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COMMUNICATION

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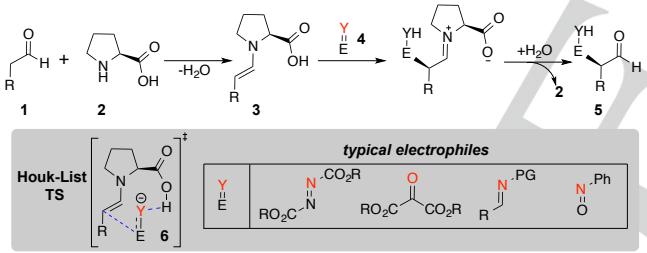
A Designed Approach to Enantiodivergent Enamine Catalysis

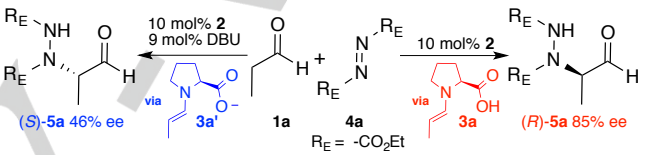
Juliet Macharia,[a] Victor Wambua,[a] † Yun Hong,[a] † Lawrence Harris,[b] † Jennifer S. Hirschi,[a] Gary B. Evans, [b] and Mathew J. Vetticatt* [a]

Abstract: *The rational design and implementation of enantiodivergent enamine catalysis is reported. A simple secondary amine catalyst, 2-methyl-L-proline, and its tetrabutylammonium salt function as an enantiodivergent catalyst pair delivering opposite enantiomers of α-functionalized aldehyde products in excellent enantioselectivities. This novel concept of 'designed enantiodivergence' is applied to the enantioselective α-amination, aldol and α-aminoxylation/α-hydroxyamination reactions of aldehydes.*

The central paradigm in asymmetric catalysis dictates that either enantiomer of a chiral catalyst/ligand can be utilized to gain selective access to either antipode of the desired chiral product. An obstacle in asymmetric synthesis is that many of these optically active catalysts are obtained from 'chiral pool' molecules such as alkaloids, amino acids, sugars, terpenes, etc. that are readily available as only one enantiomer.[1] Access to the other enantiomer is often quite difficult and sometimes requires lengthy synthetic sequences. An attractive solution to this well-known limitation of asymmetric catalysis is the concept of enantiodivergent catalysis – an approach that utilizes *a single enantiomer of a chiral catalyst/ligand to gain selective access to both enantiomers of the chiral product.* Isolated examples have garnered significant attention;[2] however, a 'designed' approach to enantiodivergent catalysis is an unaddressed goal.



The field of asymmetric organocatalysis – catalysis by small organic molecules – has witnessed explosive growth in the past two decades and is currently one of the main branches of enantioselective synthesis.[3] Organocatalytic reactions are classified based on 'activation modes' i.e. the mechanism of activation of the reacting substrate.[4] One of these activation modes – enamine catalysis – effects the enantioselective α-functionalization of carbonyls. In this mode of catalysis a simple chiral organocatalyst such as L-proline (**2**) reacts with an aldehdye (**1**) to form a transient enamine carboxylic acid intermediate (**3**), which can react with a variety of electrophiles (**4**) in a series of mechanistically related reactions to deliver an array of enantioenriched α-functionalized aldehydes (**5**). Each one of these reactions proceed via a key stereodetermining transition state (TS) – known as the Houk-List TS (**6**) – where the carboxylic acid proton directs the approach of **4** to one face of the prochiral enamine via hydrogen (H)-bonding interactions.[5]



We envisioned that the rational design of an enantiodivergent reaction within a particular activation mode (such as enamine catalysis) could lead to a diverse array of mechanistically related enantiodivergent chemistries – a valuable addition to the rich toolbox of enantioselective synthesis – and provide "proof-of-principle" for the logical development of enantiodivergent catalysis. The basis for our work was a 2010 study by Blackmond and Armstrong, which reports an unusual reversal of enantioselectivity in the α-amination reaction of propanal (**1a**) and diethylazodicarboxylate (**4a**, R_E=CO_2Et) in dichloromethane.[6] Utilizing 10 mol% of **2** as catalyst, 85% ee of the *R*-product **5a** was obtained. Addition of 9 mol% of a tertiary amine base, such as diazobicycloundecane (DBU), to the reaction mixture results in an unexpected reversal in facial selectivity, now delivering the (*S*)-product **5a** in 46% ee. In a series of follow-up kinetic and NMR studies, Blackmond and Armstrong established that the key intermediate in the reaction involving DBU additive is a prolinate species – enamine carboxylate **3a´**.[7] Sunoj and co-workers used density functional theory (DFT) calculations to show that (*S*)-**5a** is the favored product when prolinate **3a´** is the key intermediate in the catalytic cycle.[8] However, this study did not address the origin of this reversed selectivity in prolinate catalysis compared to proline catalysis.

