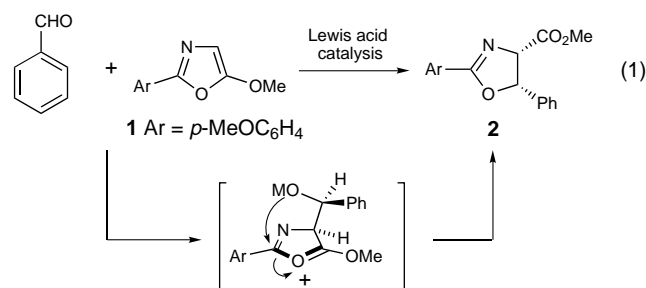


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Chiral Salen–Aluminum Complexes as Catalysts for Enantioselective Aldol Reactions of Aldehydes and 5-Alkoxyoxazoles: An Efficient Approach to the Asymmetric Synthesis of *syn* and *anti* β -Hydroxy- α -amino Acid Derivatives**

David A. Evans,* Jacob M. Janey, Nabi Magomedov, and Jason S. Tedrow

The stereoselective synthesis of α -amino- β -hydroxy acids is a topic of ongoing interest as these structures are found in numerous peptide-based natural products including the vancomycin antibiotics.^[1] The stereoselective synthesis of *trans*-5-substituted 2-oxazoline-4-carboxylates has been reported using an aldol reaction between aldehydes and methyl isocyanoacetate,^[2] and the enantioselective version of this reaction has subsequently been developed by Ito and Hayashi et al.^[3] A related aldol addition/acyl transfer process wherein 5-methoxyoxazole **1** functions as the glycine enolate synthon has been described by Suga and Ibata et al. [Eq. (1)].^[4] In



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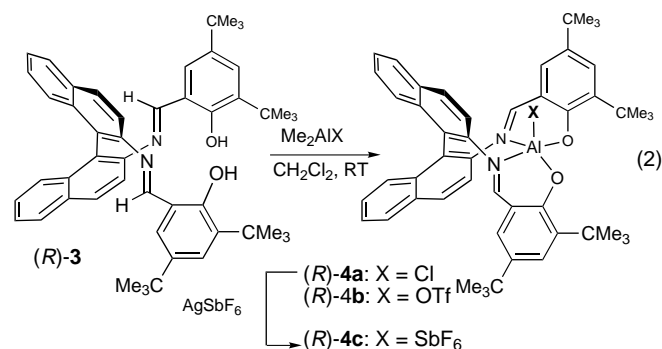
[**] Financial support has been provided by the National Institutes of Health (GM 43912-11 and GM 33328-18).

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contrast to the Hayashi–Ito reaction, this addition affords the more versatile *cis*-2-oxazoline-4-carboxylates **2**. These substrates may be cleanly isomerized to their *trans* counterparts, thus providing access to both α -amino- β -hydroxy acid diastereomers from the same reaction sequence.

In the current rendition, the Suga–Ibata reaction [Eq. (1)] is mediated by an uncharacterized metal complex derived from trimethylaluminum and (*R*)- or (*S*)-BINOL. This chiral complex affords *cis*-**2** with good diastereoselection (4:1–20:1) but variable enantioselectivities. As described, this reaction suffers from high catalyst loading (30%), long reaction times, and the requirement of excess aldehyde to drive the reactions to completion.^[4] Here we describe the synthesis and characterization of the chiral aluminum complexes (*R*)-**4** and their use in the catalysis of this *cis*-diastereoselective aldol reaction with enantioselectivities in excess of 90% for a range of aromatic aldehydes.

Chiral aluminum complex (*R*)-**4a** was prepared in quantitative yield by reaction of the enantiomerically pure diaminoBINOL-derived ligand^[5] (*R*)-**3** with dimethylaluminum chloride [Eq. (2); CH₂Cl₂, 25 °C]. Complex (*R*)-**4a** was



