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COMMUNICATION

Diastereoselective Synthesis of Spiro[2,n]alkanes via Intramolecular Carbolithiation

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Spirocycles are appealing motifs for drug design owing to their inherently rigid three-dimensional structure, but synthetic strategies to construct highly substituted spiroalkanes remain scarce. We report a highly diastereoselective protocol for the synthesis of spiro[2.n]alkanes via intramolecular carbolithiation of cyclopropenes. The methodology provides straightforward access to spiro[2.n]alkanes sizes as single diastereomers, with up to three contiguous quaternary centres. The trapping of a generated intermediate with an electrophile provides access to functionalized spirocycles bearing halo, silyl, alcohol or carbonyl functionalities.

Spirocycles—molecular architectures composed of two rings connected through a single atom—have attracted significant attention in medicinal chemistry.[1-6] This growing interest results from the recognition that three-dimensional, sp^3-rich scaffolds enhance drug-likeness by improving solubility and oral bioavailability.[7-10] In particular, spirocyclic structures featuring adjacent quaternary carbon stereocenters[11] provide additional vectors for installing binding motifs in multiple spatial directions, thereby enhancing target binding affinity.[2, 12] Despite these potential advantages, the broader application of spiroalkanes, especially those incorporating stereochemically defined small to medium-sized rings,[13, 14] remains limited by significant synthetic challenges.[1, 2, 12, 15] In this context, synthetic strategies have emerged to tackle the synthesis of spiro[2.n]alkanes (Scheme 1A),[16-20] mostly relying on cyclopropanation chemistry. Despite recent advances in spirocycle synthesis,[20-28] the diastereoselective synthesis of highly substituted cyclopropyl-containing spirocycles remains relatively underexplored.[17, 18] As part of our ongoing efforts to develop stereoselective strategies for the construction of polysubstituted small rings via carbometallation reaction,[29] we recently reported an approach to access stereodefined, highly substituted spiropentanes[30] and bicyclopropanes[31] from readily available cyclopropenes (Scheme 1B). We envisaged expanding the methodology to the synthesis of spiro[2,*n*]alkanes beyond spiropentanes, by reversing the strategy from an intermolecular to an intramolecular carbometallation pathway (Scheme 1C). To enable the synthesis of all-carbon spirocycles via this approach, we required a functional group on the cyclopropene that could be efficiently converted into an organometallic species. Alkyl iodide **1** was selected for this purpose, as it should undergo a fast and quantitative iodine-lithium exchange with *t*BuLi resulting into the linear alkyllithium species **2**, that can eventually be transmetallated if required. The resulting organometallic species is then expected to undergo an intramolecular carbometallation into the desired spirocyclic organometallic intermediate **3**. To control the diastereoselectivity of this cyclization step, a coordinating substituent on the three-membered ring was designed to direct the incoming nucleophile to the same face of the cyclopropene. Finally, the spirocyclopropyl metal species could be further functionalized by reaction with suitable electrophiles, providing various spirocyclic scaffolds **4**. During the course of this study, Waser and coworkers reported an elegant palladium-catalyzed intramolecular etherification strategy,[32] which provides pentasubstituted trifluoromethylated spirooxazolidines as single diastereomers. However, this approach is conceptually distinct from carbolithiation strategy described herein and is not applicable to the synthesis of spiro[2.*n*]alkanes.

