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Catalytic Kinetic Resolution of a Dynamic Racemate: Highly Stereoselective β-Lactone Formation by *N*-Heterocyclic Carbene Catalysis

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Abstract

This study describes the combined experimental and computational elucidation of the mechanism and origins of stereoselectivities in the NHC-catalyzed dynamic kinetic resolution (DKR) of α-substituted-β-ketoesters. Density functional theory computations reveal that the NHC-catalyzed DKR proceeds by two mechanisms, depending on the stereochemistry around the forming bond: 1) a concerted, asynchronous formal (2+2) aldol-lactonization process, or 2) a stepwise spiro-lactonization mechanism where the alkoxide is trapped by the NHC-catalyst. These mechanisms contrast significantly from mechanisms found and postulated in other related transformations. Conjugative stabilization of the electrophile and non-classical hydrogen bonds are key in controlling the stereoselectivity. This reaction constitutes an interesting class of DKRs in which the catalyst is responsible for the kinetic resolution to selectively and irreversibly capture an enantiomer of a substrate undergoing rapid racemization with the help of an exogenous base.

Introduction

β-Lactones are highly useful building blocks for the synthesis of target compounds, especially in the area of natural product synthesis.[2–13] Catalytic asymmetric methods have provided new approaches to access this valuable strained ring system, and additional selective routes from different substrate classes open new synthetic possibilities.[14–19] We recently disclosed the first NHC-catalyzed dynamic kinetic resolution (DKR) reaction that furnishes β-lactones and cyclopentenes in good yields with high stereoselectivities from racemic α-substituted-β-keto esters (eq. 4).[20] Here, we report a collaborative computational study of the origins of stereoselectivities and the reaction mechanism. We have discovered

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how the degree of conjugation to an electrophile controls the stereoselectivity of this reaction, and how the stereochemical environment around the forming bond leads to a divergence in mechanism. In the process, we have also discovered that this reaction is part of an unusual class of DKRs in which the catalyst is responsible for the kinetic resolution that irreversibly traps an enantiomer of a dynamically racemizing substrate in a stereocontrolled manner.

The conversion of racemic starting materials to enantioenriched products is an ongoing goal in chemical synthesis with significant impact on the production of high value medicinal compounds.[21–27] Dynamic kinetic resolutions (DKRs) are one particularly efficient and widely used approach to convert racemic substrates to stereochemically pure products with a theoretical yield of 100%.[28–36] During the reaction sequence, a catalyst rapidly racemizes the substrate and stereospecifically transforms one enantiomer of the substrate. The ongoing catalyst driven racemization driven by Le Chatelier's principle eventually leads to the accumulation of a stereochemically pure product. Substituted-β-ketoesters are the archetypal substrate for DKR reactions due to their configurational lability at the α-position (Scheme 1, eq. 1).[37] Examples of DKRs with α-substituted-β-ketoesters include several asymmetric hydrogenations (eq. 2),[38,39] and a Baeyer-Villiger oxidation (eq. 3).[40] In 2007, we reported the NHC-catalyzed desymmetrization of 1,3-diketones, a kinetic resolution process.[41] In this process, the chiral NHC-generated enol undergoes selective addition to one of the two ketones, to allow for the formation of enantioenriched lactones and cyclopentenes. Our 2012 report, the title reaction (Scheme 2), is an expansion of this reaction to a dynamic kinetic resolution process.

N-Heterocyclic carbenes (NHCs) have greatly advanced the fields of organic and inorganic chemistry as ligands[42–49] and as catalysts.[50–61] These unique Lewis bases have been used to generate acyl anion,[62–76] homoenolate,[77–94] and enolate equivalents,[41,95–105] as well as promote hydroacylation[106–111] and an exciting variety of non–*Umpolung* processes.[112–115] These carbene-catalyzed processes have been used to access numerous challenging compound classes with high levels of diastereo- and enantioselectivities. With all of the different reaction manifolds accessed through carbene catalysis, it is interesting to note that before our 2012 report, there had been no previous examples in the literature of NHCs facilitating a DKR.[116]

Computational Methods

The mechanism and origins of stereoselectivity of this reaction were studied using M06-2X[117]/6-31+G**[118,119]/PCM(DCE)[120]//M06-2X/6-31G* as implemented in the Gaussian 09 suite of programs.[121] This method has previously been shown by Sunoj to reproduce experimentally observed stereoselectivity in a related NHC process.[122] Ethyl groups were modeled as methyl to reduce the degrees of freedom. Manual, exhaustive conformational searches were performed to ensure all relevant intermediates and transition structures were located. Intrinsic reaction coordinates (IRCs) were computed for all transition structures to verify reaction pathways.

