Allylic Compounds

Deutsche Ausgabe: DOI: 10.1002/ange.201602393
Internationale Ausgabe: DOI: 10.1002/anie.201602393

Preparation and Reactivity of Acyclic Chiral Allylzinc Species by a Zinc-Brook Rearrangement

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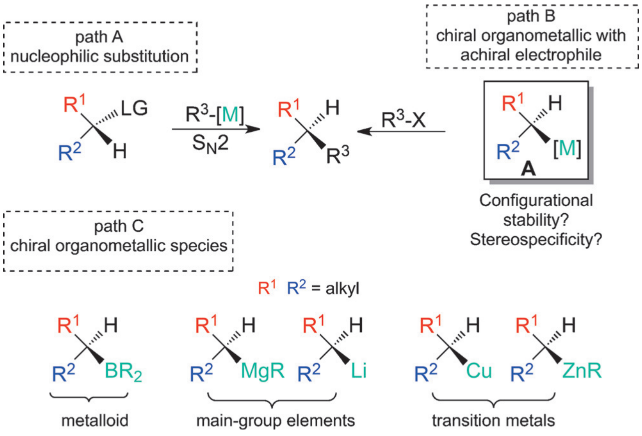
Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: *The zinc-Brook rearrangement of enantiomerically enriched α-hydroxy allylsilane produces a chiral allylzinc intermediate, which reacts with retention of configuration in the presence of an electrophile. Two remarkable features of this transformation are the stereochemical outcome during the formation of the allylzinc species and the complete stereocontrol in the organized six-membered transition state, which leads to an overall and complete transfer of chirality within the reaction sequence.*

Numerous methods have been developed to prepare carbon–metal bonds and subsequently harness its reactivity for the creation of stereodefined C–C bonds.[1] For instance, if one wants to create a new stereogenic center, the displacement of an electrofuge by an organometallic species (nucleophilic substitution) is one of the tools commonly used in organic synthesis.[2] However, if one could create stereogenic centers in acyclic systems, not through a classical S_N2 reaction between a chiral electrophile and an achiral nucleophile (Scheme 1, path A), but rather through the reaction of a chiral nucleophile (that would be used as a new chiral building block for stereoselective synthesis) with an achiral electrophile, it would broaden the synthetic possibilities in organic synthesis (Scheme 1, path B). Such a strategy is only possible if the carbanion intermediate **A** is configurationally stable under the reaction conditions and proceeds with complete stereocontrol of the electrophile (either pure retention or pure inversion of configuration).[3] To fulfill the requirements of configurational stability for secondary carbanions ($R^1 \neq R^2 =$ alkyl, **A**) metalloids such as organoboronates were intensively investigated.[4,5] More recent developments have shown that few main-group organometallic species, such as organomagnesium[6] and organolithium,[7] as well as transition-metal species, such as alkylcopper[8] and alkylzinc,[9] present some configurational stability under particular circumstances (Scheme 1, path C). However, going from an sp^3-centered to delocalized organometallic species drastically decreases the configurational stability. Further complications arise for unsymmetrical 1,3-disubstituted η^1-allylmetal derivatives as up to eight regioisomers and torsional isomers may be in equilibrium (Scheme 2, path A).[3,10]



Scheme 1. General principles for the preparation of chiral organometallic species.

As each of these isomers can react with electrophiles through four different pathways ($S_E$ret, $S_E$inv, *syn*-S'_E, and *anti*-S'_E), only the introduction of strongly complexing groups such as *N,N*-dialkylcarbamoyloxy[11] or *N*-(alkoxycarbonyl)-amino[12] led to selective transformations, either through deprotonation of optically active secondary allyl carbamates[13] or through a dynamic thermodynamic resolution process (Scheme 2, path B).[14] As we have recently reported the formation of enantiomerically enriched allenyl zinc species by a zinc-Brook (Zn-Brook) rearrangement of propargyl alcohols,[15] we were intrigued to extend this concept to the formation of chiral allylzinc species. Our proposal was to transform the model α-allyl hydroxysilane **1** into the corresponding allylzinc species **3** by simple deprotonation with Et_2Zn and subsequent reaction with electrophiles (Scheme 2, Path C). The proposed reaction is appealing because of its simplicity, but the success of this challenging one-pot reaction, in which a chiral allylzinc intermediate would be formed to give **4** in high enantiomeric ratio, requires complete control of all the elementary steps. To our delight, Harutyunyan and co-workers have recently reported the preparation of enantiomerically enriched α-