The origin of enantioselective formation of (*R*)-**5a** in proline catalysis is well understood based on the Houk-List TS model. A detailed transition state analysis of the origin of modest enantiodivergence (46% ee of (*S*)-**5a**) in the Blackmond prolinate reaction is the first step in our enantiodivergent catalyst design strategy. This analysis will provide design principles for a prolinate derivative that catalyzes a highly (*S*)-selective reaction. Based on the mechanism for proline catalysis, the protonated analogue of this 'designed' catalyst will mediate the (*R*)-selective reaction via a TS similar to **6**. Thus, TS analysis will lead to a truly enantiodivergent catalyst – defined here as a single

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enantiomer of chiral catalyst that delivers >90% ee for both enantiomeric products. We report herein, the rational design of a simple L-proline derivative that catalyzes the perfectly enantiodivergent α-amination reaction of aldehydes. From this "proof-of-principle" example, we extend this approach to other reactions within the enamine catalysis framework.

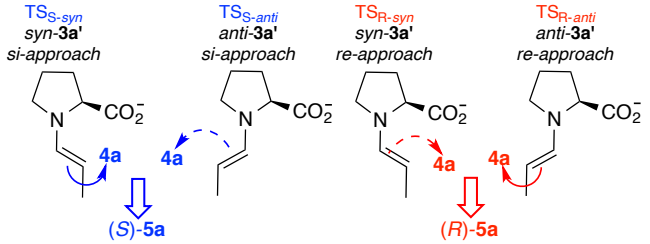


Figure 1. TS analysis of the prolinate catalyzed α-amination reaction of propanal (**1a**) and diethylazodicarboxylate (**4a**, R_E= CO_2Et)

Transition structures for the approach of **4a** to the *re*- and *si*-face of *anti*-**3a´** and *syn*-**3a´** (Figure 1) were identified using B3LYP/6-31+G** calculations with a polarizable continuum model (PCM) for dichloromethane as implemented by Gaussian 09.[9,10,11] Approach of **4a** from the same face as the carboxylate – *re*-face of *anti*-**3a´** ($TS_{R\text{-}anti}$) and *si*-face of *syn*-**3a´** ($TS_{S\text{-}syn}$) – is disfavored due to repulsive electrostatic interactions between the carboxylate and the developing negative charge on **4a** during carbon-carbon bond formation. This unfavorable approach is highlighted by the obvious proximity of the areas of increased electron density (red) in the electrostatic potential map of $TS_{R\text{-}anti}$ (Figure 2). Consistent with the Sunoj study,[8] the lowest energy structures leading to the two enantiomers of product result from the approach of **4a** from the face opposite to the carboxylate moiety. The electrostatic potential map for $TS_{S\text{-}anti}$, the lowest energy transition structure, involves approach of **4a** to the *si*-face of *anti*-**3a´** and exhibits areas of increased electron density on opposite sides of the pyrrolidine ring – minimizing the electrostatic repulsion between areas of increased electron density (Figure 2). The modest enantioselectivity observed in this reaction is attributable to the 0.9 kcal/mol energy difference between $TS_{S\text{-}anti}$ and $TS_{R\text{-}syn}$ (Figure 3). This energy difference corresponds to a predicted ee of 63% for (*S*)-**5a**, which is in reasonable agreement with the experimental 46% ee (*S*).

