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Diastereoselective addition of organolithiums to 1,3-oxazolidines complexed with aluminum tris(2,6-diphenylphenoxide) (ATPH)

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Abstract—1,3-Oxazolidines were easily obtained by condensation of N-substituted (*R*)-phenylglycinol with aldehydes. Addition of organolithium reagents to 1,3-oxazolidines by complexation with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH) readily produced the corresponding chiral amines with good yield and high diastereoselectivity. The configuration of the new stereogenic center was shown to be opposite to that of adducts obtained for the same 1,3-oxazolidines using Grignard reagents. The best diastereoselectivity was achieved using *N*-isopropyl-1,3-oxazolidines. The mechanism of addition was deduced by determining the stereochemistry of the iminium–aluminum complex by NOE experiments.

1. Introduction

The diastereoselective addition of organometallic reagents to the C═N bond of chiral imines and their derivatives is useful for the asymmetric synthesis of chiral amines.[1] We have previously described a synthetic method for stereoselective preparation of both enantiomers of chiral amines from a single-enantiomer source, (*R*)-phenylglycinol, proceeding via the diastereoselective addition of Grignard reagents to 1,3-oxazolidines with excellent yield and diastereoselectivity.[2] It was previously alleged that addition of Grignard reagents occurred after formation of the ring-opened iminium intermediate, but addition of an organolithium reagent to 1,3-oxazolidine did not proceed for the unopened ring. It was considered that the reaction required activation to open the 1,3-oxazolidine ring. We tried to react 1,3-oxazolidines with organolithium reagents using various Lewis acids. Aluminum compounds might be effective additives to facilitate the reaction. One additive, bulky C_3 symmetrical ATPH, has been shown to have unique properties in various reactions by Yamamoto.[3] ATPH has a small opening in the ligand sphere and is known to give stable complexes with carbonyl compounds. Herein we report the diastereoselective addition of organolithium to 1,3-oxazolidine via activation with ATPH. Interestingly, the absolute configuration of the adducts obtained in the presence of ATPH was the opposite to that obtained by addition of Grignard reagents (Scheme 1). Other groups have also reported that some reactions with ATPH resulted in the reversal events of diastereoselectivity.[4]

2. Results and discussion

2.1. Addition of MeLi to 1a using various Lewis acids

For the addition of MeLi to 1,3-oxazolidines, an activator such as a Lewis acid is needed for cleavage of the 1,3-oxazolidine ring. To activate a diastereomer mixture of 1,3-oxazolidine **1a**,[2a] prepared easily from (*R*)-phenylglycinol, we tried various Lewis acids as additives (Scheme 2, Table 1). As expected, addition of MeLi to **1a** did not proceed without a Lewis acid (run 1). Some Lewis acids provided methylation to the 1,3-oxazolidine but with low yields and diastereoselectivity (runs 2, 3, and 8). Diastereoselective addition of MeLi was possible in the presence of $MgBr_2$ and Me_3Al (runs 9 and 12). Interestingly, the major adduct of methyl addition using ATPH, (*R*,*R*)-**2a**, differed from that obtained using the other Lewis acids (runs 13–16). This result also differed from previous research in which addition of MeMgBr to **1a** gave (*S*,*R*) **2a** in 94% yield and 68% de.[2a] It was assumed that the change in diastereoselectivity was caused by a virtually blocking of the reaction site due to the bulky structure of ATPH. After a series of activating experiments, the optimum activation time of **1a** with ATPH was found to be 2 h at rt. When the reaction time was prolonged, it resulted in a decreased yield (runs 13–15). As ATPH showed encouraging activity,