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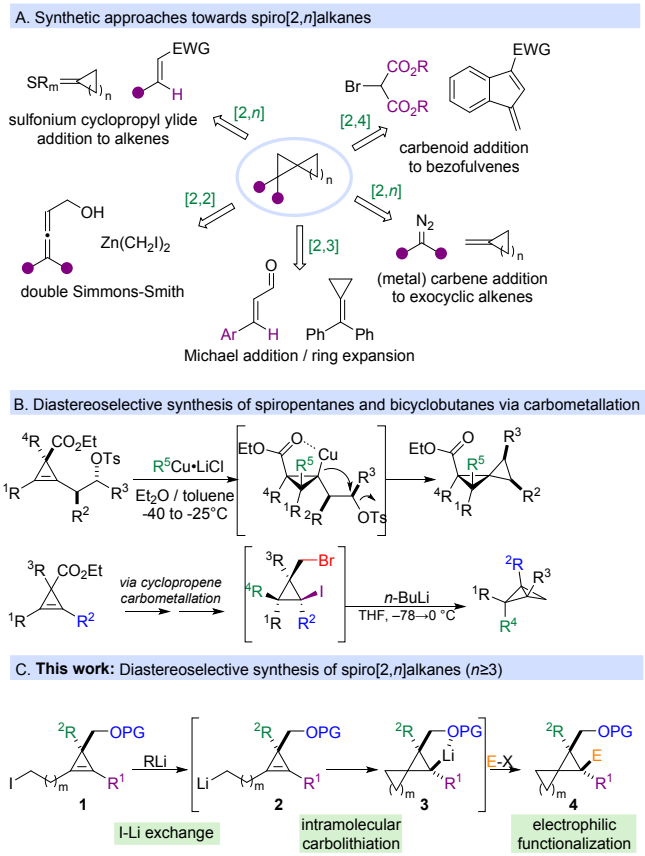
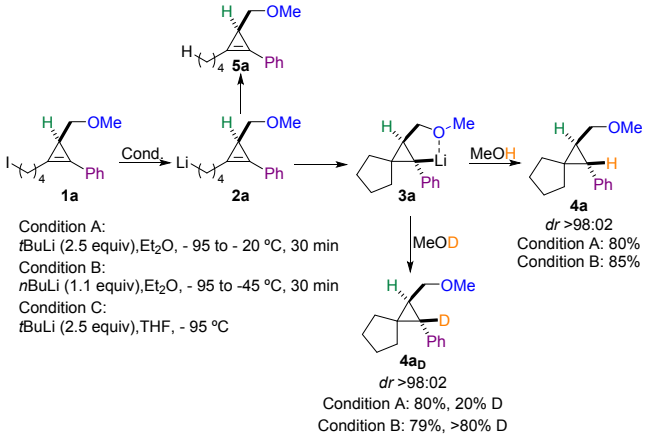


Scheme 1. Key precedent and proposed research.

Building on our earlier work on the enantioselective catalytic carbolithiation of cinnamyl derivatives,[33] we hypothesized that the substituent on the cyclopropenyl ring (R^1) should promote the carbometallation step, with aromatic or silyl groups expected to provide the required slight activation. However, this design also necessitates a rapid and quantitative iodine-lithium exchange, to minimize undesired intermolecular addition of alkyllithium species to the reactive double bond of the cyclopropenyl ring.[34] It also required to provide a configurationally stable cyclopropyl benzyl (or silyl) lithium intermediate before addition of the electrophile.[35] To begin our investigation, we developed a straightforward and efficient method for the preparation of the starting materials **4** (see Supporting Information for all details). Enantiomerically enriched sp^2-monosubstituted cyclopropenyl ester are readily accessible,[36] and undergo direct palladium-catalyzed cross-coupling reaction with a wide range of aryl iodides.[37]

