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# Enantioselective addition of diethylzinc to aldehydes catalyzed by titanium(IV) complexes of *N*-sulfonylated amino alcohols with two stereogenic centers

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**Abstract**—Bidentate *N*-sulfonylated amino alcohols with one or two stereogenic centers were prepared and applied as chiral ligands in the titanium(IV)-catalyzed asymmetric addition of diethylzinc to aldehydes, affording excellent enantioselectivities of up to 98% e.e. 

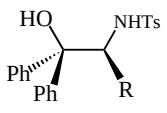
## 1. Introduction

The application of chiral β-amino alcohols as versatile ligands for a variety of asymmetric reactions has been extensively studied.[1] Most notable among these reactions are the asymmetric additions of organometallic reagents to aldehydes.[2] Traditionally, Grignard and alkyllithium reagents have been used together with amino alcohols in stoichiometric amounts to obtain high enantioselectivity.[3] Over the past 10 years, the asymmetric addition of organozinc reagents to aldehydes in the presence of a catalytic amount of chiral ligand has attracted much attention, and many excellent ligands inducing high enantioselectivity have been reported.[4] Chiral titanium complexes have proven remarkably successful in the asymmetric addition of dialkylzinc to aldehydes and the effective catalytic systems were, in general, prepared in situ by mixing a chiral ligand with excess Ti(O-*i*-Pr)$_4$.[5–8] The most successful catalysts in these reactions have been titanium complexes which employ chiral diol-based or bis(sulfonamide) ligand systems.

Following our interest in developing the titanium ligand chemistry,[9] we report herein the synthesis of bidentate *N*-sulfonylated amino alcohols with one or two stereogenic centers. The asymmetric additions of diethylzinc to aldehydes catalyzed by titanium(IV) complexes of the chiral *N*-sulfonylated amino alcohols was carried out and proceeded with excellent enantioselectivities (up to 98% e.e.).

## 2. Results and discussion

We first prepared the *N*-sulfonylated amino alcohols (*S*)-**1a–c** with only one stereogenic center from L-phenylglycine, L-alanine or L-phenylalanine, respectively. The asymmetric addition of diethylzinc to aldehydes using titanium complex systems prepared in situ from Ti(O-*i*-Pr)$_4$ and the bidentate *N*-sulfonylated amino alcohols (*S*)-**1** were examined (Eq. (1)) and the results are listed in Table 1. It was found that these catalytic systems afforded poor enantioselectivities with an e.e. value of 18% (*R*) (entry 1) when (*S*)-**1a** (R = $CH_3$) was used as a ligand and no enantioselectivity for (*S*)-**1b** (R = Ph; entry 2). For (*S*)-**1c** with R = $PhCH_2$ (entry 3), moderate enantioselectivity was obtained with an e.e. of 64% (*R*). The above results prompted us to synthesize a series of amino alcohols with two stereogenic centers, hoping to improve the enantioselectivity and to learn more about the structural features of the ligand that influences the enantioselectivity and catalytic activity.




(*S*)-**1**

**1a:** R = $CH_3$
**1b:** R = Ph
**1c:** R = $PhCH_2$

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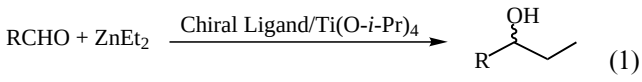


(1)

**Table 1.** Enantioselective addition of diethylzinc to benzaldehyde catalyzed by bidentate *N*-sulfonylated amino alcohol ligands/Ti(O-*i*-Pr)$_4$ in situ-formed systems[a,b,c]

