Simple iodoalkyne-based organocatalysts for the activation of carbonyl compounds

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ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

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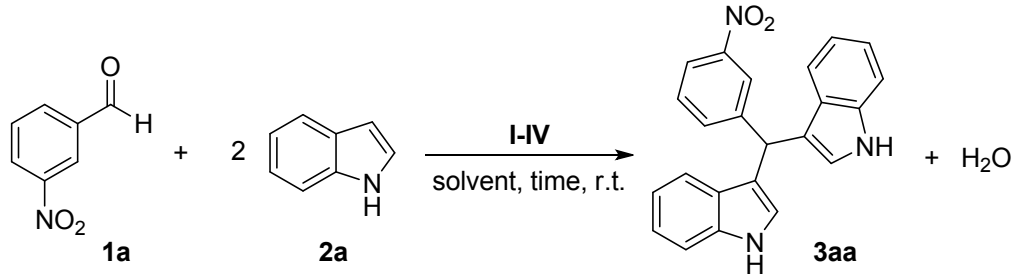
1. General experimental methods and instrumentation

Purification of reaction products was carried out either by flash chromatography using silical-gel (0.063-0.200 mm). Analytical thin layer chromatography was performed on 0.25 mm silica-gel 60-F plates. ESI ionization method and mass analyser type MicroTof-Q were used for the ESI measurements. ^{1}H and $^{13}C\{^{1}H\}$-APT NMR were recorded at room temperature on a BRUKER AVANCE 400 spectrometer (^{1}H, 400 MHz; ^{13}C, 100.6 MHz) in $CDCl_3$ or CD_3COCD_3 as solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.28 ppm) and CH_3COCH_3 (2.05 ppm) for ^{1}H NMR and to the central line of $CHCl_3$ (77.16 ppm) and CH_3COCH_3 (29.84 ppm) for $^{13}C\{^{1}H\}$-APT NMR. All commercially available solvents and reagents were used as received. ^{1}H- and $^{13}C\{^{1}H\}$-APT NMR spectra for compounds **3aa**,[1] **3ba**,[2] **3ca**,[3] **3da**,[4] **3ea**,[3] **3fa**,[1] **3ha**,[1] **3ia**,[1] **3ka**,[5] **3hb**[6] and **3hc**[7] are consistent with values previously reported in the literature.

2. Screening of the reaction conditions

Table S1. Screening of catalysts I-IV.[a]



Entry	Catalyst	Solvent	Time (days)	Yield (%)[b]
1	**I** (30)	CH_2Cl_2	1	>95
2	**II** (30)	CH_2Cl_2	1	>95
3	**III** (30)	CH_2Cl_2	1	79
4	**IV** (30)	CH_2Cl_2	1	>95
5	**I** (30)	CH_3CN	2	n.d.[c]

[1] H.-E. Qu, C. Xiao, N. Wang, K.-H. Yu, Q.-S. Hu and L.-X. Liu, *Molecules*, 2011, **16**, 3855.
[2] R. Martínez, A. Espinosa, A. Tárraga and P. Molina, *Tetrahedron*, 2008, **64**, 2184.
[3] L.-T. An, F.-Q. Ding, J.-P. Zou, X.-H. Lu and L.-L. Zhang, *Chin. J. Chem.* 2007, **25**, 822.
[4] C. J. Magesh, R. Nagarajan, M. Karthik and P. T. Perumal, *Appl. Catal. A: Gen.* 2004, **266**, 1.
[5] A. Khalafi-Nezhad, A. Parhami, A. Zare, A. R. M. Zare, A. Hasaninejad and F. Panahi, *Synthesis*, 2008, 617.
[6] M. L. Deb and P. J. Bhuyan, *Synthesis*, 2008, 2891.
[7] R. Ramachandiran, D. Muralidharan and P. T. Perumal, *Tetrahedron Lett.*, 2011, **52**, 3579.

6	**I** (30)	THF	2	n.d.[c]
7	**I** (30)	Dioxane	2	n.d.[c]
8	**I** (30)	AcOEt	2	70

[a] Experimental conditions: to a mixture of catalyst **I-IV** (0.03 mmol) and aldehyde **1a** (0.1 mmol) in the corresponding solvent (250μL), indole **2a** (0.4 mmol) was further added in a test tube at room temperature. After the reaction time, adduct **3aa** was isolated by chromatography (Hexano:AcOEt 8:2). [b] Isolated yield. [c] Not determined.

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3. Computational details

The ωB97X-D[8]/Def2-TZVP[9] method was employed to optimize the geometries of the stationary points (including the corresponding effective core potential (ECP) for iodine atoms). This functional has proven to be accurate for systems with long-range interactions.[8,10] Vibrational frequency calculations were performed in order to verify that the stationary points were energy minima. Solvent effects (solvent=toluene) were also taken into account using the integral equation formalism variant of the polarizable continuum model (IEF-PCM)[11] using the SMD solvation model. All the calculations were carried out using Gaussian 16.[12]

In order to reduce basis set superposition errors (BSSEs) and basis set incompleteness errors (BSIEs) in the bonding energy (BE) calculations, after the geometry optimizations, we performed single point energy calculations using ωB97X-D/Def2-QZVPP (using the SMD solvation model as well and including the corresponding ECP for iodine atoms). We employed a quadruple zeta basis set (Def2-

[8] a) A. D. Becke, *J. Chem. Phys*., 1997, **107**, 8554; b) J.-D. Chai and M. Head-Gordon *Phys. Chem. Chem. Phys*., 2008, **10**, 6615.
[9] a) F. Weigend and R. Ahlrichs *Phys. Chem. Chem. Phys.,* 2005, **7**, 3297; b) F. Weigend, *Phys. Chem. Chem. Phys.,* 2006, **8**, 1057.
[10] a) L. Goerigk and S. Grimme, *Phys. Chem. Chem. Phys*., 2011, **13**, 6670; b) J. V. Alegre-Requena, E. Marqués-López and R. P. Herrera, *ACS Catal.,* 2017, **7**, 6430; c) J. V. Alegre-Requena, E. Marqués-López and R. P. Herrera, *Chem. Eur. J*., 2017, **23**, 15336.
[11] a) E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.,* 1997, **107**, 3032; b) B. Mennucci, E. Cancès and J. Tomasi, *J. Phys. Chem. B,* 1997, **101**, 10506; c) B. Mennucci and J. Tomasi, *J. Chem. Phys.,* 1997, **106**, 5151; d) J. Tomasi, B. Mennucci, and E. Cancès, *J. Mol. Struct. (Theochem),* 1999, **464**, 211; e) A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, 113, 6378; f) G. Scalmani and M. J. Frisch, *J. Chem. Phys.,* 2010, **132**, 114110.
[12] Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

QZVPP) because this type of basis set typically shows less than 2% of Δ*E* due to BSSEs in combination with different DFT functionals.[13] The BE were calculated by measuring the energy difference of the complexes and the individual components. For example, the BE created in the complex **I--1h** is calculated as follows: BE = E(**I--1h**) – E(**I**) – E(**1h**). The geometries of the individual components **I** and **1h** were optimized before the single-point calculations in order to account for the corresponding fragment relaxation energies.

Electrostatic potentials at nuclei (EPN) of the carbonyl C atoms were calculated with the pop=CHelpG[14] option implemented in Gaussian 16 at the ωB97X-D/Def2-QZVPP(SMD)//ωB97X-D/Def2-TZVP(SMD) level of theory. For the CHelpG calculations, an atomic radius of 2.2 Å was used for the iodine atoms.[15] Graphical representations of the geometries were generated using PyMOL.[16] NCIPLOT[17] was used to generate the surfaces of noncovalent interactions and these surfaces were represented using PyMOL.

Electronic Energies (E), BE and EPN

Table S2. E, BE and EPN of the different complexes and individual components measured at the ωB97X-D/Def2-QZVPP(SMD)//ωB97X-D/Def2-TZVP(SMD) level. Negative values in the BE values correspond to attractive interactions.

System	E (au)	BE (kcal/mol)	EPN (au)	EPN (kcal/mol)
1h	-345.61110054	-	-14.687880	-9216.6
IH	-384.56449073	-	-	-
IH--1h	-730.17937329	-2.37	-14.680684	-9212.1
I	-978.92800462	-	-	-
I--1h	-1324.54494772	-3.67	-14.670153	-9205.5

[13] R. Sure and S. Grimme, *J. Chem. Theory Comput.,* 2015, **11**, 3785.
[14] C. M. Breneman and K. B. Wiberg, *J. Comp. Chem*., 1990, **11**, 361.
[15] S. Reiling, M. Besnard and P. A. Bopp, *J. Phys. Chem. A,* 1997**, 101***,* 4409.
[16] The PyMOL Molecular Graphics System, version 2.0.7, Schrödinger, LLC.
[17] NCIPLOT Version 3.0. a) E.R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen and W. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 6498; b) J. Contreras-Garcia, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan and W. Yang, *J. Chem. Theory Comput.*, 2011, **7**, 625.

Molecular Coordinates

I--1h

0 1

C	1.35359114	2.49539587	0.00000000
C	2.00959414	3.14958987	1.04514400
C	1.25821314	3.66451087	2.10389300
C	-0.11539886	3.52887587	2.11661900
C	-0.77235886	2.87512387	1.07141400
C	-0.02010286	2.35999587	0.01307000
H	1.93036514	2.09378687	-0.82274200
H	1.76079514	4.17191787	2.91678100
H	-0.69226586	3.92970787	2.93963000
H	-0.52274686	1.85204787	-0.79938800
C	3.43069314	3.29065887	1.03129300
C	-2.19363486	2.73581587	1.08539200
C	4.62816914	3.41048987	1.01973200
C	-3.39230286	2.61896387	1.09854600
I	6.60413414	3.60872487	1.00024800
I	-5.38107286	2.42938587	1.12320700
C	-10.27733586	3.71182387	0.92506700
C	-10.73950186	5.00764487	0.71501100
C	-12.10071086	5.26275587	0.68493200
C	-12.99775086	4.22049287	0.86462500
C	-12.54011886	2.92378987	1.07442000
C	-11.18307886	2.66711787	1.10519100
H	-10.02831486	5.81442687	0.57618100
H	-12.46200686	6.26994787	0.52229900
H	-14.06251386	4.41720887	0.84170600
H	-13.24789286	2.11664587	1.21340900

H	-10.80866286	1.66433187	1.26725600
C	-8.82713586	3.47125187	0.95298700
O	-8.31039386	2.39140187	1.13144900
H	-8.19991086	4.36908687	0.79492900

I

0 1

C	3.50828724	2.27440140	0.00000000
C	4.23783924	2.31888940	1.19023000
C	3.55765124	2.26463540	2.40890700
C	2.18096724	2.16819740	2.43671900
C	1.45143224	2.12369340	1.24652100
C	2.13164324	2.17796940	0.02781300
H	4.03039224	2.31611840	-0.94677700
H	4.11805824	2.29875840	3.33384000
H	1.65890124	2.12649240	3.38351800
H	1.57119124	2.14385240	-0.89709300
C	5.66213824	2.41865640	1.16143800
C	0.02713824	2.02386640	1.27524100
C	6.86242024	2.50273340	1.13759500
C	-1.17312576	1.93969340	1.29987000
I	8.84310824	2.64179840	1.09814200
I	-3.15380976	1.80043540	1.34024300

