] A broad scope of Lewis and Brønsted acids were then screened, and the results are listed in Table 1. Most of the Lewis acids were quite effective for the domino reaction. In most cases under Lewis acid catalysis (0.03 equiv.), the reactions were finished within 2 h at 60 °C, and the products were delivered in excellent yields. Several Brønsted acids were also screened for this process. HCl, *p*-toluenesulfonic acid (TsOH), and trifluoroacetic acid (TFA) gave only Meinwald rearrangement product **3** (Table 1, entries 27–29). However, to our surprise, we found that TfOH

was quite effective for the domino process. The reaction was completed within 12 h at room temperature and the product was obtained in an excellent yield (96%; Table 1, entry 26). This was important, because Brønsted acids have been rarely reported to be effective catalysts in cycloaddition reactions of carbonyls with donor–acceptor cyclopropanes.

Table 1. Optimization for the intramolecular [3+2] domino cycloaddition of cyclopropane 1,1-diester **1a** in the presence of acid catalysts.[a]

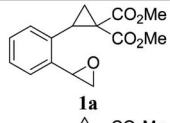
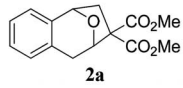
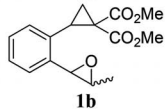
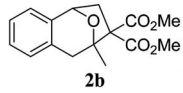
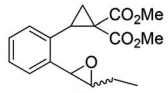
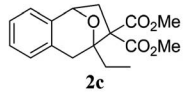
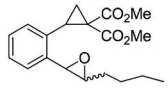
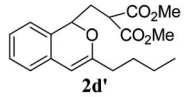
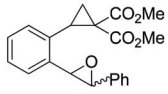
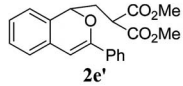
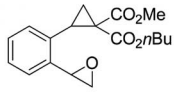
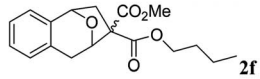
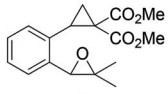
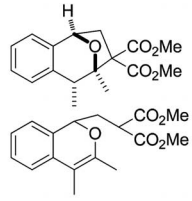
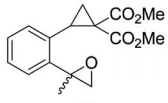
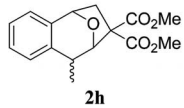
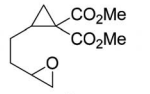
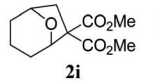
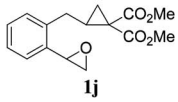
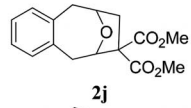
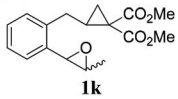
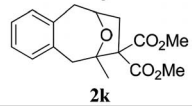


Entry	Cat.	T [°C]	t [h]	Yield[b] [%] 2	3
1	$Sc(OTf)_3$	–10	0.5		65
2[c]	$Sc(OTf)_3$	60	2	89	
3	$Er(OTf)_3$	60	2	38	50
4	$Sn(OTf)_2$	60	2	98	
5	$Yb(OTf)_3$	60	2	70	15
6	$Bi(OTf)_3$	60	2	95	
7	$Ga(OTf)_3$	60	2	96	
8	Cu(OTf)	60	2	93	
9	$Cu(OTf)_2$	60	2	81	
10	$Cu(OTf)_2$·Ph	60	2	71	
11	$Em(OTf)_3$	60	2		67
12	$In(OTf)_3$	60	2	91	
13	$Lu(OTf)_3$	60	2	65	10
14	$Ha(OTf)_4$	60	2	85	<5
15	$Al(OTf)_3$	60	2	92	
16	AgOTf	60	2	82	<5
17	PPh_3·AuCl/AgOTf	60	2	69	<5
18	$Ag(PF_6)$	60	2		10
19	$Ag(SbF_6)$	60	2	75	
20	TMSOTf	60	2	94	
21	AuCl	60	2	31	12
22	$PtCl_2$	60	2		27
23	$SnCl_4$	60	2		28
24	$Ni(ClO_4)_2$·$6H_2O$	60	2	31	47
25	BF_3·OEt_2	–78 to 40	12		62
26[c,d]	TfOH	r.t.	12	96	
27[d]	HCl	60	2		88
28[d]	TsOH	60	2		91
29[d]	TFA	60	2		90