Results and Discussion

Previous computational studies of NHC-catalyzed processes have elucidated the mechanisms, reactivities, and stereocontrol in various NHC-organocatalyzed processes.[66,122–136] This study builds on these earlier reports and reveals not only an unusual method of stereocontrol, but also an unprecedented mechanism. The computed catalytic cycle and the reaction coordinate diagram are shown in Figure 1. The attack of the NHC catalyst on the ω-aldehyde, proton transfer, and two tautomerizations lead to the key enolate intermediate **IV**. The subsequent irreversible aldol cyclization diverges to two pathways, depending on the stereochemistry around the forming bond (Figure 1): 1) For the major (*R*,*S*,*S*)-product, a concerted asynchronous aldol lactonization pathway is operative. This is a formal (2+2) cyclization where the forming alkoxide simultaneously attacks the regenerating adjacent carbonyl, leading directly to the catalyst-lactone adduct **VIII**. 2) For all minor products, a stepwise spiro-lactonization mechanism is operative, where the aldol irreversibly leads to a spiro compound **VIb**, the collapse of which leads to the catalyst-lactone adduct **VIII**. In all cases, the facile dissociation of the NHC catalyst regenerates the catalyst and releases the product lactones **IX**.

The discovery of two divergent mechanisms for the aldol-lactonization step contrast to the originally proposed mechanism in two ways: 1) originally, a stepwise mechanism that involves the formation of the zwitterionic aldol adduct **VIa** was postulated (Figure 1). This is unusual considering how frequently it is invoked and found in related reactions, most recently in the elegant work by Paddon-Row and Lupton.[127] Surprisingly, neither this adduct nor the subsequent transition state (**VIIa**) to form the catalyst-lactone adduct **VIII** exist on the potential energy surface. All our efforts to locate these structures have led to intermediate **VIb** and transition state **VIIb**, respectively. 2) Computations unequivocally reveal that the aldol-cyclization occurs via the enolate rather than the enol. In fact, the aldol-lactonization TS involving the enol does not exist. In line with these computational observations, we observed that Lewis acid and thiourea additives either significantly slowed, or completely shut down the reaction.[137]

The aldol transition states (TSs) for all observed products where R_1 = Ph are shown in Figure 2. The **TS-V-(*R*,*S*,*S*)**, which leads to the major product, is favored by 2.7 kcal/mol compared to minor enantiomer **TS-V-(*S*,*R*,*R*)**. This compares favorably with experimental enantioselectivity of 2.9 kcal/mol. In contrast, the computed diastereoselectivity is overestimated by ∼1 kcal/mol compared to experiments – major **TS-V-(*R*,*S*,*S*)** is favored by 2.2 kcal/mol compared to the minor diastereomer **TS-V-(*S*,*S*,*S*)**, while the experimental diastereoselectivity is 1.1 kcal/mol.

The energetic preference for the major **TS-V-(*R*,*S*,*S*)** stems from a double activation of the electrophilic ketone. First, there is significant electrostatic stabilization of the developing negative charge on the ketone undergoing nucleophilic attack by a critical C–H···O non-classical hydrogen bonding interaction[138] from the catalyst pyranyl C–H (indicated by thin green lines, Figure 2). Moreover, the phenyl substituent of the electrophilic ketone is in conjugation with the carbonyl (–0.2°), maximizing the reactivity of the ketone.