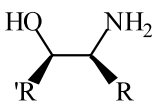
| Entry | Ligand (mol%) | Ti(O-*i*-Pr)$_4$ (mmol) | Yield (%) | % e.e. |
|---|---|---|---|---|
| 1 | **1a** (10) | 0.5 | 96 | 18 (*R*) |
| 2 | **1b** (10) | 0.5 | 100 | 0 |
| 3 | **1c** (10) | 0.5 | 93 | 64 (*R*) |
| 4 | **3a** (10) | 0.5 | 100 | 96 (*R*) |
| 5 | **3a** (20) | 1.0 | 100 | >99 (*R*) |
| 6 | **3a** (5) | 0.25 | 96 | 91 (*R*) |
| 7 | **3b** (10) | 0.5 | 100 | 94 (*R*) |
| 8 | **3c** (10) | 0.5 | 75 | 8 (*S*) |
| 9 | **3d** (10) | 0.5 | 81 | 4 (*R*) |
| 10 | **3e** (10) | 0.5 | 100 | 90 (*R*) |

[a] Reaction conditions: Under a nitrogen atmosphere, the ligand and Ti(O-*i*-Pr)$_4$ were mixed in dry dichloromethane at room temperature. The mixture was stirred for 1 h and $Et_2Zn$ (1.0 M solution in hexane, 0.75 mmol) was added at 0°C. After 30 min, benzaldehyde (0.5 mmol) was added and the mixture was allowed to react at 0°C for 12 h.

[b] The yields were based on the $^1$H NMR spectra.

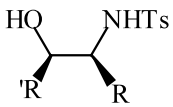
[c] The e.e. values were determined by HPLC with a Chiralcel-OD column from Daicel. The absolute configurations of the products were derived by comparison of optical rotation data with literature values.

Based on the route described by Reetz et al.,[10] amino alcohols (*R*,*S*)-**2** with two stereogenic centers were synthesized and an array of bidentate *N*-sulfonylated amino alcohols (*R*,*S*)-**3** were synthesized by condensation of amino alcohols with TsCl in the presence of an excess of triethylamine and a catalytic amount of DMAP (4-dimethylaminopyridine).



(*R*,S)-**2**

**2a**: R = $PhCH_2$; R' = Ph
**2b**: R = $PhCH_2$; R' = *p*-$CH_3C_6H_4$
**2c**: R = $PhCH_2$; R' = cyclohexyl
**2d**: R = $PhCH_2$; R' = *t*-Bu



(*R*,*S*)-**3**

**3a**: R = $PhCH_2$; R' = Ph
**3b**: R = $PhCH_2$; R' = *p*-$CH_3C_6H_4$
**3c**: R = $PhCH_2$; R' = cyclohexyl
**3d**: R = $PhCH_2$; R' = *t*-Bu
**3e**: R = Ph; R' = Ph

When 10 mol% of (*R*,*S*)-**3a** was used as a ligand in the asymmetric reaction under the same conditions as used for entries 1–3, with a molar ratio of Ti(O-*i*-Pr)$_4$/(*R*,*S*)-**3a** of 10, the reaction gave (*R*)-1-phenyl-1-propanol in 100% yield with an excellent e.e. of 96% (entry 4). When 20 mol% of (*R*,*S*)-**3a** was used, the addition of diethylzinc to benzaldehyde gave the product in 100% yield with an e.e. value of 99% (entry 5). On reducing the loading of (*R*,*S*)-**3a** to 5 mol%, excellent enantioselectivity of 91% e.e. was still obtained (entry 6). When the phenyl group R′ was replaced with a *p*-tolyl substituent in (*R*,*S*)-**3b**, the asymmetric addition reaction also gave excellent enantioselectivity of 94% e.e. (entry 7). However, when R′ was an aliphatic substituent such as cyclohexyl [(*R*,*S*)-**3c**] or *t*-Bu [(*R*,*S*)-**3d**], very poor enantioselectivities were obtained (8% e.e. of the (*S*)-configured product and 4% e.e. of the (*R*)-configured product, respectively, entries 8 and 9). When R and R′ were both phenyl groups, the reaction gave an of the (*R*)-configured product with e.e. of 90% (entry 10). The above study clearly demonstrates that differences in the ligand structure strongly influence the enantioselectivity of the substitution reaction. For substitution at the hydroxyl-bearing stereogenic center, several trends were noted for the asymmetric alkylation reactions. First, changing the tertiary alcohol functionality to a secondary alcohol led to a significant improvement in the enantioselectivity (entry 4 versus 1). Second, the presence of aryl substituents on the hydroxyl-bearing stereogenic center proved to be much superior to alkyl groups (entries 4 and 7 versus entries 8 and 9). Third, substitution of the flexible benzyl group in (*R*,*S*)-**3a** for a rigid phenyl group in (*R*,*S*)-**3e** resulted in a slight drop in the e.e. (entry 4 versus entry 10). These results indicate that the enantioselectivity relies mainly on the stereogenic center bearing the hydroxyl group rather than the one bearing the amino group. In addition, the effect of changing the solvent on the asymmetric addition was examined employing (*R*,*S*)-**3a** as a ligand and $CH_2Cl_2$ was found to be the best solvent for these reactions.

