Amino-Sugar Modular Ligands – Useful Cores for the Formation of Asymmetric Copper 1,4-Addition Catalysts

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Supplementary Data

General

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. Solvents were dried prior to use: THF and toluene were distilled on Na/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX270, Bruker 400, Varian-Gemini 300 and Varian-Gemini 200 spectrometers. For all other samples δ values were referenced to residual $CHCl_3$. All *J* values are in Hz. Specific optical rotatory powers [α] were measured with a ADP 440 Polarimeter in dichloromethane (c= 1.0 g/100 mL). Enantioselectivities were determined by chiral GC. GC analyses were performed on a Varian 3900 gas chromatograph using an octakis (6-*O*-methyl-2,3-di-*O*-pentyl)-γ-CD column under the conditions given. Yields were determined by calibration against authentic samples using undecane or dodecane as an internal standard. Thin layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254+366}$ pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating. Liquid chromatography was by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 (220-240 mesh) supplied by Fluka. The diorganozinc samples used were commercial products from the following sources: $ZnMe_2$ (2.0 M toluene solution; Aldrich) and $ZnEt_2$ (1.0 M hexane solution; Aldrich). All enones were commercially available (Aldrich). The compound 5-methylhex-3-en-2-one was available from Aldrich as a 75-80% mixture with isomeric 5-methylhex-4-en-2-one. This was removed from commercial product by selective MCPBA epoxidation followed by flash chromatography. All other compounds were used as supplied. Ligands $\mathbf{L_H}$ and $\mathbf{L_I}$ are commercially available.
The ligands $\mathbf{L_A}$[1], $\mathbf{L_C}$[1]and $\mathbf{L_J}$[2] and the sugars precursors $\mathbf{L_D}$[3]**,** $\mathbf{L_E}$[4]**,** have been described in the literature -instead of- The ligands $\mathbf{L_A}$[1] , $\mathbf{L_D}$[1]and $\mathbf{L_J}$[2] and the sugars precursors $\mathbf{L_F}$[3]**,** $\mathbf{L_G}$[4]**,** have been described in the literature.

Preparation of Ligands

Synthesis of $\mathbf{L_B}$
A solution of 2-(diphenylphosphino)naphtoic acid (2.6 mmol), 4-dimethylaminopyridine (0.60 mmol) and 1,3-dicyclohexylcarbodiimide (6.1 mmol) in dry dichloromethane (7 mL) was added to a solution of the appropriate amino sugar $\mathbf{L_D}$ (2.6 mmol) in the same solvent (7 mL). The resulting mixture was stirred at room temperature under inert atmosphere affording a yellow suspension. After 12 hours 2-

(diphenylphosphino)benzoic acid (2.6 mmol) was added and the suspension was stirred for other 12 hours. The residue was removed by filtration. The resulting yellow solution was evaporated under vacuum and the residue was chromatographed on silica gel (4:9 ethyl acetate:hexane) affording the pure product as a white solid (yield: 60-65%).
^{1}H NMR (200MHz, $CDCl_3$): δ 6.42 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 9.3Hz), 5.66 (t, 1H, H3, $^{3}J_{H3-H4}$ = 20.4Hz, $^{3}J_{H3-H2}$ = 10.0Hz), 5.35 (m, 2H, H1 e H7, $^{3}J_{H1-H2}$ = 3.9Hz), 5.01 (dt, 1H, H2, $^{3}J_{H2-H3}$ = 11.1Hz), 4.60 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 12Hz), 4.37 (d, 1H, CH*H*Ph), 4.17 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4.4, $^{3}J_{H6eq-H6ax}$ = 9.8 Hz), 3.90 (dt, 1H, H5, $^{3}J_{H5-H6ax}$ = $^{3}J_{H5-H4}$ = 9.3Hz), 3.78 (s, 3H, OCH_3) 3.68 (m, 2H, H4, $H6_{ax}$).
^{13}C NMR (200MHz, $CDCl_3$): δ 169.6,166.8,160.3,138.7-126.2,113.8,101.4,98.7,80.0, 70.7,69.1,63.6,55.7,53.2.
^{31}P NMR (400MHz, $CDCl_3$): δ -4.95, -13.38.
$[\alpha]_D^{20}$ = + 54.20 (c= 0.60, CH_2Cl_2).
HRMS (ESI) M+Na calcd: 1014.3265 m/z, found: 1014.3319 m/z.