1h

0 1

C	0.54327808	1.29834250	0.00000000
C	-0.06575592	2.53681850	0.17292100
C	-1.43794692	2.66450450	0.02709300

C	-2.20043692	1.55111350	-0.29222900
C	-1.59583492	0.31071950	-0.46618700
C	-0.22746192	0.18244050	-0.32083600
H	0.54008308	3.40111450	0.42242600
H	-1.91206892	3.62829950	0.16172200
H	-3.27308992	1.64740550	-0.40697900
H	-2.19786092	-0.55386050	-0.71546800
H	0.26031908	-0.77523050	-0.45244100
C	2.00786308	1.18917950	0.16130900
O	2.64289508	0.17255050	0.03739600
H	2.51581508	2.14131950	0.41521500

IH--1h

0 1

C	-0.56169428	1.66666661	0.00000000
C	-1.21652028	1.64714261	-1.23271600
C	-0.57481428	2.17681661	-2.35363200
C	0.69271872	2.71333061	-2.24426700
C	1.34823772	2.73283061	-1.01169800
C	0.70584172	2.20324761	0.10908900
H	-1.05506328	1.25840561	0.87222400
H	-1.07839428	2.16518061	-3.31130300
H	1.18534472	3.12367261	-3.11591700
H	1.20865972	2.21701261	1.06711700
C	-2.53000028	1.09238361	-1.34562300
C	2.66163372	3.28779661	-0.89871200
C	-3.63208028	0.62832061	-1.44002200
C	3.76319372	3.75518261	-0.80351800
C	8.33752272	2.06222861	-1.19608300

C	8.32622672	0.70254861	-1.49060400
C	9.51913572	0.01515061	-1.64601800
C	10.72274372	0.68974961	-1.50642600
C	10.73876572	2.04905661	-1.21202600
C	9.54995472	2.73599661	-1.05671700
H	7.37859072	0.18631161	-1.59730400
H	9.51158372	-1.04273639	-1.87514800
H	11.65660672	0.15474461	-1.62741800
H	11.68265872	2.56814061	-1.10472500
H	9.54311472	3.79411861	-0.82742800
C	7.05406372	2.76786461	-1.03622000
O	6.93961072	3.94325361	-0.78090200
H	6.15399672	2.13517761	-1.16842000
H	4.75263472	4.15980361	-0.72130600
H	-4.61162928	0.21719961	-1.52362700

IH

0 1

C	2.99263347	1.83241247	0.00000000
C	2.18203347	2.05340447	-1.11506000
C	2.65148447	2.86465147	-2.14986900
C	3.90333647	3.44209947	-2.07125700
C	4.71383447	3.22133547	-0.95604900
C	4.24450447	2.40988247	0.07862400
H	2.63307547	1.20422847	0.80433500
H	2.02681447	3.03856747	-3.01611900
H	4.26305547	4.06999847	-2.87574700
H	4.86929947	2.23564547	0.94471300

C	0.88529747	1.45526847	-1.19651400
C	6.01067847	3.81927747	-0.87464400
C	-0.20211553	0.95341647	-1.26422000
C	7.09790947	4.32175847	-0.80851300
H	8.06470447	4.76653947	-0.74655200
H	-1.16823653	0.50753247	-1.32383900

4. NMR spectra

Figure S1. ^{1}H and ^{13}C NMR spectra of catalyst I

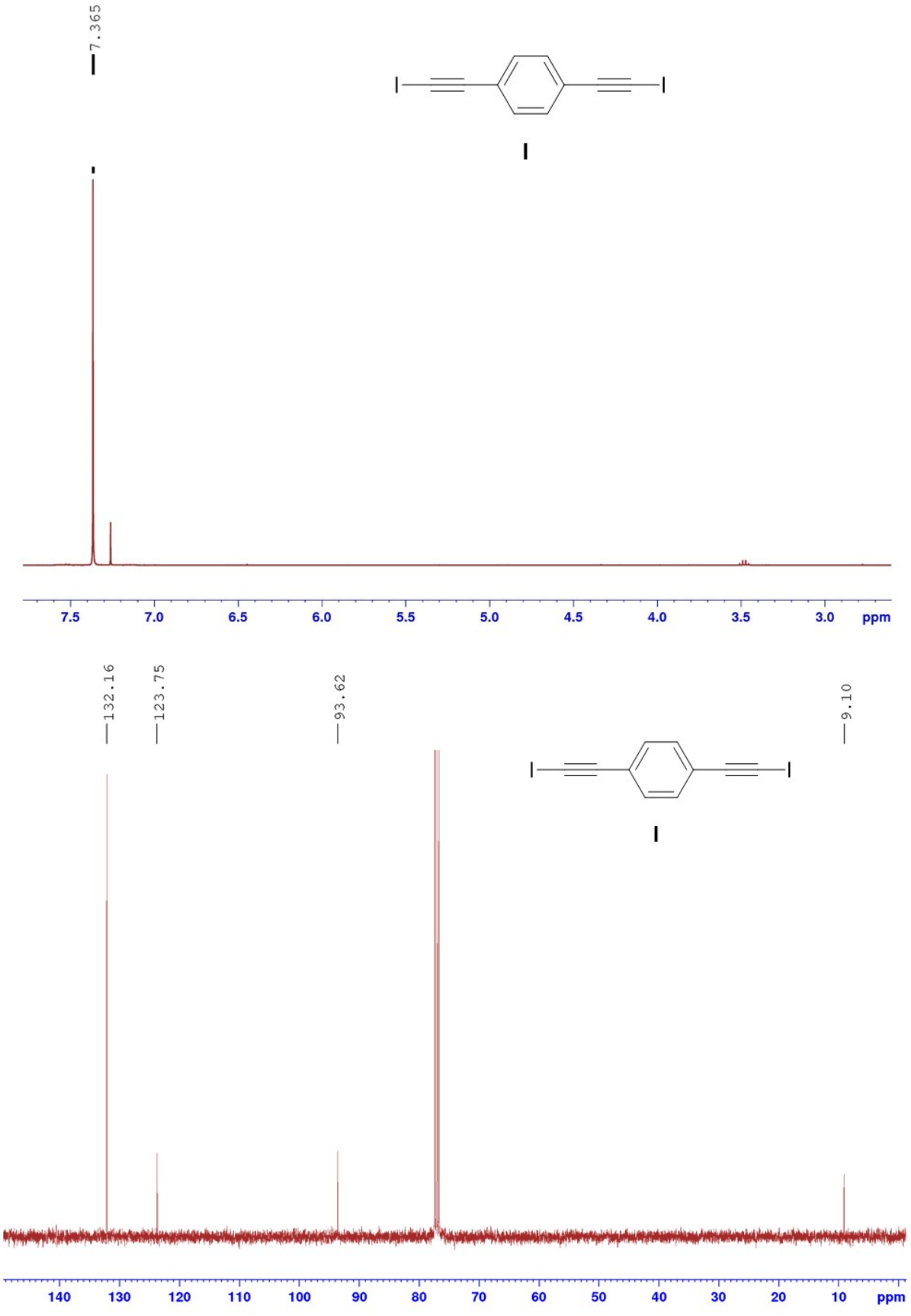
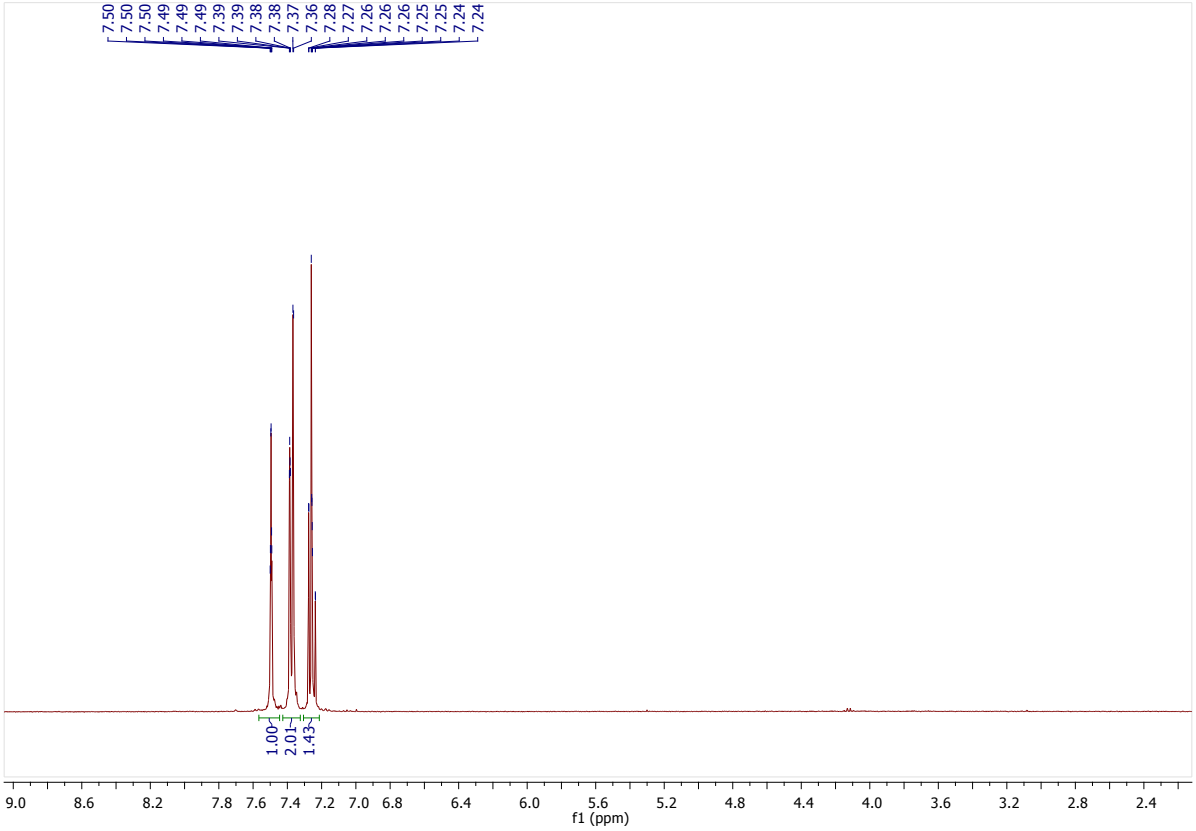


