Supporting Information for:

Development of a Kilogram-Scale Process for the Enantioselective Synthesis of 3-Isopropenyl-cyclohexan-1-one via Rh/DTBM-SEGPHOS-Catalyzed Asymmetric Hayashi Addition Enabled By 1,3-Diol Additives

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General Information

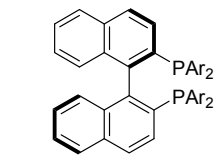
All reactions were performed under a nitrogen atmosphere unless otherwise noted. Monitoring of headspace oxygen levels was performed using a Teledyne O_2 analyzer. Reagents were used as received from the vendors, unless otherwise noted. Quoted yields are for isolated material, and are corrected for potency. NMR spectra were recorded on a Bruker DRX-400 instrument, and are referenced to residual undeuterated solvents. The following abbreviations are used to explain multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra (HRMS) were recorded on an Agilent 6230B TOF instrument. Chiral GC analysis was performed using a Supelco AlphaDEX 120 column (30 m x 0.25 mm x 0.25 μm), front inlet at 200 °C, split ratio 30:1, helium carrier gas with constant flow 1.9 mL/min (40 cm/s), oven program: 80 °C for 0 min, then 2 °C/min to 110 °C for 0 min, then 20 °C/min to 220 °C (20.5 min run time), front detector: FID, 250 °C, 35/350/30 hydrogen/air/makeup (He), 20 Hz acquisition, auto zero on. HPLC analysis was performed using a Phenomenex Lux Cellulose-4 column (3 μm, 4.6 x 150 mm), mobile phase A = 0.05% TFA in 5% acetonitrile, 95% water; mobile phase B = 0.05% TFA in 95% acetonitrile, 5% water; gradient: 0 min 10% B, 15 min 90% B, 20 min 90% B, injection volume = 10 μL, flow rate = 1 mL/min, oven temperature = 40 °C, wavelength = 210 nm.

Ligand Screening

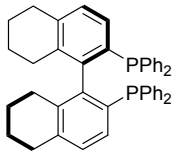
General Procedure for Ligand Screening

In an N_2-filled glovebox, a 96-well block was loaded with 1 mL glass vials containing the appropriate chiral ligand (0.5 μmol for bidentate ligands, 1.0 μmol for monodentate ligands). To each vial was added 50 μL (0.5 μmol Rh) of a solution of the appropriate Rh precursor, and the resulting mixture was aged at RT for 20 min and then concentrated to dryness using a Genevac. A micro stir bar was charged to each vial, followed by water and then the sequential addition of solutions of (isopropenyl)pinacolboronate (**3d**), DIPEA and 2-cyclohexen-1-one (**2**) in the appropriate solvent (100 μL total organic solvent volume). The block was sealed under N_2 and then removed and heated on a shaker plate at 60 °C for 16 h. Upon cooling to RT, the reaction mixtures were diluted with toluene and analyzed by chiral GC.

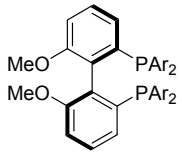
Ligand Chart



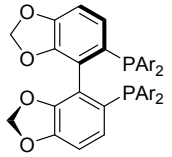
Ar=Ph **BINAP-*R***
Ar=4-Me-Ph **Tol-BINAP-*R***



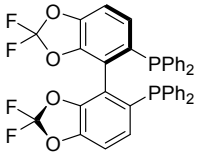
H8-BINAP-*R*



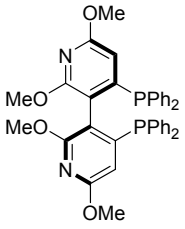
Ar=Ph **SL-A101-1**
Ar=3,4,5-OMe-Ph **SL-A104-1**



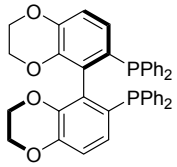
Ar=Ph **SEGPHOS-*R***
Ar=3,5-tB-4-MeO-Ph **DTBM-SEGPHOS-*R***