The origin of diastereocontrol arises from the reduced reactivity of the electrophilic ketone in the minor diastereomer **TS-V-*(S,S,S)***. The epimer at the ester stereocenter changes the torsion around the forming C–C bond such that although the stabilizing C–H···O interaction is maintained, it forces the electrophilic ketone to be twisted out of conjugation (–36°) with the phenyl ring to avoid steric interactions with the catalyst.[139]

We have computed a model system to quantify the effect of conjugative electrophilic activation on transition state stabilities. Shown in Table 1 are the energetic penalty from the loss of conjugation in various substituted benzaldehydes by comparing the fully conjugated planar (0° dihedral between the carbonyl and the Ph) with the phenyl twisted out of conjugation to the same degree as found in the minor transition state (34° dihedral average, across **TS-V-*(S,S,S)*** involving substrates where R = H, F, and OMe). In the ground state, the loss of conjugation amounts to ∼2 kcal/mol destabilization, regardless of the identity of the phenyl substitution. However, in model transition states of hydride addition to the carbonyl where the hydride approach has been fixed at 2Å, conjugative stabilization was worth significantly more, ∼2-7 kcal/mol, depending on the electronic nature of the aryl substituent (entries 2 and 3, Table 1). This highlights a unique conjugative stabilization effect present only in the transition state but absent in the ground state that is strong enough to effect excellent stereocontrol.

The importance of this conjugative stabilization may explain why alkyl ketone substrates are not compatible under these reaction conditions.[140] This NHC-catalyzed DKR proved to be general for α-substituted-β-ketoesters with aryl ketones. The decreased electron-withdrawing ability of alkyl and alkenyl substrates led to either no reaction or formation of side products.

The minor enantiomeric product is formed via **TS-V-*(S,R,R)***. The pyranyl non-classical hydrogen bonding C–H···O interaction controls the enantioselectivity. In the major TS, the pyranyl C–H is sandwiched between the enolate oxygen and the approaching electrophilic carbonyl, stabilizing the developing negative charges. However, approach to the opposite face of the enolate, as in the minor enantiomer pathway **TS-V-*(S,R,R)***, precludes stabilization with the pyranyl C–H. Instead, stabilization is realized by weaker alkyl C–H···O interactions. The weakness of these interactions is the cause for the destabilization of this transition state. A related investigation of electrostatic control of stereoselectivity in NHC-catalyzed [4+2] annulation reactions has been recently reported by Bode and Kozlowski.[132]

After we had computed the reaction coordinate, we questioned whether the NHC catalyst was indeed involved with the epimerization of the α-proton or was simply playing the role of a kinetic resolution catalyst. To test these two possibilities, we carried out a series of deuterium exchange experiments. α-Allylated β-keto ester **30** was dissolved in CD_2Cl_2/CD_3OD mixture (0.07 M).[141] Addition of cesium carbonate (30 mol %) as the base led to virtually instantaneous and complete deuterium incorporation at 23 °C as seen by ^1H NMR spectroscopy (time = 0). The same experiment performed at −10 °C showed significant deuterium exchange after 5 minutes (Figure 3), and complete exchange after 30 minutes. These results demonstrate that the optimal basic conditions used in our DKR reaction

promote extremely rapid keto/enol tautomerization and epimerization of these α-substituted β-keto esters.

An alternative possibility exists where the NHC azolium salts (pKa ∼17-25)[142–152] itself drives the deprotonation.[153] While experiments involving preparation of pre-generated carbene using strong bases (LDA or NaH) led to decomposition of starting materials, this possibility cannot be completely excluded.

We designed a stereodivergent reaction on a racemic mixture (RRM) experiment to verify that the aldol-lactonization process, not the epimerization is rate-limiting. In contrast to a standard kinetic resolution, a divergent RRM converts both enantiomers of a racemic mixture to non-enantiomeric products.[154–156] We employed racemic α-disubstituted β-ketoesters, which are configurationally stable (Scheme 4). Complete cyclization to diastereomeric β-lactone products **29a** and **29b** was achieved in excellent yield (50% maximum theoretical yield for each) and enantioselectivity in 12 hours, considerably slower than the exogenous base-mediated epimerization of the substrate.

Together these results suggest that the basic conditions needed to generate the activated catalyst additionally promote substrate racemization at a faster rate than the overall DKR reaction process. We suspect that the NHC catalyst simply plays the role of a kinetic resolution catalyst that captures and irreversibly transforms one enantiomer of the substrate. The current DKR process is different from the classical DKR where the catalyst is involved with both the racemization and kinetic resolution; the racemization occurs tangentially to the kinetic resolution (Figure 4). The stark differences in the role of the catalyst prompt us to suggest differentiating these two DKRs. Such processes, in fact, though rarely reported, have been observed by others.[157–159] We suspect that this unusual DKR is more common than is currently recognized.