isolated as a yellow, bench-stable amorphous solid. The structure of *rac*-**4a** was determined by X-ray crystallography.^[6] The complex exhibits a distorted trigonal bipyramidal geometry with the chlorine atom located in the equatorial plane (Figure 1). The dihedral angle between the two naphthyl planes is 62°, creating a chiral environment around the aluminum metal center. The corresponding triflate complex (*R*)-**4b** was prepared by the reaction of (*R*)-**3** with dimethylaluminum triflate^[7] (CH₂Cl₂, 0–25 °C) in 94% yield. The structure of *rac*-**4b** was also determined by X-ray analysis. In contrast to the aluminum chloride complex *rac*-**4a**, the triflate complex *rac*-**4b** crystallized as the diaqua aluminum complex *rac*-**5**, and exhibited a distorted octahedral geometry with two *cis* water molecules coordinated to the metal center (Figure 1). According to the triflate–aluminum distance of 4.5 Å the triflate anion is fully dissociated. Inspection of the X-ray structure of *rac*-**5** indicates that the (*R*)-**3** ligand is bound to the aluminum center of (*R*)-**4b** in a Δ -*cis*- β configuration.^[8]

Initial experiments revealed that [Al(OH₂)₂]{(*R*)-**3**}[OTf] (**5**) (20 mol%) catalyzes the reaction of oxazole **1** with benzaldehyde (1.2 equiv, CH₂Cl₂, 3 Å MS, 25 °C, 20 h) to furnish (4*S*,5*S*)-oxazoline **2** in 98% *ee* and with high diastereoselection (93:7 *dr*) favoring *cis*-**2**. However, catalyst turn-

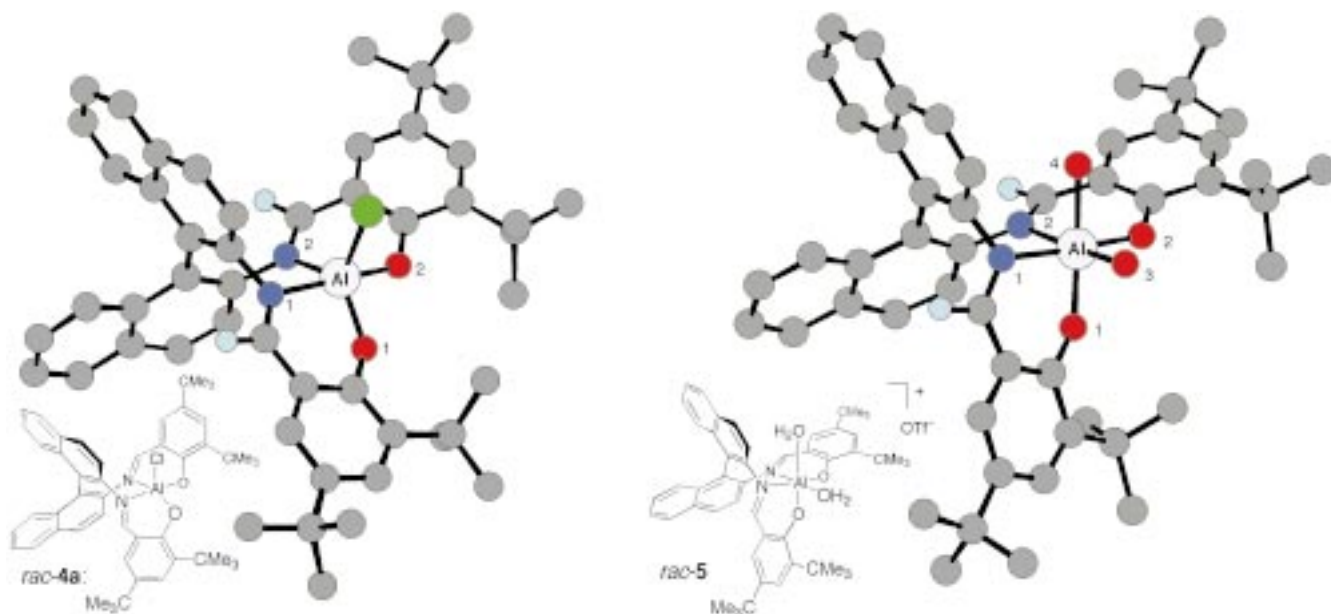


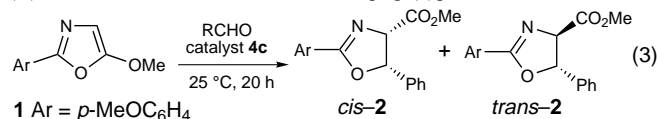
Figure 1. X-ray structure of chiral aluminum complexes *rac-4a* and *rac-5*. The dissociated triflate counterion is not illustrated in *rac-5*.

