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Lanthanum(III) Triflate-Catalyzed Cyclopropanation via Intramolecular Methylene Transfer

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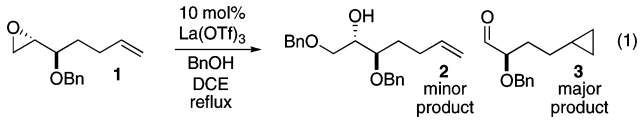
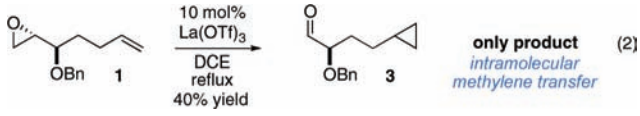
The value of cyclopropyl ring systems as unique structural elements and as reactive starting materials has inspired the invention of numerous methods for their preparation.[1] Although many of these methods have proven to be profoundly useful for the construction of a range of important cyclopropyl architectures, the stereoselective synthesis of cyclopropanes, particularly those remote from other functionality, remains a significant challenge. We report here the development of a novel catalytic method for cyclopropanation involving intramolecular methylene transfer from epoxides to olefins.

During the course of an attempted alcoholysis of epoxide **1** with benzyl alcohol catalyzed by lanthanum(III) triflate, we were surprised to observe as the major product the cyclopropyl aldehyde **3**, along with minor amounts of the target alcohol **2** (eq 1). Further investigation of this surprising transformation revealed that the benzyl alcohol was superfluous to cyclopropane formation, and that the product **3** could be isolated in approximately 40% yield simply by refluxing **1** in DCE in the presence of 10 mol % $La(OTf)_3$ (eq 2).

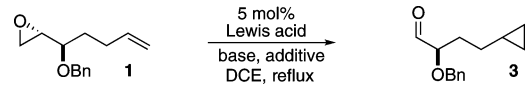




We are aware of only two examples of this type of methylene-transfer cyclopropanation: the first by Sharpless, who observed similar rearrangement products as components of a complex reaction mixture,[2] and more recently by Marson, who described methylene-transfer cyclopropanation in a constrained system with concomitant ring expansion.[3] In both of these cases, multiple equivalents of Lewis acid promoter were used, and little about the potential scope or stereoselectivity of this process was revealed.[4] In this Communication, we describe the first Lewis acid-catalyzed methylene-transfer cyclopropanation and demonstrate that a range of epoxy olefins participate efficiently and with high stereoselectivity.

To further optimize the reaction shown in eq 2, we first investigated a variety of Lewis acids for their effectiveness at catalyzing methylene-transfer cyclopropanation (Table 1). Although certain other metal salts (especially other lanthanide triflates) provided some amount of cyclopropane product (entries 1−6), $La(OTf)_3$ proved to be the most effective (entry 7).[5] Because the yield (40%) was significantly lower than conversion (100%), we hypothesized that the product might not be stable under the acidic reaction conditions. We thus screened base additives in the hopes of remedying this problem (entries 8−11), and indeed 2,6-lutidine was found to increase the product yield significantly (entry 11). Finally, we found that optimal yields could be obtained with $LiClO_4$ as an additive (entry 12). The role of $LiClO_4$[6] is not clear, since neither $LiClO_4$ in the absence of $La(OTf)_3$ (entry 13) nor $La(ClO_4)_3$ (entry 14) was as effective at promoting this reaction.

Table 1. Optimization Studies for $La(OTf)_3$-Catalyzed Intramolecular Methylene-Transfer Cyclopropanation[a]



entry	catalyst	base (0.05 equiv)	$LiClO_4$ (equiv)	time (h)	% yield
1	$Mg(OTf)_2$		0	12	4
2	$Zn(OTf)_2$		0	12	15
3	$Al(OTf)_3$		0	12	7
4	$Bi(OTf)_3$		0	12	<5
5	$Yb(OTf)_3$		0	12	22
6	$Eu(OTf)_3$		0	12	22
7	$La(OTf)_3$		0	12	40
8	$La(OTf)_3$	NEt_3	0	18	49
9	$La(OTf)_3$	TMU	0	18	40
10	$La(OTf)_3$	pyridine	0	18	25
11	$La(OTf)_3$	2,6-lutidine	0	18	54
12	$La(OTf)_3$	2,6-lutidine	0.75	3	72
13		2,6-lutidine	0.75	18	46
14	$La(ClO_4)_3$	2,6-lutidine	0	6	38