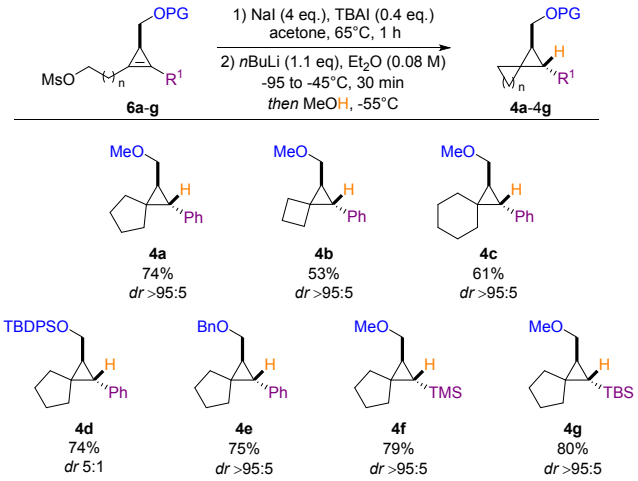
We then set out to identify reaction conditions that would promote a clean iodine-lithium exchange followed by an efficient intramolecular carbolithiation reaction on our model substrate **1a**. Upon dropwise addition of *t*BuLi (2 equiv)[38] to iodide **1a** at -95 °C, the reaction mixture was gradually warmed to the desired temperature to enable the carbometallation (condition A, Scheme 2). For this substrate, cyclization occurred even at -95°C, but the transformation tolerated temperatures up to -20°C (see Supporting Information for all details) to provide **4a** in excellent yield as a single diastereomer. However, when MeOH-d_4 was used as the electrophile, only low levels of deuterium incorporation were observed (**4a$_D$**, 20% D). This suggests that the tertiary cyclopropyllithium intermediate **3a** formed during carbolithiation is more reactive than *t*BuLi itself towards the in-situ generated *t*Butyl iodide under the reaction conditions. As a result, **3a** reacts competitively with *t*Butyl iodide leading to protonated spirocycle **4a**. Since this undesired side reaction could not be suppressed, we investigated the use of *n*BuLi for the iodine–lithium exchange, despite the likelihood of an equilibrium between linear iodide **2a** and the corresponding *n*-alkyllithium.[39] Gratifyingly, the intramolecular carbolithiation provided sufficient driving force to push the reaction forward, yielding results comparable to *t*BuLi. When MeOH-d_4 was used in the condition B, a significantly higher degree of deuteration (>80% D) was achieved for **4a$_D$** (Condition B). When THF was used instead of diethyl ether, the iodine-lithium exchange proceeded completely, but carbometallation was incomplete, and the major side product was the reduced linear product **5a** (Condition C).



Scheme 2. Conditions for the intramolecular carbolithiation.

With the optimized conditions established, we next explored the substrate scope. As some of the alkyl iodides proved unstable toward chromatographic purification and prolonged storage, the crude iodides were used directly after simple filtration (see Supporting Information for details). Consequently, the isolated yields of all spiro[2.n]alkanes in Schemes 3-5 were calculated over two steps. A series of spirocycles ranging from spiro[2.3]hexane **4c** to spiro[2.5]octane **4d** were obtained in high yields as single diastereomers (Scheme 3), consistent with a *syn*-selective carbolithiation directed by the methyl ether substituent. The formation of spiro[2.3]hexane **4b** with *n*BuLi was also efficient, although this transformation required higher temperatures compared to the synthesis of spiro[2.4]heptane **4a**. To achieve full conversion, the reaction mixture was gradually warmed to -45 °C and stirred for an additional 30 minutes at that temperature. Interestingly, in all cases, the benzyl lithium species is configurationally stable under these experimental conditions. To clarify the role of the cyclopropylcarbinol ether in directing the carbolithiation event, we designed substrate **4d** as a control experiment. Introduction of the

sterically demanding tert-butyldiphenylsilyl (TBDPS) protecting group led to a marked erosion of diastereoselectivity, furnishing the product in 5:1 dr, in contrast to the excellent selectivities observed with the corresponding methyl and benzyl ethers (>95:5 dr). This outcome is consistent with a directing effect exerted by the carbinol ether, which is diminished when coordination is attenuated or sterically hindered by the bulky silyl protecting group. The relative configurations of the major and minor diastereomer of **4d** were assigned by NMR analysis, through detailed examination of coupling constants and NOE experiments, confirming that the minor product corresponds to the spirocycle formed through carbolithiation anti to the silyl carbinol substituent. Thus, the stereochemical outcome of substrate **4d** directly supports the proposed directing role of the cyclopropylcarbinol ether. Benzyl ethers were well tolerated, providing the desired product **4e** in 75% yield, whereas ester protecting groups as well as the shortest substrate (n = 1) (not described in Scheme 3) failed to deliver the ester-derived spirocyclic products and spiro[2.2]pentanes (see the Supporting Information for details on unsuccessful substrates). Modifying the anion-stabilizing group allowed access to TMS-substituted spiro[2.4]heptane **4f**, obtained in excellent yield (79% over two steps) as a single diastereomer. Remarkably, even the bulky TBS group was tolerated on the cyclopropene, affording silylated spiro[2.4]heptane **4g** in 80% yield.



Scheme 3. Substrate scope.