over appeared to be a problem as the reaction proceeded to only 60% conversion. While the aluminum chloride complex (*R*)-**4a** was not catalytically active, activation by AgSbF₆ provides a highly reactive species, presumably the cationic complex (*R*)-**4c**. Reaction of oxazole **1** with benzaldehyde in the presence of 20 mol % of (*R*)-**4c** afforded oxazoline **2** with good conversion (80%; 20 h) and the same enantio- and diastereoselection (93:7 *dr*, 98% *ee*). The same reaction performed in the absence of molecular sieves afforded similar stereoselectivity, but decreased conversion (60%). In subsequent experiments it was established that the problem of low conversion was not due to product inhibition.

Solvent effects were next investigated in an attempt to improve catalyst turnover. In general, poorly coordinating solvents provide higher conversions than reactions conducted in THF or acetonitrile [Table 1, Eq. (3)]. Ultimately, toluene was found to be the optimal solvent affording oxazoline **2** (80% conversion, 95:5 *dr*, 99% *ee*) in the presence of only 10 mol % of (*R*)-**4c**. It is noteworthy that asymmetric induction and reaction diastereoselection are virtually solvent insensitive.

A salt additive sharply increases the catalyst efficiency (Table 1). For example, the reaction of **1** with 1.2 equiv of benzaldehyde (PhMe, 3 Å MS, 25 °C, 5 mol % of (*R*)-**4c**) furnishes oxazoline **2** in 99% yield with excellent stereoselectivity (95:5 *dr*, 99% *ee*) when conducted in the presence of 20 mol % of LiClO₄. The same reaction performed in the absence of any additive proceeds with only 35% conversion. Low conversion (40%) is also observed when lithium perchlorate is replaced with 20 mol % of tetramethylammonium perchlorate. The latter experiments suggest that a hard cation such as Li⁺ (or Na⁺) might serve to promote the breakdown of the proposed aluminum–alkoxide aldolate intermediate [Eq. (1)]. A practical extension of this effect was made by utilizing Na₂SO₄ as both additive and drying agent. This reaction may be readily scaled up. Thus, on a one-gram scale, reaction of oxazole **1** and benzaldehyde (1M in toluene,

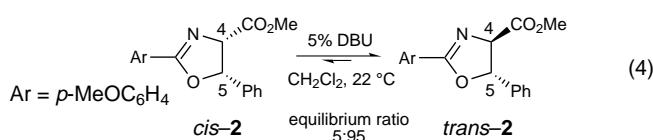
Table 1. Enantioselective reaction of **1** with PhCHO catalyzed by complex (*R*)-**4c**. Assessment of reaction variables [Eq. (3)]



Solvent ^[a]	Additive ^[b]	mol % 4c	conv. [%]	<i>dr</i> ^[c]	<i>ee</i> [%] ^[c]
MeCN	none	20	10	97:3	99
THF	none	20	19	95:5	98
CH ₂ Cl ₂	none	10	50	95:5	98
MeC ₆ H ₅	none	10	80	95:5	99
MeC ₆ H ₅	none	5	34	95:5	99
MeC ₆ H ₅	LiClO ₄	5	94	95:5	99
MeC ₆ H ₅	Me ₄ NClO ₄	5	42	95:5	99
MeC ₆ H ₅	Na ₂ SO ₄ ^[d]	1	96	96:4	99
MeC ₆ H ₅	NaBPh ₄	5	94	95:5	99

[a] The reaction was carried out in the indicated solvent at room temperature in the presence of crushed 3 Å molecular sieves (200 mg for 0.4 mmol **1**). [b] The indicated additive was used in 20 mol %. [c] *cis:trans* ratio and enantiomeric excess (*cis-2*) determined by HPLC (Chiralcel AD). [d] Use of molecular sieves replaced by additive on 1-g scale reaction.

1 g Na₂SO₄, 25 °C, 20 h) with 1 mol % of (*R*)-**4c** furnished the desired adduct *cis-2* in 92% yield (96% conversion, 96:4 *dr*, 99% *ee*). In addition, *cis-2* (>99% *ee*) was epimerized to *trans-2* by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (*cis:trans* 5:95, >99% *ee*) [Eq. (4)]. The absolute configuration of the known (4*S*,5*S*)-*cis-2* was readily determined by its optical rotation.^[4] This experiment also establishes that the sample of (4*R*,5*S*)-*trans-2*



obtained by epimerization has the same absolute configuration as the minor aldol reaction product [Eq. (3)].

