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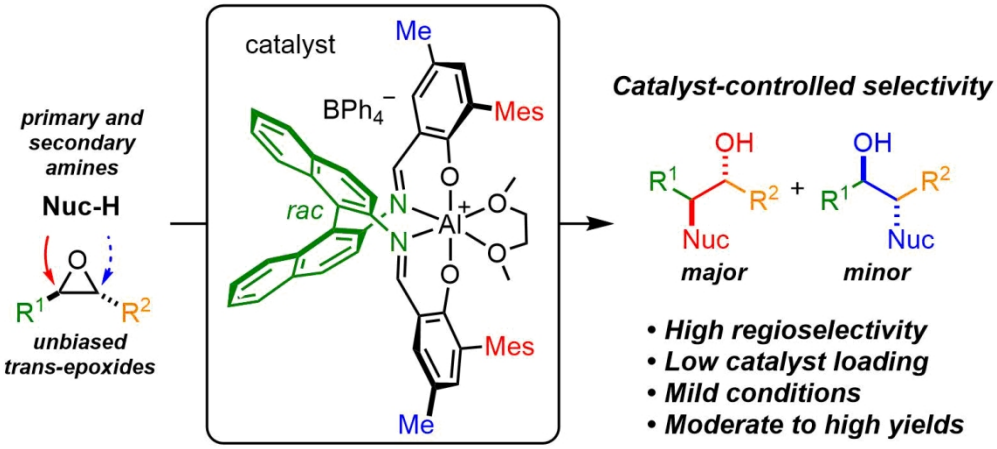
primary and secondary amines
Nuc-H
R1
R2
unbiased trans-epoxides
catalyst
Me
BPh4−
Mes
rac
N
N
Al
O
O
O
O
Mes
Me
Catalyst-controlled selectivity
OH
R1
R2
Nuc
major
OH
R1
R2
Nuc
minor
• High regioselectivity
• Low catalyst loading
• Mild conditions
• Moderate to high yields

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Nucleophilic ring opening of *trans*-2,3-disubstituted epoxides to β-amino alcohols with catalyst-controlled regioselectivity

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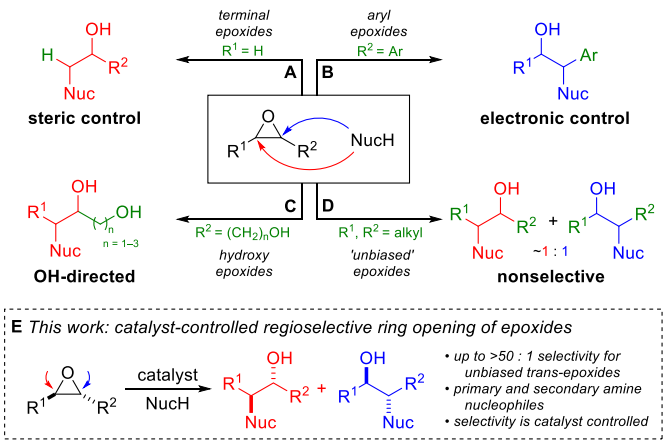
We report the nucleophilic ring opening of unsymmetrical *trans*-epoxides to β-amino alcohols with *catalyst-controlled regioselectivity*. This cationic aluminum salen catalyst, which contains bulky mesityl groups in the *ortho*-position of the phenoxide and a 2,2'-diamino-1,1'-binaphthalene backbone, transforms a variety of epoxides with high regioselectivity using nitrogen-containing nucleophiles. Unlike most reports, in which regioselectivity is substrate controlled, the regioselectivity in this system is catalyst controlled and allows selective nucleophilic ring opening of unbiased *trans*-epoxides.