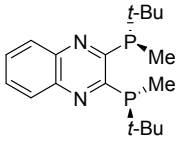
DIFLUORPHOS-*R*



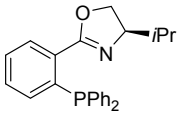
P-Phos-*R*



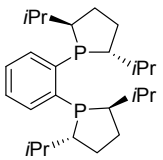
SYNPHOS-*R*



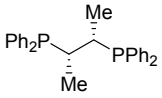
QuinoxP*-*R*



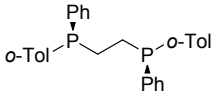
iPrPHOX-*R*



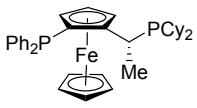
iPr-DuPhos-*R*



Chiraphos-*S*



Tol-DiPAMP-*R*



SL-J001-1

General Procedure for Small-scale Optimization Experiments

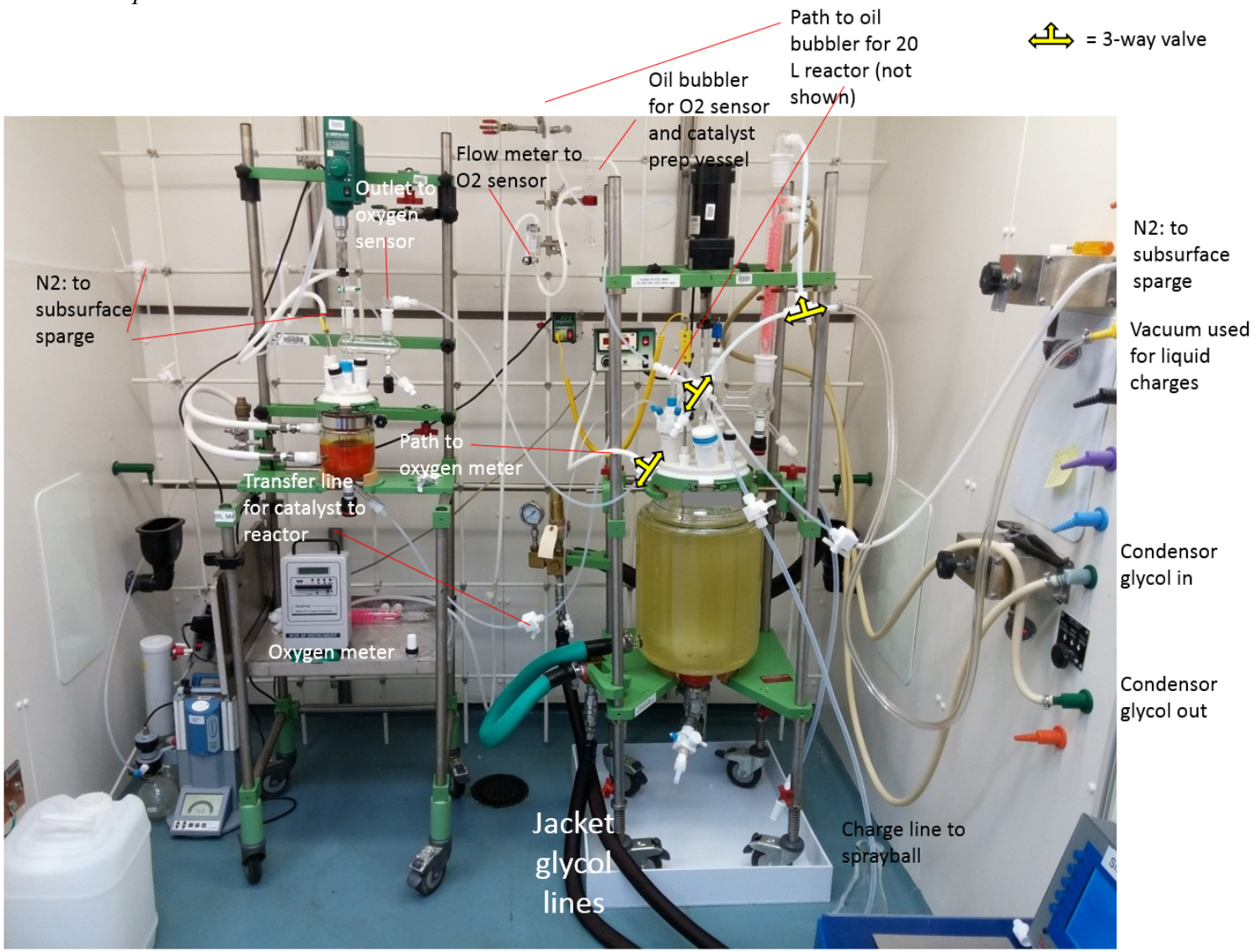
In an N_2-filled glovebox, a stock solution of $[Rh(cod)Cl]_2$ (0.020 M) and DTBM-SEGPHOS-*S* (0.044 M) was prepared in MeOH and aged on a shaker plate for 60 min, resulting in a dark orange solution with a small amount of undissolved white solid (residual DTBM-SEGPHOS). Aliquots of this solution were added to empty 4 mL vials and then concentrated to dryness using a Genevac. A 3 x 10 mm stir bar was charged to each vial, followed by the sequential addition of (isopropenyl)pinacolboronate (**3d**) (600 μmol, 1.1 equiv), dodecane (40 μL, internal standard), DIPEA, and 2-cyclohexen-1-one (**2**) (500 μmol, 1.0 equiv), along with solvent(s), water and appropriate additives. The vials were sealed under N_2 with a Teflon-lined screw cap and heated at 50 °C. At appropriate time intervals, 10 μL aliquots were withdrawn from the organic layer and diluted with 1.0 mL toluene for chiral GC analysis.