Synthesis of $\mathbf{L_F}$
A solution of 2-(diphenylphosphino)benzoic acid (2.6 mmol), 4-dimethylaminopyridine (0.60 mmol) and 1,3-dicyclohexylcarbodiimide (6.1 mmol) in dry dichloromethane (7 mL) was added to a solution of the appropriate amino sugar $\mathbf{L_D}$ (2.6 mmol) in the same solvent (7 mL). The resulting mixture was stirred for 12 hours at room temperature under inert atmosphere affording a yellow suspension.
The residue was removed by filtration. The resulting yellow solution was evaporated under vacuum, and the residue was chromatographed on silica gel (4:9 ethyl acetate:hexane) affording the pure product as a white solid (yield: 60-65%).
^{1}H NMR (400MHz, $CDCl_3$): δ 6.27 (d, 1H, NH-C2, $^{3}J_{NH-H2}$ = 8.0Hz), 5.56 (s, 1H, H7), 4.95 (d, 1H, H1,$^{3}J_{H1-H2}$ = 4.0Hz), 4.66 (d, 1H, C*H*HPh, $^{2}J_{gem}$ = 12Hz), 4.45 (d, 1H, CH*H*Ph), 4.39(dt, 1H, H2, $^{3}J_{H2-H3}$ = 12Hz), 4.22 (dd, 1H, $H6_{eq}$, $^{3}J_{H6eq-H5}$ = 4.0, $^{3}J_{H6eq-H6ax}$ = 12Hz), 3.93 (t, 1H, H3, $^{3}J_{H3-H4}$ = 20.4Hz, $^{3}J_{H3-H2}$ = 12Hz), 3.83 (s, 3H, OCH_3), 3.85-3.75(m, 2H, H5 and $H6_{ax}$), 3.67 (t, 1H, H4, $^{3}J_{H4-H5}$ =7.9Hz).
^{13}C NMR (400MHz, $CDCl_3$): δ 169.8, 160.2, 136.8-127.7, 113.6, 101.9, 97.2, 81.6, 70.5, 69.8, 68.8, 63.0, 55.3, 54.9.
^{31}P NMR (400MHz, $CDCl_3$): δ -11.37.
$[\alpha]_D^{20}$ = + 46.85 (c= 0.815, CH_2Cl_2).
HRMS (ESI) M+H calcd: 676.2459 m/z, found: 676.2449 m/z.

Synthesis of $\mathbf{L_G}$
A solution of 2-(diphenylphosphino)benzaldehyde (2.6 mmol) in toluene (5 mL) was added to a solution of the amino sugar $\mathbf{L_D}$ (2.6 mmol) in the same solvent (5 mL). The resulting mixture was stirred for 2 hours at 80°C affording a yellow solution. The volume of the solvent was reduced under vacuum at ca. 1 mL and hexane (5-6 mL) was slowly added to afford the product as a yellow microcrystalline powder, which was washed with hexane and dried under vacuum (yield: 60%).
^{1}H NMR (200MHz, C_6D_6): δ 9.06 (d, 1H, N=CH), 5.55 (s, 1H, H7), 4.73 (d, 1H, H1, $^{3}J_{H1-H2}$ = 4.0Hz), 4.66 (m, 2H, C*H*HPh, H3), 4.44 (d, 1H, CH*H*Ph, $^{2}J_{gem}$ = 12Hz), 4.35-4.30 (m, 2H, H5 and $H6_{eq}$), 3.74 (t, 1H, $H6_{ax}$, $^{3}J_{H6ax-H5}$ = 8.0Hz), 3.64 (t, 1H, H4, $^{3}J_{H4-H5}$= 12Hz, $^{3}J_{H4-H3}$= 12Hz), 3.47 (dd, 1H, H2, $^{3}J_{H2-H3}$= 12Hz), 3.38 (s, 3H, OCH_3).

^{13}C NMR (200MHz, C_6D_6): δ 162.5, 138.5-127.5, 113.5, 102.1, 99.7, 82.3, 75.3, 72.9, 69.4, 69.2, 64.3, 62.7, 54.6.
^{31}P NMR (400MHz, $CDCl_3$): δ -11.62.
$[\alpha]_D^{20}$ = + 37.97 (c= 0.52, CH_2Cl_2).
HRMS (ESI) M+H calcd: 660.2510 m/z, found: 660.2495 m/z.

