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Synthesis of Complex Glycolates by Enantioconvergent Addition Reactions

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Conspectus

The unique role that stereochemistry plays in molecular recognition events continues to provide a driving force for synthesizing organic compounds in enantioenriched form. The tendency of enantioenriched organic compounds to revert to an entropically favored racemic state in the presence of viable racemization pathways (e.g., the enolization of stereogenic carbonyl derivatives) can sometimes interfere with this objective; however, beginning with Noyori's foundational disclosure of a dynamic kinetic transfer hydrogenation, the ability to channel racemic, configurationally labile starting materials through stereoconvergent reaction pathways has been recognized as a powerful strategy in asymmetric synthesis. Proton transfer, retro-aldol, retro-Michael, reversible redox events, and other processes that can be deleterious to asymmetric synthesis are exploitable in enantioconvergent reactions using chiral small molecules and enzymes as asymmetric catalysts. Enantioselective reduction of configurationally labile carbonyl derivatives bearing a C–H acidic chiral center are particularly common. Because facile racemization is vital to stereocontrol in these transformations, hydrogenations of β -dicarbonyls are commonplace, while less activated substrates have been used less commonly. Our entry into enantioconvergent catalysis evolved from a long-standing interest in the synthesis of complex glycolates and began with the development of a general Noyori-type transfer hydrogenation of α -keto esters. Key innovations in this work include the identification of a new terphenylsulfonamide–Ru(II) complex, which displays unusual preference toward reduction of α -keto esters, and the observation that α -keto esters racemize under mildly basic conditions. This work was extended to the dynamic kinetic hydrogenation of racemic acyl phosphonates. Moreover, the recent recognition that the mechanistic paradigm underlying enantioconvergent hydrogenation chemistry can be extended to diverse carbon-centered nucleophiles has led to advances in the art. Our lab has developed a number of enantioconvergent tertiary alcohol syntheses. In the context of carbon-centered nucleophiles, we have focused on the use of α -keto esters; however, in the latter part of this Account, we will briefly describe our nascent efforts to develop dynamic kinetic additions of carbon-centered nucleophiles to β -oxo acid derivatives. While the enantioconvergent hydrogenation of β -keto acid derivatives is carried out on 100-ton scale annually, non-hydrogenative transformations of these compounds constitute an underexplored subclass of enantioconvergent reactions.

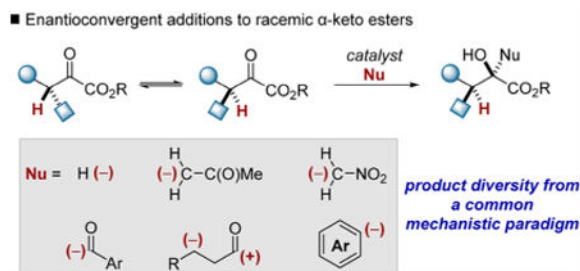
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With regard to future prospects, a trend toward transformations that afford increasing levels of molecular complexity is apparent. It can be expected that the burgeoning field of asymmetric 1,2-addition chemistry will further drive this chemistry to encompass a wider array of enantioconvergent additions. Additionally, the continued exploration of these chemistries in the context of less conventional electrophiles, as well as identifying novel or overlooked modes of racemization, holds considerable potential.

Graphical abstract



1. Introduction

Nucleophilic addition to α -stereogenic carbonyl derivatives is a robust strategy for the synthesis of complex alcohols.¹ The requisite chiral electrophiles are readily prepared by the functionalization of enolate derivatives. The addition of acyl anion equivalents to prochiral electrophiles constitutes an alternative approach that can be deployed in the synthesis of α -stereogenic carbonyls.^{2,3} Both approaches require basic reaction conditions, and the inclination of optically active carbonyls bearing acidic protons to racemize via enolization can pose a significant challenge.⁴ Enantioconvergent catalysis represents a powerful solution to this problem.⁵ The ability to channel configurationally labile starting materials through stereoconvergent reaction pathways, disclosed by Noyori and co-workers in their foundational report of a dynamic kinetic hydrogenation (Scheme 1A),⁶ represents a significant advance in organic synthesis. Racemization, typically viewed as a nuisance, can be harnessed to achieve streamlined syntheses of complex molecular frameworks.⁷ Numerous transformations that operate under this mechanistic paradigm have been developed.⁵ The complexity found in the products ascends according to the number of stereocenters centers formed and the reagents coupled in the enantioselective step (Scheme 1B). Beginning with enantioconvergent reactions that furnish a single stereo-center,^{8,9} the next stratum of complexity includes Noyori-type hydrogenations that establish two chiral centers.^{6,10,11} In many enantioconvergent reactions, facile substrate racemization is a prerequisite for obtaining high stereoselectivity;^{5,12} therefore, β -oxo ester derivatives have emerged as the factotum substrate class for dynamic kinetic hydrogenations. Non-hydrogenative transformations that establish two chiral centers constitute the third echelon of complexity.¹³ The final echelon of complexity comprises a handful of reactions that involve the addition of prochiral nucleophiles and create three chiral centers.¹⁴

This Account highlights our laboratory's ongoing development of two underexplored subtypes of enantioconvergent transformations: those employing α -keto esters as

electrophiles and non-hydrogenative transformations of β -oxo acid derivatives. Enantioconvergent additions are classified as either dynamic kinetic resolutions (DKRs) or Type I dynamic kinetic asymmetric transformations (DyKATs).^{5,12} In a DKR, the racemization is independent of the chiral catalyst (Scheme 1C), and the stereoselectivity is affected by the rate of racemization, which generally must be greater than the rate of reaction for the fast reacting enantiomer. In a Type I DyKAT, racemization is promoted by the chiral catalyst. The rates of formation and transformation of epimeric catalyst/substrate complexes and their concentrations influence stereoselectivity.

2. Transfer Hydrogenation Dynamic Kinetic Resolutions of α -Keto Esters and Acyl Phosphonates

Our work utilizing silyl glyoxylates as glyoxylate anion equivalents opened the door to our studies of dynamic 1,2-additions.¹⁵ During the development of a nucleophilic glyoxylation employing silyl glyoxylate **4** and aldehydes (i.e., benzaldehyde **5**), the sensitivity of the derived β -silyloxy- α -keto ester **6** toward base promoted conversion to isomeric β -keto ester **7** was noted. This observation prompted the realization that α -keto esters such as **6** might succumb to facile racemization and thereby hold potential as precursors to diol derivatives such as **8** via dynamic reduction (Scheme 2). Enantioselectivity was obtained with the Noyori-type Ru(II)-diamine catalyst **9** under transfer hydrogenation conditions (Cs_2CO_3 , HCO_2H).¹⁶ Unfortunately, conditions could not be identified that both suppressed the intervention of the unreactive α -silyloxy- β -keto ester **7** and engendered high stereoselectivity. Nevertheless, the utilization of α -keto esters in enantioconvergent hydrogenation remained attractive to us as a means to generate diverse glycolate architectures.

We sought to embed functional handles within the α -keto ester framework that would trigger complexity building events in the same flask. For instance, incorporation of γ -diester functionality might trigger a diastereoselective lactonization, providing access to γ -butyrolactone derivatives characterized by three contiguous stereocenters (Scheme 3).¹¹

We aimed to develop an efficient route to the α -keto ester starting materials so that the utility of the forecasted complexity-generating hydrogenation/lactonization event would not be undermined by unduly inconvenient or costly procedures.

Accordingly, inspired by a glyoxamidation reaction developed by Rovis and co-workers,⁴ we developed an *N*-heterocyclic carbene-catalyzed Stetter addition utilizing benzylidene malonate derivatives **10** and commercially available ethyl glyoxylate **11** (Scheme 3). Notably, the process can produce multigram quantities of α -keto esters **13** and is characterized by 100% atom economy.¹⁷ For the key hydrogenation reaction, we returned to Noyori's (arene)RuCl(monosulfinamide-DPEN) framework and employed formic acid/triethylamine azeotrope (5:2) as both the organic reductant and racemization promoter. A new *m*-terphenyl substituted α -naphthylethylene diamine derived ruthenium(II) complex **14** was developed for optimal performance. At the time, the α -naphthyl ethylene diamine scaffold had rarely been used in asymmetric catalysis,¹⁸ while examples of *m*-terphenyl groups in enantioselective catalysis were even less common.¹⁹ These two structural elements

operate synergistically to relay asymmetry; corresponding ligands with a DPEN backbone and *m*-terphenylsulfonamide group or an α -naphthyl ethylene diamine backbone with other sulfonamides failed to provide satisfactory selectivity.