Keywords: Lewis acid; Phenylglycinol; NOE experiment; Iminium–aluminum complex; Allylic strain.
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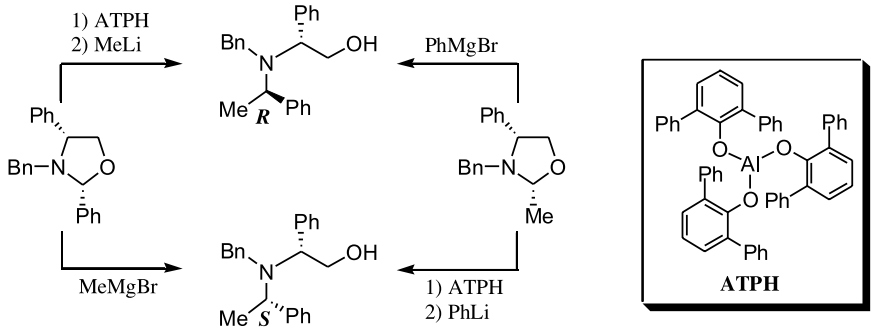
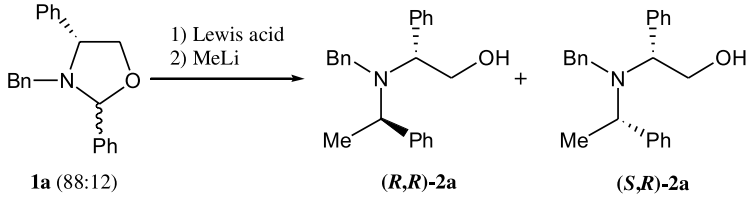


Scheme 1.



Scheme 2.

Table 1. Addition of MeLi to **1a** with Lewis acid

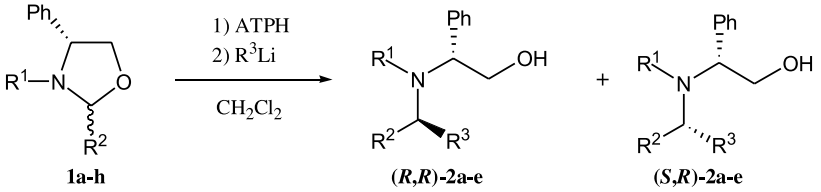
Run	Lewis acid	Activation time (h)	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Ratio (*R*,*R*/*S*,*R*)[a]
1	—	—	rt	20	NR	—
2[b]	BF_3OEt_2	1	rt	20	34	43:57
3[b]	BCl_3	1	rt	20	17	38:62
4	$SnCl_2$	2	−50	20	NR	—
5	$MnBr_2$	2	−50	20	NR	—
6	Et_2Zn	2	−50	20	NR	—
7	$Ln(Otf)_3$	2	−50	20	NR	—
8	$Yb(Otf)_3$	2	−50	20	41	37:63
9	$MgBr_2$	2	−50	20	68	15:85
10	YCl_3	2	−50	20	NR	—
11[b]	Me_3Al	1	rt	20	Trace	—
12[b]	Me_3Al	2	−50	20	72	20:80
13	ATPH	1	−50	20	62	79:21
14	ATPH	1	−50	72	56	67:33
15	ATPH	1	−50	168	19	80:20
16	ATPH	2	−50	20	86	78:22

[a] Estimated by ^{1}H NMR spectrum.
[b] This reaction was carried in THF solvent.

further research looked into the effect of the *N*-substituent of 1,3-oxazolidines at −50 °C.

2.2. Diastereoselective additions of organolithium reagents to N-substituted 1,3-oxazolidines complexed with ATPH

To probe the influence of the *N*-substituent of 1,3-oxazolidine, organolithium reagents were added to various 1,3-oxazolidines complexed with ATPH (Scheme 3, Table 2). N-Substituted 1,3-oxazolidines (**1a–c**,[2a] **1d**,[2b,c] **1f–h**[2a]) were prepared from (*R*)-phenylglycinol in three steps as noted in the literature. **1e** was also prepared from (*R*)-phenylglycinol in the same manner. The diastereomers of **1a–h** were confirmed to be inseparable mixtures in thermodynamic equilibrium differing at the 2 position of the 1,3-oxazolidine ring, and their ratios in $CDCl_3$ were determined from the ^{1}H NMR peak intensities of the 2-H of 1,3-oxazolidine. Addition of organolithium reagents to **1a–h** with ATPH as the Lewis acid gave **2a–e** in 62–98% yield with 78:22 ∼ >99:1 diastereoselectivity. The adducts obtained with ATPH, with the exception of substrate **1b**, showed opposite diastereoselectivities to the adducts obtained with Grignard reactions. The isomer ratios of the adducts were determined from the ^{1}H NMR peak intensity of the 2-Me. The absolute configurations of **2a–c**,[2a] **2d**[2b,c] were previously reported. Treatment of the single isomers (*R*,*R*)-**2e** and (*S*,*R*)-**2e** with TFA gave (*R*,*R*)-**3** in 77% yield



1a-h (*R*,*R*)-2a-e (*S*,*R*)-2a-e

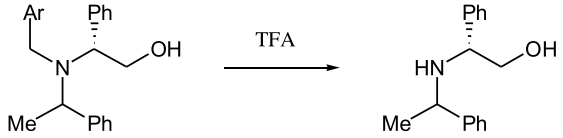
Scheme 3.

