Stereoselective Synthesis of Polysubstituted Spiropentanes

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ABSTRACT: A new approach to polysubstituted spiropentanes is developed through a regio- and diastereoselective carbometalation of sp²-disubstituted cyclopropenes. The control of selectivity originates from a combined syn-facial diastereoselective carbometalation with a regio-directed addition. The regio-controlling element subsequently serves as a leaving group in an intramolecular nucleophilic substitution. This method allows the preparation of various polysubstituted spiropentanes with up to five contiguous stereocenters.

Spiropentane, the smallest spiro-connected cycloalkane, has been known since the end of the 19th century. First synthesized by Gustavson in 1896, the correct structure was proposed by Zelinsky two decades later, and spectroscopically characterized by Murray in 1944. Since then, spiropentanes have aroused the imagination of theoretical, physical, and synthetic chemists, as well as biologists as some members display interesting biological activities. The synthesis of these highly strained spirocyclic hydrocarbons has been extensively investigated, initially through 1,3-reductive dehalogenation reactions (Scheme 1a). To reach a slightly higher degree of substitution, cyclopropyl sulfur ylides were added to α-β unsaturated carbonyl derivatives (Scheme 1b). Another approach is the carbene (in situ generated by metal-catalyzed decomposition of diazo compounds) addition to alkylidene-cyclopropane or allene to produce spiropentanes with different substitution patterns (Scheme 1c). Using zinc carbenoid in the presence of chiral dioxaborolane ligand led to a substituted spiropentane structure with excellent enantiomeric ratios (Scheme 1d). In a real tour de force, de Meijere reported the first enantiomerically enriched unbranched [4]triangulane synthesis (Scheme 1e). Nevertheless, all reported methods mentioned above, among others, lack flexibility with a rather limited number of substitution patterns, particularly if one is interested in the formation of quaternary carbon stereocenters. In our recent study concerning the selective ring opening of spiropentane derivatives towards the formation of distant stereocenters in acyclic systems (Scheme 1f), we indeed realized the difficulty to prepare polysubstituted spiropentane with high diastereomeric and enantiomeric ratios.

Based on the limited number of synthetic approaches allowing a convergent preparation of polysubstituted spiropentanes as a single diastereomer, we decided to start a new program to handle this issue. For the past few years, we and others have developed several strategies to prepare polysubstituted cyclopropanes including the formation of per(hexa)-substituted cyclopropanes as a single diastereomer through regio- and diastereoselective carbometalation reactions of cyclopropanes. During this study, we have established a protocol for a regio- and diastereoselective copper-catalyzed addition of alkylmagnesium halide to electronically biased sp²-disubstituted cyclopropanes, as well as to sp²-dialkylated substituted cyclopropanes where the regioselectivity is controlled by a template effect (Scheme 2a).

In the latter case, the organometallic nucleophile is doubly directed: (i) the alcoholate induces a syn-facial diastereoselectivity of the addition and (ii) a directing group tethered to one end of the double bond dictates the regioselectivity of the addition. Several directing groups (DGs) could govern the regioselectivity such as free and protected alcohols, tertiary amines, and sulfides.

Based on this directing group ability to control the regioselectivity of addition to 1,2-dialkylated cyclopropanes, we envisioned the use of a functionality that not only possessed the capacity to direct the addition step but also could serve as a good leaving group. It should allow a subsequent intramolecular nucleophilic substitution reaction giving rise to the preparation of polysubstituted spiropentane derivatives (Scheme 2b). Obviously, several challenges and pitfalls need to be overcome. First and foremost, an easy and efficient preparation of all starting materials as a single diastereomer should be delineated. Then, the regioselectivity as well as the diastereoselectivity of addition should be controlled implying that the nature of the directing group/leaving group should match the syn-facial effect of the ester of 1 (matched pair, Scheme 3). Assuming that the carbometalation reaction will be fully regio- and diastereoselective (1 into 2), the subsequent step consists of an intramolecular nucleophilic substitution of a tertiary cyclopropyl metal species 2 to a secondary halide or pseudo halide that might lead to elimination reactions rather than substitution. Finally, the required substitution should proceed faster than a ring-fragmentation that is a known side-