Preparation of racemic $ZnEt_2$ addition products

A solution of the copper-catalyst precursor CuTC (1mol%, 0.015 mmol) and the corresponding ligand (2 equiv., 0.03 mmol) in 5 mL of dry diethyl ether was stirred for 12 hours at room temperature. The alkylating organometallic reagent $ZnEt_2$ (1.2 equiv., 3.6 mmol) was added dropwise and then the substrate (3 mmol).
After 12 hours the reaction was quenched with 2M HCl (2 mL). The organic layer was filtered twice through a plug of silica and dried.

Preparation of racemic $ZnMe_2$ addition products

To a suspension of CuI (5 mmol) in diethyl ether 25 ml at -10°C was added MeLi (2 eq., of a 1.6M solution in hexane, 10 mmol), dropwise. The cloudy yellow mixture was allowed to warm at 0°C over a 30 min period, affording a clear solution. The flask was cooled at -78°C and a solution of enone (3.2 mmol) in diethyl ether was added dropwise. The mixture was kept at 0°C and became again yellow. The reaction was quenched with 2M HCl and the product was extract with diethyl ether.

Table S1 describes the columns and conditions used to determine the ee value from the catalytic reactions.

Table S1. Enantioselectivity determinations of products.

R^1	R^2	R^3	Column[a]	Programme	Retention times/mins
C_5H_{11}	CH_3	CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 16.2 *R* 17.5
C_5H_{11}	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 30.0 *R* 31.1
C_6H_{13}	CH_3	CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 33.9 *R* 35.9
C_6H_{13}	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	60 °C isothermal	*S* 64.0 *R* 65.9
Pr^i	CH_3	CH_3	6-Me-2,3-pe-γ-CD	45 °C isothermal	*S* 8.75 *R* 9.65
Pr^i	CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	50 °C isothermal	*S* 12.4 *R* 12.9
CH_3	CH_2CH_3	CH_2CH_3	6-Me-2,3-pe-γ-CD	45 °C isothermal	*S* 9.87 *R* 11.0

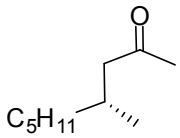
[a] 6-Me-2,3-pe-γ -CD is 25 m octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin 0.25 μm internal diameter (60% in OV1701, w/w).

Catalytic Reaction: General procedure for additions to enones

A solution of the copper-catalyst precursor $Cu(OTf)_2$ (1mol%, 0.003 mmol) and the corresponding ligand (2.5 equiv., 0.0075 mmol) in 2 mL of dry toluene was stirred for 30 minutes at room temperature. The alkylating organometallic reagent ZnR_2 (2 equiv., 0.24 mmol) was added dropwise and then the substrate (0.12 mmol).
After 12 hours the reaction was quenched with 2M HCl (2 mL). Undecane or dodecane (10 μL) was then added as internal standard and the organic layer filtered twice through a plug of silica. Yields and enantiomeric excesses were measured by GC using a octakis (6-*O*-methyl-2,3-di-*O*-pentyl)-γ-CD column.

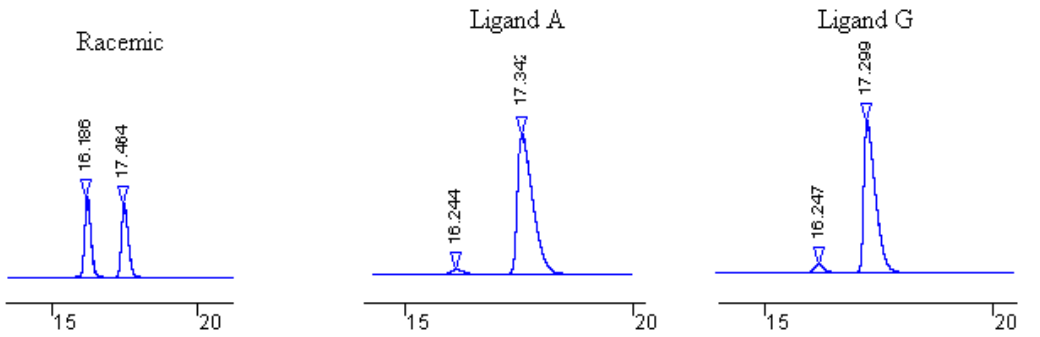
Chiral GC traces for individual compounds