Table 2. Addition of R^3Li to **1a–h** with ATPH (cf. Grignard reaction)[a]

Run	Substrate	R^1	R^2	R^3	Yield (%)	Ratio (*R*,*R*/*S*,*R*)[b]	Ratio (*R*,*R*/*S*,*R*)[b]
1	**1a** (88:12)	Bn	Ph	Me	86	78:22	16:84[c]
2	**1b** (97:3)	Me	Ph	Me	98	19:81	34:66[c]
3	**1c** (95:5)	*i*-Pr	Ph	Me	86	97:3	3:97[c]
4	**1d** (89:11)	Diphenylmethyl	Ph	Me	62	84:16	6:94[d]
5	**1e** (90:10)	2,4,6-Trimethylbenzyl	Ph	Me	94	97:3	6:94
6	**1f** (90:10)	Bn	Me	Ph	90	3:97	77:23[c]
7	**1g** (98:2)	Me	Me	Ph	83	27:73	78:22[c]
8	**1h** (98:2)	*i*-Pr	Me	Ph	80	1:>99	88:11[c]

[a] Reaction with R^3MgBr in THF.
[b] Estimated by ^1H NMR spectrum.
[c] See Ref. 2a.
[d] See Ref. 2c.

and (*S*,*R*)-**3** in 84% yield, respectively. The stereochemistry of **3** was established by comparing ^1H NMR spectra with published data[2a–d] (Scheme 4).



2e **3**

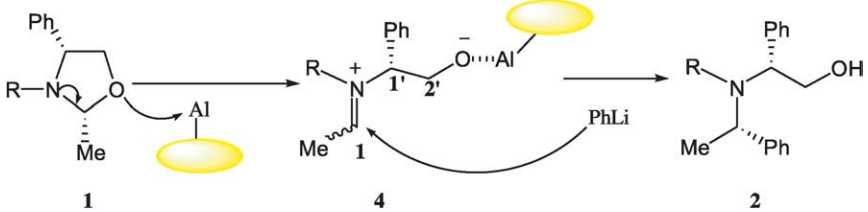
Ar; 2,4,6-trimethylphenyl

Scheme 4.

2.3. Discussion about the diastereoselective addition of organolithium reagents to 1,3-oxazolidines with ATPH based on the geometry of the iminium–aluminum complex

The mechanism of the ring opening of chiral 1,3-oxazolidines has been previously described.[5] First, the metal coordinates to oxygen, and then the C–O bond of the oxazolidine ring is cleaved. As a result, an iminium–metal complex intermediate is formed, with addition of the organometallic reagent giving the chiral amine. We considered the mechanism of addition of organolithium reagents to 1,3-oxazolidines with ATPH to be similar (Scheme 5). However, the geometry of the iminium–aluminum complex (**4**) at the 1 position is not certain, and the diastereoselective process as a whole has not yet been elucidated. To examine the mechanism of addition we determined the geometry of the iminium–aluminum complex by NOE experiment.

A model compound, *N*-isopropyl-2-methyl-1,3-oxazolidine (**1h**), was preferred to the comparative intelligible chart. The ^1H NMR spectra of iminium–aluminum complex (**4h**) prepared from **1h** under usual conditions was assigned by comparison of the decoupling spectra (Fig. 1) with an equivalent C2′ deuterated compound additionally prepared.[6] Trace a shows the high-field region of the spectra of non-deuterated **4h**. Traces b–d show the spin decoupling spectrum acquired by irradiating H2′a, H2′b, and H1″, respectively. In traces b and c, irradiation at H2′a and H2′b was reflected by a change in the H1′ peak from a doublet–doublet to a doublet. Trace d shows that irradiation at H1″ converted the doublet at H2″ into a singlet. Based on these experiments, assignment of the ^1H NMR spectra of **4h** was judged to be consistent. Both NOE difference experiments identified correlation between H2 and H1′ at rt (Fig. 2). The iminium–aluminum complex with an *N*-isopropyl group (**4h**) was found to adopt the *Z* form in $CDCl_3$ (Fig. 3). This result was unexpected because the geometry seemed to be more unstable, as the steric repulsion of the phenethyl group with ATPH would be expected to be greater than that with the isopropyl group. The stereochemistry at the 2 and 3



1 **4** **2**

Scheme 5.

