Reactivity Enhancement for Chiral Dirhodium(II) Tetrakis(Carboxamidates)

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Abstract: Difluorinated ligands from azetidinone-4-carboxylates and pyrrolidinone-5-carboxylate have been prepared, substituted onto dirhodium(II), and the reactivities and selectivities of the resulting catalysts have been examined. The fluorinated catalysts exhibit enhanced reactivity towards diazo decomposition but diminished enantioselectivities for cyclopropanation. Selectivity for ylide formation and rearrangement or Si–H insertion is enhanced or similar to that with unfluorinated analogues.

Introduction

The enhancement of catalyst effectiveness through ligand modification is a time-honored approach. This has been especially true for the development of chiral dirhodium(II) catalysts for metal carbene transformations.[1] Dirhodium(II) compounds with chiral carboxamidate ligands are highly effective towards diazo decomposition of diazoacetates and diazoacetamides.[2] However, these catalysts are generally unreactive towards vinyldiazoacetates[3] and diazomalonates,[4] and alternative reactions or thermal processes occur instead of catalytic diazo decomposition.[1]

By substitution of fluorine for hydrogen on the carbon position alpha to the carboxamide carbonyl, one could expect increased reactivity while retaining nearly the same selectivity as the unsubstituted parent carboxamide. Fluorine substitution does influence significantly the reactivity of dirhodium(II) carboxylates.[5,6] We describe here the synthesis of difluoroazetidinones and a difluoropyrrolidinone ligand for dirhodium(II) and the reactivities and selectivities drawn from the corresponding catalysts in their applications with diazocarbonyl compounds.

Results and Discussion

Enantiomerically pure 3,3-difluoro-2-oxaazetidine-4-carboxylates were prepared from D-mannitol (**1**) by the sequence of synthetic steps that is described in Scheme 1. Thus oxidative cleavage of the acetone ketal of D-mannitol,[7] followed by imine formation, afforded **3** which was then treated with zinc dust and ethyl bromodifluoroacetate[8] to produce **4** as a mixture of diastereoisomers whose ratio was dependent on R^1 (Bn, *syn/anti* = 4.7; *p*-$MeOC_6H_4CH_2$, *syn/anti* = 4.0; Ph_2CH, *syn/anti* = 2.0). Chromatographic separation of the *syn*-isomer, alcoholysis, oxidation,[9] and esterification produced the azetidin-2-one product **5** that was deprotected[10] to afford the desired ligand. The key to this synthesis was the success of the Reformatsky reaction (step *d*), for which the only deficiency was the stereoisomer ratio with imines whose R^1 substituent was removable at a later stage. With these considerations the *p*-methoxybenzyl group was determined to be optimal for the construction of **5** (R^1 = H). Although several esters of **5** (R^1 = H) were prepared, only two (R = *i*Bu and *c*Hex) were converted by the standard procedure[11] to dirhodium(II) tetrakis(carboxamidates) **6**. In spite of extensive efforts, we were not able to prepare crystals suitable for X-ray structural analysis.

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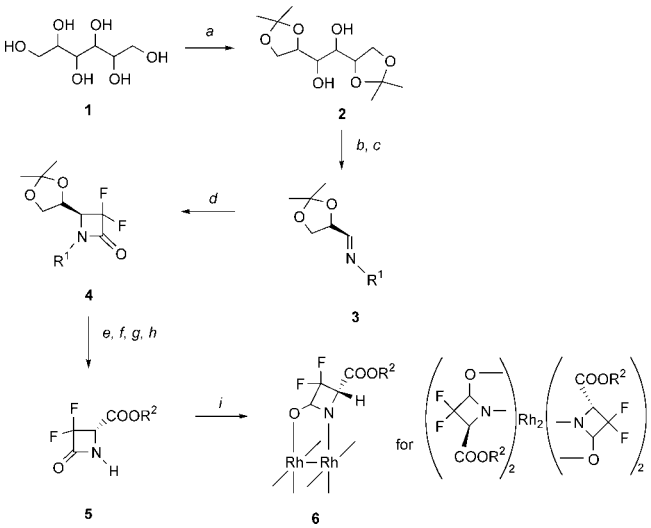
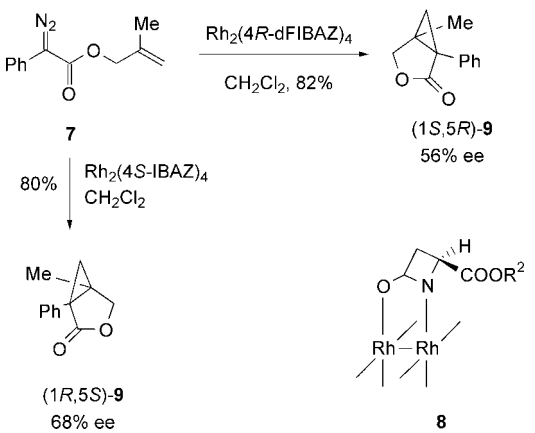


