Stereoselective Synthesis of Highly Functionalized Cyclohexenes *via* Strong Acid Mediated Endocyclic C-C Bond Cleavage of Monocyclopropanated Cyclopentadienes

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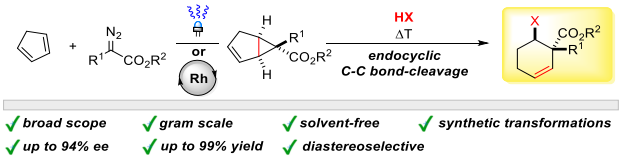
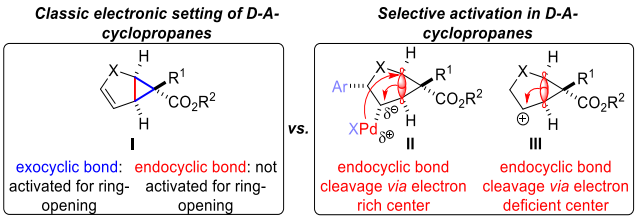


ABSTRACT: A stereoselective, solvent- and metal-free endocyclic C-C bond cleavage of monocyclopropanated cyclopentadienes mediated by strong acids was developed, leading to highly functionalized six-membered carbocycles with high stereocontrol. The critical step for this ring-expansion is the formation of a cyclopropyl carbocation that undergoes endocyclic ring-opening *via* an SN_2'-attack of various nucleophiles. Subsequent synthetic transformations demonstrate the versatility of the cyclohexenes obtained as synthetic building blocks.

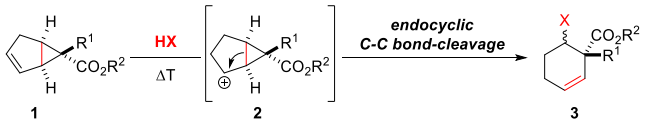
Donor-acceptor (D-A) cyclopropanes are known to be valuable for the synthesis of new synthetic building blocks.[1] Our synthetic interests focus on using bicyclic D-A cyclopropanes to generate novel chiral cyclic building blocks. In the presence of nucleophiles and/or electrophiles, the general reactivity of these bicyclic D-A cyclopropanes **I** involves an exocyclic ring opening due to the intrinsic electronic setting of the activated exocyclic bond. These exocyclic ring-opening reactions have been demonstrated in many stereo-, regio-, and chemoselective transformations (Figure 1).[1c,2]

Figure 1. Electronic setting of D-A-cyclopropanes.



In contrast, C-C bond cleavage of the endocyclic bond in bicyclic D-A cyclopropanes remains challenging and underexplored.[2c,3] In earlier works, we have demonstrated the utility of endocyclic ring-opening reactions by generating 1) an electron-rich center of type **II** vicinal to the endocyclic C-C bond *via* a Pd-catalyzed Heck-type reaction, resulting in the desired endocyclic ring-opening of bicyclic vinyl cyclopropanes[3a,3c] or 2) an electron-deficient center of type **III** vicinal to the endocyclic C-C bond *via* a base-mediated, metal-free, and microwave-assisted endocyclic ring-opening of bicyclic D-A cyclopropanes.[4] Additionally, metal halides and Brønsted acids have been demonstrated as effective reagents for ring-opening of cyclopropanols and importantly, cyclopropyl vinyl compounds in a few previous studies.[5] However, the scope has been mostly limited to heterocyclic ring systems for endocyclic ring-expansions,[3a,4] provoked by the "push-effect"[4,6] of the embedded heteroatom within the ring system, which consequentially activates the endocyclic C-C bond. This study aimed to develop a selective endocyclic C-C bond cleavage protocol with corresponding carbocyclic analogs.

Scheme 1. Proposed endocyclic C-C bond cleavage mediated by (Brønsted) acids.

