Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2014

Electronic Supporting Information for

Metal controlled regioselectivity in the cyclometallation of 2-(1-naphthyl)-pyridine

Mikhail Kondrashov, Sudarkodi Raman and Ola F. Wendt*

Centre for Analysis and Synthesis, Department of Chemistry,

PO Box 124, 22100 Lund, Sweden.

Ph: +46-46-2228153. E-mail: ola.wendt@chem.lu.se

Contents

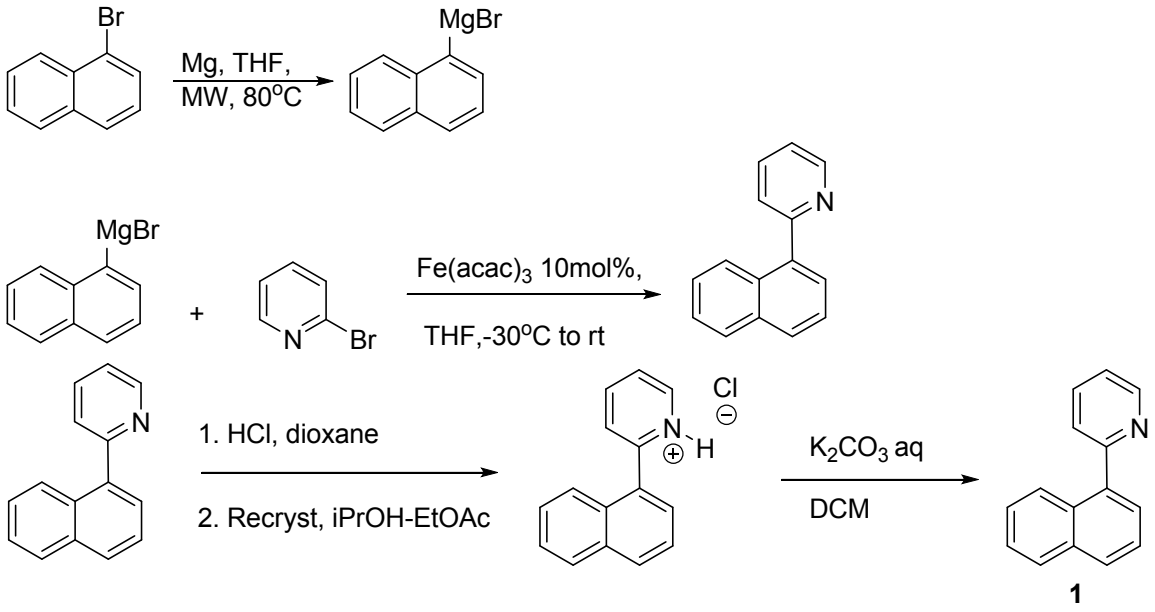
Experimental procedures

General

All manipulations were conducted under ambient conditions, unless noted. Solvents and chemicals were purchased from commercial suppliers and used as received. NMR spectra were acquired on a Bruker Avance 400 FT-NMR spectrometer (^{1}H: 400.1 MHz) or a Varian Unity INOVA 500 spectrometer (^{1}H: 499.76 MHz). For ^{1}H and ^{13}C NMR spectra the residual solvent peak was used as an internal reference. Elemental analyses were performed by H. Kolbe Microanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Microwave experiments were performed on Biotage Initiator 2.5 microwave synthesizer with automatic power adjustment using "high absorption" setting.

Synthesis of 1

2-(1-Naphthyl)-pyridine was synthesised according to a modified literature procedure as shown below:[1]



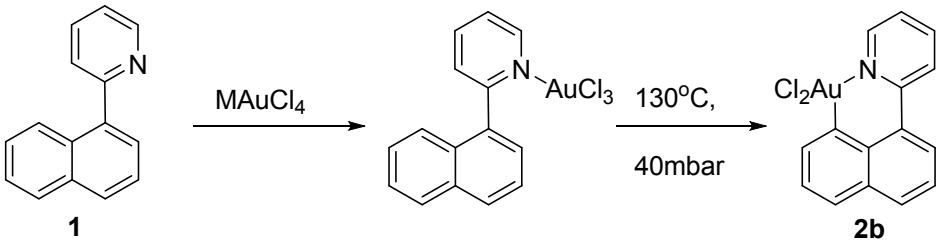
Preparation of the Grignard reagent. Mg turnings (422 mg, 17.6 mmol, 1.1 eq) were placed in a 20 ml microwave vial. The vial was sealed, evacuated and refilled with nitrogen. Dry THF (14 ml) was added via syringe followed by 1-bromonaphthalene (3.313 g, 16 mmol, 1 eq). The vial was subjected to quick heating to 60°C under MW conditions followed by immediate cooling. After the heat evolution stopped the reaction was heated under MW conditions at 80°C for 20 min. The resulting 1M solution of 1-naphthylmagnesium bromide was used immediately after preparation.