Scheme 1. *a*: $Me_2C(OMe)_2$, *p*TsOH (46%). *b*: $NaIO_4$/CH_2Cl_2–H_2O. *c*: R^1NH_2/$MgSO_4$/CH_2Cl_2. *d*: Zn/THF/TMSCl/$BrCF_2COOEt$ (61% from **2**). *e*: CH_2Cl_2/TFA/MeOH/PhMe. *f*: Me_2CO–H_2O (3:1)/$NaIO_4$/$KMnO_4$/HOAc. *g*: *i*BuOH/*p*TsOH/Dean-Stark trap (57% from **4**). *h*: CAN/ MeCN–H_2O (2:1) with R^1 = *p*-$MeOC_6H_4CH_2$ (69%). *i*: $Rh_2(OAc)_4$/PhCl (65% with R^2 = *i*Bu, 73% with R^2 = *c*Hex)

To ascertain that the fluorinated ligand did confer higher reactivity to the associated catalyst,[12] we selected the intramolecular cyclopropanation reaction of 2-methyl-2-propen-1-yl phenyldiazoacetate (**7**)[13] by both Rh_2(4*R*-dFIBAZ)$_4$ (**6a**, R^2 = *i*Bu) and its hydrogen-substituted analogue **8a** (Scheme 2). Separately, these two catalysts gave the cyclopropane product **9** in good yield, modest % ee values, but opposite configuration. With equal amounts of the two catalysts and under exactly the same reaction conditions, however, (1*S*,5*R*)-**9** was the major enantiomer (43% ee), indicating that **6a** is at least eight times more reactive towards diazo decomposition of **7** than is **8a**.



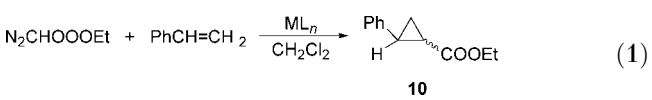
Scheme 2.

Lower % ee values for the reactions of **7** catalyzed by **6a** compared to **8a** are a result of the higher reactivity of the intermediate metal carbene, and this outcome is also seen in more traditional reactions. For example, with ethyl diazoacetate and styrene (Eq. 1) **6** was less selective diastereoselectively and enantioselectively than its non-fluorinated counterparts (**8**).[14]

Table 1. Reaction of allyl iodide with ethyl diazoacetate[a]

Catalyst	Product yield %[b]	**11**:**12**	**11** % ee	**12** *cis*:*trans*	***cis*-12** % ee
$Rh_2(OAc)_4$	75	90:10	–	45:55	–
Rh_2(4*S*-IBAZ)$_4$	36	37:63	26	50:50	66
Rh_2(4*R*-dFIBAZ)$_4$	46	62:38	52	50:50	39
Rh_2(4*R*-dFCHAZ)$_4$	45	59:41	47	50:50	45
Rh_2(5*S*-dFMEPY)$_4$	41	89:11	30	43:57	28
Rh_2(5*S*-MEPY)$_4$	44	76:24	0	37:63	44

[a] Reaction performed in refluxing CH_2Cl_2 with 1.0 mol % of catalyst and 10 equiv of allyl iodide.
[b] Weight yield after chromatography.