Conclusion

In summary, computations have uncovered the mechanism and origins of stereoselectivity in the first NHC-catalyzed dynamic kinetic resolution of α-substituted-β-keto esters that provide β-lactones in high yields and selectivity. This study has uncovered two new mechanisms for the aldol-lactonization that challenge the currently accepted mechanism: 1) A concerted, asynchronous formal (2+2) aldol-lactonization process that leads to the major product, or 2) a stepwise spiro-lactonization mechanism that traps the forming enolate with the NHC catalyst iminium for all other products. The previously proposed stepwise mechanism, originally proposed by us, also invoked in other related reactions, is not operative.[20] Additionally, we have uncovered how conjugative stabilization to the electrophile and C–H···O non-classical hydrogen bonds are key to stereocontrol. Finally, we have also discovered that that the current reaction exhibits an unusual DKR, one we coined as non-classical due to the atypical role of the catalyst. The combined experimental and theoretical efforts described in this manuscript have led to discoveries that refine and further distinguish the current understanding of carbene-catalyzed reactions and DKR processes. These advances will continue to be enhanced and employed towards the discovery and advancement of new processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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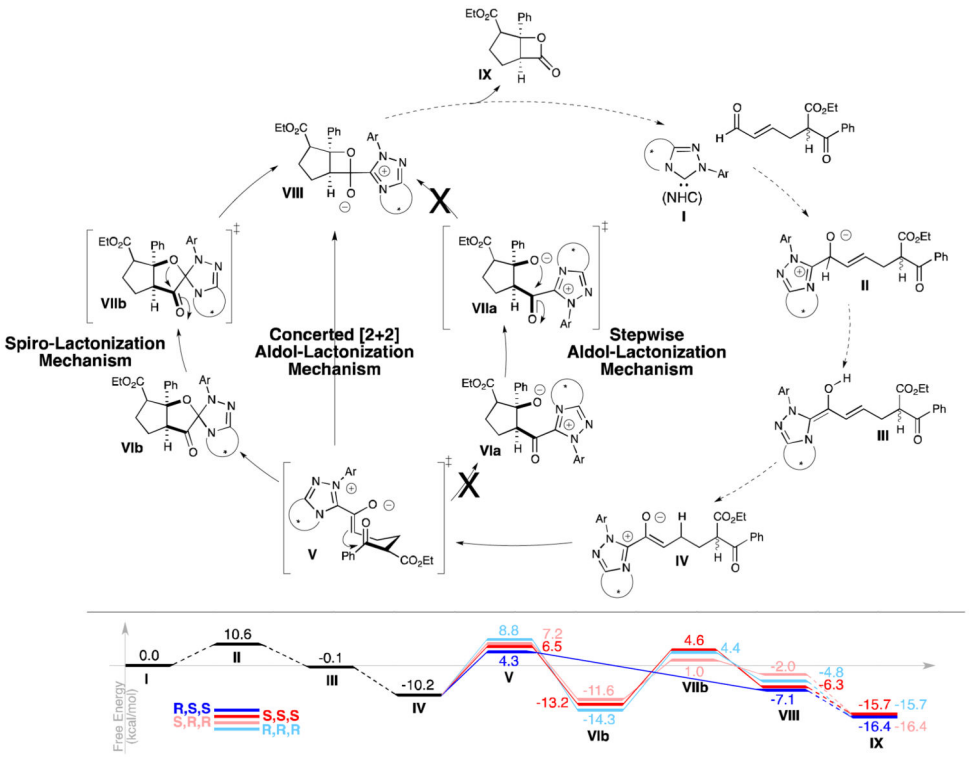


Figure 1.

The computed catalytic cycle (top) and reaction coordinate diagram (bottom). The pathway that leads to the major product is a concerted asynchronous (2+2) aldol-lactonization process while all minor products undergo a spiro-lactonization mechanism that traps the forming enolate with the catalyst iminium. Previously postulated pathway, involving the formation of the zwitterionic aldol adduct, does not exist on this potential energy surface.