A range of γ -butyrolactones **15a–i**, characterized by a *syn,anti*-configured stereotriad were furnished (Scheme 3). The reduction could be carried out with ease on 10 g scale, using 1 mol % Ru in the synthesis of piperonyl derivative **15i**. The overall sequence of three catalytic steps transforms four feedstock starting materials, aldehyde, malonate, ethyl glyoxylate, and formic acid, into stereochemically complex γ -butyrolactone frameworks.

The terphenylsulfonamide of catalyst **14** is a uniquely effective design element in hydrogenations of diverse β -stereogenic- α -keto esters. For instance, α, γ -diketoesters **17**, produced by a Stetter reaction between ethyl glyoxylate **11** and chalcones **16**, underwent highly chemo- and stereoselective hydrogenation to α -hydroxy- γ -keto esters **18** (Scheme 4).^{10b} The products of this reduction are formal glycolate Michael adducts, a bond construction that is otherwise difficult to achieve without recourse to auxiliary control or protecting group manipulation.²⁰ This methodology was applied to the synthesis of the α -benzylidene- γ -butyrolactone natural products mega-cerotonin acid **19f** and shimobashiric acid **19g** (Scheme 4B).^{10e} The simplicity of the hydrogenation and the flexibility of substitution on the α, γ -diketoesters **17** should facilitate the preparation of unnatural congeners for biological studies.

The high chemoselectivity imparted by the *m*-terphenylsulfonamide/*di- α* -naphthylethylenediamine-Ru(II) system **14** toward reduction of α -keto esters is remarkable considering (arene)RuCl(sulfonamide) catalysts are used for reductions of aryl ketones. Acetophenone **20** and ethyl-3-oxo-butanoate **21**, archetypal substrates for the development of transfer hydrogenations,¹⁷ were not hydrogenated by complex **14**. We surmise that the bulky nature of the novel ligand motif suppresses reduction of less activated carbonyls.

β -Aminoglycolates could also be generated by the asymmetric transfer hydrogenation DKR (ATH-DKR, Scheme 5).^{10d} Racemic Mannich adducts **24** were treated with Oxone to provide access to Boc or Cbz protected β -amino- α -keto esters **25**. In this instance, the terphenylsulfonamide/ diphenylethylenediamine–Ru(II) complex **26** provided levels of enantioselectivity comparable to **14**. The unpurified α -keto ester starting materials could be employed in the transfer hydrogenation reaction, highlighting the robust nature of the catalyst system. An array of β -amino- α -hydroxy esters **27** were prepared in good to high yield with high levels of stereocontrol (Scheme 5, **27a–i**). Different amine protecting groups can be employed, although higher selectivities were obtained with Boc-protected substrates (**27a** vs **27b**). As the series of **27c–e** shows, the ability of the catalyst to enforce enantiocontrol is marginally influenced by *ortho*-substitution in this system, although the diastereoselectivity displayed higher sensitivity. An arylpinacol boronate was tolerated in the reduction to β -aminoglycolate product **27h**.

The hydrogenation of a common platform containing a malleable β -functionality was compelling from the standpoint of rapidly generating diverse glycolates from a single hydrogenation product. Thus, the deployment of β -chloro- α -keto esters **28** was undertaken

with the assumption chlorohydrins **29** would be amenable to downstream substitution chemistry (Scheme 6).^{10b}

Ultimately, catalyst **26** was effective for the synthesis of diverse chlorohydrin derivatives **29a–i**. In accord with our hypothesis that the β -nucleofuge could be displaced to introduce various heteroatomic substitution, halohydrin **29g** was converted to its derived glycidic ester **30g** and β -aminoglycolic acid **31g**.

The diastereoselectivity of this process exhibits a striking response to ligand structure (Scheme 6). For instance, the ethylene diamine derivative **32** provided >20:1 preference for the syn isomer. In contrast, the novel terphenylsulfonamide scaffolds **14** and **26** were highly *anti*-selective.

At this juncture we began to consider the extension of the ATH-DKR to other substrate classes. Acyl phosphonates share some characteristics with α -keto esters and can behave analogously in catalytic asymmetric reactions.²¹ The use of the former in the ATH-DKR was appealing as a means to test the generality of this mechanistic paradigm.^{10c} In analogy to the transfer hydrogenation of β -chloro- α -keto esters, the diastereoselectivity of this transformation could be tuned by altering the ligand structure. Ultimately, we found complex **14** to be optimal in the reduction of acyl phosphonates **34** to a wide array of hydroxy phosphonates **35**, but with the opposite facial selectivity relative to analogous β -aryl-substituted α -keto esters: the diastereomeric (1*R*, 2*R*) configuration was obtained (Scheme 7B).

The dichotomy in diastereofacial selectivity observed between acyl phosphonates and α -keto esters stands in contrast to other asymmetric transformations for which both have been employed;²¹ however, the steric environment surrounding the reactive carbonyl center is different for acyl phosphonates, which are tetrahedral at the phosphorus center, and α -keto esters, which are trigonal at the adjacent carbon. This difference apparently influences the facial selectivity in the (arene)RuCl-(monosulfonamide-diamine) catalyzed transfer hydrogenation.

3. Dynamic Kinetic 1,2-Addition of Carbon-Centered Nucleophiles

3.1. Aminocatalyzed Aldol and Henry Reactions of α -Keto Esters

By extending Noyori-type hydrogenations to β -stereogenic α -keto esters and acyl phosphonates, an array of complex glycolate and hydroxyphosphonate frameworks were accessed; however, enantioconvergent processes that proceed via C–H bond formation are limited with respect to the complexity they can generate. In contrast, the addition of carbon-nucleophiles should provide expanded access to diverse scaffolds. Due to our group's interest in complex glycolates,¹⁵ the development of enantioconvergent C-centered nucleophile additions to α -keto esters emerged as a compelling means to generate tertiary glycolates. We first targeted the addition of pro-nucleophiles nitromethane and acetone to β -bromo- α -keto esters **36** (Scheme 8).^{13c} Ultimately, a simple, readily accessed quinidine-derived catalyst **37** was found to promote high reactivity and excellent stereoselectivity in the Henry reaction, while the acetone aldol reaction was realized by enamine catalysis using

cinchona alkaloid derived primary amine **38**. A diverse array of α -keto ester substrates participated in both reactions, providing tertiary glycolates **39a–h** (MeNO₂ addition) or **40a–h** (Me₂CO addition).

To gain a deeper understanding of the mechanism of the dynamic kinetic aldol and Henry reaction, we sought to elucidate the racemization mode. We first measured the enantiomeric composition of enantioenriched α -keto ester **36a** and product **39a** during the course of the Henry reaction (Scheme 9A). Complete racemization of **36a** occurred within 10 min, and the starting material remained racemic throughout the remainder of the reaction, while the product was formed with uniform selectivity throughout the course of the reaction. Notably, the observation that **36a** underwent complete racemization in under 30 min in the presence of **37** alone suggests general base catalysis as a mode of substrate racemization in the case of **36** (Scheme 9B). Additionally, when the catalytic Henry addition was conducted with CD₃NO₂, a kinetic isotope effect of 2.8 and only 36% deuterium incorporation at the β position of **39a** was observed, suggesting that racemization of **36a** primarily involves an intimate ion process with protonation occurring from the ammonium salt rather than nitromethane and that nitronate formation contributes to the observed reaction rate. In situ monitoring of the reaction by NMR spectroscopy revealed no intermediates, thus confirming the resting state as the neutral amine **37** and suggesting that nitronate formation is endergonic. The observation that **36a** undergoes racemization in the presence of the amine catalyst, likely via an enolate– ammonium ion pair intermediate, in combination with the observed moderate deuterium incorporation, suggests that the Henry reaction proceeds via a DyKAT Type I mechanism (Scheme 9C).

