Electronic Supplementary Material (ESI) for Green Chemistry

Supporting Information

Asymmetric Hydrogenation of Unprotected Indoles Using Iridium Complexes derived from P–OP Ligands and (Reusable) Brønsted acids

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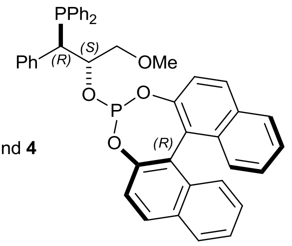
(A) General considerations

All syntheses were carried out using chemicals as received from commercial sources unless otherwise stated. All manipulations and reactions were run under inert atmosphere using anhydrous solvents, in either a glove box or with standard Schlenk-type techniques. Glassware was dried under vacuum and heated with a hot air gun before use. All solvents were dried by using a Solvent Purification System (SPS). Silica gel 60 (230–400 mesh) was used for column chromatography. NMR spectra were recorded in $CDCl_3$ unless otherwise cited, using a 400 MHz or 500 MHz spectrometer. ^1H NMR and $^{13}C\{^1H\}$ NMR chemical shifts are quoted in ppm relative to residual solvent peaks. IR spectra were recorded using Attenuated Total Reflection (ATR) technique unless otherwise stated. High resolution mass spectra (HRMS) were recorded by using ESI ionisation method in positive mode (characterisation purposes) unless otherwise stated. Melting points were measured in open capillaries and are uncorrected. Enantiomeric excesses were determined by HPLC on chiral stationary phases.

The preparation of the iridium complex derived from P–OP ligand **4** has previously been reported by our group.[1]

P–OP Ligand **4**



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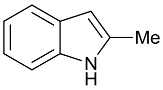
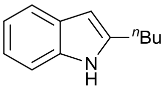
[1] (a) J. L. Núñez-Rico, H. Fernández-Pérez, J. Benet-Buchholz and A. Vidal-Ferran, *Organometallics*, 2010, **29**, 6627; (b) J. L. Núñez-Rico and A. Vidal-Ferran, *Org. Lett.*, 2013, **15**, 2066.

(B) Preparation and characterisation of indoles (1a–1f)

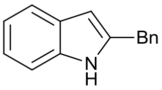
2-methyl-1*H*-indole (**1a**), 5-fluoro-2-methyl-1*H*-indole (**1d**), 2,5-dimethyl-1*H*-indole (**1e**) and 2,3,4,9-tetrahydro-1*H*-carbazole (**1f**) are all commercially available substrates which were used as received. 2-butyl-1*H*-indole (**1b**) and 2-benzyl-1*H*-indole (**1c**) were prepared following reported procedures[2] and spectroscopic data for these compounds were in agreement with the reported ones.



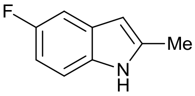
1a



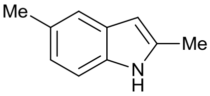
1b



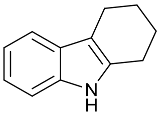
1c



1d



1e



1f

(C) General procedure for the Ir-mediated asymmetric hydrogenation

A solution of the required amount of iridium precursor ([{Ir(μ-Cl)(cod)}$_2$]) (0.00125 mmol) and the P–OP ligand **4** (0.00275 mmol) in the corresponding dry and deoxygenated solvent (0.75 mL) was added under N_2 into an autoclave containing the substrate (0.25 mmol) and the additive (0.25 mmol) in the deoxygenated solvent (0.5 mL). In all cases the molar concentration of the substrate in the reaction medium was adjusted to a final concentration of 0.20 M. The autoclave was purged three times with H_2 (at a pressure that did not exceed the selected one) and finally, the autoclave was pressurised with H_2 at the desired pressure. The reaction mixture was stirred at the desired temperature for the stated reaction time. After the hydrogen had been carefully released, the resulting mixture was concentrated under vacuum and then treated with saturated $NaHCO_3$ (4 mL). After stirring for 10 min, the mixture was extracted with EtOAc (2 × 4 mL), dried over $MgSO_4$, filtered through a short pad of SiO_2 and, finally, concentrated *in vacuo*. Conversions were determined at this point by ^{1}H NMR analysis. The hydrogenation products were isolated after chromatography on SiO_2. The enantioselectivities were determined by HPLC analysis on chiral stationary phases and

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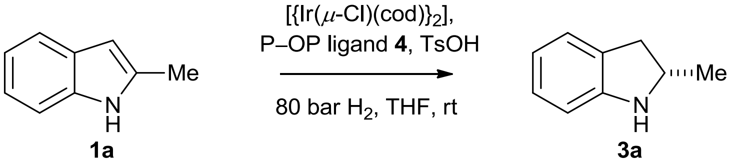
[2] D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou and X. Zhang, *J. Am. Chem. Soc*., 2010, **132**, 8909.

the configuration of the products was established by comparison with reported HPLC data on chiral stationary phases.

