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Achiral Co-Catalyst Induced Switches in Catalytic Asymmetric Reactions on Racemic Mixtures (RRM): From Stereodivergent RRM to Stereoconvergent Deracemization by Combination of Hydrogen Bond Donating and Chiral Amine Catalysts

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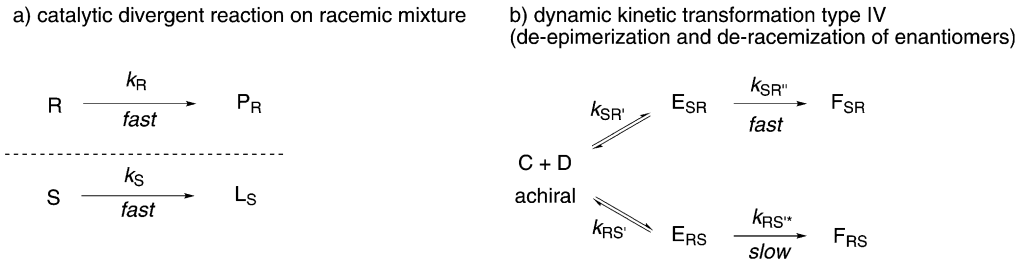
Abstract: A stereochemical divergent approach for the highly enantioselective synthesis of distinct bicyclic products with multiple stereocenters from a racemate using a single chiral catalyst is disclosed. It is based on switches of the overall reaction pathways in the chiral amine-catalyzed cascade reactions between racemic γ-nitro ketones and α,β-unsaturated aldehydes using different achiral co-catalysts. The utility of the method is exemplified by the highly diasteroselective switch and stereoconvergent deracemization process by combination of chiral amine and achiral hydrogen-bond-donating catalysts.

Keywords: cascade reactions; deracemization; dynamic asymmetric catalysis; hydrogen-bond donor; organocatalysis; reactions on racemic mixtures; stereodivergence

Chiral small molecules with multiple stereocenters are essential for life on earth and the betterment of human health. A striking aspect of nature is that chiral molecules (e.g., sugars) with several stereocenters are made as single enantiomers (e.g., D-glucose).[1–3] In contrast, to achieve similar levels of selectivity in one-pot by chemical synthesis is a very challenging task since a molecule containing n number of chiral centers can form 2^n possible stereoisomers. Chemical research is addressing this challenge and one growing area is the development of catalytic asymmetric multi-component and cascade reactions that include advantages of reducing synthetic steps and other green chemistry parameters.[4–7] Despite these and other advances in asymmetric catalysis,[7] during the last 50 years industrial processes often have to deal with stereomeric mixtures. Consequently, enzymatic or chemical resolution is applied where 50% (racemate) or more (diastereomeric mixtures) of the starting material is disposed.[8] In order to improve kinetic resolutions (KR), the less reactive enantiomer can be removed by a parallel reaction to yield a different product that can be readily separated.[8c,9] If this process is carried out by a single chiral reagent it is called "divergent reactions on a racemic mixture" (divergent RRM)[9] where a variation is the parallel kinetic resolution (PKR) in which two complementary chiral reagents are employed to afford distinct products (Scheme 1, a).[8c] Thus, a diastereo- and enantio-(stereo)divergent RRM or PKR can give four possible products (the four enantiomers of the two products) but in 50% theoretical yield. To overcome the limitations of KR and allow for deracemization (the complete transformation of a racemate into a single stereoisomeric product) different protocols have been developed. Among the most popular are dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT, Scheme 1, b) that allow for the synthesis of two possible products (the two enantiomers of the product) in 100% theoretical yield.[10,11]