(1)

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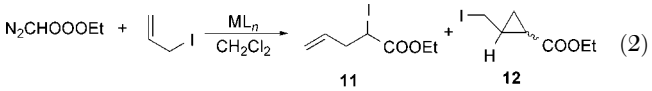
However, in ylide formation and [2,3]-sigmatropic rearrangement with allyl iodide and ethyl diazoacetate (Eq. 2),[15] a transformation that was only moderately successful (12–15% yield of **11**, up to 39% ee) with other chiral dirhodium(II) carboxamidates, moderate yields and significantly higher % ee values were achieved for **11** with fluorinated catalysts **6** (Table 1), and these results suggest that there may be further advantages for these catalysts in ylide transformations.



(2)

11 **12**

In addition, **6** is effective for diazo decomposition of RCN_2COOEt (R = CF_3 and COOEt) in refluxing dichloromethane, but enantiomeric excesses of cyclopropanation are less than 40%.

We have also prepared the fluorinated analogue of Rh_2(5*S*-MEPY)$_4$ through modification with significantly higher yield of a recently published procedure for the preparation of ligand **13**.[16] In this case we were able to ibtain crystals suitable for X-ray structural analysis. The structure of **14b** is shown in Figure 1; the new catalyst possesses the same (*cis*-2,2) geometry as Rh_2(5S-MEPY)$_4$. Reaction with phenyl diazoacetate **7** occurred within minutes at room temperature in dichloromethane using **14b** even though there was no reaction with **14a** under the same conditions. However, as found with **6** in comparison with **8**, enantiocontrol was low (6% ee for **9** catalyzed by **14b**). Comparable results for ylide reactions were more promising (Table 1), both in chemoselectivity for iodonium ylide formation and in enantioselectivity for **11**.

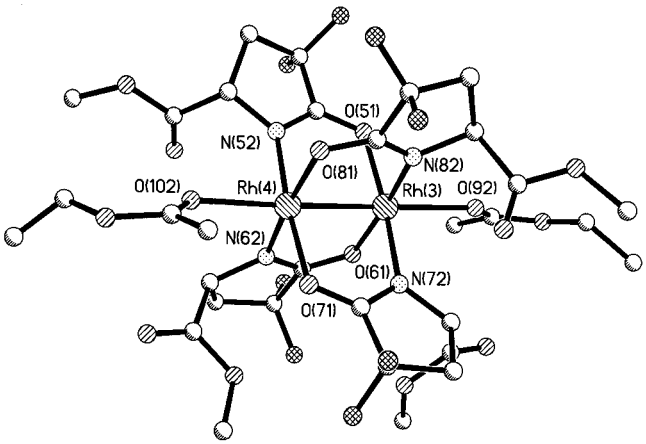
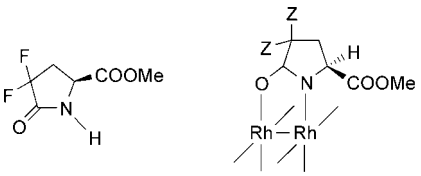
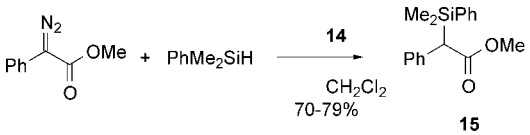


Figure 1. X-Ray crystal structure of dirhodium(II) tetrakis[mcthyl 3,3-difluoro-2-oxopyrrolidine-(5S)-carboxylate] (bis ethyl acetate complex) **14b**



13 **14a** Z = H: Rh_2(5*S*-MEPY)$_4$
14b Z = F: Rh_2(5*S*-dFMEPY)$_4$

A comparison of results for Si–H insertion with **14**[17] describes a similar outcome, Eq. (3). Reaction times are an order of magnitude less with Rh_2(5*S*-dFMEPY)$_4$ than with Rh_2(5*S*-MEPY)$_4$, but enantiocontrol is diminished (38% ee for **15** with **14b** versus 58% ee for **15** with **14a**). However, when tri(isobutyl)silane is used in place of phenyldimethylsilane, enantiomeric excesses for the Si-H insertion products are comparable (58% ee with **14b** and 56% with Rh_2(5*R*-MEPY)$_4$).