(R)-4-methylnonan-2-one



Literature compound,[5] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$):δ 2.38 (dd, 1H, CH*H*=COMe, J=15.8, 5.7), 2.22 (dd, 1H, C*H*H=COMe), 2.11 (s, 3H, *Me*CO), 2.0-1.9 (m, 1H, nPentC*H*Me), 1.4-1.1 (m, 8H, $(CH_2)_4$), 0.9-0.88 (m,6H, $(CH_2)_4$*Me*, *Me*CH); ^{13}C NMR (400MHz, $CDCl_3$):δ 209.3 (C=O), 51.3, 36.9, 32.0, 30.4, 39.3, 26.6, 22.6, 19.8, 14.1.

Comparitive GC chromatograms of racemic, 95% ee (**L$_A$**) and 92% ee (**L$_G$**) materials below.

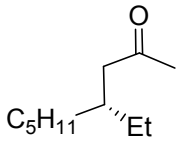


Peak No.	Peak Name	Result ()
1		49.9144
2		50.0856
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		2.4724
2		97.5276
	Totals:	100.0000

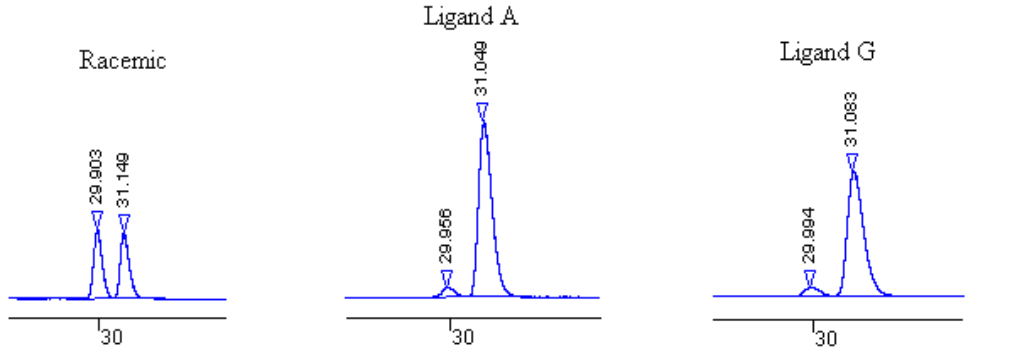
Peak No.	Peak Name	Result ()
1		4.1307
2		95.8693
	Totals:	100.0000

(R)-4-ethylnonan-2-one



Literature compound,[6] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.33 (m, 2H, C*H*$_2$=COMe, J=7.0Hz), 2.11 (s, 3H, *Me*CO), 1.83 (m, 1H, nPentC*H*Et), 1.31-1.16 (m, 10H, (C*H*$_2$)$_4$, C*H*$_2$ of Et), 0.88-0.80 (m, 6H, (CH$_2$)$_4$*Me*, C*H*$_3$ of Et); ^{13}C NMR (400MHz, $CDCl_3$):δ 209.3 (**C**=O), 48.4, 35.4, 33.5, 32.1, 30.3, 26.4, 26.4, 22.6, 14.0

Comparitive GC chromatograms of racemic, 91% ee (**L$_A$**) and 87% ee (**L$_G$**) materials below.

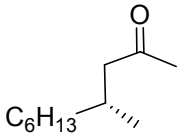


Peak No.	Peak Name	Result ()
1		50.0948
2		49.9052
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		4.5503
2		95.4497
	Totals:	100.0000

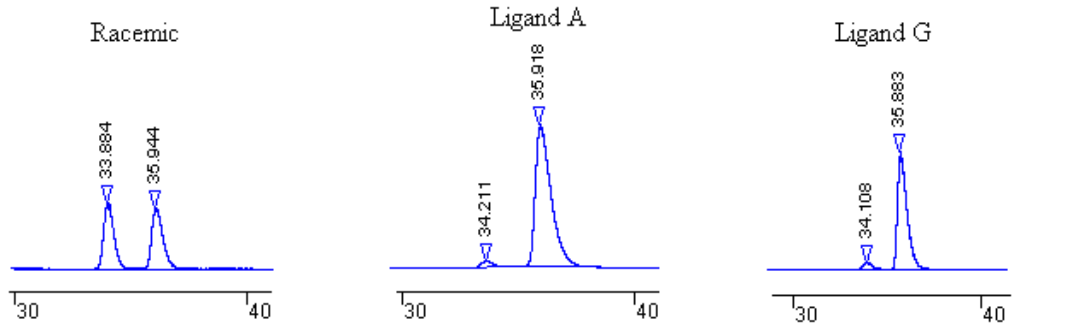
Peak No.	Peak Name	Result ()
1		6.2463
2		93.7537
	Totals:	100.0000

