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Supplementary Material for

Improved Synthesis of Symmetrically & Asymmetrically N-Substituted Pyridinophane Derivatives

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I. Synthesis Optimization for 7

Table S1: Optimization Trials for the Synthesis of **7** from 1 g of **4b**

Run	Variable	Ratio (7:8)[a]	Yield of 7 (%)[b]	Yield of 8 (%)[b]
1	Control	2.66:1	8.2	3.1
2	Time (add'l 2 days)	11.88:1	12.2	1.0
3	Heat (120°C)	0:2.9	0	2.9
4	Dilution (6-fold)	0:2.0	0	2.0

[a] **7**:**8** Product ratio were determined by NMR. [b] The yields are artificially low due to the small scale of reactions. Upon scale up, the yield typically increases to ~40%**.**

II. NMR Spectra

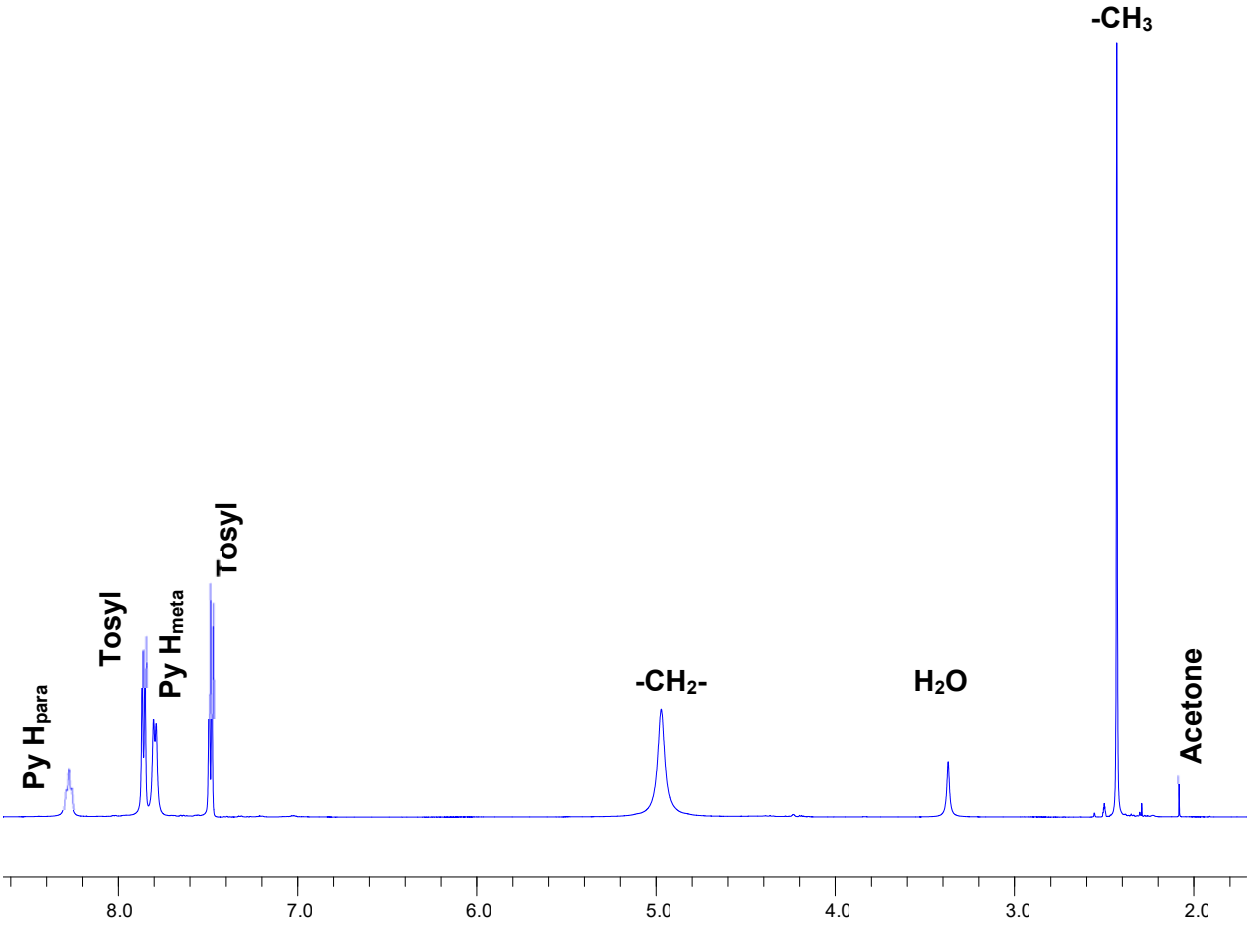

Figure S1. ^{1}H NMR spectrum of ^{Ts}N4·HCl (**7·HCl**) in DMSO-*d*$_6$.