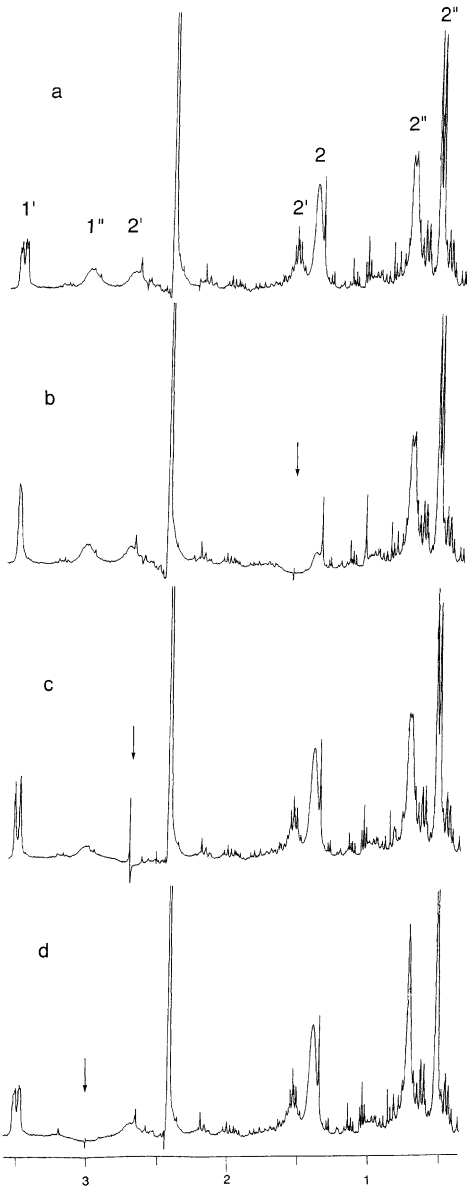


Figure 1. Partial 270 MHz ^{1}H NMR spectrum of **4h** in $CDCl_3$ at 22 °C. (a) Original. (b) Decoupling at 1.6 ppm. (c) Decoupling at 2.7 ppm. (d) Decoupling at 3.0 ppm.

positions of 1,3-oxazolidine might have been important in setting the geometry of the iminium–metal complex. Further, due to the effect of the 1,3-allylic strain, the conformation at C1′ of **4h** is fixed. As a result, the bulky ATPH would situate on the *si* face and the organolithium reagent would attack the iminium–aluminum complex from the *re* face, avoiding ATPH to give (*S*,*R*)-**2c** (Scheme 6). We are still unsure of the exact reason why only ATPH produced this effect when other bulky Lewis acids did not. It may be a result of the remarkable properties of the C_3 symmetrical ATPH, an aluminum center surrounded by bulky ligands in which the aluminum 'peeks out' from a small opening in the ligand sphere. Supposing the mechanism by the observations, the geometry of **4h** related with the configuration at 2 position of oxazolidine (**1h**) and diastereoselectivity of the addition could be a clear explanation. However, in the reactions of **1a**-**1g**, the cause

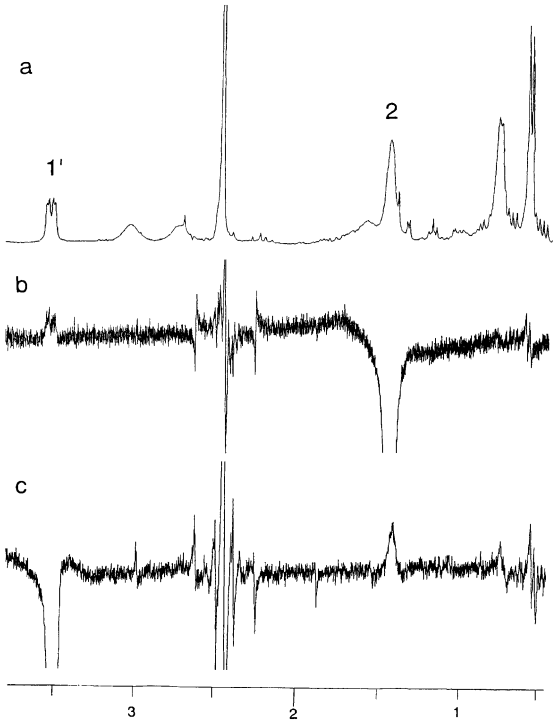


Figure 2. Trace a shows the partial one-dimensional 270 MHz ^{1}H NMR spectrum of **4h** in $CDCl_3$ at 22 °C. Traces b and c are the steady-state NOE difference spectra obtained, when H2 and H1′ are saturated.

