Cyclopropanation

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Defying Ring Strain: New Approaches to Cyclopropanes**

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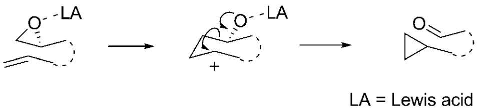
allylpalladium · asymmetric catalysis · cyclization · methylene transfer · ring strain

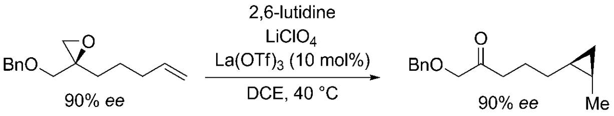
Cyclopropanes are important subunits with unique reactivity that are present in many biologically important compounds.[1] Many cyclopropanation reactions have been developed,[2] notably the Simmons–Smith reaction,[3] the transition-metal-catalyzed decomposition of diazo compounds,[4] the Kulinkovich-de Meijere reaction,[5] and Michael-initiated ring closure reactions.[6] Many of these approaches are based on highly reactive metal carbene reagents that can overcome the ring strain (28 kcal mol^{-1}) generated in the newly formed cyclopropane unit; in particular, methylene transfer reagents like the Simmons–Smith reagents or substituted metal carbenes derived from copper, rhodium, ruthenium, or cobalt catalysts rely on this strategy. Alternatively, other approaches have relied on irreversible ring closure processes that are entropically favored. Although many mild cyclopropanation conditions have been reported, synthetically useful approaches to enantiomerically pure cyclopropane derivatives remain scarce. However, two independent reports published recently developed new avenues in this field.

In the constant search for safer and greener cyclopropanation reactions with increased functional-group tolerance, efforts have been directed towards the development of methylene sources that are easier to handle and more stable than currently used reagents. One very attractive method was developed by Sharpless and co-workers,[7] demonstrating that an epoxide can be used as a methylene source for the intramolecular cyclopropanation of an alkene using a stoichiometric amount of Lewis acid (Scheme 1). Unfortunately, this unprecedented transformation was in competition with other rearrangements and led to a mixture of products. A few years later, the epoxide methylene-transfer cyclopropanation reaction was observed by Marson et al.[8] on a constrained system using a stoichiometric amount of $SnBr_4$. In this case, no other side products were formed, although only one example was reported. In both these reports, an excess of Lewis acid was required, and little about the potential scope or stereoselectivity of these processes was revealed.



Scheme 1. The epoxide methylene-transfer cyclopropanation reaction.

The breakthrough was recently disclosed by Lambert and Hardee,[9] who demonstrated that enantioenriched cyclopropanes can be obtained as the only product using epoxide as methylene source and $La(OTf)_3$ as the catalyst (Scheme 2).



Scheme 2. Catalytic epoxide methylene-transfer cyclopropanation using $La(OTf)_3$. TfO = CF_3SO_3, DCE = 1,2-dichloroethane, Bn = benzyl.

The key development of the method was using the Lewis acid (0.05 equiv) in the presence of 2,6-lutidine (0.05 equiv) and $LiClO_4$ (0.75 equiv). A variety of cyclopropane units remote from other functionalities were formed using these mild conditions with excellent diastereoselectivities. Moreover, an enantioenriched cyclopropane derivative was produced from an epoxide with a complete transfer of the stereochemical information. The mechanism proposed by the authors, which is in accordance with that proposed by Marson et al., is the opening of the epoxide by the nucleophilic attack of the alkene and subsequent semipinacol-type rearrangement to form the cyclopropane (Scheme 1).

It will be interesting to see whether future developments of this strategy will expand the substrate scope to other chain lengths and other directing groups. Moreover, these studies open the door to an enantioselective catalytic version using chiral Lewis acids, and ultimately to the use of epoxide as a methylene source in intermolecular cyclopropanation.