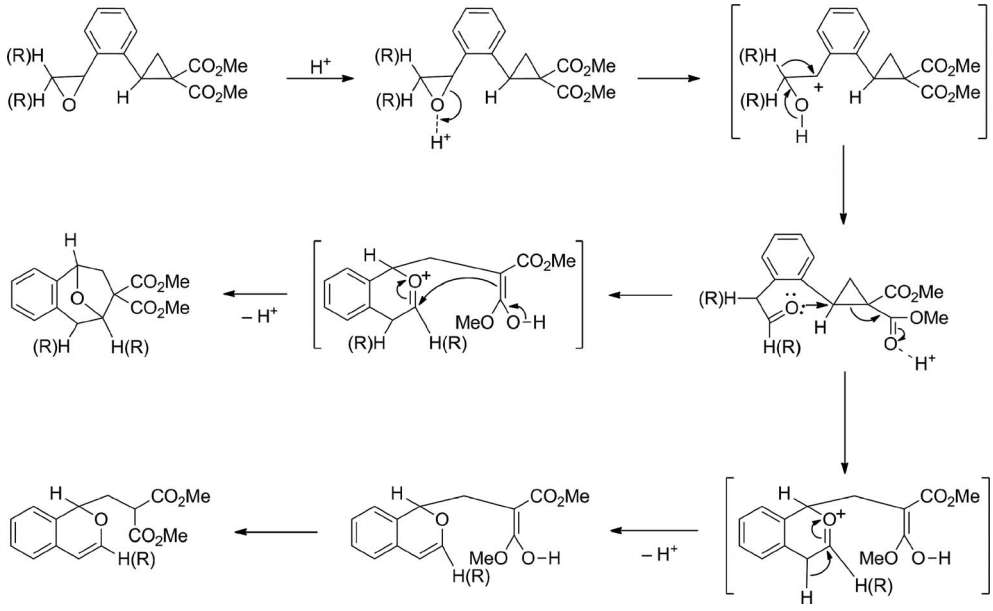
[a] The reaction was conducted with **1a** (0.1 mmol), Lewis or Brønsted acid (0.03 equiv.), and 1,2-dichloroethane (DCE, 5 mL). [b] Estimated by analysis of the crude product by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Cat. (0.2 equiv.).

The scope of substrates **1** was then investigated (Table 2). Substrates **1** with various substituents were investigated (Table 2, entries 1–8). Substrates **1b** and **1c** with methyl and ethyl groups at the external carbon atom of the epoxy moiety gave corresponding cycloaddition products **2b** and **2c**, respectively, in excellent yield (Table 2, entries 2 and 3). However, instead of the cycloaddition products, substrates **1d** and **1e** with *n*-butyl and phenyl substituents gave **2d′** and **2e′**, respectively (Table 2, entries 4 and 5). Substrate **1f** also gave cycloaddition product **2f** as a mixture of two diastereoisomers (Table 2, entry 6). Substrate **1g** with two methyl groups at the external carbon atom of the epoxy moiety gave cycloaddition product **2g** together with **2g′** (Table 2, entry 7). Formation of **2d′**, **2e′**, and **2g′** implied a stepwise

Table 2. Acid-catalyzed domino Meinwald rearrangemement/[3+2] IMCC.[a]

Entry	Cyclopropane **1**	Product **2**	Yield[b] [%]
1[c]	 **1a**	 **2a**	96
2[d]	 **1b**	 **2b**	97
3[e]	 **1c**	 **2c**	89
4	 **1d**	 **2d'**	37
5	 **1e**	 **2e'**	46
6	 **1f**	 **2f**	86 (3.3:1 *dr*)
7	 **1g**	 **2g + 2g'**	28 + 37
8	 **1h**	 **2h**	89 (1:1 *dr*)
9[f]	 **1i**	 **2i**	43
10	 **1j**	 **2j**	65 (40[c])
11	 **1k**	 **2k**	81 (61[c])

[a] Reaction conditions: cyclopropane (0.1 mmol), TfOH (0.2 equiv.), DCE (5 mL), 65 °C 4 h, Ar. [b] Yield of isolated product. [c] T = 25 °C, 12 h. [d] TMSOTf (0.2 equiv.). [e] T = 32 °C, 12 h. [f] $Sc(OTf)_3$ (0.2 equiv.), 80 °C, 8 h.