(3)

Conclusion

Overall, the fluorinated analogues of Rh_2(IBAZ)$_4$ and Rh_2(MEPY)$_4$ do exhibit enhanced reactivity for diazo decomposition. However, and to our surprise, these catalysts show significantly diminished selectivity in cyclopropanation reactions, which may be attributed to an earlier transition state. In contrast, selectivity in and for ylide transformations appear to benefit from this increased reactivity, and in Si–H insertion reactions the influence may be minimal. Additional investigations are warranted.

Experimental Section

General Experimental Details
The tetrahydrofuran used was distilled prior to use from sodium and benzophenone; all other solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard, Me_4Si (TMS), using either an AM-250, DRX-400, DRX-500, or DRX-600 NMR spectrometer. Optical rotations were measured using a JASCO DIP-1000 digital polarimeter. *N*-Fluorobenzenesulfonimide was recrystallized from ethyl acetate : hexanes prior to use.

1,2 : 5,6-Diisopropylidene-D-mannitol (2)
A mixture of powdered D-mannitol (28 g, 0.154 mol), *p*-toluenesulfonic acid (0.5 g) and 2,2-dimethoxypropane (46 mL, 0.375 mol) in dry Me_2SO (50 mL) was stirred at room temperature under nitrogen. Within 1 hour the suspended solids had dissolved, and after 16 hours the reaction solution was poured into 150 mL of 3% $NaHCO_5$. The mixture was extracted with ethyl acetate (3×200 mL), and the extracts were concentrated under reduced pressure until a solid mass occurred. Hexanes (300 mL) was added, and the mixture was dissolved under refluxing conditions. The solution was allowed to cool slowly overnight. The resulting crystalline material was collected by filtration and then washed with 100 mL of cold ether/hexanes (1 : 20) and dried to give the diacetonide; yield: 18 g (0.07 mol, 46%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.23–4.05 (m, 1-H, 4 H), 3.97 (dd, J = 8.1, 5.6 Hz, 2 H), 3.74 (t, J = 6.2 Hz, 2 H), 2.63 (br s, 2 H), 1.41 (s, 6 H), 1.35 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 109.4, 76.3, 71.2, 66.7, 26.7, 25.2.

(4*R*)-1-(4′-Methoxylbenzyl)-3,3-difluoro-4-(1′*R*-1′,2′-*O*-isopropylideneethyl)azetidin-2-one (4)
To a stirred solution of **2** (5.0 g, 19.0 mmol) in CH_2Cl_2 (50 mL) was added sodium periodate (8.1 g, 38.0 mmol) followed by addition of saturated sodium hydrogen carbonate (2.0 mL). The mixture was stirred at room temperature for 2 hours. Magnesium sulfate (3 g) was added and stirring was continued for 20 min. The slurry was filtered through a plug of celite to give a CH_2Cl_2 solution of crude 2,3-*O*-isopropylidene-D-glyceraldehye (**3**).[7] To the above solution was added anhydrous magnesium sulfate (10 g) then *p*-methoxybenzylamine (4.69 g, 34 mmol) during 30 min. After an additional 30 min the resulting slurry was filtered, and the filtrate was washed with CH_2Cl_2 (2×20 mL). Imine that was recovered after the solvent evaporated was subjected to the Reformatsky reaction according to the literature procedure,[8] and the resulting product was fully characterized. The *syn* to *anti* ratio was determined by ^{1}H NMR, and the *syn*-lactam **4** was isolated; yield: 7.6 g (23.2 mmol, 61%); $[\alpha]_D^{25}$ = –93.8 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26–7.21 (comp, 2 H), 6.90–6.71 (comp, 2 H), 4.85 (d, J = 14.7 Hz, 1 H), 4.27–4.16 (comp, 3 H), 3.38 (s, 3 H), 3.76–3.68 (comp, 2 H), 1.38 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.9, 130.1, 126.1, 119.9 (t, $J_{F,C}$ = 292 Hz), 114.1, 110.5, 74.8, 66.3 (t, $J_{F,C}$ = 23.7 Hz), 66.1, 55.3, 44.8 (t, $J_{F,C}$ = 2.8 Hz), 26.5, 24.9.

