Synthetic Methods

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Brook Rearrangement as a Trigger for the Ring Opening of Strained Carbocycles

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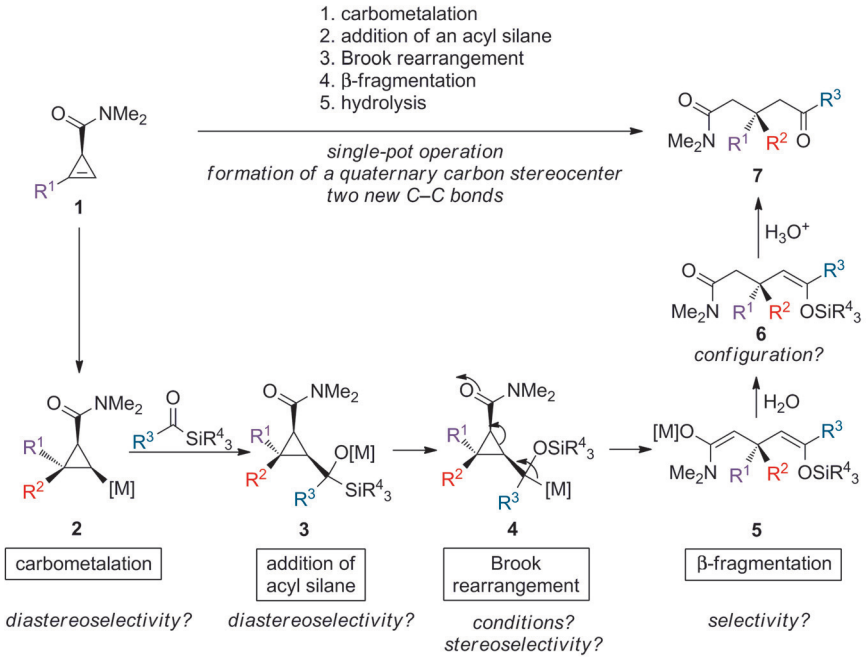
Abstract: *The combined regio- and stereoselective carbometalation of cyclopropenyl amides, followed by the addition of an acyl silane, led to the formation of polysubstituted cyclopropyl derivatives as unique diastereoisomers. Upon warming of the reaction mixture to room temperature, a Brook rearrangement proceeded with inversion of configuration to provide ready access to δ-ketoamides possessing a quaternary carbon center with high enantiomeric ratios through selective C–C bond cleavage of the ring.*

From the initial creation of a single carbon–carbon bond per chemical step in the early days of organic synthesis, numerous strategies, such as domino, cascade, tandem, sequential, multicomponent, and one-pot reactions, have appeared in the last few decades that have drastically improved overall efficiency in synthesis.[1] However, when the structural complexity of the target molecule increases, only a handful of methods maintain their efficiency.[2] One structural combination that invariably increases the complexity of the target molecule is the formation of quaternary carbon stereocenters,[3] particularly in acyclic systems.[4] The construction of such stereocenters with high enantioselectivity through the creation of several C–C bonds per chemical step in a single-pot operation would certainly open new perspectives towards solving problems in organic synthesis.[5] In this context, the use of polyfunctional intermediates,[6] such as bismetalated,[7] oxenoid,[8] and carbenoid species,[9] can enable the consecutive generation of the same number of carbon–carbon bonds as in a multistep process. Alternatively, as the stereoselective formation of quaternary carbon stereocenters in cyclic systems is easier than in acyclic systems,[3] a particularly interesting approach would rely on the initial formation of the desired quaternary carbon stereocenter in a cyclic motif, followed by selective ring opening of the carbocycle into the expected linear fragments.[10] Indeed, since pioneering studies on the C–C bond cleavage of cyclopropylcarbinyl Grignard reagents,[11] the metal-promoted β-fragmentation of strained rings has been recognized as a useful and powerful approach to the synthesis of acyclic building blocks.[12]

Inspired by such ring-fragmentation reactions, we devised a new approach for the rapid construction of quaternary carbon stereocenters with the formation of several new C–C bonds in a one-pot operation (Scheme 1). The planned sequence began with the regio- and diastereoselective carbometalation[13] of enantiomerically enriched cyclopropenyl amides **1**, which are readily accessible by the metal-catalyzed enantioselective addition of diazoester derivatives to alkynes.[14] The addition of acyl silanes to the diastereoisomerically pure carbometalated products **2** should then lead to the formation of the corresponding tertiary α-silylated alcohols **3**, which possess an additional stereogenic center. Acyl silanes are powerful substrates owing to a potential 1,2-anion transposition, defined as the Brook rearrangement, which would lead to a new organometallic species that may



Scheme 1. Proposed one-pot synthesis of δ-ketoamides from cyclopropenyl amides.