For recycling the acidic resin (DOWEX^{TM} 50WX8), it was filtered from the aqueous solution, then suspended in aq. HCl (10% solution; 8 mL/mmol resin), stirred for 10 minutes, filtered and sequentially washed with a series of solvents (5 mL of each solvent/mmol resin; solvents: H_2O, H_2O/MeOH (1:1), MeOH) and diethyl ether. The resin was then dried under vacuum prior to its reuse.

(D) Complete set of results regarding the effect of the TsOH amount in the Ir-mediated asymmetric hydrogenation of indole 1a

Table SI 1 Studies on the effect of the TsOH amount in the hydrogenation of indole **1a** with Ir catalyst derived from P–OP ligand **4**.[a]



Entry	Additive	Loading	Conv. [%][b]	ee [%][c] (config.)[d]
1	–	–	11	n. d.
2	TsOH	10%	22	90 (*S*)
3	TsOH	40%	42	90 (*S*)
4	TsOH	80%	65	88 (*S*)
5	TsOH	100%	69	88 (*S*)

[a] Reaction conditions: *In situ* formed pre-catalyst, [{Ir(μ–Cl)(cod)}$_2$]/P–OP ligand **4**/substrate molar ratio = 0.5:1.1:100, variable additive loading, 80 bar H_2, room temperature, 20 h, 0.2 M in THF, unless otherwise indicated.

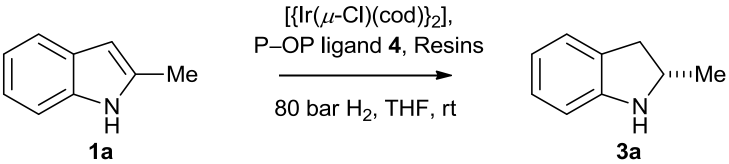
[b] Conversion determined by ^{1}H NMR.

[c] Enantiomeric excess determined by HPLC on chiral stationary phases.

[d] Absolute configuration was assigned by comparison with reported data.

(E) Complete set of results regarding the use of different ion-exchange resins in the Ir-mediated asymmetric hydrogenation of indole 1a

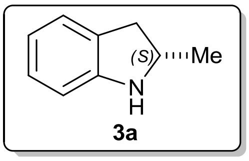
Table SI 2 Acid cation exchange resins as additives in the hydrogenation of model indole **1a** with Ir catalyst derived from P–OP ligand **4**.[a]



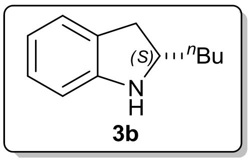
Entry	Acid cation exchange resin	Conv. [%][b]	ee [%][c] (config.)[d]
1	Amberlyst™ 15 Dry	23	90 (*S*)
2	Amberlite™ IRN77	3	n. d.
3	DOWEX™ 50WX8	37	90 (*S*)

[a] Reaction conditions: *In situ* formed pre-catalyst, [{Ir(μ–Cl)(cod)}$_2$]/P–OP ligand **4**/acidic resin/substrate molar ratio = 0.5:1.1:100:100, 80 bar H_2, room temperature, 65 h, 0.2 M in THF.
[b], [c], [d] See the corresponding footnotes in Table SI 1.

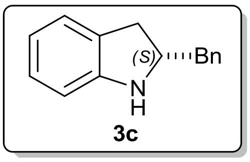
(F) Characterisation of hydrogenation products and determination of ees


3a

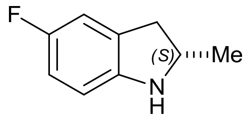
Hydrogenation product 3a: Known compound,[2] HPLC conditions: Daicel Chiralcel® OD-H (25 cm x 0.46 cm), 97:3 *n*-hexane/2-propanol, 0.80 mL/min, 254 nm, $t_R(R)$ = 11.3 min, $t_R(S)$ = 13.1 min.


3b

Hydrogenation product 3b: Known compound,[2] HPLC conditions: Daicel Chiralcel® OD-H (25 cm x 0.46 cm), 99:1 *n*-hexane/2-propanol, 1.00 mL/min, 254 nm, $t_R(R)$ = 8.9 min, $t_R(S)$ = 13.2 min.

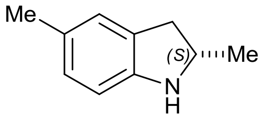

3c

Hydrogenation product 3c: Known compound,[2] HPLC conditions: Daicel Chiralcel® OD-H (25 cm x 0.46 cm), 99:1 *n*-hexane/2-propanol, 1.00 mL/min, 254 nm, $t_R(R)$ = 16.7 min, $t_R(S)$ = 19.5 min.