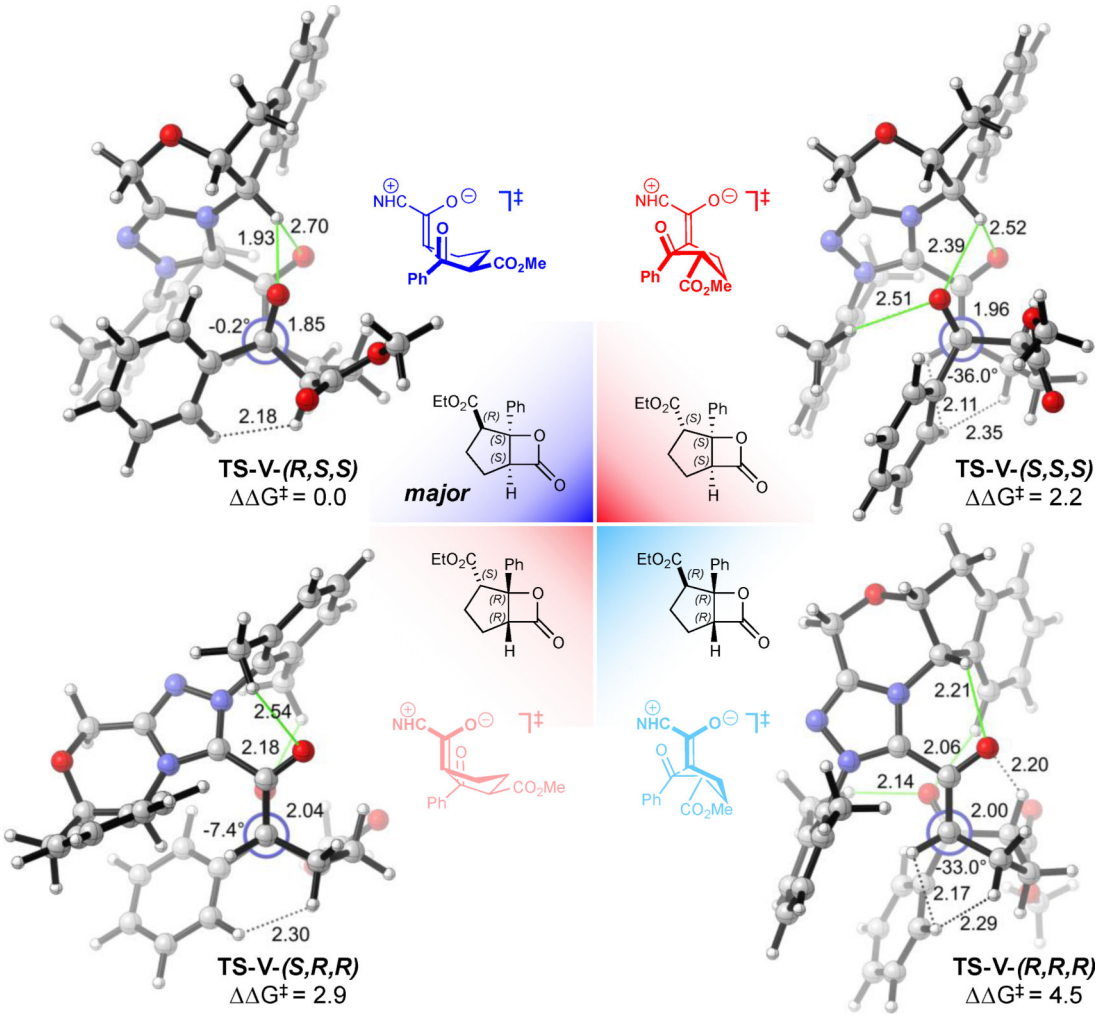


Figure 2.

Rate- and stereodetermining aldol cyclization transition states. Green lines indicate electrostatic stabilizations, and dotted lines indicate steric repulsions. Dihedral angles describe the planarity of the phenyl group with the electrophilic carbonyl (degree of conjugation). Distances are in Ångströms, dihedrals in degrees and free energies in kcal/mol. Colors correspond to diastereomeric pathways in Figure 1.