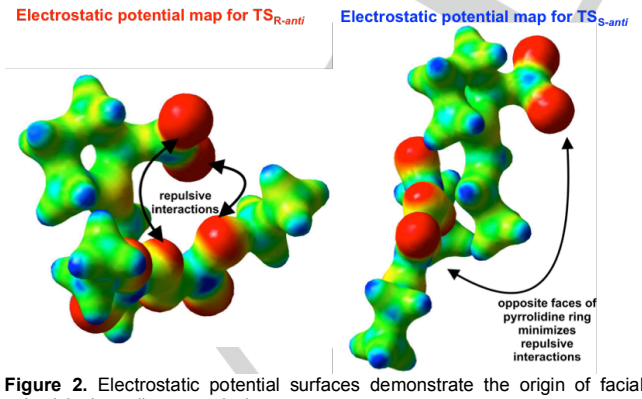
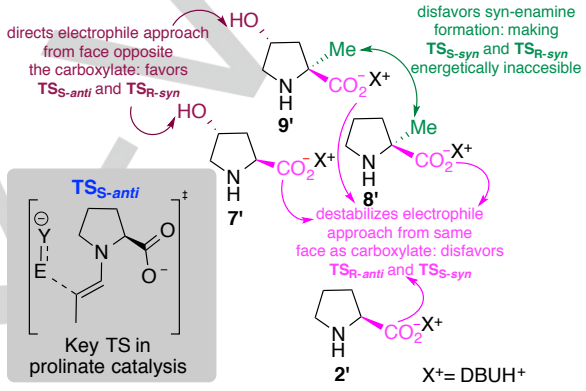


Figure 2. Electrostatic potential surfaces demonstrate the origin of facial selectivity in prolinate catalysis

This transition state analysis provides vital clues for the design of a *prolinate* catalyst that will deliver high enantioselectivity for (*S*)-**5a**. The first strategy involves incorporation of an H-bond donor, such as a hydroxyl group, at C-4 of L-prolinate and *trans* to the carboxylate. This prolinate catalyst (**7´**, Figure 3) is easily generated from commercially available 4-*trans*-hydroxy L-proline (**7**) and a base. The hypothesis is that while the carboxylate moiety of **7´** destabilizes 'front attack' of the electrophile ($TS_{R\text{-}anti}$ and $TS_{S\text{-}syn}$), the potential of the 4-hydroxyl group to form a stronger H-bond in $TS_{S\text{-}anti}$ compared to $TS_{R\text{-}syn}$ (since **4a** can H-bond better to the hydroxyl group while approaching the *anti* enamine due to proximity) will lead to increased selectivity for (*S*)-**5a**.[12] Accordingly, transition structures analogous to those shown in Figure 1 were located using **7´** as the catalyst. Consistent with our hypothesis the energy difference between $TS_{S\text{-}anti}$ and $TS_{R\text{-}syn}$ increased from 0.9 kcal/mol (**2´** as catalyst) to 1.4 kcal/mol (**7´** as catalyst), leading to an increase in the predicted selectivity from 63% ee to 78% ee (*S*) (Figure 3).



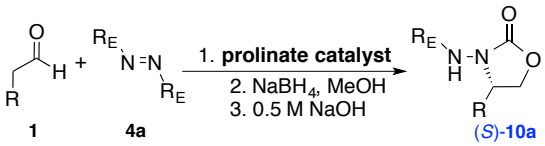
catalyst	*Relative E+zpe in kcal/mol*				predicted ee (%)
	$TS_{S\text{-}syn}$	$TS_{S\text{-}anti}$	$TS_{R\text{-}syn}$	$TS_{R\text{-}anti}$	
2'	5.8	**0.0**	**0.9**	3.4	63 (*S*)
7'	12.7	**0.0**	**1.4**	7.6	78 (*S*)
8'	11.2	**0.0**	5.2	**2.1**	95 (*S*)
9'	11.6	**0.0**	5.3	**3.3**	99 (*S*)

Figure 3. Catalyst design considerations for highly enantioselective prolinate catalysis. Bolded and underlined values represent energies of lowest energy transition structures for each enantiomer. Transition structures modeled without counterion using E-Y = **4a** (R_E = -CO_2Et)

