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Enantioselective aminolytic kinetic resolution (AKR) of epoxides catalyzed by recyclable polymeric Cr(III) salen complexes

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Abstract—Polymeric chiral Cr(III) salen complexes catalyzed regio-, diastereo-, and enantioselective aminolytic kinetic resolution (AKR) of *trans*-stilbene oxide, *trans*-β-methyl styrene oxide, and 6-CN-chromene oxide proceeded smoothly at room temperature, providing the desired *anti*-β-amino alcohols in high yields and enantiomeric excess (up to 100%).

1. Introduction

Enantiomerically pure β-amino alcohols are important structural units in many biologically active molecules as well as chiral auxiliaries/ligands that are used in asymmetric synthesis.[1] Although direct synthesis of *syn*-β-amino alcohols via Sharpless osmium catalyzed aminohydroxylation of alkenes,[2] direct addition of α-hydroxy ketones to imines,[3] and ring opening of *meso* epoxides with amines[4] has resulted in highly enantio-enriched *syn*-β-amino alcohols, the synthesis of enantiomerically pure *anti*-β-amino alcohols has been scarcely studied.[5] Among the various methods, the kinetic resolution[6,7] of readily accessible racemic 1,2-disubstituted epoxides with amines as nucleophiles is an attractive approach for the synthesis of enantiomerically pure *anti*-β-amino alcohols with high diastereoselectivity. In this direction, Bartoli et al. have recently reported for the first time the ring opening of *trans* and *meso* epoxides with anilines for the synthesis of *anti*/*syn*-β-amino alcohols using Jacobsen Cr(III) salen[8] catalyst, but separation and recycling of the catalyst is tedious which makes the system economically non-viable on the industrial scale. As chiral catalysts are expensive, their separation and repeated recycling is highly desirable. Attempts were made in the past for immobilization of chiral homogeneous catalysts[9] either by anchoring the catalyst on a solid support,[10a] by use of a two-phase system,[10b] or by using ionic liquids.[10c] All these approaches are interesting but usually require additional modifications of the catalyst. Moreover, such approaches frequently lead to partial loss of activity and/or enantioselectivity. In our continuing effort for making the catalytic system recyclable for enantioselective epoxidation of non-functionalized alkenes[11b,c] and hydrolytic kinetic resolution (HKR) of racemic epoxides,[11a] we report herein novel polymeric chiral Cr(III)(X) salen complexes **1**–**3** derived from (1*R*,2*R*)-(−)-cyclohexanediamine with 5,5′-methylene di-3-*tert*-butylsalicylaldehyde and X = Cl, NO_3, and ClO_4. These complexes proved to be recyclable (four times) catalysts for aminolytic kinetic resolution (AKR) of *trans*-stilbene oxide, *trans*-β-methyl styrene oxide, and CN-chromene oxide with aniline and substituted anilines to give β-amino alcohols in high yields (49% out of maximum 50% theoretical yield) with high regio- and diastereo/enantioselectivity (ee, up to 100%) leaving behind the corresponding valuable epoxide in high enantiomeric excess (ee, up to 98%).

2. Results and discussion

The polymeric salen ligand was synthesized according to the literature method[11,12] and catalysts **1**–**3** (Scheme 1) were prepared according to the procedure reported earlier.[13] Catalysts **1**–**3** (5 mol %) based on a monomeric salen unit were used for the AKR of *trans*-stilbene oxide and *trans*-β-methyl styrene oxide with aniline at room temperature, providing high yields (49%) of *anti*-β-amino alcohols **7a** and **8a** with high enantioselectivity (ee, 87%) of product

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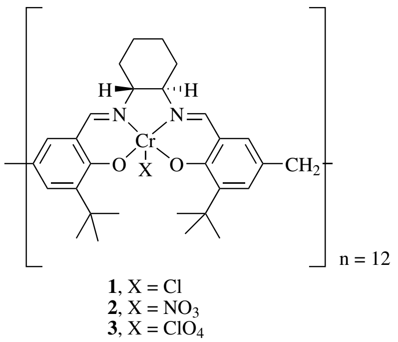


Scheme 1. Schematic representation of catalysts **1**–**3**.