Another cyclopropanation reaction that attracted the attention of chemists is the cyclization of a π allylpalladium complex promoted by nucleophilic addition. Formally, in this

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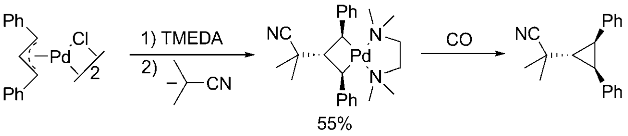
process a nucleophile attacks at the center carbon atom of an allyl cation, which pushes the electron doublet of the alkene to perform a three-membered-ring cyclization (Scheme 3). In most cases, π allylpalladium complexes react at the terminal carbon atoms (allylic alkylation reactions) and thereby avoid the high ring strain generated by the cyclopropanation. Despite this challenging issue, considerable attention has been directed toward this reaction, although with moderate success until recently.

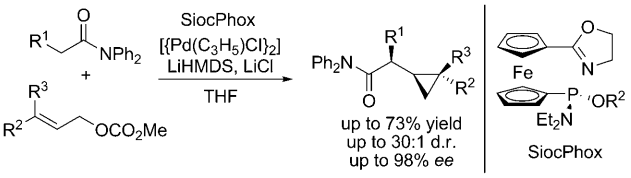
Scheme 3. Nucleophile-promoted intramolecular cycloaddition.

Hegedus and co-workers[10] were the first to observe the formation of a cyclopropane ring by this method. They reported that, under specific conditions, ester enolates can add to the center carbon atom of a π allylpalladium complex to form the three-membered ring. Other hard nucleophiles such as amides, esters, ketones, and sulfonamides proved to be efficient in this transformation, although a stoichiometric amount of π allylpalladium reagent was required.[11] Insight into the mechanism was gained by labeling experiments and through the isolation of a palladacyclobutane (Scheme 4).[10,11d] A catalytic version of this reaction was later developed by Musco and co-workers[12] employing ketene silyl acetals as nucleophiles, albeit with low yields. Substantial improvement was achieved by Satake and co-workers[13] by using pyridinylpyrazole and pyridinylimidazole as ligands with a catalytic amount of palladium. The intramolecular version of this process was achieved by the Grigg group[14] and the Hayashi group,[15] but either narrow substrate scope or low selectivity was observed. A catalytic enantioselective version was also reported,[13b] but the highest enantioselectivity obtained until recently was 54 % *ee*.



Scheme 4. Synthesis of a palladacyclobutane and its conversion to a cyclopropane. TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine.

The major breakthrough was achieved by Hou and co-workers[16] through the use of the chiral ligand SiocPhox with a catalytic amount of palladium, which not only promotes the attack of the center carbon atom on a π allylpalladium complex but generates cyclopropanes in good yields and excellent enantioselectivities (Scheme 5). The presence of lithium had a great impact on promoting the cyclopropanation reaction, as not only LiHMDS was the optimal base, but also LiCl as an additive greatly improve the selectivity. Under these conditions, a variety of cyclopropanes were synthesized with moderate to good yields and *ee* values ranging from 89 to 98 %. These results are remarkable considering that three stereogenic centers are formed in one process from two easily accessible starting materials.



Scheme 5. Asymmetric palladium-catalyzed cyclopropanation of acyclic amides with substituted allyl carbonates. HMDS = bis(trimethylsilyl)-amide.

Several technical issues are likely to be addressed in the continued development of this reaction. The selectivity of the cyclopropanation/allylic alkylation is not yet perfect, and the diastereoselectivity is low in certain cases. Although the allylic alkylation products can be removed by oxidation, this procedure narrows the functional-group tolerance. Undoubtedly, a better understanding of the mechanism of this reaction will help to address these issues. In the near future we should expect to see other nucleophiles than amides that can perform this transformation with a high level of enantioselectivity as well as its application in the synthesis of difficult-to-access enantioenriched 1,2,3-substituted cyclopropanes.

Aiming at the discovery of new synthetically useful cyclopropanation reactions, Lambert and Hardee demonstrated that epoxides could be a source of methylene in the synthesis of enantioenriched cyclopropanes.[9] Hou and co-workers pushed the limit of the well-established allylic alkylation chemistry to the synthesis of three-membered rings with excellent *ee* values.[16] These reactions will certainly inspire the development of new methodologies that defy the ring strain of the cyclopropane.

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