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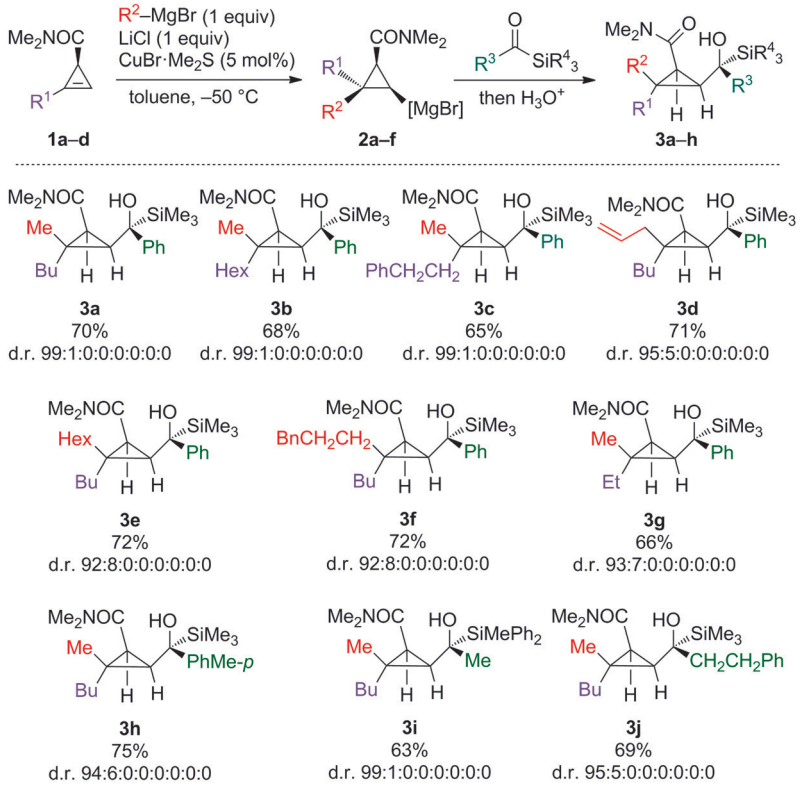
undergo further reactions.[15] In this particular case, the Brook rearrangement should therefore generate a cyclopropylmethyl metal species **4**, which would undergo β-fragmentation[16] to give the corresponding enolate **5**, potentially with a stereodefined disubstituted silyl enol ether functionality (i.e. **6**). After acidic hydrolysis, δ-ketoamide **7**—the targeted acyclic system with a quaternary carbon stereocenter—should be obtained. Thus, **7** could be synthesized in a one-pot operation from the starting cyclopropenyl amide **1**.