Nucleophilic ring opening (NRO) of epoxides is a well-established method to access diverse, highly-functionalized molecules, such as β-amino alcohols.[1] These products are an important class of compounds used as catalysts, chiral auxiliaries, and intermediates for the synthesis of natural products and pharmaceuticals.[2] Classically, highly regioselective, catalytic systems for epoxide ring opening rely on strong substrate bias to control the regioselectivity.[1] For example, terminal epoxides are often used to sterically bias the nucleophilic attack to the less-hindered methylene carbon (Scheme 1A). Aromatic epoxides are also commonly employed to electronically bias the nucleophilic attack to the benzylic position. (Scheme 1B). Additionally, alcohol-, ether-, and sulfonamide-directed variants have been developed to achieve high regioselectivity through a chelating effect (Scheme 1C),[3] but the requirement for a nearby directing group limits the scope of the reaction. Most existing methods, however, cannot achieve good regioselectivity for 2,3-disubstituted epoxides with different alkyl substituents that are both sterically and electronically similar (referred to as 'unbiased' substrates). When non-aromatic 2,3-disubstituted epoxides are used in these reactions, symmetrical substrates are generally used to show activity, or enantioselectivity through *meso*-desymmetrization, while avoiding the issue of regioselectivity.[4] Examples using unsymmetrical, unbiased substrates lead to a mixture of products (Scheme 1D).[3c,5,6] One report from Kobayashi and coworkers demonstrated good regio- and enantioselectivity for unsymmetrical, unbiased *cis*-epoxides using a *meso*-desymmetrization catalyst, but no *trans*-epoxides were reported.[7] A general, catalyst-controlled regioselective NRO of unbiased *trans*-epoxides has not been reported and would be a useful addition to current methodology.

Scheme 1. Regioselective ring opening of different classes of epoxides[1,3c,e,f]



Our group has reported the regioselective carbonylation[8] and isomerization[9] of unbiased internal epoxides using bimetallic Al–salen cobaltate complexes. Additionally, one of the catalyst precursors could be used to promote the nucleophilic ring opening of *cis*-epoxides with similarly high selectivities using a latent HCl source.[8b] Herein, we expand upon this work by optimizing a cationic Al–salen Lewis acid paired with a non-nucleophilic anion for the regioselective ring opening of various unbiased *trans*-epoxides using nitrogen-containing nucleophiles (Scheme 1E).

We first optimized the salen ligand by varying the diamine linker as well as the *ortho*- and *para*-positions of the phenoxide (R^1 and R^2, respectively) (Chart 1). The catalyst variations (**1a**–**h**) were screened in THF for the ring opening of *trans*-2-octene

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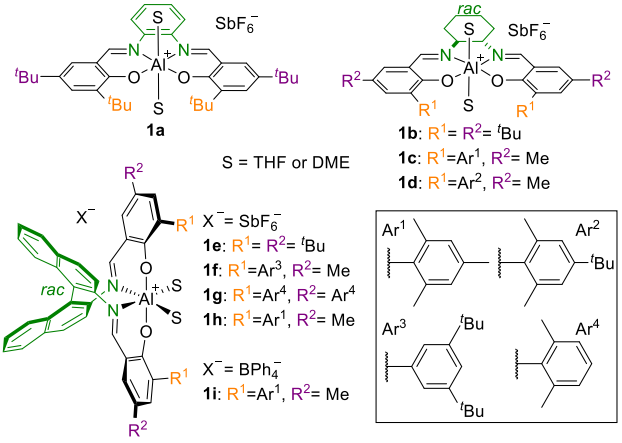
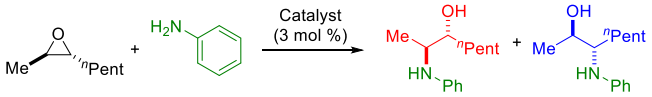
Chart 1. Catalysts screened for the regioselective ring opening of epoxides[13]



oxide (**2a**) with aniline (**3a**) (Table 1). Initially, we tested the first-generation catalysts [salphAl(THF)$_2$]$^+$[SbF$_6$]$^-$ (**1a**)[10] and [*rac*-salcyAl(THF)$_2$]$^+$[SbF$_6$]$^-$ (**1b**),[11] resulting in minimal regioselectivity (Table 1, entries 1 and 2), which was expected for unbiased internal epoxides.[5a] In our previous work, we observed that bulky aryl-substituents, particularly in the *ortho*-position, greatly improved regioselectivity for 2,3-disubstituted epoxides,[8,9] but only marginal improvement in regioselectivity was observed when *ortho*-aryl groups were paired with the 1,2-cyclohexyldiamine backbone (**1c** and **1d**, Table 1, entries 3 and 4).