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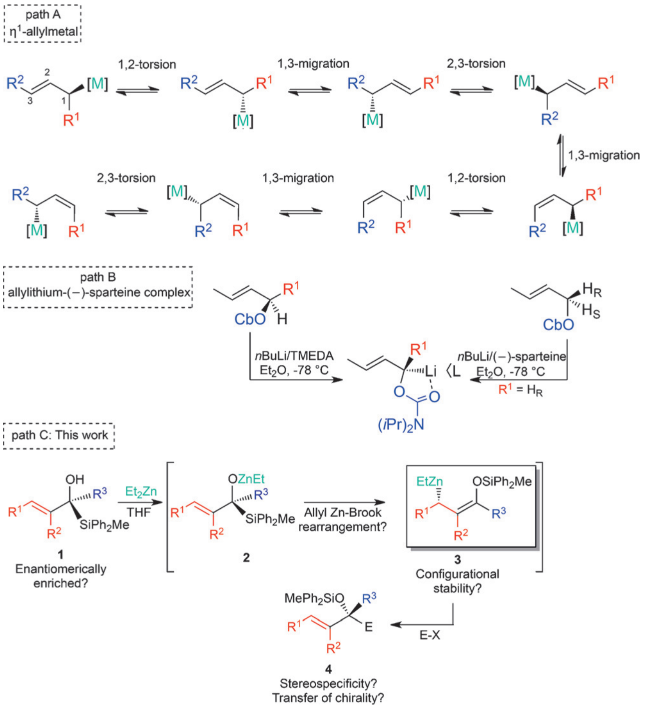
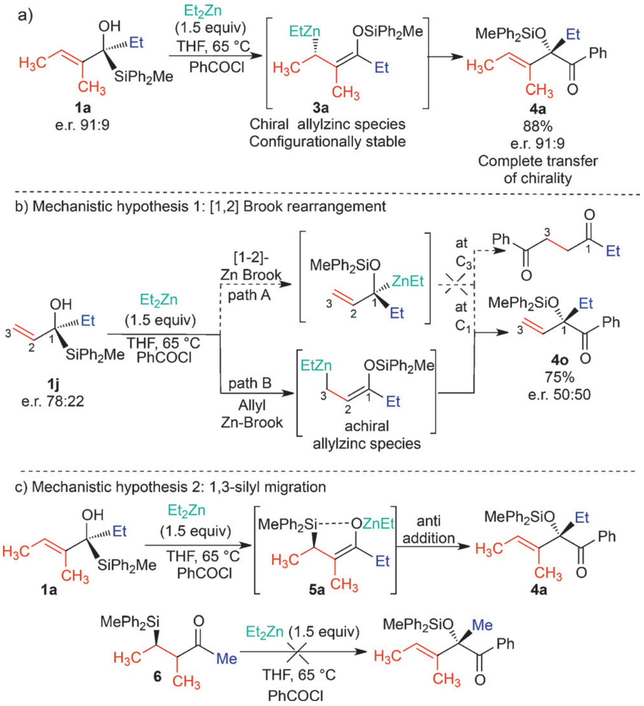


Scheme 2. Chiral allylmetal species and proposed research. TMEDA = *N*,*N*,*N'*,*N'*-tetramethylenediamine.



