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. 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. 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 C₃ symmetrical ATPH, has been shown to have unique properties in various reactions by Yamamoto. 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.

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, 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 MgBr₂ and Me₃Al (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). As ATPH showed encouraging activity,
further research looked into the effect of the N-substituent of 1,3-oxazolidines at \(-50^\circ\text{C}\).

### 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) 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 $\text{w}$O 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, 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.

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**Scheme 1.**

**Scheme 2.**

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

<table>
<thead>
<tr>
<th>Run</th>
<th>Lewis acid</th>
<th>Activation time (h)</th>
<th>Reaction temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>Ratio ((R,R,\overline{S}, \overline{R})^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>——r</td>
<td>r t 2 0N R —</td>
<td>20</td>
<td>NR</td>
<td>—</td>
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<tr>
<td>2b</td>
<td>BF$_3$OEt$_2$</td>
<td>1</td>
<td>rt</td>
<td>20</td>
<td>34</td>
<td>43:57</td>
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<tr>
<td>3b</td>
<td>BCl$_3$</td>
<td>1</td>
<td>rt</td>
<td>20</td>
<td>17</td>
<td>38:62</td>
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<tr>
<td>4</td>
<td>SnCl$_2$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>MnBr$_2$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Et$_2$Zn</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Ln(OtF)$_3$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>41</td>
<td>37:63</td>
</tr>
<tr>
<td>8</td>
<td>Yb(OtF)$_3$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>68</td>
<td>15:85</td>
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<tr>
<td>9</td>
<td>MgBr$_2$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>NR</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>YCl$_2$</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>72</td>
<td>20:80</td>
</tr>
<tr>
<td>11b</td>
<td>Me$_3$Al</td>
<td>1</td>
<td>rt</td>
<td>20</td>
<td>Trace</td>
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</tr>
<tr>
<td>12b</td>
<td>Me$_3$Al</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>72</td>
<td>20:80</td>
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<tr>
<td>13</td>
<td>ATPH</td>
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<td>−50</td>
<td>72</td>
<td>56</td>
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<tr>
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<td>−50</td>
<td>168</td>
<td>19</td>
<td>80:20</td>
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<tr>
<td>16</td>
<td>ATPH</td>
<td>2</td>
<td>−50</td>
<td>20</td>
<td>86</td>
<td>78:22</td>
</tr>
</tbody>
</table>

$^a$ Estimated by $^1$H NMR spectrum.

$^b$ This reaction was carried in THF solvent.
and \((S,R)-3\) in 84% yield, respectively. The stereochemistry of \(3\) was established by comparing \(^1\)H NMR spectra with published data\(^{2a-d}\) (Scheme 4).

**Scheme 3.**

![Scheme 3](image)

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

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

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

**Scheme 4.**

![Scheme 4](image)

**Scheme 5.**

![Scheme 5](image)

A model compound, \(N\)-isopropyl-2-methyl-1,3-oxazolidine (1h), was preferred to the comparative intelligible chart. The \(^1\)H 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\(^0\) deuterated compound additionally prepared.\(^5\) 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\(^0\)a, H2\(^0\)b, and H1\(^0\)0, respectively. In traces b and c, irradiation at H2\(^0\)a and H2\(^0\)b was reflected by a change in the H1\(^0\) peak from a doublet–doublet to a doublet. Trace d shows that irradiation at H1\(^0\) converted the doublet at H2\(^0\) into a singlet. Based on these experiments, assignment of the \(^1\)H NMR spectra of 4h was judged to be consistent. Both NOE difference experiments identified correlation between H2 and H1\(^0\) 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

**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.
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 C3 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
of diastereoselectivity is imprecise, because we were unable to characterize their complexes.

3. Conclusion

1,3-Oxazolidinones 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-oxazolidinones having 1,3-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. 1H and 13C NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical shifts are reported in ppm on the 1H and 13C NMR spectra were obtained on a JEOL GSX 270 instrument. Melting points were measured with a Yanagimoto Micro melting Point apparatus without collection. IR spectra were taken as the solution in CHCl3. 1H NMR (CDCl3) δ: 7.40 (1H, 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). 13C NMR (CDCl3) δ: 136.4q, 20.15q, 20.82q, 45.44q, 54.96d, 62.39d, 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 C28H27NO: C, 83.60; H, 8.32; N, 3.64. Found: C, 83.64; H, 8.32; N, 3.64.

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 Me2Al (1.75 mL, 0.75 mmol; 1 M in hexane) in dry CH2Cl2 (2 mL) was stirred at rt under nitrogen for 30 min to afford the solution of ATPH. To this solution was added the solution of oxazolidine (1a–h) (0.5 mmol) in dry CH2Cl2 (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 Na2SO4 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. (1R,1′R)-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 (2:1) to give pure (R,R-2e) as colorless oil. [α]D20 = −115.5 (c 1.27, CHCl3). MS m/z: CI, 374 (M+ + 1, base peak); EI, 373 (M+), 342 (M+ − CH2OH), 133 (base peak). IR (CHCl3), cm−1: 3500 (O–H), 3050, 2950, 2860 (C–H). 1H NMR (CDCl3) δ: 2.12 (3H, s), 3.84 (4H, m), 4.01 (1H, q, J = 7.1 Hz), 6.84 (2H, s), 7.20–7.46 (10H, m). 13C NMR (CDCl3) δ: 136.4q, 20.15q, 20.82q, 45.44q, 54.96d, 62.39d, 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 C28H27NO: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.64; H, 8.32; N, 3.64.

4.2.2. (1S,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 NH4Cl (10 mL). The aqueous phase was extracted with ether (2 × 10 mL). The combined organic extract was washed with brine, dried over anhydrous Na2SO4, 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. [α]D24 = −68.0 (c 1.40, CHCl3). MS m/z: Cl, 374 (M+ + 1, base peak); E1, 373 (M+), 342 (M+ − CH2OH), 133 (base peak). IR (CHCl3, cm−1): 3440 (O–H).

1H NMR (CDCl3) δ: 1.53 (3H, d, J = 12.7 Hz), 1.69 (3H, d, J = 12.7 Hz), 4.26 (1H, q, J = 7.1 Hz), 4.15 (1H, d, J = 10.7, 4.9 Hz), 4.32 (1H, dd, J = 10.7, 9.4 Hz). 13C NMR (CDCl3) δ: 16.03q, 19.75q, 20.78q, 43.82t, 54.71d, 61.01t, 61.65d, 126.49d, 126.99d, 127.57d, 128.08d, 128.25d, 128.78d, 129.23d, 132.45s, 136.27q, 138.21s, 139.96s, 143.97s. Anal. Calcd for C26H31NO: 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 CH2Cl2 (3 × 20 mL). The combined extracts were washed with brine, dried over anhydrous Na2SO4, 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 Me3Al (0.1 mL, 0.2 mmol; 2 M in toluene) in dry CH2Cl2 was stirred at rt under nitrogen for 30 min to afford the solution of ATPH. Then the solution was concentrated under reduced pressure and residue was solved in CDC13 (0.5 mL). To this solution was added the solution of oxazolidine (1e) (0.1 mmol) in CDC13 (0.5 mL) and stirred at rt for 2 h to obtain the CDC13 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 (CDCl3) 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).

Acknowledgements

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References and notes


6. The assignment of 1H NMR spectrum on 1’ and 2’ position of 4h determined as follows, 2’-Dideuterium iminium–aluminum complex (4h′) was obtained from (R)-phenylglycine with LiAlD4 for 5 steps by the similar procedure. 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.