Scheme 3. Proposed mechanism of the domino reaction.

mechanism of the [3+2] IMCC (Scheme 3). In these cases, proton elimination was favored in the final cyclization step owing to steric hindrance, which was also observed in our previous study. This is important for understanding the mechanism. If the methyl substituent was on the internal carbon atom of the epoxy moiety, **2h** was obtained as a mixture (1:1) of two diastereoisomers in a total yield of 89% (Table 2, entry 8). Reaction of aliphatic substrate **1i** proceeded at 80 °C under catalysis of $Sc(OTf)_3$ to afford the product in 43% yield (Table 2, entry 9). Reactions of **1j** and **1k** were also successfully performed to afford **2j** and **2k** containing a bridged oxa-[4.2.1] skeleton (Table 2, entries 10 and 11).

On the basis of the above results, a Meinwald (Pinacol) rearrangement/[3+2] IMCC domino process is proposed (Scheme 3). A Meinwald (Pinacol) rearrangement of the epoxide affords phenylacetaldehyde, which gives either the bridged skeleton through a [3+2] IMCC (a S_N2-aldol domino process) or the enol ether through an elimination (interrupted [3+2] IMCC).[7]

Conclusions

In summary, we developed an acid-catalyzed domino Meinwald rearrangement/[3+2] intramolecular cross-cycloaddition (IMCC) of cyclopropane 1,1-diesters with epoxides. Besides Lewis acids, the Brønsted acid TfOH also effectively catalyzed the reactions. With the in situ generation of acetaldehydes from epoxides, this further expands the scope of the IMCC strategy for the construction of bridged oxa-[3.2.1] and oxa-[4.2.1] skeletons.

Experimental Section

General Procedure: Under an argon atmosphere, the cat. (0.1 M in DCE, 0.2 mL, 0.02 mmol) was added at room temperature to a solution of cyclopropane **1** (0.10 mmol) in DCE (5 mL). TLC was used to monitor the reaction. After the mixture was cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography to afford product **2**.

Dimethyl 8,9-Dihydro-5*H*-5,8-epoxybenzo[7]annulene-7,7(6*H*)-dicarboxylate (2a): White solid, yield: 96%, m.p. 65–66 °C. R_f = 0.24 (EtOAc/petroleum ether, 1:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.09 (m, 2 H), 6.98 (dd, J = 9.2, 3.8 Hz, 2 H), 5.40 (d, J = 6.1 Hz, 1 H), 5.10 (d, J = 7.1 Hz, 1 H), 3.77 (s, 3 H), 3.66 (s, 3 H), 3.38 (dd, J = 17.8, 6.1 Hz, 1 H), 2.94 (d, J = 13.1 Hz, 1 H), 2.58 (dd, J = 13.1, 7.2 Hz, 1 H), 2.53 (d, J = 17.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.45, 169.19, 139.51, 130.19, 128.25, 127.56, 126.13, 123.85, 78.71, 77.46, 64.88, 53.13, 52.80, 44.11, 31.05 ppm. IR (thin film): $\tilde{\nu}$ = 3024.1, 2954.0, 2846.2, 1739.2, 1434.35, 1359.8, 1270.1, 1244.3, 1158.0, 1045.4, 758.9, 615.8 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}O_5$ $[M + Na]^+$ 299.0890; found 299.0894.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

The authors thank the National Natural Science Foundation of China (NSFC) (grant numbers 21172109, 21121002) and the Ministry of Science and Technology of the People's Republic of China (MOST) (grant numbers 2010CB126106, 2011BAE06B05).

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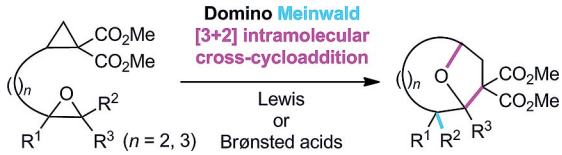
Received: February 27, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Cycloaddition



An acid-catalyzed domino Meinwald rearrangement of epoxides/intramolecular [3+2] cross-cycloaddition of cyclopropane 1,1-diesters is developed, which supplies a method for the construction of bridged oxa-[*n*.2.1] (*n* = 3, 4) skeletons.

Keywords: Rearrangement / Cycloaddition / Domino reactions / Small ring systems / Epoxides