The scope of the reaction was explored using the optimized conditions described in the preceding paragraph (PhMe, 20% LiClO₄, 3 Å MS, 25 °C, 20 h; Table 2). A wide range of aromatic aldehydes were found to be excellent substrates. The reactions of densely functionalized benzaldehydes containing both electron withdrawing and donating substituents afford oxazoline adducts (**8c**, **9a–c**, and **10**) in high yield (90–100%) and good stereoselection (74:26–96:4 *dr*, 92–98% *ee*). Furfural affords oxazoline **12** with good stereoselection (77:23 *dr*, 96% *ee*), but in moderate yield (58%). We speculate that the longer reaction times necessary for higher conversion lead to epimerization of the *cis*-oxazoline **12** to the *trans* isomer (6:94 *dr*, 68% *ee trans*; 20 h). The absolute configurations of the above products were assigned by analogy to the known *cis*-oxazoline **2**. Surprisingly, aliphatic aldehydes, such as dihydrocinnamaldehyde and cyclohexane carbaldehyde, were found to be unreactive under the standard reaction conditions.

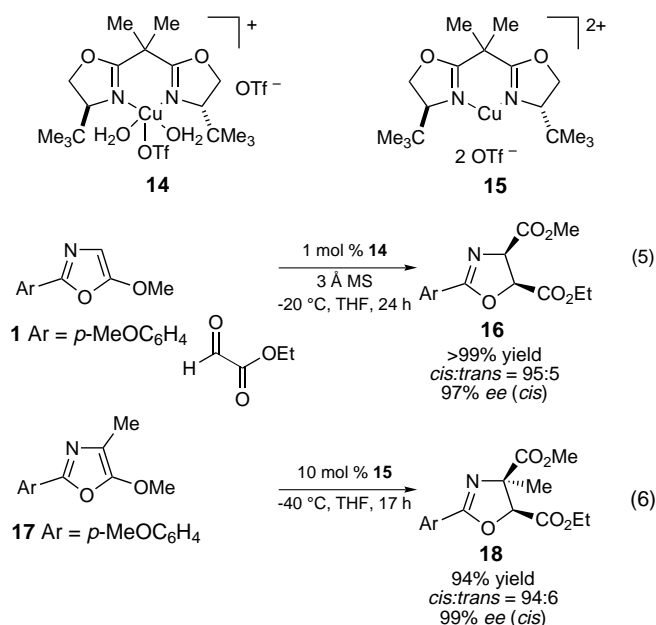
This reaction is not limited to catalysis by aluminum-derived Lewis acids. We have found that Cu^{II}-bis(oxazoline) complexes are efficient catalysts for chelating aldehydes. For example, the reaction between oxazole **1** and ethyl glyoxylate, mediated by [Cu(OTf)(OH)₂]{(*S,S*)-*t*Bu-box}}[OTf] (**14**) (1 mol %, THF, 3 Å MS, –20 °C, 24 h) afforded adduct **16** in quantitative yield and excellent stereoselectivity (95:5 *dr*, 97% *ee*) [Eq. (5)].^[9] Furthermore, 4-methyl substituted oxazole **17** reacts in an analogous fashion with ethyl glyoxylate in the presence of **15** (10 mol %, THF, –40 °C, 17 h) to provide a 94% yield of oxazoline **18** (94:6 *dr*, 99% *ee*) [Eq. (6)]. The absolute configuration of the cycloadduct^[10] is consistent with the previously proposed model for asymmetric induction with Cu^{II}-bis(oxazoline) and glyoxylate esters.^[9, 11] The observed stereochemistry may be rationalized by assuming an aldol-like addition of the nucleophilic oxazole to the Lewis acid-activated aldehyde.

Based upon the published X-ray structure of complex **14**,^[12] semiempirical calculations (PM3) were employed to model the complex between ethyl glyoxylate and **15**. For simplicity,

Table 2. Enantioselective reaction of aldehydes with oxazole **1** catalyzed by chiral aluminum complex (*R*)-**4c** [Eq. (3)].

