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Communication

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Dynamic Kinetic Resolution of Alkenyl Cyanohydrins Derived from α,β-Unsaturated Aldehydes: Stereoselective Synthesis of *E*-Tetrasubstituted Olefins

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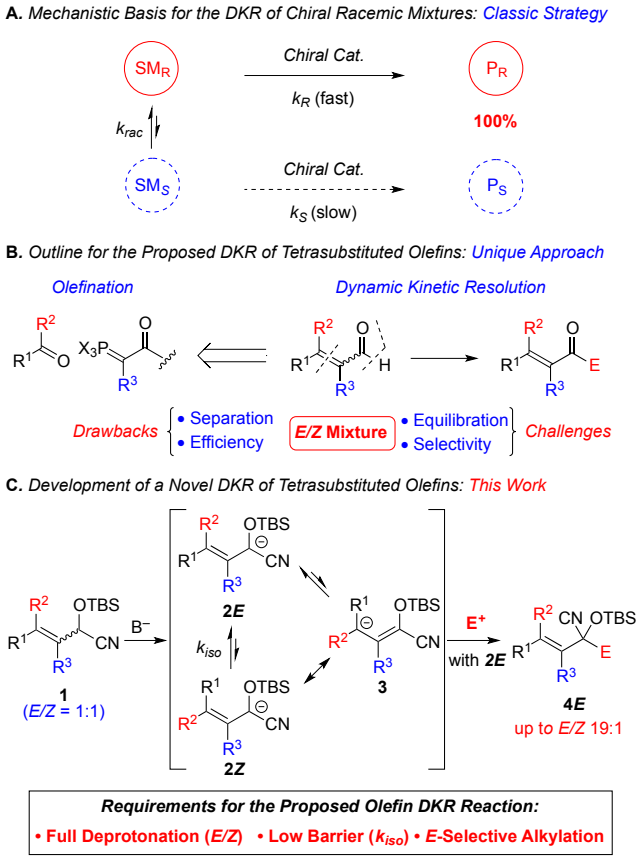
Supporting Information

ABSTRACT: A novel *dynamic kinetic resolution* (DKR) of tetrasubstituted alkenyl cyanohydrins prepared from the corresponding α,β-unsaturated aldehydes is described. The deprotonation of a geometrical mixture of tetrasubstituted alkenyl cyanohydrins with sodium diisopropylamide (NaDA) enables the equilibration of the *E*- and *Z*-olefins and the *selective* functionalization of former to selectively afford the *E*-adduct. Theoretical studies indicate that the nature of the alkali metal cation is a critical component to lowering the barrier for interconversion between the two geometrical isomers, which provides the mechanistic basis for the DKR reaction. In addition, we demonstrate that the DKR reaction can be combined with a transition-metal-catalyzed allylic substitution to generate a stereodefined *E*-tetrasubstituted olefin and quaternary center in a single cross-coupling reaction.

The exponential growth in the field of asymmetric synthesis over the last few decades has resulted in the development of an array of methods for the preparation of chiral nonracemic molecules.[1] Among the particularly attractive strategies to accomplish this goal are dynamic kinetic asymmetric transformations (DYKATs), which facilitate the construction of enantiomerically enriched products *via* the selective functionalization of a racemate (Scheme 1A).[2] In this context, the process generally relies on the formation of two diastereomeric complexes, which undergo differential reaction governed by the Curtin-Hammett principle to furnish a single stereoisomer. Nevertheless, despite the widespread utility of dynamic kinetic resolutions (DKR) in the field of asymmetric synthesis, the extension of this strategy to other stereochemical motifs, namely olefins, has not been forthcoming (*cf.* Scheme 1B). Herein, we describe the first example of a *dynamic kinetic resolution* of a mixture of tetrasubstituted alkenyl cyanohydrins **1** (*E*/*Z* = 1:1), which affords the *E*-tetrasubstituted olefins **4*E*** with exquisite selectivity, thereby providing a convenient and stereoselective method for preparing this challenging class of olefins (Scheme 1C).