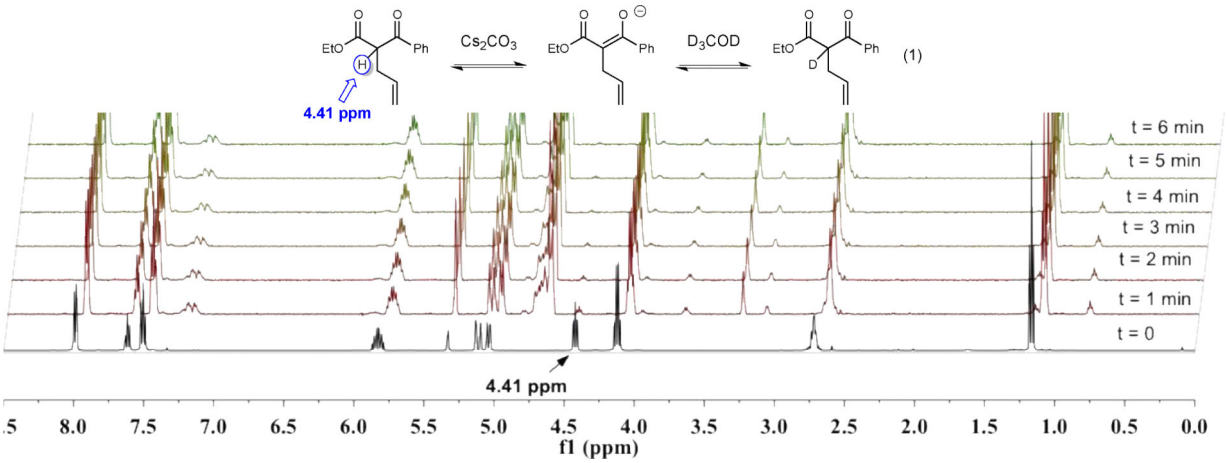


Figure 3.

^{1}H NMR (500 MHz) spectroscopic deuterium exchange experiment. The chemical shift at 4.41 ppm represents the α-proton of the α-allylated β-keto ester **30**.