Catalyst Formation NMR Studies

The catalyst was formed in the usual manner using *d*4-methanol. Samples were taken and diluted with $CDCl_3$ (20x). Spectra of $[Rh(cod)Cl]_2$ and DTBM-SEGPHOS-*R* were previously taken in 20:1 $CDCl_3$:*d*4-methanol at the same concentration. After 30 min, the initial slurry transformed to a deep-red solution with a small amount of the solids (excess ligand). Sample transfers and the spectra were taken under inertion. ^{1}H NMR indicated complete disappearance of the cod signals, and ~90% consumption of the ligand; a new entity was formed. ^{31}P NMR indicated disappearance of the free ligand signal at -13.1 ppm and the appearance of two signals for the newly formed complex at 26.1 ppm and 27.0 ppm.

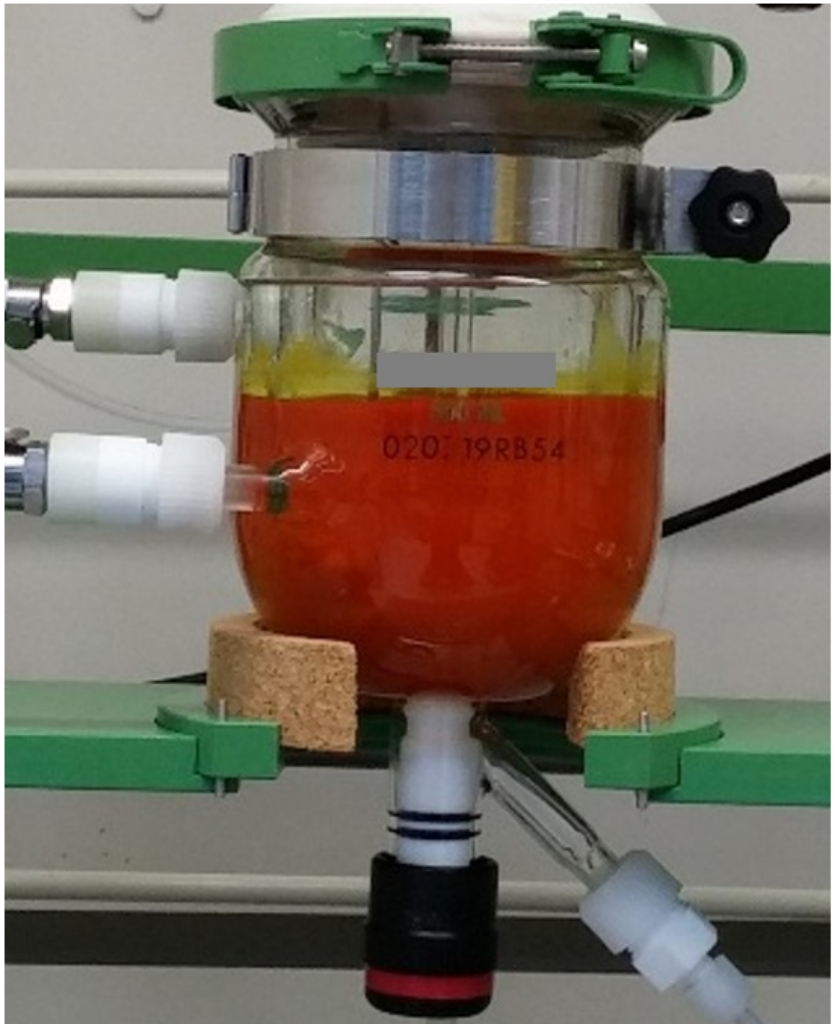
1 kg Scale (20 L) Synthesis of 1 via Addition of 3d to 2

Overall Setup



Catalyst Ligation

~10 min after solid charges
(orange; slurry)



~30 min
(deeper red; light slurry)