Coupling procedure. 2-Bromopyridine (1.264g, 8.0 mmol) and iron(III) acetylacetonate (280mg, 0.8 mmol, 0.1 eq) were dissolved in dry THF (60 ml) under Schlenk conditions and the solution was cooled down to -30°C. The solution of naphthylmagnesium bromide (1M, 16 ml, 2 eq) was added dropwise at -30°C. Then, the reaction mixture was allowed to warm up to room temperature overnight, quenched with brine and aqueous NaOH and extracted with diethyl ether (3x20ml). The organic fraction was extracted with 2M HCl (3x10 ml) and the new aqueous phase was washed with DCM, then an excess NaOH was added and the mixture was extracted with ether (3x10ml). The organic phase was dried over potassium carbonate, filtered through a pad of silica and evaporated to dryness to give the crude product as a yellow oil (1.440 g, 88%).

Further purification. Crude 2-(1-naphthyl)-pyridine was dissolved in EtOAc (15ml) and a solution of HCl (4M in dioxane, 4 ml) was added. The resulting precipitate was washed with EtOAc, dried under vacuum and recrystallised from a hot mixture of *i*-PrOH:EtOAc (1:1) to produce white crystals of 2-(1-naphthyl)-pyridine hydrogen chloride (1.354g, 70%), which can be stored indefinitely and quantitatively converted to the free-base **1** by treating with aqueous potassium carbonate, extraction with ether and drying over potassium carbonate. The spectral properties of the compound were identical to the published data.[2]

Synthesis of auracycle 2b

Method A



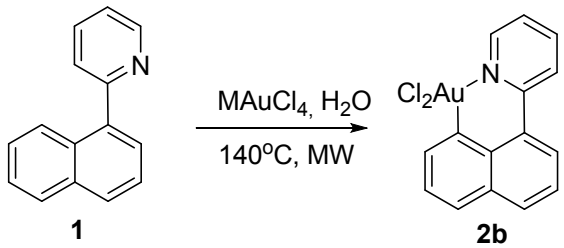
1 **2b**

2-(1-Naphthyl)-pyridine (91 mg, 0.44 mmol, 1 eq) was dissolved in acetonitrile (1 ml) and a solution of potassium or sodium or hydrogen tetrachloroaurate (0.48 mmol, 1.1 eq) in water (1 ml) was added. After one minute of stirring, a precipitate starts forming. The mixture was stirred for 3h, and the product was filtered, washed with water and dried under vacuum. The resulting brick-red powder of 2-(1-naphthyl)-pyridino gold trichloride (215 mg, 95%) was used without further purification. 2-(1-Naphthyl)-pyridino gold trichloride (32 mg, 63 μmol) was placed in a vial equipped with a

magnetic stirrer and a septa and heated with stirring at 135°C under a pressure of 40 mbar (house vacuum) for 30 h. The product was formed as a yellow powder (28 mg), which is almost pure by NMR spectroscopy, but contaminated with Au particles.

Purification of 2b. The crude product was dissolved in hot DMSO, and the solution was filtered through a pad of Celite and evaporated to ~10% volume under vacuum. Then an excess of DME was added; the precipitate formed was washed with DME and dried resulting in a light-yellow powder (25 mg, 84%).