Several other aminocatalyzed dynamic aldolizations have been reported in the literature. For instance, prior to our work, Calter reported a highly enantioselective interrupted Feist–Bénary reaction (Scheme 10A).^{13a} Additionally, Ward and co-workers developed an enantioconvergent aldolization of cyclocarbaldehydes (Scheme 10B),^{14a} while Zhang employed β -keto esters in a highly enantioselective dynamic acetone aldol reaction (Scheme 10C).^{13b} Finally, the tandem chlorination/aldol reaction developed by Britton and co-workers was leveraged for synthesis of furanose derivatives (Scheme 10D).^{14c}

3.2. NHC-Catalyzed Additions to α -Keto Esters

3.2.1. Dynamic Kinetic Cross-Benzoin Additions—Having developed highly enantio- and diastereoselective Henry and aldol reactions of racemic α -keto ester electrophiles, we sought to expand the scope to the addition of other carbon-centered nucleophiles. The benzoin addition is a valuable reaction that furnishes α -hydroxycarbonyl products with 100% atom economy. At the time we began to examine this issue, benzoin reactions that established more than one stereocenter were not commonplace.^{3d,f} Thus, the formation of two stereocenters via dynamic kinetic cross-benzoin reactions of aldehydes **42** and racemic, configurationally labile, α -keto esters (i.e., **28** or **36**) was attractive to us as a means to generate complex glycolate frameworks. While highly selective homo-benzoin reactions have been developed, cross-benzoin additions between different donor and acceptor carbonyls are more difficult to implement due to competitive homobenzoin reactions.²² Nevertheless, a highly selective cross-benzoin reaction of aryl aldehydes **42** and

β -halo- α -keto esters could be realized when triazolium salt **43** was employed in conjunction with K_2CO_3 to facilitate formation of the active carbene (Scheme 11A). The β -chloro- α -keto esters **28-Me** afforded lower levels of diastereocontrol (i.e., **44a**); therefore, the scope of this transformation was studied using the β -bromo-derivatives **36-Me**. An array of α -keto esters underwent a highly diastereo- and enantioselective cross-benzoin addition with benzaldehyde leading to products **44a-e**. Currently, γ -branched electrophiles represent a limitation, as only 60% conversion was observed in the formation of product **44h**, which was isolated in low yield.

A gram scale benzoin reaction between **36b** and **42a** revealed a minor amount of the benzoin **45** (9% isolated yield); however, subjecting **45** to the reaction conditions with α -keto ester **36a** produced none of the cross-benzoin product **44b** (Scheme 11B), indicating that benzoin formation is irreversible under the reaction conditions and that the high selectivity for the cross-benzoin product is likely due to the heightened reactivity of the β -bromo- α -keto esters **36-Me** relative to the less activated aryl aldehydes **42**. The cross-benzoin product **44i** could be reduced by sodium borohydride to complex β -hydroxyglycolate framework **46** bearing three contiguous stereocenters with exquisite levels of diastereoselection (Scheme 11C).

The observed selectivity in the cross-benzoin reaction was rationalized through the interplay of Felkin-Anh²³ diastereofacial addition opposite to the large electronegative bromide and approach from the convex face of the Breslow intermediate imposed by the bicyclic framework of the NHC catalyst (Scheme 11D). It should be emphasized that the reactive conformation proposed by the Cornforth model, where the halogen is *anti* with respect to the carbonyl to achieve dipole minimization, predicts the same stereochemical outcome.²⁴

3.2.2. Dynamic Kinetic Homoenoate Additions—Enantioconvergent reactions that establish three stereogenic centers are unusual. Examples include the transfer hydrogenation/lactonization sequence developed by our laboratory (Scheme 3), processes that involve Michael/retro-Michael induced enantiomerization,²⁵ and the aldol reactions developed by Ward^{14a} and Britton^{14c} (Scheme 10B,D). Building on the theme of enantioconvergent umpolung reactions, the extension to extended Breslow intermediates^{3e,f} was a logical next step. We anticipated that the integration of homoenoates would not be trivial due to the potential formation of eight stereoisomers. Additional perceived challenges to our reaction design included potential acyl anion reactivity and competitive dimerization of the enal (Scheme 12A, paths a and c). Nevertheless, we were compelled by the potential of the dynamic kinetic homoenoate addition of α,β -unsaturated aldehydes **47** and α -keto esters (path b) to furnish γ -butyrolactones bearing three stereogenic centers and a fully substituted glycolic acid motif. The β -chloro substituted α -keto esters **28** employed in previous DKR reactions by our lab were chosen as a model substrate. Concomitant formation of undesired cross-benzoin products was suppressed by employing the pyroglutamic acid derived triazolium precatalyst **48**, which allowed the highly chemo-, diastereo-, and enantioselective formation of the desired γ -butyrolactones **49**. An array of enals **47** could be employed in the process, but the NHC catalyzed homoenoate addition was sensitive to the steric nature of the nucleophile as *o*-tolylcinnamaldehyde was not a productive reaction partner. However, thiophene-substituted lactone **49d** could be obtained in 84% yield, >30:1 dr, and 99:1 er on 1

g scale. In analogy to the enantioconvergent cross-benzoin addition, the diastereoselectivity of the homoenolate addition reaction is in accord with the Felkin–Anh model.

An important precedent for NHC-catalyzed enantioconvergent reactions described here was provided in the form of the intramolecular tandem aldol/lactonization developed by Scheidt and co-workers (Scheme 13A; also relevant to Section 4).^{14b} Additionally, Wang and co-workers have developed an elegant NHC/Lewis acid catalyzed vinylogous aldol/lactonization reaction (Scheme 13B).^{13f} Finally, Fang recently developed an intramolecular enantioconvergent benzoin reaction (Scheme 13C).^{13h}

3.3. Enantioconvergent Addition of Nonstabilized Nucleophiles: Chiral(diene)rhodium(I)-Catalyzed Arylboronic Acid Addition

The transition metal-catalyzed addition of nonstabilized carbon nucleophiles to ketones recently emerged as a compelling opportunity to generate complex tertiary alcohols inaccessible through other methods. The enantioselective addition of arylboronic acids to carbonyl derivatives, including α -keto esters, has been widely developed.²⁶ Considering their chemical stability, ease of handling and broad commercial availability, we envisioned the deployment of arylboronic acids in an enantioconvergent addition to racemic α -keto ester electrophiles would facilitate the production of stereochemically complex glycolate architectures.¹³ⁱ The β -alkyl, aryl substituted α -keto ester derivatives **50** were chosen as a model substrates for this process (Scheme 14A). Catalyst screening led to the identification of chiral(diene)rhodium(I) complexes **52a** and **52b** as highly selective catalysts for the enantioconvergent arylation reaction. The optimal conditions employed CsF to promote transmetalation, and chloroform as solvent at 40 °C. The presence of an amine base was necessary to achieve high levels of enantioselectivity.

The reaction delivered a diverse array of tertiary arylglycolate products **53a–53i**. A notable example involves addition of 6-indoleboronic acid to an indole substituted α -keto ester, producing bis(indole) derivative **53g** in good yield with high levels of diastereo- and enantiocontrol. Pyridine containing α -keto esters could also be employed in this process, and product **53i** could be obtained in good yield with high levels of enantio- and diastereocontrol. Compact scaffolds containing heterocyclic motifs such as **53g** and **53i** represent interesting targets in the field of medicinal chemistry.²⁷

The observed stereochemistry can be attributed to the C_2 -symmetry of (*R,R*)-catalyst **52b** (and **52a**), which enforces high levels of enantiocontrol by blocking the shaded quadrants in the model shown in Scheme 14B; the bulky sp^3 center is guided to the top left region. In the reaction of the (*S*)-enantiomer, the less sterically demanding hydrogen projects toward the catalyst assembly.

