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An enantiopure galactose oxidase model: synthesis of chiral amino alcohols through oxidative kinetic resolution catalyzed by a chiral copper complex

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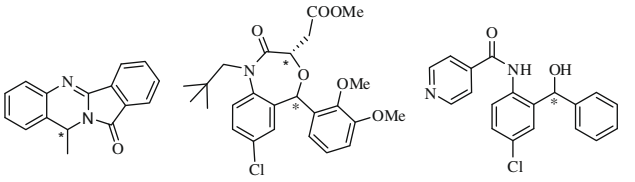
ABSTRACT

An enantiopure galactose oxidase (GO) enzyme model has been synthesized from readily available (*R*)-BINAM and $Cu(OTf)_2$, and the enantiopure GO model has been effectively used in situ as an efficient chiral catalyst for the synthesis of chiral amino alcohols through oxidative kinetic resolution (OKR), where molecular oxygen is used as the sole oxidant. Under the proposed catalytic conditions, both *ortho*- and *para*-substituted amino alcohols were resolved with good to excellent enantiomeric excesses through oxidative kinetic resolution.

1. Introduction

The synthesis of chiral amino alcohols is very important in organic synthesis, since intermediates of this type are major building blocks in the synthesis of many pharmaceutically important molecules including antihistaminic, anesthetic, diuretic, antidepressive, antiarrhythmic, antitumoral, and anticholinergic compounds (Fig. 1).[1] Gerearly, these chiral amino alcohols can be synthesized by reduction of optically active α-amino acids[2] or enantioselective reduction of the corresponding prochiral amino ketones.[3] Kinetic resolution of amino alcohols through enzyme-catalyzed acylation or deacylation is also one of the most efficient methods for the synthesis of chiral amino alcohols.[4] Non-enzymatic kinetic resolution (NKR) is an alternative for the enzymatic process, which is considered to be a challenging issue in organic synthesis.[5]



batracylin (antitumoural agent) | 4,1-benzoxazepine derivative (squalene synthase inhibitor) | *N*-isonicotinoyl derivarive of 2-aminoalcohol (rice plant growth regulator)

Figure 1. Some of the pharmaceutically important molecules, where chiral amino alcohols are used as important building blocks.

Although various efficient transition metal-based catalysts are reported in the literature for the NKR of racemic secondary benzylic alcohols,[6] NKR of racemic amino alcohols that will produce the corresponding enantiopure amino alcohols is a less explored method in the literature. The pioneering works done by Sharpless using stoichiometric quantities of a chiral titanium tartrate complex through N-oxide formation in the early eighties[7] followed by Nishiyama where he used stoichiometric quantities of a chiral-halogenating agent [(*R*)-BINAM-NCS] for the NKR of an amino alcohol[8] are the only few reports in the literature. Herein, for the first time we report the catalytic NKR of racemic amino alcohols using a chiral copper complex as a bio-mimetic model of galactose oxidase enzyme.

Galactose oxidase (GO) is a copper-containing fungal enzyme, which oxidizes alcohols to the corresponding aldehydes with concomitant reduction of molecular oxygen.[9] Its crystal structure reveals a unique mononuclear copper site with two nitrogens (from histidine imidazole groups) and two oxygens (from tyrosine groups) as donor atoms, plus an exogenous water or acetate molecule in a distorted square-pyramidal co-ordination.[10] GO enzyme contains chiral copper in its active site, wherein chirality is due to the histidine and tyrosine residues. This enzyme has so far inspired several research groups to design a variety of achiral or racemic synthetic analogues.[9,11]

2. Results and discussion

As a continuation to our copper-catalyzed oxidation chemistry,[12] very recently, for the first time we have synthesized an enantiopure model of galactose oxidase enzyme from readily available (*R*)-BINAM and $Cu(OTf)_2$ in our laboratory, and this enantiopure GO model has been successfully used as an efficient chiral catalyst for the first chiral copper-catalyzed oxidative kinetic resolution of racemic benzoins.[13] Further, we wish to extend our investigations

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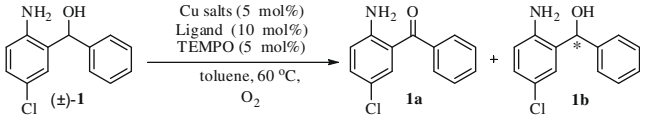
Table 1
Screening of different chiral ligands and copper salts for the OKR of amino alcohol (±)-1[a]



