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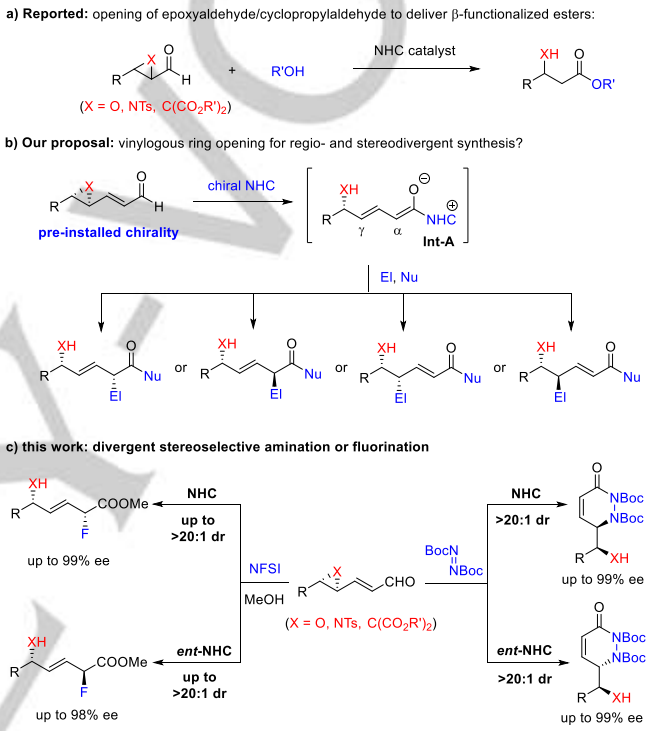
Highly Regio- and Stereodivergent Access to 1,2-Amino Alcohols or 1,4-Fluoro Alcohols by NHC-Catalyzed Ring Opening of Epoxy enals

Si Bei Poh, Jun-Yang Ong, Shenci Lu* and Yu Zhao*

Abstract: We describe herein an unprecedented NHC-catalyzed stereoselective ring opening of epoxy- or cyclopropyl-enals to deliver valuable compounds bearing multiple stereocenters. A straightforward three-step procedure involving two catalytic enantioselective transformations has been developed that leads to a regio- and stereodivergent synthesis of 1,2-amino alcohols/diamines or 1,4-fluoro alcohols with excellent diastereo- and enantiopurity.

The efficient generation of structural diversity in organic compounds remains an important goal in synthetic chemistry and other applied areas such as chemical biology.[1] Accordingly, the development of catalytic regio- or diastereodivergent transformations from the same starting material has gained much significance in recent years.[2] For the preparation of important compounds bearing multiple stereocenters, it is undoubtedly more attractive to access different isomers in a highly diastereo- and enantiocontrolled fashion. To achieve this, however, the catalytic system has to be able to accomodate a variety of functional groups and overcome the inherent stereo-control from the existing stereogenic center in the substrate. Heading towards this goal, we have developed an NHC-catalyzed process in which essentially complete catalyst control is realized to deliver valuable compounds in highly diasteo- and enantiopure fashion.

During the past few decades, N-heterocyclic carbene catalysis has emerged as a powerful and versatile tool in stereoselective synthesis.[3] Aldehydes bearing a α-leaving group have found much use as the substrate to access diverse reactivites under NHC-catalysis. In particular, epoxy- or cyclopropyl-aldehydes were shown by the Bode group to undergo ring opening to deliver β-functionalized esters (Scheme 1a).[4] Inspired by this, we became interested in the vinylogous ring opening of cyclopropyl- or epoxy-enals by NHC catalysis;[5] the intermediate generated this way (**Int-A**) may undergo various regio- and diastereodivergent transformations to produce valuable structures bearing multiple stereocenters (Scheme 1b).[6] It is noteworthy that elegant examples on NHC-catalyzed transformations of aldehydes bearing a γ-carbonate as the leaving group has been reported by the Sun group and the Ye group for the synthesis of allenes, α-fluoroesters and dihydropyridazinones.[7] In our proposed transformations, the incorporation of reactive functionalities such as epoxide in the substrate may raise serious compatibility issues. As one particular complication, **Int-A** may undergo an undesired intramolecular cyclization leading to lactone side products (when X = OH).[8] On the other hand, these processes also provides great opportunities for stereodivergent synthesis of more functionalized compounds. We present herein the realization of such strategy in 1,2-amino alcohol/diamine and 1,4-fluoro alcohol synthesis. A straightforward three-step procedure involving an iminium catalysis-Wittig olefination-NHC catalysis sequence has been achieved for a regio- and stereodivergent synthesis of these important compounds with excellent diastereo- and enantiocontrol (Scheme 1c).[9]



Scheme 1. Divergent Reactions Enabled by Dual Catalytic System.