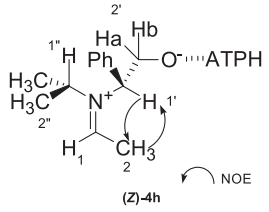
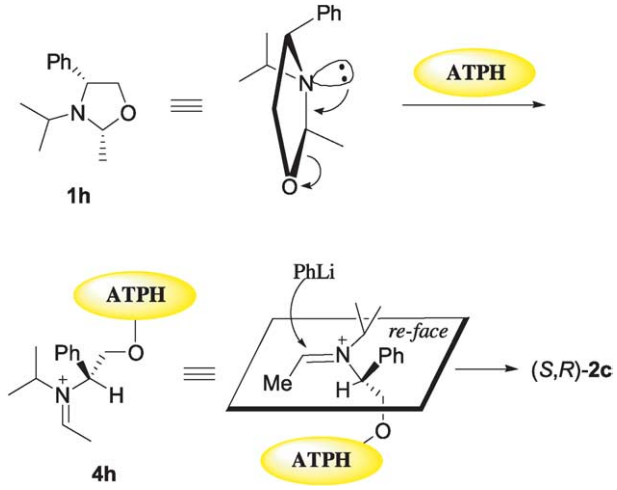


Figure 3.



Scheme 6.

of diastereoselectivity is imprecise, because we were unable to characterize their complexes.

3. Conclusion

1,3-Oxazolidines were reacted with organolithium reagents using the bulky Lewis acid ATPH. The reactions were achieved with high yield and high diastereoselectivity, and the products showed opposite diastereoselectivity to products of Grignard reaction. The best diastereoselectivities were obtained for addition of 1,3-oxazolidines having *N*-isopropyl and 2,4,6-trimethylbenzyl groups. Chiral amines could be synthesized with opposite diastereoselectivity from a chiral 1,3-oxazolidine depending on whether Grignard reagents or ATPH-organolithium reagents were used. ATPH was shown to have activating ability due to effective coordination of the iminium–aluminum complex with the *N*,*O*-acetal. A variation of this method may be useful for the asymmetric synthesis of compounds with medical applications, including physiologically active natural products.

4. Experimental

4.1. General

Melting points were measured with a Yanagimoto Micro melting Point apparatus without collection. IR spectra were recorded on a 215 Hitachi Granting IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. MS spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization (CI) with isobutene and the electron impact (EI) methods. Elemental analyses were performed on a Perkin–Elmer 240-B instrument. Optical rotation were taken with a JASCO-DIP-370 polarimeter at rt. Sibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on silica gel (45–75 μm, Wakogel C-300). The reaction solvents were prepared as the following. THF was distilled over potassium metal. Dichloromethane was distilled over phosphorus pentoxide. Ether and toluene were distilled over sodium metal.

