Asymmetric Synthesis

Dynamic Kinetic Resolution during a Cascade Reaction on Substrates with Chiral All-Carbon Quaternary Centers**

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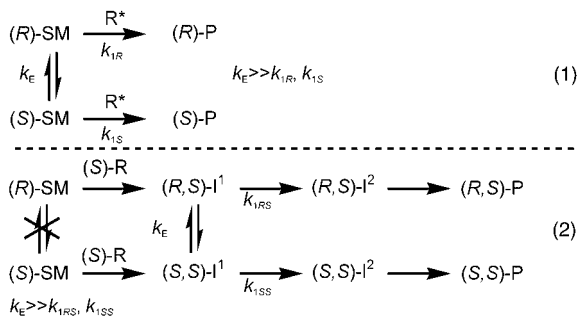
Dynamic kinetic resolution has become a useful method for the diastereoselective and enantioselective synthesis of organic compounds.[1] Dynamic kinetic resolution, presented in Equation (1) (Scheme 1), in its most common form results in greater than 50% conversion of a mixture of stereoisomers into products enriched in one enantiomer or diastereoisomer.[2]

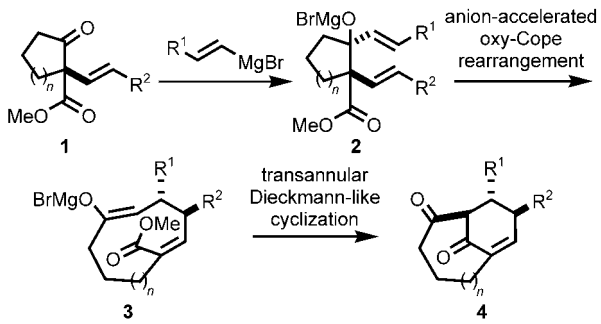


Scheme 1. Dynamic kinetic resolution with enantiomerization of the starting materials (SM; Eq. (1)). Dynamic kinetic resolution with epimerization in the second step (Eq. (2)). I^1 = first intermediate, I^2 = second intermediate, P = product.

Most dynamic kinetic resolutions require rapidly equilibrating enantiomeric starting materials that undergo a slower second step, in which the enantiomers react with enantiomerically enriched reagents at different rates ($k_{1R} \neq k_{1S}$; Scheme 1, Eq. (1)). Conceptually, it is difficult to imagine how starting materials that are not directly susceptible to enantiomerization, such as molecules where the only chirality present is in all-carbon quaternary stereocenters, could take part in dynamic kinetic resolutions. However, if a molecule incapable of direct enantiomerization were to undergo a cascade reaction (a reaction comprising one or more intermediates) and if any one of the intermediates in the reaction was capable of epimerization or enantiomerization (I^1, Scheme 1, Eq. (2)), then dynamic kinetic resolution could be achieved. Furthermore, equilibration of stereoisomers in dynamic kinetic resolutions is most often achieved by proton transfer,[3] addition–elimination reactions,[4] oxidation–reduction reactions,[5] or isomerization of configurationally labile carbanions,[6] whereas equilibration between stereoisomers containing all-carbon quaternary stereocenters can only be achieved through reversible C–C bond-forming reactions, which have rarely been used so far in dynamic kinetic resolutions.

Therefore, it may be possible to generate complex structures as single stereoisomers from a racemic starting material and an enantiopure reagent by developing cascade reactions with dynamic kinetic resolutions. Despite the potential of this concept, there are few examples of cascade reactions that incorporate dynamic kinetic resolution, especially ones involving the formation of multiple C–C bonds.[7] Herein, we report on dyanmic-kinetic-resolution cascade reactions that occur with racemic starting materials that contain all-carbon quaternary stereocenters.

During our synthesis of CP-263,114, we developed a diastereoselective cascade reaction comprising an alkylation, an anion-accelerated oxy-Cope rearrangement, and a transannular Dieckmann-like cyclization.[8] Using this latter reaction, we synthesized a wide range of complex polycyclic bridgehead enone compounds (Scheme 2).[9] The possible



Scheme 2. A cascade reaction for the synthesis of polycyclic bridgehead enone compounds.

participation of intermediate **2** in a retro-aldol/aldol equilibrium and the consequences of this equilibrium on the transfer of stereochemistry from C2 of **1** to the product **4** was of particular interest to us (Scheme 3).[10]

The occurance of the retro-aldol/aldol equilibration during the cascade reaction was tested with β-ketoester **5**, which was prepared in 99% *ee* by the enantioselective reduction of the corresponding racemate with the Corey–Bakshi–Shibata (CBS) catalyst and catecholborane[11] followed by separation and oxidation of the resulting diastereomers. Compound **5** was subjected to the conditions previously developed for the cascade reaction (see above), and the bicyclic product **6** was isolated as a racemate in 67% yield. The reaction was stopped after 15 minutes at 0°C by the addition of AcOH and addition product **7** was isolated in