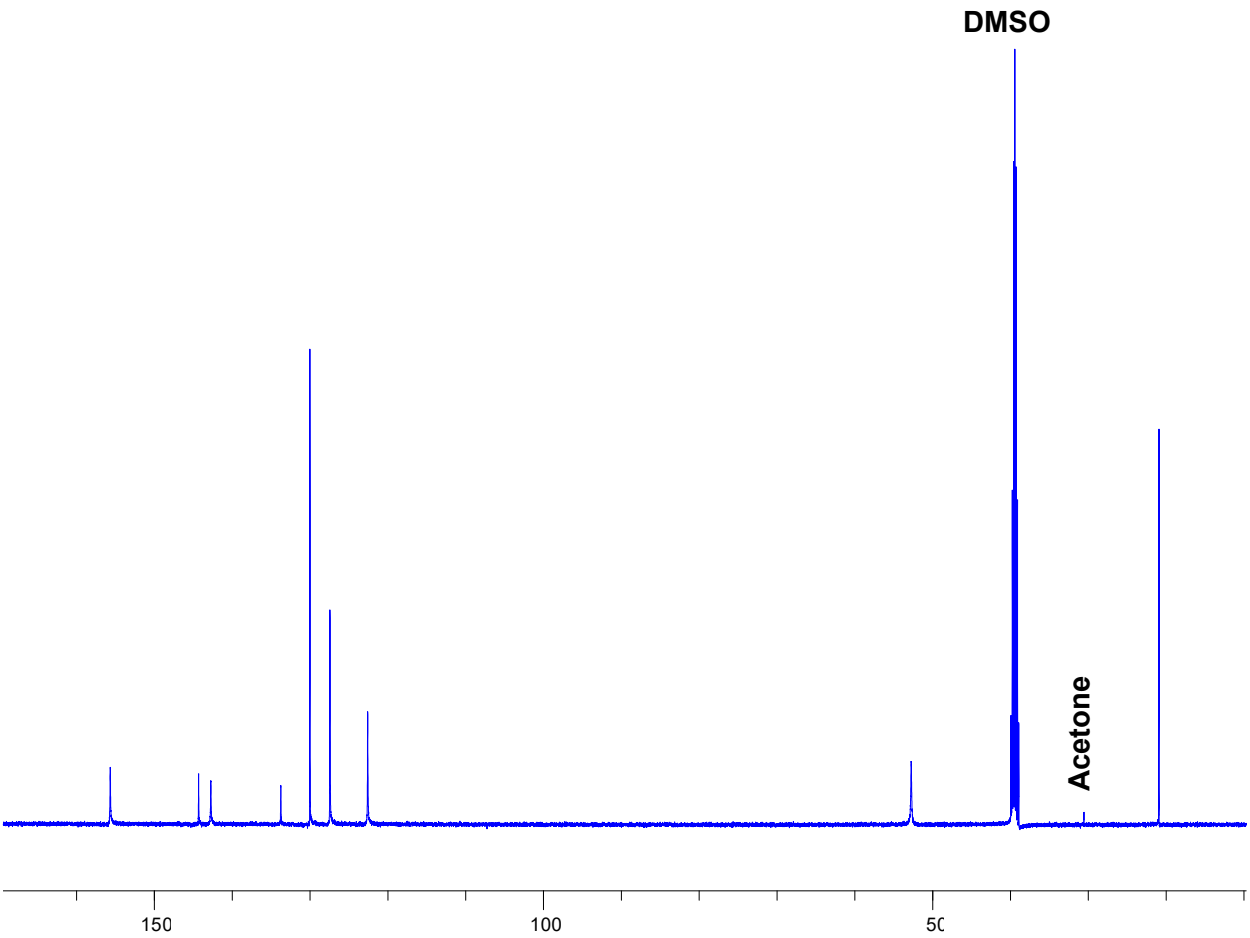

Figure S2. ^{13}C NMR spectrum of ^{Ts}N4·HCl (**7·HCl**) in DMSO-d_6.