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reaction of cyclopropyl metal possessing an electron withdrawing group (donor−acceptor cyclopropane, Scheme 3). With these potential pitfalls in mind, we started our study by devising a synthesis of our starting materials. Cyclopropenyl esters 4 are easily obtained by a Rh-catalyzed decomposition of diazoester in the presence of an alkyne. From racemic 4, a simple metalation at low temperature and addition of epoxides in the presence of a Lewis acid led to the equimolar amount of the two diastereomers 5a and 5b (see the Supporting Information). It should be noted that formally a single enantiomer as well as diastereomer could be obtained by using the enantioselective Rh-catalyzed cyclopropenation of alkynes that would provide 4 in excellent enantiomeric ratios followed by addition of enantiomerically pure epoxide. However, as the two diastereomers were easily separated by purification by column chromatography, we have initially opted to continue with racemic 4. It is interesting to note that 6-membered ring lactone was not detected in the crude reaction mixture underlining the unfavorable cyclization process. Then, the corresponding alcohols were transformed into tosylate 1 that would serve, on one hand, as a directing template to control the regioselectivity of the carbometalation reaction and, on the other hand, as a good leaving group toward intramolecular nucleophilic substitution. The chemistry described above could be easily run on a preparatory scale (0.5 to gram scale) which makes the method attractive despite unoptimized modest yields in some cases (please note that yields for 5a and 5b are after separation of the two diastereomers by column chromatography and are based on a maximum 50%, Scheme 4). In some cases, the ester was also reduced into alcohols 7. The relative configuration was determined by X-ray analysis of 1a-8, and all other configurations were assigned by analogy.

Having in hand an easy access to a large variety of starting materials 1a and 1b, we then turned our attention to the tandem regio- and diastereoselective carbometalation reaction followed by intramolecular nucleophilic substitution as a new route to polysubstituted spiropentanes 3. When our model substrate 1a-1 was treated with an organocopper reagent (easily prepared by addition of 1 equiv of alkyllithium to 1 equiv of CuI) in a mixture of Et₂O/toluene as solvent, the carbometalation reaction proceeded smoothly at low temperature. The resulting cyclopropyl copper species could not be isolated as it undergoes a rapid cyclization to provide spiropentane 3a-1 as a single diastereomer in excellent yield (Scheme 5). We were happy that no ring fragmentation of the cyclopropyl copper species was observed, owing to the relatively high covalent nature of the carbon−copper bond. The nature of the alkyl group of the organocopper can be varied as various primary and even secondary alkyl lithiums could be used as precursors of the organocopper (3a-1 to 3a-4, Scheme 5). It should be noted that the diastereoselectivity in the latter case is lower due to potential steric hindrance in the carbometalation step. Both diastereomers at the quaternary carbon center could be easily prepared by simply permuting the nature of the alkyl groups on the cyclopropene and organocopper (compare 3a-2 and 3a-3, Scheme 5). Similarly, various alkyl chains R₁ of different nature are compatible, including a phenyl substituent (3a-5 to 3a-7, Scheme 3). The nature of the substituents on the epoxide could be varied
including with a more functionalized group (3a-8 and 3a-9). We were equally delighted to observe a smooth transformation of cyclopropene 1a-9 possessing two substituents on the tether. This transformation allowed the preparation of spiropentane 3a-10 possessing five contiguous stereocenters as a single diastereomer out of 8 possible isomers. The relative configuration was determined by X-ray analysis of an hydrazine-derived from 3a-7 (for details, see Supporting Information), and all the other configurations were assigned by analogy. Interestingly when the stereocenter on the cyclopropenyl ring is inverted as in cyclopropene 1b, the overall diastereoselectivity of the process is lower. If the intramolecular nucleophilic substitution of the cyclopropyl copper intermediate occurs with pure inversion of configuration, this discrepancy could only originate from a less diastereoselective carbocupration of 1b-1 and 1b-2, leading to 3b-1 and 3b-2 (compared to 3a-2 and 3a-6, Scheme 5). This inconsistency suggests that some steric interactions occur in the conformer that has a chelation between the ester, the tosylate, and the organometallic species, leading to minor addition from the opposite diastereotopic face (mismatched isomer; see molecular modeling in the Supporting Information). Following the same logic, similar steric interactions should be observed for the carbometalation of the fully substituted cyclopropene 1a-10 (R^4 ≠ H). Indeed, the diastereoselectivity of the process is slightly lower (compare 3a-11 with 3a-2, Scheme 5). This result implies that the presence of an alkyl substituent R^4 (for 1a-10, R^4 = Me) as it was for 1b provides a certain amount of the opposite diastereomer (see molecular modeling in the Supporting Information). To avoid the formation of this minor isomer, we therefore hypothesized that a substrate devoid of this double chelation should lead to a higher diastereoselective carbometalation reaction and consequently to a better overall selectivity for the formation of spiropentane. Therefore, the secondary chloride 6a-1 was prepared as a single diastereomer by an S_N2 reaction on the tosylate. Treatment of 6a-1 with the same organocopper and under the same experimental conditions led
to the formation of a new spiropentane 3a-12 as a single diastereomer. It should be noted that this diastereomer is different from the two diastereomers of 3a-11. This underlines the fact that the diastereoselectivity in the formation of 3a-12 is directed exclusively by the ester, without influence of the chloride on the facial diastereocent.