As noted, the presence of a tertiary amine had a bearing on the enantioselectivity. Low levels of selectivity were observed when Hunig's base was employed; however, simply switching to the more compact base triethylamine allowed the formation of the desired product with high levels of enantioselectivity. Subjecting enantioenriched **50a** to the reaction conditions and an array of amine bases revealed that the structure of the basic additive impacted the rate of racemization (Scheme 15). More specifically, less sterically encumbered bases promote

faster racemization. In the presence of Hunig's base, α -keto ester **50a** is enriched after 100 min, while complete racemization is observed within 2 min in the presence of *N*-methylpyrrolidine. The observed trend suggests that the kinetic basicity of the amine additive is more important to racemization rate than minute differences in thermodynamic basicity. These findings have since guided the design of other novel enantioconvergent addition reactions in our laboratory.

4. Non-Hydrogenative Enantioconvergent Transformations Of β -Oxo Carboxylic Acid Derivatives

The use of β -oxo carboxylic acid derivatives in dynamic kinetic reactions is attractive, but the markedly diminished carbonyl electrophilicity represents a considerable challenge. This substrate class is routinely employed in dynamic kinetic hydrogenation reactions, but the use of these compounds in non-hydrogenative enantioconvergent reaction manifolds is rare.^{14b,13h} Nevertheless, 1,2-addition products of β -oxocarboxylate derivatives constitute formal aldol (or Mannich) products of carboxylic acid derived nucleophiles; therefore, non-hydrogenative enantioconvergent reactions of such substrates can facilitate access to structures that are difficult to obtain or altogether unknown in enantioenriched form via alternative direct methods.

Initially, we chose to build upon the findings of Rueping and Wulff who disclosed chiral Brønsted acid-catalyzed asymmetric aminoallylations of aldehydes that proceed via a 2-aza-Cope rearrangement (Scheme 16A).^{28,29} Our attempt to induce rearrangement of the β -formyl ester-derived iminium **55** was unsuccessful due to a strong thermodynamic preference for the inert enamine tautomer **55'**. In contrast, β -formyl amide derived **56a** underwent a facile 3,3-rearrangement to the desired homoallylamine upon its formation *in situ*. The manifestation of A^{1,3} interactions in tautomer **56'** presumably destabilizes this species relative to the analogous ester derivative **55'** resulting in heightened reactivity. Thus, the aminoallylation of β -formylamides **57** in combination with **58** was targeted for the production of homoallyl amines **59**. Among the chiral phosphoric acids tested, (S)-TRIP **60** provided optimal levels of enantioselectivity. The reaction tolerated a number of β -formyl amide substrates (Scheme 17). A variety of benzyl-substituted aldehydes could be transformed to the corresponding amine products, including furan- and thiophene-containing **59d** and **59e**. The alkyl branched products **59f** and **59g** were formed with similar levels of selectivity. An internally substituted allylamine derivative could be used to generate **59i**, albeit with reduced levels of stereocontrol. Finally, in addition to morpholine derived amides, pyrrolidine, piperidine, and dimethylamine derived substrates could also be employed.

5. Summary and Outlook

By capitalizing on the inherent tunability of the basic Ru(II)-sulfonamide framework developed by Noyori, we identified a novel terphenylsulfonamide variant that made possible chemo- and enantioselective reduction of the α -keto ester moiety. This system was applied in the enantioconvergent hydrogenation of a diverse array of α -keto esters as well as related acyl phosphonates. The mechanistic paradigm underlying this chemistry has been extended

by us and others for the generation of higher molecular complexity by means of enantioconvergent carbon-centered nucleophile additions to carbonyl derivatives as well as processes that furnish up to three chiral centers in one step. The advancement of this chemistry should occur in tandem with the remarkable advancements that are occurring in the realm of asymmetric 1,2-addition chemistry. The continued exploration of these chemistries in the context of less conventional electrophiles as well as identifying novel or overlooked modes of racemization holds considerable potential for the generation of novel, stereo-chemically complex molecular architectures.

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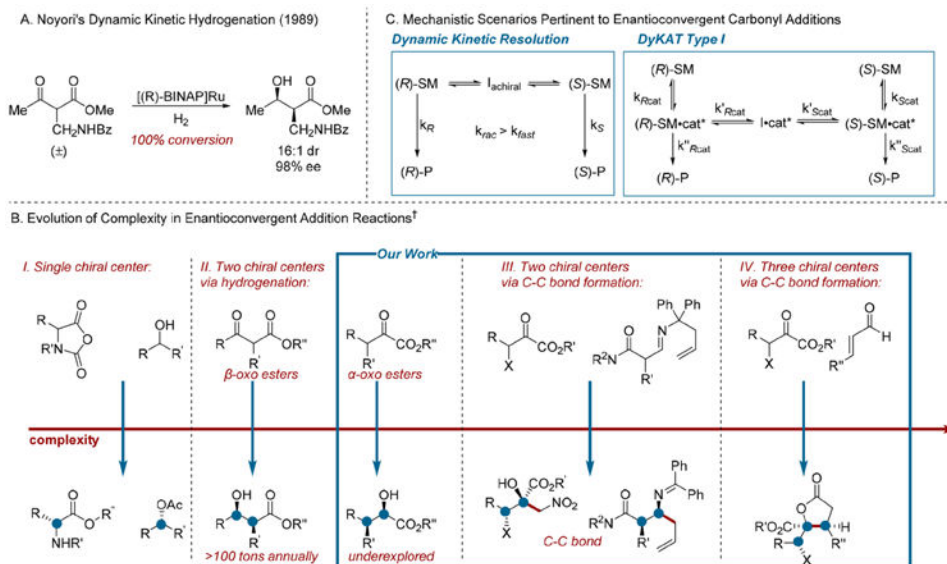
Abbreviations

DKR	dynamic kinetic resolution
ATH	asymmetric transfer hydrogenation
DyKAT	dynamic kinetic asymmetric transformation
Ts	tolylsulfonyl
DPEN	diphenylethylenediamine

Biographies

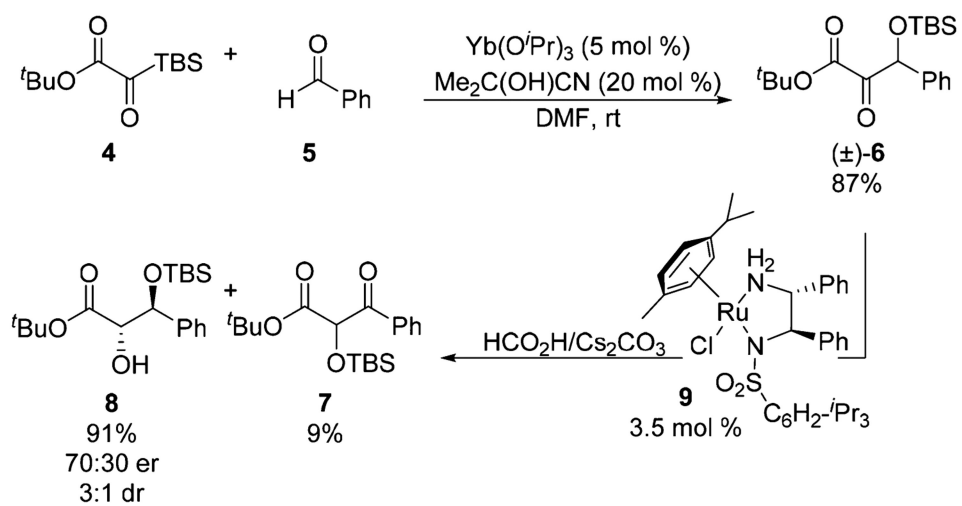
Samuel L. Bartlett received his B.S. in chemistry from Oregon State University in 2012 where he conducted research with Prof. Chris Beaudry. He is currently a fifth year Ph.D. candidate in the laboratory of Prof. Jeffrey Johnson. During his doctoral studies, he has also been an NSF EAPSI Fellow with Prof. Mikiko Sodeoka at RIKEN in Japan.