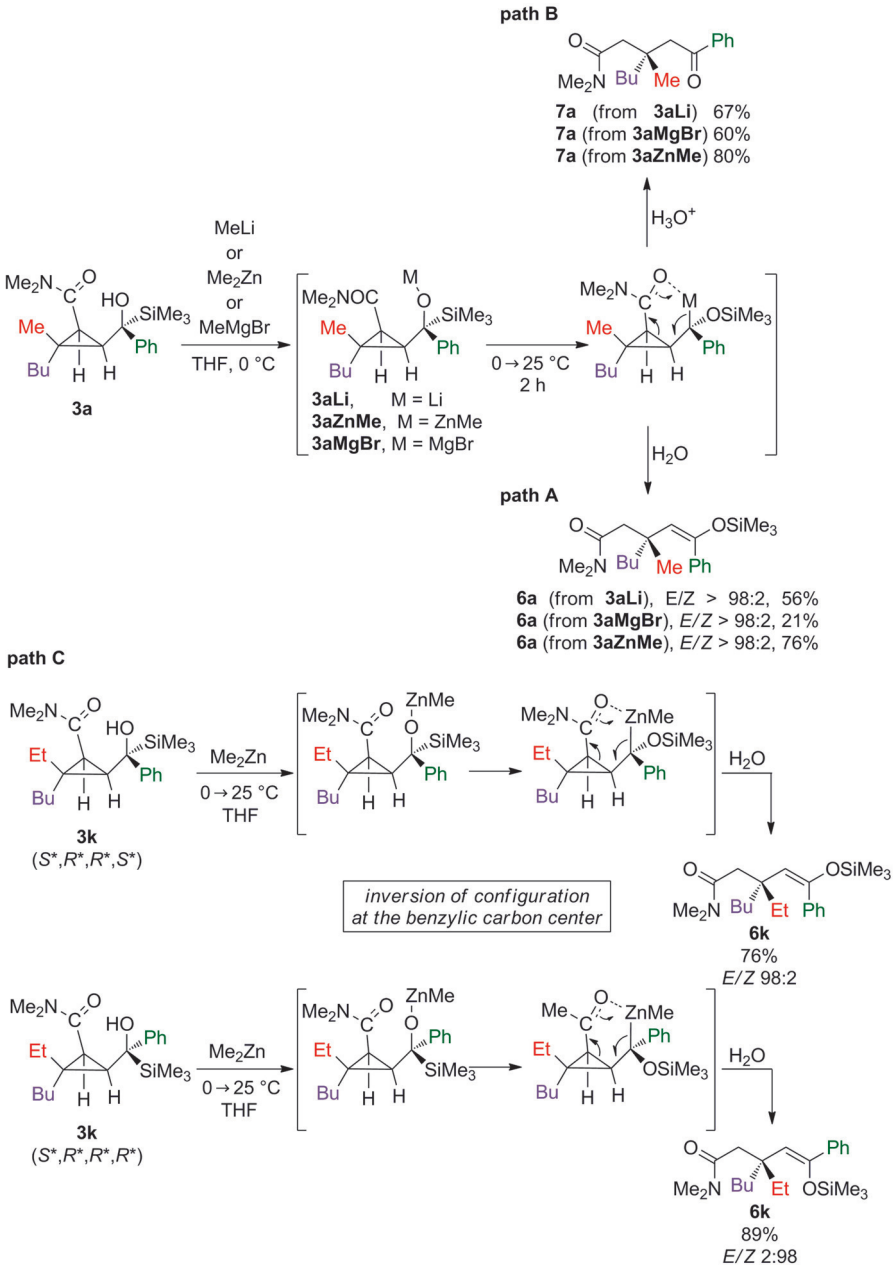
Although this proposed sequence is very appealing, the formation of the ketoamide **7** directly from **1** in high chemical yield with a high enantiomeric ratio requires a cascade of diastereoselective high-yielding events and perfect control of all the elementary steps (Scheme 1): 1) control of the regio- and diastereoselectivity of the carbometalation reaction (**1**→**2**); 2) control of the diastereoselectivity of the reaction with the acyl silane (**2**→**3**) and determination of the configuration of the resulting α-hydroxysilane **3**; 3) control of the stereoselectivity of the Brook rearrangement (**3**→**4**) and of the selectivity of the ring cleavage (**4**→**5**); 4) control of the configuration of the disubstituted silyl enol ether **6** generated in situ; 5) control of the enantiomeric ratio of **7**. Before performing the entire one-pot transformation of **1** into **7**, we initially had to develop experimental conditions that would not only enable a completely diastereoselective carbometalation reaction of **1**, but also a high-yielding reaction with the acyl silane. After extensive experiments, we were pleased to find that the copper-catalyzed carbomagnesiation of **1** in toluene at −50 °C and in the presence of LiCl gave the cyclopropyl magnesium species **2** as a single diastereoisomer (as determined after hydrolysis). The *syn* diastereoselectivity of the copper-catalyzed carbomagnesiation of **1** was determined by comparison of the formed product **2**, after hydrolysis, with authentic samples[13a] and can be rationalized by the existence of a transition state in which chelation occurs between the carbonyl moiety of the amide and the organometallic species. Several cyclopropyl magnesium species **2** reacted diastereoselectively with various acyl silanes to give the corresponding cyclopropyl derivatives **3** in good yield after hydrolysis (Scheme 2). The configuration of **3d** was confirmed by X-ray crystal-structure analysis,[17] and the configuration of other products was assigned by analogy (see the Supporting Information). The addition reaction proceeded with acyl silanes possessing aryl (R^3 = Ar, formation of **3a**–**h**) and alkyl groups (R^3 = alkyl, formation of **3i**,**j**) and led to various polysubstituted cyclopropane derivatives with excellent diastereoisomeric ratios.

We next investigated the Brook rearrangement independently by treating α-hydroxysilane **3a** with different bases (MeLi, Me_2Zn, and MeMgBr) in THF at 0 °C. The resulting metal alcoholates **3aLi**, **3aZnMe**, and **3aMgBr** all underwent the Brook rearrangement followed by regioselective ring opening of the three-membered ring to give, after hydrolysis under neutral conditions, the corresponding silyl enol ether **6a** in moderate to good yield as a single *E* isomer (*E*/*Z* > 98:2, path A, Scheme 3).