Method B

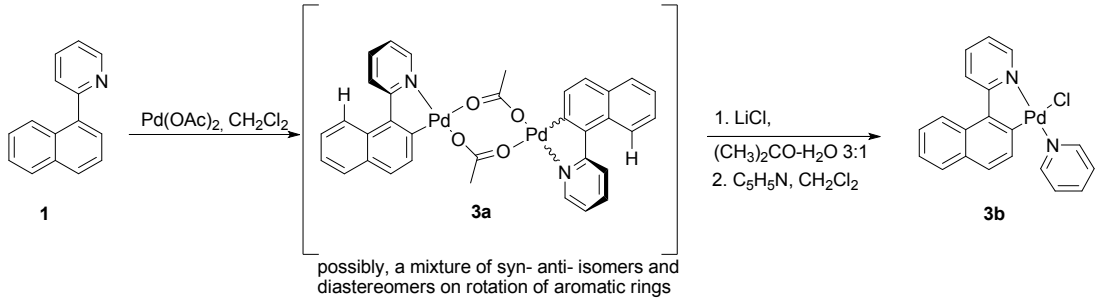


1 **2b**

2-(1-Naphthyl)-pyridine (30 mg, 0.15 mmol) and potassium or sodium or hydrogen tetrachloroaurate (0.17 mmol, 1.1 eq) were mixed in water (1 ml) in a 2 ml microwave vial. The vial was heated for 20 minutes at 140°C under microwave irradiation. The resulting light-yellow suspension was filtered, and the precipitate was washed with water, cold acetone and dried under vacuum. The crude product was subjected to purification identical to method A, resulting in 31 mg (45%) of the pure product. Single crystals suitable for X-ray analysis were obtained by slow crystallisation from DMSO.

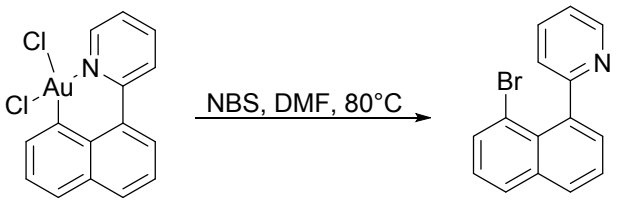
^{1}H NMR (DMSO-*d6*, 400MHz, δ, ppm): 9.51 (1H, dd *J*= 6.4 Hz 1.2Hz); 8.67 (1H, d *J* = 7.6Hz); 8.44-8.35 (2H, m); 8.27 (1H, d, *J* =8.0Hz); 7.98 (1H, d, *J* =8.0Hz); 7.83-7.75 (3H, m); 7.50 (1H, vt, *J* =4.0Hz). ^{13}C NMR (DMSO-*d6*, 125MHz, δ, ppm): 152.6, 148.6, 142.6, 133.7, 133.2, 133.0, 132.5, 132.2, 128.33, 128.27, 126.8, 126.4, 126.2, 125.0, 122.5. HR-MS ES^{+} (H_2O-CH_3CN): 493.9743, calculated for $C_{15}H_{10}NNaCl_2Au$ ([M+Na]$^{+}$) 493.9754. Elemental analysis, calculated for $C_{15}H_{10}NCl_2Au$: C, 38.16; H 2.13; N, 2.94; found C, 37.91; H 2.45; N, 3.05.

Synthesis of palladacycle 3b



2-(1-Naphthyl)-pyridine (45 mg, 0.22 mmol, 1.05 eq) was dissolved in CH_2Cl_2 (4ml). Palladium acetate (47mg, 0.21mmol) was added and the solution was stirred overnight at 40˚C. The resulting turbid, yellow solution was filtered through a pad of Celite and evaporated to dryness. The yellow solid formed was washed twice with Et_2O and dried. The product was dissolved in an acetone-water (3:1) mixture and LiCl (90 mg, 2.1 mmol, 10 eq) was added resulting in an immediate precipitation; water (2 ml) was added to precipitate the rest of the product. The precipitate of (2-(1-naphthalene)pyridine-$C^{2'},N$) palladium chloride dimer was filtered off, washed with water and dried to afford 65mg (85%) of a bright yellow powder. The product was suspended in CH_2Cl_2 (2 ml) and pyridine (15 µl, 0.19 mmol) was added to result in a yellow solution that was stirred for 10 min, filtered through a plug of Celite and evaporated to result in a bright orange solid. Vapour-exchange recrystallisation from CH_2Cl_2 - pentane afforded 54 mg (57%) of orange crystals. Single crystals suitable for X-ray analysis were obtained in a vapour exchange chamber with CH_2Cl_2 and Et_2O. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ ppm: 9.581 (2H, br d, J =4 Hz), 8.960 (1H, br d, J =5Hz), 8.448 (1H, d, J =9Hz), 8.217 (1H, d, J =8Hz), 7.957-7.858 (2H, m), 7.808 (1H, d, J =8Hz), 7.573-7.514 (3H, m), 7.445-7.413 (2H, m), 7.215 (1H, t, J =14 Hz), 6.440 (1H, d, J =8Hz); ^{13}C NMR (CD_2Cl_2) δ ppm: 168.1, 157.0, 153.2, 152.8, 139.6, 138.7, 138.3, 132.4, 130.2, 129.6, 129.3, 129.0, 127.2, 125.6, 124.3, 122.5, 122.2, 121.3. MS ES$^+$: 398.8 ([M-Cl+H]$^+$), 350.9 ([M-Cl-C_5H_5N+CH_3CN]$^+$), 309.9 ([M-Cl-C_5H_5N]$^+$). Elemental analysis, calculated for $C_{20}H_{15}ClN_2Pd$: C, 56.49; H 3.56; N, 6.59. Found: C, 56.35; H, 3.87; N, 6.34.