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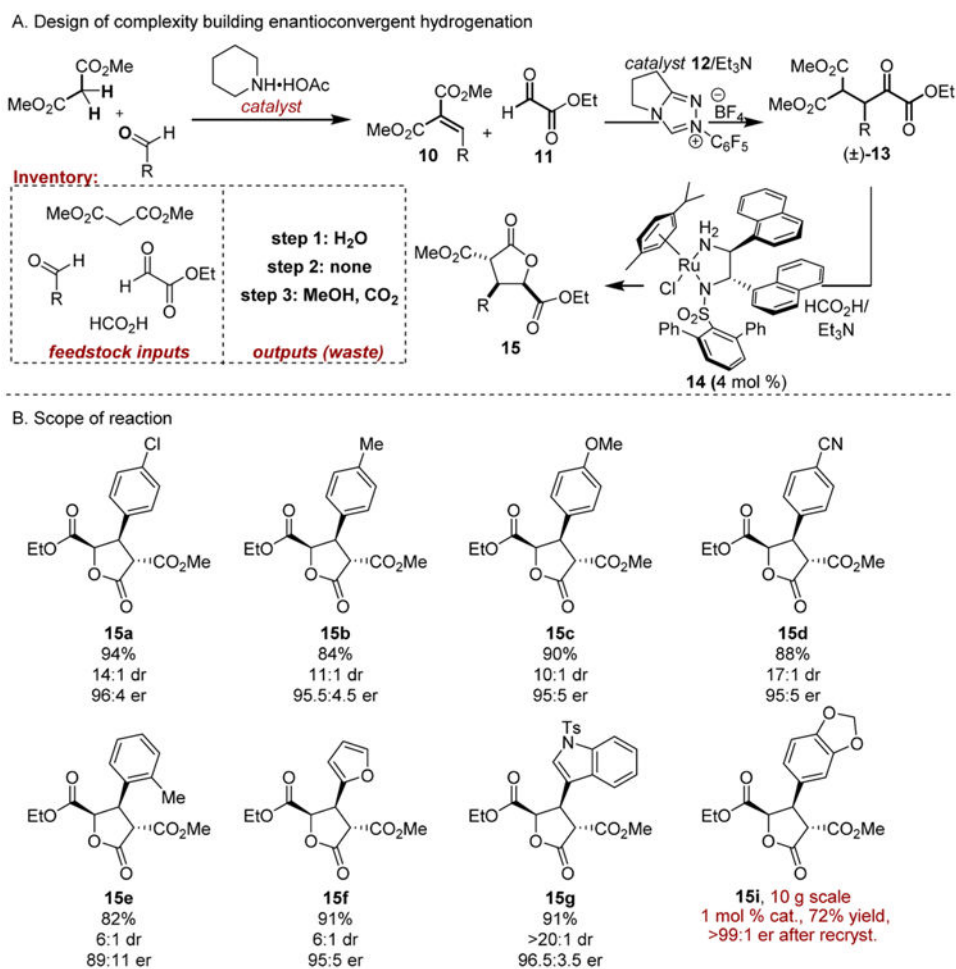


Scheme 1. Enantioconvergent Reactions of Carbonyl Compounds

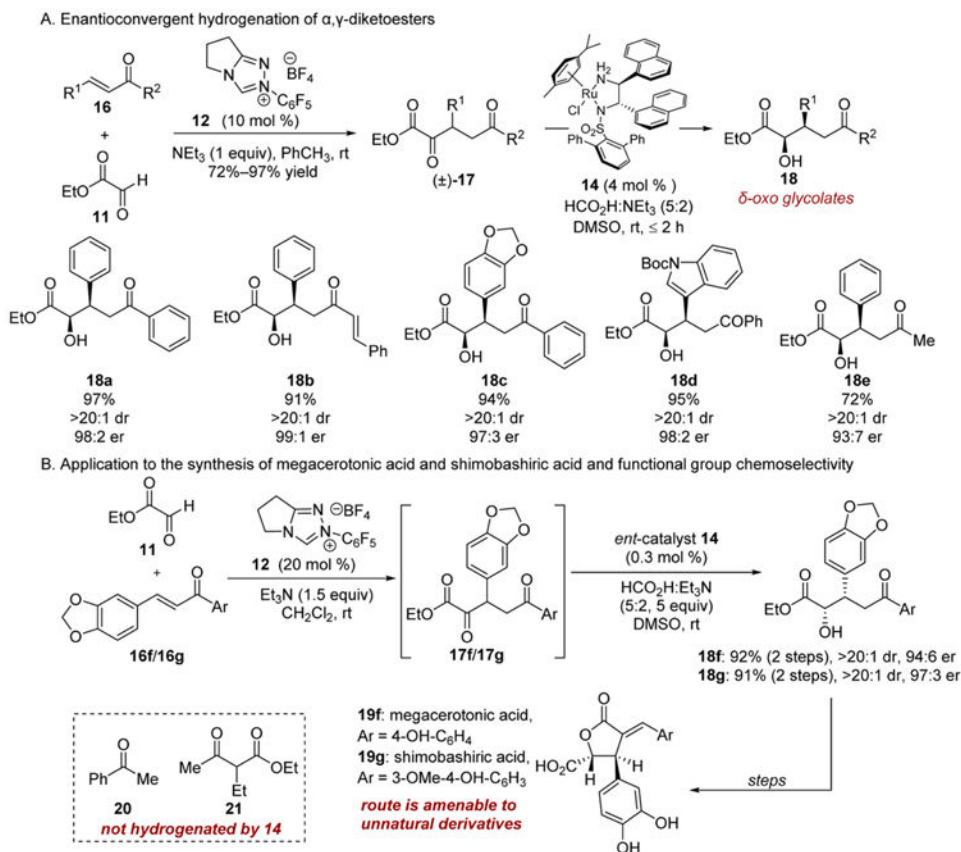
[†]All transformations shown employ racemic starting materials.