The second strategy to obtain high selectivity for (*S*)-**5a** involves a prolinate catalyst with an additional substituent at the 2-position, 2-methyl-L-prolinate (**8´**). We predicted the second substituent at the 2-position would essentially shut down the formation of the *syn*-enamine pathway (due to unfavorable steric interactions) thereby destabilizing $TS_{R\text{-}syn}$ and $TS_{S\text{-}syn}$ (Figure 3). The enantioselectivity will then result from a competition between $TS_{S\text{-}anti}$ and $TS_{R\text{-}anti}$. Since the carboxylate moiety of **8´** destabilizes $TS_{R\text{-}anti}$ (vide supra), $TS_{S\text{-}anti}$ becomes the dominant pathway using this catalyst. Consistent with this hypothesis, transition structures located using **8´** as catalyst reveal a 2.1 kcal/mol difference in energy between $TS_{S\text{-}anti}$ and $TS_{R\text{-}anti}$, leading to a prediction of 95% ee for (*S*)-**5a**. Also consistent with our proposal, the transition structures involving *syn*-**3a´** are energetically inaccessible using **8´** as catalyst (Figure 3). The third and final strategy involves a combination of the above two described approaches i.e. the use of 4-hydroxy-2-methyl-L-prolinate (**9´**) as a catalyst for the highly selective formation of (*S*)-**5a**. With the carboxylate group destabilizing approach of **4a** from the 'front side', the 2-methyl group virtually eliminating both *syn* transition states, and the 4-trans-hydroxy group stabilizing

4a via H-bonding, the only viable transition state using **9´** as catalyst should be **TS**$_{S\text{-}anti}$. This hypothesis is confirmed by our calculations, which predict a 3.3 kcal/mol energy difference between **TS**$_{S\text{-}anti}$ and **TS**$_{R\text{-}anti}$, a predicted 99% ee for (*S*)-**5a** (Figure 3).

Table 1. Optimization of enantioselective prolinate catalysis



1 **4a** (*S*)-**10a**

R = Bn R_E = -CO_2Et

entry	catalyst[a]	yield[b] (%)	ee[c] (%)
1	**2'**[X=DBUH]	58	27 (*S*)
2	**7'**[X=DBUH]	59	54 (*S*)
3	**8'**[X=DBUH]	61	84 (*S*)
4	**8'**[X=N(Me)$_4$]	51	80 (*S*)
5	**8'**[X=P(Ph)$_3$Et]	61	94 (*S*)
6	**8'**[X=N(Bu)$_4$]	60	93 (*S*)
7	**8'**[X=N(Bu)$_4$] @(-20°C)	64	94 (*S*)
8	**8'**[X=N(Bu)$_4$] (3 mol%)	53	93 (*S*)
9	**8'**[X=N(Bu)$_4$] (10 mol% AcOH additive)	61	92 (*S*)
10	**8** + 10 mol% [N(Bu)$_4$]$^+$[OAc]$^-$	60	75 (*S*)
11	**9'**[X=N(Bu)$_4$]	51	96 (*S*)

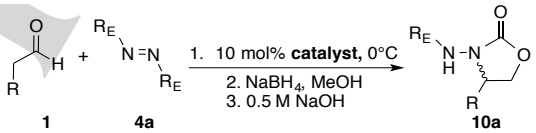
[a] 10 mol% catalyst at 0°C unless otherwise noted [b] isolated yield of derivatized product **10a** [c] determined by chiral HPLC using Chiralcel AD-H column

We then tested our computational predictions using the prolinate-catalyzed α-amination of 3-phenylpropanal (**1**, R=Bn) and diethylazodicarboxylate (**4a**, R_E = CO_2Et) as a model reaction (Table 1). The computational trend is qualitatively reproduced with an experimentally observed increase in ee for (*S*)-**5a** upon going from **2´** to **7´** to **8´** (Table 1, entries 1-3), when 10 mol% of catalyst is used as a pre-formed DBU salt in reactions performed at 0°C in dichloromethane. The 84% ee obtained using 2-methyl-L-prolinate (**8´, [**X=DBUH]) is the highest reported enantioselectivity to date, for this reaction, using a prolinate catalyst. We proceeded to explore the effect of varying the counter-ion of **8´**. While the tetramethylammonium salt of **8´** gives slightly reduced ee (entry 4), the tetrabutylammonium and ethyltriphenylphosphonium salts of **8´** give 93 and 94% ee for (*S*)-**5a** (entries 5-6). Based on these results and considering the cost and ease of preparation, we chose **8´[**X=N(Bu)$_4$] as the catalyst of choice for further optimization of reaction conditions. Lowering the temperature to -20° C leads to a minimal increase in yield and enantioselectivity. Lowering the catalyst loading to 3 mol% results in slightly diminished yields but identical enantioselectivity. Addition of 10 mol% acetic acid as additive gives almost identical results compared to entry 6; however, the reaction is complete in 10 minutes as compared to the 0.5 h for entry 6. In-situ generation of the prolinate salt **8´**[X=N(Bu)$_4$] by using 10 mol% each of **8** and tetrabutylammonium acetate resulted in similar yield but slightly diminished enantioselectivity (entry 10). Finally, consistent with our theoretical predictions, catalyst **9´**[X=N(Bu)$_4$] gives the highest ee (entry 11). However, the protonated analogue (**9**) produces only 30% ee and sluggish reaction rates for the formation of (*R*)-**5a**.[13] We therefore proceeded with **8**/**8´**[X=N(Bu)$_4$] as the catalyst pair of choice to examine the substrate scope of our newly discovered enantiodivergent chemistry.