(R)-4-methyldecan-2-one



Literature compound,[5b,6]authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.40 (dd, 1H, CH*H*=COMe, J=16, 5.7), 2.22 (dd, 1H, C*H*H=COMe), 2.13 (s, 3H; *Me*CO), 1.89 (m, 1H; nHexC*H*Me), 1.1-1.35 (m, 10H, (C*H*$_2$)$_5$), overlapped by 0.89 (m, 6H, *Me*CH, (CH$_2$)$_5$*Me*); ^{13}C NMR (400MHz, $CDCl_3$): δ 209.6 (C=O), 51.7, 37.3, 32.3, 30.8, 29.8, 29.7, 27.3, 23.0, 20.2, 14.5.

Comparitive GC chromatograms of racemic, 91% ee (**L$_A$**) and 90% ee (**L$_G$**) materials below.

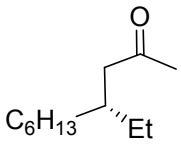


Peak No.	Peak Name	Result ()
1		49.9134
2		50.0866
	Totals:	100.0000

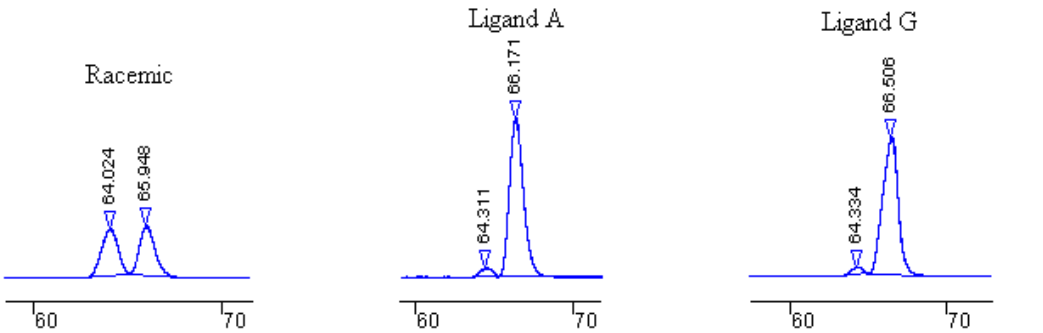
Peak No.	Peak Name	Result ()
1		4.5306
2		95.4694
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		4.9690
2		95.0310
	Totals:	100.0000

(R)-4-ethyldecan-2-one



Literature compound,[7] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.33 (m, 2H, C*H*$_2$=COMe, J=7.0Hz), 2.14 (s, 3H, *Me*CO), 1.83 (m, 1H, nHexC*H*Et), 1.31-1.16 (m, 12H, (C*H*$_2$)$_5$, C*H*$_2$ of Et), 0.88-0.80 (m, 6H, (CH$_2$)$_4$*Me*, C*H*$_3$of Et);^{13}C NMR (400MHz; $CDCl_3$): δ 209.7 (**C**=O), 48.4, 35.4, 33.5, 32.0, 30.4, 29.6, 26.6, 26.4, 22.7, 14.0, 10.83.
Comparitive GC chromatograms of racemic, 93% ee (**L$_A$**) and 90% ee (**L$_G$**) materials below.