Figure S2. ^{1}H and ^{13}C NMR spectra of catalyst II



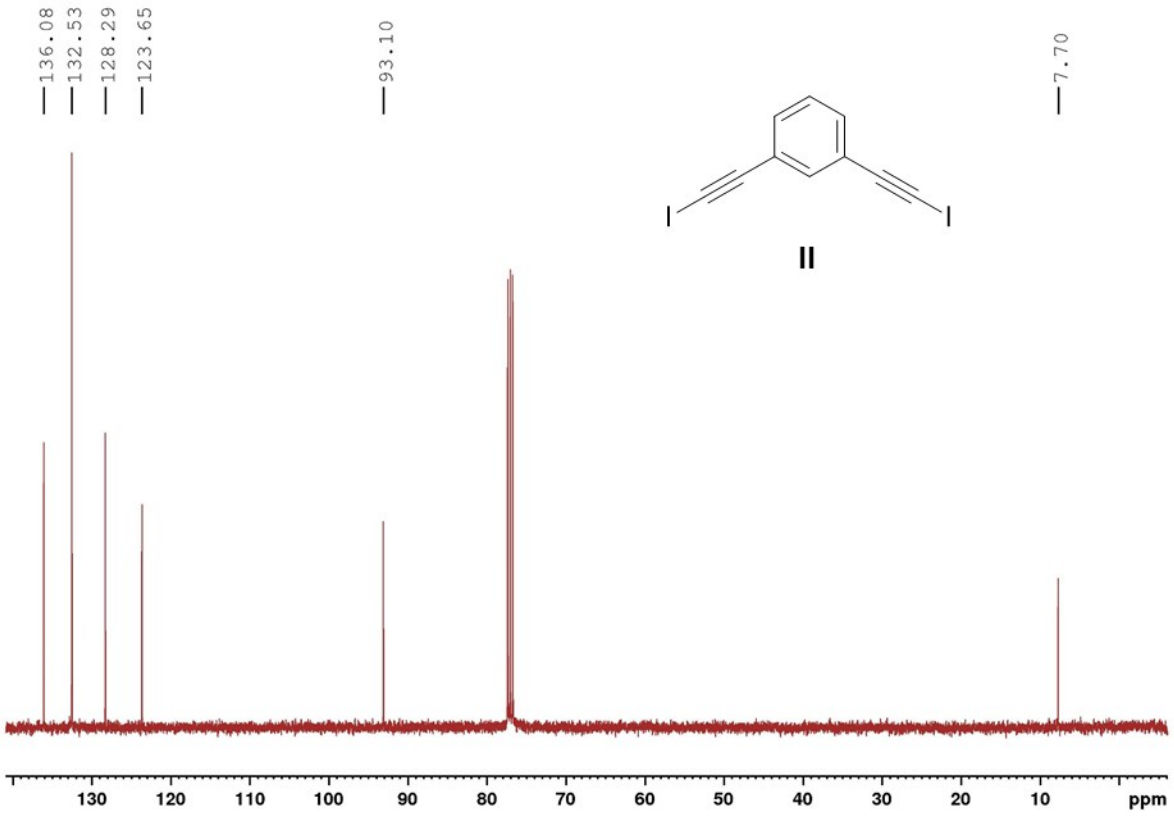
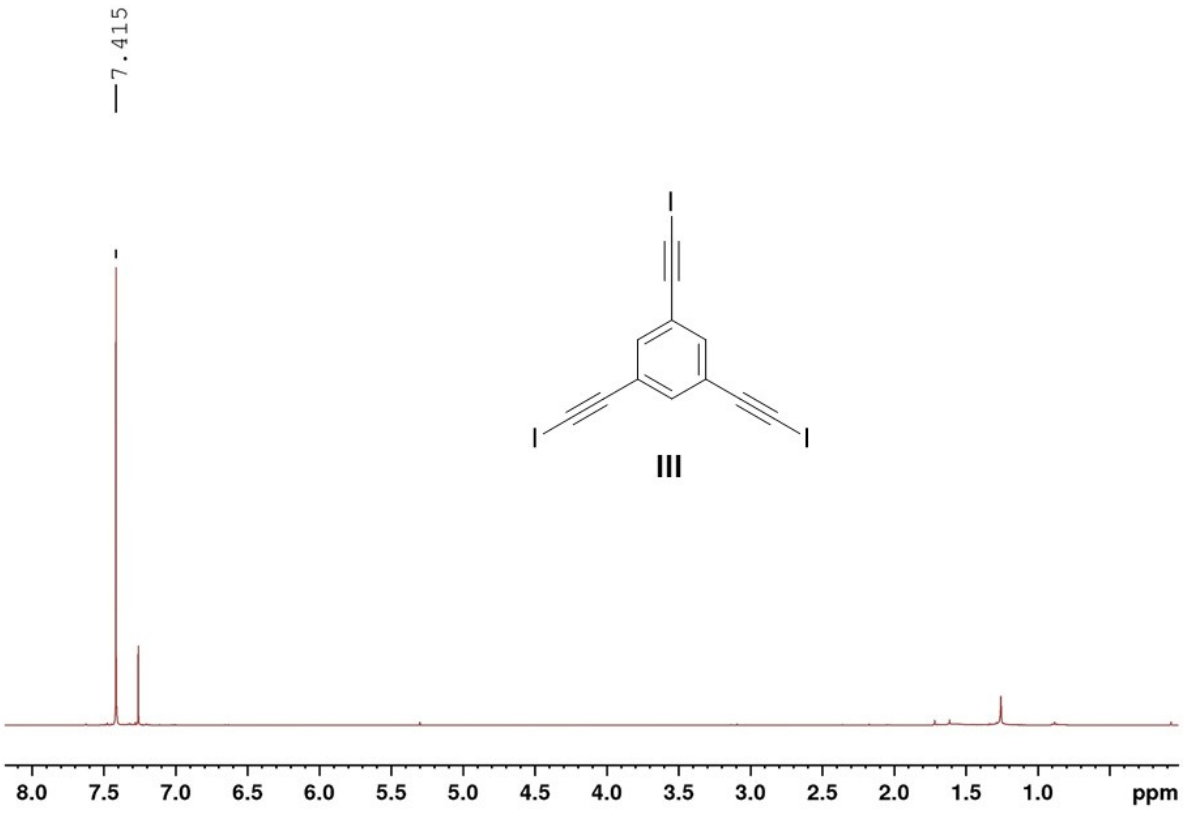


Figure S3. ^{1}H and ^{13}C NMR spectra of catalyst III



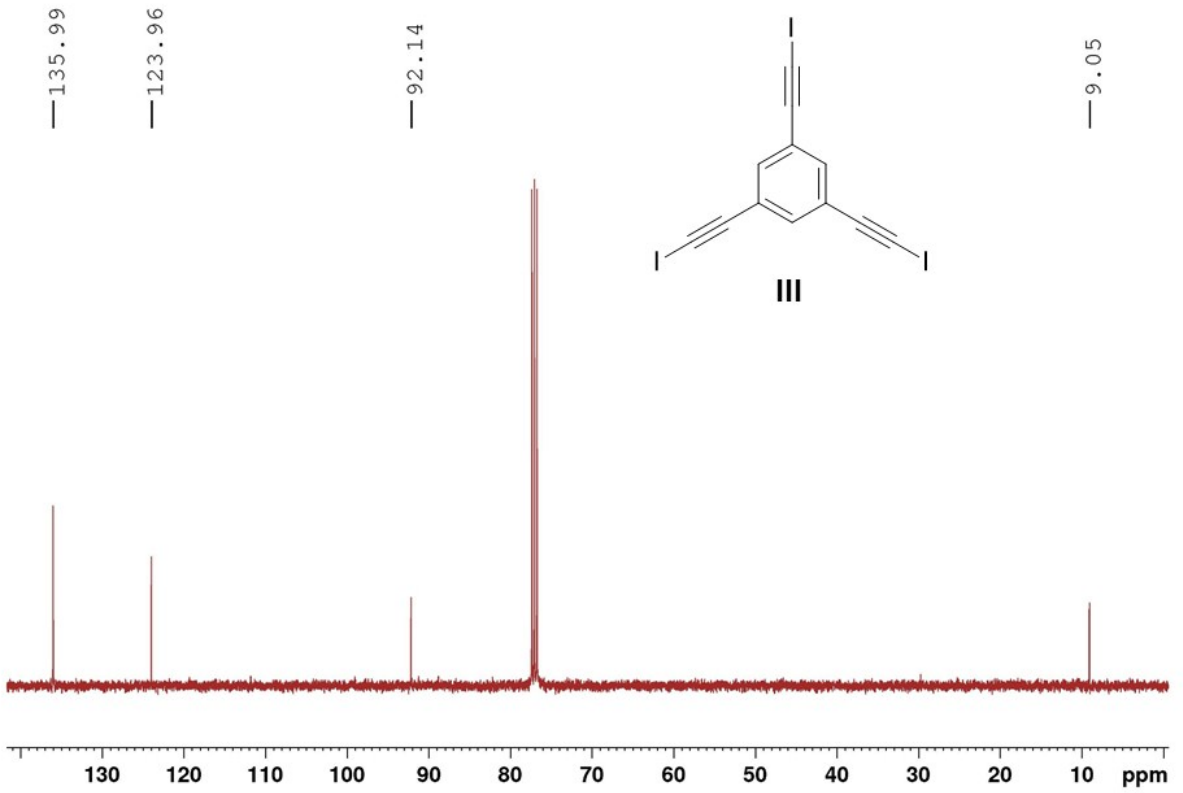
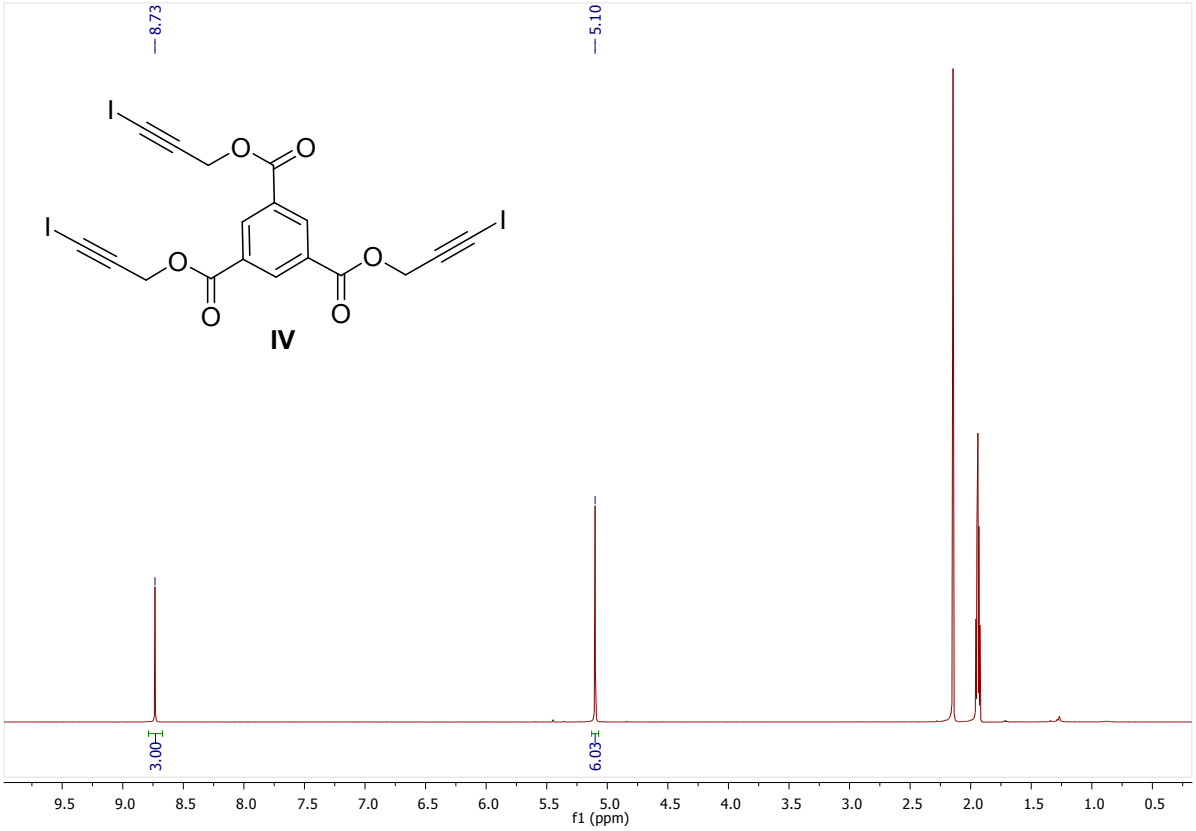