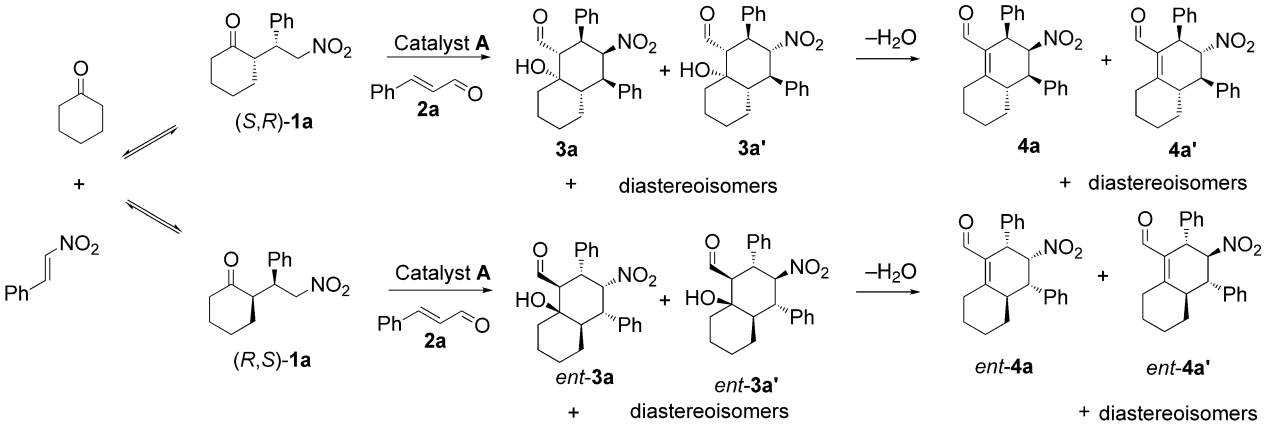


Scheme 1. a) RRM. R = *R*-enantiomer. S = *S*-enantiomer. b) Simplified DYKAT type IV. E_{SR} and E_{RS} are the two enantiomers of the starting racemate.[10a]

From a stereochemical divergent strategy perspective,[12,13] it would be highly appealing to be able to switch between the above described systems since it could allow for the synthesis of distinct products from a racemate using a single chiral catalyst. For example, if the overall process and diastereoselectivity of a stereodivergent RRM were switched to a stereoconvergent deracemization, six diffrent products (the six enantiomers of the three products) would be obtained. Herein, we disclose that this systems strategy is indeed possible by the synergistic action of an achiral catalyst.

We initially began our studies of finding a suitable model system. In this context, the catalytic asymmetric cascade transformation on racemic γ-nitro ketone **1a** with cinnamic aldehyde **2a** could in theory deliver polyfunctionalized [4.4.0] bicyclic compounds **3** with 6 chiral centers as a mixture of 64 different possible stereoisomers **3** and dehydrated products **4** (Scheme 2). As a consequence, this type of reaction has to date only been performed on enantiopure (*S*,*R*)-**1a** with a chiral amine as the catalyst to give the bicyclic compound **3a** together with a minor unidentified diastereoisomer.[14,15] The use of supramolecular interactions (e.g., hydrogen bonding) is very important for controlling the reaction outcome and selectivity of dynamic processes.[16] These types of interactions are also a powerful activation mode in asymmetric catalysis.[17,18] In this context, we recently found that the generation of an achiral hydrogen bond-donating network could switch the chemoselectivity of a chiral amine-catalyzed one-pot three-component reaction.[18j] Thus, we believed that the kinetics of the cascade transfromation depicted in Scheme 2 should be different in the presence of a suitable achiral hydrogen bond-donating co-catalyst. In addition, we envisioned that the achiral non-covalent hydrogen bond interactions could induce a diastereoselective switch in the transition state of the cascade transformation. For example, redirecting the equatorial γ-nitro group of **1** in transisition state **I** to an axial position as in transition state **II** by the hydrogen bond-donating catalyst (Figure 1).

At the onset of our catalyst and conditions screening (Supporting Information), we discovered that the reaction between racemic **1a** and **2a** in the presence of a chiral amine catalyst **5** delivered bicyclic compounds **3a** and *ent*-**4a**$^{\mathbf{II}}$ as the major diastereoisomers (Table 1). Thus, this transformation is a formal stereodivergent RRM. We also found that the reaction was accelerated by the co-catalysis of an achiral acid and amine (entry 1 *vs.* entry 2; the reaction with only chiral amine **5a** as the catalyst gave less than 50% conversion after 24 h so the products were not isolat-



Scheme 2. Some of the possible pathways of the for catalytic asymmetric transformations on racemic *syn*-**1a**. The possible pathways of the *anti*-**1a** are not shown.