7a being achieved in case of catalyst **1** (Table 1, entry 1). The ee of product **7a** was further improved up to 100% by a single crystallization. The order of reactivity[14] of complexes as determined by the initial rate constant of the three catalysts is **3** > **1** > **2** > Jacobsen Cr(III) salen as shown in Figure 1 and the enantiomeric excess of *anti*-β-amino alcohols **7a** was better in the case of catalyst **1** (Fig. 2). In comparison with Jacobsen Cr(III) salen catalyst, catalyst **1** (based on a monomeric salen unit) was found to be superior in terms of total turnover number (~5 times, due to recyclability) with retention of enantioselectivity (selectivity factor = 38 and 28 for catalyst **1** and the Jacobsen Cr(III) salen,[8] respectively) under identical experimental conditions for AKR of *trans*-stilbene oxide with aniline.[8] The increased reactivity of polymeric Cr(III) salen catalyst

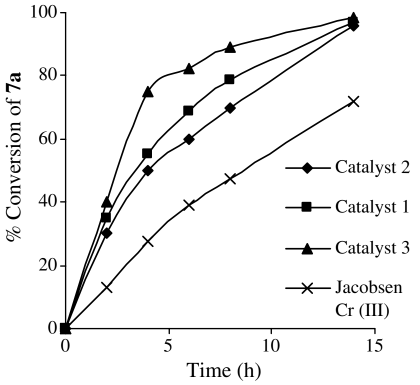
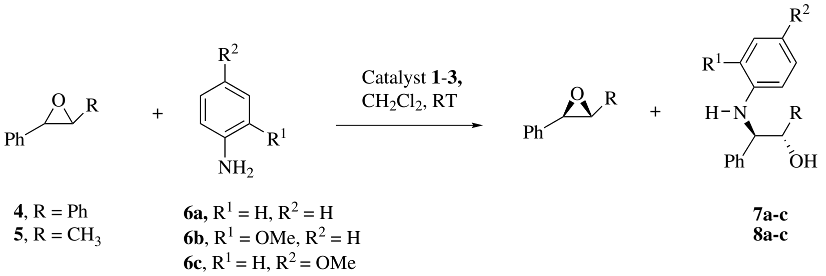


Figure 1. Time versus % conversion of the amino alcohols (based on maximum theoretical yield of 50%) with different catalysts.

Table 1. Enantioselective kinetic resolution of *trans*-epoxides using recyclable catalysts by anilines[a]



Entry	Catalyst	Epoxide	Amine	Time (h)	*trans*-Epoxide		Amino alcohols (**7a**–**c**, **8a**–**c**)		Selectivity factor[d]
					ee (%)[b]	Yield (%)[c]	ee (%)[b]	Yield (%)[c]	
1	**1**	**4**	**6a**	14	80	48	87 (100)[e]	49	38
2	**1**	**4**	**6a**	36	32	76	99[f]	23	266
3	**2**	**4**	**6a**	14	75	49	72	49	13
4	**3**	**4**	**6a**	14	75	48	79	49	19
5	**1**	**4**	**6a**	12	92	41	78 [g]	58	—
6	**1**	**4**	**6a**	10	98	30	60 [h]	68	—
7	**1**	**4**	**6b**	10	80	50	87	48	35
8	**1**	**4**	**6c**	16	85	50	76	47	15
9	**1**	**5**	**6a**	12	87	49	73	49	13
10	**1**	**5**	**6b**	24	70	50	59	48	7
11	**1**	**5**	**6b**	36	42	62	72[f]	35	9
12	**1**	**5**	**6c**	24	92	51	56	47	6

[a] 5 mol % catalyst was taken in 150 μl CH_2Cl_2 and epoxides (0.2 mmol) and aniline (0.1 mmol) were added and stirred at rt.