We subsequently explored the scope of the asymmetric addition of diethylzinc to aldehydes using the best performing ligand (*R*,*S*)-**3a**, and the results are listed in Table 2. For aromatic aldehyde substrates such as 4-chlorobenzaldehyde, 1-naphthaldehyde or 2-naphthaldehyde as excellent enantioselectivities of 96, 94, and 98% e.e. (entries 2–4) of the (*R*)-configured product were obtained, respectively. For aromatic aldehydes bearing an electron-donating substituent such as 2-methoxybenzaldehyde (entry 5) or 4-methoxybenzaldehyde (entry 6), the reaction gave the desired chiral product in slightly lower yield but with excellent enantioselectivities of 95 and 97% e.e., respectively. The reactions of aldehydes with an alkyl group between the aromatic ring and the carbonyl group, such as *trans*-cinnamaldehyde or 3-phenylpropionaldehyde and *n*-hexaldehyde were also examined. The catalytic reaction gave 96% e.e. for *trans*-cinnamaldehyde as the substrate

**Table 2.** Enantioselective addition of diethylzinc to aldehydes catalyzed by **3a**/Ti(O-*i*-Pr)$_4$ in situ-formed system[a,b,c]

| Entry | Aldehyde | Yield (%) | % e.e. |
|---|---|---|---|
| 1 | Benzaldehyde | 100 | 96 (*R*) |
| 2 | 4-Chlorobenzaldehyde | 100 | 96 (*R*) |
| 3 | 1-Naphthaldehyde | 100 | 94 (*R*) |
| 4 | 2-Napthaldehyde | 100 | 98 (*R*) |
| 5 | 2-Methyoxybenzaldehyde | 90 | 95 (*R*) |
| 6 | 4-Methyoxybenzaldehyde | 94 | 97 (*R*) |
| 7 | *trans*-Cinnamaldehyde | 100 | 96 (*R*) |
| 8 | 3-Phenylpropionaldehyde | 100 | 94 (*R*) |
| 9 | *n*-Hexaldehyde | 94 | 79 (*R*)[d] |

[a] The same conditions as described in the footnote of Table 1.
[b] The yields were based on the $^1$H NMR spectra.
[c] The e.e. values were determined by HPLC with a Chiralcel-OD column from Daicel. The absolute configurations of the products were derived by comparison of optical rotation data with literature values.
[d] Reaction time of 24 h. The alcohol was converted to the benzoate ester for HPLC analysis.

(entry 7). However, in the reaction of *n*-hexaldehyde, a lower e.e. of 79% was obtained (entry 9). Because high enantioselectivity is generally more difficult to achieve with aliphatic aldehydes than with benzaldehydes, we were delighted to find that the addition to 3-phenylpropionaldehyde also proceeded in 94% e.e. (entry 8).

## 3. Conclusion

In summary, we have developed a family of *N*-sulfonylated amino alcohols with two stereogenic centers for application as chiral ligands. The titanium complexes of these bidentate ligands are demonstrated as excellent catalysts in the addition of diethylzinc to aldehydes at the convenient temperature of 0°C. The (*R*,*S*)-**3a**/Ti(O-*i*-Pr)$_4$ catalytic system also works successfully with 3-phenylpropionaldehyde.