Scheme 1. Inspiration and Challenges for the Development of a Dynamic Kinetic Resolution of Tetrasubstituted Olefins



The alkene moiety is among the most ubiquitous functional groups present in a variety of organic frameworks. In this regard, tetrasubstituted alkenes

feature prominently in many natural products,[3] pharmaceuticals[4] and materials[5] and as important synthetic intermediates,[6] in which the olefin geometry often plays a critical role in the biological function and/or the chemical reactivity of a specific compound.[7] Consequently, the stereocontrolled construction of these types of olefins remains an important goal for modern synthetic methodology development. Nevertheless, the preparation of geometrically defined tetrasubstituted olefins represents a formidable challenge because of the congested nature of the carbon–carbon double bond, which presents problems associated with controlling both regio- and stereochemistry.[8-10] Although a wide variety of classical synthetic strategies to construct olefins have been developed,[8] namely the Wittig and Horner-Wadsworth-Emmons (HWE) carbonyl olefination reactions, the Julia-Lythgoe and Peterson eliminations and cross-metathesis,[11] many of these methods are optimal for di- and trisubstituted olefins. Hence, the application of the aforementioned methods to the preparation of acyclic tetrasubstituted alkenes is often limited in the context of selectivity,[12] which has led to the development of several novel approaches.[8-11,13]

We envisioned an alternative strategy, which permits the formal conversion mixtures of α,β-unsaturated aldehydes to the corresponding *E*-tetrasubstituted α,β-unsaturated carbonyl derivatives using a simple C-C bond forming reaction (Scheme 1B).[14,15] To this end, the process is initiated by the deprotonation of a geometrical mixture of an alkenyl cyanohydrins **1** (*E*/*Z* = 1:1), prepared in one-step from the corresponding α,β-unsaturated aldehydes, to generate anions **2*E*** and **2*Z*** in a uniform ratio (Scheme. 1C). The isomerization between these two geometrical isomers is possible *via* intermediate **3** in order to relieve $A^{1,3}$-strain between the cyanohydrin and/or the larger of the two substituents (R^1/R^2).[16] Hence, the rate of equilibration (k_{iso}) was expected to be heavily influenced by the steric and electronic nature of these substituents (R^1/R^2). Furthermore, the stereoelectronic nature of the carbanion is a critical component that should impact the rate of attack of the specific anions **2*E*** and **2*Z*** with an electrophile. Hence, if the rate of reaction for **2*E*** is faster than **2*Z***, itwould permit a *dynamic kinetic resolution* (DKR).

In accord with the proposed hypothesis, the *tert*-butyldimethylsilyl protected cyanohydrin of α , β -dimethylcinnamaldehyde **1a** (R^1 = Ph, R^2, R^3 =Me; *E*/*Z* = 1:1) was selected to demonstrate proof-of-principle (Table 1). After careful optimization of the reaction conditions (see the SI. S27), we established an efficient protocol using sodium diisopropylamide as the base, which is critical for achieving good selectivity.[17,18] Table 1 summarizes the application of the optimized reaction conditions to a number of electrophiles and substituted alkenyl cyanohydrins.[19] Gratifyingly, the reaction is tolerant of a variety of alkyl (Table 1A, entries 1 and 2), allylic (entries 3–5) and propargylic halides (entry 6), furnishing the products in good yields and with excellent selectivity for the *E*-isomer. Interestingly, the reaction is also amenable to alkylation with a variety of more functionalized electrophiles, namely, MOM-Cl, BOM-Cl (entries 7 and 8) and carbonyl-based electrophiles such as ethyl chloroformate and dimethylcarbamoyl chloride (entries 9 and 10). A key and striking feature with this approach is the ability to provide utility to *isomeric olefin mixtures* prepared *via* classical olefination strategies and thereby avoiding tedious chromatography separations.[20]