Entry	Ligand	Cu salts	Time (h)	Yield[b]		% ee of Amino alcohol[c]
				Ketone	Amino alcohol	
1	**L1**	$Cu(OTf)_2$	24	57	29	71
2	**L2**	$Cu(OTf)_2$	35	59	29	12
3	**L3**	$Cu(OTf)_2$	29	58	31	07
4	**L4**	$Cu(OTf)_2$	33	60	33	05
5	**L5**	$Cu(OTf)_2$	31	57	32	02
6	**L1**	CuCl	36	65	29	06
7	**L1**	$CuCl_2$	29	59	27	05
8	**L1**	CuBr	27	60	31	00
9	**L1**	CuI	48	61	32	00
10	**L1**	$Cu(OAc)_2$	29	57	27	06

[a] Reaction conditions: 10 mol % ligand, 5 mol % Cu salt, 5 mol % TEMPO, 1 mmol amino alcohol, O_2 at 60 °C.
[b] Isolated yields.
[c] % Ee was determined by HPLC using Diacel chiral AS-H column.

by employing the enantiopure GO model that is a (*R*)-BINAM–$Cu(OTf)_2$ complex as an efficient catalyst for the oxidative kinetic resolution of racemic amino alcohols to synthesize biologically important, optically active amino alcohols. It is important to mention that this is the first chiral copper-catalyzed OKR of racemic amino alcohols, where molecular oxygen is used as sole oxidant.

During our initial optimization studies, we had taken racemic (2-amino-5-chlorophenyl)(phenyl)methanol **1** as the model substrate for the chiral copper-catalyzed OKR, and the results are summarized in Table 1. Treatment of **1** with the (*R*)-BINAM–$Cu(OTf)_2$ complex at 60 °C in the presence of TEMPO and molecular oxygen provided 29% of the recovered alcohol **1b** in 24 h with 71% ee, which encouraged us to continue our optimization with the same racemic amino alcohol **1.** Later, we screened reactions with different nitrogen-containing ligands (Fig. 2)[14] to improve the *enantiomeric excess* of the recovered amino alcohol. Unfortunately, none of these ligands were successful and provided very poor enantiomeric excess for the recovered amino alcohol **1b** (Table 1).

Then we screened different copper salts, which revealed that $Cu(OTf)_2$ is the best source of copper salt along with (*R*)-BINAM (Table 1, entry 1). Later, we employed different ratios of $Cu(OTf)_2$ and (*R*)-BINAM, where 5 mol % $Cu(OTf)_2$ and 10 mol % of (*R*)-BINAM (1:2 complex) provided the best result (Table 2, entry 2) over 1:1 and 1:4 Cu-BINAM complex (entry 2 vs entries 1 and 3). This result clearly shows that an optimized 2:1 ratio of (*R*)-BINAM and $Cu(OTf)_2$ is the appropriate combination for effective catalytic activity, and this ratio corresponds unequivocally exactly to the ratio obtained from our crystal structure of GO model.[15] Examination of various organic solvents showed that toluene was the best choice of the solvent (Table 3). There was no significant reaction observed without using either $Cu(OTf)_2$ or (*R*)-BINAM or both. Similarly, there was no reaction without TEMPO. Based on the above results, we have a strong insight that TEMPO might act as a hydrogen acceptor during the catalytic cycle.[16]

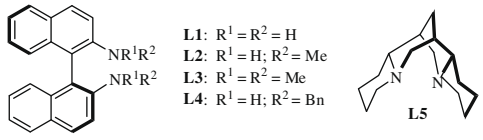
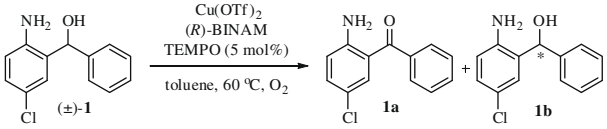


Figure 2. Different chiral ligands screened for the OKR of (±)-**1**.

