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Brook Rearrangement as a Trigger for the Formation of Carbene: Formation of Stereodefined Fully-Substituted Cyclobutene Derivatives

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Brook Rearrangement as Trigger for Carbene Generation: Synthesis of Stereodefined and Fully Substituted Cyclobutenes

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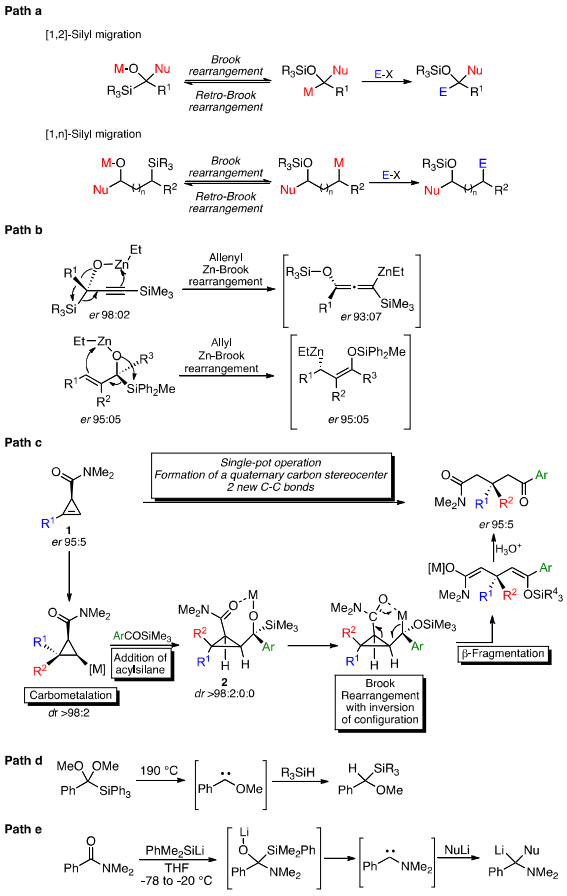
Supporting Information Placeholder

ABSTRACT: Through a sequence that can be performed in a single vessel, involving regio- and diastereoselective copper-catalyzed carbomagnesiation of cyclopropenes, reaction with acylsilanes and addition of THF as co-solvent, Brook rearrangement can be triggered to furnish a wide range of cyclobutenes with exceptional diastereoselectivity. Accordingly, stereodefined and highly substituted cyclobutenes with contiguous quaternary carbon centers can be synthesized easily and in high yield. The new strategy constitutes an unprecedented application of Brook rearrangement, one which involves the intermediacy of carbene species.

I. INTRODUCTION

Brook originally reported the intramolecular 1,2-anionic migration of a silyl group from a carbon to an oxygen atom.[1] This was later extended to structures where the migrating silyl unit is more distal from the oxygen atom (Scheme 1, path a).[2] Such [1,2]- and [1,n]-rearrangements are used[3] in sequential relay processes,[4] with the ability to generate C–C bonds through in situ functionalization of the carbanionic intermediate. In this context, we have recently been interested in the Zn-Brook rearrangement to generate configurationally stable chiral allenylzinc compounds[5] as well as their enantiomerically enriched variants[6] (Scheme 1, path b). Notably, the carbanionic species derived from the Brook rearrangement might react with retention[7] or inversion[8] of stereochemistry depending on the nature of the substrates involved. For instance, we have shown that [1,2]-Brook rearrangement of benzylic α-hydroxysilane **2** proceeds with complete inversion of configuration to give, after acidic hydrolysis, an enantiomerically enriched δ-ketoamide that contains a quaternary carbon stereocenter. The transformation was performed in a single vessel from easily accessible cyclopropene **1** through a sequence of carbometalation, addition of acylsilane, Brook rearrangement, and ring fragmentation (Scheme 1, path c).[9] Nonetheless, and despite being less common, α-alkoxysilane proved to be a source of carbene.[10] In particular, Brook reported that α,α-dimethoxybenzylsilane thermally rearranges at 190 °C to afford methoxysilane and phenylmethoxycarbene (Scheme 1, path d).[11] Because relatively harsh conditions were necessary for degradation of the α,α-dimethoxybenzylsilane precursor, this approach has received scant attention for carbene synthesis despite a more recent report demonstrating that Ph-C:-NMe_2 can be easily synthesized at low temperature by subjection of tertiary amides to $PhMe_2SiLi$ (Scheme 1, path e).[12] Intrigued by the above findings, we wondered whether Brook rearrangement might serve as the in situ trigger for carbene formation and, if so, might it serve as the basis for reaction development.