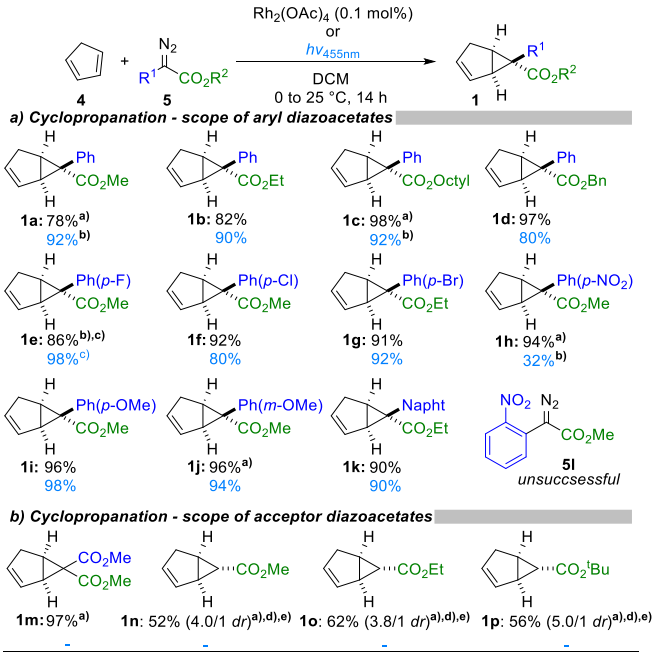


We hypothesized that protonation of **1** to the cyclopropyl carbocation **2** should result in endocyclic rather than exocyclic C-C bond cleavage in order to avoid a positive charge next to the ester group. This results in cyclohexenes **3**, which should be valuable synthetic building blocks that are difficult to synthesize otherwise, especially if they can be obtained stereoselectively (Scheme 1).

To synthesize the required starting materials **1**, cyclopropanation of cyclopentadiene **4** with diazo compounds **5** could be effectively achieved by two distinct methods. Monocyclopropanated carbocycles **1a-1k** were generated with high yields (78-98%) and high diastereoselectivity (>20:1 *d.r.*) either by dirhodium-tetraacetate catalyzed or by light-mediated cyclopropanation of **4** with the corresponding aryldiazoacetates **5a-5k** following protocols from the literature with some modifications.[7,8] Both approaches gave comparable yields, however, diazo compound **5l** was not tolerated and the yields differ significantly when using **5h**. Blue light-promoted photolysis with diazo compounds lacking the aryl moiety was not possible, but

the rhodium-catalyzed cyclopropanation was also effective with diazomalonate **5m** (leading to **1m**, 97%) and with acceptor-diazoacetates **5n-5p** (leading to **1n-1p**, 52-62%, 3.8-5.0:1 *d.r.*). Gram-scale synthesis of **1a, 1c**, **1h, 1j** and **1m-1p** was possible by rhodium catalyzed cyclopropanation. (Scheme 2)

Scheme 2. Rh(II) or photocatalyzed cyclopropanation of cyclopentadiene.

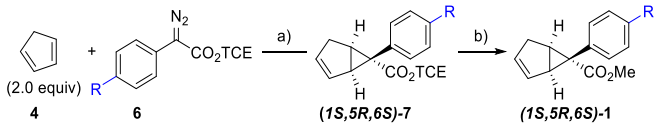


Reactions were performed on a 1.0 – 2.0 mmol scale. 2.5 – 5.0 equiv cyclopentadiene (**4**) were used. [a] Gram-scale synthesis: **5a** (59.0 mmol) to **1a** (9.90 g), **5c** (9.11 mmol) to **1c** (2.79 g), **5h** (9.09 mmol) to **1h** (2.22 g), **5j** (29.3 mmol) to **1j** (6.87 g), **5m** (15.6 mmol) to **1m** (2.96 g), **5n** (43.2 mmol) to **1n** (3.08 g), **5o** (23.8 mmol) to **1o** (2.24 g), **5p** (12.0 mmol) to **1p** (1.21 g) [b] Yield was determined using fumaronitrile as internal standard. [c] Reactions were performed on a 3.0 mmol scale. [d] Diastereomeric ratio was determined from crude ^{1}H-NMR. [e] Major diastereomer is shown.