An alternative approach to overcome this lower diastereoselectivity would be to have a stronger directing group that would counterbalance the conformational bias of the mismatched isomer. Therefore, a simple reduction of the ester 6b-1 into the strongly chelating alcohol derivative 7b-1 was prepared as described in Scheme 6. The addition of MeCu at low temperature promotes a fully diastereoselective carbometalation reaction followed by a subsequent intramolecular nucleophilic substitution to give 8b-1 as a single diastereomer. The same stereochemical outcome was obtained by using the tosylate 7a-1 as starting material, and in all cases, a single diastereomer of the corresponding spiropentane methanols 8a-1 to 8a-3 was obtained.

In conclusion, by recognizing the potential of directed diastereoselective carbometalation of \( \text{sp}^3 \)-disubstituted cyclopropene, a new approach to polysubstituted spiropentanes was developed. This reaction requires the combined effect of a syn-facial diastereoselective carbometalation with a regio-directing group that serves as a leaving group in a subsequent intramolecular nucleophilic substitution. This method allows the preparation of diverse polysubstituted spiropentanes with up to five stereocenters including three quaternary carbon centers. Preparation of enantiopure spiropentanes are therefore easily accessible by using enantiopure epoxides during the preparation of the starting materials.

\section*{ASSOCIATED CONTENT}

\subsection*{Supporting Information}

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07370.

Experimental procedures, characterization data for all new compounds, along with copies of spectra (PDF)

\subsection*{Accession Codes}

CCDC 2172799–2172800 contain the supplementary crystallographic 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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\subsection*{Notes}

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De la R.’s group has investigated the potential of spiropentanes as chiral auxiliaries in asymmetric synthesis and catalysis. Their work has led to the development of new methods for the enantioselective synthesis of cyclopropanes, which are key intermediates in the synthesis of natural products and pharmaceuticals. These methods have been widely adopted in the field, and have contributed to the advancement of chiral catalysis and asymmetric synthesis.

The discovery of new synthetic methods, such as those reported in this paper, is a testament to the ongoing efforts of researchers in the field of organic chemistry. The ability to control the stereochemistry of the resulting cyclopropanes is crucial for the development of new drugs and materials. The development of these new methods is expected to have a significant impact on the field, and will likely lead to the discovery of new pharmaceuticals and materials in the near future.