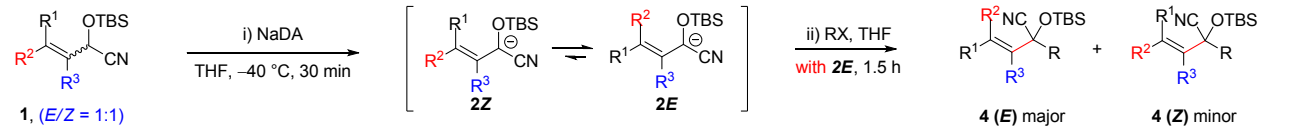
In an attempt to garner the breadth of alkene substitution, various substituents on the olefin were examined. For instance, the reaction is tolerant to a range of electron-withdrawing and electron-donating aryl substituents with benzyl bromide as an electrophile (Table 1B, entries 11–14), in which only the iodo-substituted aryl group afforded slightly reduced selectivity (entry 15).[21] Furthermore, the reaction is applicable to polyaromatic systems and a number of heteroaromatic alkenyl substituted cyanohydrins (entries 16–20). Perhaps the most remarkable feature with this process is the ability to employ a range of alkyl groups at the α- and β-position relative to the cyanohydrin (Table 1C).[22] For example, linear alkyl substituents such as ethyl and *n*-hexyl are well tolerated at both the α - and β - positions, in addition to more sterically demanding substituents such as isobutyl, isopropyl and cyclohexyl groups proceed exquisite selectivity (entries 21–30). *Hence, the DKR reaction of tetrasubstituted alkenyl cyanohydrins has a useful scope, providing a convenient approach to E-tetrasubstituted olefins for applications in target directed synthesis.*

The construction of tetrasubstituted olefins and enantioenriched quaternary-substituted stereocenters are amongst the most challenging functional groups to prepare in selective manner. To this end, we combined the DKR with a metal-catalyzed allylic substitution to install these functionalities in a single operation. Consequently, the stereospecific rhodium-catalyzed allylic alkylation of the linalool-derived allylic carbonate **5** (98% *ee*) with the tetrasubstituted alkenyl cyanohydrin **1b** furnished after *in situ* deprotection, the enantioenriched α,β-unsaturated ketone **6** (99% *cee*)[23] in 76% yield[24] and with excellent geometrical selectivity (Table 1D). This process highlights the utility of the DKR reaction to prepare *acyclic* tetrasubstituted α , β - unsaturated ketones in combination with a metal-catalyzed cross-coupling reaction, which we envision may be applicable to related transformations.

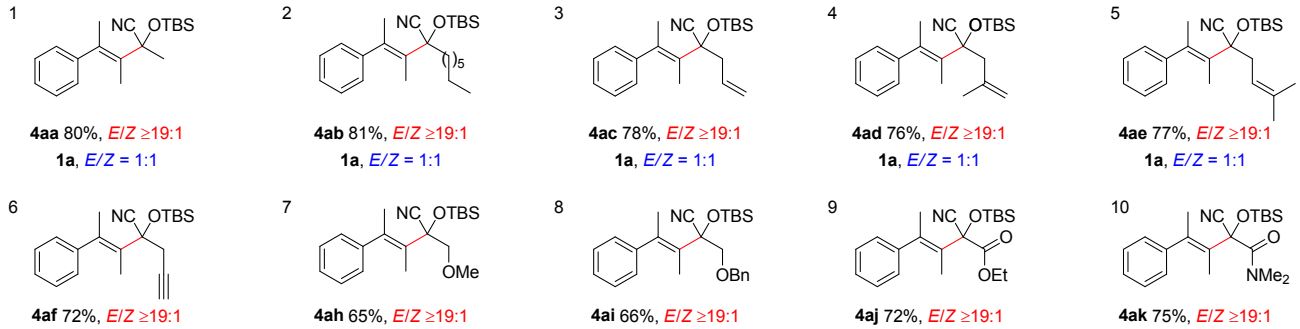
To gain insight into the underlying mechanism of this novel transformation we constructed a computational model using density functional theory (DFT) and extensively explored the putative reaction mechanism by identifying all plausible intermediates. Special attention

was given to how the alkali metal cations could interact with the intermediate anions **2a*E*** and **2a*Z***, as we envisioned that they presumably reduce the rate of alkylation of one of the two isomers and thereby shift the equilibrium in a way to facilitate the dynamic kinetic resolution. The