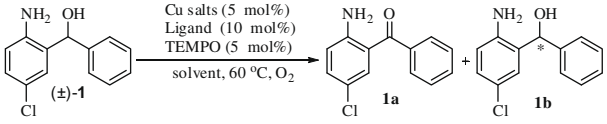
Table 2
Effect of different ratios of (*R*)-BINAM and $Cu(OTf)_2$ on the OKR of (±)-**1**[a]



Entry	$Cu(OTf)_2$ (mol %)	(*R*)-BINAM (mol %)	Time (h)	% Yield[b]		% ee of Amino alcohol[c]
				Amino alcohol	Ketone	
1	5	5	48	29	55	33
2	5	10	24	29	57	71
3	5	20	10	25	59	63

[a] Reaction conditions: different ratios of Cu salts and ligands, 5 mol % TEMPO, 1 mmol alcohol, O_2 (balloon) at 60 °C.
[b] Isolated yields.
[c] % Ee was determined by HPLC using Diacel chiral AS-H column.

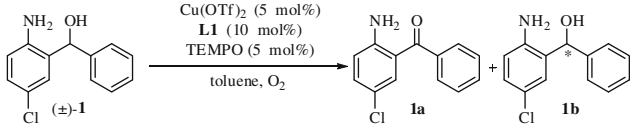
Table 3
Screening of different solvents for the OKR of amino alcohol (±)-**1**[a]



Entry	Solvent	Time (h)	% Yield[b]		% ee of Amino alcohol[c]
			Amino alcohol	Ketone	
1	Toluene	24	29	57	71
2	Xylene	28	27	59	52
3	DCM	23	32	60	12
4	Benzene	31	34	61	23
5	THF	21	29	63	15
6	DMF	14	30	62	19
7	DMSO	9	28	64	12
8	CH_3NO_2	21	32	65	05

[a] Reaction conditions: 5 mol % $Cu(OTf)_2$, 10 mol % (*R*)-BINAM, 5 mol % TEMPO, 1 mmol alcohol, O_2 (balloon) at 60 °C.
[b] Isolated yields.
[c] % Ee was determined by HPLC using Diacel chiral AS-H column.

Table 4
Effect of temperature on OKR of (±)-**1**[a]



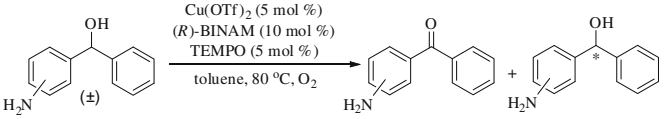
Entry	$Cu(OTf)_2$ (mol %)	(*R*)-BINAM (mol %)	Temp (°C)	Time	Yield[b]		% ee of Amino alcohol[c]
					Ketone	Amino alcohol	
1	5	10	60	24 h	59	29	71
2	5	10	70	19 h	61	29	75
3	5	10	80	11h	57	27	92
4	5	10	90	6 h	58	25	37
5	5	10	rt	2 days	No reaction		00[d]

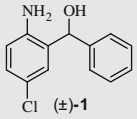
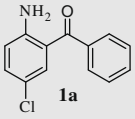
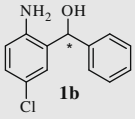
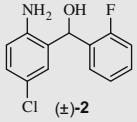
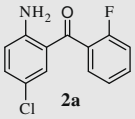
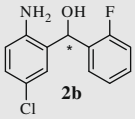
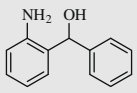
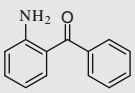
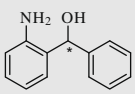
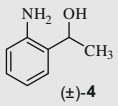
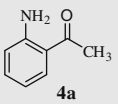
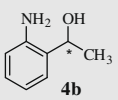
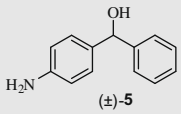
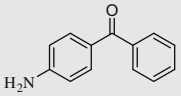
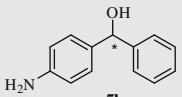
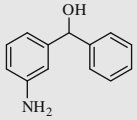
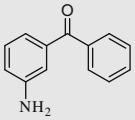
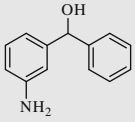
[a] Reaction conditions: 10 mol % (*R*)-BINAM, 5 mol % $Cu(OTf)_2$ 5 mol % TEMPO, 1 mmol alcohol, O_2 (balloon) at different temperatures.
[b] Isolated yields.
[c] % Ee was determined by HPLC using Diacel chiral AS-H column.
[d] Reaction was not proceeded beyond 10–15% even after longer hours.