To establish the substrate scope, we performed the α-amination of five distinct aldehyde-alkyl diazodicarboxylate pairs using the 2-methyl-L-proline/2-methyl-L-prolinate (**8**/**8´**[X=N(Bu)$_4$]) catalyst pair. Using dibenzylazodicarboxylate (**4a**, R_E = CO_2Bn) as the electrophile, reactions were performed using propanal, isovaleraldehyde and 3-phenylpropanal (Tables 2, entries 1-3 & 6-8). Diisopropyl and diethyl azodicarboxylates were then tested as electrophiles for the reaction with 3-phenylpropanal as the aldehyde (Table 2, entries 4-5 & 9-10). In reactions utilizing **8** as the catalyst, good isolated yields of (*R*)-**10a** were obtained in >90% ee for each of the reactant pairs, while for reactions utilizing **8´** X=N(Bu)$_4$ as catalyst, >90% ee for (*S*)-**10a** were obtained in good yields for all except one substrate pair (entry 7).[14] *Comparison of entries 1-5 to entries 6-10 establish that catalyst pair **8**/**8´**[X=N(Bu)$_4$] functions as near-perfect enantiodivergent catalysts for the α-amination reaction for all tested reactant pairs*.

Next, we sought to establish the generality of 'designed enantiodivergence' using the enantiodivergent catalyst pair **8**/**8´** to test another reaction within the enamine catalysis framework. In 2002, Jorgensen and co-workers reported the L-proline catalyzed reaction between propanal (**1**, R=Me) and diethylketomalonate (**4b**), giving high yields and enantioselectivities of the aldol product (*S*)-**5b**.[15] We performed this reaction using both **8** and **8´**[X=N(Bu)$_4$] as catalyst in dichloromethane. Reactions employing **8** as catalyst result in 82% yield and 93% ee for (*S*)-**5b** and the switch to **8´**[X=N(Bu)$_4$] results in a complete reversal in enantioselectivity, giving 84% yield and 82 % ee for (*R*)-**5b** (Figure 4a). This result suggests that this novel approach to 'designed' enantiodivergence has potentially broad scope in proline-enamine catalysis.

Table 2. Scope of enantiodivergent α-amination reaction



1 **4a** **10a**

entry	R	R_E	time (h)	yield[a] (%)	ee (%)
catalyst = **8**, CH_2Cl_2					
1	Me	CO_2Bn	20	62	94[c] (*R*)
2	i-Pr	CO_2Bn	21	64	96[c] (*R*)
3	Bn	CO_2Bn	16	69	92[b] (*R*)
4	Bn	CO_2*i*Pr	20	63	92[b] (*R*)
5	Bn	CO_2Et	23	63	93[b] (*R*)
catalyst = **8'** [X = N(Bu)$_4$], $CHCl_3$					
6	Me	CO_2Bn	1	70 (88)	91[c] (*S*)
7	i-Pr	CO_2Bn	0.75	66 (81)	85[c] (*S*)
8	Bn	CO_2Bn	1	68 (83)	91[b] (*S*)
9	Bn	CO_2*i*Pr	1	59	96[b] (*S*)
10	Bn	CO_2Et	0.5	68	92[b] (*S*)

[a] isolated yield of derivitized product **10a**; yields in parenthesis are isolated yield of $NaBH_4$ reduced **5a.** ee determined by chiral HPLC using [b]Chiralcel AD-H column or [c]Chiralcel OD-H column.