We then tested the 2,2'-diamino-1,1'-binaphthalene (BINAM)[14] backbone because these ligands have previously been used to improve both regio- and enantioselectivity in NRO reactions of epoxides.[3c] Additionally, our group has used BINAM-based salen catalysts to achieve high selectivity for internal epoxide carbonylations.[8b,15] Similar to the salph and salcy catalysts, the di-*tert*-butyl variant (**1e**) resulted in unselective ring opening (entry 5), but further optimization led to 10 : 1 regioselectivity with catalyst **1h**, which features a bulky mesityl substituent in the *ortho*-position and a methyl group in the *para*-position (Table 1, entry 8). Changing the counter-anion

Table 1. Catalyst optimization[a]



Entry	Catalyst	Conv. (%)[b]	**4a** : **5a**[b]
1	**1a**	17	1 : 1.4
2	**1b**	22	1.2 : 1
3	**1c**	50	3.6 : 1
4	**1d**	85	2.5 : 1
5	**1e**	67	1.5 : 1
6	**1f**	13	1.2 : 1
7	**1g**	7	1.6 : 1
8	**1h**	90	10 : 1
9[c]	**1i**	77	12 : 1

[a] Conditions: 3 mol % catalyst (formed *in situ* from L$_n$Al–Cl + NaSbF$_6$),[12] THF (0.3 M), 22 °C, 18 h. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] NaBPh$_4$ used instead of NaSbF$_6$.

from SbF$_6^-$ to BPh$_4^-$ (**1i**) improved the regioselectivity even further to 12 : 1 (Table 1, entry 9).[16] While the exact mechanism through which regioselectivity is conferred is unknown, we hypothesize that a favorable epoxide binding geometry is dictated by the salen ligand and that a combination of the bulky mesityl substituents and the tight ion pair[12] between the cationic aluminum metal center and tetraphenylborate anion blocks nucleophilic attack to one epoxy carbon.

The reaction conditions for **1i** were then further optimized for regioselectivity, conversion, and reaction time (Table 2). A solvent screen revealed no activity in non-donating toluene and

Table 2. Reaction optimization for **1i** using epoxide **2a** and aniline (**3a**)[a]

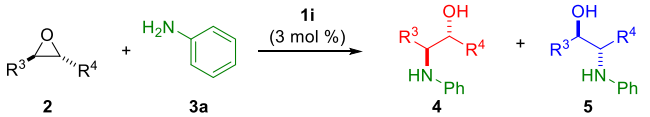
Entry	Solvent	Conc. (M)	Conv. (%)[b]	**4a : 5a**[b]
1	THF	0.3	77	12 : 1
2	Toluene	0.3	<5	n.d.
3	1,4-Dioxane	0.3	30	15 : 1
4	Et$_2$O	0.3	92	14 : 1
5	DME	0.3	69	15 : 1
6	DME	0.6	95	16 : 1
7	DME	1.2	>99	16 : 1
8	DME	2.0	>99	19 : 1
9[c]	DME	3.6	>99	19 : 1

[a] Conditions: 3 mol % **1i** (formed *in situ* from L$_n$Al–Cl and NaBPh$_4$),[12] 22 °C, 18 h. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] 40 °C, 4 h. n.d. = not determined.

high selectivity in 1,4-dioxane, diethyl ether, and DME (Table 2, entries 1–5). 1,4-Dioxane significantly slowed the reaction and the volatility of ether resulted in lower reproducibility, so DME was chosen as the optimal solvent. Increasing the substrate concentration from 0.3 to 2.0 M led to both an increase in conversion and selectivity (Table 2, entries 5–8). Further increasing the concentration to 3.6 M and heating the reaction to 40 °C allowed the reaction to proceed to full conversion in 4 h while maintaining 19 : 1 regioselectivity (entry 9). This result can be directly compared to recent reports which yield a 1 : 1 mixture of **4a** and **5a** when ring-opening *trans*-2-octene oxide with aniline.[3c]