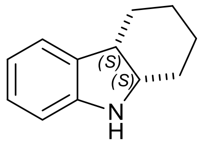
3d

Hydrogenation product 3d: Known compound,[2] HPLC conditions: Daicel Chiralcel® OD-H (25 cm x 0.46 cm), 99:1 *n*-hexane/2-propanol, 1.00 mL/min, 254 nm, $t_R(R)$ = 9.5 min, $t_R(S)$ = 14.5 min.



3e

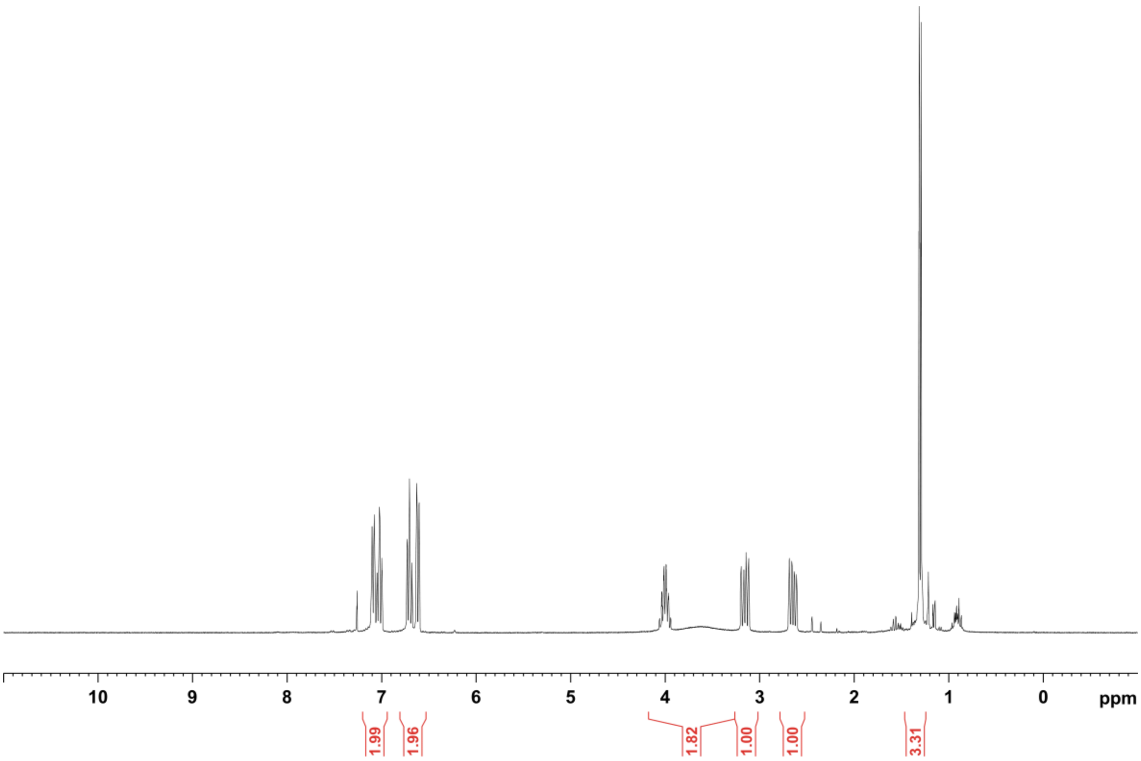
Hydrogenation product 3e: Known compound,[2] HPLC conditions: Daicel Chiralcel® OD-H (25 cm x 0.46 cm), 99:1 *n*-hexane/2-propanol, 1.00 mL/min, 254 nm, $t_R(R)$ = 9.4 min, $t_R(S)$ = 11.7 min.

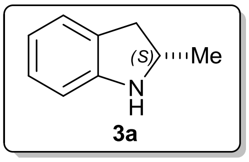


3f

Hydrogenation product 3f: Known compound,[2] 91% *ee*, $[\alpha]_D^{25}$ = −22.7 (*c* 1.20, $CHCl_3$) [lit.:[2] $[\alpha]_D^{23}$ = +23.4 (*c* 1.20, $CHCl_3$) for the 4a*R*,9a*R* enantiomer, 91% *ee*], HPLC conditions: Daicel Chiralcel® IC (25 cm x 0.46 cm), 99:1 *n*-hexane/2-propanol, 1.00 mL/min, 254 nm, $t_R(+)$ = 6.2 min, $t_R(-)$ = 10.2 min.