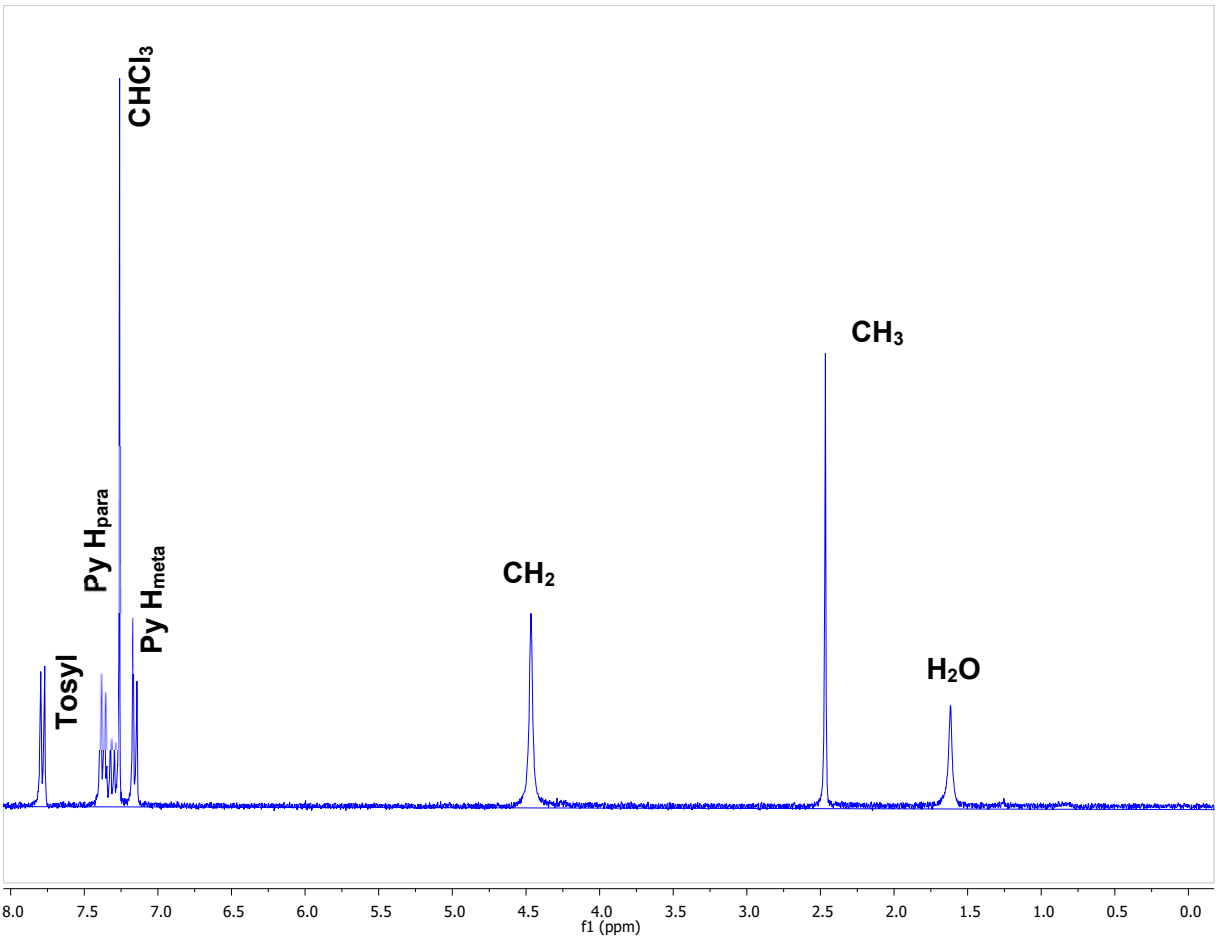

Figure S3. ^{1}H NMR spectrum of ^{Ts}N4 (**7**) in $CDCl_3$.

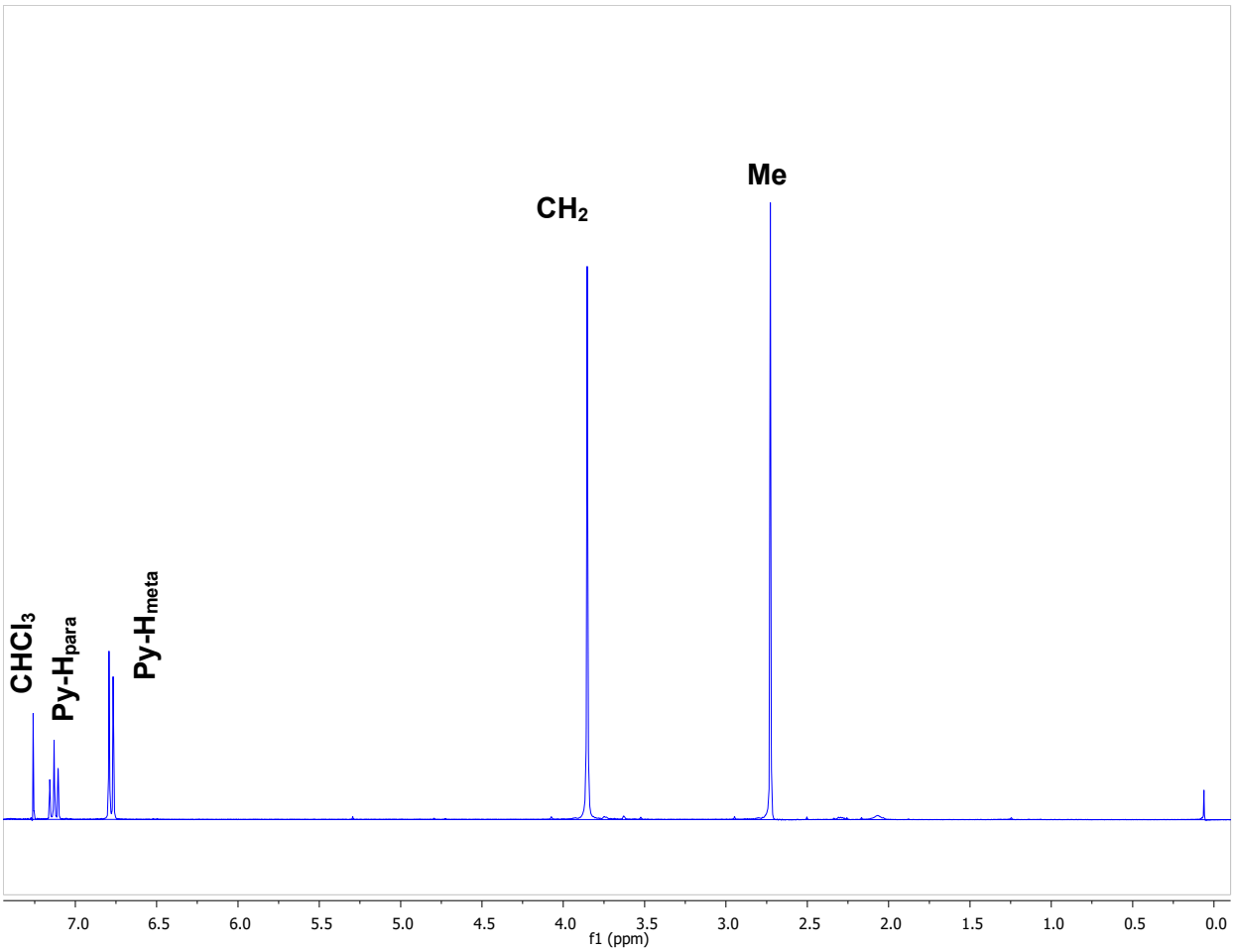

Figure S4. ^{1}H NMR spectrum of ^{Me}N4 (**10**) in $CDCl_3$.