1 could also be obtained enantiomerically enriched, improving on a previous report by the Davies group that achieved moderate levels of enantioselectivity (78% *ee*) for **1i**[9] using Rh_2(*S*-DOSP)$_4$ (*S*-DOSP = (*S*)-(-)-N-(*p*-dodecylphenylsulfonyl)prolinato) as the chiral catalyst. Enantioselectivities of 90-94% *ee* were achieved when 2,2,2-trichloroethyl (TCE) esters **6** of the aryldiazoacetates in combination with Rh_2(*R-p*-PhTPCP)$_4$[10] (*R-p*-PhTPCP = (*R*)-1-(4-phenyl(phenyl))-2,2-diphenylcyclopropanecarboxylate)) were used, which was followed by transesterification to furnish **(1S,5*R*,6*S*)-1** (Table 1). A loading of 0.05 mol% of this chiral rhodium catalyst (for screening details evaluating other chiral rhodium catalysts see the SI) was sufficient to obtain the monocyclopropanated cyclopentadienes **(1S,5*R*,6*S*)-7** in up to 97% yield (see the SI, Table S9 and S10).

With robust and scalable access to **1** in hand, we screened various acids that could promote the desired endocyclic ring-opening using **1a** as the model substrate (Table 2). HI, HBr, HCl, and H_2SO_4 indeed gave rise to the halogen substituted cyclohexenes **8-10** or to the hydroxy/alkoxy substituted cyclohexene **12**, depending on the conjugate base present as a nucleophile (Table 2).

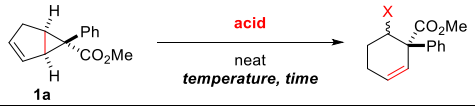
Table 1. Asymmetric cyclopropanation of cyclopentadiene followed by transesterification.[a]



Entry	**6**-R	Yield of **1**[b] [%]	*ee* of **1** [%]
1[c]	**6a:** H	(*1S,5R,6S*)-**1a**: 71	90
2	**6i:** OMe	(*1S,5R,6S*)-**1i**: 65	94
3	**6q:** Br	(*1S,5R,6S*)-**1q**: 56	90
4	**6r:** CF_3	(*1S,5R,6S*)-**1r**: 56	90

Reactions were performed on a 0.7 – 1.0 mmol scale. [a] Reaction conditions: a) Rh_2(*R-p*-PhTPCP)$_4$ (0.05 mol%), HFIP (10 equiv), 4 Å MS, DCM, 25 °C. b) i. Zn-dust (<10 µm, 5.0 equiv), AcOH as solvent (0.1 M), 24 h, 25 °C; ii. K_2CO_3 (5.0 equiv), DMF, MeI (5.0 equiv), 24 h, 25 °C. [b] Overall yield is reported over 3 steps starting from compound **6**. [c] 10 equiv of Zn-dust (<10 µm), 1.5 equiv of potassium carbonate and 1.5 equiv of iodomethane were used. The absolute configuration of **1a**, **1g**, and **1i** was determined by Xray structure analysis, see SI for details.

Table 2. Screening of different acids with different *pK*$_a$-values for endocyclic ring-opening reaction.[a]