In general, increasing the temperature of an enantioselective organic transformation reduces the selectivity.[17] So, we proceeded to monitor the effect of temperature in this chiral copper-catalyzed OKR, and the results are summarized in Table 4. We were surprised to observe a totally different behavior in the OKR of amino alcohol (±)-**1**. When the amino alcohol **1** was subjected to OKR at 60 °C, the recovered amino alcohol **1b** was obtained with 71% ee, and the corresponding ketone **1a** was obtained 59% in 24 h (Table 4, entry 1). When the temperature was increased to 70 °C, the ee was increased to 75% with 29% and 61% isolated yields of recovered alcohol **1b** and ketone **1a,** respectively (entry 2). Similarly, when the temperature was raised to 80 °C, the ee was drastically increased to 92% with 27 and 57% isolated yields of recovered alcohol **1b** and ketone **1a,** respectively (entry 3). However, a further increase in temperature from 80 °C to 90 °C meant that the % ee of **1b** dropped drastically to 37% (entry 4). Similarly, when the reaction was carried out at room temperature, no oxidation was observed even after two days (entry 5). The best catalytic conditions for the oxidative kinetic resolution of **1** after optimization studies turned out to be 5 mol % $Cu(OTf)_2$/10 mol % (*R*)-BINAM/5 mol % TEMPO/O_2 at 80 °C.

Having the optimized condition in hand, we next investigated the substrate scope of this enantioselective oxidation with several amino alcohols[18], and the results are summarized in Table 5. Different *ortho* amino alcohols such as (2-amino-5-chlorophenyl)(phenyl)methanol **1**, (2-amino-5-chlorophenyl)(2-fluoro-

Table 5
Oxidative kinetic resolution of different amino alcohols[a]



Entry	(±)-Amino alcohol	Time (h)	Ketone	Yield[b]	Amino alcohol	Yield[b]	% ee[c]	Config[d]
1	 (±)-**1**	11	 **1a**	57	 **1b**	29	92	–
2	 (±)-**2**	18	 **2a**	59	 **2b**	23	91	–
3	 (±)-**3**	24	 **3a**	57	 **3b**	25	87	(*S*)
4	 (±)-**4**	22	 **4a**	51	 **4b**	20	93	(*S*)
5	 (±)-**5**	21	 **5a**	53	 **5b**	21	71	(*S*)
6	 (±)-**6**	10 days	 **6a**	55	 **6b**	35	00	–

[a] Reaction conditions: 10 mol % (*R*)-BINAM, 5 mol % $Cu(OTf)_2$ 5 mol % TEMPO, 1 mmol alcohol, O_2 (balloon) at 80 °C.
[b] Isolated yields.
[c] % Ee was determined by HPLC using Diacel columns.
[d] Absolute configuration was determined by comparing the literature values.

phenyl)methanol **2**, (2-aminophenyl)(phenyl)methanol **3**, and 1-(2-aminophenyl)ethanol **4** were resolved with enantiomeric excess varying from 87% to 93% in 11–24 h (Table 5, entries 1–4). *para* Amino alcohol such as (4-aminophenyl)(phenyl)methanol **5** was also resolved with 71% enantiomeric excess, and the isolated yields of recovered alcohol and ketone were 21% and 53%, respectively (entry 6). In the case of *meta* amino alcohol (3-aminophenyl)(phenyl)methanol **6** the resolution rate was very slow (10 days), and the recovered alcohol was racemic with an isolated yield 35% (entry 6). It can be seen clearly from Table 5 that in case of *ortho* amino alcohols the enantiomeric excess of the recovered amino alcohols is high (entries 1–4), and the enantiomeric excess decreases when the amino substitution is at the *para* position (entry 5). When the amino group is substituted at the *meta* position, the enantiomeric excess is further reduced, and only racemic alcohols were recovered, and the reaction took very long time to progress (entry 6). Enantiomeric excess (% ee) of recovered amino alcohols was determined by HPLC on a chiral stationary phase (see Section 4 for full details). This copper-catalyzed OKR is very versatile in that the sole by-product accompanying our oxidation process is water, making our system more eco-friendly and green as well.