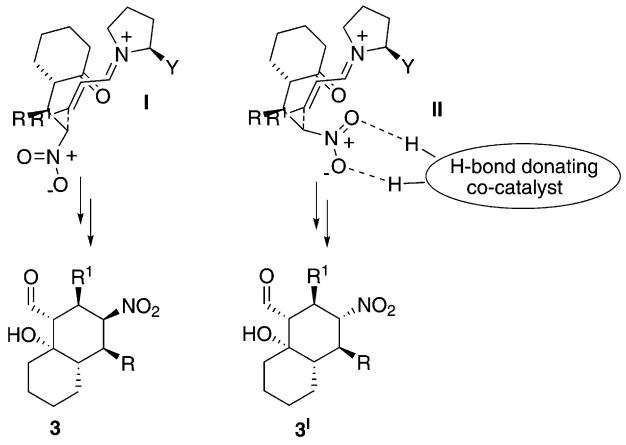
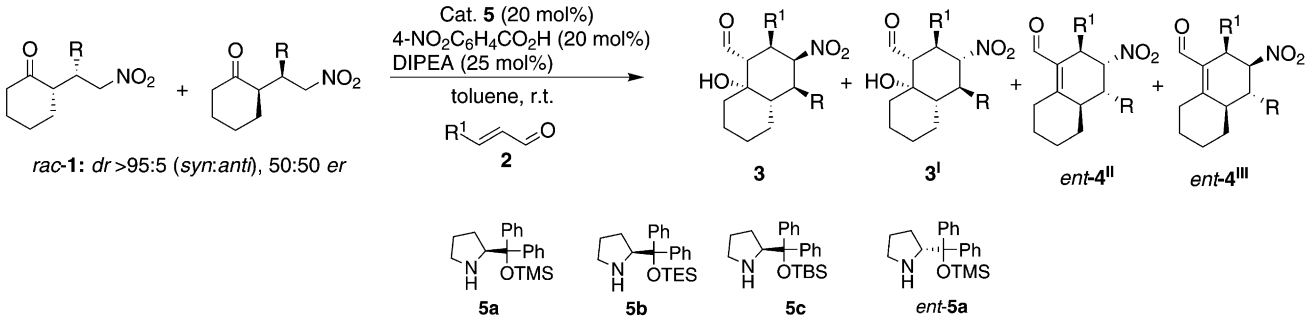


Figure 1. Possible transition states **I** and **II**.

ed). The optimal conditions to perform the stereodivergent RRMs were use of the combination of chiral protected diarylprolinols **5**,[19] 4-nitrobenzoic acid and DIPEA as the co-catalysts in toluene at room temperature (Table 1).

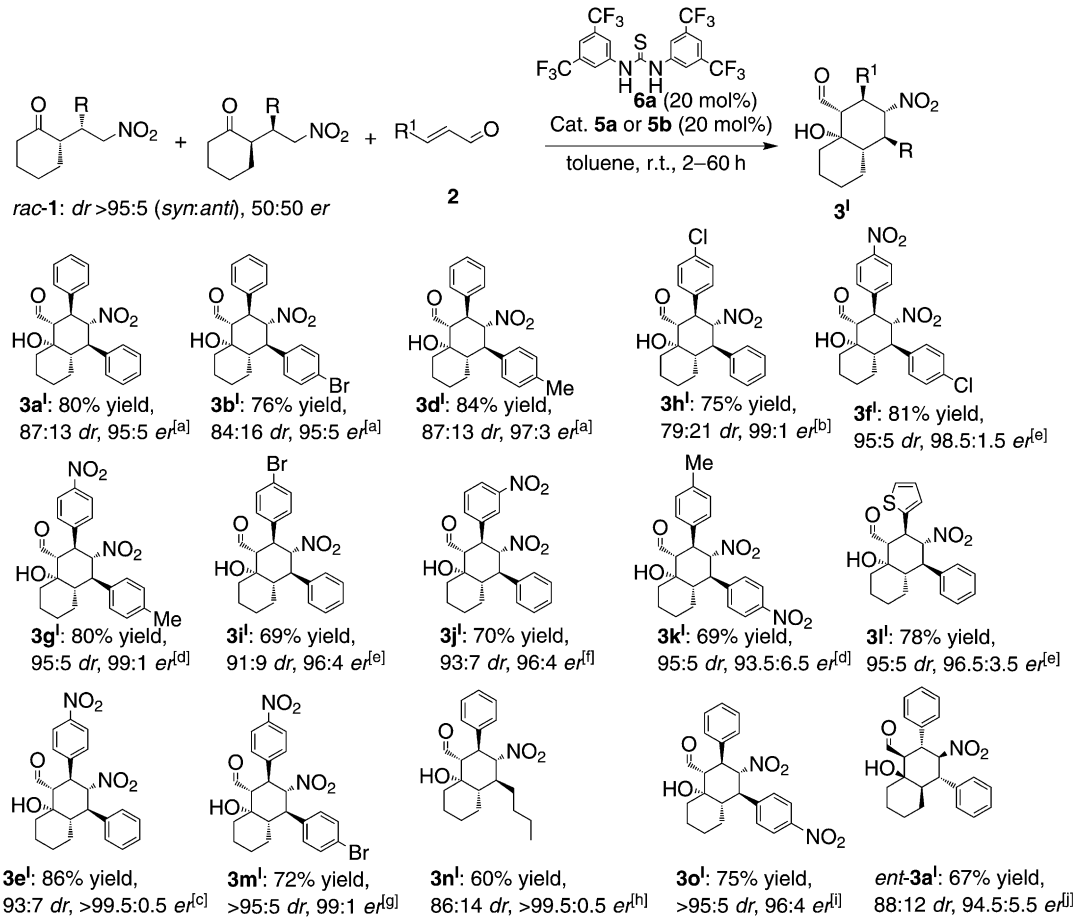
Compounds **3a**–**3g** and *ent*-**4a**^{II}-*ent*-**4g**^{II} were obtained with good to high *dr*s and high *er*s, respectively (entries 2–10). Furthermore, bicyclic compounds **3** were readily separated from bicyclic compounds *ent*-**4**^{II} by silica-gel column chromatography. The ratio of **3** to *ent*-**4**^{II} was slightly higher than 50:50 demonstrating that γ-nitro ketone enantiomers (*S*,*R*)-**1** reacted faster than enantiomers (*R*,*S*)-**1** under these reaction conditions. The use of (*R*)-**5a** as the catalyst gave the opposite enantiomers *ent*-**3** and **4**^{II}, respectively (entry 11). The reactions on racemic γ-nitro ketones **1** showed that it should be possible to synthesize predominantly *ent*-**4**^{II} when starting with enantioenriched (*R*,*S*)-**1**. Indeed performing the reaction with (*R*,*S*)-**1a** as the starting material (96.5:3.5 *er*) gave nearly enantiomerically pure *ent*-**4a**^{II} in 61% yield (entry 12). Having discovered this chiral amine-catalyzed stereodivergent RRM process, we began to investigate whether we could convert it to a stereoconvergent de-