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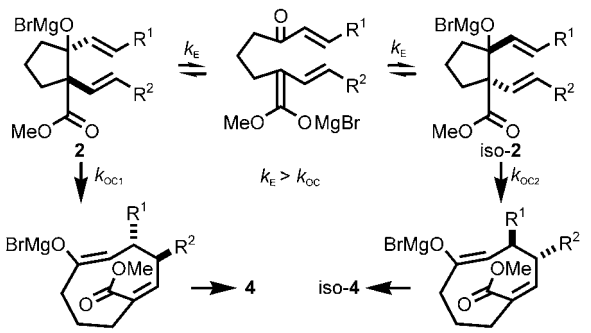
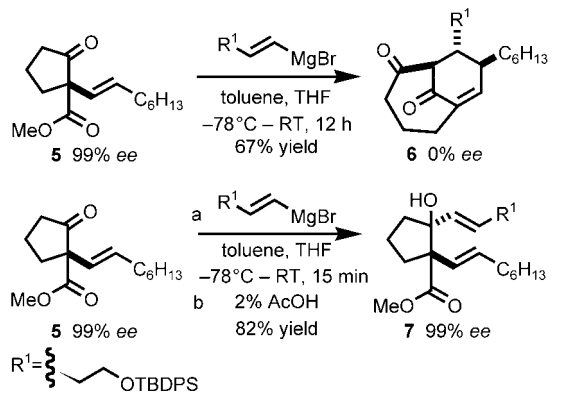


Scheme 3. Racemization in the cascade reaction. k_E = rate of the equilibration, k_{OC1} and k_{OC2} = rates of the anion-accelerated oxy-Cope rearrangements.

99% ee and in 82% yield (Scheme 4). The results of these experiments indicate that there was a retro-aldol/aldol equilibrium between the two enantiomers of the addition



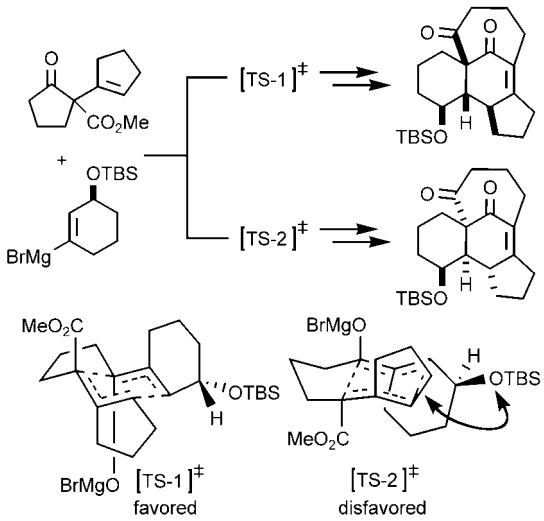
Scheme 4. Mechanism of racemization. TBDPS = *tert*-butyldiphenylsilyl.

product **2** and iso-**2** and that the rate of the equilibration (k_E) was significantly higher than the rate of the anion-accelerated oxy-Cope rearrangements (k_{OC1} and k_{OC2}; see Scheme 3). These results also establish that epimerization of the quaternary stereocenter of **1** occurred only after addition of the Grignard reagent.

The rapid enantiomerization between **2** and iso-**2** provided an intriguing opportunity for the dynamic kinetic resolution of **1**. A single enantiomer of a chiral vinyl Grignard reagent added to a racemic β-ketoester should result in two diastereomeric products (Scheme 3, **2** and iso-**2**, chiral R^1).

The fast retro-aldol/aldol reactions would result in equilibration of **2** and iso-**2** (with chiral R^1) at a rate higher than the rate of the ensuing anion-accelerated oxy-Cope rearrangements ($k_E \gg k_{OC1}$ and $k_E \gg k_{OC2}$). Considering a highly organized transition state of the anion-accelerated oxy-Cope rearrangement, with appropriately substituted chiral vinyl Grignard reagents, we anticipated that the two diastereomers would react at different rates ($k_{OC1} \neq k_{OC2}$), thus leading to dynamic kinetic resolution.