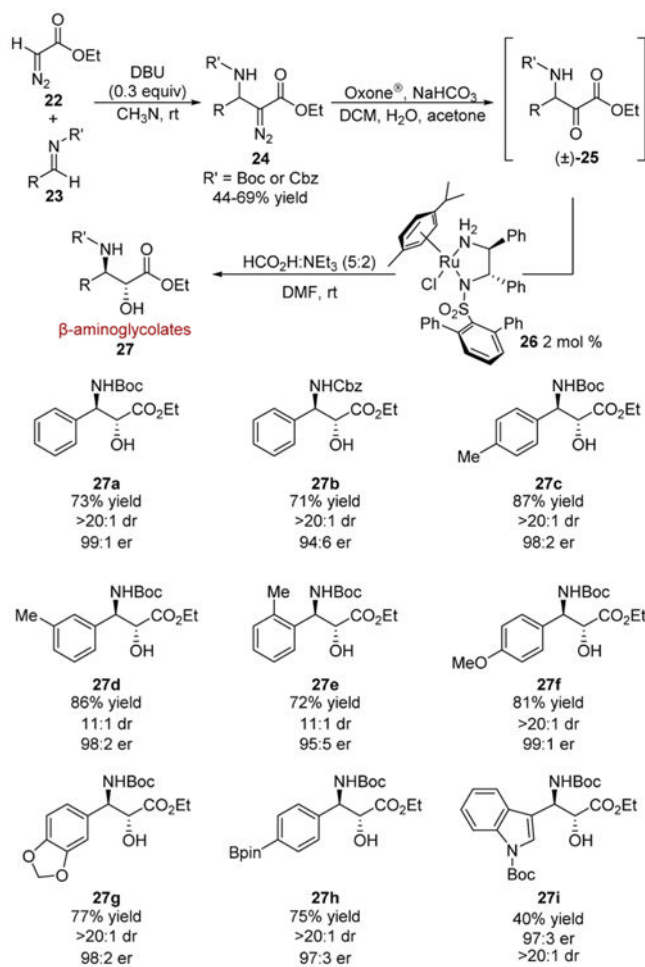


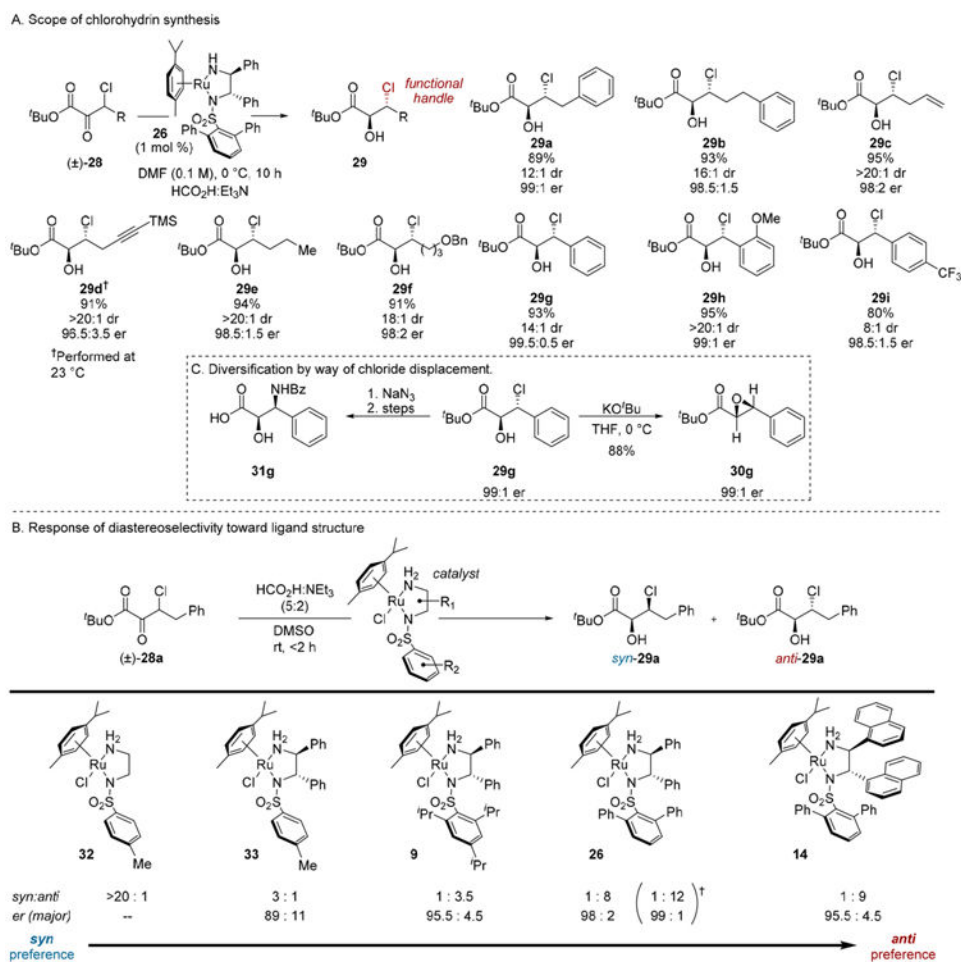
Scheme 2. Initial Findings



Scheme 3. Complexity Generating Enantioconvergent Hydrogenation

Scheme 4. Chemoselective Transfer Hydrogenation DKRs of α -Keto Esters

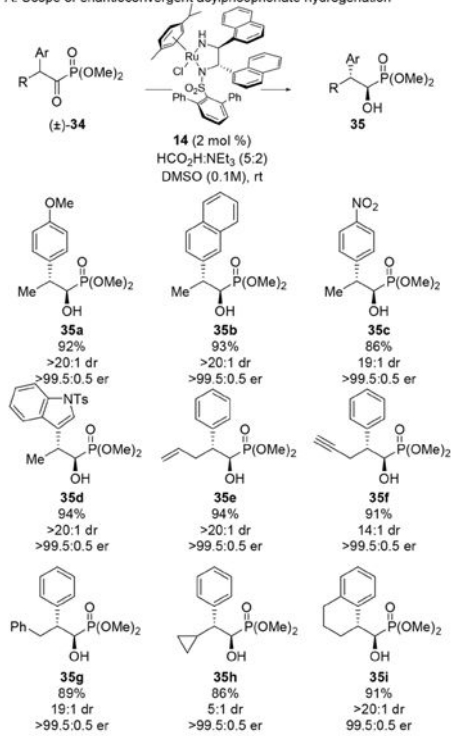
Scheme 5. Enantioconvergent Hydrogenation of β -Amino- α -keto Esters



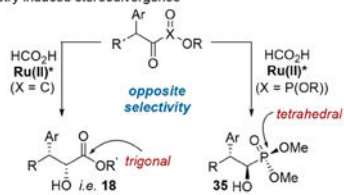
Scheme 6. Enantioconvergent Hydrogenation of β -Chloro- α -keto Esters

[†]Experiment conducted in DMF at $0\text{ }^\circ\text{C}$ for 10 h.

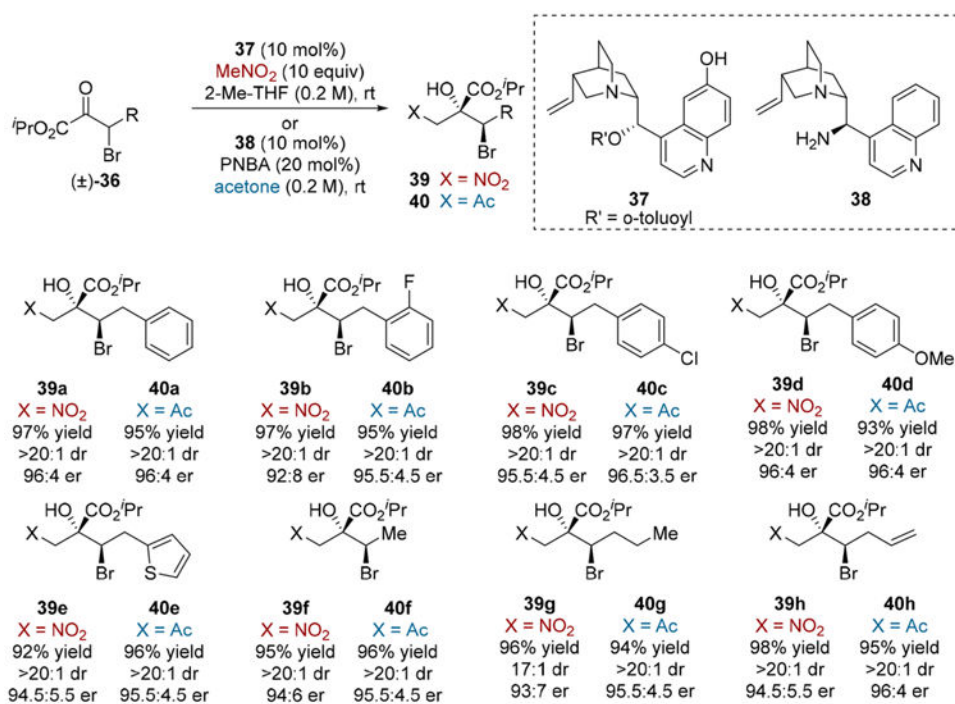
A. Scope of enantioconvergent acylphosphonate hydrogenation



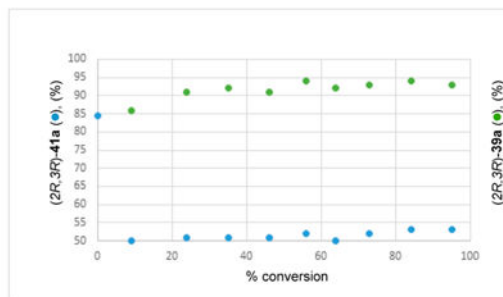
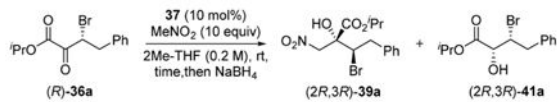
B. Geometry induced stereodivergence