We also sought to investigate the replacement of the aryl group with heteroaromatic substituents. However, access to the corresponding heteroarene-substituted cyclopropyl carbinols proved challenging, and these substrates were therefore not pursuit further. Alkyl-substituted cyclopropenes were likewise not examined, as the corresponding intramolecular carbolithiation is not expected to proceed efficiently in the absence of a substituent capable of stabilizing the resulting tertiary alkyllithium species. Shorter tether lengths that would form spiropentanes are not proceeding under the current conditions. To further increase the complexity of the final spiroalkanes, we subsequently trapped the cyclopropyllithium intermediate with various electrophiles. As discussed previously, deuteration with MeOH-d_4 proceeded smoothly, regardless of the nature of the anion-stabilizing group, giving 69% of **4a$_D$** with 83% of deuterium incorporation and 76% of **4g$_D$** with 95% of deuterium incorporation (Scheme 4). Iodination of these cyclopropyl lithium intermediates furnished **4h** and **4i** in 44% and 66% yield, respectively, with the only detectable side products being the proton-quenched products. The higher yield of the TBS-substituted product **4i** as compared to **4h** is attributed to both the efficiency of the preparation and stability of the linear alkyl iodide starting material. Attempts to synthesize cyclopropyl bromides in the same manner by quenching with NBS led to decomposition (for details on unsuccessful substrates please consult the supporting information). Despite their steric bulk, silicon electrophiles proved to be viable coupling partners, as demonstrated by the formation of TMS-functionalized spiro[2.4]heptane **4j**, albeit in a low 30% yield. Carbon–carbon bond formation was also achieved using various electrophiles, affording spiro[2.4]heptanes **4k**-**4p**, each being pentasubstituted cyclopropane derivatives, in moderate to good yield as single diastereomers. Interestingly, trapping with sterically demanding electrophiles such as TMSCl and acetone-d_6 proved more efficient for spiro[2.3]hexanes than for spiro[2.4]heptanes (compare **4j** with **4q** and **4l** with **4r**, Scheme 4). This enhanced reactivity is likely attributed to the angle strain inherent in the cyclobutyl ring, which reduces steric congestion around the cyclopropyllithium center. The steric differences between these spirocyclic systems are further reflected in their NMR spectra. For the acetone-trapped derivatives, spiro[2.4]heptane **4l** exhibits restricted phenyl ring rotation at room temperature, as evidenced by six distinct aromatic signals in its ^{13}C NMR spectrum. In contrast, spiro[2.3]hexane **4r** and all other phenyl-substituted spirocycles examined display rapid phenyl rotation, leading to only four aromatic signals, with the ortho/ortho' and meta/meta' carbon atoms rendered magnetically equivalent. Alcohol **4s** was easily prepared via addition of benzaldehyde, yielding a 1:1 mixture of alcohol diastereomers (while retaining a single diastereomer at the spirocyclic core) in 57% yield. Introduction of carbonyl groups was achieved through reactions with acetyl chloride and DMF, affording ketone **4t** (44%) and aldehyde **4u** (62%), respectively. Carboxylic acid **4v** was obtained in 42% yield over two steps, and single X-ray crystallographic analysis[40] confirmed the relative configuration. Finally, installation of a double bond via allylation proceeded in good yield (**4o**, 61%), though with diminished diastereoselectivity (Scheme 4). Finally, we were interested to extend the intramolecular carbolithiation strategy to the synthesis of spiroalkanes bearing three contiguous quaternary carbon centers on the cyclopropyl ring.[41] For this purpose, mesylate **6h** having an additional phenyl substituent, was easily prepared.[42]