[b] The diastereoselectivity of *anti* product was found to be >99% determined by ^1H NMR and HPLC. The ee's of amino alcohols and epoxides were determined on Chiralpak OD column and the absolute configuration was assigned by comparing the specific rotations with literature values.[8]

[c] The conversion of product **7a** was determined on Chiralpak OD column using calibration curve of epoxide and amino alcohols and the rest given as isolated yield.

[d] Selectivity factor was calculated using the equation shown in Section 4.

[e] Value in parentheses refers to ee % after a single recrystallization.

[f] Reaction was carried at −10 °C.

[g] Reaction was performed with 0.6 equiv of aniline.

[h] Reaction was performed with 0.75 equiv of aniline.

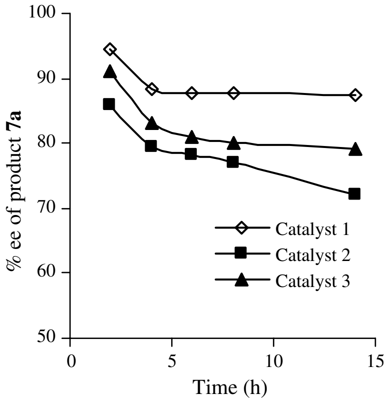


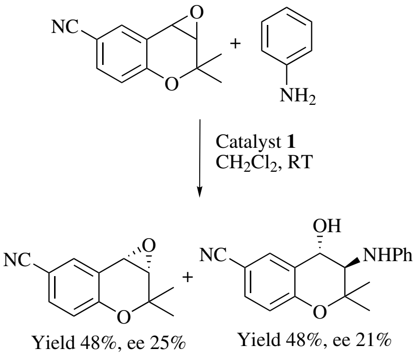
Figure 2. Time versus ee % of the amino alcohols with different catalysts.

1 as compared to Jacobsen Cr(III) salen is due to the presence of 12 active catalytic centers.

Furthermore, the kinetic resolution of racemic epoxide is temperature dependent.[6] On conducting the reaction at -10 °C, the reaction occurred slowly (conversion 23% in 36 h) but there was an increase in ee up to 99% and selectivity factor of *anti*-β-amino alcohol **7a** compared to when the reaction was carried out at rt (Table 1, entries 1 and 2). The effect of equivalents of nucleophile (0.5–0.75 equiv) on product yield for **7a** was also studied. When the amount of nucleophile is increased, there is an increase in the product yield of **7a** (Table 1, entries 5 and 6) with a decrease in its ee; concomitantly there is an enhancement in the ee of *trans*-stilbene oxide 98% (Table 1, entry 6).

It has been reported in the literature[15] that in the simple and synthetically useful preparation of chiral *anti*-β-amino alcohol, there is the need of an easily removable N-protecting group. On carrying out the AKR of *trans*-stilbene oxide and *trans*-β-methyl styrene oxide in the presence of substituted anilines, 2-methoxy and 4-methoxy anilines as easily removable N-protecting group, we have observed ee's of epoxides **4** in the range of 80–85% and 76–87% for the corresponding *N*-aryl amino alcohols **7b**–**7c** (Table 1, entries 7 and 8), respectively. In the case of epoxide **5**, the yield was in the range of 48–49% with moderate ee's 56–59% for the corresponding *N*-aryl amino alcohols **8b**–**8c** (Table 1, entries 10 and 12), which can be efficiently deprotected by oxidative dearylation without erosion of stereochemical integrity.[15] The absolute configuration of all products was found to be (1*S*,2*R*) and assigned by comparing the specific rotations with literature values.[8]