γ-Amination of epoxy enals for stereodivergent 1,2-amino alcohol synthesis

We chose epoxy enal **1a** as the model substrate for our investigation, which could be prepared in high enantiopurity following the previous report on enantioselective epoxidation of enals via iminium catalysis,[10] followed by Wittig olefination (Procedure shown in Scheme 2a). We decided to explore amination of **1a** using **2**[7c] as such transformation could lead to stereodivergent synthesis of functionalized 1,2-amino alcohols that are important structural motifs in synthesis and catalysis.[11]

When the reaction of **1a** and **2** was examined using different azoliums, only the use of **4b** led to the formation of the desired product *(R, S)*-**3a**, albeit with a moderate 40% yield (entries 1-4). To our delight, *(R, S)*-**3a** was formed as a single diastereomer with a high 97% ee. Different reaction conditions were screened at this stage. The use of other bases such as K_2CO_3 and DBU resulted in a complex mixture (results not shown). The different loading of base or **2** was also examined. 2 equiv. of NaOAc proved to be a better choice (entry 5 vs entry 4), while a higher loading of **2** lead to an improved chemical yield (entry 6). Finally, decreasing the catalyst loading of **4b** to 10 mol% led to a cleaner reaction and further improvement in the chemical yield to 62% with the same level of stereoselectivity (entry 7).

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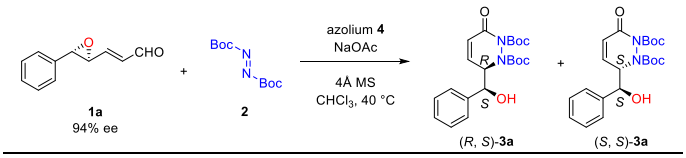
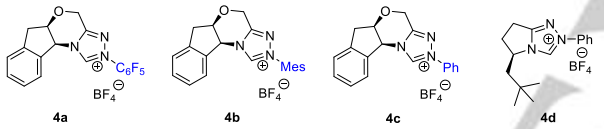
Aiming towards a divergent synthesis of the *anti*-amino alcohol series, we also examined the amination of **1a** by the use of the enantiomeric azolium *ent*-**4b** under otherwise identical conditions (entry 8). We speculated that the selectivity for this transformation would be much more challenging to achieve, considering the catalytic control has to overcome the inherent substrate control. To our excitement, the reaction proceeded smoothly with a complete switch of diastereoselectivity, producing (*S*, *S*)-**3a** as a single diastreomer in an excellent ee of 99%.[12]

Table 1. Optimization of Enantioselective Amination of **1a**[a]