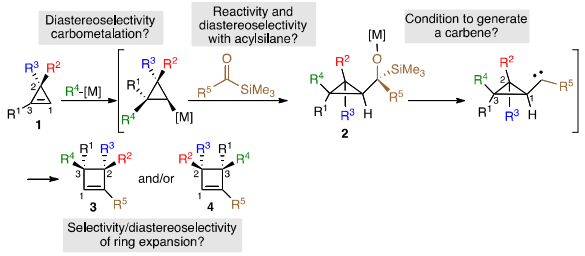
Scheme 1. Brook Rearrangement and its Application to Carbene Formation



Based on our past experience regarding development of diastereoselective synthesis of cyclopropyl-containing α-

hydroxysilane derivatives **2**, we chose to explore the possibility of using Brook rearrangement as a carbene equivalent and trigger selective ring-expansion leading to polysubstituted cyclobutene-containing products (Figure 1).[13] If successful, the above strategy would provide an attractive option for synthesis of highly functionalized cyclobutenes. Unsaturated four-membered rings are important class structural motifs present in many natural products and biologically active compounds,[14] and may be utilized for synthesis of complex organic molecules.[15] Compared to cyclobutanes and cyclobutanones, efficient routes for synthesis of cyclobutenes are uncommon and their development, especially in a stereocontrolled manner, represents a compelling goal in organic synthesis.[14a,16] Selective ring expansion of cyclopropanes to cyclobutenes is well established.[17] We therefore argued that stereoselective formation of cyclopropanes followed by their in situ and diastereoselective conversion to an assortment of highly functionalized cyclobutenes would constitute an attractive single vessel strategy (Figure 1).[18] Fully diastereoselective carbometalation of cyclopropenyl amides that are followed by reaction with an acylsilane have previously been developed (Scheme 1, path c).[9] We anticipated that the same sequence could be performed with various cyclopropenes (**1**), affording **2** in high dr. We would then devise a method for in situ conversion of **2** under relatively mild conditions followed by an ensuing ring expansion to afford various cyclobutenes. Formation of Brook rearrangement products, capable of undergoing ring-cleavage, would have to be excluded.[9] The above strategy requires the ability to control selectivity the ring expansion, since C_1–C_2 as well as C_1–C_3 bonds may migrate to generate **3** and **4** in diastereoisomerically pure form if migration proceeds with stereocontrol.[19] The envisioned one-pot approach would be successful if the issues shown on Figure 1 could be appropriately addressed.