We have also tried AKR of (±)-6-cyano-2,2-dimethyl-chromene oxide with aniline as the nucleophile using catalyst **1** at room temperature where the reaction was complete within 3 h but the ee's of (3*S*,4*S*)-6-cyano-2,2-dimethyl-chromene oxide and corresponding β-amino alcohol were not very encouraging (Scheme 2). Furthermore, the AKR of (±)-6-cyano-2,2-dimethyl-chromene oxide with aniline at -10 and -30 °C took a longer reaction time (12 and 20 h, respectively) for completion without any improvement in the ee of the product. The absolute configuration of (3*S*,4*S*)-6-cyano-2,2-dimethyl-chromene oxide was assigned by comparing the specific rotation with the literature value.[16] On repeating the similar experiment with Jacobsen Cr(III) salen, the catalytic system behaved in a similar manner. Solvent plays a crucial role for AKR of epoxides with amines as the nucleophile.[8] In view of this, the effect of solvents (CH_2Cl_2, THF, CH_3OH and DMF) in AKR of *trans*-stilbene oxide with aniline was carried out using complex **1** as a catalyst (Table 2). Out of all the solvents used, non-coordinated solvents such as CH_2Cl_2 (Table 3, entry 15) were found to be better than coordinating solvents such as THF and CH_3OH (Table 3, entries 13 and 14). Further, the strongly coordinating solvent DMF (entry 16) does not at all favor this reaction.



Scheme 2. AKR of 6-cyano-2,2-dimethyl-chromene oxide.

The interesting feature of these novel polymeric Cr(III) salen complexes is their inherent tendency to precipitate out in non-polar solvents such as hexane due to their higher molecular weight and lower solubility. We have

Table 2. Aminolytic kinetic resolution (AKR) of *trans*-stilbene oxide using catalyst **1** by aniline in the presence of different solvents

Entry	Solvents	Time (h)	ee of epoxide	ee of amino alcohols	Yield of amino alcohols
13	THF	10	75	80	49
14	MeOH	18	70	82	48
15	DCM	14	80	87	49
16	DMF	24	—	—	No reaction

Table 3. Recycling data of catalyst **1** for AKR of *trans*-stilbene oxide using aniline as nucleophile[a]

Catalytic run	Time (h)	ee of epoxide[b]	ee of amino alcohols[b]	Yield of amino alcohols
1	14	80	87	49
2	14	80	86	48
3	15	79	85	47
4	17	75	87	46
5	20	71	86	45

[a] 5 mol % catalyst was taken in 150 μl CH_2Cl_2 and epoxides (0.2 mmol) and aniline (0.5 equiv) were added and stirred at rt.

[b] The diastereoselectivity of *anti* product was found to be >99% as determined by ^{1}H NMR and HPLC. The ee of amino alcohols and epoxides are determined on Chiralpak OD column and the absolute configuration was assigned by comparing the specific rotation with the literature value.[8]

recovered catalyst **1** which worked well in up to four cycles with gradual loss in reactivity but with retention of enantioselectivity of the β-amino alcohols and epoxides in the AKR of the *trans*-stilbene oxide with aniline (Table 3).

3. Conclusion

In conclusion, we have developed the recyclable polymeric Cr(III) salen complexes for AKR of *trans*-stilbene oxide, *trans*-β-methyl styrene oxide with different amines and obtained highly enantio- and diastereoselectively *anti*-β-amino alcohol in excellent yield. Catalyst **1** was successively recovered and reused four times with retention of enantioselectivity.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker F113V. The chemical shifts (δ) for ^{1}H and ^{13}C are given in parts per million relative to the signals of TMS. Coupling constants are given in hertz. FTIR spectra were recorded on a Perkin Elmer Spectrum GX spectrophotometer in a KBr/Nujol mull. Purification of reaction products was carried out by flash chromatography on silica gel (230–400 mesh). Melting points are uncorrected. Diastereomeric purity was determined by NMR analysis of the crude mixture and by HPLC analysis. Optical rotations are reported as follows: $[\alpha]_D^{27}$ (c = in g per 100 ml, solvent) were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments. Enantiomeric excesses (ee) were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak OD and OJ chiral columns (wavelengths 243 nm) with 2-propanol/hexane as eluent. HPLC traces were compared to racemic samples prepared with racemic Jacobsen Cr(III) salen as the catalyst. High-resolution mass spectra were obtained with LC–MS (Q-TOFF), LC (Waters), and MS (Micromass) instruments. The selectivity factor or k_{rel} for the product was calculated using the equation $s = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$, where the c is the conversion of amino alcohol and ee is the enantiomeric excess of amino alcohol.

Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[17] Racemic epoxide of *trans* β-methyl styrene was prepared by *m*-CPBA oxidation of the corresponding alkenes.[18] *trans*-Stilbene oxide and anilines **6a**–**6c** were purchased from Aldrich and used as received. (*R*,*R*)-Polymeric salen ligand was synthesized according to the literature procedure[11c,12] and polymeric Cr(III) salen was prepared as described below.

4.1.1. Synthesis of poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine chromium(III)] chloride 1. Following the procedure described by Jacobsen et al.,[19] a 100 ml two necked round bottom flask with a nitrogen inlet and outlet was charged with a solution of poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine] (641 mg, 1.31 mmol) in dry degassed THF (26 ml). To the yellow solution, anhydrous chromium(II) chloride (175 mg, 1.44 mmol) was added in a glove box and the resulting brown solution which turned dark green was stirred for 4 h under a blanket of nitrogen and then exposed to air for a further 3 h. The dark green solution was precipitated with *tert*-butyl methyl ether, which was filtered and washed with water to remove the coarse chromium chloride, dried overnight under vacuum (yielded 70%). The filtrate was washed with saturated NH_4Cl solution followed by brine and dried over anhydrous Na_2SO_4. It was concentrated under a vacuum to give the desired complex (yield 15%). The overall yield was found to be 85%. This complex is soluble in methanol and the color of the complex is dark brown. Mp >250 °C; Anal. Calcd for $C_{29}H_{37}ClCrN_2O_2\cdot 3/2H_2O\cdot 1/2THF$: C, 62.78; H, 6.97; N, 4.72. Found: C, 61.98; H, 6.89; N, 4.68; IR (KBr): 2944, 2361, 2340, 1619 (C=N), 1536, 1434, 1350, 1316, 1161, 831, 738, 658, 563 cm^{-1}; $[\alpha]_D^{27} = -646$ (c 0.024, CH_2Cl_2); Λ_M (MeOH) 114 mho cm^{-1} mol^{-1}; UV–vis: (MeOH) $\lambda_{max}(\varepsilon)$ 221 (18,560), 256 (11,305), 425 (2115).

4.1.2. Synthesis of poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine chromium(III)] nitrate 2. Poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine chromium(III)] chloride (281 mg, 0.5 mmol) was dissolved in a minimum amount of MeOH (20 ml), and a solution of silver nitrate (126 mg, 0.75 mmol) in water (4 ml) was added.[13] The resulting suspension was stirred for 30 min and a white precipitate of silver chloride was filtered off. The filtrate was concentrated to yield a brown solid and dried under vacuum (yield 72%). Anal. Calcd for $C_{29}H_{37}CrN_3O_5\cdot H_2O\cdot CH_3OH$: C, 59.10; H, 7.11; N, 6.89. Found: C, 58.39; H, 6.98; N, 6.84; IR (KBr): 2946, 2865, 1620 (C=N), 1536, 1433, 1384 (N–O), 1160, 831, 783, 689, 564 cm^{-1}; $[\alpha]_D^{27} = -514$ (c 0.024, CH_2Cl_2); Λ_M (MeOH) 153 mho cm^{-1} mol^{-1} UV–vis: (MeOH) $\lambda_{max}(\varepsilon)$ 219 (18,074), 258 (11,217), 424 (2116).