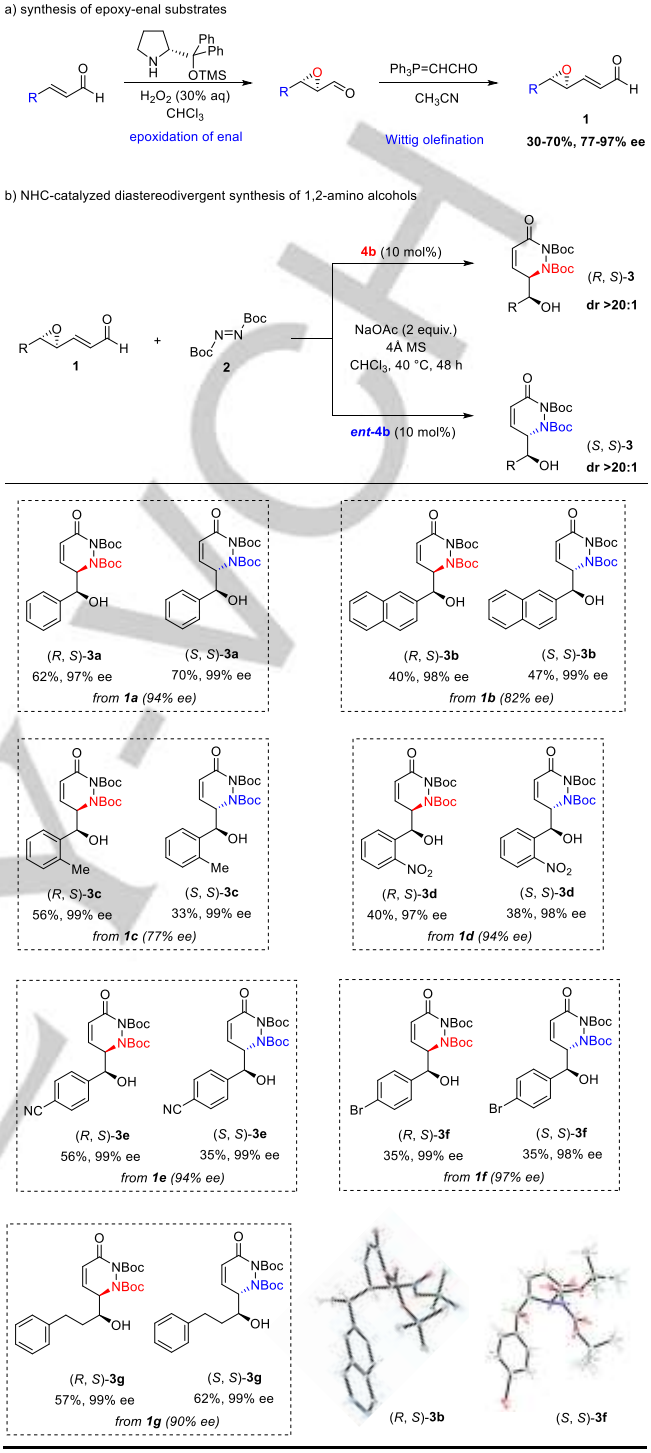
Entry	azolium	NaOAc	2	yield[b]	dr[c]	ee (%)[d]
1	20 mol% **4a**	2 equiv	2 equiv	<5%	-	n.d.
2	20 mol% **4b**	2 equiv	2 equiv	40	>20:1	97
3	20 mol% **4c**	2 equiv	2 equiv	<5%	-	n.d.
4	20 mol% **4d**	2 equiv	2 equiv	<5%	-	n.d.
5	20 mol% **4b**	1 equiv	2 equiv	37	>20:1	95
6	20 mol% **4b**	2 equiv	3 equiv	50	>20:1	95
7	10 mol% **4b**	2 equiv	3 equiv	62	>20:1	97
8	10 mol% ***ent*-4b**	2 equiv	3 equiv	70	1:>20	99

[a]Unless otherwise specified, the reactions were carried out using **1a** (0.1 mmol), **2**, chiral azolium species **4** and base in solvent (0.1 M in **1a**) for 48 h at 40 °C with. [b]Isolated yield. [c]Ratio of (*R*,*S*)-**3a**/(*S*,*S*)-**3a**. [d]Determined by chiral-phase HPLC analysis.

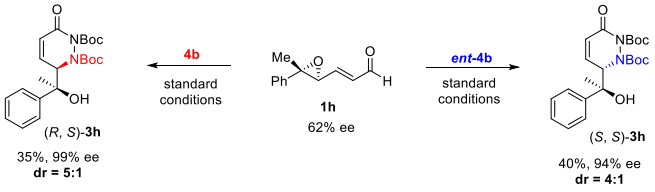


The scope of this stereo-divergent reaction proved to be very general. As shown in Scheme 2a, a range of epoxy enals **1** were prepared following the same procedure in good to excellent enantioselectivity and subjected to the amination reaction catalyzed by **4b** or ***ent*-4b** (Scheme 2b). In all the cases, either the *(R, S)- or (S, S)*-series of the amino alcohols **3** bearing aryl (**3a-f**) or alkyl substituents (**3g**) could be accessed with uniformly excellent level of diastereo- and enantioselectivity. Different functionalities such as nitro, cyano and halogen could be well-tolerated in the NHC-catalyzed amination step. Such a complete switch of diastereoselectivity represents a rare example in asymmetric catalysis. With this catalytic procedure incorporating two catalytic enantioselective steps, all the possible stereoisomers of the 1,2-amino alcohols could thus be accessed in a pure form. The relative and absolute configuration of *(R, S)*-**3b** as well as *(S, S)*-**3f** were unambiguously assigned by single crystal x-ray analysis.