## 4. Experimental

### 4.1. Reagents and general techniques

L-Phenylalanine, L-alanine, L-phenylglycine, DMAP (4-dimethylaminopyridine), sulfur trioxide pyridine complex, and diethylzinc (1.0 M solution in hexane) were purchased from Fluka and were used directly. Ti(O-*i*-Pr)$_4$ was freshly distilled prior to use. Aldehydes were distilled or recrystallized before use. (1*R*,2*S*)-2-Amino-1,2-diphenylethanol, Grignard reagents, *p*-toluenesulfonyl chloride (TsCl) and 20% Pd(OH)$_2$–C were purchased from Aldrich and used without further purifications. Amino alcohols (*R*,*S*)-**2a**–**2d** were synthesized according to literature procedures.[10] Solvents were dried by heating under refluxing for at least 24 h over $P_2O_5$ (dichloromethane), sodium/benzophenone (*n*-hexane, diethyl ether, THF or toluene) or sodium (methanol) and were freshly distilled prior to use. All syntheses and manipulations were carried out under a dry nitrogen atmosphere.

### 4.2. Physical measurements

$^1$H NMR spectra were obtained with a Varian Mercury-400 (400 MHz) or a Varian Gemini-200 (200 MHz) spectrometer and $^{13}$C NMR spectra were recorded with the Varian Mercury-400 (100.70 MHz) or the Varian Gemini-200 (50.289 MHz) spectrometer. The $^1$H and $^{13}$C NMR chemical shifts were measured relative to tetramethylsilane as the internal reference. Melting points were taken on a Büchi 535 instrument and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-RAPID instrument. The high resolution FAB-mass spectra and EI-mass spectra were obtained using a JEOL JMS-SX/SX 102A instrument. Optical rotations were determined on a Perkin–Elmer 241 polarimeter.

### 4.3. General procedures for the addition of $Et_2Zn$ to aldehydes

Under a dry nitrogen atmosphere, the ligand and Ti(O-*i*-Pr)$_4$ were mixed in dry (1.5 mL) dichloromethane at room temperature. After stirring the mixture for 1 h, a solution of $Et_2Zn$ (1.0 M in hexane, 0.75 mmol) was added at 0°C. The mixture was stirred for 0.5 h and the resulting orange solution cooled to 0°C and treated with the aldehyde (0.5 mmol). The mixture was allowed to react at 0°C for 12 h and quenched with 1N aqueous HCl. The aqueous phase was extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexane/ethyl acetate) gave the carbinol. The enantiomeric purity of the product was determined by HPLC.

### 4.4. General procedures for synthesis of (*S*)-sulfonyl-amino alcohols, (*S*)-1

L-Amino acid (50.0 mmol) was dissolved in aqueous sodium hydroxide (1.67 M, 60 mL) at 0°C. An ethereal solution of *p*-toluenesulfonyl chloride (50.0 mmol) was added dropwise with stirring over 4 h. The ethereal solution was then separated off and the aqueous solution was acidified to pH 2.0 with hydrochloric acid. The product crystallized immediately and was collected by filtration to give the (*S*)-*N*-sulfonylated amino acid.

The (*S*)-*N*-*p*-toluenesulfonylated amino acid (12.3 mmol) was suspended in methanol (45 mL) and cooled to 0°C in an ice bath. $SOCl_2$ (1.4 mL) was then added dropwise at this temperature. The mixture was stirred at room temperature for 24 h, and the solvent was then removed. The product was dried in vacuo to give the (*S*)-*N*-*p*-toluenesulfonyl amino acid methyl ester as a pale yellow solid. The crude (*S*)-*N*-*p*-toluenesulfonyl amino acid methyl ester (12.1 mmol) was dissolved in dry THF (80 mL) and then phenylmagnesium bromide (1.0 M solution in THF, 50 mL) was added dropwise under a nitrogen atmosphere at 0°C over 0.5 h. The resulting solution was stirred for 24 h at room temperature. The reaction mixture was cooled to 0°C and hydrolyzed with a saturated aqueous $NH_4Cl$ solution (20 mL). The organic layer was separated and the