3. Conclusion

In conclusion, we have developed an efficient (*R*)-BINAM–$Cu(OTf)_2$ complex-catalyzed oxidative kinetic resolution method for the synthesis of highly important enantiomerically enriched amino alcohols. To the best of our knowledge, this is the first chiral copper-catalyzed oxidative kinetic resolution of racemic amino alcohols, where molecular oxygen is used as the sole oxidant. Under the proposed catalytic conditions, *ortho* amino alcohols were resolved with high enatioselectivities when compared to the *para* amino alcohols, where the enantioselectivities were moderate.

4. Experimental

4.1. General methods

All oxidation reactions were performed under an oxygen atmosphere using an oxygen balloon. All the solvents used in the experiments were obtained from Merck, and dried by Vogel's procedure. Reactions were monitored by TLC plates (Silica Gel 60 F254, obtained from Merck) using an appropriate mixture of ethyl acetate and hexane. Product purification was done by silica gel (100–200 mesh) column chromatography using hexane and ethyl acetate mixture as eluent. $Cu(OTf)_2$, CuI, (−)- sparteine, and TEMPO were obtained from the Sigma–Aldrich company. CuCl, CuBr, $Cu(OAc)_2$, and $CuCl_2{\cdot}2H_2O$ were obtained from SRL chemicals, India. (*R*)-1,1′-Binaphthyl-2,2′-diamine (BINAM) ligand was purchased from GERCHEM chemicals, Hyderabad, India, and some of the ligands were synthesized using literature procedures. Racemic amino alcohols used in Table 5 were prepared from the corresponding amino ketones by reduction with $NaBH_4$. All the products were characterized by ^1H and ^{13}C NMR (Bruker 400 MHz), FT-IR (Thermo Nicolet 6700), mass spectra (Q-Tof micro hybrid quadruple time of flight mass spectrometer), and melting points (Toshniwal melting point apparatus). ^1H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ peak (δ 7.26 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). All yields reported in this publication refer to isolated yields of compounds. Optical rotations were determined at 589 nm (sodium D line) by using Rudolph, AUTOPOL IV digital polarimeter. Enantioselectivities were determined by HPLC using JASCO PU-2080 with Diacel chiral columns (Chiralpak/Chiralcel AS-H, OD-H, AD-H and OJ columns).

4.2. General procedure for the oxidative kinetic resolution of racemic amino alcohols

To a 10 mL reaction tube equipped with a magnetic stir bar that was charged with $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and (*R*)-BINAM (14.20 mg, 0.05) was added toluene (5.0 mL). The reaction mixture was allowed to stir for 5 min at room temperature. Then TEMPO (3.92 mg, 0.025 mmol) was added to the reaction mixture. To the resulting reaction mixture amino alcohol (±)-**1** (116.9 mg, 0.5 mmol) was added, and the reaction mixture was allowed to stir at 80 °C until 50–60% completion of the reaction (monitored by TLC). After that, the reaction mixture was allowed to cool to room temperature, and the solvent was evaporated by rotary evaporator. The residue left after evaporation was purified by a silica gel column chromatography to give corresponding ketone (65.83 mg, 57%) and recovered alcohol **1b** (33.79 mg, 29%) whose enantiopurity was measured by HPLC using chiral column. Spectral data of Product **1a**:[19] Brownish solid, mp 95–99 °C (lit. 95–98 °C); R_f = 0.60 (30% ethyl acetate in hexane); IR (neat): 3414, 3308, 1609 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.2 Hz, 2H), 7.50–7.32 (m, 4H), 7.19–7.13 (m, 1H), 6.61 (d, J = 8.8 Hz, 1H), 6.00 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 149.5, 139.5, 134.3, 133.4, 131.7, 129.3, 128.5, 120.1, 119.0, 118.6; HRMS (ESI): *m/z* calcd. for $C_{13}H_{11}NOCl$ $[M+H^+]$: 232.0529; found: 232.0527.