We assumed that the transition state for the anion-accelerated oxy-Cope rearrangement had a chairlike structure and so anticipated that 3-silyloxy-substituted cyclopentenyl and cyclohexenyl Grignard reagents would lead to different rates of the anion-accelerated oxy-Cope rearrangements (Scheme 5). Specifically, a nonbonded interaction



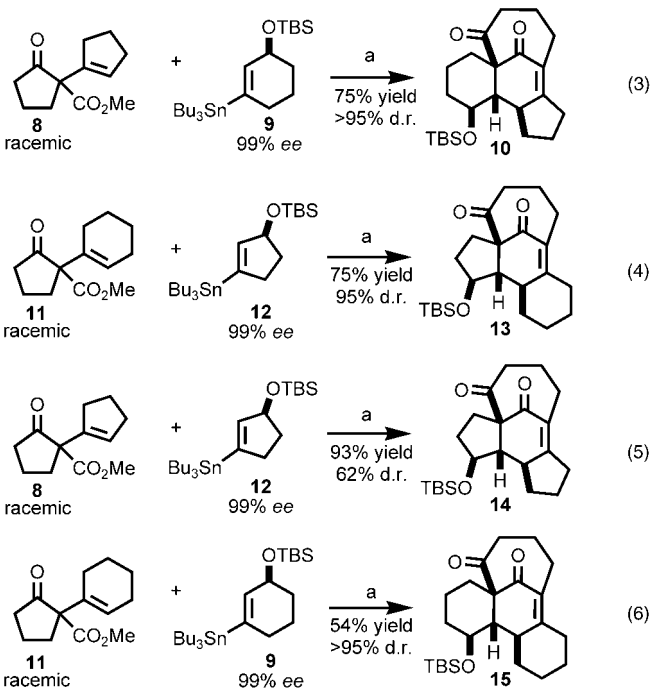
Scheme 5. Dynamic kinetic resolution of the polycyclic products. TBS = *tert*-butyldimethylsilyl.

between the silyloxy group and the cyclopentene that would exist in the second transition state (TS-2) but not the first transition state (TS-1) would differentiate between these two transition states, thus leading to the formation of the diastereomer derived from TS-1.

Indeed, treatment of racemic β-ketoester **8** with a single enantiomer of a Grignard reagent derived from vinyl stannane **9** (Scheme 6, Eq. (3)) afforded the product **10** of the expected cascade reaction as a single diastereomer in 75% yield, which is indicative of dynamic kinetic resolution. The product would have been generated as a 1:1 mixture of diastereomers in 99% *ee* if dynamic kinetic resolution had not occurred. However, the products would have been formed in 99% *ee* as a single diastereomer but in a maximum yield of 50% if only a kinetic resolution had occurred.

The diastereoselectivity of these reactions are, predictably, sensitive to the degree of nonbonded interactions between the silyloxy group and the olefin substituent on the β-ketoester. For example, the lowest diastereoselectivity was obtained in the reaction of **8** with **12** [Eq. (5)], in which both five-membered rings diminish the nonbonded interaction between the silyloxy group and the olefin substituent. The diastereoselectivity was high (≥95% d.r.) as long as one of the olefin substituents is part of a six-membered ring [Eqs. (3)–(5)]. The stereochemistry of the cascade reaction product **10** was confirmed by X-ray crystallographic studies (Figure 1).

The cascade reactions reported here are unique because they involve dynamic kinetic resolutions that required the formation and cleavage of multiple C–C bonds. Although



Scheme 6. Dynamic kinetic resolution during the cascade reaction. Conditions: a) *n*BuLi, THF, −78 °C,; $MgBr_2$, Et_2O/benzene, 0 °C; THF/toluene, 23 °C, 18 h.

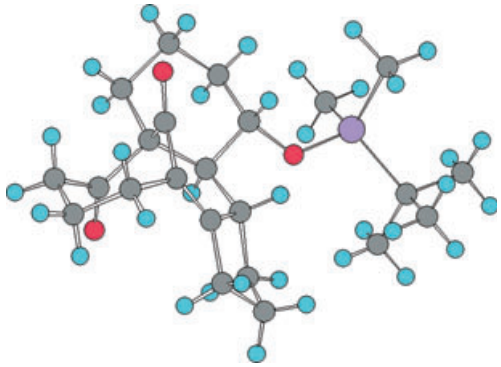


Figure 1. X-ray structure of **10**.

dynamic kinetic resolution is used more often in organic synthesis, this process is still rare for substrates with chiral all-carbon quaternary centers. The reactions reported in Scheme 6 demonstrate the necessity of reversible C–C bond-forming reactions in the dynamic kinetic resolution of starting materials with all-carbon quaternary stereocenters. Furthermore, the products generated in these reactions are among the most complex prepared to date involving dynamic kinetic resolution, which suggests that cascade reactions that comprise dynamic kinetic resolution may be useful for the stereoselective synthesis of complex molecules.

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