4.1.3. Synthesis of poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine chromium(III)] perchlorate 3. Poly[(*R*,*R*)-(−)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}-cyclohexene-1,2-diamine chromium(III)] chloride (281 mg, 0.5 mmol) was dissolved in a minimum amount of MeOH (20 ml), and a solution of silver perchlorate (126 mg, 0.75 mmol) in water (4 ml) was added.[13] The resulting suspension was stirred for 30 min and a white precipitate of silver chloride was filtered off. The filtrate was concentrated to yield a brown solid and dried under vacuum (yield 72%). Anal. Calcd for $C_{29}H_{37}ClCrN_2O_6\cdot H_2O\cdot CH_3OH$: C, 55.68; H, 6.70; N, 4.33. Found: C, 54.89; H, 6.59; N, 4.26; IR (KBr): 2947, 2865, 2360, 1617 (C=N), 1538, 1314, 1100 (Cl–O), 831, 688, 565 cm^{-1}; $[\alpha]_D^{27} = -531$ (c 0.024, CH_2Cl_2); Λ_M (MeOH) 144 mho cm^{-1} mol^{-1}; UV–vis: (CH_2Cl_2) $\lambda_{max}(\varepsilon)$ 220 (17,867), 257 (11,195), 424 (2073).

4.2. General procedure for asymmetric catalytic ring opening of *trans*-aromatic epoxides

All the reactions were carried out in undistilled CH_2Cl_2 without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, catalysts **1–3** (0.01 mmol, based on the monomeric salen unit) and the epoxide (0.20 mmol) were dissolved in 0.15 ml of CH_2Cl_2, but the catalysts are not soluble in CH_2Cl_2. The tube was closed with a rubber stopper and the mixture was stirred at room temperature for 5 min. Then the solution was cooled to the indicated temperature, aniline (0.10 mmol) was added and the catalyst was solubilized. The resulting reaction mixture was stirred until the disappearance of the amine. The crude reaction mixture was directly charged on the chromatography column and purified on silica.

4.2.1. (1*R*,2*R*)-1,2-Diphenyl-oxirane 4.[8] The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a white solid; Mp 62 °C; $[\alpha]_D^{27} = +310$ (*c* 2.5, C_6H_6, ee 98%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 90:10, flow rate = 0.5 ml/min, PDA detector at 228 nm, $t_R = 13.60$ (1*S*,2*S*), $t_R = 19.26$ (1*R*,2*R*); LCMS: $m/z = 197.1$ $[M+H]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 3.88 (s, 2H), 7.15–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm): 63.0, 128.5, 128.8, 135.7, 137.3.

4.2.2. (1*S*,2*R*)-1,2-Diphenyl-2-phenylanilino-ethanol 7a.[8] The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a white solid; Mp 122–125 °C; $[\alpha]_D^{27} = +45.6$ (*c* 1, $CHCl_3$, ee 87%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 90:10, flow rate = 0.5 ml/min, PDA detector at 243 nm, $t_R = 29.60$ (1*R*,2*S*), $t_R = 50.43$ (1*S*,2*R*); LCMS: $m/z = 290$ $[M+H]^+$, 312 $[M+Na]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 2.32 (br s, 1H), 4.44 (br s, 1H), 4.66 (d, 1H, $J = 3.8$ Hz), 5.05 (d, 1H, $J = 3.4$ Hz), 649–6.53 (m, 1H), 6.60–6.67 (m, 2H), 7.06–7.15 (m, 2H), 7.21–7.25 (m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm): 63.7, 77.1, 113.9, 117.9, 126.5, 127.6, 127.9, 128.0, 128.2, 128.3, 129.1, 138.4, 140.0, 146.7.

4.2.3. (1*S*,2*R*)-1,2-Diphenyl-2-(2-methoxy-phenylanilino)-ethanol 7b.[8] The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a colorless foam; $[\alpha]_D^{27} = +26$ (*c* 1.2, $CHCl_3$, ee 87%); enantiomeric excess was determined by HPLC analysis using Chiralpak OJ column, hexane/isopropanol = 70:30, flow rate = 0.5 ml/min, PDA detector at 254 nm, $t_R = 21.69$ (1*R*,2*S*); $t_R = 31.75$ (1*S*,2*R*); LCMS: $m/z = 320$ $[M+H]^+$, 342 $[M+Na]^+$, 662 $[2M+Na]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 2.35 (br s, 1H), 3.80 (s, 3H), 4.63 (d, 1H, $J = 4.8$ Hz), 5.05 (m, 2H), 6.32–6.37 (m, 1H), 6.57–6.73 (m, 3H), 7.09–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm): 55.6, 63.7, 77.3, 109.6, 111.5, 117.1, 121.2, 126.5, 127.5, 127.7, 127.9, 128.1, 136.8, 138.8, 140.3, 147.1.