4.1.1. (2*R*,4*R*)-*N*-(2,4,6-Trimethylbenzyl)-2,4-diphenyl-1,3-oxazolidine (1e). A mixture of (*R*)-phenylglycinol (6.85 g, 50 mmol) and 2,4,6-trimethylbenzylaldehyde (7.41 g, 50 mmol) in benzene (100 mL) was refluxed for 1 h with a Dean–Stark trap. After being cooled, the mixture was concentrated under reduced pressure, and the residue was dissolved in methanol (100 mL). To this solution was added portionwise $NaBH_4$ (4.73 g, 125 mmol) at rt. After the reaction mixture was stirred for 40 min, it was added with water (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized (EtOAc–hexane) to afford (*R*)-*N*-2,4,6-trimethylbenzylphenylglycinol (89%) as colorless needles. Mp 98–99 °C. $[\alpha]_D^{22}=-72.5$ (*c* 1.00, $CHCl_3$). MS *m*/*z*: CI, 270 ($M^+ +1$, base peak); EI, 269 (M^+), 238 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3440 (O–H, N–H). ^{1}H NMR ($CDCl_3$) δ: 1.42 (1H, br), 2.25 (9H, s), 2.69 (1H, br), 3.47–3.76 (4H, m), 3.83 (1H, dd, $J=9.2$, 4.8 Hz), 6.84 (2H, s), 7.29–7.42 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 19.39q, 20.95q, 45.53t, 65.40d, 66.56t, 127.30d, 127.66d, 128.62d, 129.06d, 133.33s, 136.59s, 137.00s, 140.71s. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.01; H, 8.95; N, 4.96. A mixture of above compound (5.38 g, 20 mmol) and benzaldehyde (6.36 g, 60 mmol) in benzene (100 mL) was refluxed for 20 h with a Dean–Stark trap. After being cooled, the mixture was concentrated under reduced pressure. The residue was distilled (231 °C, 4 mm Hg) to afford **1e** (88%, 90:10 mixture) as colorless oil. $[\alpha]_D^{20}=-7.40$ (*c* 1.00, $CHCl_3$). MS *m*/*z*: CI, 358 ($M^+ +1$, base peak); EI, 357 (M^+), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3030, 2950, 2860 (C–H). ^{1}H NMR ($CDCl_3$) δ: major component; 2.03 (3H, s), 2.09 (6H, s), 3.64 (1H, d, $J=$ 12.4 Hz), 3.68 (1H, d, $J=12.4$ Hz), 3.97 (2H, m), 4.32 (1H, m), 5.12 (1H, s), 6.41 (2H, s), 7.12–7.41 (10H, m). ^{13}C NMR ($CDCl_3$) δ: major component; 20.33q, 20.66q, 49.59t, 69.05d, 74.52t, 98.66d, 127.15d, 127.35d, 127.73d, 127.77d, 127.88d, 128.44d, 128.48d, 130.77s, 136.21s, 137.20s, 139.98s, 140.11s. HRMS calcd for $C_{25}H_{27}NO$: 357.2093. Found: 357.2071.

4.2. General procedure for the addition of organolithium reagent to 1a–h with ATPH

A mixture of 2,6-diphenylphenol (0.55 g, 2.25 mmol) and Me_3Al (1.75 mL, 0.75 mmol; 1 M in hexane) in dry CH_2Cl_2 (2 mL) was stirred at rt under nitrogen for 30 min to afford the solution of ATPH.[6] To this solution was added the solution of oxazolidine (**1a–h**) (0.5 mmol) in dry CH_2Cl_2 (3 mL) and stirred at rt for 2 h. The solution was cooled to −50 °C, and organolithium (1.5 mL, 1.5 mmol, 1 M solution) was added dropwise to it. After being stirred at −50 °C for 20 h, the reaction mixture was treated with a small amount of water, and the resulting white precipitate was filtered off. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–ether (2:1) to give a diastereomeric mixture of amine (**2a–e**).

4.2.1. (1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*-2,4,6-trimethylbenzyl-1-phenylethylamine (*R*,*R*-2e). Yield 86% (97:3 mixture). Diastereomers were separated by column chromatography on silica gel with hexane–ether (3:1) to give pure (*R*,*R*)-**2e** as colorless oil. $[\alpha]_D^{22}=-115.5$ (*c* 1.27, $CHCl_3$). MS *m*/*z*: CI, 374 ($M^+ +1$, base peak); EI, 373 (M^+), 342 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3500 (O–H). ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, d, $J=$ 7.1 Hz), 1.82 (1H, br), 2.24 (3H, s), 2.28 (6H, s), 3.39 (1H, m), 3.85 (4H, m), 4.01 (1H, q, $J=7.1$ Hz), 6.84 (2H, s), 7.20–7.46 (10H, m). ^{13}C NMR ($CDCl_3$) δ: 13.64q, 20.15q, 20.82q, 45.44t, 54.96d, 62.39t, 62.94d, 126.95d, 127.60d, 128.34d, 128.36d, 2×129.54d, 132.13s, 136.62s, 138.03s, 139.06s, 144.42s. Anal. Calcd for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.64; H, 8.32; N, 3.64.