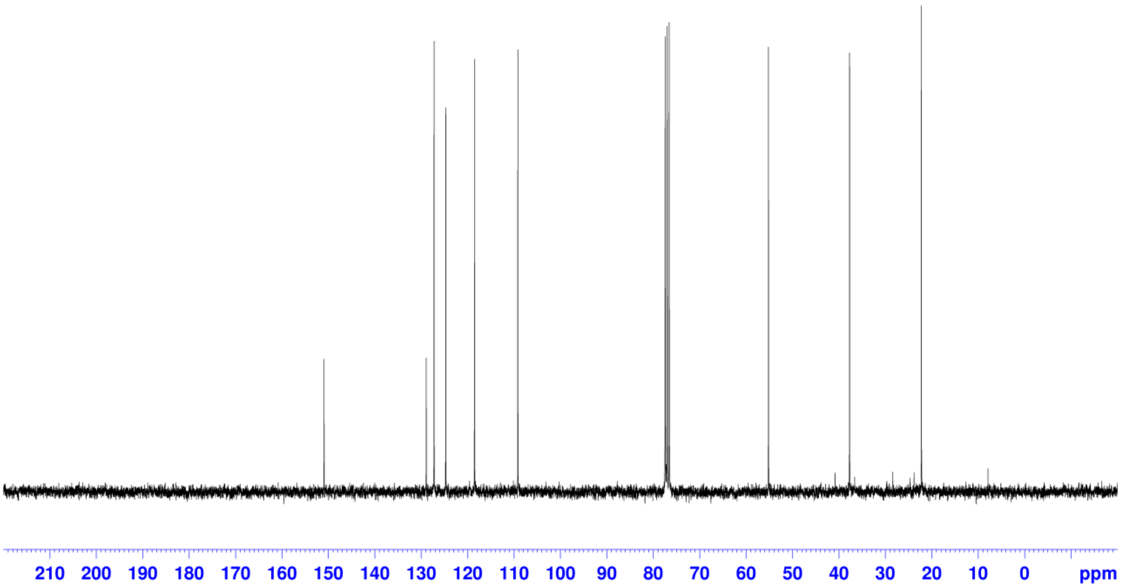
(G) NMR spectra of hydrogenation products 3 under homogeneous conditions

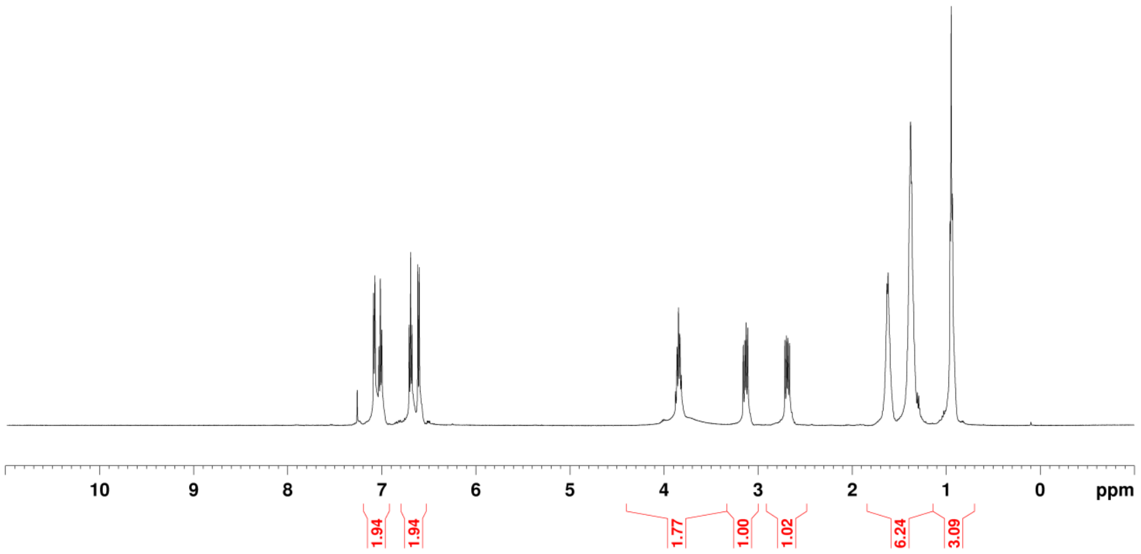


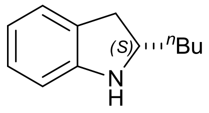


3a

^{1}H-NMR ($CDCl_3$, 300 MHz)
^{13}C{^{1}H}-NMR ($CDCl_3$, 75 MHz)