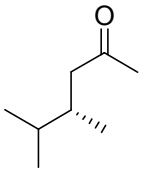


Peak No.	Peak Name	Result ()
1		50.1445
2		49.8555
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		3.6837
2		96.3163
	Totals:	100.0000

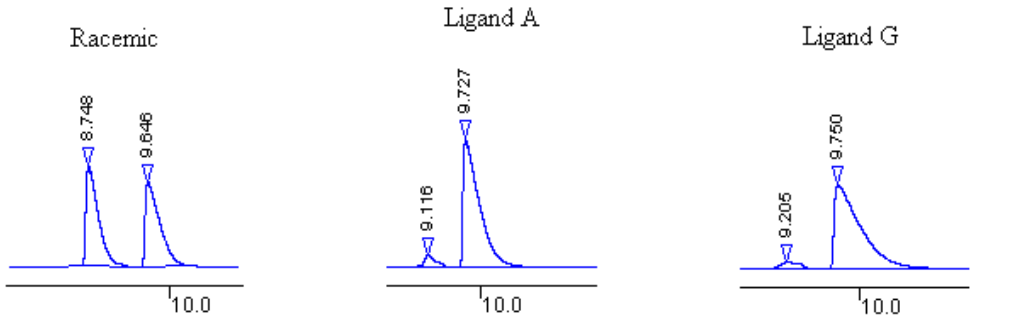
Peak No.	Peak Name	Result ()
1		4.8601
2		95.1399
	Totals:	100.0000

(R)-4-methyl-5-methylhexan-2-one



Literature compound,[8] authenticated by comparison against an existing sample and by ^{1}H NMR (270MHz, $CDCl_3$): δ 2.20 (dd, 1H, CH*H*=COMe, J=16, 5.4), 2.18 (dd, 1H, C*H*H=COMe), 2.15 (s, 3H; *Me*CO), 1.90 (m, 1H; C*H*$(Me)_2$), overlapped by 0.86 (m, 6H, *Me*$_2$CH, *Me*), ^{13}C NMR (400MHz, CDCl3) δ= 209.5 (C=O), 48.5, 34.75, 32.2, 30.4, 19.8, 18.4, 16.0.

Comparitive GC chromatograms of racemic, 89% ee (**L$_A$**) and 94% ee (**L$_G$**) materials below.

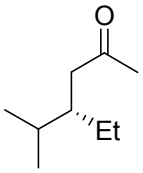


Peak No.	Peak Name	Result ()
1		49.8576
2		50.1424
	Totals:	100.0000

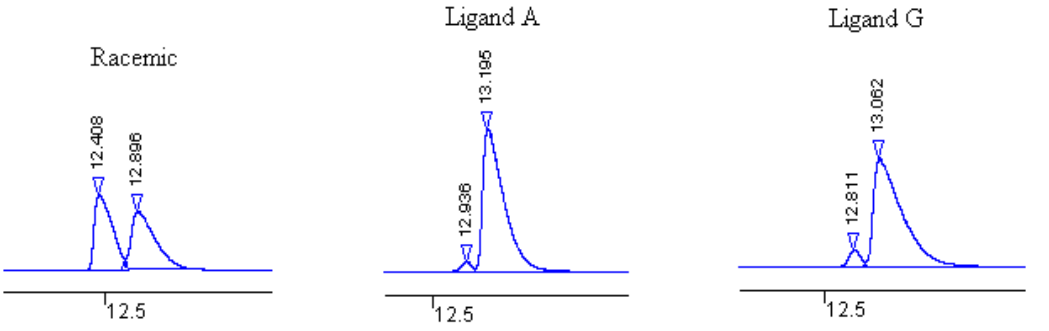
Peak No.	Peak Name	Result ()
1		5.3238
2		94.6762
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		2.9639
2		97.0361
	Totals:	100.0000

(R)-4-ethyl-5-methylhexan-2-one



Literature compound,[9] authenticated by comparison against an existing sample and by ^{1}H NMR (270 MHz, $CDCl_3$)**:** δ 2.40 (dd, 1H, CH*H*=COMe, J= 16.0Hz, 5.6Hz), 2.25 (dd, 1H, C*H*H=COMe, J=16Hz, J=7.6Hz), 2.15 (s, 3H; *Me*CO), 1.80-1.65 (m, 2H, C*H*Me$_2$ and C*H*Et), 1.38-1.30 (m, 1H, CH*H* of Et), 1.16-124 (m, 1H, C*H*H of Et), 0.90 (t, 3H, CH_3 of Et, J= 7.4Hz), 0.86 (t, 3H, *Me*CHMe, J= 7.4Hz), 0.82 (t, 3H, MeCH*Me*, J= 7.0Hz); ^{13}C (270MHz; CDCl3) 209.6 (**C**O), 45.1, 41.1, 30.3, 29.3, 23.9, 19.5, 18.5, 11.7.
Comparitive GC chromatograms of racemic, 93% ee (**L$_A$**) and 88% ee (**L$_G$**) materials below.