Table 1. Examples of catalytic RRM of *rac*-**1**.[a]



Entry	R	R^1	Cat.	Time (h)	Products 3	Products *ent*-4^{II}	Yield (%)[b] 3	Yield (%)[b] *ent*-4^{II}	Ratio[c] (3+3')/(*ent*-4^{II}+*ent*-4^{III})	*dr*[c] 3:3^{I}	*dr*[c] *ent*-4^{II}:*ent*-4^{III}	*er*[d] 3	*er*[d] 3^{I}	*er*[d] *ent*-4^{II}
1[e]	Ph	Ph	**5a**	48	**3a**	*ent*-**4a**^{II}	49	21	66:34	71:29	77:23	95:5	n.d.	99:1
2	Ph	Ph	**5a**	24	**3a**	*ent*-**4a**^{II}	50	32	58:42	80:20	78:22	95:5	98.5:1.5	99.5:0.5
3	Ph	Ph	**5b**	24	**3a**	*ent*-**4a**^{II}	43	25	63:37	72:28	78:22	92:8	98.5:1.5	99.5:0.5
4	Ph	Ph	**5c**	24	**3a**	*ent*-**4a**^{II}	28	15	79:21	79:21	79:21	96:4	99.5:0.5	99.5:0.5
5	4-BrC_6H_4	Ph	**5a**	22	**3b**	*ent*-**4b**^{II}	56	37	60:40	61:39	80:20	98.5:1.5	98.5:1.5	99.5:0.5
6	4-ClC_6H_4	Ph	**5a**	23	**3c**	*ent*-**4c**^{II}	56	34	62:38	62:38	81:19	98.5:1.5	98:2	>99.5:0.5
7	4-MeC_6H_4	Ph	**5a**	32	**3d**	*ent*-**4d**^{II}	51	33	60:40	72:28	79:21	90:10	99.5:0.5	99.5:0.5
8	Ph	4-$NO_2C_6H_4$	**5a**	29	**3e**	*ent*-**4e**^{II}	46	29	61:39	86:14	94:6	95:5	98.5:1.5	>99.5:0.5
9	4-ClC_6H_4	4-$NO_2C_6H_4$	**5a**	23	**3f**	*ent*-**4f**^{II}	67	23	75:25	79:21	91:9	91:9	99:1	>99.5:0.5
10	4-MeC_6H_4	4-$NO_2C_6H_4$	**5a**	36	**3g**	*ent*-**4g**^{II}	55	36	60:40	78:22	92:8	96:4	99.5:0.5	>99.5:0.5
11	Ph	Ph	*ent*-**5a**	24	*ent*-**3a**	**4a**^{II}	48	31	60:40	74:26	79:21	95:5	99:1	99.5:0.5
12[f]	Ph	Ph	**5a**	48	**3a'**	*ent*-**4a**^{II}	11	61	18:82	18:82	79:21	61:39	n.d.	>99.5:0.5