Once the optimized reaction conditions were determined, we explored the scope of the reaction using aniline as the nucleophile (Table 3). To ensure full conversion of all epoxides, the reaction was run for 6 hours instead of 4 hours. A series of unbiased *trans*-epoxides with one methyl and one alkyl substituent were ring-opened with excellent regioselectivity for attack at the 2-position (yielding **4**) instead of the 3-position (yielding **5**) (Table 3, entries 1–4). Longer alkyl substituents generally led to higher regioselectivity, demonstrating additional substrate-control, but all of the β-amino alcohols were isolated in high yields. For epoxide **2e**, in which neither substituent is a methyl group, the selectivity dropped substantially to 2.4 : 1 (Table 3, entry 5), but this still represents a significant improvement on existing methods that yield ~1 : 1

Table 3. Epoxide substrate scope using aniline (**3a**) as the nucleophile

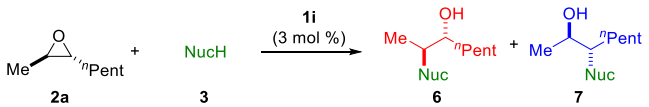


2 **3a** **4** **5**

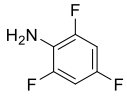
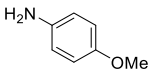
Entry	Epoxide	R^3	R^4	Yield (%)[b]	**4 : 5**[c]
1	**2b**	Me	Et	63	6 : 1
2	**2c**	Me	^{n}Pr	88	8 : 1
3	**2a**	Me	^{n}Pent	98	17 : 1
4	**2d**	Me	^{n}Hex	97	15 : 1
5	**2e**	Et	^{n}Bu	82	2.4 : 1
6	**2f**	Me	*p*-MeBn	91	>50 : 1
7	**2g**	Me	*m*-MeBn	78	>20 : 1
8	**2h**	Me	*o*-MeBn	86	14 : 1
9	**2i**	Me	CH_2OTBS	84	>50 : 1
10	***cis*-2j**	Me	^{n}Pent	95	1 : 1

[a] Conditions: 3 mol % **1i**, 0.46 mmol of epoxide, **3a** (1.1 eq, 8 M stock solution in DME), 40 °C, 6 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Table 4. Nucleophile scope using **2a** as the substrate[a]



2a **3** **6** **7**

Entry	NucH	**3**	Conv. (%)[b]	Yield (%)[c]	**6 : 7**[d]
1		**3b**	97	51	>20 : 1
2[e]		**3c**	88	55	12 : 1
3		**3d**	78	32	>50 : 1
4		**3e**	86	60	>20 : 1
5		**3f**	<5	<1	n.d.

[a] Conditions: 3 mol % **1i**, [epoxide] = 3.6 M in DME, 40 °C, 20 h. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] Determined by ^{1}H NMR spectroscopy of the isolated yield. [e] t_{rxn} = 6h. n.d. = not determined.

selectivity for dialkyl substrates using *racemic* catalysts.[3c,5a,c,e,f] This is in agreement with our previous results with these types of catalysts[9] and can be explained by the exceedingly similar sterics and electronics of the ethyl and *n*-butyl substituents.

Additional substrates with larger substituent differences, such as benzyl-substituted epoxides (**2f–2h**), resulted in excellent regioselectivities and good yields (Table 3, entry 6–8). The TBS-protected epoxy alcohol **2i** showed high regioselectivity and a single regioisomer was isolated in 84% yield (Table 3, entry 9). As previously seen,[9] the relative stereochemistry of the epoxide (i.e. *cis* versus *trans*) strongly influences the efficacy of the catalyst. When *cis*-2-octene oxide (**2j**) was subjected to the standard reaction conditions, no regioselectivity was observed, but the product mixture was still isolated in high yield (Table 3, entry 10).