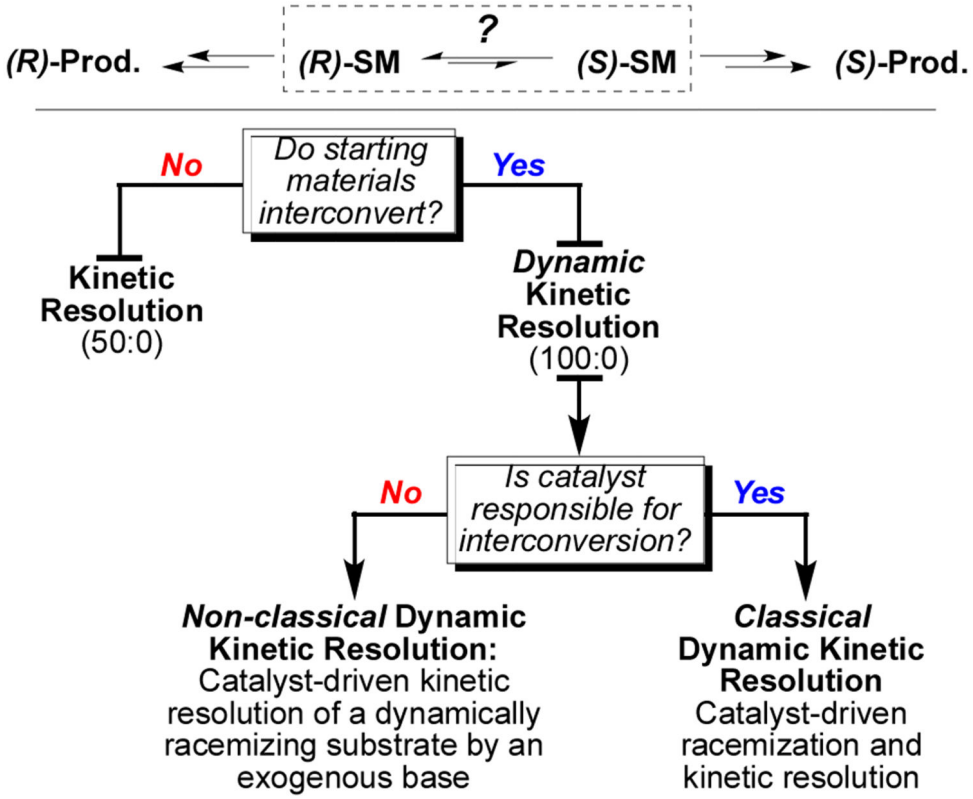
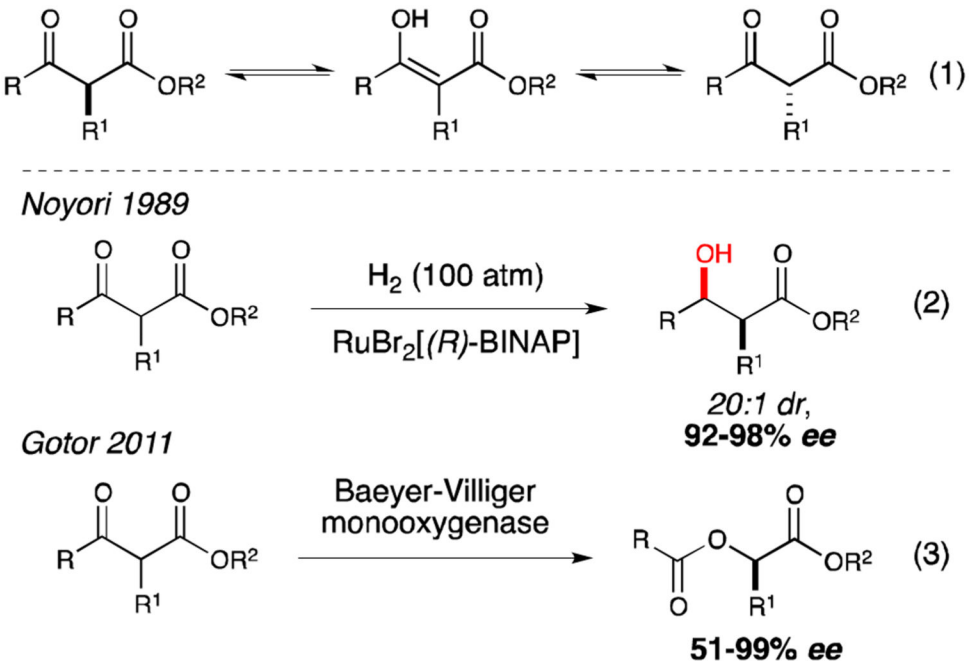
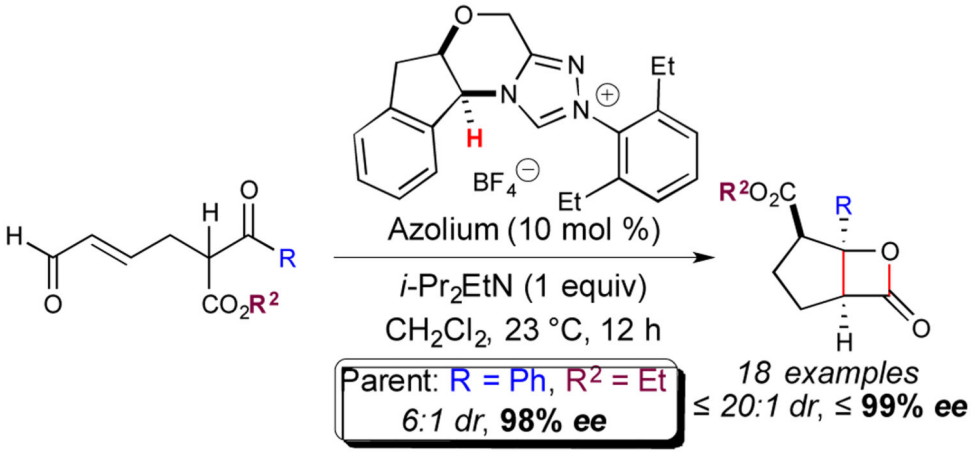


Figure 4.

Types of kinetic resolution processes. In a kinetic resolution, starting materials do not racemize. Only one enantiomer is transformed to product (maximum 50% yield). Dynamic kinetic resolutions (DKRs) occur when starting materials racemize to the more reactive form, leading to a maximum 100% yield. In a classical DKR, the catalyst is responsible for the racemization and conversion to product. In *non-classical* DKRs, the racemization of starting materials occurs independent of the kinetic resolution catalyst.