Figure S4. ^{1}H and ^{13}C-APT NMR spectra of catalyst IV



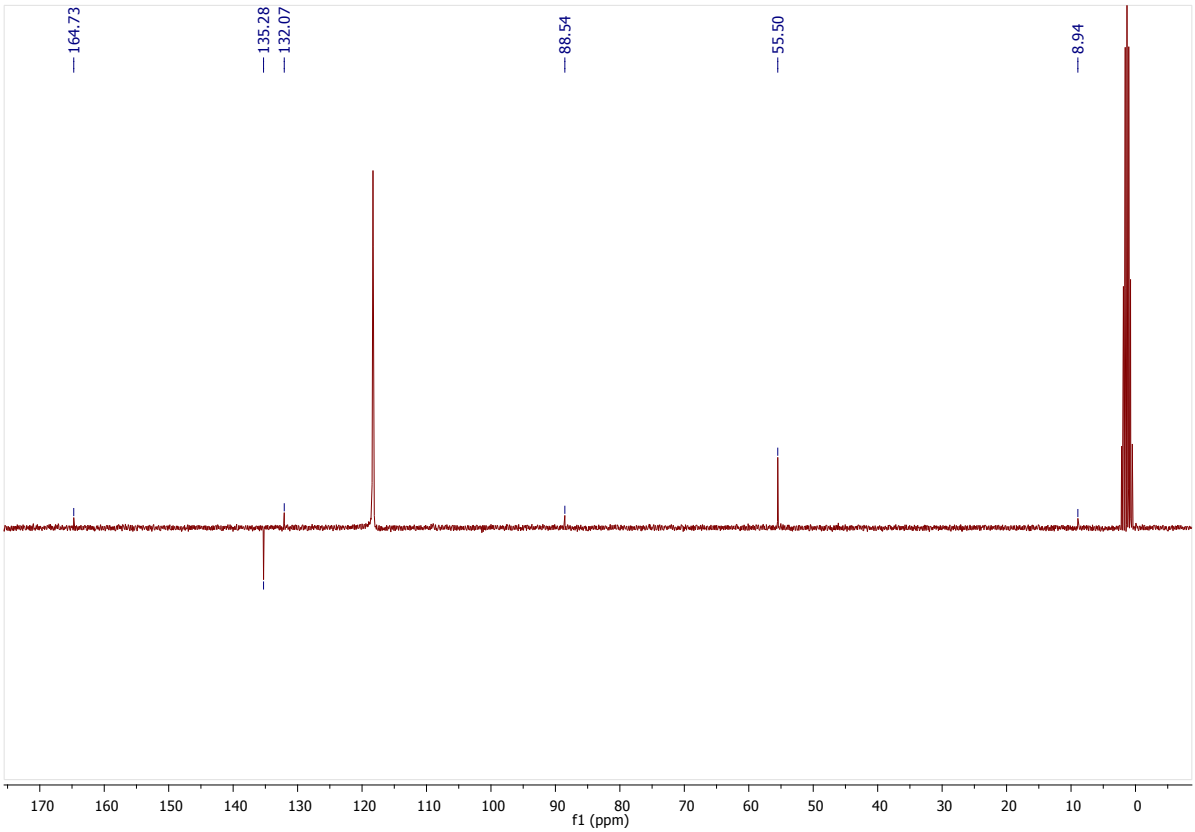


Figure S5. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 3,3'-((3-nitrophenyl)methylene)bis(1*H*-indole) (3aa)

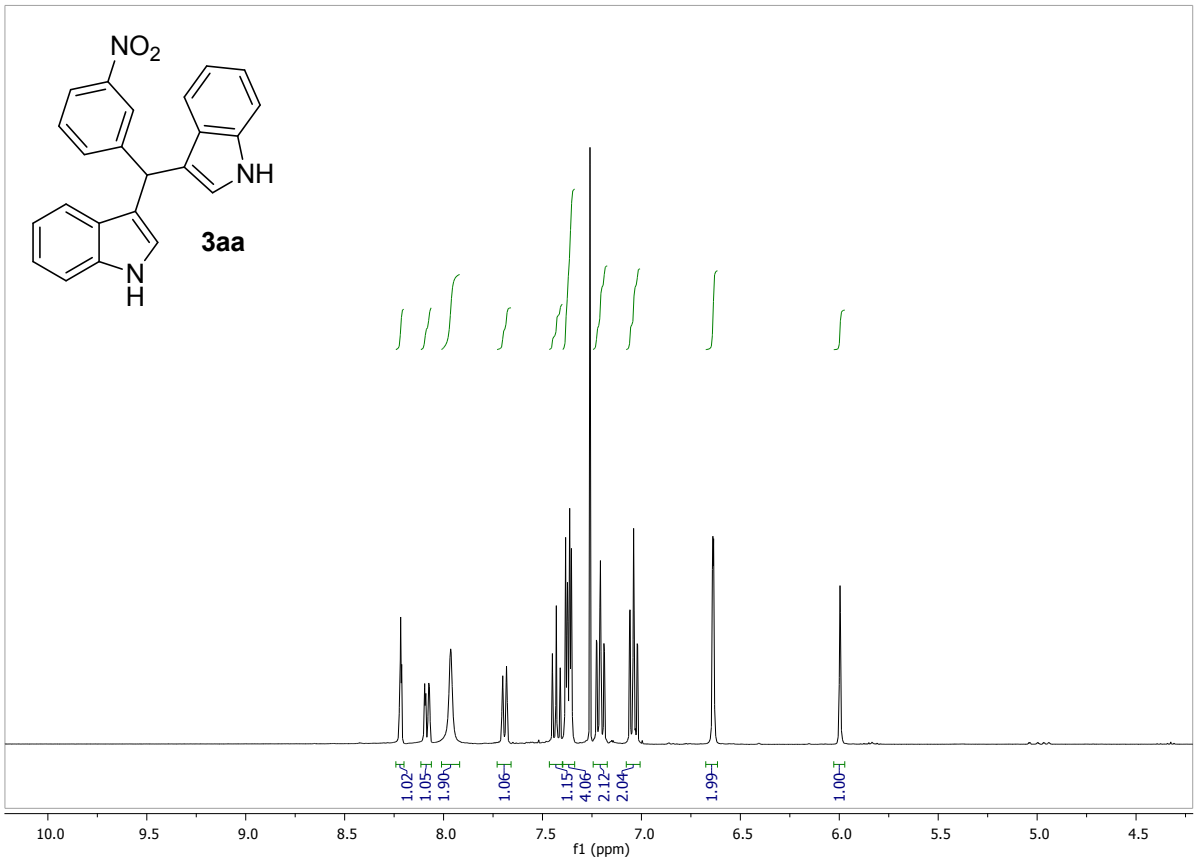


Figure S6. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 3,3'-((4-nitrophenyl)methylene)bis(1*H*-indole) (3ba)

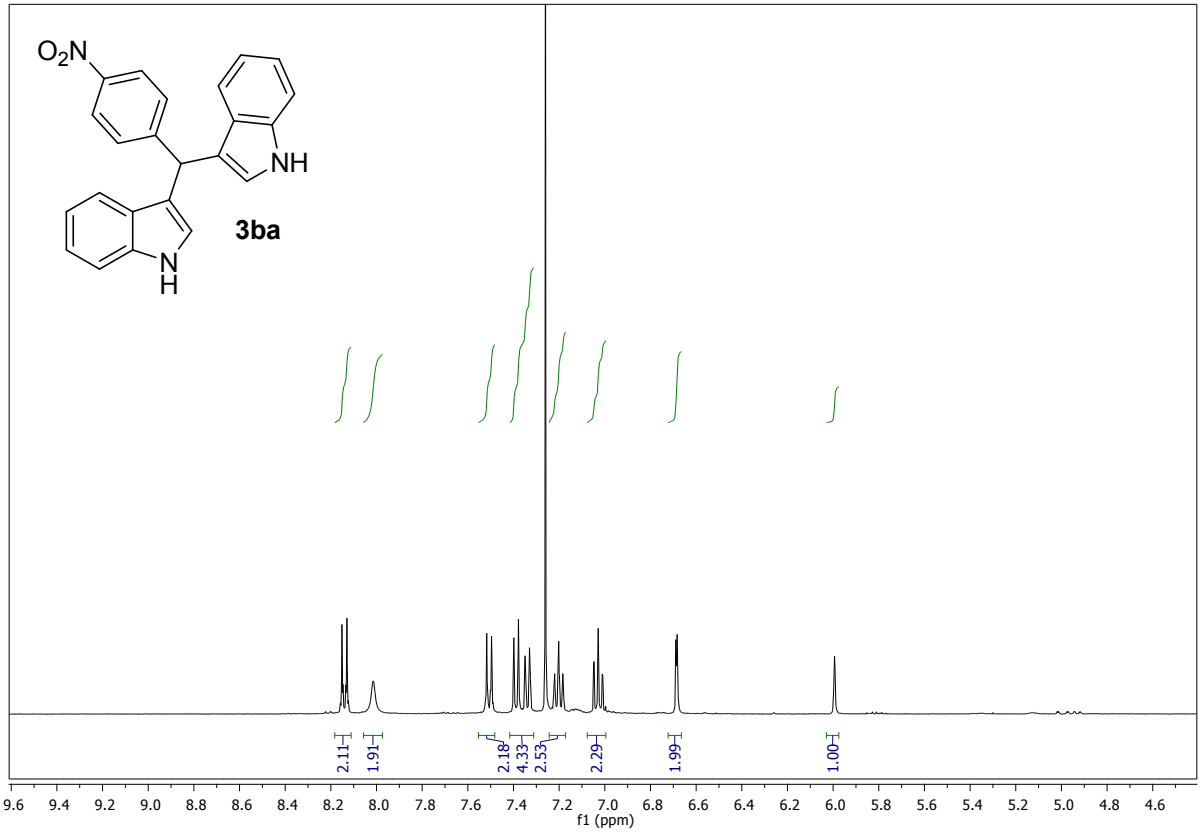


Figure S7. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 4-(di(1*H*-indol-3-yl)methyl)benzonitrile (3ca)