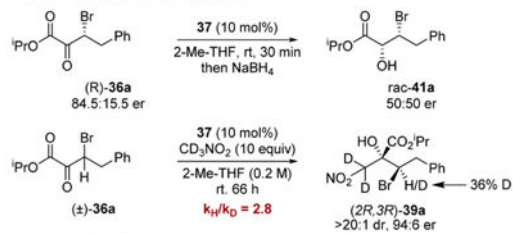
Scheme 7. Enantioconvergent Hydrogenation of Acylphosphonates

Scheme 8. Enantioconvergent Aldol Reaction of β -Bromo- α -keto Esters

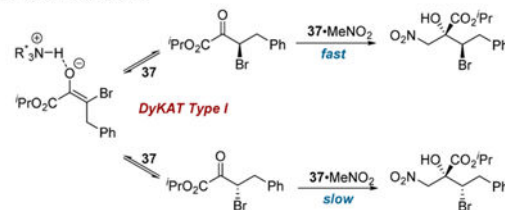
A. In-situ monitoring of enantiomeric composition



B. Racemization and deuterium labeling studies

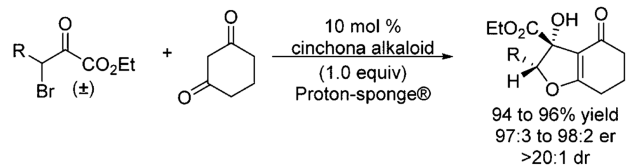


C. Mechanistic proposal

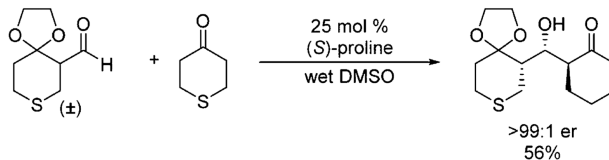
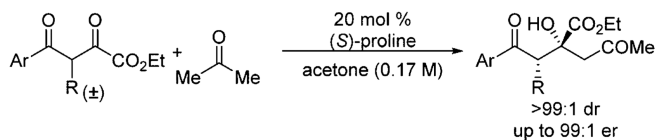


Scheme 9. Mechanistic Studies of Enantioconvergent Henry Addition

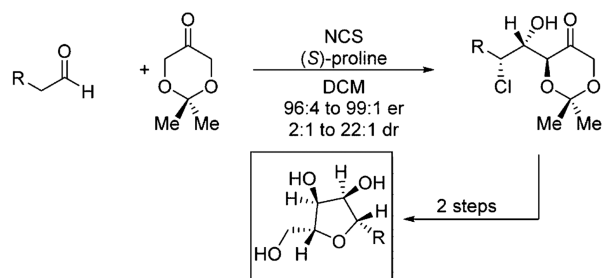
A. Calter's interrupted Feist-Bénary reaction

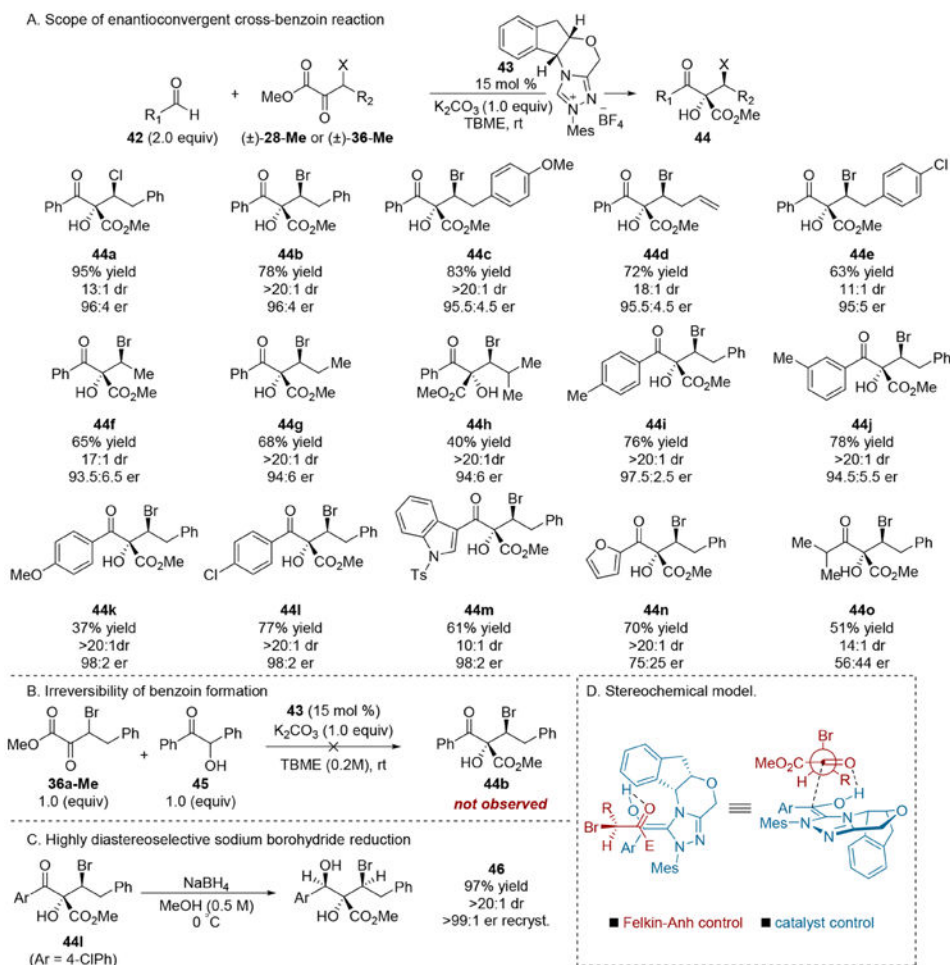


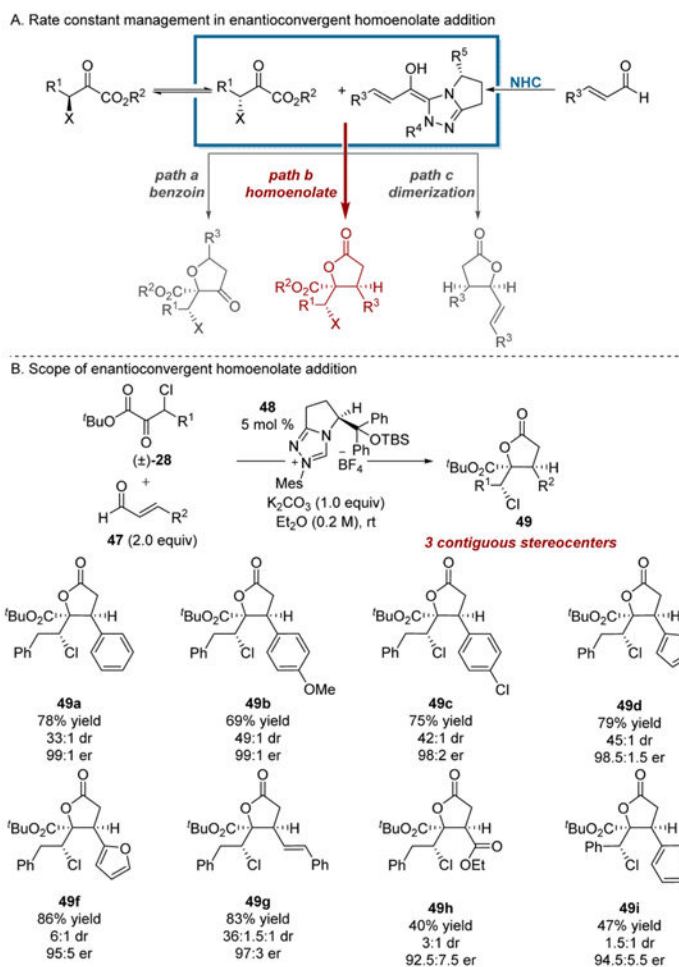
B. Ward's aldol addition to racemic cycloaldehydes