(4*R*)-1-(4′-Methoxylbenzyl)-3,3-difluoro-4-(isobutyloxycarbonyl)azetidin-2-one

A solution of γ-lactam **4** (7.6 g, 23.2 mmol) in 166 mL of 6:3:1 CH_2Cl_2/TFA/CH_3OH (100:50:16 mL) was stirred at room temperature for 1 h (step *e*, Scheme 1). The solvent was evaporated under vacuum, and to the residue was added toluene (50 mL) which was evaporated to remove residual TFA. The residue was dried thoroughly under vacuum, then a mixture of 320 mL of 3:1 acetone/H_2O (240:80 mL) was added to dissolve the residue, then $NaIO_4$ (9.93 g, 46.4 mmol) was added (step *f*, Scheme 1). The mixture was stirred at room temperature for 2 hours. $KMnO_4$ (10.6 g, 93.6 mmol) was added, followed by acetic acid (10 mL). The resulting red mixture was stirred at room temperature for 3 h then filtered, and the filter cake was washed with acetone until the acetone eluent was colorless. The aqueous eluent was extracted with ethyl acetate (2×200 mL). The resulting organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to give crude acid. To the crude acid was added benzene (150 mL), 2-methyl-1-propanol (20 mL) and *p*-toluenesulfonic acid (0.43 g). The resulting solution was refluxed (step g, Scheme 1) until water was no longer evolved in a Dean-Stark apparatus. Solvent was evaporated and the residue was subjected to column chromatography on silica gel (hexanes:ethyl acetate = 20:1) to afford product as a colorless viscous oil; yield: 4.3 g (13.2 mmol, 57%); $[\alpha]_D^{29}$ = +37.4 (*c* 0.4, CH_3CN); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.93 (d, J = 15.0 Hz, 1H), 4.25 (dd, $J_{F,H}$ = 6.8, 2.5 Hz, 1H), 4.22 (dd, J = 15.0, 1.8 Hz, 1H), 4.05 (dd, J = 10.5, 7.6 Hz, 1H), 3.98 (dd, J = 10.5, 7.6 Hz, 1H), 3.82 (s, 3H), 2.01–1.91 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8, 159.8, 159.3 (t, $J_{F,C}$ = 30 Hz), 130.0, 126.1, 124.7, 119.5 (t, $J_{F,C}$ = 292 Hz), 114.6, 72.4, 64.0 (t, $J_{F,C}$ = 25.3 Hz), 55.3, 44.7, 27.6, 18.8.

2-Methyl-1-propyl 3,3-Difluoro-2-oxaazetidine-(4*R*)-carboxylate (5a)

To the above *N*-protected azetidinone (2.7 g, 8.3 mmol) was added 75 mL of 2:1 CH_3CN/H_2O (50:25 mL). The resulting solution was cooled to 0 °C under an ice-water bath. Ceric ammonium nitrate (18.1 g, 33.2 mmol) was added to the mixture which was stirred at the same temperature for 1 h.[10] The solution was allowed to warm to room temperature, and stirring was continued for another 3 h. The reaction mixture was extracted with ethyl acetate (2×200 mL). The combined organic layer was washed with water (30 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (hexanes:ethyl acetate = 10:1) to afford product as a colorless oil; yield: 1.18 g (5.7 mmol, 69%); $[\alpha]_D^{25}$ = +26.6 (*c* 5.0, CH_3CN); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40 (br s, 1H), 4.60 (dd, $J_{F,H}$ = 6.5, 3.5 Hz, 1H), 4.09 (dd, J = 10.5, 6.9 Hz, 1H), 3.98 (dd, J = 10.5, 6.6 Hz, 1H), 2.01–1.91 (m, 1H), 0.93 (d, J = 6.8 Hz, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 165.6, 160.3, 120.9 (t, $J_{F,C}$ = 292 Hz), 72.7, 62.2 (t, $J_{F,C}$ = 24.8 Hz), 27.6, 18.7; MS(FAB): *m/z* 208 $(MH)^+$.