Catalyst Transfer

Experimental Procedure

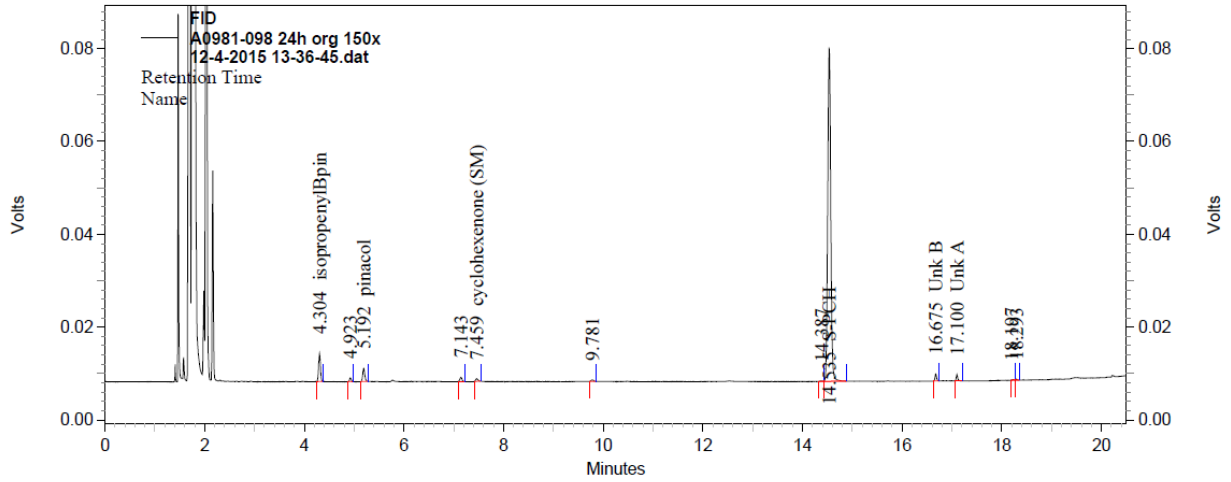
Catalyst preparation: Methanol (320 mL) was charged into a 500 mL inerted reactor equipped with an overhead agitator, nitrogen sparging tube and an outlet connected to an oxygen meter. The reactor was inerted by sparging nitrogen subsurface through methanol until <300 ppm O_2 was detected in the headspace. *S*-(+)-DTBM-SEGPHOS (77.3 g, 65.6 mmol) and $[Rh(cod)Cl]_2$ (15.4 g, 31 mmol) were charged and the nitrogen sparging was continued until <300 ppm O_2 was detected in the headspace. The mixture was agitated at RT under constant positive nitrogen pressure for 30 min by sweeping a low flow of nitrogen through the headspace, during which time the initial yellow slurry gradually transformed into a deep-red solution containing a small amount of solids (excess ligand). **Reaction**: A 20 L jacketed reactor, equipped with an overhead agitator, a thermocouple, nitrogen sparging tube, a sampling port, a condenser connected to the glycol supply and a nitrogen outlet connected sequentially to a bubbler, flow meter and an oxygen meter, was inerted using a vigorous nitrogen sweep. Heptane (4.0 L), 2-cyclohexen-1-one (**2**, 1 kg, 10.4 mol) in heptane (1.0 L), (2-isopropenyl)pinacolboronate (**3d**, 1.92 kg, 11.4 mol, 1.1 equiv) in heptane (1.0 L), DIPEA (0.91 L, 0.67 kg, 0.50 equiv), a solution of 2,2-dimethyl-1,3-propanediol (neopentylglycol, 1.19 kg, 1.1 equiv) and methanol (0.12 L) in water (3 L), and the rest of heptane (2.55 L) were sequentially charged to the reactor via vacuum. After the charges were complete, nitrogen was sparged subsurface through the agitated biphasic mixture until <300 ppm oxygen level was reached in the headspace, then the nitrogen flow was reduced to maintain a slight positive pressure in the reactor. The catalyst slurry, prepared as above, was transferred from the bottom valve of the 500 mL reactor to the 20 L reactor through an inerted teflon tubing by applying slight positive pressure of nitrogen. After the transfer was complete, the nitrogen flow was reduced to maintain a slight positive pressure to minimize solvent loss. The jacket was set to 60 °C on the 20 L reactor and the biphasic mixture was

vigorously heated and agitated under nitrogen. Reaction progress was monitored by both chiral GC (organic phase) and HPLC (aqueous phase) of a composite sample that was taken from the vigorously agitated mixture (200 RPM), and the phase split was done in a vial. The mol % conversion was then calculated as follows:

$$mol\ \%\ conversion = (mol\ \%\ product_{org} + mol\ \%\ product_{aq}) / (mol\ \%\ product_{org} + mol\ \%\ product_{aq} + mol\ \%\ SM_{org} + mol\ \%\ SM_{aq})$$