To test the generality and limitations of this catalytic procedure, we prepared epoxy enal **1h** with a tri-substituted epoxide following the same two-step procedure, although the enantioselectivity from the asymmetric epoxidation step was only moderate (62% ee) as shown in Scheme 3. When **1h** was subjected to the standard NHC-catalyzed amination conditions, the diastereomic ratio of *(R, S)*-**3h:** *(S, S)*-**3h** dropped to 5:1 when using **4b** or 1:4 when ***ent*-4b** was employed. Importantly, the enantioselectivity for the final products were as high as 94-99% ee. In these transformations, the combination of two enantioselective steps boosted the enantiopurity of the major diastereomer of the products to a higher level by the sacrificial formation of the minor diastereomer.[9a]



Scheme 2. Scope of NHC-Catalyzed Amination of Chiral Epoxy Enals.



Scheme 3. Access to α-Amino Tertiary Alcohol.

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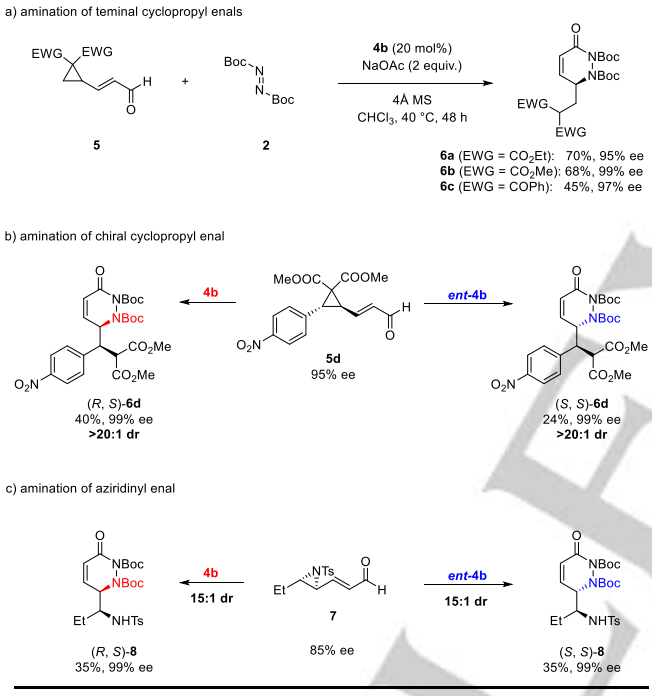
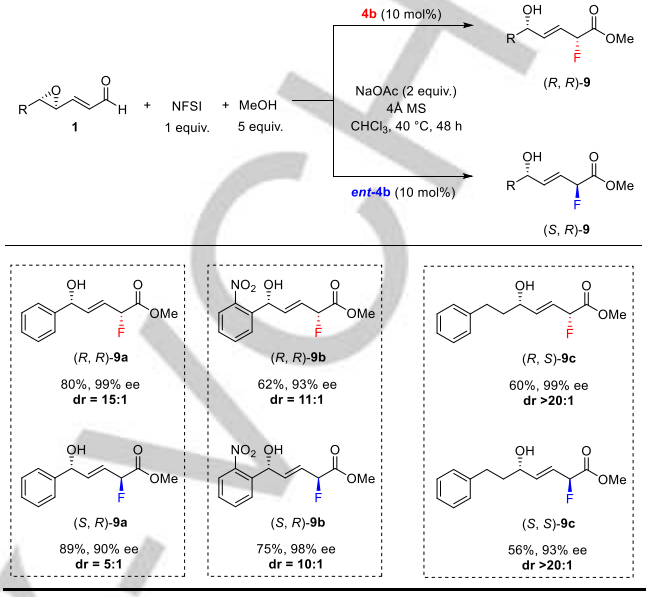
To further extend the scope of this catalytic procedure, we decided to explore substrates bearing other strained ring system such as cyclopropanes and aziridines. As shown in Scheme 4a, enals **5a**-**c** bearing a terminal cyclopropane were prepared and examined in the NHC-catalyzed amination step first. The ring opening amination reaction proceeded smoothly in these cases; different electron-withdrawing substitutents on the substrate including different diesters or diketone were all well-tolerated to produce **6a-c** in moderate to good yields with excellent enantiopurity. We then turned to the chiral cycloproyl enals such as **5d**, which was prepared in 95% ee via enantioselective cyclopropanation[13] followed by Wittig olefination. When **5d** was subjected to the NHC-catalyzed amination conditions using **4b** or ***ent*-4b**, to our delight, similar level of excellent dr and ee were obtained to deliver *(R, S)*-**6d** or *(S, S)*-**6d** as a pure stereoisomer, albeit with a low chemical yield. In addition, we also prepared and examined the analogous aziridinyl enal **7**,[14] which also underwent similar stereodivergent amination under the standard conditions to produce either *(R, S)*-**8** or *(S, S)*-**8** in high dr and excellent ee (Scheme 4c). These studies dramatically expanded the scope of this catalytic procedure to prepare more diverse multi-functional compounds bearing continuous stereogenic centers.