Dirhodium(II) Tetrakis[2-methyl-l-propyl 2-oxa-3,3-difluoroazetidine-4(*R*)-carboxylate] (6a)

Prepared and purified in 65% overall yield by standard methods;[11,13,14] $[\alpha]_D^{25}$ = +250.8 (*c* 0.43, MeCN); anal. found: C, 38.3; H, 4.1; N, 6.9, calcd. for $C_{32}H_{40}N_4O_{12}F_8Rh_2 \cdot CH_3CN$ C, 38.1; H, 4.1; N, 6.5; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.91–4.89 (m, 2H), 4.43–4.41 (m, 2H), 4.10–3.92 (m, 8H), 2.02–1.86 (m, 4H), 0.96 (d, J = 6.6 Hz, 12H), 0.92 (d, J = 6.8 Hz, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 168.2, 167.2, 72.2, 72.1, 66.4, 66.1, 52.7, 27.7, 27.5, 18.7; MS (FAB): *m/z* 1031 $([MH]^+$, 100%); HRMS (FAB) for $(C_{32}H_{40}N_4O_{12}F_8Rh_2H)^+$, *m/z* calcd. 1031.0703, found 1031.0712.

2,2-Dimethyl-7-fluoro-8-oxo-1-aza-3-oxabicyclo[3.3.0]-octane

Prepared by a modification to the method reported by Coward and Konas.[16] To a cooled stirred solution of diisopropylamine (5.4 mL, 41.9 mmol) in dry THF (30 mL) at –78 °C, *n*-butyllithium in hexanes (14.2 mL, 35.5 mmol) was added via a syringe pump over a 1 h period and the resulting mixture stirred for 1 h. A solution of (5*S*)-2,2-dimethyl-8-oxo-1-aza-3-oxabicyclo-[3.3.0]octane[18] (5.00 g, 32.3 mmol) in dry THF (20 mL) was added over a 1 h period to the LDA mixture during which time an orange color developed. After 2 h, *N*-fluorobenzenesulfonimide (11.2 g, 35.5 mmol) in dry THF (30 mL) was added dropwise over a 1 h period, and the reaction mixture was stirred for a further 1 h. The reaction mixture was then quenched with aqueous saturated ammonium chloride (20 mL) and allowed to warm to room temperature, then THF was removed under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (3×50 mL), the organic layers were combined and dried ($MgSO_4$), and the solvent was removed under vacuum to yield a yellow oil which was subjected to silica gel column chromatography [EtOAc:hexanes (3:2) as eluent]. The title compound was isolated as a yellow oil which was a mixture of diastereoisomers; yield: 5.22 g (94%); ^{1}H NMR (600 MHz, $CDCl_3$) *syn*-isomer: δ = 5.31 (ddd, J = 52, 10, 8 Hz, 1H), 4.19 (dd, J = 16, 6 Hz, 1H), 3.93–3.98 (m, 1H), 3.50 (dd, J = 9, 9 Hz, 1H), 2.79 (ddd, J = 13, 8, 6 Hz, 1H), 1.87–1.96 (m, 1H), 1.71 (s, 3H), 1.48 (s, 3H); *anti*-isomer: δ = 5.08 (dd, J = 52, 6 Hz, 1H), 4.46 (m, 1H), 4.15 (dd, J = 8, 6 Hz, 1H), 3.42 (dd, J = 9, 9 Hz, 1H), 2.42 (ddd, J = 21, 15, 6 Hz, 1H), 1.96–2.06 (m, 1H), 1.66 (s, 3H), 1.52 (s, 3H).