Spectral data of recovered amino alcohol **1b**:[20] Brownish solid, mp 129–132 °C (lit.[20] 131–132 °C); R_f = 0.36 (30% ethyl acetate in hexane); $[\alpha]_D^{20} = -36.0$ (*c* 1, $CHCl_3$); IR (neat): 3385, 3308, 3206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.22 (m, 5H), 7.02–6.94 (m, 2H) 6.58 (d, J = 8.0 Hz, 1H), 5.75 (s, 1H), 3.20 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 141.2, 129.6, 128.9, 128.8, 128.4, 128.2, 126.8, 123.9, 118.9, 74.4. The enantiomeric excess (ee) was determined to be 92% by HPLC using Diacel, ChiralPAK AS-H column (10% *i*-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 14.142 min), Retention time (major, 11.825 min).

4.3. Spectroscopic data for the products amino ketones

4.3.1. (2-Amino-5-chlorophenyl)(2-fluorophenyl)methanone, 2a[21]

Brownish solid, mp 96–99 °C (lit.[26] 95–98 °C); R_f = 0.70 (30% ethyl acetate in hexane); IR (neat): 3439, 3331, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.07 (m. 6H), 6.66 (d, J = 8.8 Hz, 1H), 4.50 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 149.8, 139.2, 135.3, 133.3, 130.9, 130.2, 128.6, 126.9, 120.4, 118.8, 118.3; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}NOClF$ $[M+H^+]$: 250.0435; found: 250.0431.

4.3.2. (2-Aminophenyl)(phenyl)methanone, 3a[22]

Brownish solid, mp 104–108 °C (lit. 103–107 °C); R_f = 0.73 (30% ethyl acetate in hexane); IR (neat): 3431, 3313, 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.64 (m, 2H) 7.58–7.45 (m, 4H), 7.35–7.29 (m, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.68–6.60 (m, 1H), 5.97 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 150.9, 140.3, 134.7, 134.3, 131.1, 129.2, 128.2, 118.5, 117.2, 115.8; HRMS (ESI): *m/z* calcd for $C_{13}H_{12}NO$ $[M+H^+]$: 198.0919; found: 198.0919.

4.3.3. (2-Aminophenyl)ethanone, 4a[23]

Light yellowish liquid; R_f = 0.53 (30% ethyl acetate in hexane); IR (neat): 3431, 3313, 1619; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.71 (m, 1H), 7.31–7.25 (m, 1H), 6.70–6.64 (m, 2H), 6.20 (br s, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 150.3, 134.5, 132.1, 118.4, 117.3, 115.9, 27.9; HRMS (ESI): *m/z* calcd for $C_8H_{10}NO$ $[M+H^+]$: 136.0762; found: 136.0766.

4.3.4. (4-Aminophenyl)(phenyl)methanone, 5a[24]

Brownish solid, mp 118–122 °C (lit. 121–124) °C; R_f = 0.79 (30% ethyl acetate in hexane); IR (neat): 3405, 3325, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77–7.70 (m, 4H) 7.58–7.44 (m, 3H), 6.69 (d, J = 8.0 Hz, 2H), 4.11 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 151.0, 138.9, 133.0, 131.5, 129.6, 128.2, 127.6, 113.9; HRMS (ESI): m/z calcd for $C_{13}H_{12}NO$ [M+H$^+$]: 198.0919; found: 198.0920.

4.3.5. (3-Aminophenyl)(phenyl)methanone, 6a[25]

Brownish solid, mp 80–85 °C (lit. 81–84 °C); R_f = 0.42 (40% ethyl acetate in hexane) IR (neat): 3383, 3309, 3201, 1646; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.29–7.13 (m, 3H), 6.93–6.89 (m, 1H), 3.61 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 146.6, 138.9, 138.0, 132.4, 130.1, 129.2, 128.3, 120.8, 119.1, 116.1; HRMS (ESI): m/z calcd for $C_{13}H_{12}NO$ [M+H$^+$]: 198.0919; found: 198.0915.

4.4. Spectroscopic data for the recovered amino alcohols

4.4.1. (2-Amino-5-chlorophenyl)(2-fluorophenyl)methanol, 2b[18]

Brownish semi solid; R_f = 0.40 (20% ethyl acetate in hexane); $[\alpha]_D^{25} = +37.5$ (c 1.0, MeOH); IR (neat): 3382, 3307, 3113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.17 (m, 4H), 6.97 (dd, J = 2.4, 6.0 Hz, 1H), 6.78 (s, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.06 (s, 1H), 3.55 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 136.8, 131.3, 128.1, 127.7, 127.0, 126.9, 126.0, 125.9, 125.6, 121.9, 116.3, 68.6; HRMS (ESI): m/z calcd. for $C_{13}H_{12}NOClF$ [M+H$^+$]: 252.0591; found: 252.0585. The enantiomeric excess (ee) was determined to be 91% by HPLC using Diacel, ChiralPAK, AS-H column (15% i-PrOH/hexanes, 1 mL/min, 220 nm): Retention time (minor, 46.233 min), Retention time (major, 40.900 min).