4.2.4. (1*S*,2*R*)-1,2-Diphenyl-2-(4-methoxy-phenylanilino)-ethanol 7c.[8] The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a white solid; Mp 121–124 °C; $[\alpha]_D^{27} = +32.5$ (*c* 1, $CHCl_3$, ee 76%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 70:30, flow rate = 0.5 ml/min, PDA detector at 254 nm, $t_R = 17.60$ (1*R*,2*S*), $t_R = 20.12$ (1*S*,2*R*); LCMS: $m/z = 320$ $[M+H]^+$, 342 $[M+Na]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 2.38 (br s, 1H), 3.66 (s, 3H), 4.13 (br s, 1H), 4.59 (d, 1H, $J = 4.4$ Hz), 5.01 (d, 1H, $J = 4.2$ Hz), 6.46 (m, 2H), 6.65 (m, 2H), 7.10–7.24 (m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm): 55.6, 64.7, 77.1, 114.7, 117.1, 115.5, 126.5, 127.5, 127.8, 127.9, 128.2, 128.3, 138.7, 140.0, 140.8, 152.4.

4.2.5. (2*R*,3*R*)-2-Methyl-3-phenyl-oxirane 5.[8] The title compound was isolated by column chromatography (hexane/AcOEt = 95:5) as a liquid; $[\alpha]_D^{27} = +66$ (*c* 1.0, CH_2Cl_2, ee 92%); enantiomeric excess was determined by GC analysis using chiral-GTA column; LCMS: $m/z = 135.1$ $[M+H]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 1.43 (d, 3H, $J = 5.2$ Hz), 3.01–3.06 (m, 1H), 3.56 (d, 1H, $J = 2.1$ Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 17.8, 58.9, 59.5, 125.5, 127.9, 128.3, 137.7.

4.2.6. (1*R*,2*S*)-1-Phenylanilino-1-phenyl-propan-2-ol 8a. The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a high dense oil; $[\alpha]_D^{27} = -20.2$ (*c* 0.9, $CHCl_3$, ee 73%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 90:10, flow rate = 0.5 ml/min, PDA detector at 245 nm, $t_R = 23.66$ (1*R*,2*S*), $t_R = 32.19$ (1*S*,2*R*); LCMS $m/z = 228$ $[M+H]^+$, 210 $[M-OH]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 1.12 (d, 3H, $J = 6.4$ Hz), 4.13–4.18 (m, 1H), 4.35 (d, 1H, $J = 4.0$ Hz), 6.51–6.67 (m, 3H), 7.07–7.11 (m, 2H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.5, 63.1, 70.5, 113.6, 117.6, 127.5, 127.7, 128.5, 129.1, 139.3, 147.1.

4.2.7. (1*R*,2*S*)-1-(2-Methoxy-phenylanilino)-1-phenyl-propan-2-ol 8b. The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as high dense oil; $[\alpha]_D^{27} = -19.5$ (*c* 0.8, $CHCl_3$, ee 72%); enantiomeric excess was determined by HPLC analysis using Chiralpak OJ column, hexane/isopropanol = 80:20, flow rate = 0.5 ml/min, PDA detector at 245 nm, $t_R = 21.17$ (1*S*,2*R*), $t_R = 29.24$ (1*R*,2*S*); LCMS $m/z = 258$ $[M+H]^+$, 280 $[M+Na]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 1.16 (d, 3H, $J = 6.4$ Hz), 3.88 (s, 3H), 4.14–4.20 (m, 1H), 4.36–4.39 (d, 1H, $J = 4.4$ Hz,), 6.35–6.39 (m, 1H), 6.60–6.78 (m, 3H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.3, 55.4, 63.2, 70.7, 109.4, 112.3, 116.8, 121.1, 127.4, 127.6, 128.5, 139.1, 141.1.