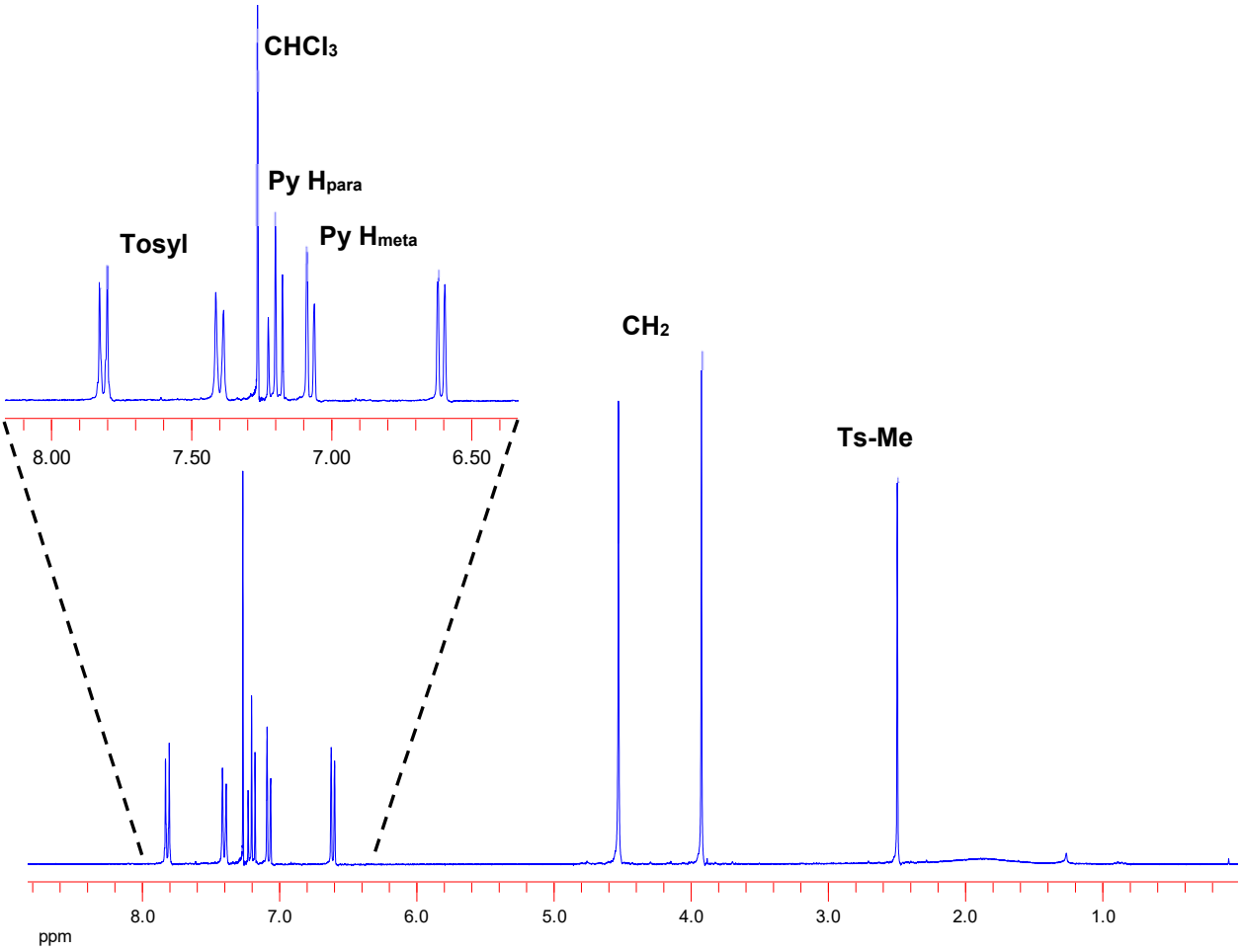

Figure S5. ^{1}H NMR spectrum of ^{TsH}N4 (**11**) in $CDCl_3$.