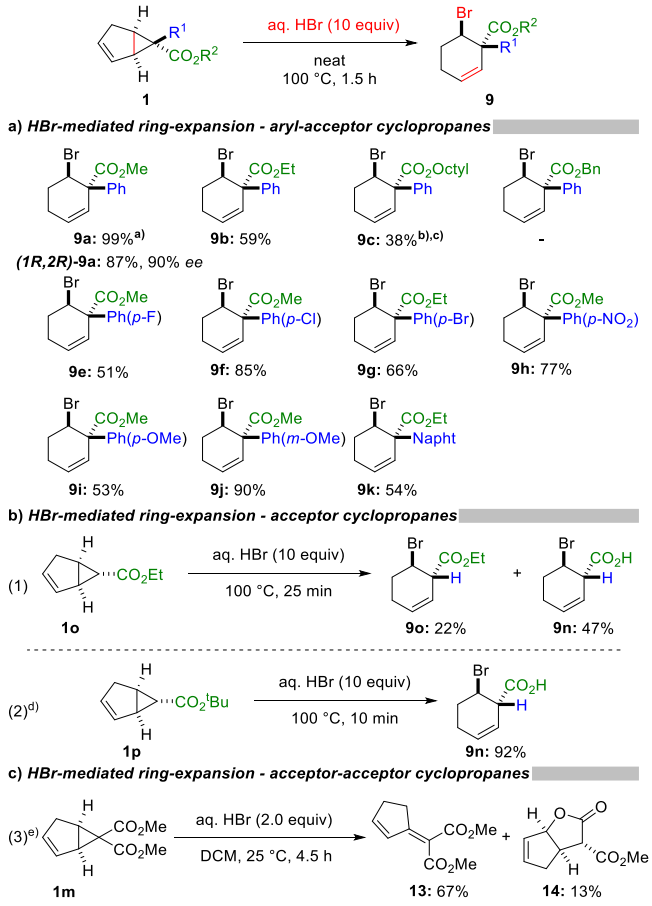


Entry	Acid	*pK*$_a$	Result
1	aq. HI (57%)	-10	**8:** 55%
2	aq. HBr (47%)	-9	**9a:** 99%
3[b]	aq. HCl (37%)	-6	**10a:** R = Me: 51% **11:** 11% **10b:** R = H: 29%
4	H_2SO_4	-3	**12a:** R = H: 31% **12b:** R = Et: 25%

[a] Reaction conditions: entry 1: **1a** (0.45 mmol), aq. HI (57 wt%, 10 equiv), 80 °C, 1 h; entry 2: **1a** (7.75 mmol), aq. HBr (47 wt%, 10 equiv), 100 °C, 1.5 h; entry 3: **1a** (0.44 mmol), aq. HCl (37 wt%, 15 equiv), 100 °C, 4 h; entry 4: **1a** (0.50 mmol), conc. H_2SO_4 (10 equiv), EtOH, 150 °C, 10 h. [b] Yield was determined using fumaronitrile as internal standard. *pK*$_a$-Values in water.[11]

Remarkably, in all cases the products were obtained completely diastereoselectively, indicating that the nucleophile is introduced from the *endo* face of the bicycle *via* an S_N2' rather than an S_N1 process (vide infra for mechanistic discussion). HBr proved to be best for the transformation, apparently providing the optimal combination of acid strength for effective protonation of **1** and nucleophilicity to assist in the ring opening. Screening of other acids remained unsuccessful (see the SI, Table S2 – S4)).

Scheme 3. Scope of endocyclic ring-opening triggered by HBr.



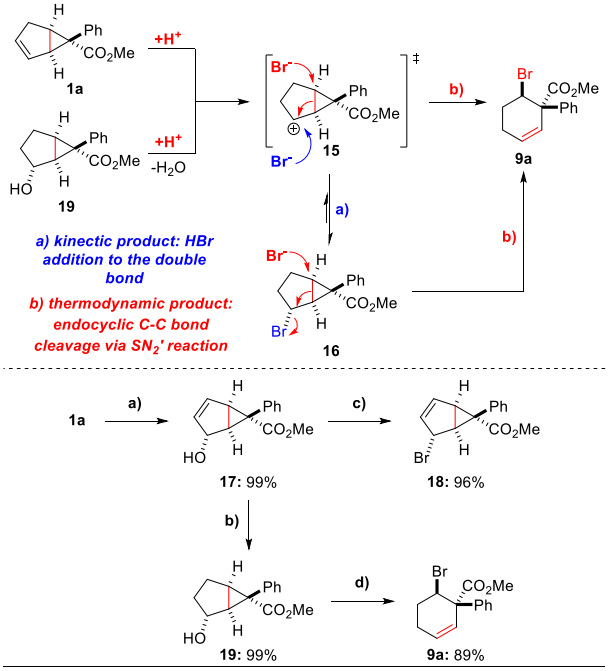
Reactions were performed on a 0.2 – 0.3 mmol scale. [a] Gram-scale synthesis: **1a** (7.75 mmol) to **9a** (2.26 g) [b] Yield was determined by NMR using fumaronitrile as internal standard. [c] MeCN was used as solvent. [d] 1.2 mmol of **1p** were used. [e] 0.53 mmol of **1m** were used.