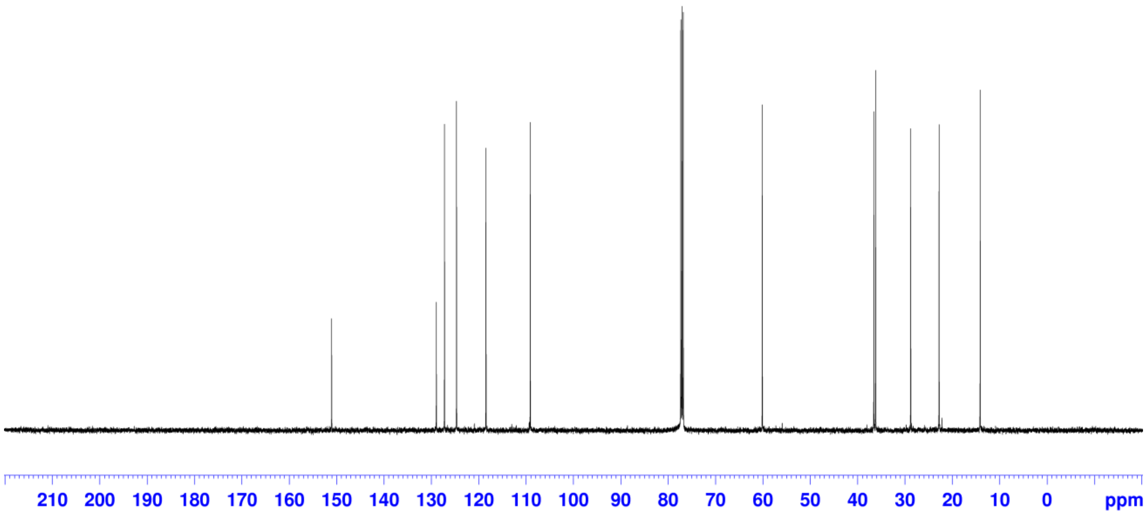


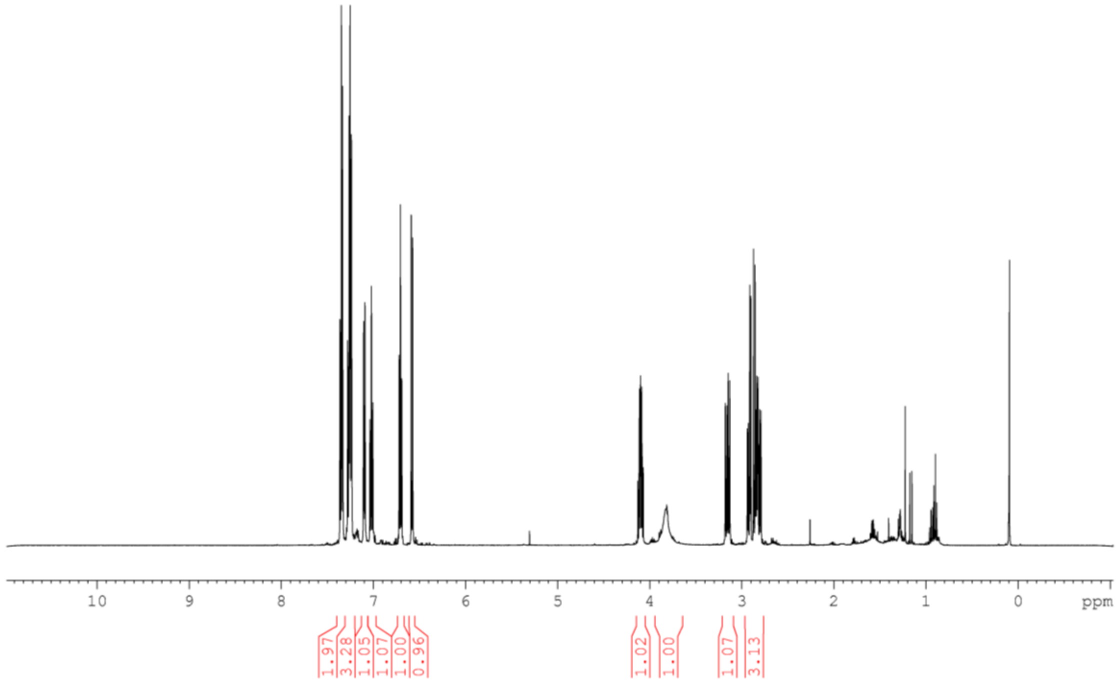


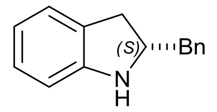


3b

^{1}H-NMR ($CDCl_3$, 500 MHz)
^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz)