Aldehyde		mol % 4c	Yield (%) ^[a]	<i>dr</i> ^[b]	<i>ee</i> [%] (product) ^[c]
	X = H	5	99	95:5	99 (2)
	X = F	10	98	96:4	> 99 (6a)
	X = NO ₂	5	99	88:12	97 (6b)
	X = CN	5	96	83:17	95 ^[d] (6c)
	X = COOMe	5	98	93:7	> 99 (6d)
	X = OPh	10	89	96:4	> 99 (6e)
	X = OAc	5	95	96:4	> 99 (6f)
	X = Me	5	96	92:8	96 (6g)
	X = Ph	5	100	96:4	99 (6h)
	X = Cl	5	93	90:10	99 (7a)
	X = NO ₂	5	99	73:27	91 (7b)
	X = OMe	5	95	93:7	99 (7c)
	X = Me	5	98	95:5	98 (7d)
	X = Cl, Y = H	5	96	> 99:1	> 99 (8a)
	X = NO ₂ , Y = H	5	93	93:7	> 99 (8b)
	X = Br, Y = OMe	5	98	96:4	95 (8c)
	X = Me, Y = H	5	86	> 99:1	> 99 (8d)
	X = F, Y = Cl	5	100	89:11	98 (9a)
	X = OMe, Y = Br	5	90	91:9	98 (9b)
	X = Cl, Y = NO ₂	5	99	74:26	92 (9c)
		5	96	90:10	98 (10)
	1-Naphthyl	10	97	96:4	> 99 (11a)
	2-Naphthyl	10	98	96:4	> 99 (11b)
		10	58	77:23	96 (12)
		10	98	90:10	98 (13)

[a] Yield of isolated product. [b] *cis:trans* ratio determined by ¹H NMR or HPLC. [c] Enantiomeric excess of the *cis* isomer determined by HPLC (Chiralcel AD). [d] Enantiomeric excess determined by ¹H NMR with BINOL as a shift reagent.



the triflate counterions were omitted from the calculations. As shown in Figure 2, the *Re* face of the bound glyoxalate is screened by the ligand's *tert*-butyl substituent, leaving the *Si* face accessible to nucleophile approach.



Figure 2. PM3 model of the **15**–glyoxalate complex.

Experimental Section

(R)-4a: To an oven-dried round-bottom flask containing a magnetic stir bar was added (**R**)-**3**^[13] (1.96 g, 2.74 mmol). The flask was charged with 20 mL of CH₂Cl₂ and cooled to 0 °C. Neat Me₂AlCl (255 μL, 2.74 mmol) was slowly added to the stirred solution with a syringe over 3 minutes. The red reaction mixture was allowed to warm to room temperature and stirred overnight (15 h). It was then concentrated in vacuo to give an orange glass. Hexane (20 mL) was added and the solvent was removed in vacuo to afford the product (**R**)-**4a** as a bright yellow amorphous solid (2.13 g, 2.74 mmol, >99% yield). Analytical data for (**R**)-**4a**: m.p. 234–236 °C; [α]_D = -977° (*c* = 0.66, CHCl₃); IR (CH₂Cl₂): $\tilde{\nu}$ = 2964, 1615, 1584, 1540, 1471, 1179 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 8.43 (s, 1H), 8.22 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.95–7.90 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.54–7.47 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.31–7.25 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 1.53 (s, 9H), 1.49 (s, 9H), 1.26 (s, 18H); ¹³C NMR (125 MHz, CDCl₃): δ = 173.9, 170.0, 165.5, 161.8, 145.1, 144.9, 141.8, 141.3, 139.6, 138.8, 133.4, 132.8, 132.7, 132.4, 132.3, 131.7, 130.5, 129.6, 128.8, 128.5, 128.0, 127.9, 127.2, 126.9, 126.7, 126.3, 126.0, 125.7, 125.2, 119.2, 118.4, 35.7, 34.2, 31.8, 31.4, 31.3,

30.0, 29.7, 22.9, 14.4; HR-MS (FAB): *m/z* calcd for C₅₀H₅₄AlN₂O₂: 741.4001 [*M* – Cl]⁺, found: 741.3980.