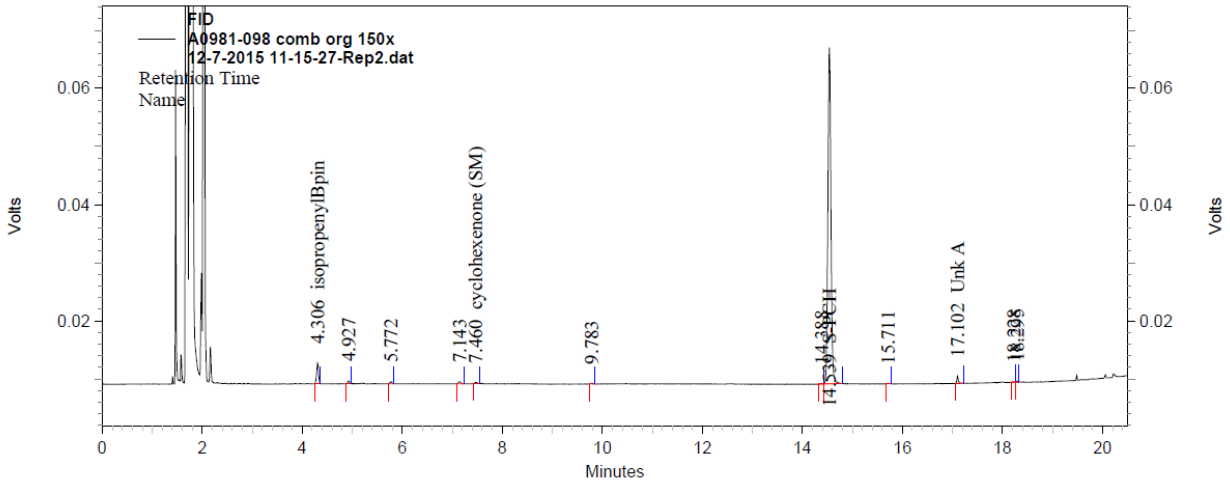
After 26 h, the reaction was judged to be complete (>97.0 mol % **1**) and the reaction mixture was cooled to 20-25 °C. **Workup**: The phases were separated (phases split in ~4 min) and the bottom aq. phase was transferred to a carboy. The organic phase was washed with 1 N HCl (5.7 L, 0.55 equiv) to remove DIPEA (phases split in ~1 min), followed by water (2.5 L) (phases split in ~1 min). Two back-extractions with heptane (2 x 2 L) from the original aq. phase were performed. The first phase split (at RT) took ~30 min to complete, and the second phase split (at 35 °C) took ~10 min. The organic phases were combined (total volume ~15 L) and the resulting solution was polished filtered back to the cleaned reactor (cleaned using MeOH). Heptane was removed under reduced pressure (30-40 °C at 45-55 Torr) to give 1.72 L (d=0.918 g/mL) of crude product. **Distillation**: The crude product was transferred to a 2 L 4-necked RB flask, equipped with a mechanical stirrer, a thermocouple, a 30 cm Vigreaux column (24/40 joint), a distillation adapter containing a thermocouple to measure the vapor temperature, a condenser (glycol) and a Teflon tubing to a receiver flask. Distillation was performed at 10 torr, and a 2 L heating mantel was used to heat the batch. The heat applied to the batch was gradually increased to assure good separation and optimal distillation rate (~300 mL/h). The forerun (90 g) distilled at 25-79 °C and contained 1.6 mol % **1**. The main fraction distilled at 85-92 °C to give 1.18 kg **1** (96.6% potency, 82.1% corrected yield, 97AP (GC), 99.6% ee).

Chiral GC trace at end of reaction (organic phase)



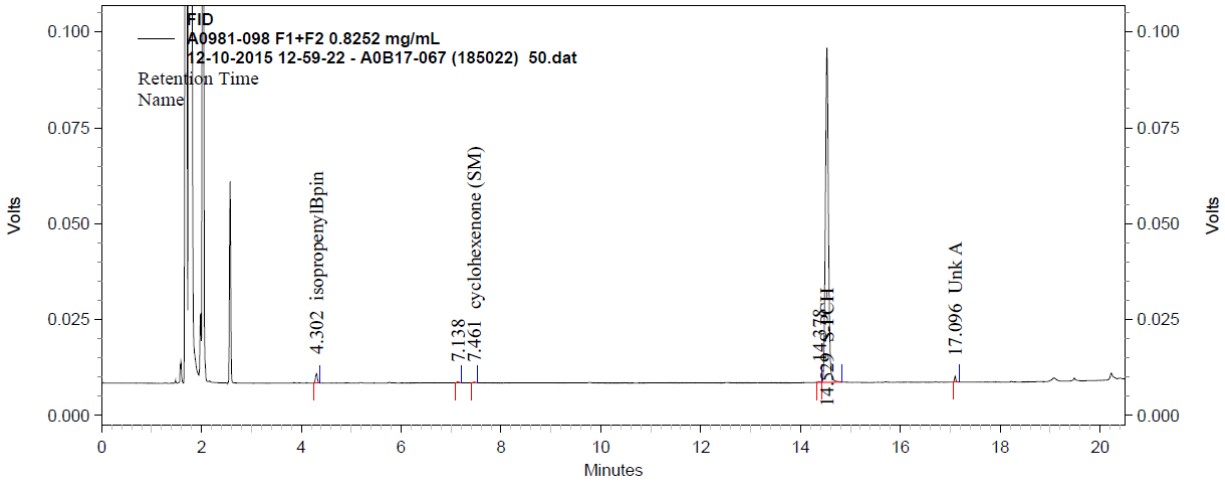
Pk #	RT (min)	Name	Area %
1	4.30	isopropenylBpin	4.62
2	4.92		0.55
3	5.19	pinacol	2.36
4	7.14	isopropenylBng	0.81
5	7.46	cyclohexenone (SM)	0.55
6	9.78		0.33
7	14.39	R-product	0.16
8	14.54	S-product	88.64
9	16.68	unknown B	0.94
10	17.10	unknown A	0.79
11	18.20		0.13
12	18.29		0.12