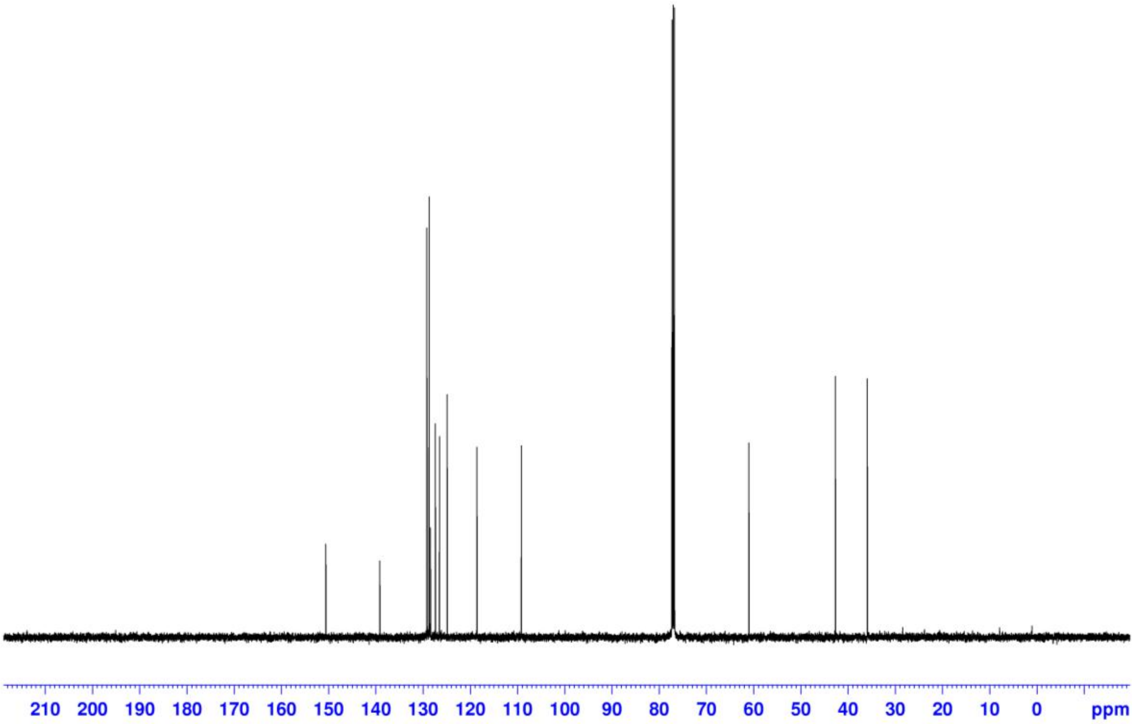


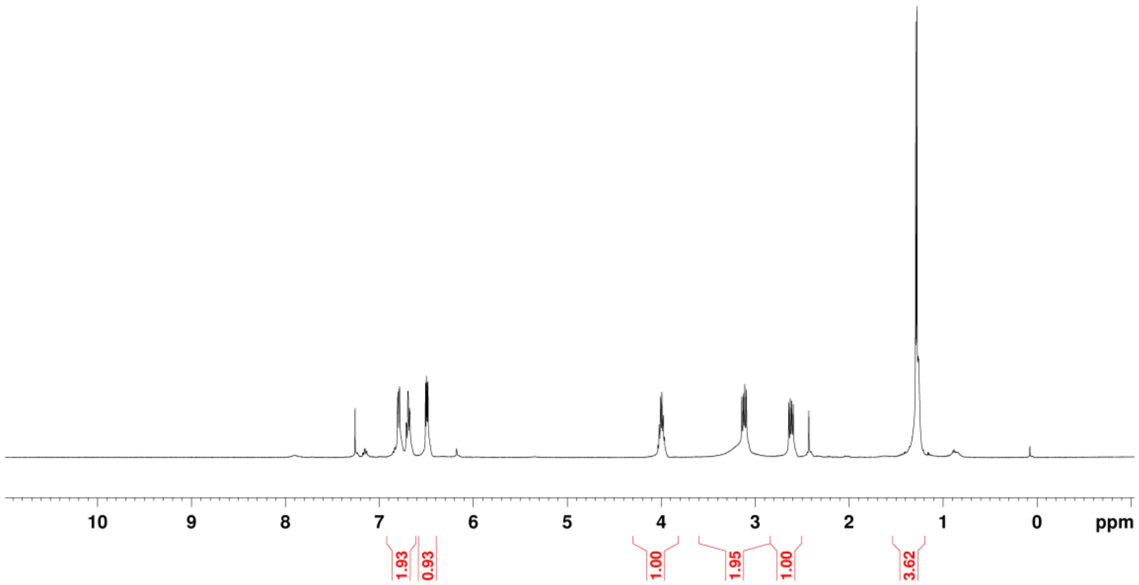


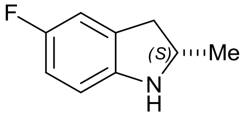


3c

^{1}H-NMR ($CDCl_3$, 500 MHz)
^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz)