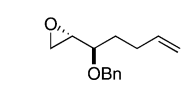
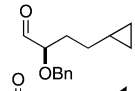
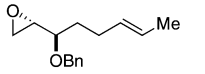
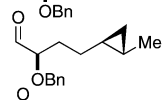
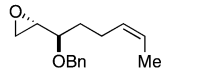
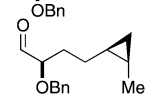
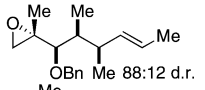
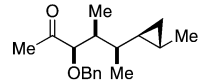
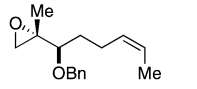
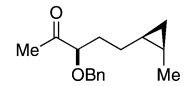
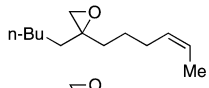
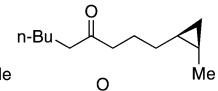
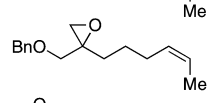
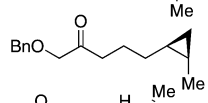
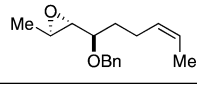
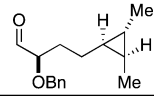
[a] Reactions were run in the presence of 5 mol % Lewis acid at a concentration of 0.2 M in DCE at reflux.

With optimized conditions identified, we next explored the scope of this cyclopropanation process (Table 2).[7] In contrast to the terminal olefinic substrate in entry 1, which requires refluxing temperatures for maximal yield, internal olefinic substrates proceeded at lower temperatures (entries 2−8). Notably, *trans* or *cis* olefins lead to *trans* or *cis* cyclopropanes respectively with complete stereospecificity (e.g., entries 2 and 3). In addition, we have found that substitution along the carbon backbone is well tolerated, allowing access to the stereochemically complex cyclopropyl aldehyde product shown in entry 4. Importantly, 1,1-disubstituted epoxides proved to be viable substrates, giving rise to cyclopropyl ketone adducts (entries 4 and 5). While a chelating substituent appears to be necessary for high yield under our optimal conditions (see entry 6), we have found that this chelating motif need not reside along the carbon backbone between the epoxide and olefin moieties. Thus, the epoxide shown in entry 7 undergoes methylene transfer to produce an α-benzyloxy ketone adduct in high yield. Realizing the potential utility of employing internal epoxides to prepare 1,2,3-trisubstituted cyclopropane adducts, we have also investigated reaction of the substrate shown in entry 8. While this reaction unfortunately gave rise to several products (see Supporting Information), the desired trisubstituted cyclopropane could be isolated in 30% yield as a single diastereomer.

Our mechanistic hypothesis for this transformation, which is in accordance with that proposed by Marson,[3] is shown in Figure 1.

10.1021/ja902137z CCC: $40.75

Table 2. Substrate Scope Studies for La(OTf)$_3$-Catalyzed Intramolecular Methylene-Transfer Cyclopropanation[a,b]

entry	substrate	product	temp (°C)	% yield	d.r.
1			80	72	--
2			40	72	>20:1
3			40	73	>20:1
4			40	71	82:18[c]
5			40	75	>20:1
6			60	26[d]	>20:1
7			40	84	>20:1
8			60	30	>20:1

[a] Reactions were run in the presence of 5 mol % La(OTf)$_3$, 5 mol % 2,6-lutidine, and 0.75 equiv of $LiClO_4$ at a concentration of 0.2 M in DCE. [b] Yields for entries 1−3 were determined using the alcohol products resulting from reduction of the crude reaction mixtures with $NaBH_4$. Diastereomeric ratios were determined by ^{1}H NMR analysis on crude reaction mixtures. [c] The starting material was an 88:12 inseparable mixture of isomers diastereomeric at the 4 and 5 (methyl-bearing) positions. [d] A major side product (~30%) appeared to be 2-pentyloct-6-enal resulting from Wagner−Meerwein rearrangement.