Scheme 4. NHC-Catalyzed Amination of Cyclopropyl and Aziridinyl Enals.

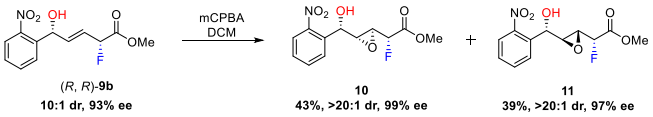
α-Fluorination of chiral epoxy enals for divergent 1,4-fluoro alcohol synthesis

In addition to the diastereodivergent synthesis of 1,2-amino alcohols bearing continuous stereogenic centers, we were also keen to explore the possibility of establishing the control of remote stereocenters by a similar three-step procedure that incorporates a different NHC-catalyzed α-functionalization of the epoxy enals. In particular, we decided to focus on the α-fluorination of **1** in an effort to prepare 1,4-fluoro allylic alcohols. As shown in Scheme 5a, when epoxy enal **1a** was subjected to the fluorination conditions using NSFI catalyzed by **4b** as previously developed by the Sun group,[7b] the corresponding 1,4-fluoro alcohol *(R, R)*-**9a** was obtained in a high yield of 80% with high dr of 15:1 and excellent 99% ee. This catalytic procedure also tolerated different substituted aryl or alkyl groups in the substrate structure to produce *(R, R)*-**9b** and *(R, S)*-**9c** in similarly high ee and high to excellent dr. More importantly, when the fluorination reactions were performed using ***ent*-4b**, we were delighted to observe a high level of diastereoselectivity (5:1 to >20:1 dr) for the formation of the other diastereomeric series of the 1,4-fluoro alcohols (shown at the bottom row of Scheme 5). Similarly, good chemical yields and high ee were obtained for these versatile multi-functionalized products.



Scheme 5. Scope of NHC-Catalyzed Fluorination of Chiral Epoxy Enals.

1,4-Fluoro alcohols **9** possess multiple functionalities and can serve as a versatile springboard to prepare valuable compounds. As a representative example, the epoxidation of the allylic alcohol moiety was attempted using mCPBA (Scheme 6). Although this acyclic substrate failed to induce a high diastereoselectivity for this transformation, the two epoxides **10** and **11** bearing four continuous stereogenic centers could be accessed in moderate yields and excellent diastereo- and enantiopurity, respectively. The relative configuration of these products was assigned by NOE measurements (see SI for details), which also helped to confirm the configuration of products **9**.



Scheme 6. Functionalization of Fluoro Allylic Alcohols.

A simplified mechanism using ***ent*-4b** is proposed to illustrate the stereocontrol of the reaction process. As illustrated in Scheme 7, chiral epoxy enal **1** undergoes vinylogous ring opening in the presence of NHC catalyst to form the key azolium dienolate intermediate, which likely undergoes fluorination or amination reaction in different conformations **I** or **I'**. For both transformations, the chiral catalyst acts as a steric shield to block the *re* face of the dienolate. The fluorination or amination reagents then approaches from the *Si* face (as shown in TS **II** or **III**) to deliver the products in high diastereoselectivity that is consistent with the experimental results. It is also noteworthy that based on the structure and conformation of these intermediates, the existing stereogenic center from the substrate does not show significant effect on the stereoselectivity of the NHC-catalyzed reactions.