The scope of the HBr-mediated endocyclic ring-opening was extended to vinyl cyclopropanes **1a-1k** (Scheme 3). Steric factors play a role (**1k** > **1a** > **1n**), agreeing with the attack of the bromide nucleophile at a neopentyl position. If the aryl substituent is missing (**1o**, **1p**), the ring-opening is greatly accelerated along with hydrolysis of the ester moiety, which allows the synthesis of carboxylic acid **9n** from **1p** in high yield. Both electron-withdrawing and donating substituents on the aryl-group in *para*- and *meta*-position are tolerated well in the transformation, however, yields differ with no discernable trend. Importantly, no erosion of enantioselectivity was observed when employing (**1S,5R,6S**)-**1a** (90% *ee*). Unexpectedly, the diester substituted derivative **1m** gave rise to products **13** and **14** due to a competitive protonation of the ester groups that is now sufficient to trigger the exocyclic cyclopropane ring opening.

Control experiments (Scheme 4) shed light on the mechanism of the ring-opening of **1**: Initially, product **16** is formed *via* cation **15**, to which bromide adds from the sterically less hindered convex face of bicycle **1a** (see the SI, Table S1). The HBr addition product regioisomeric to **16** was not observed. Considering the high diastereoselectivity in the ring-opening in which bromide has been introduced *anti* to the leaving group of **16,** ring-opening mus occur *via* an S_N2' type attack of bromideat the neopentyl position, notably from the sterically hindered concave face of the bicycle.

We also investigated if the α-carbinyl cation and subsequent ring-opening can be achieved from oxygenated precursors. Indeed, alcohol **19** was converted to **9a** with comparable yield as **1a**. However, the analogous cation derived from **17** resisted the ring-opening at room temperature but instead, led to the substitution product **18** with retention of configuration in high yield (96%) (Scheme 4). Attempting to carry out the HBr-reaction with **17** at higher temperatures led to the decomposition of the starting material. Other precursors, such as epoxides derived from **1a,** can also undergo the title transformation, however, the yields were significantly lower (see the SI, Scheme S1).

Scheme 4. Proposed reaction mechanism and further ring-opening of oxygenated precursors.[a]



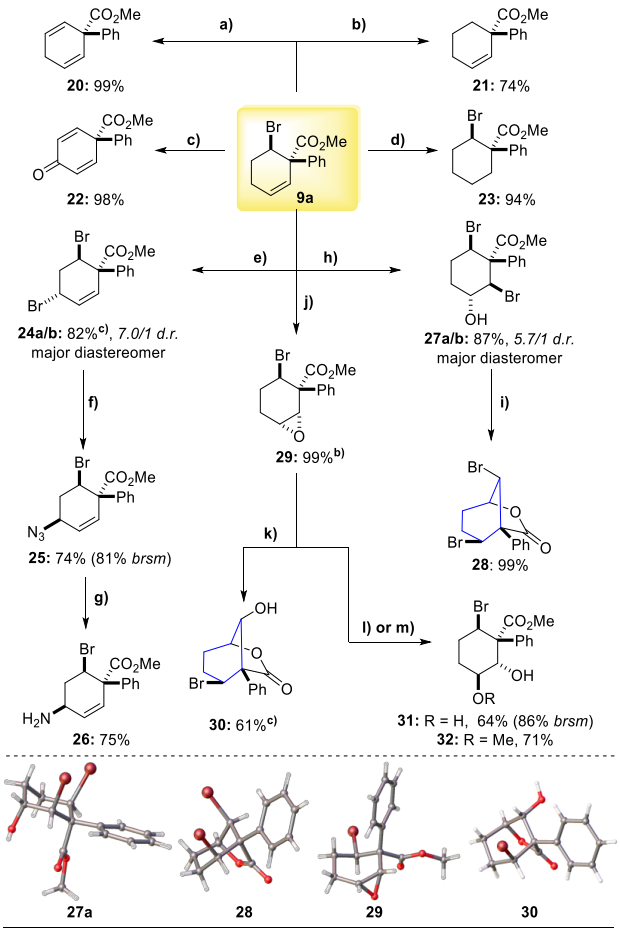
[a] Reaction conditions: a) **1a** (5.10 mmol), SeO_2 (1.1 equiv), 1,4-dioxane, 130 °C MW, 1 h. b) **17** (0.86 mmol), H_2 (60 bar), Pd/C (10 mol%), EtOAc, 25 °C, 4 h. c) **17** (0.31 mmol), aq. HBr (3.0 equiv), DCM, 25 °C, 72 h. d) **19** (0.35 mmol), aq. HBr (10 equiv), 100 °C, 1.5 h.