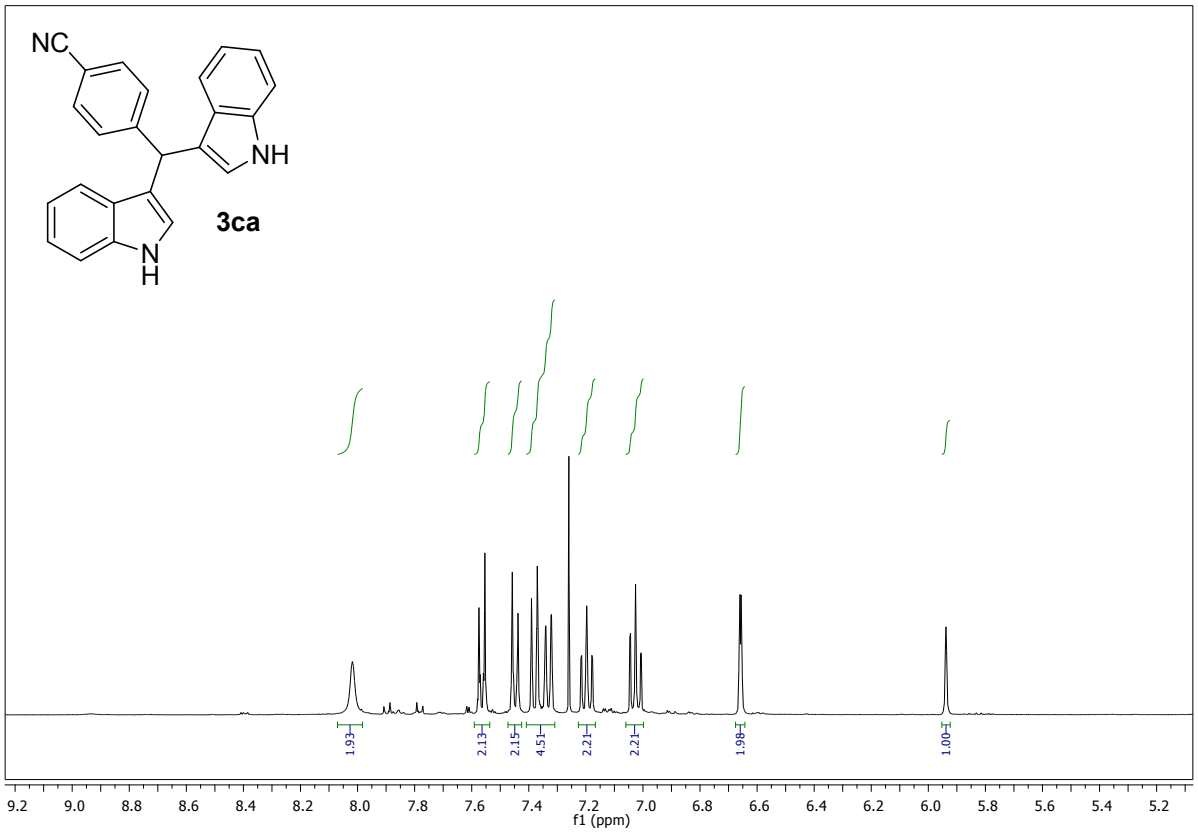


Figure S8. ^{1}H-NMR (CD_3COCD_3, 400 MHz) spectrum of 3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole) (3da)

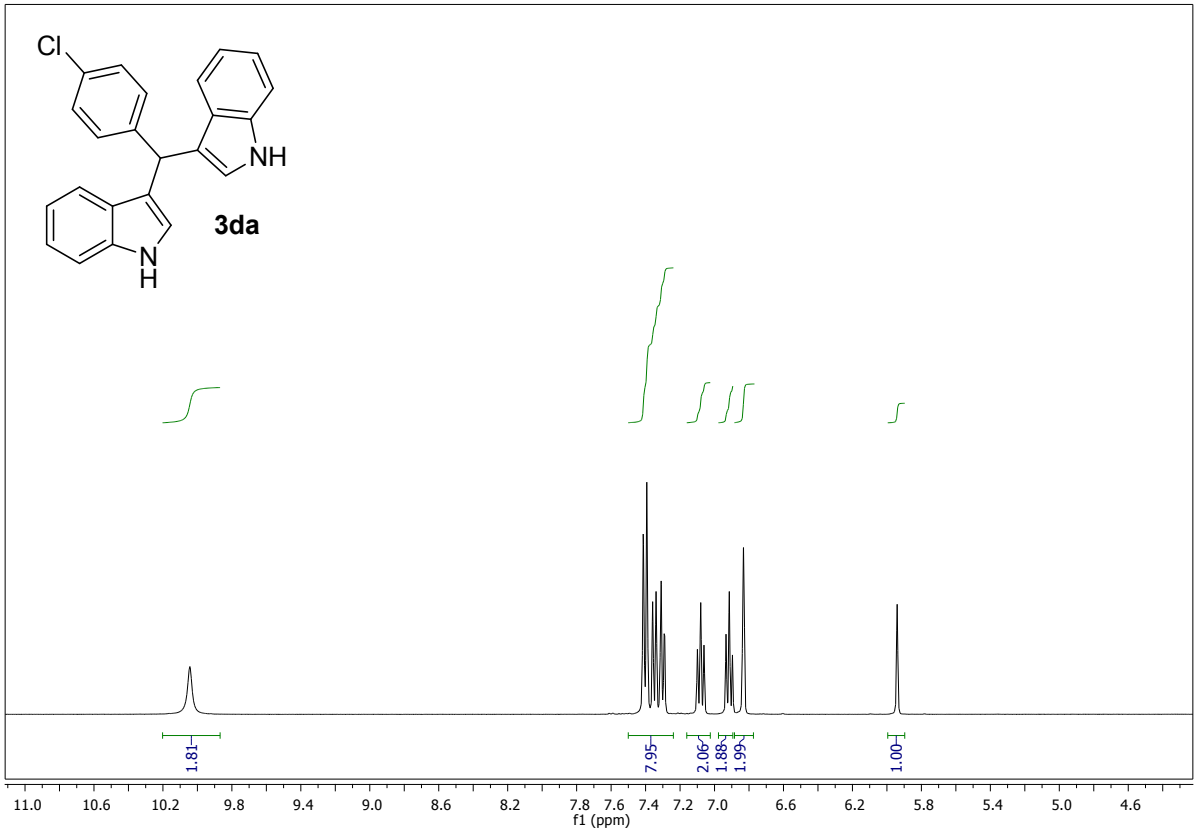


Figure S9. ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum of 3,3'-((4-bromophenyl)methylene)bis(1*H*-indole) (3ea)

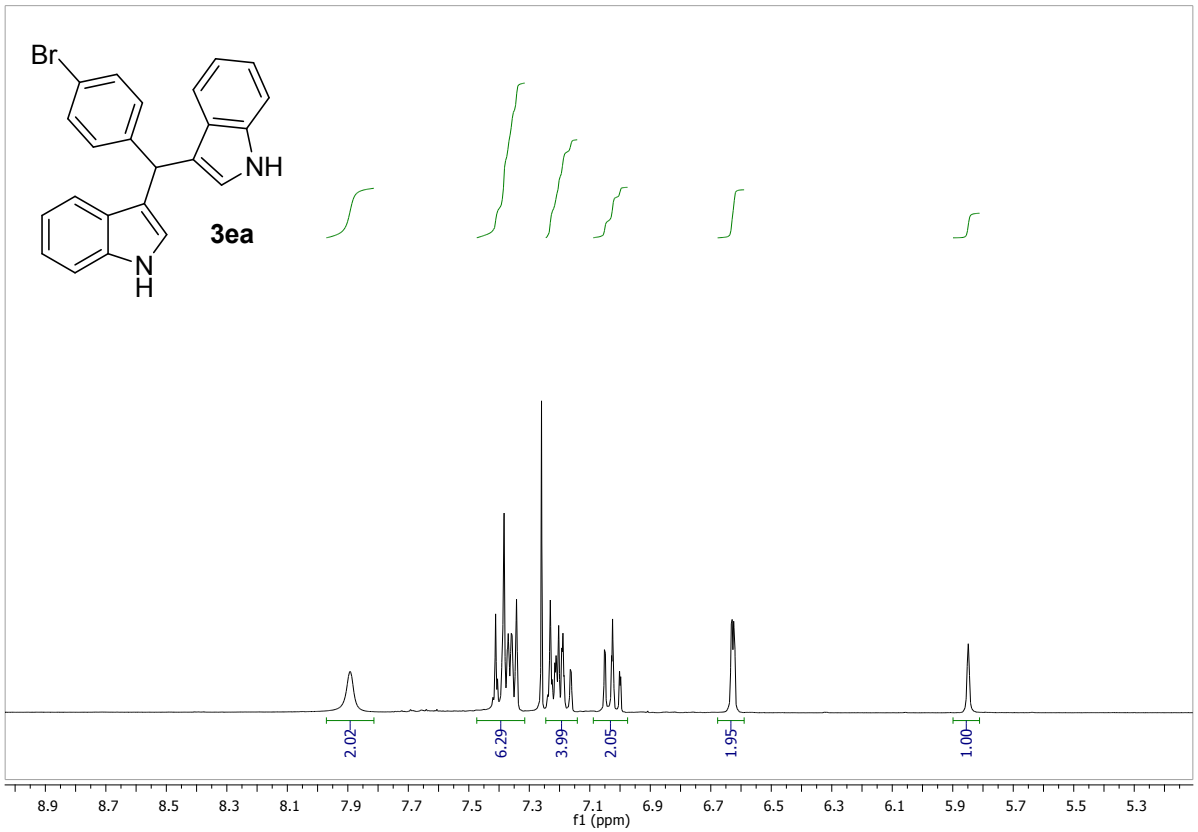


Figure S10. ^{1}H-NMR (CD_3COCD_3, 400 MHz) spectrum of 3,3'-((3-chlorophenyl)methylene)bis(1*H*-indole) (3fa)