[a] A mixture of **1** (0.2 mmol), enal **2** (0.4 mmol), **5** (20 mol%) 4-$NO_2C_6H_4CO_2H$ (20 mol%) and DIPEA (25 mol%) in toluene (0.4 mL) was stirred at room temperature for the time shown.
[b] The isolated yields of pure **3** and *ent*-**4**^{II} after silica-gel column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis (see Supporting Information).
[e] No acid and base additive.
[f] The reaction was performed with (*R*,*S*)-**1a** (96.5:3.5 *er*) as the starting material. DIPEA = *N*,*N*-diisopropylethylamine.

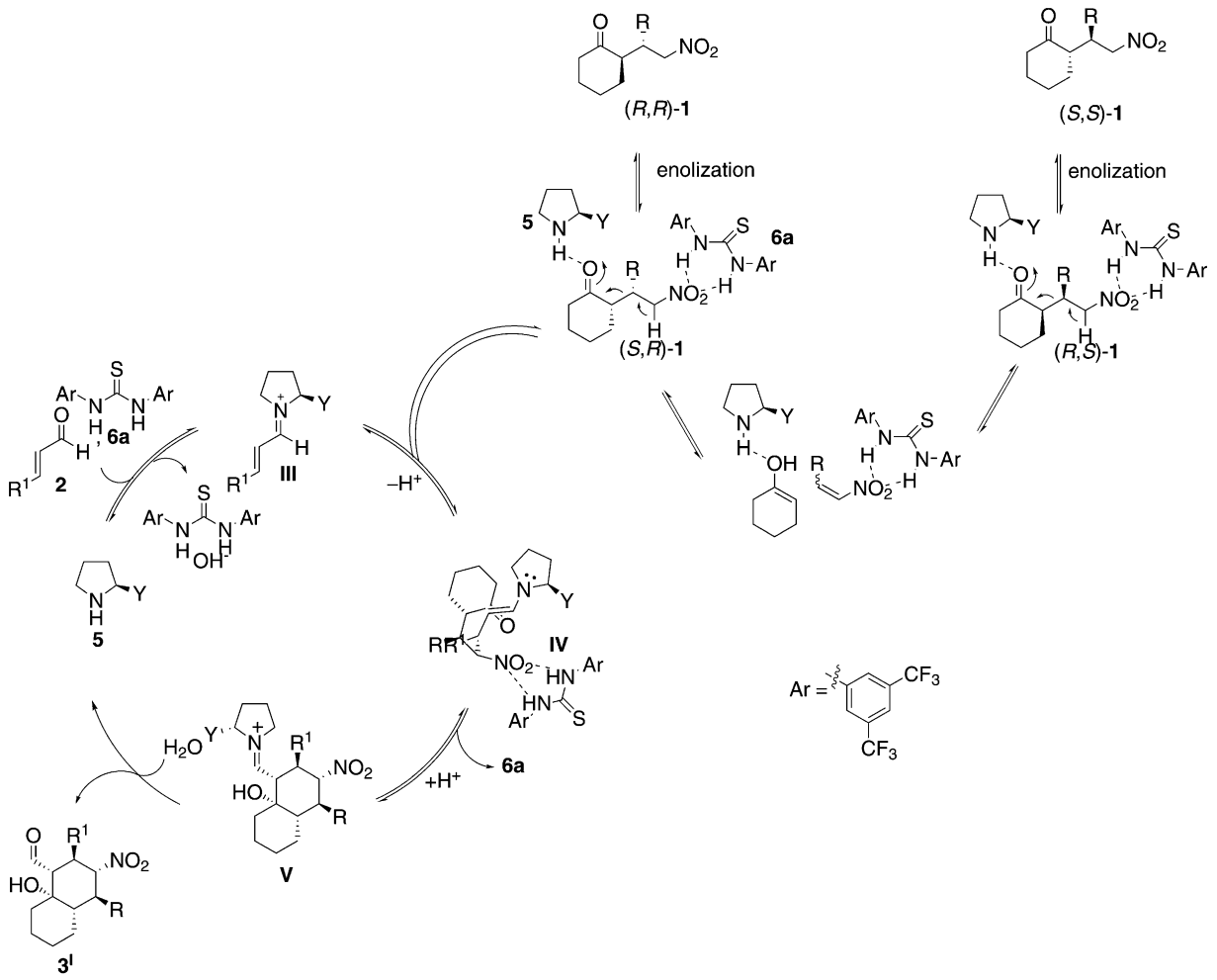


Scheme 3. [a] **5b**, 6 h; [b] **5a**, 16 h; [c] **5b**, 4 h; [d] **5b**, 5 h; [e] **5a**, 10 h; [f] **5b**, 13 h; [g] **5a**, 2 h; [h] **5a**, 60 h, **1f** [>95:5 *dr*, 71:29 *er* (*S*,*S*-**1f** major enantiomer)]; [i] **5a**, 4 h, **1e** [>95:5 *dr*, 70.5:29.5 *er* (*S*,*R*-**1e** major enantiomer)]; [j] *ent*-**5b**, 8 h.

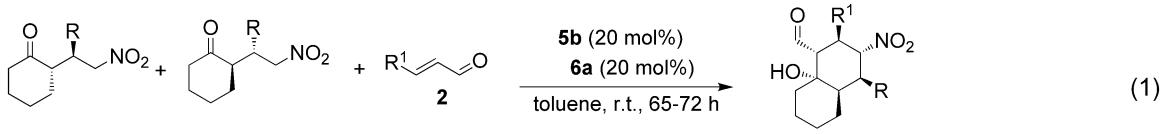
racemization using a hydrogen bond-donating co-catalyst. We found that achiral hydrogen bond-donating co-catalysts **6** accelerated the chiral amine **5**-catalyzed cascade transformation on racemic **1a**. To our delight, the overall system converted from a RRM to a dynamic deracemization process when thiourea derivatives were used as the co-catalysts (Supporting Information and Scheme 3). In particular, the use of Schreiner's thiourea derivative **6a**[17c] in combination with diarylprolinols **5a** or **5b** induced a diastereoselective switch in the cascade transformation to form $\mathbf{3a^I}$ instead of **3a** as the major diastereoisomer (Scheme 3). Thus, we decided to probe the scope of this deracemization process for a set of γ-nitro ketones **1** with enals **2** using **5a** or **5b** as the chiral amine catalyst and **6a** as the hydrogen bond-donating catalyst in toluene at room temperature (Scheme 3).

The synergistic co-catalysis was highly stereoselective and enabled the isolation of bicyclic compounds $\mathbf{3a^I}$–$\mathbf{3m^I}$ in high yields. Thus, the thiourea **6a** was essential in assisting the dynamic conversion of enantiomer (*R*,*S*)-**1** to the fast reacting enantiomer (*S*,*R*)-**1** as well as inducing the diastereomeric switch from **3** to $\mathbf{3^I}$ (Scheme 4, TS **IV**). The reaction was also readily performed on a gram-scale on racemic **1a** to give the corresponding $\mathbf{3a^I}$ with 84:16 *dr* and 96:4 *er*. We also investigated the co-catalyzed stereoselective reaction on scalemic mixtures of (*S*,*S*)-**1f** (71:29 *er*) and (*S*,*R*)-**1e** (70.5:29.5 *er*) and the corresponding products $\mathbf{3n^I}$ and $\mathbf{3o^I}$ were isolated in high yields, *dr*s and *er*s, respectively. The co-catalytic stereoconvergent deracemizations with *ent*-**5a** or *ent*-**5b** as the chiral amine catalysts gave as expected the opposite enantiomer *ent*-$\mathbf{3^I}$. In attempts to fill the other quadrants of stereochemical space, the co-catalytic asymmetric cascade transformation on racemic mixtures of the *anti*-isomer **1a** was investigated (Eq. [1]).

The reactions were highly stereoselective and the corresponding bicyclic *ent*-$\mathbf{3^{IV}}$ were obtained in high yields with >95:5 *dr* and 95:5 *er*, respectively. Thus, we were able to synthesize different stereoisomers and products (e.g., **3**, $\mathbf{3^I}$, *ent*-$\mathbf{4^{II}}$ and *ent*-$\mathbf{3^{IV}}$) with high *er*s by chiral amine **5**-catalyzed asymmetric cascade recations on racemic *syn*- or *anti*-**1**, respectively. The relative stereochemistries of **3**, $\mathbf{3^I}$, *ent*-$\mathbf{4^{II}}$, *ent*-$\mathbf{4^{III}}$ and *ent*-$\mathbf{3^{IV}}$ were determined by NOE experiments and X-



Scheme 4. Proposed reaction pathway for the formation of $\mathbf{3^I}$.



rac-anti-**1a**: R = Ph, 94.5:5.5 *dr* (*anti:syn*), 50:50 *er*
rac-anti-**1b**: R = 4-BrC_6H_4, >95:5 *dr*, 50:50 er

ent-$\mathbf{3a^{IV}}$: R^1 = Ph, 66% yield, >95:5 *dr*, 95:5 *er*
ent-$\mathbf{3b^{IV}}$: R^1 = 4-BrC_6H_4, 60% yield, >95:5 *dr*, 95:5 *er*

ray analyses. The absolute stereochemistry of compounds **3**, $\mathbf{3^I}$ and $\mathbf{4^{II}}$ were confirmed by the X-ray analysis of **3b** (1*R*,2*S*,3*S*,4*R*,4a*S*,8a*S*), $\mathbf{3b^I}$ (1*R*,2*S*,3*R*,4*R*,4a*S*,8a*S*) and *ent*-$\mathbf{4b^{II}}$ (2*R*,3*R*,4*S*,4a*R*), respectively.[20] The analyses revealed that the stereochemistry was the same for all compounds at the C-1 and C-2 positions which was controlled by the (*S*)-**5** catalyst. The absolute stereochemistries of compounds *ent*-$\mathbf{3^{IV}}$ were confirmed by these experiments and the X-ray analysis of *ent*-$\mathbf{3b^{IV}}$ (1*R*,2*S*,3*R*,4*R*,4a*R*,8a*S*).[20] The ability of chiral amine **5a** or Schreiner thiourea **6a** to epimerize and racemize (*S*,*R*)-**1a** or (*R*,*S*)-**1a**, respectively, was examined next. None of these catalysts could catalyze these processes alone (see the Supporting Information). However, in combination a significant loss of both the *dr* and the *er* of both (*S*,*R*)-**1a** and (*R*,*S*)-**1a** was observed with the latter epimerizing and racemizing at a higher rate. Thus, the slow reacting enantiomer of the cascade reaction (*R*,*S*)-**1a** was converted to the fast reacting enantiomer (*S*,*R*)-**1a** by the essential synergistic non-covalent self-assembled bifunctional catalysis (Scheme 4). However, product **1a** was not formed when 2-(nitrovinyl)benzene was reacted with cyclohexanone in the presence of co-catalysts **5a** and thiourea **6a**. HR-MS and ^{1}H NMR analysis established that no detectable covalent intermedi-

ates between **6a** and **1a** were formed during this process. Based on our experimental results, ^{1}H NMR, X-ray analyses, and HR-MS analyses, we propose the following mechanistic reasoning to account for the stereoconvergent deracemization of racemic *syn*-**1** to stereoisomer $\mathbf{3^I}$ (Scheme 4). The catalytic cascade cycle starts with hydrogen bond-donating **6a**-accelerated iminium intermediate **III** formation between chiral amine **5** and enals **2**. The bulky chiral group efficiently shields the *Re*-face of **III**. Next, of all the possible stereoisomers of **1** the fast reacting enantiomer (*S*,*R*)-**1** will perform a nucleophilic *Si*-facial conjugate attack on **III** to form enamine intermediate **IV** *via* transition state **II**, which involves hydrogen bond activation by co-catalyst **6a**.

The subsequent cascade intramolecular **6**-*exo*-*trig* aldol reaction at the *Re*-face of the keto moiety of **IV** results in intermediate **V**. Subsequent hydrolysis regenerates the chiral catalyst **5** and delivers $\mathbf{3^I}$. In parallel to this catalytic proposed cycle, the achiral hydrogen bond-donating catalyst **6a** together with chiral amine **5** co-catalyze the dynamic conversion of enantiomer (*R*,*S*)-**1** to (*S*,*R*)-**1** so that all of the starting racemic mixture is converted to $\mathbf{3^I}$ (deracemization). The presence of intermediates **III**, **IV** and **V** was experimentally confirmed by HR-MS analysis[21] on the crude reaction mixture. With respect to the formation of stereoisomers *ent*-$\mathbf{4^{II}}$ and *ent*-$\mathbf{3^{IV}}$, we propose transition states **VI** and **VII** to account for the enantioselective conjugate attack of (*R*,*S*)-**1** and (*R*,*R*)-**1** to iminium intermediate **III**, respectively (Figure 2).

In summary, we have disclosed a stereochemical divergent approach to distinct products with multiple stereocenters from a racemate using a single chiral catalyst. It is based on switches of the overall system in catalytic asymmetric reactions on racemic mixtures using achiral co-catalysts. As demonstrated by the highly diastereoselective switch in a catalytic asymmetric RRM to a stereoconvergent deracemization by the combination of chiral amine and achiral hydrogen bond-donating catalysts. The racemization and the iminium-enamine-activated asymmetric cascade transformation processes were both accelerated by the non-covalent hydrogen-bond activation. In fact, enzymes use the same type of activation modes (hydrogen bond-donation, iminium and enamine actvation) as the disclosed primitive small molecule cooperative catalysis system to bring stereochemical "order" in their biosynthesis of complex molecules essential for life. Beyond nature, the presented approach accomplished stereochemical diversification with a single chiral catalyst by achiral co-catalyst-induced switches in the overall reaction system. Further mechanistic investigations to understand, control and eventually design other such processes are ongoing in our laboratories.

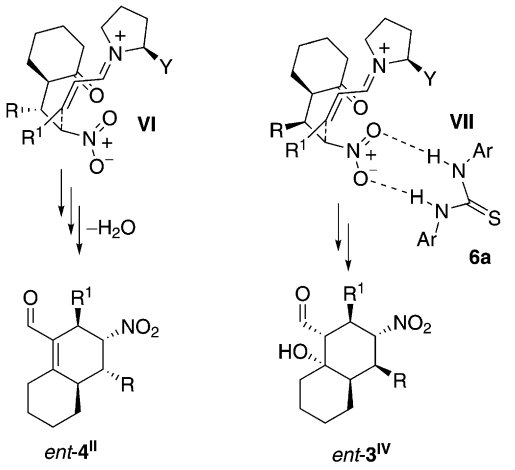


Figure 2. Possible transition states **VI** and **VII**.

Experimental Section

General Procedure for the Co-Catalytic Deracemization Reaction (Scheme 3)

To an 8-mL vial equipped with a magnetic stir bar was added organocatalyst **5a** or **5b** (0.02 mmol, 20 mol%), enal **2** (0.2 mmol, 2.0 equiv.), Schreiner's thiourea **6a** (10.0 mg, 0.02 mmol, 20 mol%) and toluene (0.2 mL). After stirring at room temperature for 10 min, the racemic γ-nitro ketone *rac*-**1** (0.1 mmol, 1.0 equiv.) was added and the mixture was vigorously stirred. The reaction progress was monitored by ^{1}H NMR analysis. After complete consumption (>95%) of γ-nitro ketone **1**, CH_2Cl_2 (5.0 mL) was added to the vial. Next, 400~500 μL of this solution were added to a vial followed by removal of the solvent under reduced pressure. The resulting pale yellow solid was dissolved in 400 μL $CDCl_3$. The ratio of $\mathbf{3}$:$\mathbf{3^I}$ was determined by ^{1}H NMR analysis. Next, all of this solution was combined with the remaining CH_2Cl_2 solution and the pure compounds $\mathbf{3^I}$ were obtained by silica-gel column chromatography (pentane/ethyl acetate = 8/1–3/1).

General Procedure for the Gram-Scale Reaction

To a 16-mL vial equipped with a magnetic stir bar were added organocatalyst **5b** (298 mg, 0.8 mmol, 20 mol%), enal **2a** (1.02 mL, 8.1 mmol, 2.0 equiv.), Schreiner's thiourea **6a** (400 mg, 0.8 mmol, 20 mol%) and toluene (8.0 mL). After stirring at room temperature for 10 min, the racemic γ-nitro ketone *rac*-**1a** (1.0 g, 4.05 mmol, 1.0 equiv.) was added to the vial in one portion and the resulting mixture was allowed to stir at room temperature for 12 h. The ratio of $\mathbf{3a^I}$/**3a** = 84:16 was determined by ^{1}H NMR analysis of the crude reaction mixture. The pure compounds $\mathbf{3a^I}$ and **3a** were obtained by flash column chromatography on silica gel (pentane/ethyl acetate = 8:1~3:1), to afford $\mathbf{3a^I}$ (yield: 940 mg, 61%, >95:5 *dr*, 95:5 *er*) and **3a** (yield: 170 mg, 11%, >95:5 *dr*, 96:4 *er*) as white solids.

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