aqueous layer was extracted with THF (3×30 mL). The combined organic extracts were washed with saturated brine (2×50 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give a yellow oil, which was recrystallized from $CH_2Cl_2$/hexane for (*S*)-**1a** and (*S*)-**1b** or EtOAc for (*S*)-**1c** to afford white needles.

**4.4.1. (*S*)-2-(*p*-Toluenesulfonylamino)-1,1-diphenyl-1-propanol, (*S*)-1a**. White needles (67% yield), mp 108–110°C. $[\alpha]_D^{25}$ +7.7 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.07 (d, $J=6.4$ Hz, 3H, $CH_3$CH), 2.40 (s, 3H, $CH_3$ in Ts), 4.36 (m, 1H, CHN), 4.76 (d, $J=8.2$ Hz, 1H, NH), 7.12–7.53 (m, 14H, 3Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 17.19, 21.48, 55.65, 80.38, 125.65, 125.71, 126.89, 126.97, 127.19, 128.25, 128.35, 129.54, 137.79, 143.01, 143.84, 143.91 ppm. HRMS (FAB) calcd for $C_{22}H_{23}N_1O_3S_1Na$ ([M+Na]$^+$): 404.1296, found: 404.1306. Anal. calcd for $C_{22}H_{23}N_1O_3S_1$: C, 69.27; H, 6.08; N, 3.67%. Found: C, 68.99; H, 6.09; N, 3.79%.

**4.4.2. (*S*)-2-(*p*-Toluenesulfonylamino)-1,1,2-triphenylethanol, (*S*)-1b**. White needles (74% yield), mp 215–216°C. $[\alpha]_D^{25}$ −251.4 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.29 (s, 3H, $CH_3$), 2.61 (s, br, 1H, OH), 5.29 (d, $J=8.00$ Hz, 1H, CHN), 5.44 (d, $J=7.6$ Hz, 1H, NH), 6.72–7.60 (m, 19H, 4Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.33, 63.19, 80.93, 125.62, 126.62, 126.86, 127.01, 127.41, 127.47, 127.80, 128.54, 128.77, 128.89, 135.46, 137.43, 142.54, 143.25, 143.72 ppm. HRMS (FAB) calcd for $C_{27}H_{25}N_1O_3S_1Na$ ([M+Na]$^+$): 466.1453; found: 466.1451. Anal. calcd for $C_{27}H_{25}N_1O_3S_1$: C, 73.11; H, 5.68; N, 3.16. Found: C, 73.27; H, 5.96; N, 3.27%.

**4.4.3. (*S*)-2-(*p*-Toluenesulfonylamino)-1,1,3-triphenyl-1-propanol, (*S*)-1c**. White needles (62% yield), mp 120–121°C. $[\alpha]_D^{25}$ +86.4 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.35 (s, 3H, $CH_3$), 2.54 (s (br), 1H, OH), 2.79 (dd, $J=5.8$, 3.8 Hz, 1H, $PhCH_AH_B$), 2.86 (dd, $J=5.4$, 3.8 Hz, 1H, $PhCH_AH_B$), 4.61 (m, 1H, CHN), 4.88 (d, $J=8.2$ Hz, 1H, NH), 6.93–7.51 (m, 19H, 4Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.41, 37.80, 61.25, 80.95, 125.38, 126.07, 126.57, 126.81, 127.41, 128.13, 128.45, 128.69, 129.33, 129.73, 137.13, 137.43, 142.46, 143.74, 143.88 ppm. HRMS (FAB) calcd for $C_{28}H_{27}N_1O_3S_1Na$ ([M+Na]$^+$): 480.1609, found: 480.1618. Anal. calcd for $C_{28}H_{27}N_1O_3S_1$: C, 73.50; H, 5.95; N, 3.06. Found: C, 73.72; H, 5.78; N, 3.50%.