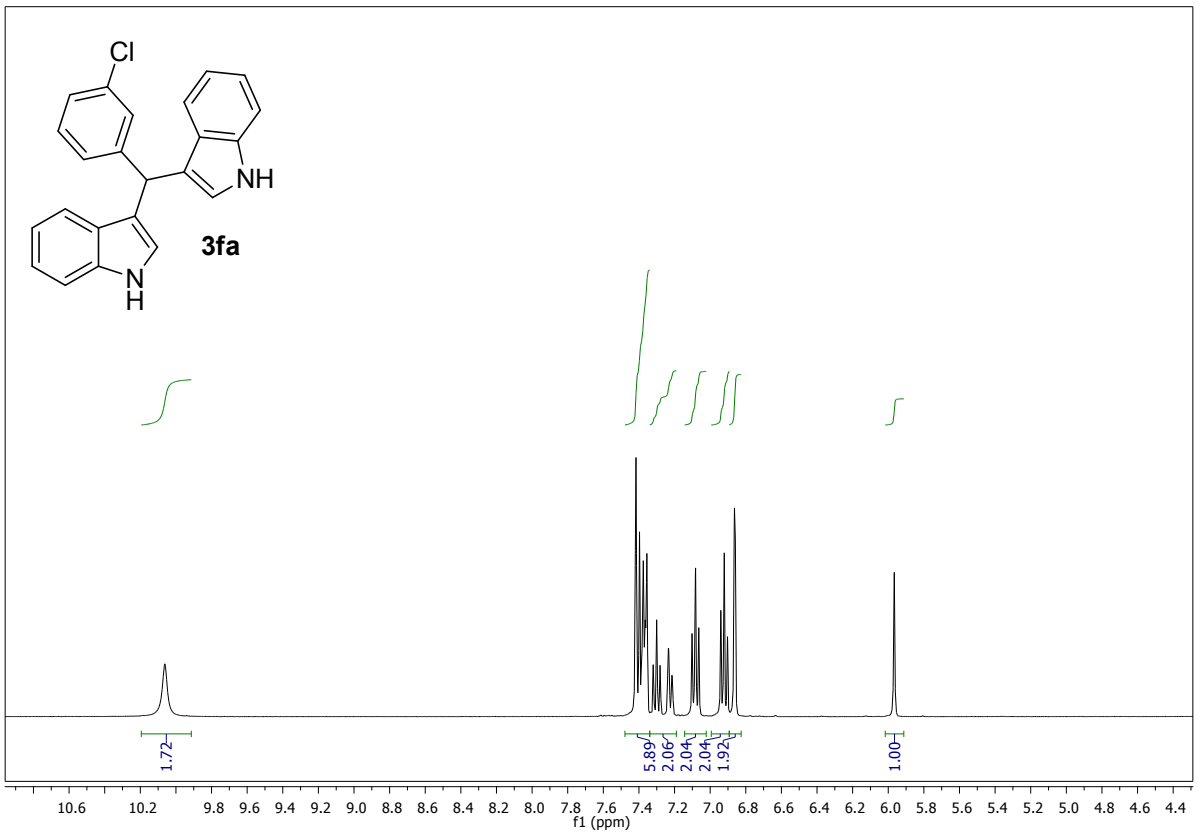
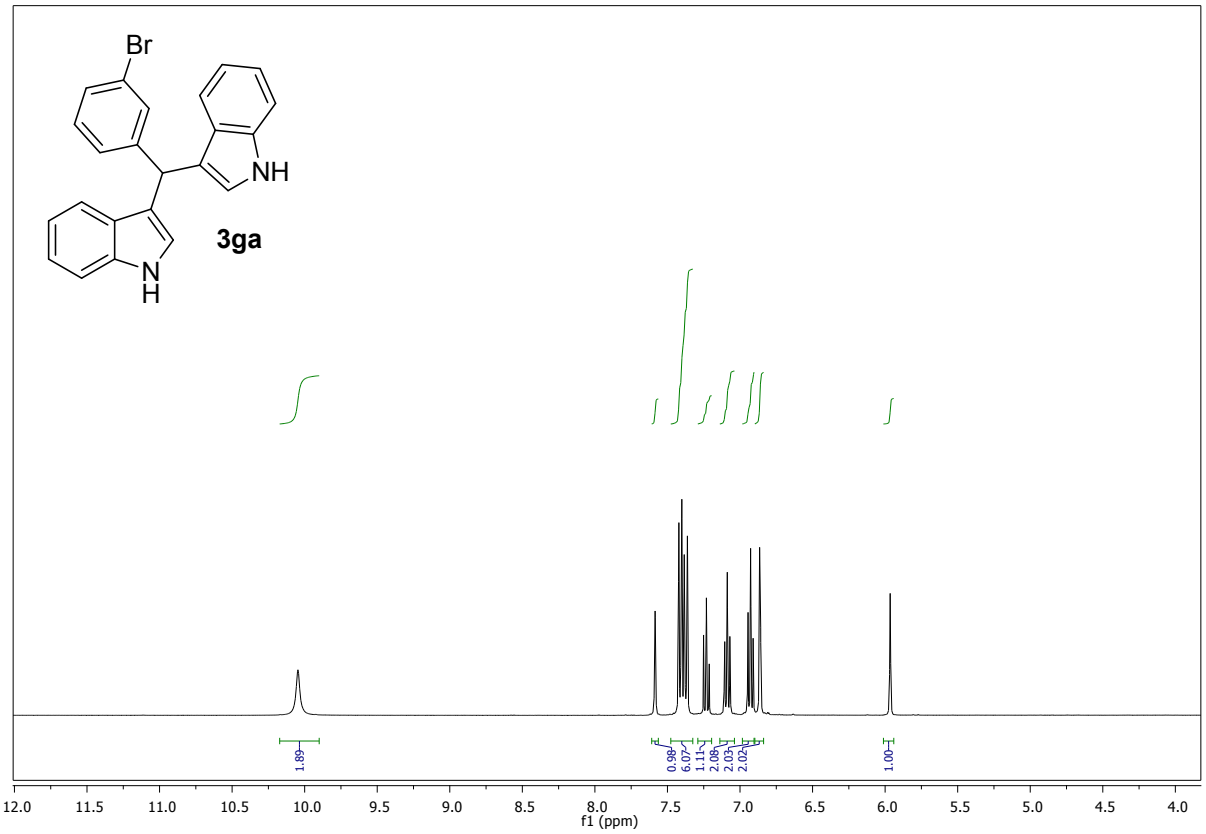


Figure S11. ^{1}H- and ^{13}C-APT NMR (CD_3COCD_3, 400 MHz) spectra of 3,3'-((3-bromophenyl)methylene)bis(1*H*-indole) (3ga)



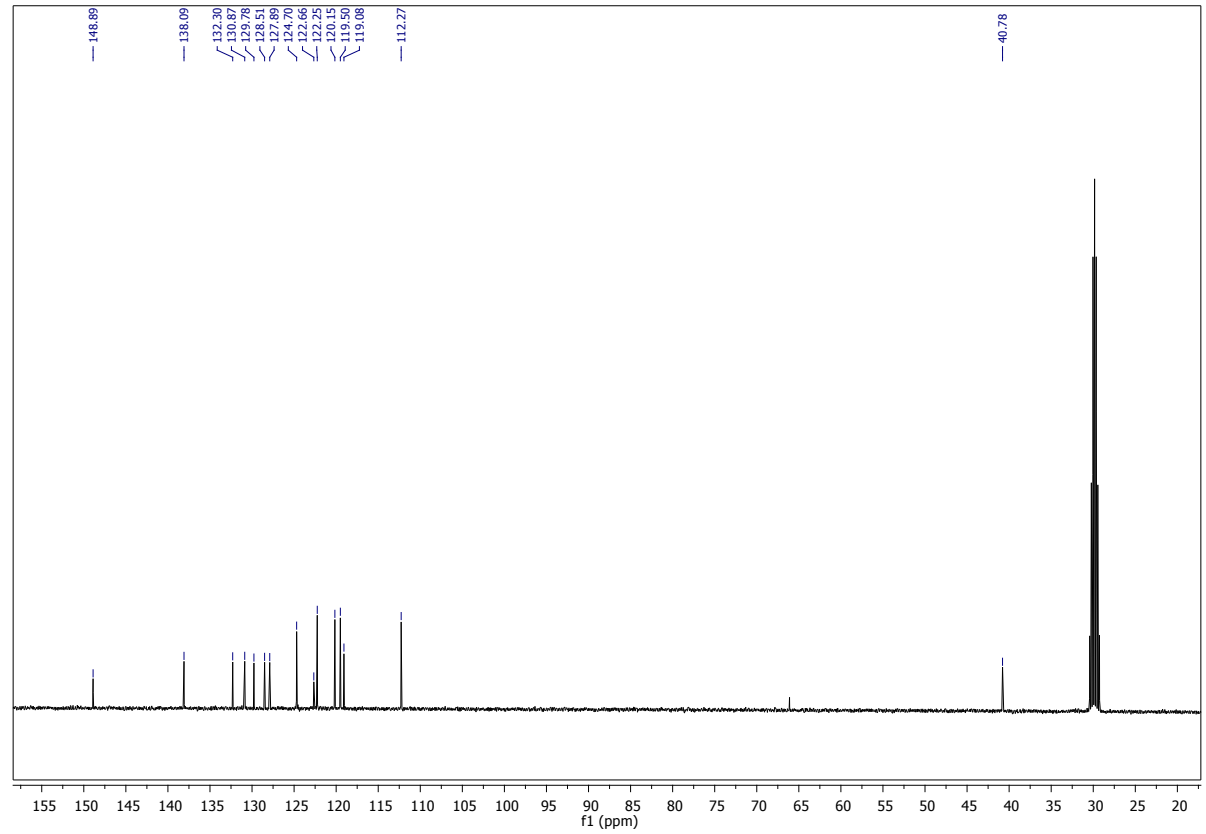


Figure S12. ^{1}H-NMR (CD_3COCD_3, 400 MHz) spectrum of 3,3'-(phenylmethylene)bis(*1H*-indole) (3ha)