The low yield of **6a** when formed by the ring fragmentation of **3aMgBr** is most probably due to the sensitivity of **6a** in the aqueous medium in the presence of magnesium salts, as acidic hydrolysis of the reaction mixture after ring fragmentation gave **7a** directly in decent yield (60%, path B, Scheme 3). Interestingly, the formation of the *E* silyl enol ether **6a** suggests that the Brook rearrangement (conversion of the silyl carbinol into the silyl ether) proceeds with inversion of configuration at the benzylic carbon center before fragmentation.[18] As a rapid equilibration of the benzylic metal species prior to β-fragmentation cannot be excluded,[19] we prepared both diastereoisomers of **3k** to probe the stereoselectivity of the zinc-promoted [1,2] Brook rearrangement. When (*S**,*R**,*R**,*S**)-**3k** was treated with Me_2Zn (1 equiv) at 0 °C and the reaction mixture was warmed to room temperature, the combined Brook rearrangement–fragmentation provided only *E*-configured **6k** (path C, Scheme 3), whereas the equivalent reaction of the opposite diastereoisomer (*S**,*R**,*R**,*R**)-**3k** gave the *Z* isomer of **6k**, as determined by NOE experiments (see the Supporting Information). As both diastereoisomers at the α-hydroxysilane center of **3k** were converted independently into both geometrical isomers of the silyl enol ether **6k**, we can safely



Scheme 2. Diastereoselective copper-catalyzed carbomagnesiation reaction followed by a diastereoselective reaction with an acyl silane. Bn = benzyl.



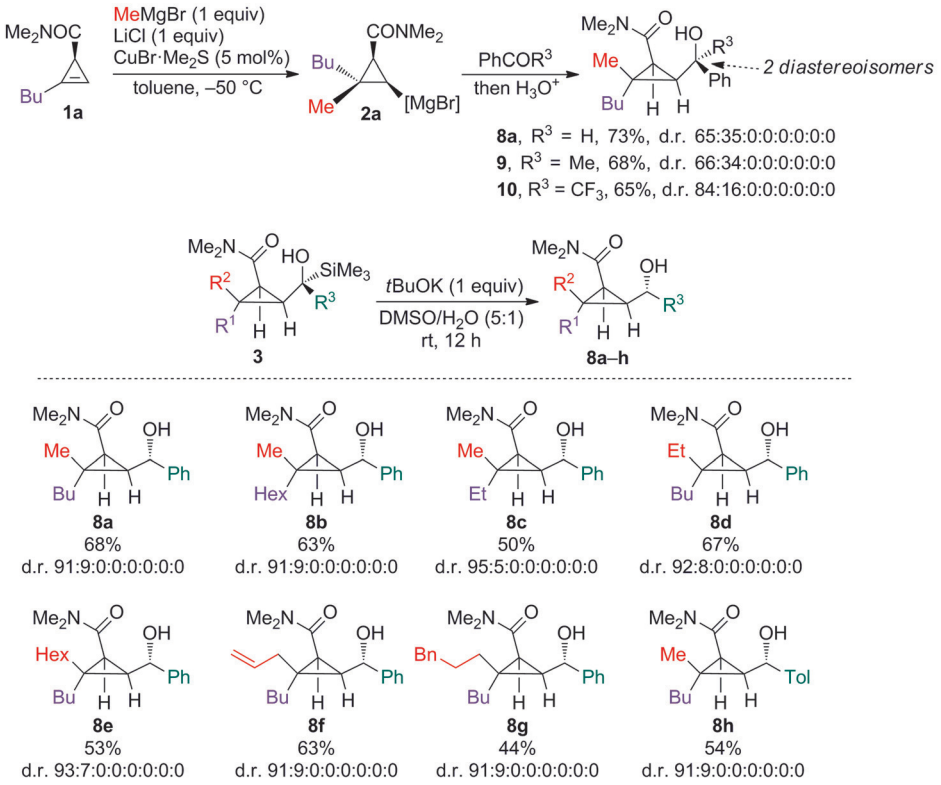
Scheme 3. Stereochemical characteristics of the Brook rearrangement–ring cleavage.

assume that the [1,2] Brook rearrangement proceeds with inversion of configuration at the benzylic carbon center.