The functional group pattern of **9a** offers various opportunities for post-functionalizations, which proceeded with remarkable chemo-, regio- and stereoselectivity: Transformation involving the bromine functionality include elimination to 1,4-cyclohexadiene **20** or reduction to **21** by halogen-abstraction *via* a radical pathway.[12] Addressing the C-C double bond, reduction to **23**, epoxidation to **29** or bromohydrin formation to **27** was possible. The major diastereomer of the latter could be transformed to the bridged structure **28** in quantitative yield. Likewise, the analogous bridged structure **30** was accessible *via* epoxide **29**, which could be subjected to nucleophilic ring opening to give rise to **31** or **32**. The allylic position in **9a** could be functionalized either by oxidation to **22** which occurred with concurrent HBr elimination, or by bromination to **24**. The latter could be selectively converted to azide **25** and subsequently to amine **26** without affecting the other bromo functionality present, which shows low reactivity due to its neopentyl position.

In conclusion, we developed a high yielding, metal-free, stereoselective method for endocyclic C-C bond cleavage of monocyclopropanated cyclopentadienes mediated by a strong acid to form highly

functionalized cyclohexenes **9**, allowing access to new scaffolds with non-conventional substitution patterns.

Scheme 5. Synthetic useful post-functionalization of 9a.[a)]



[a)] Reaction conditions: a) **9a** (0.46 mmol), 4CzIPN (2 mol%), $Co(dmgH)_2PyCl$ (5 mol%), *i*-Pr_2Net (20 mol%), K_2CO_3 (1.0 equiv), MeCN, 16 h , 25 °C, blue LED (*hv = 455 nm*). b) **9a** (0.30 mmol), TTMSS (1.3 equiv), AIBN (10 mol%), dry MeCN, 60 °C, 72 h. c) **9a** (0.38 mmol), SeO_2 (2.1 equiv), 1,4-dioxane, 120 °C MW, 7 h. d) **9a** (0.40 mmol), Pd/C (10 wt%, 0.05 equiv), EtOH, 60 bar H_2, 25 °C, 4 h. e) **9a** (0.38 mmol), NBS (1.5 equiv), AIBN (10 mol%), cyclohexane, 70 °C, 2.5 h. f) **24a** (0.34 mmol), NaN_3 (1.5 equiv), DMSO, 2 h, 25 °C. g) **25** (0.18 mmol) i. PPh_3 (1.2 equiv), dry THF, 25 °C, 24 h. ii. H_2O (50 equiv), 25 °C, 24 h. h) **9a** (0.51 mmol), NBS (2.0 equiv), acetone/H_2O (3/1), 25 °C, 6 h, exclusion of light. i) **27a** (0.21 mmol), Amberlyst® 15 (20 wt%), toluene, 80 °C, 2 h. j) **9a** (5.23 mmol), *m*-CPBA (3.5 equiv), DCM, 25 °C, 24 h. k) **29** (0.24 mmol), H_2SO_4 (1.5 equiv), toluene, 80 °C MW, 0.5 h. l) **29** (0.25 mmol), R = H: H_2SO_4 (3.0 equiv), H_2O/MeCN (1/1), 50 °C, 6 h. m) **29** (0.33 mmol), R = OMe: H_2SO_4 (1.0 equiv), MeOH, 50 °C, 6 h. [b)] Gram-scale synthesis: **9a** (5.23 mmol) to **29** (1.62 g) [c)] Yield was determined by NMR using fumaronitrile or ethylene carbonate as internal standard.

ASSOCIATED CONTENT

Supporting Information

Supporting information including experimental details, further optimization, quantum yield calculation, gram-scale functionalization and copies of NMR spectra is available free of charge *via* the internet at htpp://pubs.acs.org.

Accession Codes

CCDC 2119362–2119366 contain the supplementary crys- tallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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