Directed Diastereoselective Cyclopropanation and Epoxidation of Alkenyl Cyclopropyl Carbinol Derivatives

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ABSTRACT: We report the directed diastereoselective Simmons–Smith cyclopropanation and vanadium-catalyzed epoxidation reactions of alkenyl cyclopropyl carbinol derivatives. The reaction furnished densely substituted stereodefined bicyclopropanes and cyclopropyl oxiranes as a single diastereomer in each case. The remarkable selectivity is obtained thanks to the rigidity of the cyclopropyl core, allowing diastereoselective reactions on the alkenyl moiety. This emphasizes the uniqueness of the cyclopropyl ring as a central platform in stereoselective synthesis.

The stereoselective synthesis of numerous contiguous stereocenters represents a constant chemical challenge: the higher the number of adjacent stereocenters, the harder is the synthesis. Although various strategies have recently appeared expanding the portfolio of tools available to practitioners,7–10 the synthesis of sophisticated organic structures requires the continuous development of new methodologies that control all selectivity issues of a given reaction. Among the several general methods to control the selectivity of a reaction,7–10 the substrate-directed approach occupies a special position.11–14 The key features of this success are the level of predictability, the high diastereo- and enantioselectivity, and the latent potential functionality of the products for subsequent transformations. Indeed, in this approach, a polar functional group (directing group), usually situated in close proximity of the reactive site, induces the stereocontrol step and can be successively manipulated toward the formation of more complex molecular architecture.7–14

Two of the most classical examples employ allylic alcohol derivatives for the diastereo- and/or enantioselective epoxidation15,16 or cyclopropanation reactions,17,18 among others,19 underlining the critical importance of the position of the directing group at a close vicinity of the reactive part of the molecule.14 When the distance between the polar group and the reactive alkene increases, the face stereodifferentiation becomes more difficult and the level of selectivity decreases. To answer such limitations, several strategies have been developed for homoallylic alcohols.13

During our studies on the diastereoselective synthesis of polysubstituted cyclopropanes17–21 as a new source of stereodefined acyclic products,22 we have recently shown that alkenyl cyclopropyl carbinol derivatives 1 exhibit an excellent directing effect for the palladium-catalyzed tandem Heck addition and ring opening reaction23–28 as well as for diboration reactions29 (Scheme 1a). Even more distant alkenyl bicyclopentyl carbinol 2 led to a completely diastereoselective Heck addition reaction before the subsequent selective double ring-opening.

Although the functional group is in a 3,4 position in 1 and 5,6 position in 2, the particular molecular structure of these alkenyl cyclopropyl carbinols induces a preferred s-trans conformation toward the s-cis conformation, favoring a diastereofacial choice in the addition reaction (Scheme 1a). Based on this diastereoselective Pd-catalyzed Heck addition on alkenyl cyclopropyl carbinols, we were initially interested in extending this substrate-directed transformation to the challenging synthesis of bicyclopentyl carbinol 3. Our previous approach based on a double-diastereoselective carboalkylation reaction of two differently substituted cyclopropanes had the major drawback of producing two geometrical isomers, even if each one was diastereomerically pure (2 in Scheme 1a).26 To access stereodefined alkenyl cyclopropyl carbinol derivatives 1, we used our previously established copper-catalyzed diastereoselective carboalkylation reaction of cyclopropanes followed by a Pd-catalyzed cross-coupling reaction (Scheme 2).24 Cyclopropanes were easily prepared via the standard Rh-catalyzed decomposition of diazo esters in the presence of alkyne30 (see the Supporting Information for full details). A simple reduction of the ester provides the desired alkenyl cyclopropyl carbinols 1.