4.2.2. (1*S*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*−2,4,6-trimethylbenzyl-1-phenylethylamine (*S*,*R*-2e). Methylmagnesium bromide (0.5 mL, 1.5 mmol, 3 M in ether) was

added dropwise to a stirred solution of oxazolidine (**1e**) (0.5 mmol) in dry THF (5 mL) at rt under nitrogen over 10 min period. After the reaction mixture was stirred for 20 h, it was quenched with a small amount of water and diluted with ether (10 mL). The resulting white precipitate was filtered off, and the filtrate was washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with ether (2×10 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with hexane–ether (2:1) to give a diastereomeric mixture of amine (**2e**) (85% yield, 94:6 mixture). Diastereomers were separated by column chromatography on silica gel with hexane–ether (3:1) to give pure (*S*,*R*)-**2e** as colorless oil. $[\alpha]_D^{24} = -68.0$ (*c* 1.40, $CHCl_3$). MS *m/z*: CI, 374 ($M^+ + 1$, base peak); EI, 373 (M^+), 342 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3440 (O–H). ^1H NMR ($CDCl_3$) δ: 1.51 (3H, d, $J=7.1$ Hz), 1.55 (1H, br), 2.05 (6H, s), 2.22 (3H, s), 3.66 (1H, d, $J=12.7$ Hz), 3.86 (1H, dd, $J=9.4$, 4.9 Hz), 4.01 (1H, d, $J=12.7$ Hz), 4.02 (1H, q, $J=7.1$ Hz), 4.15 (1H, dd, $J=10.7$, 4.9 Hz), 4.26 (1H, dd, $J=10.7$, 9.4 Hz), 6.77 (2H, s), 6.87–7.01 (4H, m), 7.13–7.29 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 16.03q, 19.75q, 20.78q, 43.82t, 54.71d, 61.10t, 61.65d, 126.49d, 126.99d, 127.57d, 128.08d, 128.25d, 128.78d, 129.23d, 132.45s, 136.27s, 138.21s, 139.96s, 143.97s. Anal. Calcd for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.79; H, 8.51; N, 3.72.

4.3. General procedure for removal of the *N*-2,4,6-trimethylbenzyl group from (*R*,*R*)- and (*S*,*R*)-2e

A single diastereomer of (*R*,*R*)- and (*S*,*R*)-**2e** (0.134 mmol) and trifluoroacetic acid (5 mL) was stirred at 50 °C for 3 days, and then diluted with water (20 mL). The resulting aqueous phase was basified with 10% NaOH solution and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with ethyl acetate–hexane (1:2) to give (*R*,*R*)- and (*S*,*R*)-**3**, respectively.

4.3.1. Synthesis of (*Z*,*R*)-*N*-isopropyliminium–aluminum complex (4h) for NOE experiment. A mixture of 2,6-diphenylphenol (0.148 g, 0.6 mmol) and Me_3Al (0.1 mL, 0.2 mmol; 2 M in toluene) in dry CH_2Cl_2 was stirred at rt under nitrogen for 30 min to afford the solution of ATPH.[6] Then the solution was concentrated under reduced pressure and residue was solved in $CDCl_3$ (0.5 mL). To this solution was added the solution of oxazolidine (**1c**) (0.1 mmol) in $CDCl_3$ (0.5 mL) and stirred at rt for 2 h to obtain the $CDCl_3$ solution of iminium–aluminum complex (**4h**). The solution was used for NOE experiment without purification and the data was showed some peak for complicated chart: ^1H NMR ($CDCl_3$) δ: 0.55 (3H, brd), 0.75 (3H, brd), 1.41 (3H, br), 1.54 (1H, br), 2.67 (1H, br), 2.99 (1H, br), 3.50 (1H, brdd), 6.52 (2H, brd).

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References and notes

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6. The assignment of ^1H NMR spectrum on 1′ and 2′ position of **4h** determined as follows. 2′-Dideuteriumed iminium–aluminum complex (**4h′**) was obtained from (*R*)-phenylglycine with $LiAlD_4$ for 5 steps by the similar procedure.[4] In **4h′**, the signals of ^1H NMR spectrum on 2′ position (δ: 1.54, 2.67 ppm) were not observed, and the signal on 1′ position (δ: 3.50 ppm) was observed. Therefore, the assignment of ^1H NMR spectrum on 1′ and 2′ position of **4h** was determined.