We also explored the nucleophile scope of the reaction using *trans*-2-octene oxide (**2a**) as the substrate (Table 4). Aromatic amines were our focus due to their attenuated nucleophilicity, which avoids the unselective background ring-opening reaction not mediated by the Lewis acid catalyst. Less nucleophilic secondary and electron-poor nucleophiles required longer reaction times compared to aniline, so all reactions – except the electron-rich *p*-anisidine – were run for 20 hours. The electron-withdrawing 2,4,6-trifluoroaniline (**3b**) resulted in higher regioselectivity (>20 : 1) but lower isolated yield (Table 4, entry 1).[17] Using *p*-anisidine (**3c**), 88% conversion was reached in only 6h, but the products were formed with slightly lower selectivity (12 : 1) and modest isolated yield (55%, Table 4, entry 2) compared to the unsubstituted aniline (98%, Table 3, entry 3). This electron-rich nucleophile is of particular interest because of the potential to reveal the free amine through deprotection.[18]

The secondary nucleophiles were also explored to expand the scope of the reaction. *N*-Methyl aniline (**3d**) yielded clean **6d** in 32% isolated yield (Table 4, entry 3). Indoline (**3e**) resulted in high regioselectivity for attack at the 2-position (**6e**) over the 3-position (**7e**) (Table 4, entry 4), but product instability and free indoline co-elution made purification difficult.[19] Bulkier diisopropylamine (**3f**) did not show appreciable product formation by ^{1}H NMR spectroscopy after 20 h, though the exact mass of the product was observed in high-resolution mass spectrometry DART analysis suggesting trace amounts of product was present (Table 4, entry 5). This result is presumably due to diisopropylamine's significantly reduced nucleophilicity as well as catalyst decomposition, indicated by ligand crashing out of the reaction solution.

In conclusion, we report a general system to achieve catalyst-controlled regioselective NRO of unbiased *trans*-2,3-disubstituted epoxides. The catalyst consists of a cationic Al–salen Lewis acid and the non-coordinating anion such as BPh_4^-. The backbone and substituents on the salen ligand framework as well as the counter-anion were found to have dramatic effects on the regioselectivity of the reaction. A variety of epoxides were successfully ring opened by aniline with very high regioselectivity and in high yields, and both primary and secondary amines were employed to access internal β-amino alcohols that could not be selectively synthesized using existing methods. Future directions include the development of enantioselective variants using the enantiopure BINAM backbone to expand asymmetric NRO methodology beyond terminal and *meso*-epoxides. With this more general method for NRO in hand, complex β-amino alcohols will be more easily accessible, facilitating future synthesis of natural products and pharmaceuticals.

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Conflicts of interest

The authors declare no competing conflicts of interest.

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(11) Salcy = *N,N'-bis*(3,5-di-*tert*-butyl-salicyl-idene)-1,2-cyclohexanediamine)

(12) See ESI for more details.

(13) The generic structure for catalysts **1e–1i** is shown as C2 symmetric on the basis of a crystal structure containing the ligand for **1i**.[15a] However, NMR data of **1i** in solution supports a C1 symmetric structure.[12]

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(16) Other counter-anions – such as PF_6^-, $BAr^F{}_4^-$ (Ar^F = 3,5-*bis*(trifluoromethyl)phenyl), and BF_4^- – were tested, but resulted in lower conversion and selectivity compared to SbF_6^- and BPh_4^-. Ion pairing may play a role in the observed selectivity differences.[12]

(17) In a preliminary trial, 4-chloroaniline resulted in no conversion after 20 h. At this time, we do not have an explanation for the difference between 4-chloroaniline and 2,4,6-trifluoroaniline.

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(19) Some free indoline can be seen in the ^{1}H and ^{13}C NMR spectra of the purified product, but the reported yield corrects for the mass of indoline based on the integrations of the ^{1}H NMR spectrum.[12]