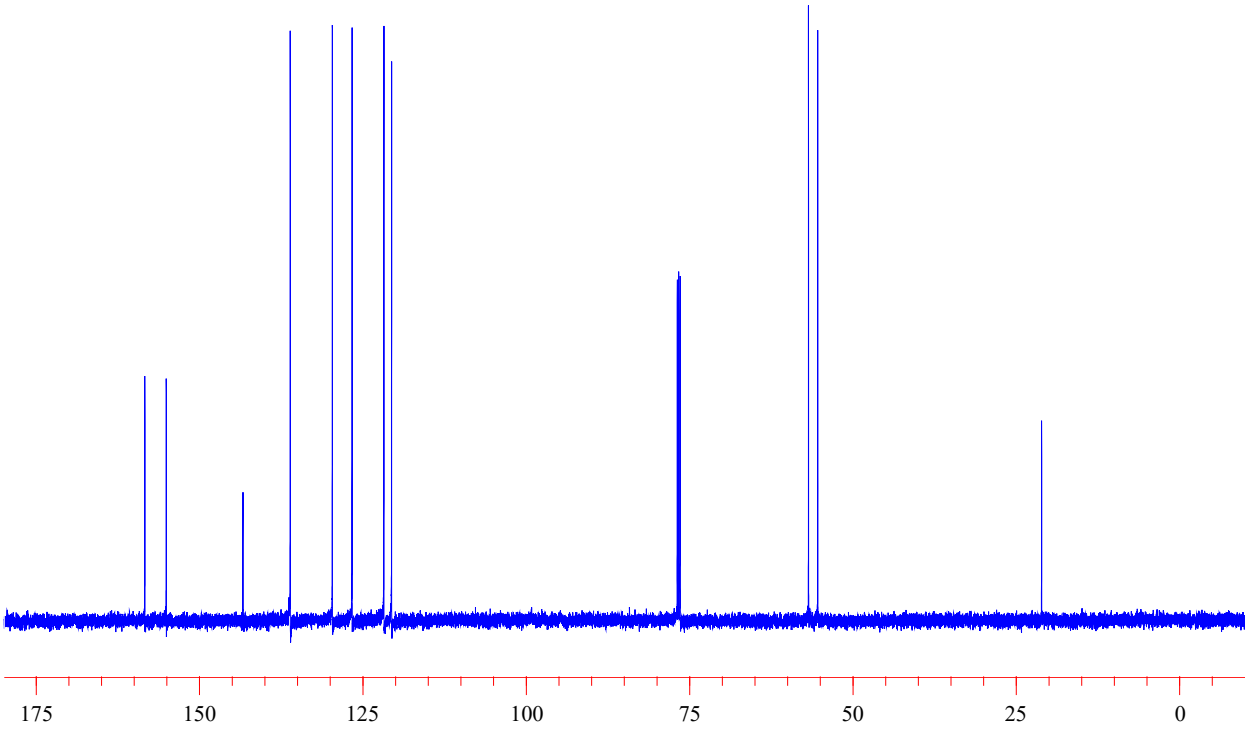

Figure S6. ^{13}C NMR spectrum of $^{TsH}N4$ (**11**) in $CDCl_3$.

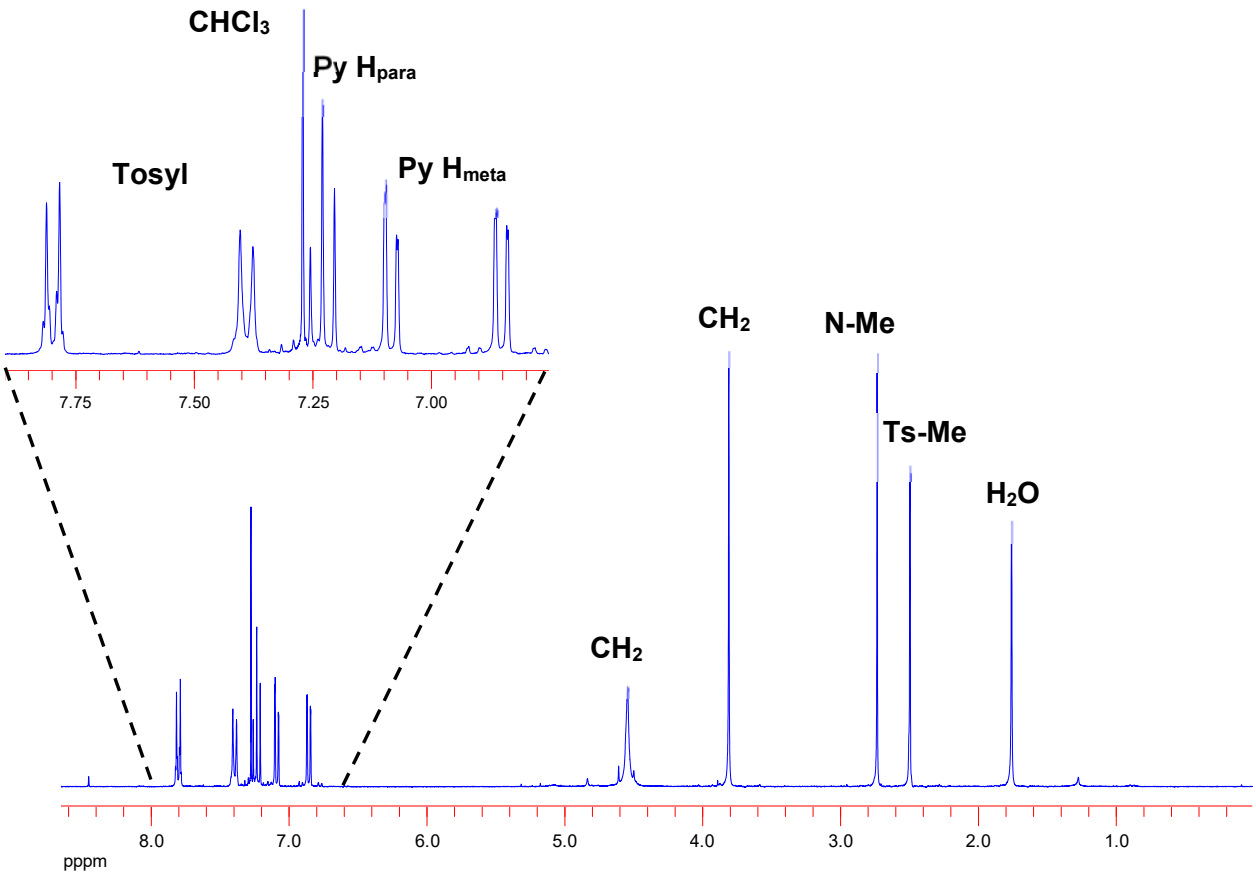

Figure S7. ^{1}H NMR spectrum of ^{TsMe}N4 (**12**) in $CDCl_3$.