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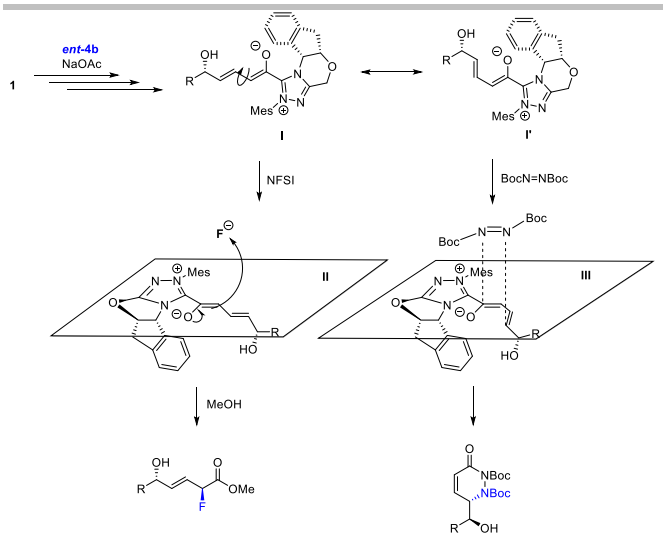

Scheme 7. Proposed mechanism and TS for amination and fluorination of chiral epoxy enals.

In conclusion, we have developed a straightforward three-step procedure that combines the power of enantioselective iminium catalysis and NHC catalysis to achieve stereodivergent preparation of functionalized 1,2-amino alcohols and 1,4-fluoro alcohols. The excellent stereocontrol from the NHC-catalyzed ring opening of epoxy-, aziridinyl or cyclopropyl enals is especially noteworthy. Further exploration of new reactivities for this class of versatile intermediates is under investigation in our laboratories.

Acknowledgements

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Experimental Section

NHC-catalyzed amination reaction: To a 4 mL vial was added epoxy enal **1, 5,** or **7** (0.10 mmol), **2** (0.20 to 0.30 mmol), triazolium salt **4b** (0.01 mmol), NaOAc (0.20 mmol) and 4Å MS (30 mg). The mixture was taken into the glovebox, where $CHCl_3$ (1.0 mL) was added using a micropipette. The reaction mixture was taken outside the glovebox and allowed to stir at 40 °C for 48 h. The reaction was cooled to ambient temperature, and the diastereoselectivity of the reaction was determined by NMR analysis of an aliquot of the crude reaction mixture. The combined crude reaction mixture was then directly purified by silica gel column chromatography with hexanes/ethyl acetate (8:1) as eluent to afford the desired products in pure form.

NHC-catalyzed α-fluorination reaction: To a 4 mL vial was added epoxy enal **1** (0.10 mmol), NFSI (0.10 mmol), triazolium salt **4b** (0.01 mmol), NaOAc (0.20 mmol) and 4Å MS (30 mg). The mixture was taken into the glovebox, where anhydrous MeOH (20 μL) and $CHCl_3$ (1.0 mL), was added using a micropipette. The reaction mixture was taken outside the glovebox and allowed to stir at 40 °C for 48 h. The reaction was cooled to ambient temperature, and the diastereoselectivity of the reaction was determined by NMR analysis of an aliquot of the crude reaction mixture. The combined crude reaction mixture was then directly purified by silica gel column chromatography with hexanes/ethyl acetate (8:1) as eluent to afford the desired products in pure form.

Keywords: divergent synthesis · *N*-heterocyclic carbene catalysis · fluorination · amination · enantioselectivity

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[12] The reaction of enantioenriched **1a** and **2** catalyzed by (±)-**4b** was carried out, which led to the formation of (*R*, *S*)-**3a** and (*S*, *S*)-**3a** in a 4:3 ratio. Similarly, the reaction with (±)-**1a** catalyzed by **4b** resulted in 4:5 dr. These experiment showed that the substrate control in the NHC-catalyzed step is not significant and the diastereoselectivity is mainly under catalyst control.

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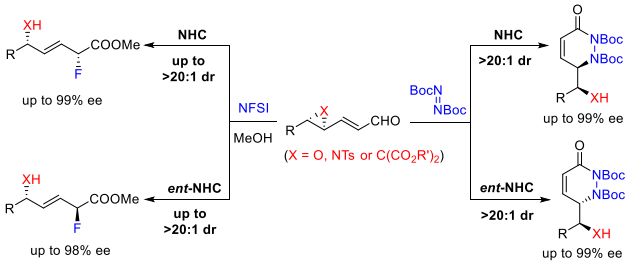

We describe herein an unprecedented NHC-catalyzed stereoselective ring opening of epoxy- or cyclopropyl-enals to deliver valuable compounds bearing multiple stereocenters. A straightforward three-step procedure involving two catalytic enantioselective transformations has been developed that leads to a regio- and stereodivergent synthesis of 1,2-amino alcohols or 1,4-fluoro alcohols with excellent diastereo- and enantiopurity.