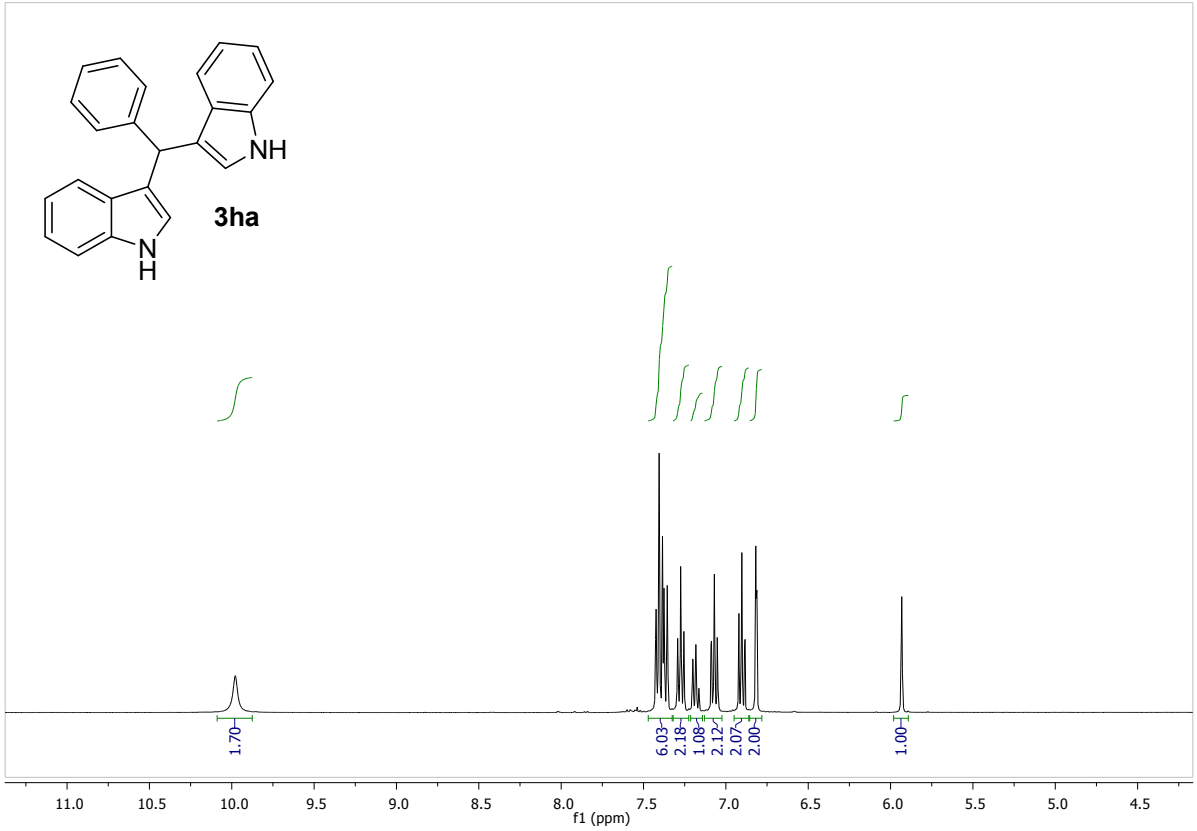


Figure S13. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 3,3'-(*p*-tolylmethylene)bis(1*H*-indole) (3ia)

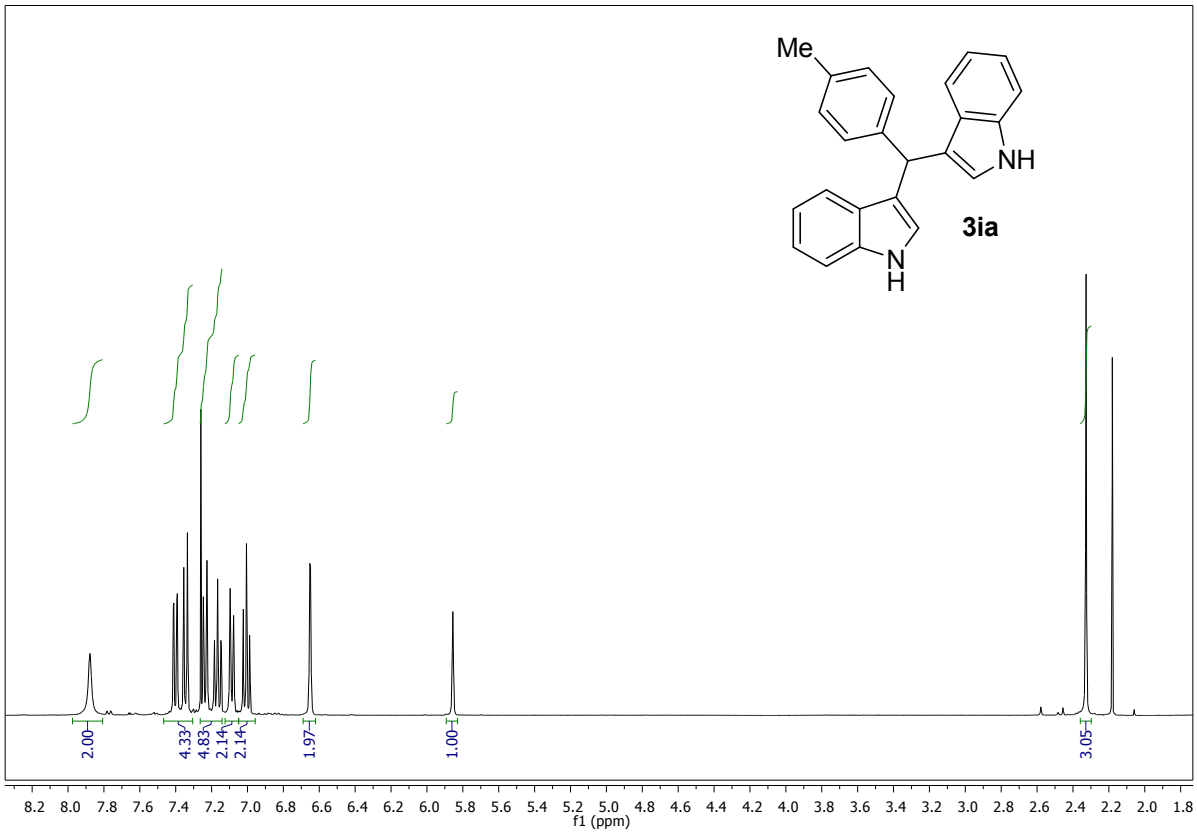
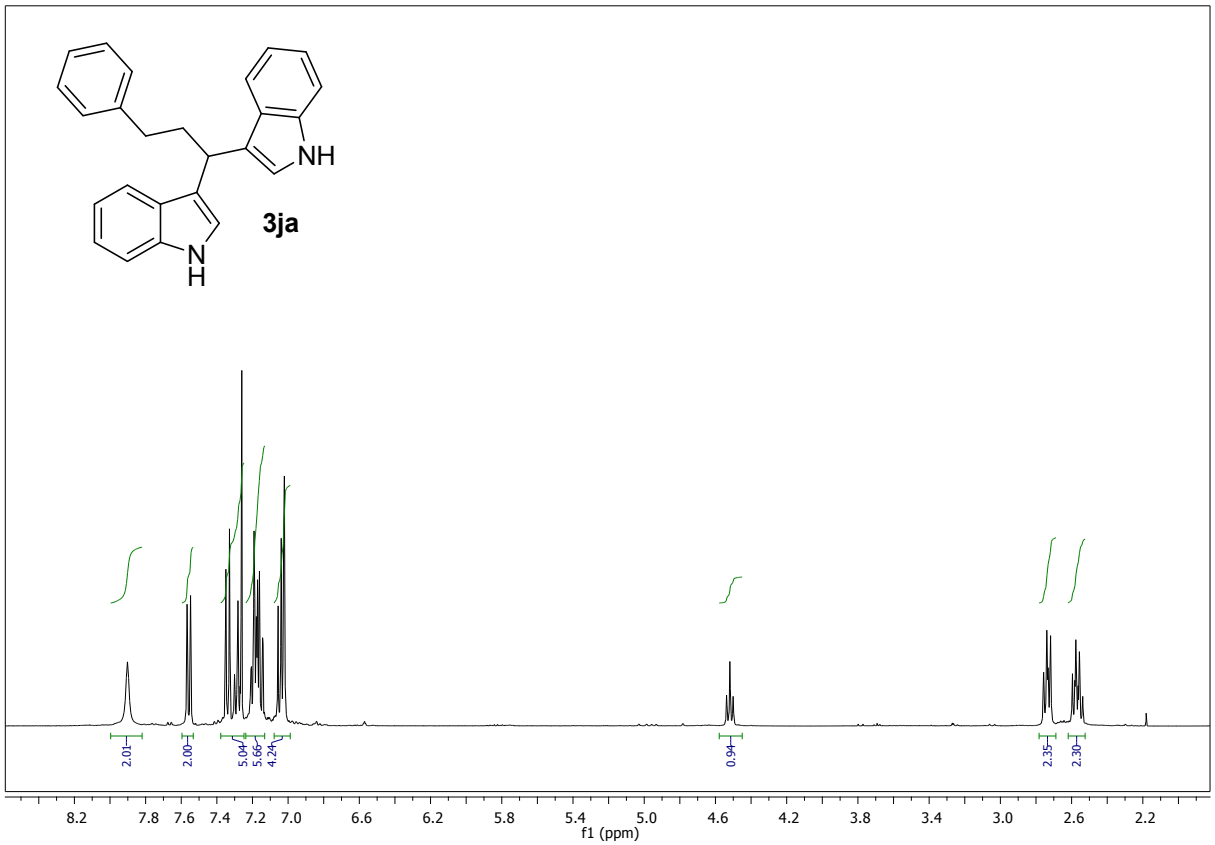


Figure S14. ^{1}H- and ^{13}C-APT NMR ($CDCl_3$, 400 MHz) spectra of 3,3'-(3-phenylpropane-1,1-diyl)bis(1*H*-indole) (3ja)



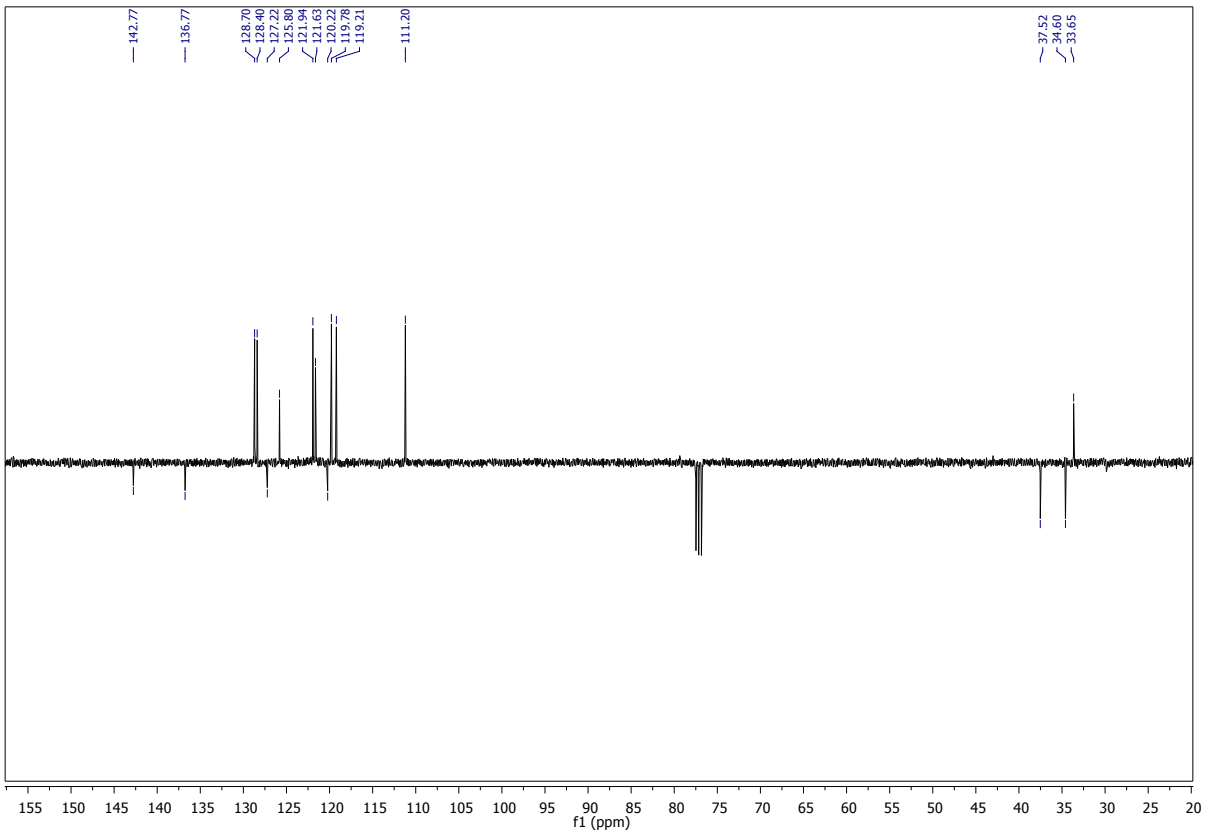


Figure S15. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 3,3'-(furan-2-ylmethylene)bis(1*H*-indole) (3ka)