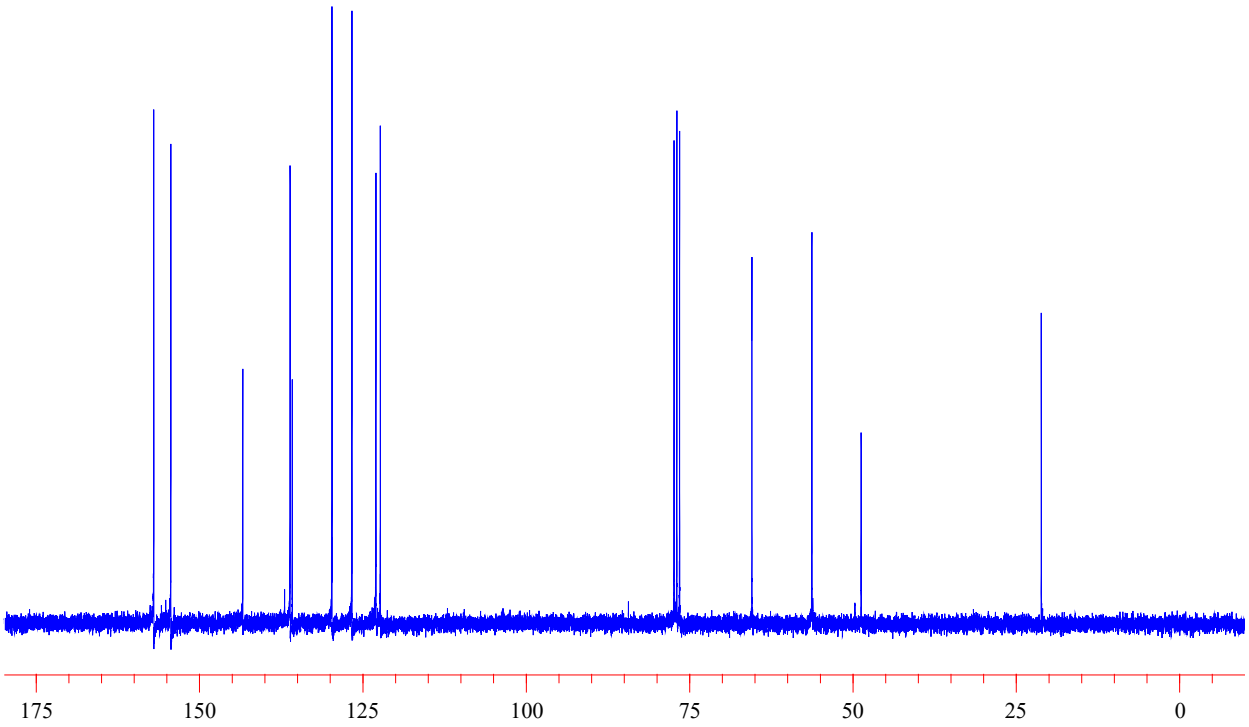

Figure S8. ^{13}C NMR spectrum of $^{TsMe}N4$ (**12**) in $CDCl_3$.

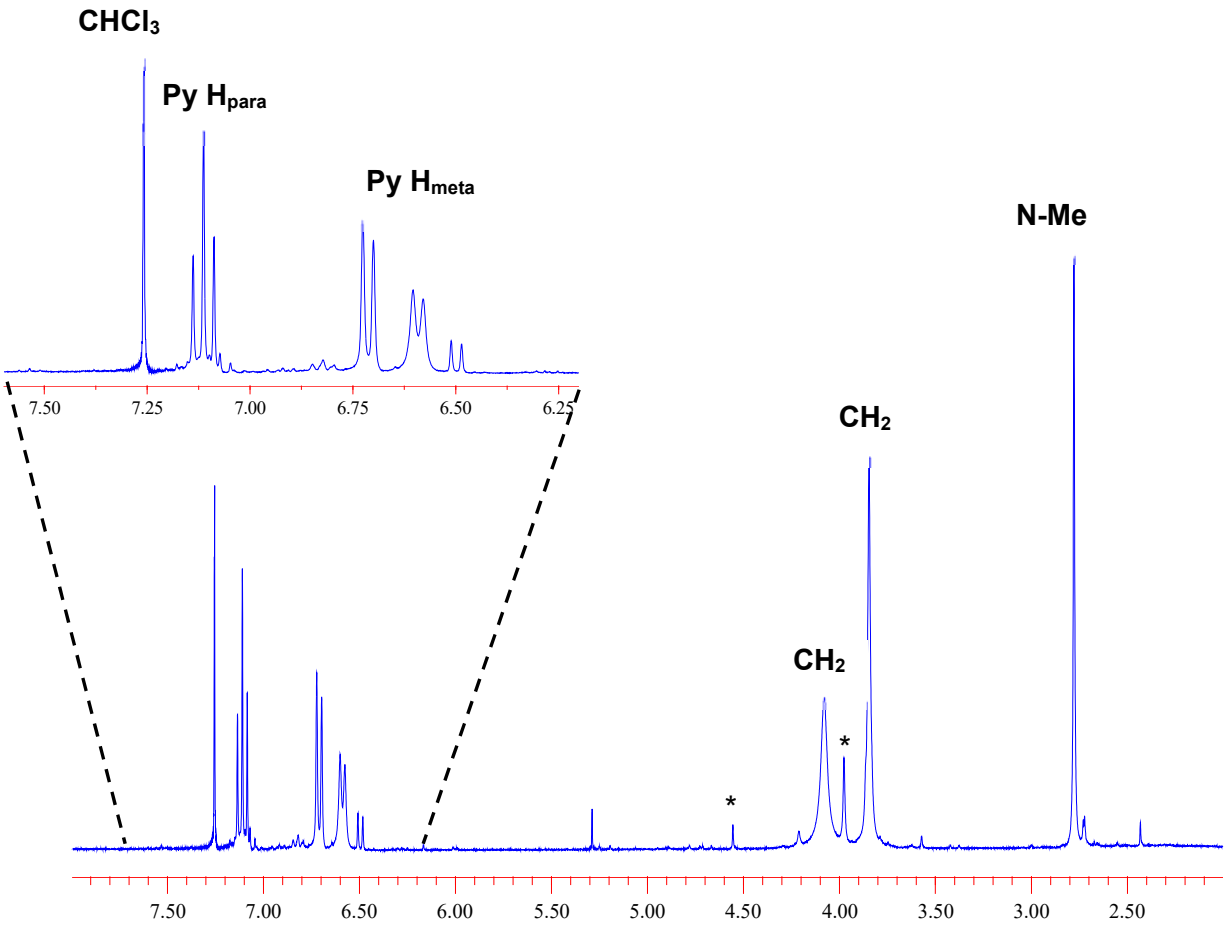

Figure S9. ^{1}H NMR spectrum of ^{MeH}N4 (**13**) in $CDCl_3$. * denotes a trace amount of unreacted ^{TsMe}N4.