C. Zhang's acetone aldol of β -diketones

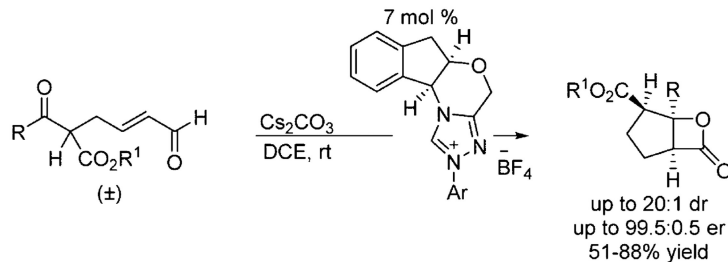
D. Britton's tandem chlorination enantioconvergent aldol of aldehydes

Scheme 10. Other Aminocatalyzed Aldol-Type Reactions of α -Keto Esters

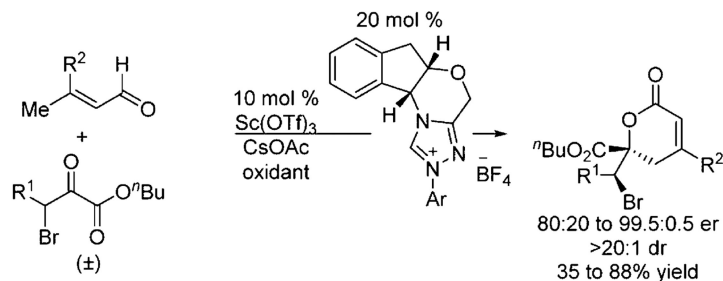
Scheme 11. Enantioconvergent Cross-Benzoin Reaction of β -Halo- α -keto Esters

Scheme 12. Enantioconvergent Homo enolate Addition to β -Chloro- α -keto Esters

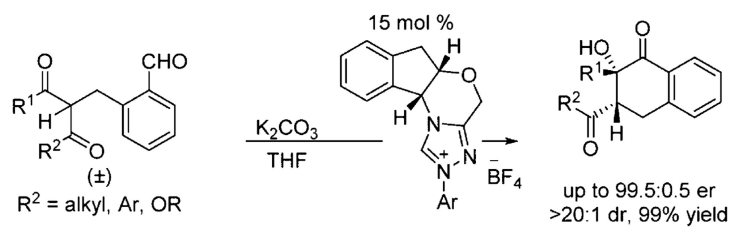
A. Scheidt's enantioconvergent NHC-catalyzed aldol/lactonization



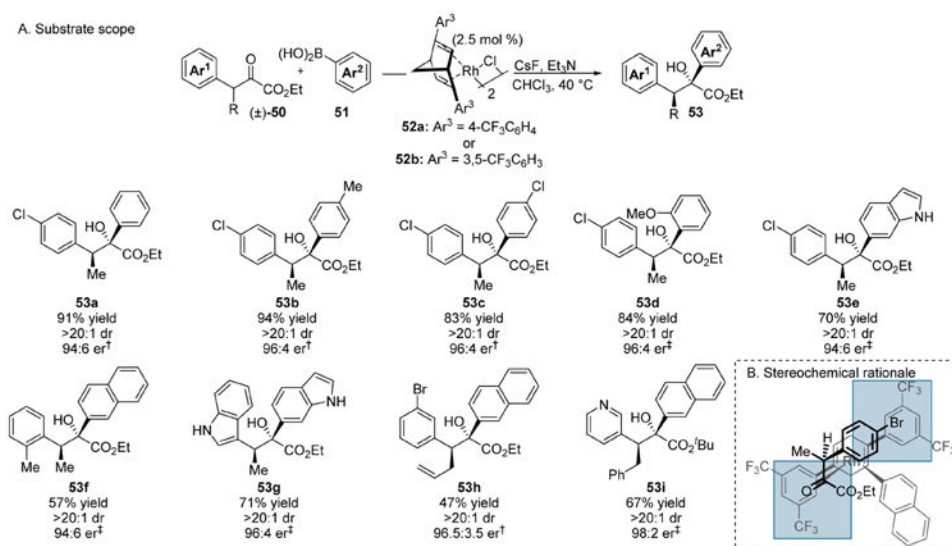
B. Wang's NHC/Lewis acid co-catalyzed vinylogous aldol/lactonization



C. Fang's enantioconvergent intramolecular benzoin reaction

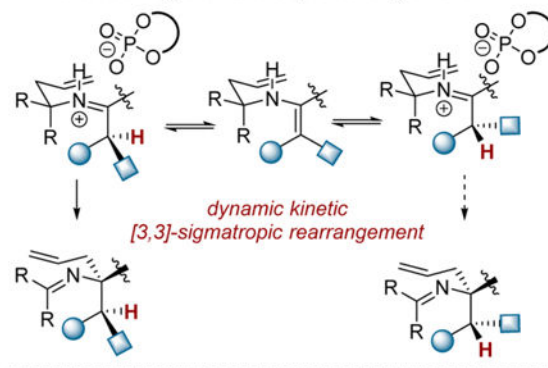


Scheme 13. Other NHC-Catalyzed Enantioconvergent Additions

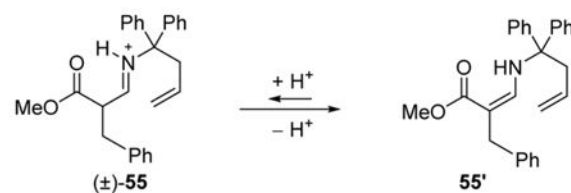


Scheme 14. Enantioconvergent Arylation of β -Alkyl- α -keto Esters
[†]52a was used as the catalyst. [‡]52b was used as the catalyst.

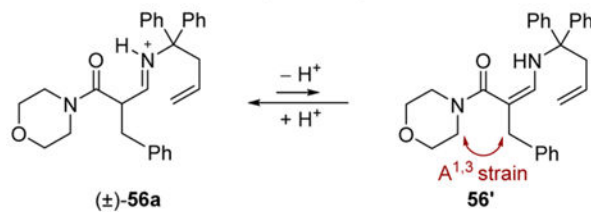
A. Enantioconvergent 2-aza-Cope rearrangement

B. Divergent reactivity of β -oxo esters and β -oxo amides

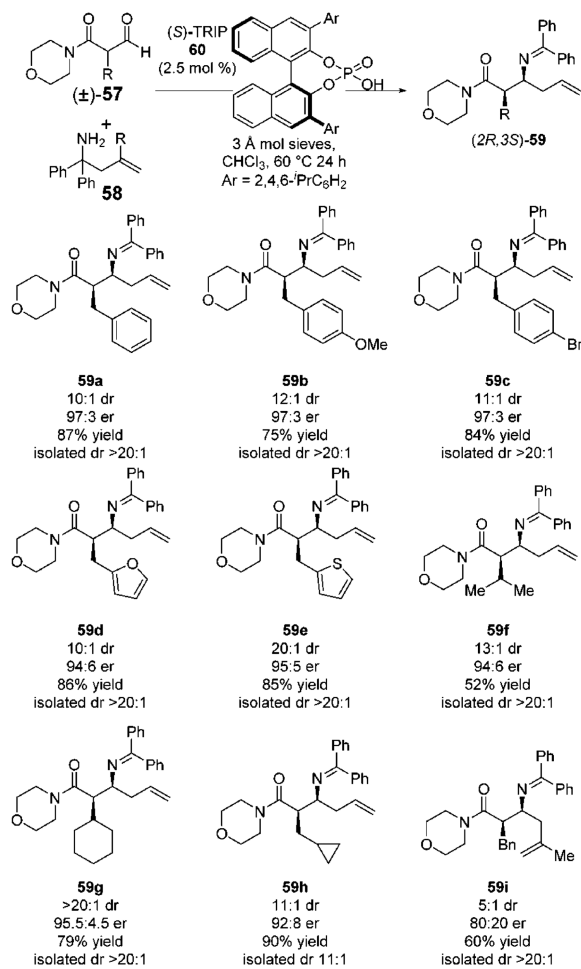
■ *enamine is too stable; low reactivity*



■ *enamine destabilized; high reactivity*



Scheme 16. Design of Enantioconvergent 2-Aza-Cope Rearrangement



Scheme 17. Scope of 2-Aza-Cope Rearrangement