Synthesis of 2-(8-bromonaphth-1-yl)pyridine (4)



2b **4**

2b (10 mg, 21 µmol, 1 eq) was dissolved in dry DMF (1ml). NBS (20mg, 112 µmol, 5.4 eq) was added and the mixture was heated to 80°C for 1h. The resulting deep red solution was quenched with aqueous NaI, then $NaOH_{aq}$ was added until the pH reached ~13. The solution was extracted with DCM (3x0.5 ml), the organic phase was shaken with a drop of saturated solution of sodium thiosulfate, dried over potassium carbonate and evaporated to result in 7 mg of a brown oil, which was subjected to preparative TLC (DCM-Et_2O, 97:3, R_f=0.6). The product was washed off the silica with diethyl ether and evaporated to result in 4.5 mg (75%) of 2-(8-bromonaphth-1-yl)pyridine as a colourless oil.

^{1}H NMR ($CDCl_3$, 400MHz, δ, ppm): 8.72 (1H, d, *J* =4.8Hz), 7.97-7.91 (2H, m), 7.83-7.77 (2H, m), 7.58-7.56 (2H, m), 7.48 (1H, d, *J* =8.0Hz), 7.37-7.32 (2H, m). MS ES$^+$: 284, 286 ($[M+H]^+$).

To obtain an NMR-spectrum with a better resolution, the compound was transformed into the corresponding hydrogen chloride salt: 2-(8-Bromonapht-1-yl)pyridine was dissolved in Et_2O, an excess of HCl (4M in dioxane) was added and the solvents were removed under vacuum. The resulting oil was redissolved in isopropanol and an excess of diethyl ether was added. After 1h, the formed precipitate was decanted and dried under vacuum.

^{1}H NMR (CD_3OD, 400MHz, δ, ppm): 8.88 (1H, d *J* =5.6Hz), 8.69 (1H, vt *J* =8.0Hz), 8.30 (1H, d *J* =7.6Hz), 8.22 (1H, d *J* =8.0Hz) 8.19-8.14 (2H, m), 7.98 (1H, d *J* =7.6Hz), 7.80-7.74 (2H, m), 7.55 (1H, vt *J* =8.0Hz). ^{13}C NMR (CD_3OD, 125MHz, δ, ppm): 156.0, 147.3, 142.0, 137.5, 135.9, 134.4, 133.8, 131.2, 130.9, 130.2, 130.1, 128.9, 127.4, 126.7, 118.8.

Crystallography

Intensity data were collected at 293 K with an Oxford Diffraction Xcalibur 3 system using ω-scans and Mo-Kα (λ = 0.71073 Å). CCD data were extracted and integrated using Crysalis RED.[3] The structures were solved using direct methods and refined by full-matrix least-squares calculations on F^2 using SHELXTL 5.1.[4] Non-H atoms were refined with anisotropic displacement parameters. Hydrogen atoms were constrained to parent sites, using a riding model. CCDC deposition numbers 1023087-1023088.

Table S1. Crystal data collection and refinement details for compounds **2b** and **3b**.

	2b	**3b**
formula	$C_{15}H_{10}AuCl_2N$	$C_{20}H_{15}ClN_2Pd$
Fw	472.11	425.19
crystal system	triclinic	monoclinic
space group	P-1	$P2_1/c$
color	orange	yellow
a/Å	8.4554(2)	12.5530(7)
b/Å	8.8766(2)	15.1519(9)
c/Å	10.4398(3)	9.3199(5)
α/deg	70.370(2)	90
β/deg	89.106(2)	111.79(4)
γ/deg	65.222(3)	90
V/Å^3	662.86(3)	1645.99(16)
temperature, K	293	120
Z	2	4
D_{calcd}/g cm^{-3}	2.365	1.716
μ/mm^{-1}	11.482	1.292
θ/ range/deg	2.68-33.03	2.69- 27.00
no. reflns collected	6911	11927
no. of unique reflns	4396	3491
$R(F)$ (I>2σ(I))[a]	0.0254	0.0277
$wR2(F^2)$ (all data)[b]	0.0547	0.0671
S[c]	0.967	0.969
R_{int}	0.0221	0.0499

[a] $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. [b] $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(F_o^2)^2]^{1/2}$. [c] $S = [\Sigma w F_o^2 - F_c^2)^2/(n\text{-}p)]^{1/2}$.