4.2.8. (1*R*,2*S*)-1-(4-Methoxy-phenylanilino)-1-phenyl-propan-2-ol 8c.[8] The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as a high dense oil; point: $[\alpha]_D^{27} = -15.8$ (*c* 1.3, $CHCl_3$, ee 56%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 80:20, flow rate = 0.5 ml/min, PDA detector at 245 nm, $t_R = 19.00$ (1*R*,2*S*), $t_R = 20.75$ (1*S*,2*R*); LCMS $m/z = 258$ $[M+H]^+$, 280 $[M+Na]^+$; ^1H NMR ($CDCl_3$) δ (ppm): 1.12 (d, 3H, $J = 6.4$ Hz), 3.69 (s, 3H), 4.14–4.20 (m, 1H), 4.30 (d, 1H, $J = 4.4$ Hz), 6.50–6.55 (m, 2H), 6.66–6.70 (m, 2H), 7.25–

7.34 (m, 5H); ^{13}C NMR (CDCl$_3$) δ (ppm): 19.2, 55.7, 64.0, 70.5, 114.7, 115.1, 127.5, 127.7, 128.5, 139.2, 141.2, 139.1, 152.2.

4.2.9. (3*S*,4*S*)-6-Cyano-2,2-dimethyl-3,4 epoxy-chromane. The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as a white solid; Mp 138–139 °C and the absolute configuration was determined by comparing optical rotation and HPLC chromatogram; $[\alpha]_D^{27} = -85.7$ (*c* 1, CH$_2$Cl$_2$, ee 98%);[15] $[\alpha]_D^{27} = -6.9$ (*c* 0.8, CH$_2$Cl$_2$, ee 25%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD column, hexane/isopropanol = 80:20, flow rate = 0.5 ml/min, PDA detector at 254 nm, $t_R = 16.92$ (3*R*,4*R*), $t_R = 19.72$ (3*S*,4*S*); LCMS: $m/z = 202$ [M+H]$^+$; ^{1}H NMR (CDCl$_3$) δ (ppm): 1.30 (s, 3H), 1.60 (s, 3H), 3.54 (d, 1H, $J = 4.4$ Hz), 3.93 (d, 1H, $J = 4.4$ Hz), 6.87 (d, 1H, $J = 8.4$ Hz), 7.50–7.55 (m, 1H), 7.65 (s, 1H); ^{13}C NMR (CDCl$_3$) δ (ppm): 22.8, 25.3, 49.6, 62.0, 74.5, 104.1, 118.8, 133.5, 133.59, 134.2, 156.31.

4.2.10. (3*R*,4*S*)-6-Cyano-2,2-dimethyl-3-(phenylanilino)-chromane-4-ol. The title compound was isolated by column chromatography (hexane/AcOEt = 90:10) as a white solid; Mp 125–128 °C; $[\alpha]_D^{27} = +14.6$ (*c* 1.2, CH$_2$Cl$_2$, ee 21%); enantiomeric excess was determined by HPLC analysis using Chiralpak OD Column, hexane/isopropanol = 80:20, flow rate = 0.5 ml/min, PDA detector at 254 nm, $t_R = 22.26$ (3*R*,4*S*), $t_R = 24.84$ (3*S*,4*R*); LCMS: $m/z = 295$ [M+H]$^+$, 317 [M+Na]$^+$; ^{1}H NMR (CDCl$_3$) δ (ppm): 1.24 (s, 3H), 1.44 (s, 3H), 2.70 (br s, 1H), 3.58 (d, 1H, $J = 8.4$ Hz), 3.75 (br s, 1H), 4.39 (d, 1H, $J = 8.8$ Hz), 6.64–6.79 (m, 4H), 7.08–7.16 (m, 2H), 7.29–7.33 (m, 1H), 7.50 (s, 1H); ^{13}C NMR (CDCl$_3$) δ (ppm): 19.3, 26.5, 53.8, 73.5, 79.8, 113.6, 118.2, 119.0, 124.8, 129.7, 132.4, 132.8, 139.3, 147.2, 156.5.

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