(5*S*)-2,2-Dimethyl-7,7-difluoro-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane

Prepared as described for the monofluorination procedure using the 2,2-dimethyl-7-fluoro-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane (4.95 g, 28.6 mmol), column chromatography [chloroform:EtOAc (4:1) as eluent] afforded the title compound as a white solid; yield: 4.37 g (80%) mp 35–37 °C (from ethyl acetate/light petroleum); $[\alpha]_D^{28}$ = +89.2 (*c* 0.85, $CHCl_3$); IR (film): ν = 1732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.26 (dd, J = 9, 6 Hz, 1H), 4.13 (m, 1H), 3.47 (dd, J = 9, 9 Hz, 1H), 2.77 (ddd, J = 15, 15, 6 Hz, 1H), 2.13 (dddd, J = 27, 15, 13, 8 Hz, 1H), 1.68 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz; $CDC1_3$): δ 159.8 (dd, $J_{C,F}$ = 33.0, 28.4 Hz), 121.2 (dd, $J_{C,F}$ = 256.9, 251.6 Hz), 92.4, 69.8, 54.0, 35.1 (dd, $J_{C,F}$ = 24.7, 21.7 Hz), 26.3, 23.3; ^{19}F NMR (376 MHz; $CDCl_3$, C_6F_6 external standard): δ = 59.77 (dd, $J_{F,F}$ = 264.4 Hz, $J_{H,F}$ = 12.9 Hz), 58.44 (ddd, $J_{F,F}$ = 264.0 Hz, $J_{H,F}$ = 26.8, 14.4 Hz); MS (CI, NH_3): *m/z* 192 $([MH]^+$, 100%).

(5*S*)-3,3-Difluoro-5-(hydroxymethyl)-2-pyrrolidinone
To a solution of the (5*S*)-2,2-dimethyl-7,7-difluoro-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane (1.91 g, 10.0 mmol) in a 1:1 mixture of dioxane and water (60 mL), Amberlite IR-120 (H^+) resin (1.91 g) was added, and the reaction mixture was heated at reflux for 4 h. After cooling to room temperature, the Amberlite resin was removed via filtration, washed with water (25 mL) and the solvent was removed under reduced pressure to give the crude product which was purified by silica gel chromatography [dichloromethane:methanol (5:1) as eluent]. The title compound was isolated as a white crystalline solid; yield: 1.38 g (91%); mp 144–145 °C (from methanol/dichloromethane); $[\alpha]_D^{21}$ = +30.6 (*c* 1.01 in MeOH); anal. found: C, 39.5, H; 4.5; N, 9.1; $C_5H_7F_2NO_2$ requires C, 39.7; H, 4.7; N, 9.3%; IR (KBr): ν = 3379, 3238, 1730 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ = 3.74–3.80 (m, 1H), 3.60 (dd, *J* = 11, 4 Hz, 1H), 3.48 (dd, *J* = 11, 5 Hz, 1H), 2.59–2.66 (m, 1H), 2.31–2.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.1 (dd, $J_{C,F}$ = 30.2, 30.2 Hz), 119.4 (dd, $J_{C,F}$ = 247.4, 245.7 Hz), 63.2, 50.2, 32.6 (dd, $J_{C,F}$ = 22.0, 21.9 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6 external standard): δ = 60.75–59.96 (br m), 59.23 (ddd, $J_{F,F}$ = 265.5 Hz, $J_{H,F}$ = 16.1, 2.3 Hz); MS (CI, NH_3): *m/z* 169 ($[M+NH_4]^+$, 100%).

Methyl (5*S*)-3,3-Difluoro-2-oxopyrrolidine-5-carboxylate (13)
Freshly prepared Jones reagent was added in portions to a solution of (5*S*)-3,3-difluoro-5-(hydroxymethyl)-2-pyrrolidinone (0.48 g, 3.20 mmol) in wet acetone (25 mL), and the reaction was monitored by TLC. Upon complete consumption of starting material, 2-propanol (10 mL) was added carefully and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with water (40 mL), and the organic solvents were removed in vacuo. The aqueous residue was adjusted to pH 3.0 with $NaHCO_3$ and continuously extracted with ethyl acetate for 2 days. The organic phase was concentrated under vacuum and the crude acid residue taken up in ether (100 mL). To this solution was added a freshly prepared solution of diazomethane in ether in portions, and upon complete consumption of intermediate acid, as judged by TLC, the reaction was quenched by addition of acetic acid (2 mL). The reaction mixture was concentrated in vacuo to give the crude product. Flash chromatography (30:5:65, ethyl acetate/methanol/light petroleum) gave the title compound as an off-white oil; yield: 0.47 g (83%); $[\alpha]_D^{25}$ = +1.5 (*c* 1.02 in $CHCl_3$); IR (film): ν = 3282 (NH), 2958, 1751, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br s, 1H), 4.35 (ddd, *J* = 7.6, 5.0, 2.1 Hz, 1H), 3.50 (s, 3H), 2.94–2.81 (m, 1H), 2.71–2.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 165.6 (dd, $J_{C,F}$ = 30.7, 30.7 Hz), 116.5 (dd, $J_{C,F}$ = 250.1, 248.6 Hz), 53.2, 50.0, 34.1 (dd, $J_{C,F}$ = 24.7, 24.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, C_6F_6 external standard): δ = 56.51–55.70 (m), 54.70 (dddd, $J_{C,F}$ = 273.0 Hz, $J_{H,F}$ = 16.7, 14.4, 2.3 Hz); MS (CI, NH_3): *m/z* 197 ($[C_6H_{11}N_2O_3F_2+NH_4]^+$, 100%); HRMS (CI) for $[C_6H_{11}N_2O_3F_2+NH_4]^+$: *m/z* calcd. 197.0738, found 197.0735.