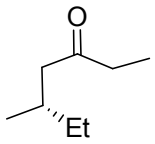


Peak No.	Peak Name	Result ()
1		50.1291
2		49.8709
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		3.2681
2		96.7319
	Totals:	100.0000

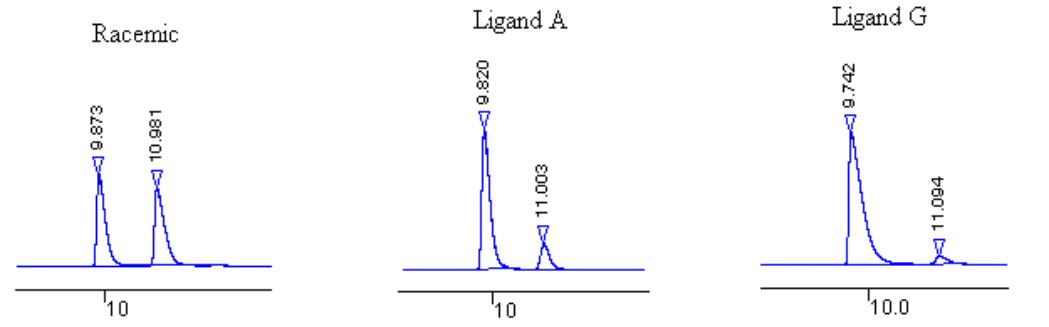
Peak No.	Peak Name	Result ()
1		5.8340
2		94.1660
	Totals:	100.0000

(S)-5-methyl-heptan-3-one



Literature compound,[10] authenticated by comparison against an existing sample and ^{1}H NMR (270MHz, $CDCl_3$)**:** δ 2.43-2.33(m, 1H, CH_3CH_2COCH*H*), 2.18 (dd, 1H, COC*H*HCH J=16Hz, J=7.6Hz), 1.80-1.65 (m, 1H, MeC*H*Et), 1.29-1.16 (m, 4H, CHC*H*$_2CH_3$, COC*H*$_2$Me), 1.02 (m, 3H, $COCH_2C$*H*$_3$), 0.88 (m, 6H, CH*Me*, $CHCH_2C$*H*$_3$); ^{13}C (400MHz; CDCl3) 211.9 (**C**O), 49.6, 36.5, 31.0, 29.7, 19.5, 11.3, 7.8.

Comparitive GC chromatograms of racemic, 67% ee (**L**$_A$) and 91% ee (**L**$_G$) materials below. The reversal of the stereochemistry is due to the use of $ZnEt_2$ (vs $ZnMe_2$) and the found selectivity was confirmed by polarimetry vs. the literature.



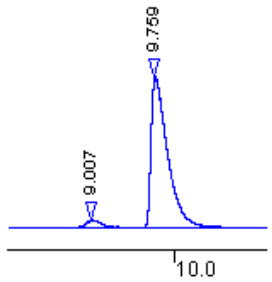
Peak No.	Peak Name	Result ()
1		50.1110
2		49.8890
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		83.5591
2		16.4409
	Totals:	100.0000

Peak No.	Peak Name	Result ()
1		95.3168
2		4.6832
	Totals:	100.0000

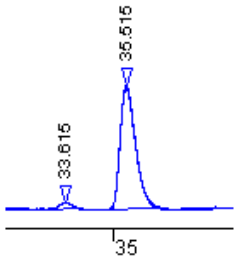
$ZnMe_2$ 1,4 addition to enones with ligand L_J

(*R*)-4-methyl-5-methylhexan-2-one



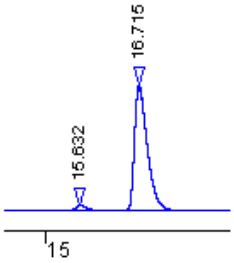
Peak No.	Peak Name	Result ()
1		2.8337
2		97.1663
Totals:		100.0000

(*R*)-4-methyldecan-2-one



Peak No.	Peak Name	Result ()
1		4.0719
2		95.9281
Totals:		100.0000

(*R*)-4-methylnonan-2-one



Peak No.	Peak Name	Result ()
1		3.2407
2		96.7593
Totals:		100.0000

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