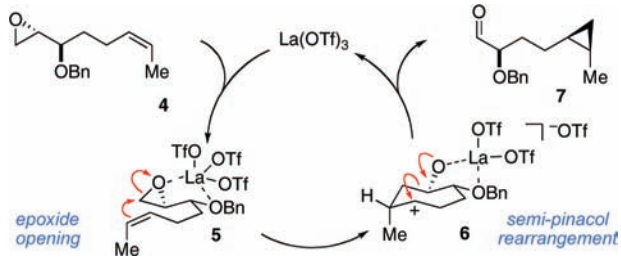
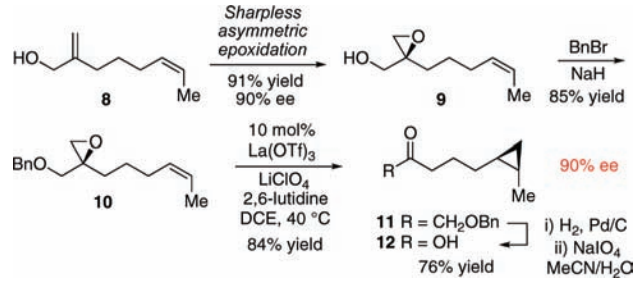


Figure 1. Proposed mechanism of methylene-transfer reaction.

Thus, chelation of lanthanum ion by alkoxy epoxide **4** activates the substrate (cf. **5**) toward intramolecular ring-opening by the olefin moiety. A semipinacol-type collapse of the resulting carbocation **6** then produces the cyclopropyl aldehyde **7**. This postulated mechanism is supported by the fact that internal olefins undergo methylene transfer more readily than terminal olefins, which is consistent with the notion of hyperconjugative stabilization of cationic intermediates.[8] Further support was gained by the isolation of a seven-membered ring product from the reaction mixture of entry 8, Table 2, which presumably arose from proton elimination of a cycloheptyl cationic intermediate (see Supporting Information).

Finally, one of the most intriguing implications of this methylene-transfer reaction is the potential to exploit asymmetric epoxidation technologies for the synthesis of enantioenriched cyclopropanes. To illustrate this concept, we have conducted the synthetic sequence shown in Scheme 1, whereby dienyl alcohol **8** was first transformed

Scheme 1. Synthesis of an Enantioenriched Cyclopropane via Asymmetric Epoxidation/Methylene Transfer



to epoxide **9** with 90% ee by Sharpless asymmetric epoxidation.[9] After standard benzyl protection, epoxide **10** was subjected to our optimized methylene-transfer conditions to furnish cyclopropane **11** in 84% yield with 90% ee.[10] Notably, ketone **11** could be further processed via a simple deprotection/oxidative cleavage protocol to produce the cyclopropyl acid **12**, which represents a potentially highly versatile synthetic building block.

In conclusion, we have developed a new cyclopropanation protocol based on intramolecular methylene transfer from epoxides to olefins. We believe this transformation provides a useful new approach for the synthesis of stereodefined cyclopropanes, particularly those relatively removed from other functionality. Further investigations of this transformation are ongoing in our laboratories.

Acknowledgment. We thank the Parkin group for determination of a crystal structure. The National Science Foundation (CHE-0619638) is thanked for acquisition of an X-ray diffractometer. We are grateful to Prof. Tom Katz (Columbia University) for providing us with helicene materials to determine the ee of product **11** (see ref 10).

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

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(4) The example reported by Marson and co-workers (ref 3) was completely stereoselective, but given the cyclic nature of their substrate, extrapolation of this finding to less constrained substrates was uncertain.
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