Chiral GC trace of the heptane solution after work up



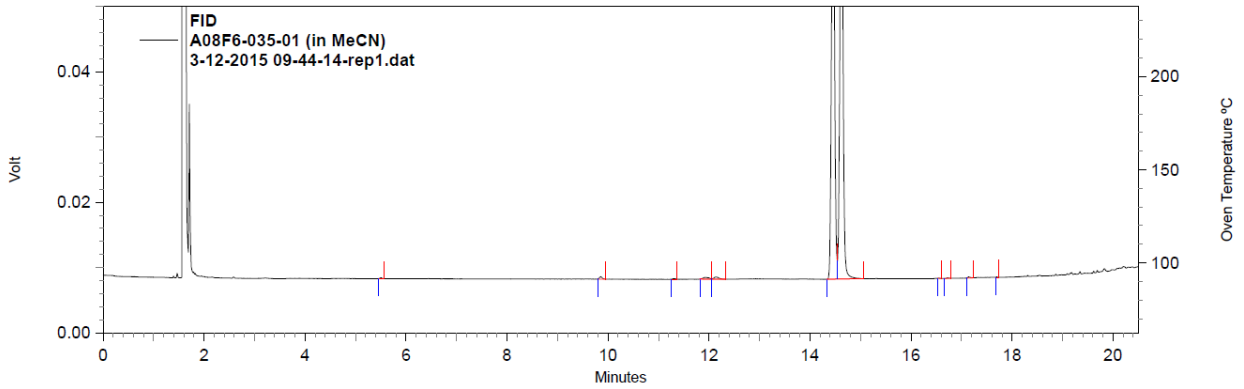
Pk #	RT (min)	Name	Area %
1	4.31	isopropenylBpin	3.53
2	4.93		0.44
3	5.77		0.37
4	7.14	isopropenylBng	0.45
5	7.46	2-cyclohexen-1-one	0.25
6	9.78		0.11
7	14.39	R-product	0.13
8	14.54	S-product	93.41
9	15.71		0.09
10	17.10	unknown A	0.99
11	18.23		0.13
12	18.30		0.10

Chiral GC trace of main fraction (1.18 kg)



Pk #	RT (min)	Name	Area %
1	4.30	isopropenylBpin	1.72
2	7.14	isopropenylBng	0.24
3	7.46	cyclohexenone (SM)	0.16
4	14.38	R-product	0.22
5	14.53	S-product	96.87
6	17.10	unknown A	0.79

*Chiral GC trace for racemic **1***



FID
Results

Pk #	Name	RT (min)	Intg Code	Height	Area	Area %
1		5.502	BB	120	324	0.054
2		9.858	BB	372	1373	0.228
3		11.313	BB	108	393	0.065
4		11.932	BV	258	2160	0.358
5		12.145	VB	344	2259	0.375
6		14.458	BV	68779	292958	48.599
7		14.623	VB	69181	302323	50.152
8		16.553	BB	47	94	0.016
9		16.720	BB	89	253	0.042
10		17.143	BB	183	516	0.086
11		17.694	BB	99	159	0.026
Totals				139580	602812	100.000

Preparation of (2-isopropenyl)neopentyl glycolboronate (3g)

To a solution of isopropenylmagnesium bromide (0.5 M in THF, 567 mL, 283 mmol) at 0 °C was added trimethyl borate (35 mL, 308 mmol). An exotherm was observed and an off-white slurry was formed. After 30 min, the reaction mixture was quenched with 1.3 equiv of 2 N HCl, resulting in an exotherm and the formation of two clear phases. The resulting mixture was held at 10 °C for 2 h and then transferred to a 1 L separatory funnel. MTBE (150 mL) was added and the layers were separated. To the organic phase (710 mL) was added neopentyl glycol (29.4 g, 282 mmol, 1.0 equiv). GC analysis after 30 min indicated an 87% solution yield of **3g**. The resulting solution was agitated with anhydrous $MgSO_4$ for 16 h and then filtered. The solvent was evaporated to give 46.3 g of an orange liquid. The product was purified by vacuum distillation (bp 55-59 °C /10 Torr) to give 23.3 g of **3g**[1] as a colorless liquid (95% potency by GC, 50% corrected yield). **^{1}H NMR** (400 MHz, DMSO-*d*6) δ 5.60 (dt, *J* = 4.0, 1.3 Hz, 1H), 5.53 – 5.42 (m, 1H), 3.61 (s, 4H), 1.69 (t, *J* = 1.5 Hz, 3H), 0.89 (s, 6H); **^{13}C NMR** (101 MHz, DMSO-*d*6) δ 127.5, 71.1, 31.2, 21.2, 21.0.