Figure 1. Proposed One-pot Synthesis of Polysubstituted Cyclobutenes

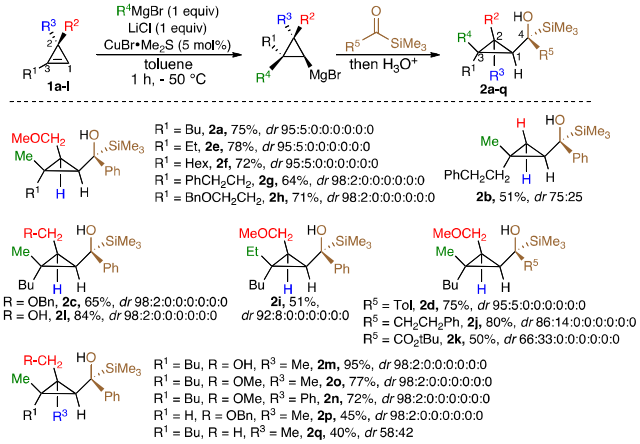


2. RESULTS AND DISCUSSION

2.1 Diastereoselective Carbometalation of Cyclopropenes.

We began by exploring the diastereoselectivity of carbometalation/acylsilane trapping of cyclopropenes **1**. We were pleased to find that the experimental conditions previously developed for diastereoselective carbometalation/acylsilane treatment[9] of cyclopropenyl amides is readily applicable to cyclopropenes containing a chelating group; the desired products were obtained in uniformly high diastereoselectivity (Scheme 2). Diastereoselectivity was low only when the cyclopropene substrate lacked a C2 functional group (compare **2a** with **2q** and **2b** with **2g**). Stereochemical identity of the products was assigned by comparing **2n** with an authentic sample the configuration of which was unambiguously confirmed through X-ray crystallography (see the Supporting Information).[20] Cyclopropenes may contain different alkyl groups (R^1 at C_3: **2a**,**b** and **2e**-**2f** and **2g**), can be unsubstituted (R^1 = H, **2p**), monosubstituted at C_2 (R^3 = H, **2a**-**2l**), or disubstituted at C_2 (R^3 = Me, Ph, **2m**-**2q**). Moreover, the acylsilane substituent (R^5) might be an aryl (**2a**-**2i** and **2l**-**2q**), alkyl (**2j**), or ester unit (**2k**), although dr is lower in the last two instances. Compounds **2l**,**m**,**r**-**t** containing an unprotected hydroxyl group, were prepared according to a slightly modified procedure (see the Supporting Information).[21]

Scheme 2. Tandem Carbometalation: Reaction with Acylsilane on Cyclopropenes 1a-l



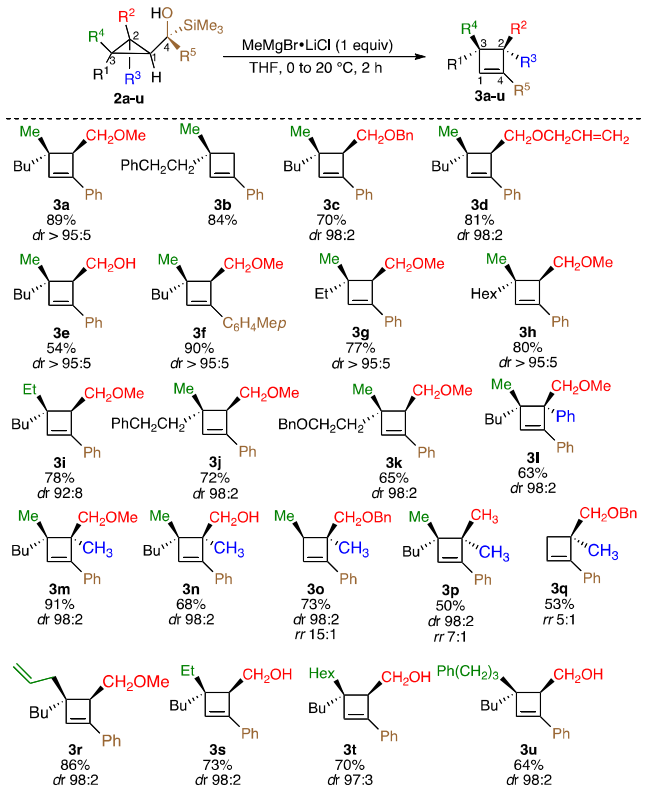
2.2 Brook Rearrangement as Trigger for Carbene Formation and Ring-Expansion.

