

DIVERGENT REACTIONS ON RACEMIC MIXTURES

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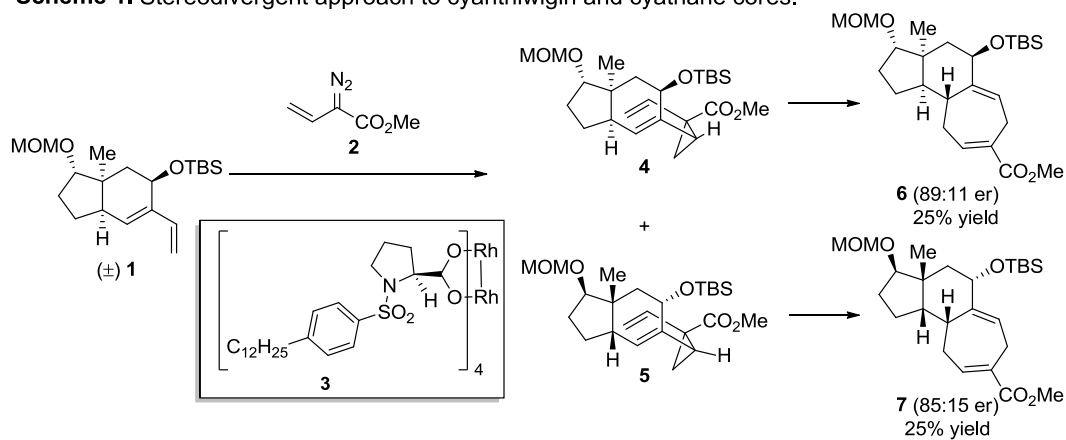
INTRODUCTION

Other than classical resolution, the methods that are currently applied to convert a racemic mixture of compounds to an enantiomerically pure product(s) include kinetic resolution, parallel kinetic resolution, dynamic kinetic asymmetric transformation, and dynamic kinetic resolution. However, these resolutions are limited by either their dependence on dissimilar reaction rates of the enantiomers, defined as the selectivity factor ($s = k_{\text{fast}} / k_{\text{slow}}$), or specific types of substrate that can undergo an epimerization process.¹ A recent method which avoids this reliance on high s values and specific substrates is that of divergent reactions on racemic mixtures (divergent RRM). Under the control of a single chiral enantiopure reagent or catalyst, the enantiomers of a racemic mixture each react via different pathways, resulting in products which are either diastereomers, constitutional isomers, or completely different compounds.^{2,3} The application of divergent RRM in synthesis is herein reported.

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In a stereodivergent RRM, each enantiomer of a racemic mixture is converted to a different diastereomer by the creation of a new stereocenter(s) under the guidance of the chiral, enantiopure reagent or catalyst. **Scheme 1.** Stereodivergent approach to cyanthiwigin and cyathane cores.

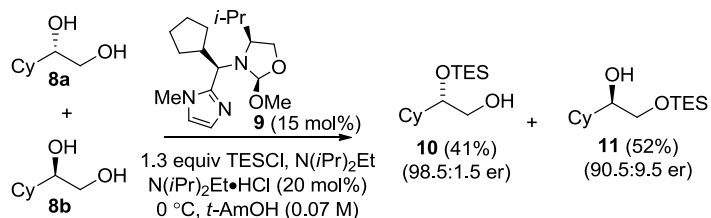
For example, Sarpong *et al.* have combined racemic diene **1** with vinyl diazoacetate **2** under the catalysis of **3**, resulting in the formation of diastereoisomeric



cyclopropanes **4** and **5**, which subsequently undergo a stereospecific Cope rearrangement to form the tricycles **6** and **7** (Scheme 1).⁴ These diastereomers constitute the epimeric cores of the natural products (–)-cyanthiwigin and (+)-cyanthin A₃ respectively. This example highlights the ability of stereodivergent RRM to produce two synthetically useful compounds from a racemic mixture with significant enantiomeric enrichment.

Tan and coworkers have recently applied regiodivergent RRM to resolve racemic terminal diols in an example of competing catalyst and substrate control (Scheme 2).⁵ The racemic diol **8** is silyl-protected in the presence of reversible covalent bonding organocatalyst **9**, which selectively protects the secondary alcohol over the more reactive primary alcohol of the **8a** enantiomer, forming silyl-protected

Scheme 2. Regiodivergent approach to silyl-protected diols.

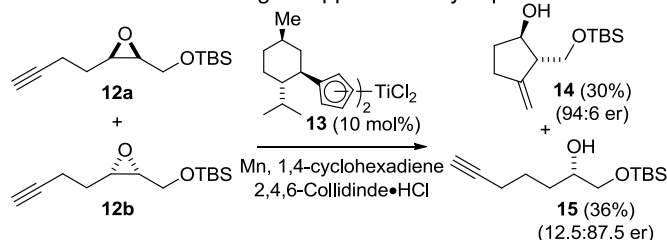


10 (catalyst control) while the enantiomer **8b** forms the primary protected diol **11** (substrate control). This study reveals the ability of catalyst **9** to overcome the strong substrate bias of the primary alcohol **8a**. Protected diols **10**

and **11** are now separable via column chromatography, highlighting one utility of regiodivergent RRM.

The Gansäuer group has employed chemodivergent RRM in the synthesis of cyclopentanols via a radical cyclization process (Scheme 3).⁶ A racemic mixture of alkyne epoxide **12** was subjected to a regioselective radical epoxide opening in the presence of Kagan's complex⁷ **13**. Cyclopentanol **14**, resulting from a 5-*exo* radical cyclization, and protected terminal diol alkyne **15**, resulting from a radical reduction of the O-Ti linkage

Scheme 3. Chemodivergent approach to cyclopentanols.



are each formed in high to moderate enantioenrichment. The application of chemodivergent RRM results in the formation of chemically distinct compounds from a racemic mixture, showing the potential for great diversity in products.

CONCLUSION

The emergence of divergent RRM has allowed for the production of enantioenriched products directly from racemic mixtures without the limitations of *s* or specific substrate types than can undergo a racemization or epimerization, shortcomings of the other resolution methods previously mentioned. The remaining obstacle of divergent RRM is the discovery of catalyst systems that can exert complete control so as to overcome any substrate control. This would allow for the catalyst to react specifically with each enantiomer to form nonenantiomeric products in high yields and enantiomeric enrichment.

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