Finally, we tested the reaction of propanal (**1**, R=Me) with the ambident electrophile nitrosotoluene (**4c**, Ar=2-tolyl). Proline and other enamine catalysts possessing an acidic functionality typically give α-aminoxylation product (**5c** from *O*-addition).[16] On the other hand, enamine catalysts lacking an acidic functional group deliver the α-hydroxyamination product (**5c´** from *N*-addition).[17] Based on these observations in the literature we speculated that in the reaction of **1** and **4c**, the catalyst pair **8**/**8´** would not only switch the facial selectivity of α-addition of **4c** but also the chemoselectivity. The rationale is that since **8** possesses a carboxylic acid proton it will facilitate *O*-attack and since **8´** lacks this acidic functional group, *N*-addition will result.

Consistent with our assumption, catalyst **8** gives 66% yield and 99% ee of (*R*)-aminoxylation product (**5c**, Ar=2-tolyl) as the exclusive product; while catalyst **8´**[X=N(Bu)$_4$] gives a 64% yield and 98% ee for enantio- and chemodivergent (*S*)-hydroxyamination product (**5c´**, Ar=2-tolyl) as the exclusive product (Figure 4b). Though chemodivergence has previously been achieved for this reaction using the Hayashi/Jørgensen catalyst (in the presence and absence of external acid additive),[16c,17b] this is the first example where both enantio- and chemodivergence is simultaneously achieved using a single chiral catalyst.

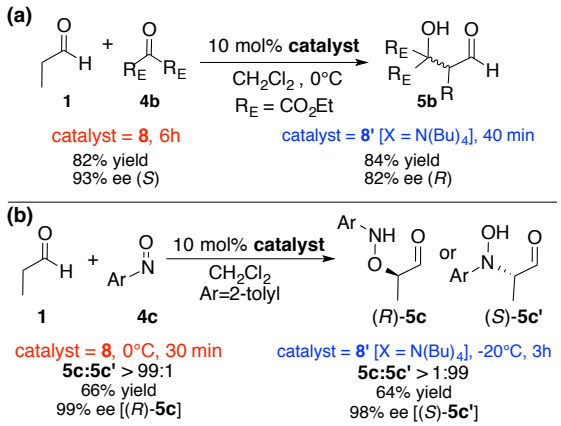


Figure 4. Prototypical examples of an (a) enantiodivergent aldol reaction of diethylketomalonate with propanal and (b) enantio- and chemodivergent addition of nitrosotoluene to propanal

In conclusion, we have developed a robust catalyst system that delivers enantiodivergent products in a series of α-functionalization reactions of aldehydes. Rational design and execution of such enantiodivergent methodologies is unprecedented. We believe that this transition state analysis-based approach can be extrapolated to other 'activation modes' within asymmetric organocatalysis and other areas of enantioselective catalysis. This approach will be of particular importance in reactions where both enantiomers of the chiral catalyst are not readily available.

Keywords: organocatalysis • enantiodivergence • prolinate catalysis • rational design • asymmetric catalysis

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[13] We believe that the catalyst **9** forms a stable product iminium carboxylate by intramolecular H-bonding with the *trans*-hydroxyl proton leading to slow hydrolysis and product release. This likely leads to epimerization and erosion of enantioselectivity. Increasing the concentration of propanal and/or addition of acetic acid additive resulted in an increase in ee to 65%.

[14] The α-amination product **5a** is derivatized to **10a** for ease of HPLC analysis, but if the derivitization is stopped at the stage of the product alcohol, excellent isolated yields are obtained (yields for product alcohol shown in parenthesis for entries 6-8 in Table 2).

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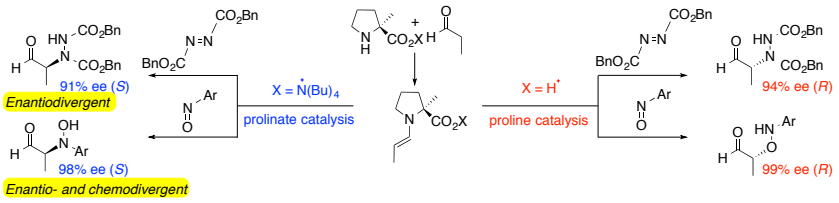

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A Designed Approach to Enantiodivergent Enamine Catalysis

The rational design and implementation of enantiodivergent enamine catalysis is reported. A simple secondary amine catalyst, 2-methyl-L-proline, and its tetrabutylammonium salt function as an enantiodivergent catalyst pair delivering opposite enantiomers of α-functionalized aldehyde products in excellent enantioselectivities. This novel concept of 'designed enantiodivergence' is applied to the enantioselective α-amination, aldol and α-aminoxylation/α-hydroxyamination reactions of aldehydes.