With a reliable and straightforward method for preparation of cyclopropyl α-hydroxysilane derivatives (**2**) in hand, we turned our attention to in situ generation of carbene by Brook-rearrangement followed by a ring expansion, which would deliver the desired cyclobutenes. Initial screening of different organometallic reagents showed that the simple deprotonation of the alcohol of the α-hydroxysilane **2a** (R^1 = Bu, R^2 = CH_2OMe, R^3 = H, R^4 = Me, R^5 = Ph) by addition of MeMgBr•LiCl (1.1 equiv, THF, 0 °C) followed by slow warming of the reaction mixture (20 °C, 2 h) resulted in the formation of **3a** in 89% yield as a single isomer (<2% **4a**) with complete stereochemical induction (**2a**, 95:5 dr; **3a** >95:5 dr; Scheme 3, path a). The presence of LiCl is not mandatory but allows for slight improvement in yield probably because it promotes solution homogeneity (Scheme 3, path a). When *n*-BuLi, Et_2Zn or catalytic amounts of a Grignard reagent were used as the base, cyclobutenes were not generated.[22] Similarly, no cyclobutane was detected when compounds containing a secondary alcohol (i.e., no C–Si bond). This latter observation clearly points to Brook rearrangement as a crucial step within the sequence.

According to the hypothesis that C_1–C_2 bond migration is exceptionally stereoselective, we wondered where the methoxy group in **2a** can influence on the aforementioned step to allow for exclusive formation of cyclobutene **3a**. In the event, treatment of compounds **2b**, which lack a methoxy unit, to the same conditions resulted in formation of cyclobutene **3b** in 84% yield as a single isomer. Rearrangements are facile

regardless of the identity of the substituents at the migrating carbon: the corresponding methyl benzyl ether (**3c**), methyl allylether (**3d**), CH_2OH (**3e**), aryl (**3l**) or even alkyl groups (**3p**) were readily converted to single rearranged product isomer. A large assortment of substituents at C_3 quaternary carbon center resulting either from the substituent on the starting cyclopropenes (R^1) or from the Grignard reagent (R^4) are tolerated and the derived cyclobutene products – including those that bear two adjacent quaternary carbon stereocenters – could be secured with high efficiency and diastereoselectivity (Scheme 3, **3i**-**3n**, **3p**-**u**). The relative configurations of the cyclobutene products were determined by X-Ray crystallographic analysis of compounds derived from **3e** and **3n** (see the Supporting Information);[24] configurations for the remaining products are by inference. The sole limitation, as far as we know, is that Brook rearrangement may triggered carbene formation when R^5 possesses an aromatic substituent. Thus, whereas **2j** (R^5 = CH_2CH_2Ph, Scheme 2) remains unchanged, **2k** (R^5 = COO*t*-Bu, Scheme 2) delivers the Brook-type product exclusively.

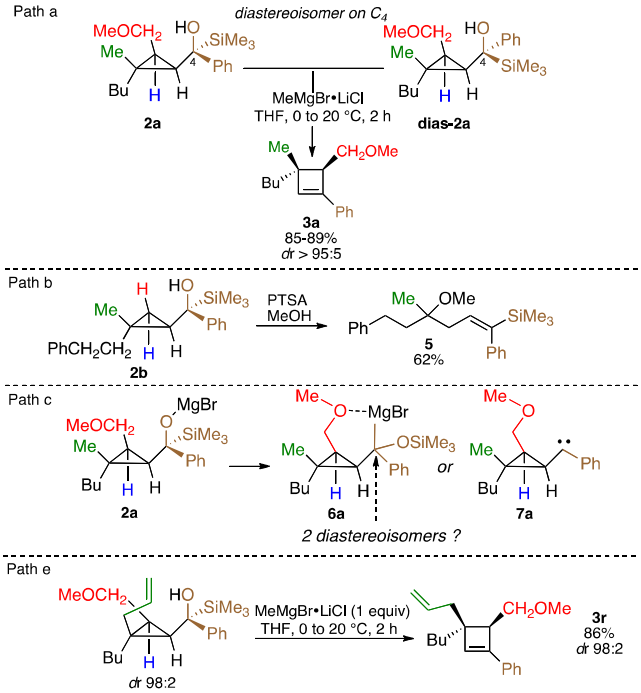
Scheme 3. Brook Rearrangement as Trigger for Carbene Formation and Ring-Expansion. Probing the Proposed Mechanism



To determine whether the migratory aptitude is independent of C_4 stereochemistry (α-hydroxysilane carbon), the two diastereoisomers of **2a** were independently synthesized and subjected to identical conditions (Scheme 4, path a). Cyclobutene **3a** was generated in both instances with nearly the same efficiency and stereoselectivity. In a similar fashion, to rule out that formation of benzylic carbocationic intermediate originates from elimination of benzylic magnesium alkoxide, we subjected **2b** to a solution of *p*-toluenesulfonic acid in MeOH: the ring-opened product **5** was obtained exclusively in 65% yield (Scheme 4, path b).