### 4.5. General procedures for the synthesis of bidentate sulfonylamino alcohols 3

The amino alcohol (*R*,*S*)-**2** (1 mmol), $NEt_3$ (3.0 mmol), and a catalytic amount of DMAP were combined in $CH_2Cl_2$ (10 mL) and cooled to −78°C. TsCl (1.05 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to the cooled, magnetically stirred solution over 20 min. After the addition was complete, the solution was allowed to stay at 0°C overnight. The resulting mixture was washed with 1N HCl (2×20 mL), saturated aqueous $NaHCO_3$ (2×20 mL) and saturated brine (2×30 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product.

**4.5.1. (1*R*,2*S*)-2-(*p*-Toluenesulfonylamino)-1,3-diphenyl-1-propanol, (*R*,*S*)-3a**. Recrystallized from EtOAc/hexane to afford white needles (81% yield), mp 116–117°C. $[\alpha]_D^{25}$ −21.2 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.37 (s, 3H, $CH_3$), 2.44 (dd, $J=9.8$, 4.4 Hz, 1H, $PhCH_AH_B$), 2.49 (dd, $J=9.8$, 4.4 Hz, 1H, $PhCH_AH_B$), 3.57 (m, 1H, CHN), 4.83 (d, $J=7.4$ Hz, 1H, Ph*CH*OH), 5.10 (d, $J=2.8$ Hz, 1H, NH), 6.76–7.38 (m, 14H, 3Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.44, 34.30, 61.06, 75.06, 126.16, 126.24, 126.79, 127.66, 128.38, 128.98, 129.46, 136.24, 136.93, 140.11, 142.97 ppm. HRMS (FAB) calcd for $C_{22}H_{23}N_1O_3S_1Na$ ([M+Na]$^+$): 404.1296. Found: 404.1288. Anal. calcd for $C_{22}H_{23}N_1O_3S_1$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.10; H, 6.28; N, 3.71%.

**4.5.2. (1*R*,2*S*)-2-(*p*-Toluenesulfonylamino)-3-phenyl-1-(*p*-tolyl)-1-propanol, (*R*,*S*)-3b**. Recrystallized from EtOAc/hexane to afford white needles (78% yield), mp 137–138°C. $[\alpha]_D^{25}$ −12.2 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.34 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 2.44 (dd, $J=9.6$, 4.4 Hz, 1H, $PhCH_AH_B$), 2.51 (dd, $J=9.6$, 4.4 Hz, 1H, $PhCH_AH_B$), 3.56 (m, 1H, CHN), 4.82 (d, $J=7.8$ Hz, 1H, $p$-$CH_3$Ph*CH*OH), 5.01 (d, $J=2.8$ Hz, 1H, NH), 6.77–7.36 (m, 13H, 3Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.09, 21.44, 34.49, 61.02, 74.91, 126.10, 126.22, 126.80, 128.36, 129.06, 129.41, 136.37, 137.00, 137.09, 137.31, 142.90 ppm. HRMS (FAB) calcd for $C_{23}H_{25}N_1O_3S_1Na$ ([M+Na]$^+$): 418.1453. Found: 418.1462. Anal. calcd for $C_{23}H_{25}N_1O_3S_1$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.74; H, 6.42; N, 3.50%.