*Stability studies of (2-isopropenyl)neopentyl glycolboronate (**3g**)*

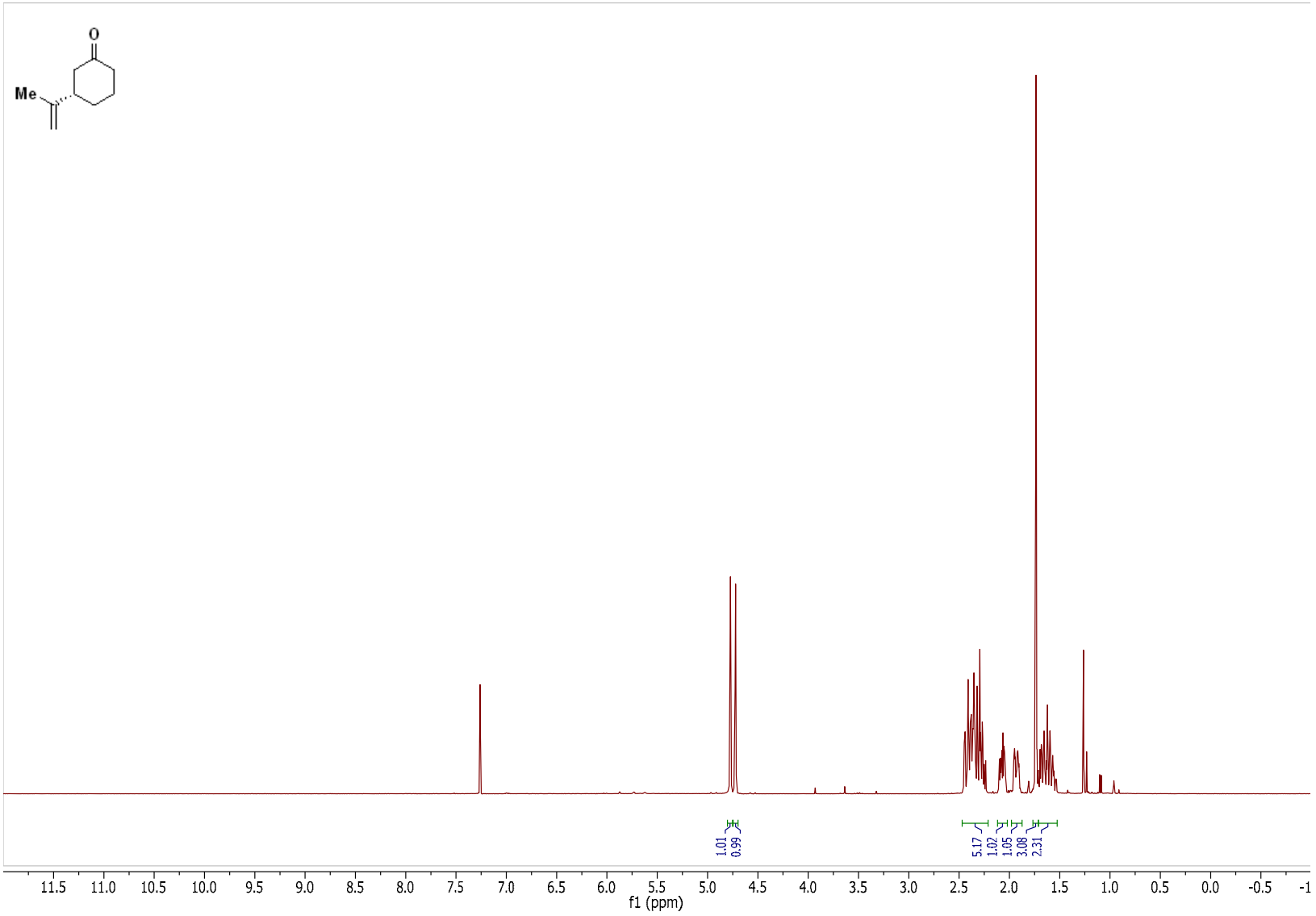
The crude product prior to distillation and the main distillate fraction were subjected to the stability studies for 6 days under the following conditions:

Sample	Form	Appearance t=0/6 days	T °C	air/N2	PT	Potency after 0 days (6 days), wt%
A	crude	light yellow liquid/	22	air	-	70.4 (71.3)
B	distilled	colorless liquid/viscous gel	22	air	-	too viscous to analyze
C	distilled	colorless liquid/viscous gel	22	N2	-	too viscous to analyze
D	distilled	colorless liquid/viscous gel	5	air	-	too viscous to analyze
E	distilled	colorless liquid/viscous gel	22	air	+	too viscous to analyze
F	distilled	colorless liquid/more viscous	22	N2	+	95.2 (81.6)
Note 1: PT=phenothiazine (0.5%)						
Note 2: After 19 days at RT, sample A was still a free-flowing liquid and sample F polymerized						