On the basis of the investigations reported by Brook[11] and Fleming,[12] we propose that ring-expansion proceeds either via a carbenoid or a carbene that is generated during Brook rearrangement. Nonetheless, as the stereochemistry of the α-hydroxysilane (C_4) is irrelevant to the migrating group selectivity (Scheme 4, path a), it might imply that either the carbenoid is configurationally unstable leading to both isomers before the ring expansion (**6a**, Scheme 4, path c) or the reaction proceeds through the formation of a carbene as a reactive intermediate (**7a**, Scheme 4, path c). However, all our attempts to trap the latter with a double bond either intermolecularly or intramolecularly (Scheme 4, path e) didn't lead to the trapping products but rather to the cyclobutene **3r** in excellent diastereoisomeric ratio.

Scheme 4. Probing the Proposed Mechanism



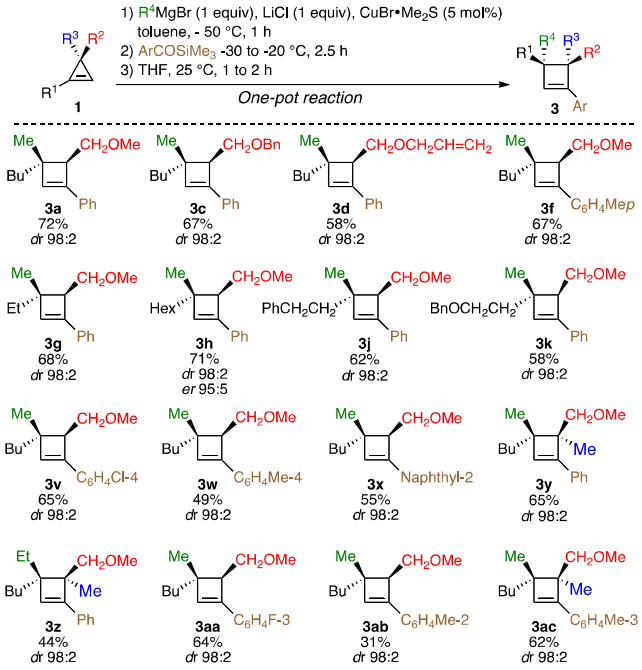
The selectivity for the ring expansion is therefore as follow: (1) When C_2 possesses a chelating group (Scheme 3, formation of **3a**, **3c**-**n**), only the C_1-C_2 ring expansion is observed even when two quaternary stereocenters are competing (Scheme 3, see **3l**-**3n**). (2) When no chelating groups are present as in **2b** (Scheme 2), the primary carbon center migrates preferentially to give only **3b** (Scheme 3) suggesting that the migrating carbon acquires a carbanion-like character in the transition state in such a way that the most stable carbanion migrates faster (primary > tertiary). (3) When a competition exists between a quaternary carbon center possessing a chelating moiety (C_2, R^2 = CH_2OBn, R^3 = Me), versus a secondary alkyl group (C_3, R^1 = H, R^4 = Me) or a primary group (C_3, R^1 = R^4 = H), the migratory aptitude could be slightly counterbalanced (Scheme 3, formation of **3o**:**4o** and **3q**:**4q** in a 15:1 and 5:1 ratio respectively indicated as *rr*). (4) When two quaternary carbon centers without any functional groups are concerned (R^1 = Bu, R^2 = R^3 = R^4 = Me), the selectivity for the migration is lower (Scheme 3, formation of **3p**) although still in a surprising 7:1 ratio for **3p**:**4p**. The unique selectivity for the ring expansion for most of the examples described therein is synthetically very appealing but further investigations

are required to fully understand the rules governing the selectivity.