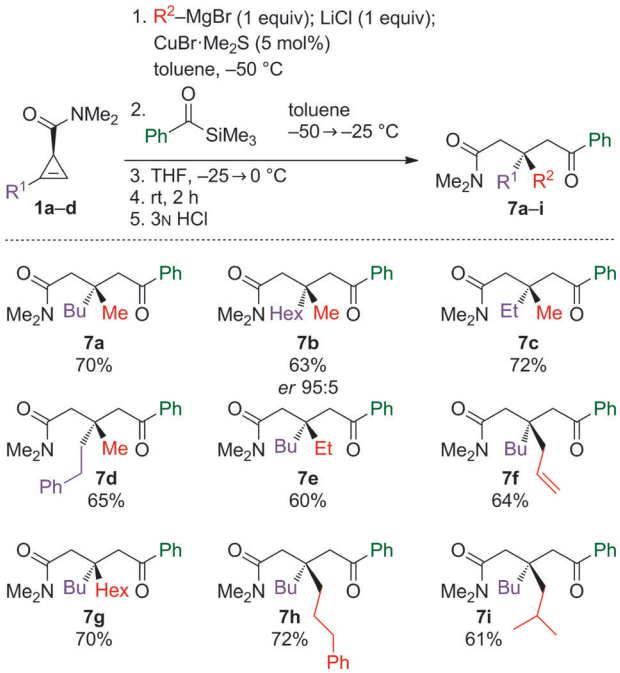
Acyl silanes showed exceptional reactivity in this reaction, particularly in terms of the control of diastereoselectivity in the formation of cyclopropane derivatives **3** (Scheme 2). Indeed, when the acyl silane was replaced with benzaldehyde, acetophenone, or trifluoroacetophenone as the electrophile, the corresponding cyclopropanes **8a–c** were formed in good yield but with low diastereoselectivity (Scheme 4). However, this drawback could be circumvented by exploiting the ability of α-hydroxysilanes **3** to undergo selective protiodesilylation. When various cyclopropyl derivatives **3** were treated with a base in the presence of a protic source, selective protiodesilylation occurred with inversion of configuration, as determined by X-ray crystal-structure analysis of **8g**,[17] to provide products **8a–h** with good diastereoselectivity.

Now that it was possible to control each independent step of the process (complete diastereoselectivity for the carbometalation of cyclopropenyl amides **1** and for the addition of the acyl silane, complete inversion of configuration during the [1,2] Brook rearrangement, and selective ring fragmentation), we focused our attention on the direct one-pot transformation of **1** into **7**. The sequence started similarly with a diastereoselective copper-catalyzed carbometalation reaction of **1** in toluene, followed by addition of the acyl silane. Once the α-silylcarbinol had been obtained quantitatively, the reaction mixture was simply diluted with THF (THF/toluene 4:1), stirred at room temperature for 2 h, and then treated with aqueous HCl (Scheme 5). By simple variation of the substituents on the cyclopropenyl ring (R^1) and the organocopper reagent (R^2), a large variety of δ-ketoamides **7a–i** possessing the expected quaternary carbon stereocenters were prepared in good overall yield in a one-pot operation from **1**. Again, the *E* silyl enol ether **6a** could be isolated from the one-pot reaction of **1a**, this time in 67% yield, when the final hydrolysis was performed under neutral conditions. Enantiomerically enriched cyclopropenylamides **1** can be prepared readily.[20] By using **1b** (R^1 = Hex) with e.r. 94:6 as the substrate for the one-pot reaction, we were able to synthesize δ-ketoamide **7b** directly with e.r. 95:5, thus demonstrating the usefulness of this strategy for the formation of fully alkylated carbon stereocenters. Although 3,3-disubstituted glutarate-type systems **7** could in principle be accessible through the desymmetrization of achiral 3,3-disubstituted glutaric anhydride, we are not aware of any example of the formation of a quaternary carbon stereocenter in such a position.[21]

In conclusion, the regio- and diastereoselective copper-catalyzed carbomagnesiation of cyclopropenyl amides led to the formation of diastereoisomerically pure cyclopropyl magnesium species. The addition of an acyl silane proceeded diastereoselectively to give the corresponding α-hydrosilane as a single diastereoisomer. Simply upon the addition of THF, this intermediate underwent a Brook rearrangement with inversion of the configuration at the benzylic carbon center to



Scheme 4. Protiodesilylation of cyclopropyl α-hydroxysilanes **3** with inversion of configuration. DMSO = dimethyl sulfoxide.



Scheme 5. One-pot preparation of δ-ketoamides with quaternary carbon centers from cyclopropenyl amides.

give, after ring cleavage, the corresponding silyl enol ether as a single geometrical isomer. Acidic hydrolysis provided, in a one-pot operation, a δ-ketoamide containing a quaternary carbon stereocenter with a high enantiomeric ratio.

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