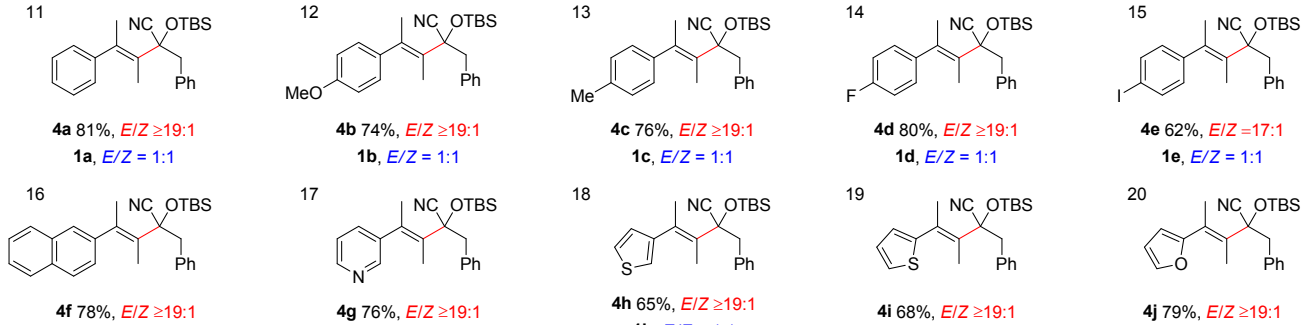
Table 1. Electrophile and Nucleophile Scope of the Stereoselective Alkylation of Tetrasubstituted Olefins[a,b,c]



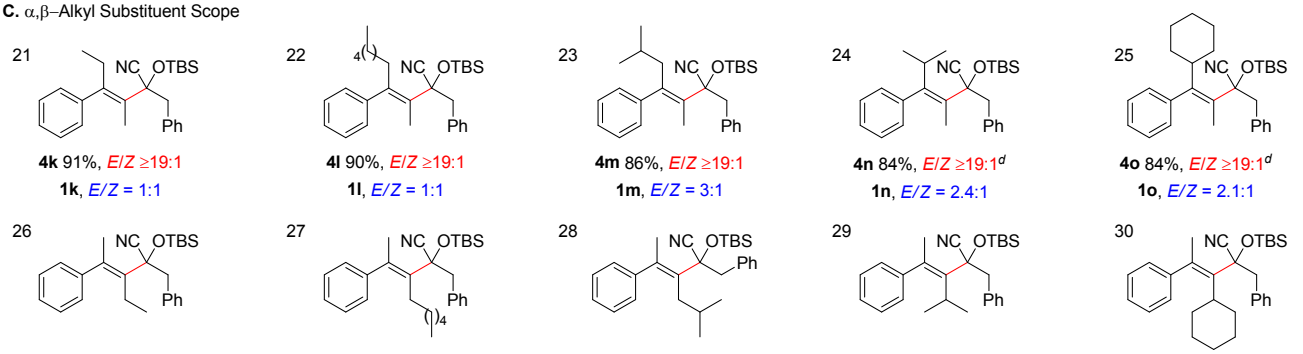
A. Electrophile Scope



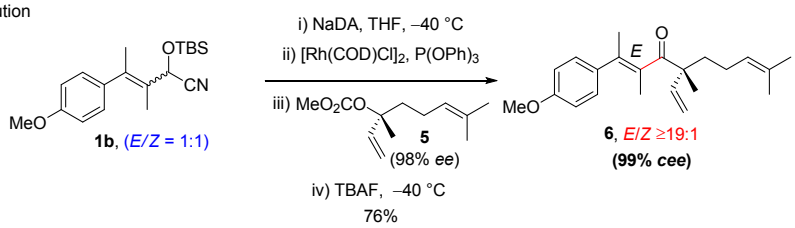
B. Aryl and Heteroaryl Scope



C. α,β–Alkyl Substituent Scope



D. Stereospecific Allylic Substitution



[a] All reactions were performed on a 0.5 mmol scale using 1.2 eqiuv. of NaDA in THF (10 mL) at –40 °C for 30 min. [b] Isolated yield. [c] *E/Z* ratios were determined by 500 MHz ^{1}H NMR on crude reaction mixture. [d] Reactions were run at –20 °C instead of –40 °C

mechanistic model suggested by the calculations is summarized in Fig. 1 and further details are provided in the supporting information. The initial deprotonation leads to the anionic species **2a*E*** and **2a*Z***, which form ion pairs with the alkali metal cations. Interestingly, we discovered that the two stereoisomers adopt very different ion pair structures. There are two functional groups that can stabilize the negative charge and bind the cation, namely, the cyano group and the aromatic moiety. In **2a*Z*** both of these elements are working in concert to accommodate the negative charge (Fig. 1A), whereas in **2a*E*** the charge primarily resides on the cyano group stabilized by the sodium cation in the lowest energy structure. Hence, our calculations indicate that the conversion of **2a*Z*** to **2a*E*** should be rapid, even at low temperatures, with a barrier of only 11.6 kcal/mol. This rapid conversion is critical to