**4.5.3. (1*R*,2*S*)-2-(*p*-Toluenesulfonylamino)-1-cyclohexyl-3-phenyl-1-propanol, (*R*,*S*)-3c**. Recrystallized from EtOAc/hexane to afford white needles (66% yield), mp 117–118°C. $[\alpha]_D^{25}$ −25.8 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.02–2.04 (m, 11H, cyclohexyl), 2.39 (s, 3H, $CH_3$), 2.54 (dd, $J=9.6$, 3.4 Hz, 1H, $PhCH_AH_B$), 2.61 (dd, $J=9.8$, 3.6 Hz, 1H, $PhCH_AH_B$), 3.48 (m, 2H, CHN and CH*CH*OH), 4.64 (d, $J=6.8$ Hz, 1H, NH), 6.88–7.36 (m, 9H, 2Ph) ppm. $^{13}$C{$^1$H} NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.46, 25.57, 25.81, 26.21, 28.61, 29.62, 33.43, 39.73, 56.87, 126.30, 126.81, 128.47, 129.14, 129.43, 136.60, 137.30, 142.84 ppm. HRMS (FAB) calcd for $C_{22}H_{30}N_1O_3S_1$ ([MH]$^+$): 388.1946. Found: 388.1950. Anal. calcd for $C_{22}H_{29}N_1O_3S_1$: C, 68.19; H, 7.54; N, 3.61%. Found: C, 68.61; H, 7.77; N, 3.64%.

**4.5.4. (3*R*,4*S*)-4-(*p*-Toluenesulfonylamino)-2,2-dimethyl-5-phenyl-3-pentanol, (*R*,*S*)-3d**. Recrystallized from hexane to afford white needles (77% yield), mp 86–88°C. $[\alpha]_D^{25}$ −55.2 ($c=0.5$, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.06 (s, 9H, $3CH_3$), 1.97 (s, br, OH, 1H), 2.37 (s, H, $CH_3$), 2.52 (dd, $J=10.6$, 3.0 Hz, 1H, $PhCH_AH_B$), 2.59 (dd, $J=11.4$, 2.8 Hz, 1H, $PhCH_AH_B$), 3.51 (m, H, CHN), 3.84 (d, $J=1.4$ Hz, 1H, CH*CH*OH),

4.84 (d, $J=7.0$ Hz, 1H, NH), 6.82–7.26 (m, 9H, 2Ph) ppm. $^{13}C\{^1H\}$ NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.43, 27.13, 34.78, 35.10, 57.32, 81.61, 126.14, 126.79, 128.42, 128.89, 129.34, 136.26, 137.72, 142.69 ppm. HRMS (FAB) calcd for $C_{20}H_{28}N_1O_3S_1$ ($[MH]^+$): 362.1790. Found: 362.1794. Anal. calcd for $C_{20}H_{27}N_1O_3S_1$: C, 66.45; H, 7.53; N, 3.87. Found: C, 66.70; H, 7.71; N, 3.62%.

**4.5.5. (1*R*,2*S*)-2-(*p*-Toluenesulfonylamino)-1,2-diphenylethanol, (*R*,*S*)-3e**. The resulting reaction mixture was filtered to afford the insoluble white product. The crude solid was washed with dichloromethane and dried under reduced pressure (85% yield), mp 211–212°C. $[\alpha]_D^{25}$ −25.0 ($c=0.5$, acetone). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.26 (d, $J=3.8$ Hz, 1H, OH), 2.34 (s, 3H, $CH_3$), 4.52 (dd, $J=4.8$, 4.4 Hz, 1H, CHN), 4.99 (t, $J=4.4$ Hz, 1H, Ph*CH*OH), 5.18 (d, $J=4.2$ Hz, 1H, NH), 6.95–7.16 (m, 14H, 3Ph) ppm. $^{13}C\{^1H\}$ NMR (50.289 MHz, $CDCl_3$): $\delta$ 21.30, 64.67, 77.18, 127.53, 127.63, 127.75, 127.99, 128.05, 128.51, 129.55, 129.95 138.75, 140.00, 142.66, 143.22 ppm. HRMS (FAB) calcd for $C_{21}H_{21}N_1O_3S_1Na$ ($[M+Na]^+$): 390.1140. Found: 390.1147. Anal. calcd for $C_{21}H_{21}N_1O_3S_1$: C, 68.64; H, 5.76; N, 3.81. Found: C, 68.10; H, 6.00; N, 4.18%.

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