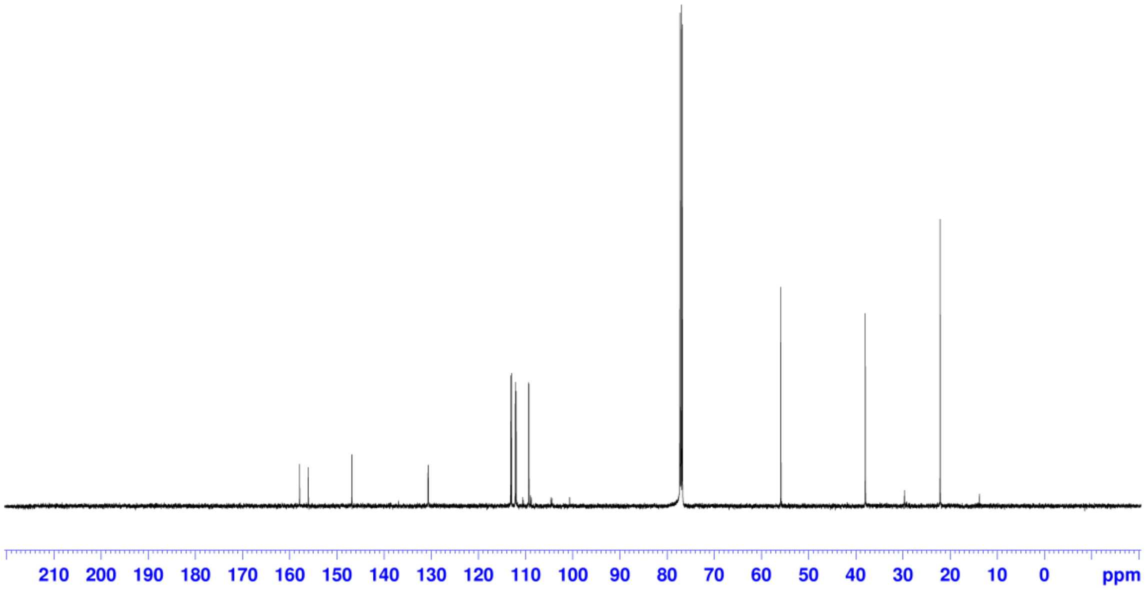


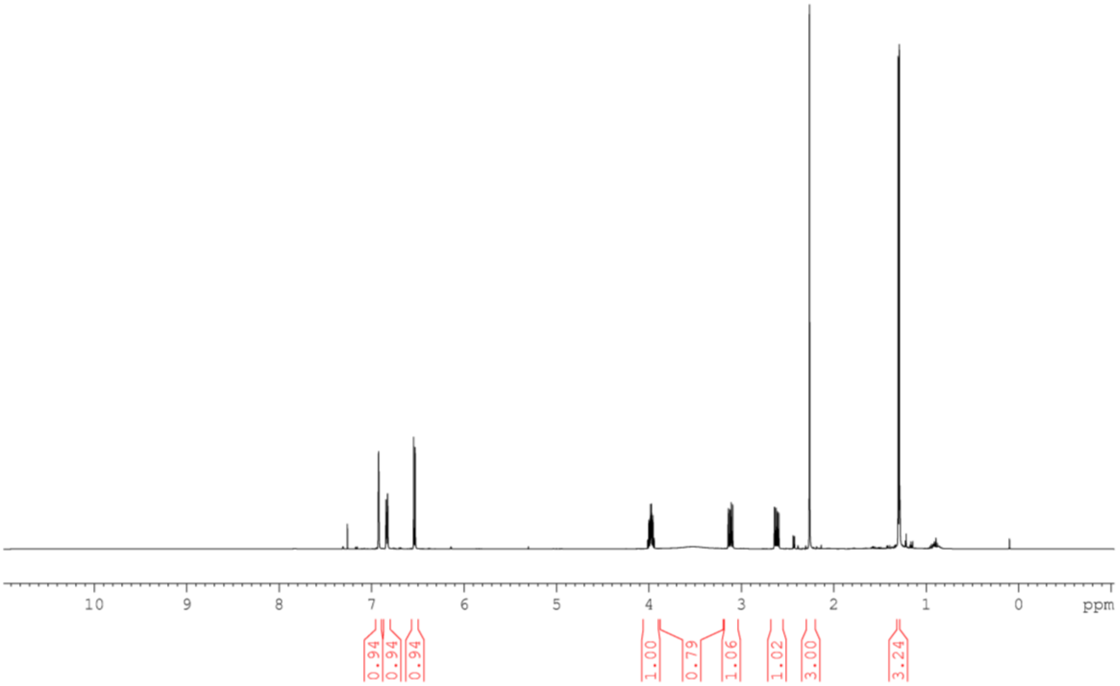


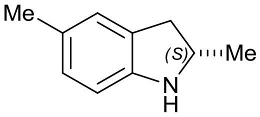


3d

^{1}H-NMR (CDCl$_3$, 500 MHz)
^{13}C{^{1}H}-NMR (CDCl$_3$, 125 MHz)