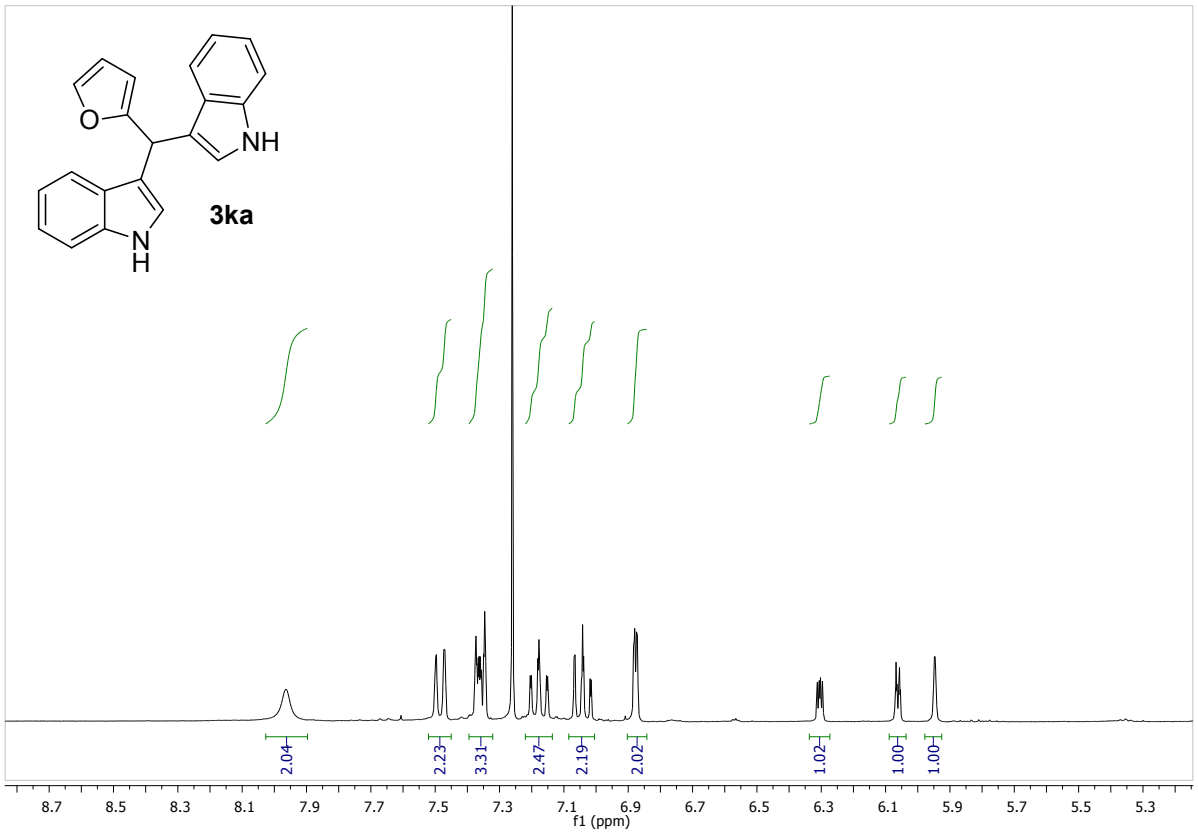


Figure S16. ^{1}H-NMR (CD_3COCD_3, 400 MHz) spectrum of 3,3'-(phenylmethylene)bis(2-methyl-1*H*-indole) (3hb)

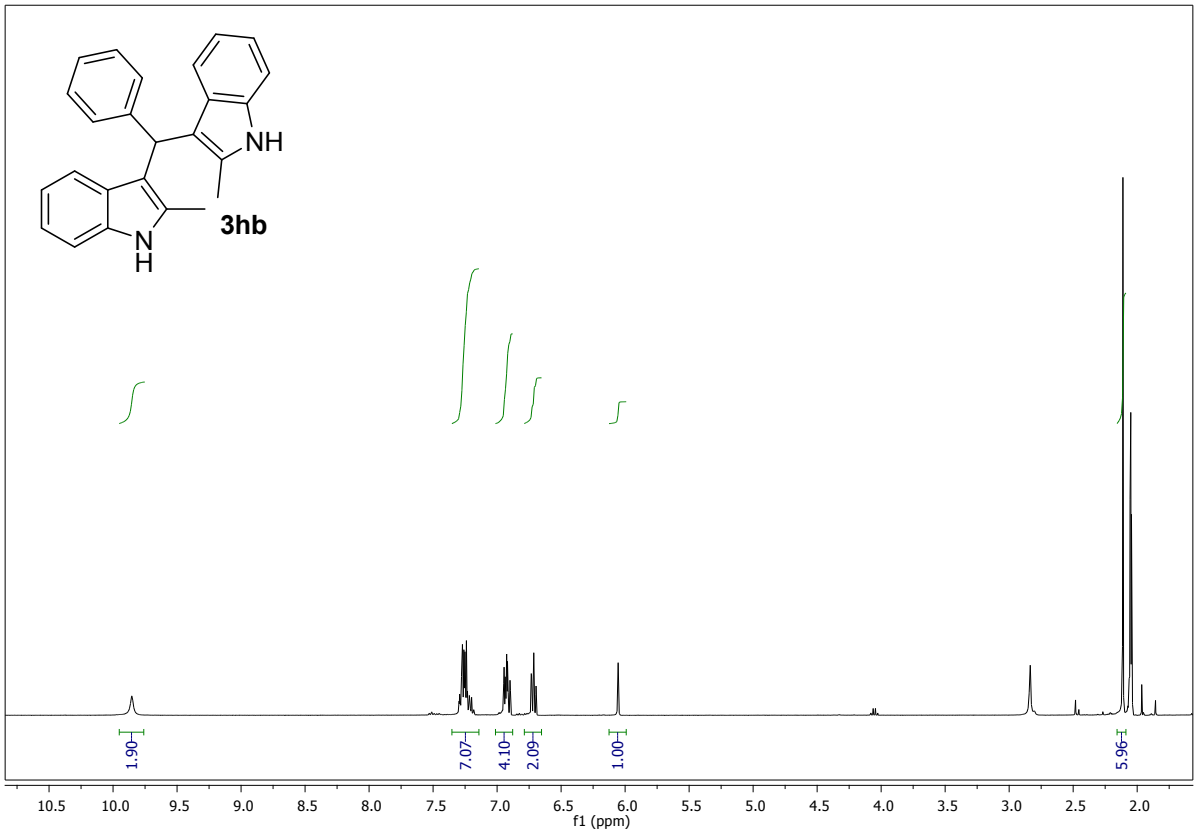


Figure S17. ^{1}H-NMR (CD_3COCD_3, 400 MHz) spectrum of 3,3'-(phenylmethylene)bis(5-methoxy-1*H*-indole) (3hc)

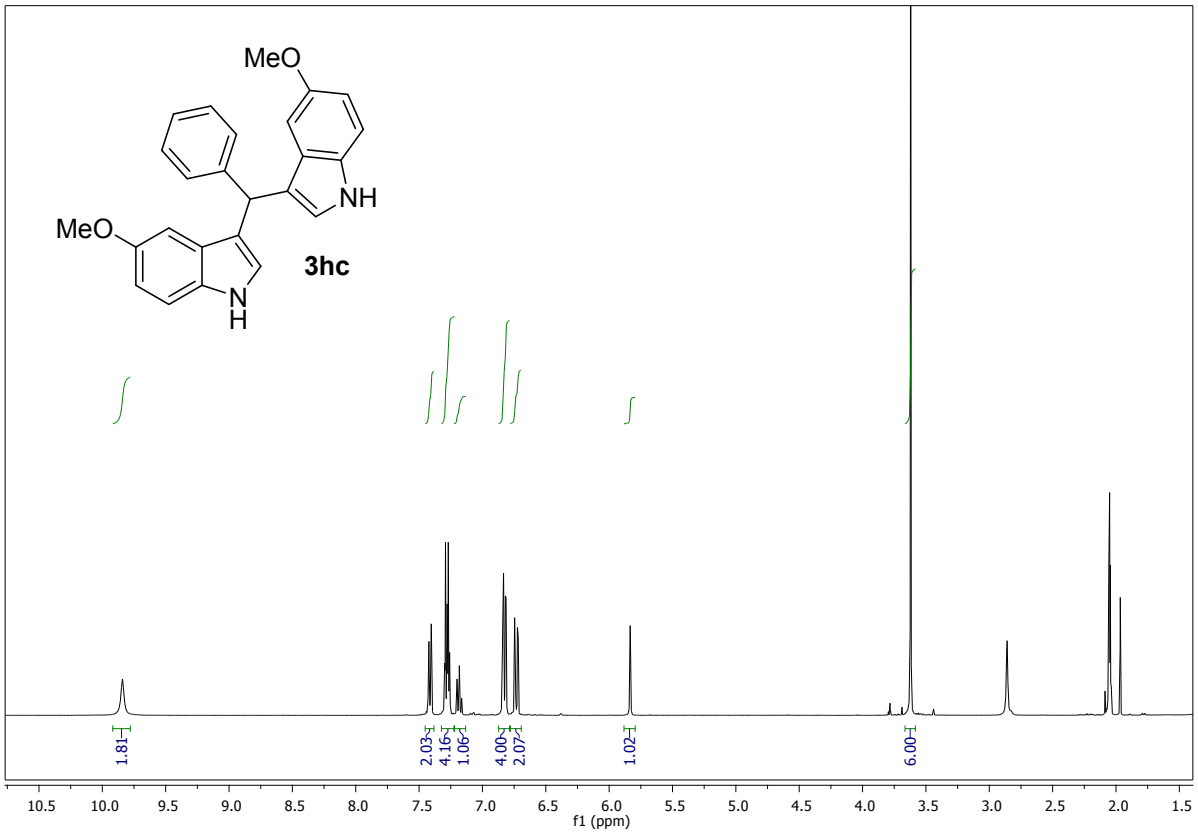


Figure S18. ^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of 3,3'-(phenylmethylene)bis(5-methoxy-1*H*-indole) (8)