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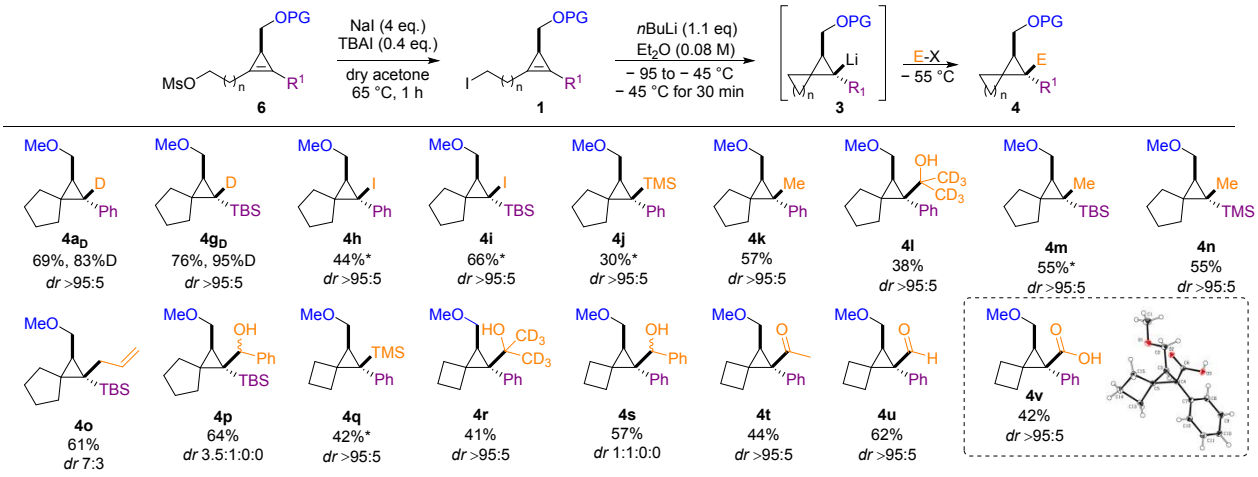
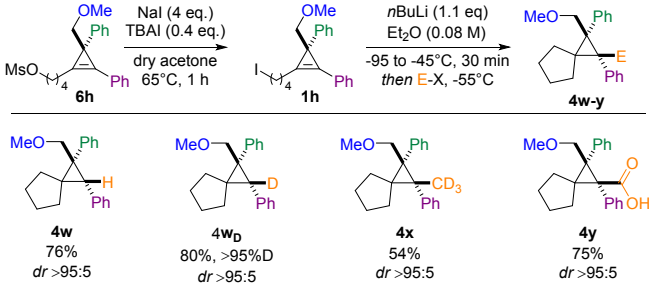


Scheme 4. Electrophile scope for the intramolecular carbolithiation – functionalization sequence. (*Contains hydrolysis product as a side product; corrected yields reported)

Gratifyingly, the presence of this substituent on the cyclopropene did not reduce its reactivity toward spirocyclisation, delivering spiro[2.4]heptanes **4w-y** in moderate to good yields (Scheme 5). Upon addition of electrophiles (with the exception of H and D), the reaction provides the expected corresponding spiro[2.4]heptanes possessing a fully substituted cyclopropyl core as a single diastereomer.



Scheme 5. Towards the diastereoselective preparation of three adjacent quaternary carbon centers on the cyclopropyl ring

Conclusions

We have developed an intramolecular carbolithiation reaction of cyclopropenes that enables the efficient synthesis of spiro[2.3]hexanes, spiro[2.4]heptanes, and spiro[2.5]octanes in moderate to high yields with excellent diastereoselectivity. Electrophilic trapping of the resulting carbolithiated intermediates proceeds with complete retention of configuration and allow for the stereospecific introduction of a wide range of substituents, including the formation of C–H, C–D, C–I, C–Si, and C–C bonds, providing a rapid access to functionalized spiro[2.n]alkanes. Furthermore, fully substituted cyclopropenes were shown to undergo a similar smooth carbolithiation, granting access to spirocyclopropanes possessing fully substituted cyclopropyl ring in excellent yields as single diastereomer — a molecular pattern that remain challenging to construct using existing synthetic approaches.[18, 22-24, 26, 43]

Author contributions

CST: investigation, data curation, project administration, Writing – initial draft, writing – reviewing & editing; CB: methodology, investigation, data curation, writing – reviewing & editing; MS: proof of concept; JZ: X-ray crystallography; IM: conceptualization, funding acquisition, supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the findings of this study are openly available in the supporting information (SI). Supplementary information:

experimental procedures, NMR spectra, high-resolution mass spectrometry data and crystallographic data. CCDC2476391 contains the supplementary crystallographic data for this paper.

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