4.4.2. (2-Aminophenyl)(phenyl)methanol, 3b[3f]

Brownish semi solid; R_f = 0.31 (30% ethyl acetate in hexane); $[\alpha]_D^{20} = +43.7$ (c 1.0, MeOH), [lit.[12] $[\alpha]_D^{25} = +44.5$ (c 1.0, MeOH)]; IR (neat): 3443, 3367, 3204; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.30 (m, 5H) 7.18–7.13 (m, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.81–6.76 (m, 1H), 6.69 (d, J = 7.6 Hz, 1H), 5.85 (s, 1H), 3.59 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 142.1, 129.0, 128.8, 128.6, 127.9, 127.7, 126.7, 118.7, 117.3, 75.0; HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ [M+H$^+$]: 200.1075; found: 200.1079. The enantiomeric excess (ee) was determined to be 87% by HPLC using Diacel, ChiralPAK, AS-H column (3% i-PrOH/ hexanes, 1 mL/min, 220 nm): Retention time (minor, 25.892 min), Retention time (major, 29.275 min).

4.4.3. (2-Aminophenyl)ethanol, 4b[3f]

Brownish semi solid; R_f = 0.29 (30% ethyl acetate in hexane); $[\alpha]_D^{20} = +52.5$ (c 1.0, $CHCl_3$); IR (neat): 3416, 3329, 3218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (t, J = 7.6 Hz, 2H), 6.70–6.49 (m, 2H), 4.71 (q, J = 6.4 Hz, 1H), 2.89 (br s, 3H); 1.38 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 146.7, 129.6, 115.8, 114.4, 112.2, 70.6, 25.1; HRMS (ESI): m/z calcd for $C_8H_{12}NO$ [M+H$^+$]: 138.0919; found: 138.0913. The enantiomeric excess (ee) was determined to be 93% by HPLC using Diacel, ChiralPAK, OD-H column (15% i-PrOH/hexanes, 0.5 mL/min, 220 nm): Retention time (minor, 22.500 min), Retention time (major, 16.058 min).

4.4.4. (4-Aminophenyl)(phenyl)methanol, 5b[3f]

Brownish semi solid: R_f = 0.56 (30% ethyl acetate in hexane); $[\alpha]_D^{20} = -27.5$ (c 1.0 MeOH); IR (neat): 3382, 3307, 3113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–6.95 (m, 6H), 6.57–6.33 (m, 3H), 5.64 (s, 1H), 2.83 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.7, 128.4, 128.1, 127.3, 126.5, 126.4, 115.4, 115.2, 76.0; HRMS (ESI): m/z calcd. for $C_{13}H_{14}NO$ [M+H$^+$]: 200.1075; found: 200.1074. The enantiomeric excess (ee) was determined to be 71% by HPLC using Diacel, ChiralPAK, OD-H column (5% i-PrOH/ hexanes, 1 mL/min, 220 nm): Retention time (minor, 15.817 min), Retention time (major, 11.258 min).

4.4.5. (3-Aminophenyl)(phenyl)methanol, 6b

Brownish semi solid; R_f = 0.23 (40% ethyl acetate in hexane); IR (neat): 3424, 3350, 3227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.13 (m, 5H), 7.01 (t, J = 7.6 Hz, 1H), 6.67–6.62 (m, 2H), 6.48 (d, J = 7.6 Hz, 1H), 5.62 (s, 1H), 3.17 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 145.4, 143.9, 129.6, 128.6, 127.6, 126.7, 117.5, 114.8, 113.6, 76.3; HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ [M+H$^+$]: 200.1075; found: 200.1073. The enantiomeric excess (ee) was determined to be 00% by HPLC using Diacel, ChiralPAK, AS-H column (10% i-PrOH/ hexanes, 1 mL/min, 220 nm).

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