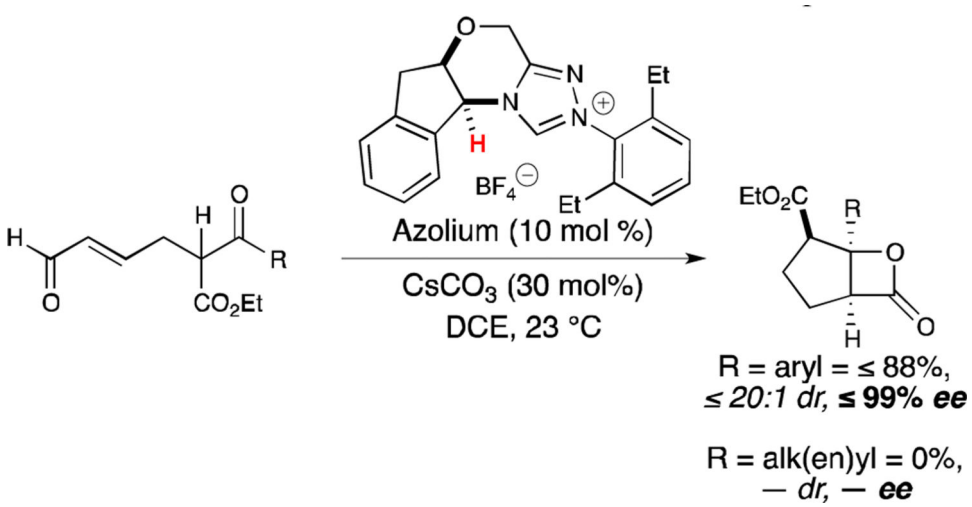


Scheme 1. DKR of α-substituted-β-ketoesters



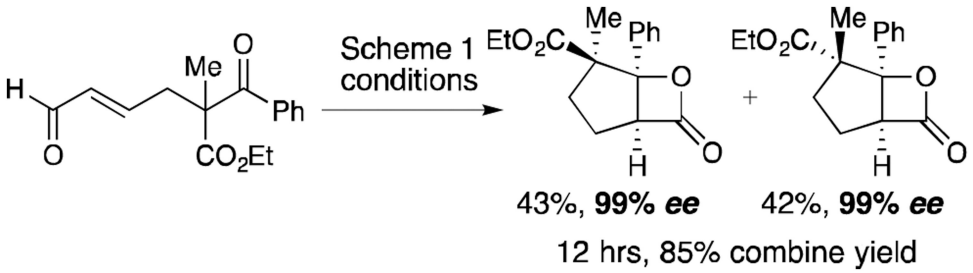
Scheme 2.

The parent transformation. Computational models abbreviated all ethyl groups to methyl.



Scheme 3.

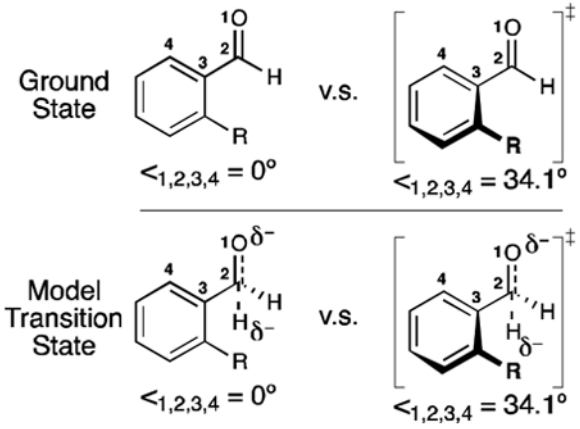
NHC-catalyzed DKR of α-substituted-β-ketoesters to β-lactones is general for aryl substitution, yet ineffective with alkyl and alkenyl substitution.



Scheme 4.
Stereodivergent reaction on a racemic mixture (RRM) study.

Table 1

[a] Energetic penalty from loss of conjugation[b] in benzaldehyde: ground state & model transition state[c]



entry	R	ΔG_{GS}	ΔG_{TS}	$\Delta G^{\ddagger}_{exp}$ *d*	$\Delta G^{\ddagger}_{comp}$ *e*
1	H	1.9	2.0	1.1	2.2
2	F	1.6	4.8	>1.7	4.4
3	OMe[g]	1.4	7.6	>1.7	5.3

[a] All energies in kcal/mol,

[b] Free energy difference between fully conjugated (0°) and twisted (34°) benzaldehyde, Torsion of twisted geometry corresponds to the average torsion found in **TS-V-(*S,S,S*)**, leading to the minor diastereomeric product.

[c] Hydride to carbonyl distance fixed at 2.0 Å,

[d] Experimental diastereoselectivity,

[e] Computed diastereoselectivity.

[g] Experimental ethoxy compound modeled computationally as methoxy.

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