Dirhodium(II) tetrakis[methyl 3,3-difluoro-2-oxopyrrolidine-(5*S*)-carboxylate] (14b)
Prepared and purified in 65% overall yield by standard methods:[11, 13, 14] mp > 275 °C (from ethyl acetate/hexane); $[\alpha]_D^{24}$ = –326.8 (*c* 0.12, CH_3CN); anal. found: C, 30.3; H, 2.8; N 5.5, $C_{24}H_{24}F_8N_4O_{12}Rh_2 \cdot 2H_2O$ requires C, 30.2; H, 3.0; N, 5.8%; IR (KBr): ν = 3448 (OH), 2960, 2924, 2852, 1749, 1653 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28–4.30 (m, 2H), 4.14–4.16 (m, 2H), 3.81 (s, 6H), 3.73 (s, 6H), 2.53–2.72, (m, 6H), 2.30 (ddd, 29, 15, 4.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.2 (dd, $J_{C,F}$ = 27.8, 27.7 Hz), 177.6 (dd, $J_{C,F}$ = 27.5, 27.5 Hz), 173.2, 172.6, 118.6 (dd, $J_{C,F}$ = 247.9, 245.4 Hz), 118.5 (dd, $J_{C,F}$ = 249.5, 246.6 Hz), 58.5, 58.0, 52.5, 52.0, 36.3 (dd, $J_{C,F}$ = 24.5, 23.9 Hz), 35.5 (dd, $J_{C,F}$ = 23.9, 23.3 Hz); ^{19}F NMR (376 MHz, DMSO-d_6, C_6F_6 external standard): δ = 66.14 (dddd, $J_{F,F}$ = 256.3 Hz, $J_{H,F}$ = 21.6, 18.6, 4.1 Hz), 64.47 (ddd, $J_{F,F}$ = 256.6 Hz, $J_{H,F}$ = 19.3, 4.7 Hz), 63.69 (ddd, *J* = 17.7, 15.2, 2.7 Hz); MS (FAB): *m/z* 917.7; HRMS (FAB) for $[C_{24}H_{24}N_4O_{12}F_8Rh_2]^+$, *m/z* calcd. 917.9373, found 917.9377.

Crystallography

Dirhodium(II)tetrakis[methyl-3,3-difluoro-2-oxopyrrolidine-(5S)-carboxylate] **14b** crystallized as two forms, one with two ethyl acetate axial ligands and one with one ethyl acetate and one water as axial ligands together with 1.5 molecules of solvent water. $C_{60}H_{77}F_{16}N_8O_{32.5}Rh_4$, *M* = 2145.94; orthorhombic, $P2_12_12_12_1$, *a* = 12.8943(4), *b* = 14.0120(3), *c* = 50.7866(13) Å, *V* = 9175.9(4) $Å^3$, $\rho_{calcd.}$ 1.553 gcm^{-1}, *Z* = 4, 46519 reflections measured, 13128 independent (R_{int} 0.1055), to yield *R* = 0.0575. Data has been deposited at the Cambridge Crystallographic Data Centre.

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