3e

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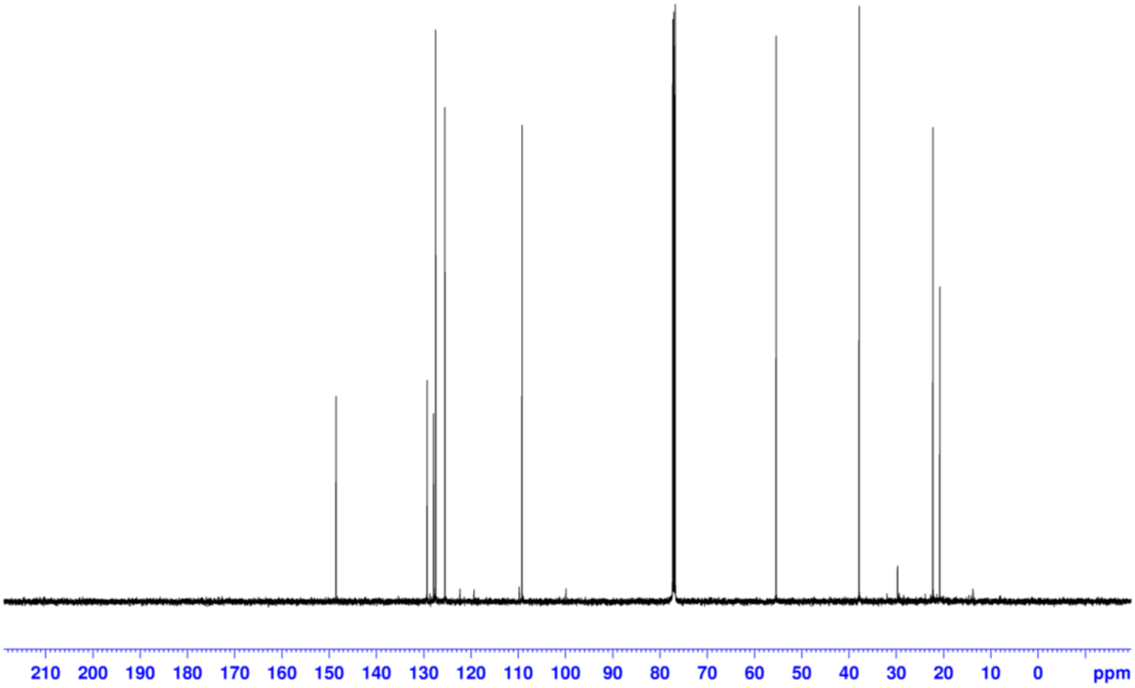
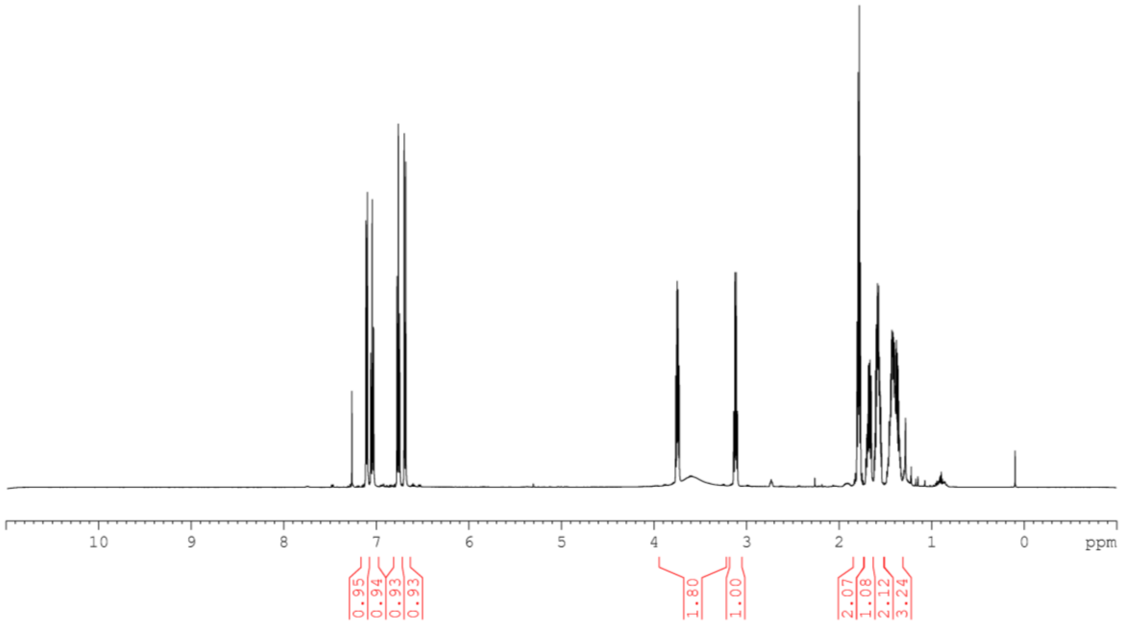
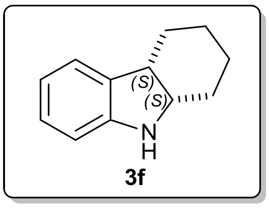
^{13}C{^{1}H}-NMR (CDCl$_3$, 125 MHz)







3f

^{1}H-NMR (CDCl$_3$, 500 MHz)
^{13}C{^{1}H}-NMR (CDCl$_3$, 125 MHz)