2.2 Direct Transformation of Cyclopropenes to Diastereomerically Pure Cyclobutenes.

Having established a straightforward access to stereodefined cyclobutenes from a selective carbon migration of α-hydroxy silane derivatives **2**, we then carried out the whole sequence, namely the preparation of polysubstituted cyclobutene derivatives **3** from simple cyclopropene species **1** through the combination of a diastereoselective carbometalation reaction, addition of an acylsilane followed by a Brook rearrangement triggering the ring expansion. To perform the desired ring expansion, we simply added THF to the *in-situ* formed $\mathbf{2}_{MgBr}$ as described in Scheme 5. We were pleased to observe that this combined transformation occurs uneventfully to give **3** in excellent overall yields as a single diastereoisomer in all cases through the creation of two new bonds and a selective ring-expansion (Scheme 5).

Scheme 5. Direct Transformation of Cyclopropenes to Diastereomerically Pure Cyclobutenes



With a practical protocol for preparation of cyclobutenes **3** from simple cyclopropenes **1** available, substrate **1h** (R^1 = Hex, R^2 = CH_2OMe, R^3 = H, R^4 = Me, Ar = Ph) were readily synthesized with high enantioselectivity (95:5 er) through catalytic decomposition of diazoester with 1-octyne.[24] The combined diastereoselective carbometalation reaction, addition of acylsilane, and selective ring-expansion through the Brook rearrangement afforded cyclobutene **3h** as a single diastereoisomer without any loss in enantiomeric purity (98:2 *dr*, 95:5 *er*, Scheme 5; see the Supporting Information). This highlights the potential utility of the present strategy regarding synthesis of enantiomerically enriched poly-substituted cyclobutenes.

3. CONCLUSION

In conclusion, regio- and diastereoselective copper-catalyzed carbomagnesiation of cyclopropenes followed by the nucleophilic addition of acylsilane may be used to access a wide range of metalated cyclopropyl α-hydroxy silanes with high diastereoselectivity. Subsequent addition of THF as the co-solvent, Brook rearrangement and ensuing ring expansion completes the single-vessel operation to furnish the corresponding cyclobutene as a single stereoisomer. The method described herein may be used for facile and exceptionally stereoselective access to polysubstituted cyclobutenes that contain two contiguous quaternary carbon stereocenters. What is more, the unique ring expansion strategy paves the way for new applications involving Brook rearrangement. Further studies to extend the chemistry of carbenes generated by Brook-type rearrangements as well as detailed mechanistic studies are in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, Crystallographic data for **2n**, **3e** and **3n**, and more details are provided.

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Notes

The authors declare no competing financial interest.

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19. If the migration proceeds with a lost of the configuration, a mixture of diastereoisomer would be expected.

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22. Whereas *n*-BuLi led to only the Brook product after hydrolysis (see the supporting information), Et_2Zn has no effect and **2** is fully recovered after hydrolysis. If the reaction is performed with a catalytic amount of Grignard reagent, the same catalytic amount of cyclobutene is obtained.

23. CCDC 1481882 (**2n**), CCDC 1484247 (**3E**) and CCDC 1518467 (**3N**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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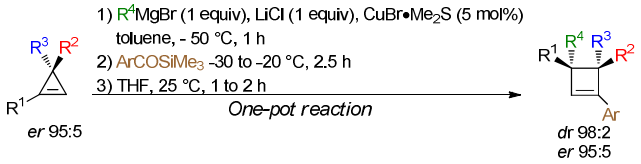
1) R4MgBr (1 equiv), LiCl (1 equiv), CuBr•Me2S (5 mol%)
toluene, - 50 °C, 1 h
2) ArCOSiMe3 -30 to -20 °C, 2.5 h
3) THF, 25 °C, 1 to 2 h
One-pot reaction
er 95:5
dr 98:2
er 95:5