8a: A dry, round-bottom flask equipped with a magnetic stirrer was charged with (**R**)-**4a** (15.5 mg, 0.020 mmol; 0.050 equiv), oxazole **1** (82 mg, 0.40 mmol; 1 equiv), AgSbF₆ (7.6 mg, 0.022 mmol; 0.055 equiv), LiClO₄ (8.5 mg, 0.08 mmol; 0.20 equiv), and powdered 3 Å molecular sieves (200 mg). To this mixture was added toluene (2 mL), followed by addition of 2-chlorobenzaldehyde (54 μL, 0.48 mmol; 1.2 equiv) with a syringe. After stirring at room temperature for 20 h, the reaction mixture was filtered through a short plug of silica gel and eluted with diethyl ether. After concentration in vacuo, the product was purified by flash chromatography on silica gel and eluted with 30% EtOAc in hexanes to afford **8a** as a thick, colorless oil (133 mg, 0.38 mmol, 96%). ¹H NMR analysis of the unpurified product showed no *trans* product. Chiral analysis by HPLC (Chiralpak AD, *i*PrOH/hexanes (20:80), flow rate 0.7 mL min⁻¹, 254 nm; *t*_r = 17.1 (minor *cis* product), 27.1 (major *cis* product)) gave the isomeric composition of the product: >99:1 *dr*, >99% *ee*. Analytical data for **8a**: [α]_D = +362° (*c* = 1.64, CHCl₃); IR (CHCl₃): 3018, 1746, 1647, 1610, 1514, 1258, 1218, 1172, 1088, 1030, 992, 842 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 8.04 (d, *J* = 8.5 Hz, 2H), 7.46–7.43 (m, 1H), 7.40–7.36 (m, 1H), 7.28–7.24 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 10.5 Hz, 1H), 5.36 (d, *J* = 10.5 Hz, 1H), 3.88 (s, 3H), 3.23 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 169.6, 166.6, 162.9, 134.4, 132.4, 130.7, 129.7, 129.2, 127.4, 127.0, 119.4, 114.1, 80.2, 72.8, 55.6, 51.8; HR-MS (EI): *m/z* calcd for C₁₈H₁₆ClNO₄: 345.0768 [*M*]⁺, found: 345.0774; satisfactory elemental analysis was obtained.

Crystal data for *rac*-**4a** (C₅₂H₆₁AlClN₂O₃):^[14] crystal dimensions 0.15 × 0.2 × 0.2 mm³, triclinic, space group *P1*, *a* = 12.1105(8), *b* = 15.4529(10), *c* = 16.5387(11) Å, β = 108°; *V* = 2559.9(3) Å³, ρ = 1.070 mg mm⁻³; Siemens SMART CCD diffractometer, 1.49 < θ < 27.85°, MoK α radiation, λ = 0.71073 Å, $\theta/2\theta$ -scans, *T* = 293(2) K; of 16249 measured reflections, 10558 were independent and 10558 were observed with *I* > 2 σ (*I*), -14 ≤ *h* ≤ 13, -19 ≤ *k* ≤ 20, -21 ≤ *l* ≤ 14; *R* = 0.0599, *wR* = 0.1720, GOF = 0.968 for 565 parameters, $\Delta\rho_{\max}$ = 0.715 e Å⁻³.

Crystal data for *rac*-**5** (C₆₈H₉₈AlF₃N₂O₁₀S₂):^[14] crystal dimensions 0.2 × 0.3 × 0.5 mm³, triclinic, space group *P1*, *a* = 13.8209(9), *b* = 15.3143(9), *c* = 18.6786(11) Å, β = 84°; *V* = 3857.7(4) Å³, ρ = 1.077 mg mm⁻³; Siemens SMART CCD diffractometer, 1.11 < θ < 22.50°, MoK α radiation, λ = 0.71073 Å, $\theta/2\theta$ -scans, *T* = 293(2) K; of 17719 measured reflections, 10033 were independent and 10033 were observed with *I* > 2 σ (*I*), -14 ≤ *h* ≤ 14, -16 ≤ *k* ≤ 10, -19 ≤ *l* ≤ 20; *R* = 0.0713, *wR* = 0.2287, GOF = 1.192 for 785 parameters, $\Delta\rho_{\max}$ = 0.826 e Å⁻³.

Received: February 5, 2001 [Z16561]

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- [14] The structures were solved by direct methods (SHELXTL Plus) and developed by least squares refinement against $|F^2|$ (SHELXL93). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-157312 (*rac-4a*) and CCDC-157313 (*rac-5*). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).