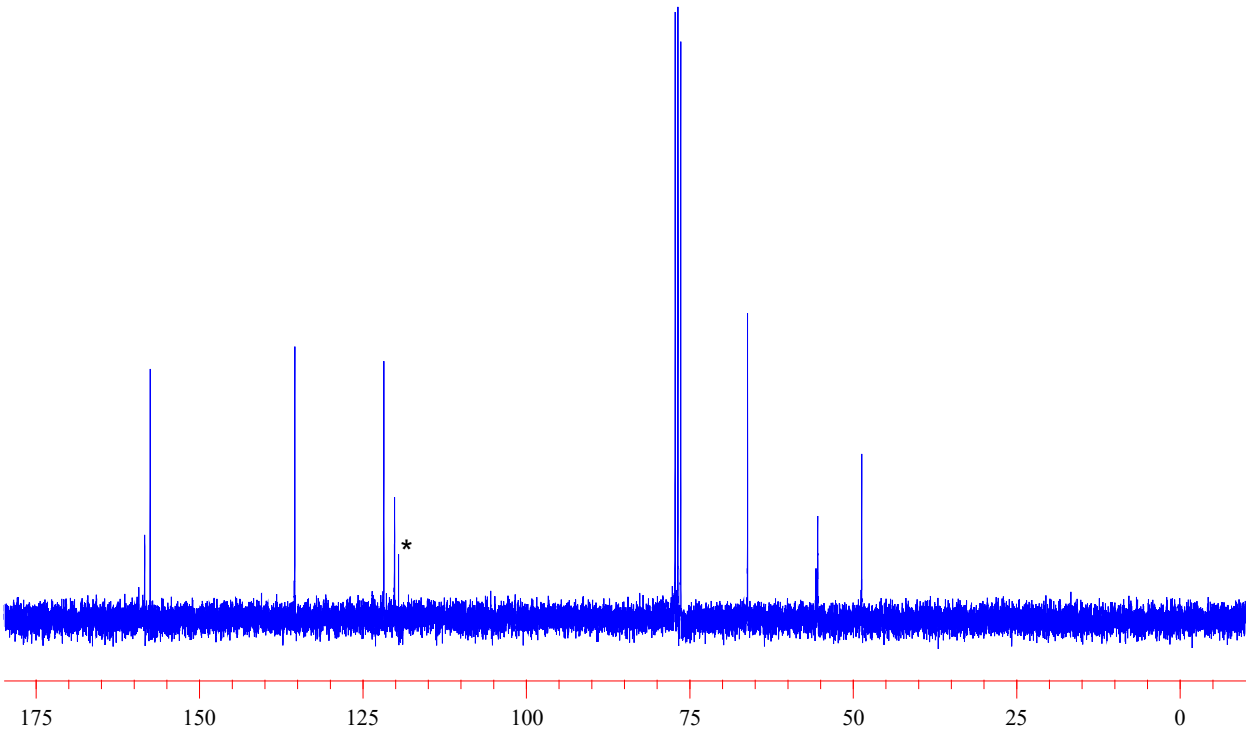

Figure S10. ^{13}C NMR spectrum of $^{MeH}N4$ (**13**) in $CDCl_3$. * denotes a trace amount of unreacted $^{TsMe}N4$.

III. X-ray structure determination

General information

Suitable crystals were mounted on MiTeGen cryoloops in random orientations in a Bruker Kappa Apex-II CCD X-ray diffractometer equipped with an Oxford Cryostream LT device and a fine focus Mo Kα radiation X-ray source (λ = 0.71073 Å). Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Typical data sets consist of combinations of ω and φ scan frames with a typical scan width of 0.5° and a counting time of 15−30 s/frame at a crystal-to-detector distance of 4.0 cm. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Apex II and SAINT software packages (Bruker Analytical X-Ray, Madison, WI, 2008) were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by global refinement of xyz centroids of reflections from the complete data sets. Collected data were corrected for systematic errors using SADABS (Bruker Analytical X-Ray, Madison, WI, 2008) based on the Laue symmetry using equivalent reflections. Crystal data and intensity data collection parameters are listed in Tables S2- 3. Structure solutions and refinement were carried out using the SHELXTL-PLUS software package. The structures were solved by direct methods and refined successfully in specified crystal systems and space groups. Full matrix least-squares refinements were carried out by minimizing $\Sigma w(Fo^2-Fc^2)^2$. The non-hydrogen atoms were refined anisotropically to convergence. Typically, the hydrogen atoms were treated using the appropriate riding model.