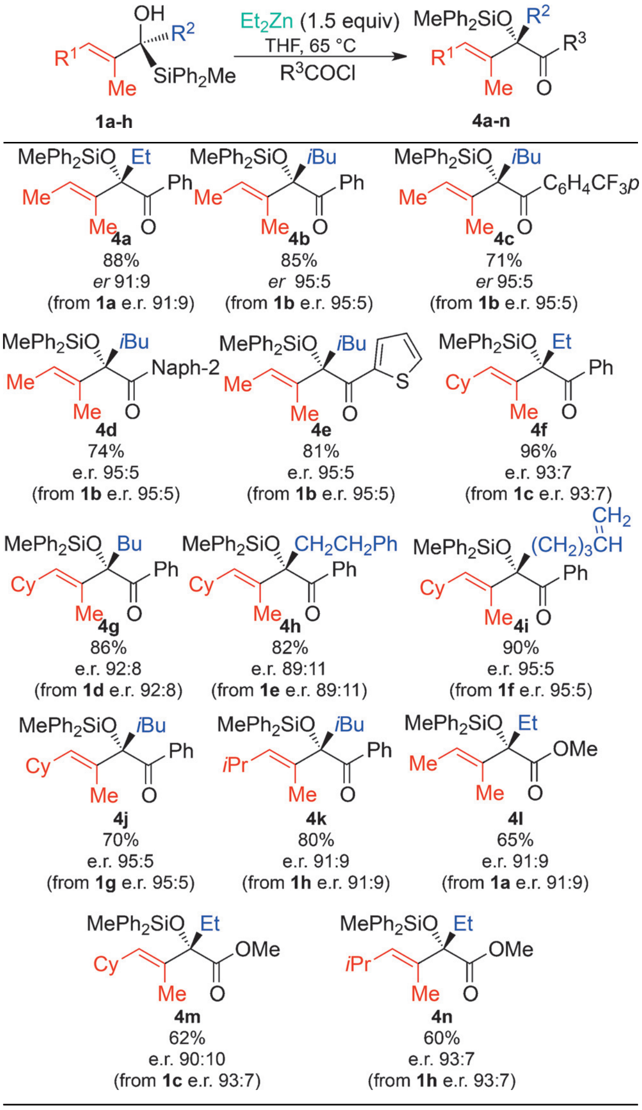
Scheme 3. Zn-Brook rearrangement and different mechanistic hypothesis. THF = tetrahydrofuran.

hydroxy allylsilanes (**1**) by the enantioselective copper-catalyzed Grignard addition to acylsilanes in good yields and high enantiomeric ratios.[16] We used this strategy to prepare various substrates (**1**) in excellent yields and enantiomeric ratios and the absolute configurations of **1** were determined by transforming **1a** ($R^1 = R^2 = Me$, $R^3 = Et$), by a Riley-type oxidation using SeO_2 and *t*BuOOH, into crystalline oxaselenolane 2-oxide,[17] which was characterized by X-ray crystallography (see the Supporting Information).[18] Having a well-established procedure in hand for the preparation of **1** through asymmetric catalysis, we then investigated the critical step, namely the allyl Zn-Brook rearrangement and subsequent reaction with electrophiles.

When **1a** (e.r. 91:9) was treated with 1.5 equivalents of Et_2Zn (1 M in hexanes) in THF at 66 °C followed by addition of PhCOCl, we were pleased to observe the formation of the product **4a** in 88 % yield with an enantiomeric ratio of 91:9 (Scheme 3a). As the enantiomeric ratio of the starting material **1a** and product **4a** are identical, we conclude that the reaction proceeded with a complete transfer of chirality. To better understand the possible mechanistic pathway of the reaction and in particular the possible formation of a chiral allylzinc intermediate versus either 1) the more classical [1,2]-Brook rearrangement followed by either a reaction at C_1 or C_3 with an electrophile (Scheme 3b) or 2) a silyl migration and subsequent reaction of the in situ formed allylsilane with the same electrophile (Scheme 3c), we had to devise two new starting materials, **1j** and **6**. For the first starting material **1j**, which does not possess the terminal vinyl substituent, conservation of the enantiomeric ratio should be observed if the reaction proceeds through a [1,2]-Brook rearrangement and direct acylation at C_1 without formation of a chiral allylzinc species (Scheme 3b, path A). However, if the reaction proceeds through the [1,2]-Brook rearrangement and acylation at C_3, a 1,4-diketone product should be obtained after hydrolysis. In contrast, if an allyl Zn-Brook rearrangement proceeds (C_3–Zn), the product should lose its stereoinformation upon reaction with an electrophile if it reacts through a six-membered chairlike transition state (Scheme 3b, path B). To verify our hypotheses, **1j** was treated under the same experimental conditions and **4o** was obtained in good yield but as a racemate, thus suggesting that the reaction may proceed through the formation of an allyl Zn-Brook rearrangement. Owing to the high migratory aptitudes of silyl groups,[19] our second hypothesis was the thermal 1,3-silyl migration of allyl silanes, a migration which is known to proceed concertedly (Scheme 3c).[20] Therefore, to check that the formation of **4a** from **1a** was not derived first from a 1,3-silyl migration to **5a** and subsequent reaction with the electrophile, an authentic sample **6**, precursor of **5a,** was independently prepared and treated under the same experimental conditions. Under such reaction conditions, no trace of the product resulting from the reaction with acyl chloride could be detected, again reinforcing our mechanistic hypothesis of an allyl Zn-Brook rearrangement leading to the chiral allylzinc intermediate **3a**.

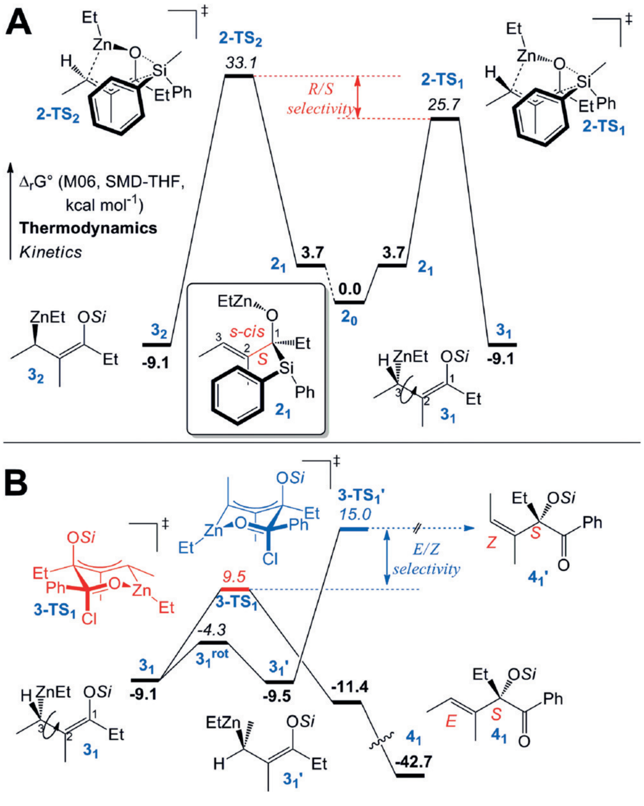
With a better understanding of the stereochemical outcome, particularly for the enantioselective formation of the chiral allylzinc intermediate, the scope of the reaction was examined for various α-hydroxy allylsilanes (**1a**–**h**) and electrophiles as represented in Table 1. The reaction proceeds smoothly for all tested α-hydroxy allylsilanes in the presence of either acid chloride or methylchloroformate derivatives, with a complete transfer of chirality in all cases.[21] The

Table 1: Substrate scope of the Zn-Brook rearrangement and reaction with electrophiles.



configurationally stable carbon–zinc bond is formed regardless of the nature of the alkyl group R^1 (primary or secondary alkyl group, compare **4a** to **4f**). Similarly the nature of the substituent R^2 is rather broad as it could be a linear or branched alkyl group (i.e., compare **4a** to **4b**). To assign the absolute configuration of the products, **4l** and **4n** were derivatized to a known compound by initial deprotection of **4l,n** and subsequent oxidative cleavage of the olefin into a known β-ketoester (see the Supporting Information). Interestingly, the reaction proceeds similarly when **1a** is treated with an alkylmagnesium species instead of R_2Zn. In this case, **4a** was obtained in 65% yield with a complete transfer of chirality. If smaller silyl groups, such as Me_3Si, are used in **1**, the reaction does not proceed as only the product resulting from O-acylation of **1** is formed. When aldehydes are added instead of acyl chlorides, the reaction proceeds similarly to give the expected products as two diastereoisomers (not represented in Table 1) in moderate yield but still with a complete transfer of chirality for both diastereoisomers.

To gain further mechanistic insights into the allyl Zn-Brook rearrangement, quantum mechanical calculations were performed (see the Supporting Information). Scheme 4 presents the energy profile of the Brook rearrangement and the subsequent reactivity with benzoyl chloride for the lead compound **1a**. The common energy reference is the trimer of (*S*)-ethyl-zinc-alkoxide ($\mathbf{2_0}$), which is the most stable complex among the monomers, dimers, trimers, and tetramers.[22] Dissociation of $\mathbf{2_0}$ into the dimer and monomer $\mathbf{2_1}$ is endergonic by 3.7 kcal mol^{-1}. From the analysis of all possible conformers, the most stable conformer of $\mathbf{2_1}$ possesses an *s-cis* configuration. In the *s-trans* conformer, the O⋯C_3 bond distance is lengthened by 0.9 Å and prevents all possible Brook rearrangements. It is interesting to note that a phenyl substituent on the $SiPh_2Me$ group in $\mathbf{2_1}$ shields one face of the double bond and therefore participates in the stereocontrol of the reaction. No transition state for the [1,2]-Zn-Brook rearrangement in which the silyl group in $\mathbf{2_1}$ migrates to the oxygen atom, and ZnEt coordinates to C_1, could be located. In contrast, two transition states for the allyl Zn-Brook rearrangement have been optimized. $\mathbf{2\text{-}TS_1}$ corresponds to a concerted antiperiplanar migration of the zinc and silyl group with a Zn-C_3-*O*-Si torsion angle of 166°, whereas these two groups are synclinal in $\mathbf{2\text{-}TS_2}$ with a Zn-C_3-*O*-Si torsion angle of 99°. As the configuration at C_3 is opposite in these two transition states, the respective products $\mathbf{3_1}$ and $\mathbf{3_2}$, are enantiomers. Calculations provide further insight into the



Scheme 4. Gibbs energy profile for the allyl Zn-Brook rearrangement and subsequent acylation reaction. Si = $SiPh_2Me$. $\mathbf{2_0} = \mathbf{2_1} + (ROZnEt)_2$.

stereochemical outcome of the reaction: whereas the rearrangement of $\mathbf{2_1}$ into $\mathbf{3_1}$ is exergonic by 13 kcal mol^{-1}, with a free-energy barrier of 22 kcal mol^{-1}, the allyl Zn-Brook rearrangement leading to $\mathbf{3_2}$ is kinetically limited by its higher activation energy of 29 kcal mol^{-1}.

The second stereochemical issue arises from the reaction of $\mathbf{3_1}$ with PhCOCl. In agreement with the Zn–allyl interaction mode previously reported in the literature (in solution, but also in solid state and in the gas phase),[23] EtZn is σ-bonded to the allyl motif in $\mathbf{3_1}$. This type of coordination frees the rotation between C_2 and C_3 (Scheme 4), thus leading to potentially fast equilibration between $\mathbf{3_1}$ and $\mathbf{3_1}'$, in agreement with the low rotation barrier of 5 kcal mol^{-1} defined by $\mathbf{3\text{-}TS_1^{rot}}$ (see the Supporting Information). Among all the possible transition states examined for the reaction of the allylzinc species with PhCOCl, the lowest in energy follows the Zimmerman–Traxler model.[24] Starting from $\mathbf{3_1}$ the transition state $\mathbf{3\text{-}TS_1}$ offers the final product in the *E*,-(*S*) configuration whereas the transition state $\mathbf{3\text{-}TS_1}'$ takes $\mathbf{3_1}'$ to the *Z*,(*S*)-product $\mathbf{4_1}'$ (Scheme 4). In the former transition state, the substituent at the stereogenic center occupies a pseudoequatorial position, and in the latter transition state the substituent occupies a pseudoaxial position, thus generating an unfavorable 1,3-diaxial interaction between the Me and the $OSiPh_2Me$ group and resulting in a higher transition state energy by 5.5 kcal mol^{-1}. This analysis is in agreement with the stereochemistry determined experimentally.

In conclusion, when enantiomerically enriched α-hydroxy allylsilanes are treated with Et_2Zn, an allyl Zn-Brook rearrangement occurs to give configurationally stable allylzinc intermediates which react with acyl chloride and methyl chloroformate with complete transfer of chirality. Experimental data as well as quantum mechanical calculations confirm that the product is obtained through the formation of a chiral allylzinc intermediate, thus bypassing the classical [1,2]-Brook rearrangement.

Acknowledgements

We are grateful for financial support by the European Research Council under the Seventh Framework Program of the European Community (ERC grant agreement no 338912). M.L. thanks the Alexander von Humboldt Foundation for a Feodor Lynen Research Fellowship and K.A.S. thanks the Center for Absorption in Science, Ministry of Immigrant Absorption, State of Israel. L.P. thanks CCIR of ICBMS and P2CHPD of Université Lyon 1 for generous computational resources allocation and technical support. I.M. is holder of the Sir Michael and Lady Sobell Academic Chair.

Keywords: allylic compounds · Brook rearrangement · chirality · olefins · zinc

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6057–6061
Angew. Chem. **2016**, *128*, 6161–6165

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Received: March 8, 2016