With alkenyl cyclopropyl carbinol derivatives 1 (and 6 and 7) as well as esters 5 at our disposal, we started to investigate if a distant functional group could direct the cyclopropanation
reaction using the classical Simmons–Smith–Furukawa condition. To our delight, subjecting our model substrate 1a (R = R1 = R2 = H, R3 = Me, R4 = Bu, R5 = Bu) to an equimolar mixture of diiodomethane and diethyl zinc in DCM at 0 °C resulted in a quantitative formation of bicyclopropyl carbinol 3a with excellent diastereoselectivity (88% yield and dr > 98:02, Scheme 3). This result indicates that the in situ formed zinc carbenoid must be preassociated with the alcoholate functional group to stereodirect the carbenoid toward one of the diastereotopic faces of the alkene.

Using this optimized condition, we demonstrated that various R2 primary (3a, 3b, 3c, 3e, and 3f) as well as secondary alkyl groups (3d) are well tolerated in the reaction without altering yields and selectivities. Similarly, the stereochemistry (E or Z) of the alkenyl side chain has no effect on the stereochemical outcome of the reaction (compare 3b and 3c, Scheme 3). Interestingly, the presence of the quaternary carbon stereocenter can be located at different places without changing the chemistry (compare 3h with 3b and 3k with 3h, Scheme 3). Importantly, the reaction is stereospecific, with E and Z-alkenyl moieties converted into their respective trans- and cis-cyclopropanes with a complete stereospecificity. Interestingly, sterically crowded trisubstituted olefins are smoothly converted under our standard conditions to bicyclopropane 3k bearing two quaternary carbon stereocenters. If the double bond is one more carbon away from the cyclopropyl core, the reaction is not diastereoselective anymore.

Finally, we decided to test other directing groups as potential promoters of the cyclopropanation reaction. We were pleased to observe that alkenyl cyclopropyl methyl ether 6a as well as alkenyl cyclopropyl silyl ether 7a were successfully converted to 3l and 3m, respectively, with excellent yields and diastereoselectivities. Subjecting compound 1l possessing a dienyl moiety to the developed cyclopropanation conditions resulted in an efficient and selective transformation to 3n in excellent yield and diastereosepecificity.

The lack of cyclopropanation at the terminal double bond further demonstrates the strong directing effect of the hydroxyl...
group. Similarly, alkenyl cyclopropyl esters 5a and 5b proved to direct the reaction equally well to give the expected products 3n and 3p as single diastereomers. Based on the outstanding abilities of the functional group to direct the cyclopropanation reaction of alkenyl cyclopropyl carbinols 1, we then set out to extend the strategy to other important synthetic transformation. We therefore turned our attention to the diastereoselective epoxidation reaction. When mCPBA or tBuOOH was added to 1b, a non-diastereoselective epoxidation reaction occurred to deliver the epoxide 4a in a 2:1 ratio. This highlights the insufficient direction provided by hydrogen-bonding interactions with the carbinol group and the importance of metal-mediated epoxidation reactions for achieving high stereoselectivity.

Indeed, when the same reaction was performed on 1b but in the presence of 10 mol % of vanadium acetylacetonate, 33–35 4a was obtained in excellent yield with complete diastereoselectivity (Scheme 4). When the opposite geometrical isomer was treated in the same conditions, the epoxide 4b was obtained with a similar selectivity featuring the specificity of the transformation. The degree of substitution has no effect on the diastereoselectivity of the process as trisubstituted alkenyl cyclopropyl carbinol 1k was epoxidized as a single diastereomer (formation of 4d, Scheme 4). In conclusion, the directed diastereoselective Simmons–Smith cyclopropanation reaction of alkenyl cyclopropyl carbinal derivatives as well as alkenyl cyclopropyl esters provides the corresponding polysubstituted stereodefined bicyclopropanes as a single diastereomer in each case. The same trend holds for the vanadium-catalyzed epoxidation reaction. The rigidity of the cyclopropyl core allows diastereoselective reactions on the alkenyl moiety, emphasizing the uniqueness of the cyclopropyl ring as a central platform in stereoselective synthesis.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03305.

Experimental procedures, characterization data for all new compounds, along with copies of spectra. Computational methods and data, geometries of computed intermediates and transition states (PDF)

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