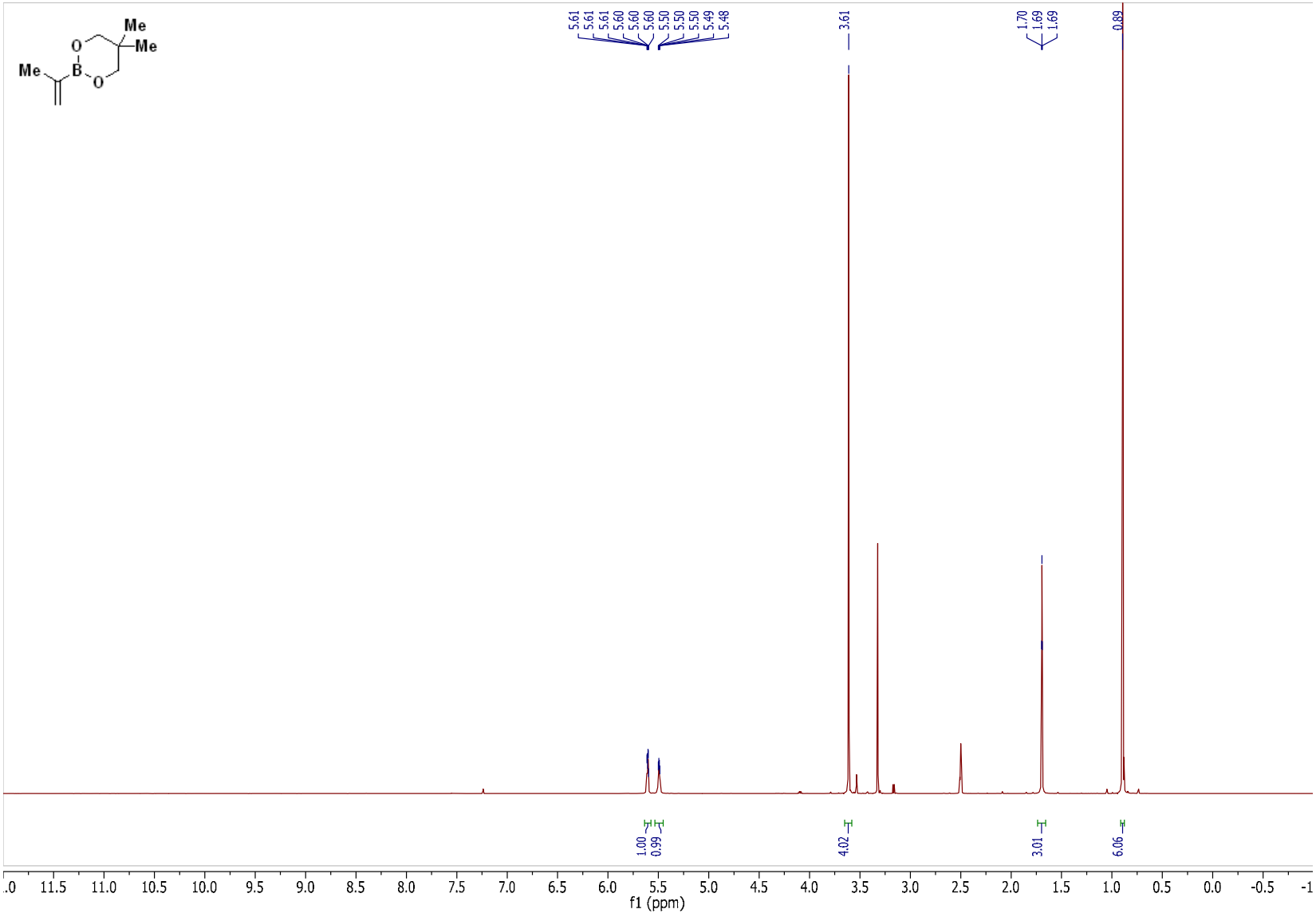
References

(1) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706.

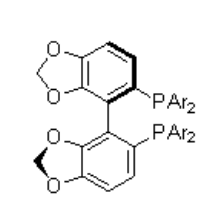
^{1}H NMR spectrum of 3-isopropenyl-cyclohexan-1-one (1)



^{1}H NMR spectrum of (2-isopropenyl)neopentylglycolboronate (3g)



^{31}P NMR spectrum of DTBM-SEGPHOS-*R*



DTBM-SEGPHOS-*R*
Ar=3,5-*t*-Bu-4-OMe-Ph

^{31}P NMR spectrum of [Rh(cod)Cl]$_2$/DTBM-SEGPHOS-*R* adduct