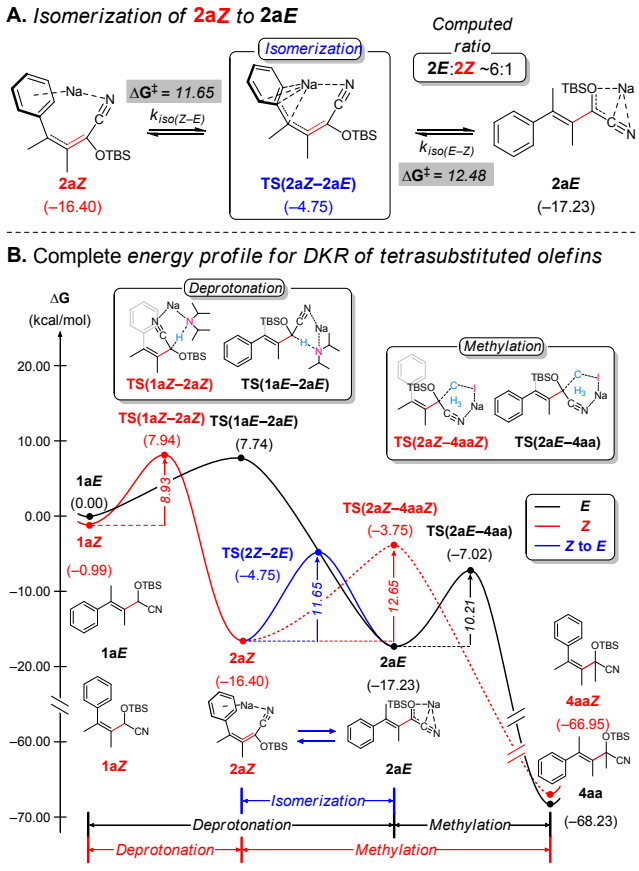


Figure 1. Computed Energy Profile of DKR. **A**. Isomerization of sodiated *E/Z*-carbanions of tetrasubstituted alkenyl cyanohydrins. **B**. Computed reaction energy profile for the DKR of tetrasubstituted alkenyl cyanohydrins. Energies are given in kcal/mol.

the dynamic kinetic resolution, as it permits the formation of the intermediate **2a*E*** from **1a*Z*** *via* **2a*Z***, in addition to the direct deprotonation of **1a*E***. The calculations also indicate that without the sodium cation, which delocalizes the negative charge across the molecule as indicated in Fig. 1A, the isomerization becomes much more challenging with an increased barrier for isomerization (~6 kcal/mol higher). While lithium and potassium are capable of behaving in an analogous manner, their size and polarizabilities are not as ideal as in the case of sodium, thereby leading to higher isomerization barriers.

The energy profiles for the reaction are detailed in Fig. 1B and they illustrate the inner workings of the dynamic kinetic resolution. The main reaction trajectory involves the generation of the sodiated adduct (**2a*E***), either by direct deprotonation of **1a*E*** or by deprotonation of **1a*Z*** followed by isomerization from **2a*Z*** to **2a*E***. Intermediate **2a*E*** may undergo methylation to produce **4aa** and we were able to locate the transition state TS(**2a*E*–4aa**) at –7.0 kcal/mol to give a barrier of 10.2 kcal/mol for the methylation of **2a*E***. To produce the undesired product **4aa*Z***, intermediate **2a*Z*** must undergo methylation and our calculations suggest a transition state TS(**2a*Z*–4aa*Z***) at –3.7 kcal/mol, which corresponds to a barrier of 12.6 kcal/mol, which is nearly 2.5 kcal/mol higher in energy than the aforementioned barrier for the formation of **4aa** (from **2a*E***). Alternatively, the energy barrier for the transition state of the isomerization (TS(**2a*Z*–2a*E***)) was located at –4.8 kcal/mol, which is 1 kcal/mol lower in energy than that of the methylation of **2a*Z***. Thus, intermediate **2a*Z*** is much more likely to undergo isomerization to **2a*E*** as opposed to direct methylation.[25] Analysis of the model concluded that the suggested mechanism implies **4aa**/**4aa*Z*** ratio of approximately 94:6, which is in good agreement with the experimental observations. *This computational analysis forms a solid foundation for the mechanism of the dynamic kinetic resolution seen in the prototype experiment.*