Table S2. Crystal data and structure refinement for ^{Ts}N4·HCl

Identification code	l12516t5/lt/x8/AJW-N4Ts2HCl	
Empirical formula	C_{28} H_{29} Cl N_4 O_4 S_2	
Formula weight	585.12	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P $\bar{1}$	
Unit cell dimensions	a = 7.7992(3) Å	α= 90.026(2)°.
	b = 9.5520(4) Å	β= 112.7594(17)°.
	c = 9.6675(4) Å	γ = 93.5164(16)°.
Volume	662.65(5) Å^3	
Z	1	
Density (calculated)	1.466 Mg/m^3	
Absorption coefficient	0.346 mm^{-1}	
F(000)	306	
Crystal size	0.439 x 0.251 x 0.218 mm^3	
Theta range for data collection	2.137 to 40.410°.	
Index ranges	-14≤h≤14, -17≤k≤17, -17≤l≤17	
Reflections collected	30030	
Independent reflections	30030 [R(int) = 0.0274]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.862764 and 0.803156	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	30030 / 0 / 184	
Goodness-of-fit on F^2	1.227	
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.1312	
R indices (all data)	R1 = 0.0651, wR2 = 0.1343	
Largest diff. peak and hole	1.164 and -0.792 e.Å^{-3}	

Table S3. Bond lengths [Å] and angles [°]

S(1)-O(2)	1.4312(12)	C(14)-H(14B)	0.9800
S(1)-O(1)	1.4319(13)	C(14)-H(14C)	0.9800
S(1)-N(2)	1.6314(14)		
S(1)-C(8)	1.7545(14)	O(2)-S(1)-O(1)	120.90(8)
N(1)-C(1)	1.3427(19)	O(2)-S(1)-N(2)	106.01(7)
N(1)-C(5)	1.3518(19)	O(1)-S(1)-N(2)	105.87(7)
N(1)-H(1)	**0.82(4)**	O(2)-S(1)-C(8)	107.71(7)
N(2)-C(7)	1.4625(19)	O(1)-S(1)-C(8)	108.09(7)
N(2)-C(6)	1.472(2)	N(2)-S(1)-C(8)	107.62(7)
C(1)-C(2)	1.387(2)	C(1)-N(1)-C(5)	120.56(14)
C(1)-C(7)#1	1.510(2)	C(1)-N(1)-H(1)	124(3)
C(2)-C(3)	1.384(2)	C(5)-N(1)-H(1)	115(3)
C(2)-H(2)	0.9500	C(7)-N(2)-C(6)	119.33(13)
C(3)-C(4)	1.389(2)	C(7)-N(2)-S(1)	117.27(11)
C(3)-H(3)	0.9500	C(6)-N(2)-S(1)	117.78(10)
C(4)-C(5)	1.375(2)	N(1)-C(1)-C(2)	120.95(14)
C(4)-H(4)	0.9500	N(1)-C(1)-C(7)#1	118.86(13)
C(5)-C(6)	1.507(2)	C(2)-C(1)-C(7)#1	120.18(13)
C(6)-H(6A)	0.9900	C(3)-C(2)-C(1)	118.75(15)
C(6)-H(6B)	0.9900	C(3)-C(2)-H(2)	120.6
C(7)-C(1)#1	1.510(2)	C(1)-C(2)-H(2)	120.6
C(7)-H(7A)	0.9900	C(2)-C(3)-C(4)	119.84(16)
C(7)-H(7B)	0.9900	C(2)-C(3)-H(3)	120.1
C(8)-C(9)	1.390(2)	C(4)-C(3)-H(3)	120.1
C(8)-C(13)	1.393(2)	C(5)-C(4)-C(3)	118.94(15)
C(9)-C(10)	1.388(2)	C(5)-C(4)-H(4)	120.5
C(9)-H(9)	0.9500	C(3)-C(4)-H(4)	120.5
C(10)-C(11)	1.397(2)	N(1)-C(5)-C(4)	120.93(14)
C(10)-H(10)	0.9500	N(1)-C(5)-C(6)	116.73(14)
C(11)-C(12)	1.390(2)	C(4)-C(5)-C(6)	122.30(14)
C(11)-C(14)	1.501(2)	N(2)-C(6)-C(5)	112.31(13)
C(12)-C(13)	1.389(2)	N(2)-C(6)-H(6A)	109.1
C(12)-H(12)	0.9500	C(5)-C(6)-H(6A)	109.1
C(13)-H(13)	0.9500	N(2)-C(6)-H(6B)	109.1
C(14)-H(14A)	0.9800	C(5)-C(6)-H(6B)	109.1
		H(6A)-C(6)-H(6B)	107.9

N(2)-C(7)-C(1)#1	113.51(12)
N(2)-C(7)-H(7A)	108.9
C(1)#1-C(7)-H(7A)	108.9
N(2)-C(7)-H(7B)	108.9
C(1)#1-C(7)-H(7B)	108.9
H(7A)-C(7)-H(7B)	107.7
C(9)-C(8)-C(13)	121.14(13)
C(9)-C(8)-S(1)	118.80(11)
C(13)-C(8)-S(1)	120.06(11)
C(10)-C(9)-C(8)	119.48(14)
C(10)-C(9)-H(9)	120.3
C(8)-C(9)-H(9)	120.3
C(9)-C(10)-C(11)	120.50(15)
C(9)-C(10)-H(10)	119.8
C(11)-C(10)-H(10)	119.8
C(12)-C(11)-C(10)	118.84(13)
C(12)-C(11)-C(14)	120.73(16)
C(10)-C(11)-C(14)	120.41(16)
C(13)-C(12)-C(11)	121.67(15)
C(13)-C(12)-H(12)	119.2
C(11)-C(12)-H(12)	119.2
C(12)-C(13)-C(8)	118.37(15)
C(12)-C(13)-H(13)	120.8
C(8)-C(13)-H(13)	120.8
C(11)-C(14)-H(14A)	109.5
C(11)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(11)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+2,-z+1

Figure S11. Projection view with 50% probability ellipsoids: