CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201003477

Deracemization of Axially Chiral α,β-Unsaturated Aldehydes through an Amino-Catalyzed Symmetry-Making–Symmetry-Breaking Cascade

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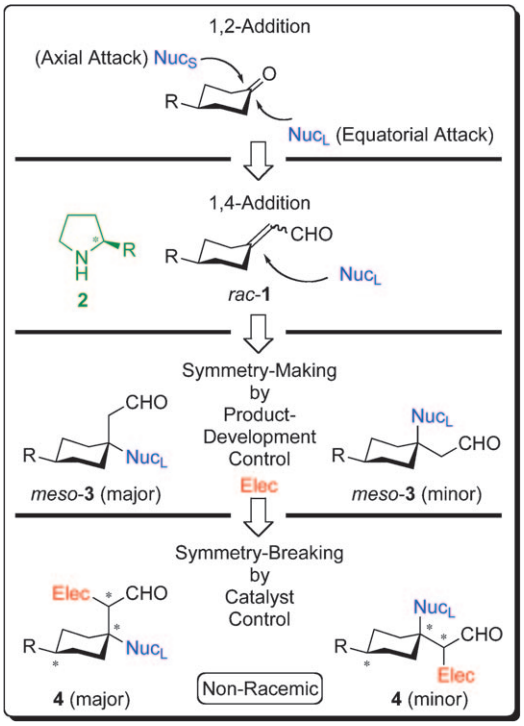
Deracemization and desymmetrization processes represent elegant and atom-efficient routes in asymmetric organic synthesis.[1] Whereas desymmetrization reactions have been extensively studied, there exist only a handful of distinct strategies that allow complete deracemization to occur with full conversion of starting substrate, hence, reaching a theoretical yield of 100% as opposed to 50% in the traditional kinetic resolution processes. In this respect, great advances have been achieved for transition-metal-catalyzed or combined metal/enzyme promoted dynamic kinetic resolution (DKR)[2] and dynamic kinetic asymmetric transformation (DYKAT) reactions.[3] On the contrary, deracemization methods based on metal-free promoters are scarce and often limited to isolated examples.[4] The obvious challenge lies in the identification of suitable substrates that permit either a rapid interconversion of the enantiomers or a simple way to introduce symmetry in the molecule. Herein, we demonstrate a novel DYKAT reaction, in which racemic substituted 2-cyclohexylidene acetaldehydes carrying axial chirality can be efficiently deracemized by a symmetry-making–symmetry-breaking cascade that utilizes amino-catalyzed functionalization strategies.[5] Moreover, a mechanistic rationale with experimental support for tandem product-development and catalyst control of selectivity is provided.

The design of the presented deracemization concept finds its inspiration in the 1,2-addition of nucleophiles to conformationally locked cyclohexanones (Scheme 1). In such addition reactions, either equatorial or axial attack may occur leading to the formation of the axial- and equatorial alcohols, respectively. Experimentally, it has been shown that nucleophiles, in which sterical hindrance is negligible (Nuc_S), prefer to add to the carbonyl from an axial trajectory, while larger and sterically more demanding nucleophiles (Nuc_L) preferentially add from the equatorial side (product-development control).[6] We questioned whether the sterically controlled diastereofacial selectivity could be extended to other "flattened" cyclic structures such as racemic enals *rac*-**1** (Scheme 1). Provided the necessary activation by an amino catalyst **2**, a sterically demanding nucleophile should attack the electrophilic double bond preferably from the equatorial side, hence exhibiting product-development control.[7] The result is that symmetry is introduced in the molecule with the formation of a diastereomeric pair of *meso*-**3**, in which the axial aldehyde is favored. In the presence of an electrophilic species, an enantioselective α-functionalization of *meso*-**3** is promoted by the optically active catalyst **2**, thus furnishing the desired enantioenriched products **4**, which contain three stereogenic centers. To have an efficient enantioconvergent process, product-development control must dominate in the symmetry-making step, while catalyst shall control the symmetry-breaking step. Notably, if full catalyst control applies in the nucleophilic addition step, a 1:1 mixture of **3** will be formed, thus minimizing the enantioconvergency of the designed strategy. Similarly, the ring-substituents may influence the enantiocontrol of the catalyst by means of mismatching sterical interactions in the subsequent step. Ideally, a tandem control provided first by the sub-



Scheme 1. Design of the symmetry-making–symmetry-breaking cascade. Elec = electrophile, Nuc_L = large nucleophile, Nuc_S = small nucleophile.

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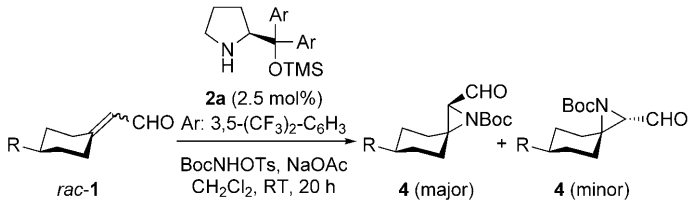
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003477.

strate and later by the catalyst, with minimum mutual interference, should give the optimum DYKAT process.

As a proof of concept, a nucleophile carrying an internal electrophilic site was selected to evaluate our designed DYKAT reaction. As such, the bulky *N*-centered aziridination reagent BocNHOTs suited this purpose (Table 1).[8]

Table 1. Deracemization by an enantioconvergent amino-catalyzed aziridination reaction.[a]

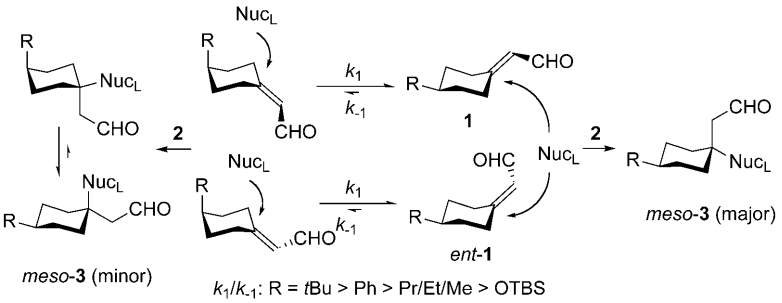


	1 (R)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (Me)	**4a**: 85	3.9:1	96 (97)[e]
2	**1b** (Et)	**4b**: 93	3.7:1	95
3	**1c** (Pr)	**4c**: 93	4:1	97
4	**1d** (Ph)	**4d**: 95	4.6:1	95 (95)[e]
5	**1e** (*t*Bu)	**4e**: 99	9:1	95
6	**1f** (OTBDMS)	**4f**: 99	1.5:1	89 (88)[e]

[a] Reactions performed with **1** (0.12 mmol), BocNHOTs (0.10 mmol), NaOAc (0.3 mmol), **2a** (0.0025 mmol) in CH_2Cl_2 (0.5 mL) at RT for 20 h. [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by CSP-HPLC after derivatizations. [e] Value in parenthesis is of the minor diastereomer. Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

Gratifyingly, by performing the aziridination reaction of *rac*-**1a** containing a methyl substituent on the ring with just 2.5 mol% (*S*)-2-[bis(bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrroli-dine **2a** as catalyst, the desired product **4a** is formed in 85% yield and 96% *ee*. More importantly, the diastereomeric ratio of the product reached 3.9:1, thus suggesting that there is indeed substrate control in the symmetry-making 1,4 addition step (Table 1, entry 1). Using other weak conformation-locking groups at the ring, such as ethyl- or propyl groups, similar results regarding yield, diastereo- and enantioselectivity were obtained (Table 1, entries 2 and 3). Larger groups like Ph- or *t*Bu proved better in controlling the diastereoselectivity and provided values of the diastereomeric ratio (d.r.) up to 9:1, whereas the excellent yields and enantioselectivities were maintained (Table 1, entries 4 and 5). Interestingly, for enals with a heteroatom substituent on the ring (-OTBDMS, **1f**) a poor 1.5:1 diastereoselectivity was obtained; however, the yield and enantioselectivity remained high (Table 1, entry 6). This observed correlation suggests that in addition to the bulkiness of the nucleophile, the conformational restrain of the cyclic enal is also crucial for the diastereoselectivity. Therefore, the ability of *rac*-**1** to perform ringflip should directly correlate to the selectivity in the symmetry-making step (Scheme 2). The observed increase in the d.r. going from R = Me to *t*Bu is thus a direct reflection on the substrate's ability to lock the conformation of the ring, as the equatorial attack to the ring-flipped compound would lead to the build-up of the undesired isomer of **3**. Additionally, it is also well-known that *O*-substituents introduce more flexibility in the cyclic structure, which transmits to the observed tendency of a drop in the d.r. value.[9] Moreover, to the best of our knowledge this represents the first general study of asymmetric amino-catalyzed aziridination reaction of β,β-disubstituted enals.[8d] The relative configuration of **4e** (major) was established by X-ray analysis and confirmed the proposed structure, whereas the absolute configuration has been assigned by correlation and an independent synthesis (see the Supporting Information). The catalyst **2a** has proven to be highly effective in steric face-shielding because it blocked the *Re*-face of the enamine intermediate while favoring the *Si*-face electrophilic attack in many α-functionalization reactions, including aziridination reactions.[5,8,10] The absolute configuration for **4** is determined to be (*2S,3R,6S*), as illustrated in Table 1 (see the Supporting Information).

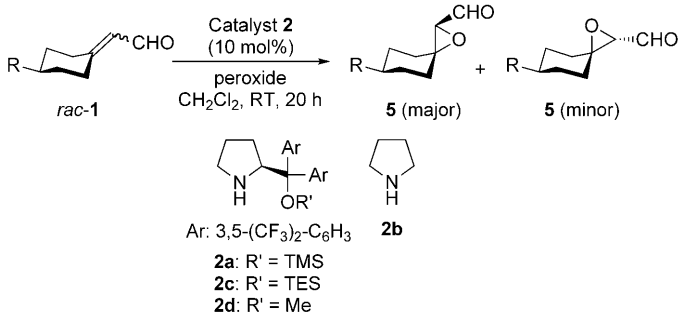
To include other amino-catalyzed functionalization reactions and to further study the role of the nucleophile and of the catalyst, we attempted the amino-catalyzed epoxidation[10] in the designed system (Table 2).



Scheme 2. Effect of ringflip and of the R group on the diastereoselectivity. TBS = tert-butyldimethylsilyl.

Treating the conformationally locked enal **1e** with aqueous H_2O_2 and catalyst **2a**, the desired epoxide product **5e** was formed in 62% yield, 4.6:1 d.r., and 92% *ee* (Table 2, entry 1). The lower d.r. obtained compared with the aziridination reaction is presumably due to the reduced size of the nucleophile, whereas the volatile nature of the resulting epoxides also diminishes the isolated yields. Other sterically more demanding oxidants result in a noticeable increase in d.r., thus furnishing **5** as a single diastereomer, albeit with lower yield or enantiomeric excess (Table 2, entries 2–4). The influence of water on the diastereoselectivity was ruled out by a control experiment (Table 2, entry 5), whereas less

Table 2. Influence of the nucleophile and catalyst on the amino-catalyzed enantioconvegent epoxidation reaction.[a]



	R	Cat.	Peroxide	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**1e** (*t*Bu)	**2a**	H_2O_2 (33%)	>95 (62)	4.6:1	92 (86)
2	**1e** (*t*Bu)	**2a**	UHP[e]	>95 (15)	20:1	96
3	**1e** (*t*Bu)	**2a**	*t*BuO_2H	>95 (38)	20:1	70
4	**1e** (*t*Bu)	**2a**	cumene peroxide	>95 (traces)	20:1	74 (60)
5	**1e** (*t*Bu)	**2a**	*t*BuO_2H+H_2O (2 equiv)	>95	20:1	72
6	**1b** (Et)	**2a**	H_2O_2 (33%)	>95 (51)	3:1	88 (91)
7	**1b** (Et)	**2b**	H_2O_2 (33%)	>95	20:1	–
8	**1c** (Pr)	**2a**	H_2O_2 (33%)	>95	3:1	87 (89)
9	**1c** (Pr)	**2c**	H_2O_2 (33%)	<25	1.5:1	84 (84)
10	**1c** (Pr)	**2d**	H_2O_2 (33%)	>95	10:1	63
11[f]	**1c** (Pr)	**2a**	H_2O_2 (33%)	>95 (traces)	4:1	89

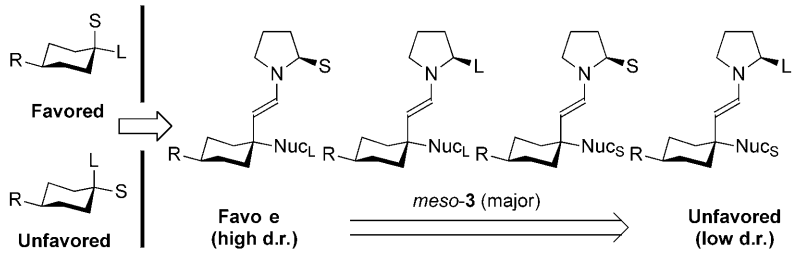
[a] Reactions were performed with peroxide (0.13 mmol), **1** (0.1 mmol), **2** (0.01 mmol) in 0.2 mL CH_2Cl_2. [b] Determined by ^{1}H NMR spectroscopic analysis. Yield of isolated product in parentheses. [c] Determined by ^{1}H NMR spectroscopic analysis or GC of the crude mixture. [d] Determined by GC or HPLC analysis with a chiral stationary phase. Results in parentheses are for the minor diastereomer. [e] Urea hydrogen peroxide. [f] EtOH (96%) was used as solvent. TES = triethylsilyl.

structurally rigid enals, such as **1b**,**c** resulted, as expected, in inferior diastereoselectivities (Table 2, entries 6 and 8). The use of the achiral pyrrolidine as catalyst in combination with H_2O_2 resulted in improved diastereoselectivity compared with the application of **2a** and H_2O_2 (Table 2, entry 7), thus confirming an interference by the chiral catalyst in the symmetry-making step. Increasing the steric bulk of the catalyst **2** by employing the O-TES prolinol analogue **2c** led to a further drop in the d.r., whereas the less sterically demanding catalyst **2d** had the opposite effect (Table 2, entries 9 and 10). However, none of the other chiral amines (**2c**,**d**) could provide the satisfactory enantioselectivity with H_2O_2 as the peroxide source. Evaluation of other polar and nonpolar solvents did not affect the selectivity of the epoxidation reaction in a positive manner. Interestingly, by employing a protic solvent such as EtOH, product **5** was furnished with improved selectivities (4:1 d.r. and 89% *ee*), albeit only traces of product could be isolated (Table 2, entry 11), presumably because of the competitive oxa-Michael reaction of the alcoholic solvent.

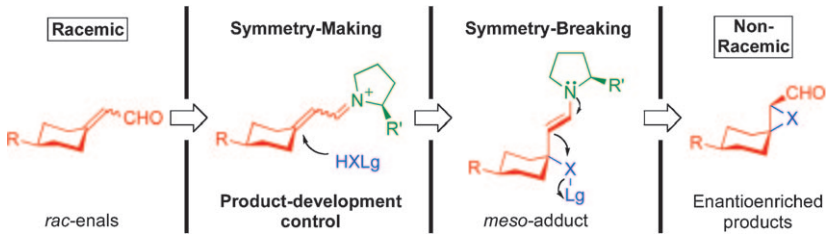
The observed correlation between diastereoselectivity and the size of catalyst and nucleophile is presumably a result of "product-development control" (Scheme 3).[7] The relative stability of the formed products favors the positioning of the larger group (L) equatorially, whereas the smaller substituent (S) is placed axially. By increasing the size of the catalyst or decreasing the bulkiness of the nucleophile, the relative stability of the major isomer of *meso*-**3** is reduced, thus disfavoring its formation and diminishing the facial selectivity of the 1,4-addition reaction. Consequently, to obtain optimal diastereoselectivity, a large nucleophile in combination with a small catalyst should be used, and vice versa.

Having studied the influence of the catalyst, solvent, and nucleophile on amino-catalyzed epoxidation, the scope of the deracemization reaction is presented (Table 3). Employing H_2O_2 as oxidant, the desired epoxides **5** were formed in 80–92% *ee*, albeit in only moderate d.r. (up to 4.6:1 d.r., Table 3, entries 1–5). Superior diastereoselectivities could also be achieved, on the expense of the enantioselectivity, by the application of a more bulky peroxide source that led to a marked improvement of the *d.r.* for all substrates (up to 20:1; Table 3, entries 6–10). It is noteworthy that in both methods, the same correlation between the size of the R group and diastereoselectivity (as that of the aziridination process) is observed, thus confirming the previously given rationale on the influence of ring-flexibility.

A summary of the reaction concept is outlined in Scheme 4. Chiral racemic enals *rac*-**1** are introduced into the

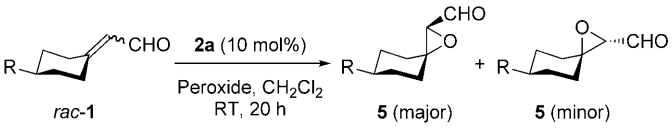


Scheme 3. Product-development controlled facial selectivity influenced by the relative size of catalyst and nucleophile.



Scheme 4. Reaction concept.

Table 3. Deracemization by an enantioconvergent amino-catalyzed epoxidation reaction.[a]



	1 (R)	Peroxide	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (Me)	H_2O_2 (33%)	**5a**: 84	3:1	91
2	**1b** (Et)	H_2O_2 (33%)	**5b**: 51	3:1	88 (91)
3	**1d** (Ph)	H_2O_2 (33%)	**5d**: 61	2.5:1	87 (91)
4	**1e** (*t*Bu)	H_2O_2 (33%)	**5e**: 62	4.6:1	92 (86)
5	**1f** (OTBDMS)	H_2O_2 (33%)	**5f**: 88	1.5:1	80 (94)
6	**1b** (Et)	*t*BuOOH	**5b**: 78	6:1	82 (76)
7	**1c** (Pr)	*t*BuOOH	**5c**: 46	5.8:1	86 (73)
8	**1d** (Ph)	*t*BuOOH	**5d**: 74	11.5:1	70
9	**1e** (*t*Bu)	*t*BuOOH	**5e**: 38	20:1	70
10	**1f** (OTBDMS)	*t*BuOOH	**5f**: 58	1.7:1	83 (91)

[a] Reactions performed with **1** (0.1 mmol), peroxide (0.13 mmol), **2a** (0.01 mmol) in CH_2Cl_2 (0.2 mL) at RT for 20 h. [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by CSP-GC or CSP-HPLC after derivatizations. TBDMS = *tert*-butyldimethylsilyl.

catalytic cycle by condensation with the amino catalyst **2**. The resulting iminium species is, preferentially, subjected to equatorial attack by the heteroatom-centered nucleophile (HXLg) because of the higher relative stability of the formed product. Importantly, the normal facial-shielding control of the amino catalyst is, in the conjugate addition step, overruled by product-development control. Upon the nucleophilic attack, symmetry is introduced in the chiral molecule (*rac*-**1**), thus generating the *meso*-compound **3**. Final cyclization from the *Si*-face of the catalyst-bound enamine species, now following catalyst-control, completes the catalytic cycle with the formation of optically active epoxides **5** and aziridines **4** in concert with the liberation of the amino catalyst.

In conclusion, we have presented a novel deracemization reaction of axially chiral α,β-unsaturated aldehydes that employs an enantioconvergent amino-catalyzed symmetry-making–symmetry-breaking cascade, in which product-development and catalyst control dominate in tandem. It is further confirmed that the size of the nucleophile and the conformational rigidity of the substrate can overrule the facial differentiation of the amino catalyst in conjugate additions (the symmetry-making step). Highly enantioenriched products were formed from chiral racemic enals, with good to excellent yields and moderate to high diastereoselectivities using as low as 2.5 mol% catalyst. The majority of current deracemization approaches are based on substrates incorporating a labile stereogenic center that equilibrates in solution; on the contrary, reports based on symmetry-introduction are very elusive. To the best of our knowledge, this represents one of the first secondary amine catalyzed DYKAT based on symmetry-introduction.

Acknowledgements

This work was made possible by grants from Carlsberg Foundation and the OChemSchool. Thanks are expressed to Drs. Steen Uttrup Petersen and Frank Jensen for the assignment of the configurations.

Keywords: deracemization · dynamic kinetic asymmetric transformation · enantioconvergent synthesis · nucleophilic addition · organocatalysis

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Received: December 1, 2010
Revised: January 28, 2011
Published online: March 4, 2011