In conclusion, we have developed a direct and highly stereoselective synthesis of *E*-tetrasubstituted olefins *via* a novel DKR of alkenyl cyanohydrins. This is a remarkable development, given that it represents the first example of a dynamic kinetic resolution of tetrasubstituted olefins and thereby circumvents the challenge of stereoselectively assembling carbon-carbon double bonds. The new approach is practical and displays a usreful substrate scope, which is in itself quite significant given the relatively close ground state energies of the *E/Z* isomers. Our understanding of the mechanism is derived from computer simulations that provide a precise model for the exquisite selectivity. Overall, given the significant challenges posed by the construction of tetrasubstituted alkenes, we envision that the DKR of olefins in this manner will provide a powerful alternative to classical methods of preparing tetrasubstituted alkenes in target-directed synthetic applications.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS publication website at http://pubs.acs.org. Computational details, experimental procedures, spectral data, ^{1}H and ^{13}C NMR spectra for all compounds including pertinent NOEs.

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(18) For an extensive investigation into different metal amide bases and counter-ions, which delineate the importance of using NaDA, see the Supporting Information.

(19) The reaction was quenched with different proton sources (see SI), albeit the results indicate that **1a** is not equilibrated to a geometrically pure isomer. This result is consistent with the DFT calculations.

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(21) An 2,6-difluoroarene example affords the product in comparable yield, albeit with significantly lower selectivity (*E/Z* = 6:1), which illustrates the necessity for the aryl group to be planar to facilitate the equilibration (*cf*. Supporting Information).

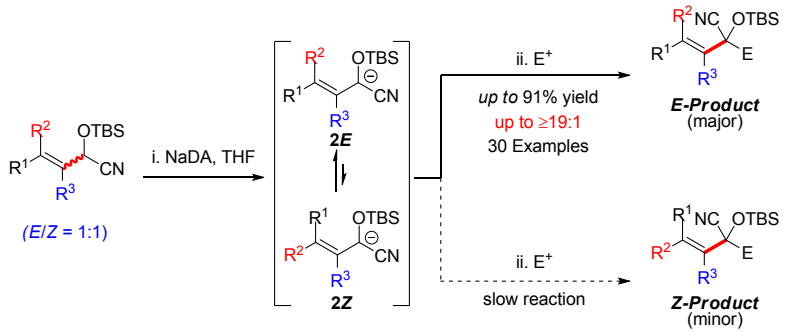
(22) Trialkyl substituted alkenyl cyanohydrins **1** ($R^1/R^2/R^3$ = alkyl) afford the benzylation product **4** with poor *E/Z* selectivity, which corroborates the importance of having an aryl substituent for the cation-pi interaction (*cf.* SI).

(23) The term conservation of enantiomeric excess (*cee*) = (*ee* of product/*ee* of starting material) × 100. See: Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc*. **1999**, *121*, 6761.

(24) The overall yield of the stereospecific reaction was 76%; however, the regioselectivity was modest (*b/l* = 4:1), albeit the olefin ratio of the tetrasubstituted olefin was *E/Z* ≥19:1 for both isomers (see SI)

(25) We developed a numerical model of the reaction kinetics using the computed reaction energy profile (Fig. S8, see Supporting Information).

Dynamic Kinetic Resolution of Alkenyl Cyanohydrins Derived from α,β-Unsaturated Aldehydes: Stereoselective Synthesis of *E*-Tetrasubstituted Olefins



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