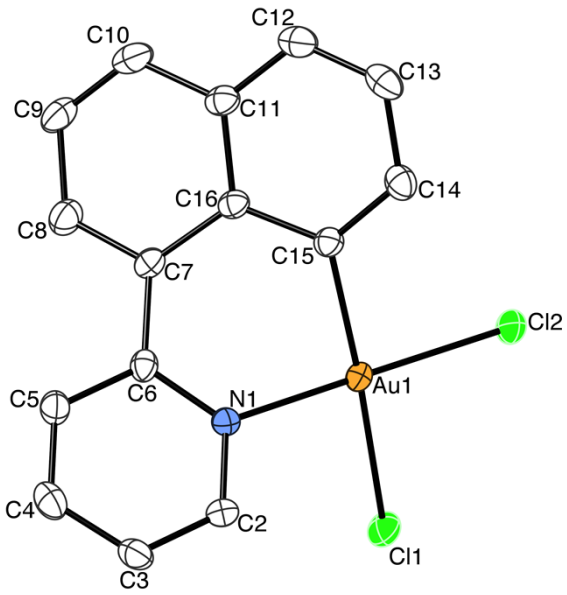


Figure S1. Molecular structure of **2b** at the 30% probability level.

Table S2. Selected distances (Å) and angles (°) in **2b**:

Au…N	2.024(3)	Cl(2)-Au-Cl(1)	89.76	Au-C(15)-C(16)-C(7)	23.97
Au…C(15)	2.024(3)	Cl(1)-Au-N	90.89	Au-C(15)- C(7)-C(6)	39.68
Au…Cl(2)	2.2771(9)	N-Au-C(15)	88.68	Au-C(15)-C(14)-H(14)	-17.23
Au…Cl(1)	2.3963(9)	C(15)-Au-Cl(2)	90.95	Cl(1)-Au-N-C(2)	46.96
C(6)…C(7)	1.458(5)	C(16)-C(7)-C(6)-N	-29.70		
Au…H(14)	3.056	C(15)-C(16)-C(7)-C(6)	21.44		

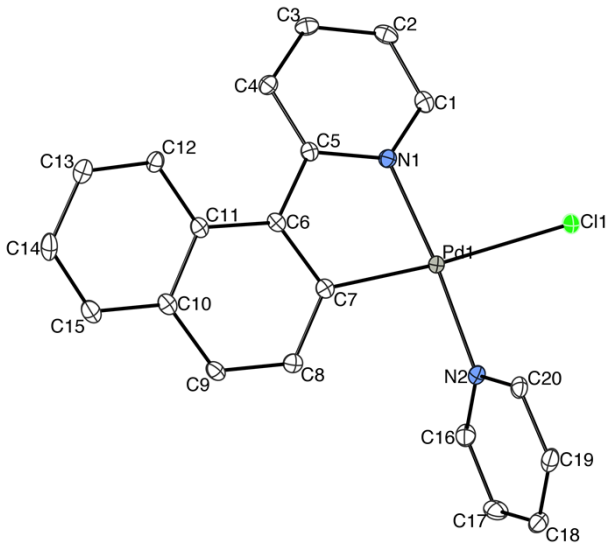


Figure S2. Molecular structure of **3b** at the 30% probability level. Hydrogen atoms are omitted for clarity.

Table S3. Selected distances (Å) and angles (°) in **3b**:

Pd…N(1)	2.017(2)	Cl-Pd-N(2)	88.95	C(5)-C(6)-C(7)-Pd	-16.29
Pd…N(2)	2.037(2)	N(2)-Pd-C(7)	94.53	C(5)-C(6)-C(11)-C(12)	21.99
Pd…Cl	2.4204(7)	N(1)-Pd-C(7)	81.03	C(5)-C(6)-C(12)-H(12)	16.54
Pd…C(7)	1.992(3)	N(1)-Pd-Cl	95.57	Pd-C(7)-C(8)-H(8)	3.42
C(5)…C(6)	1.473(4)	Cl-Pd-N(2)-C(20)	-69.69		
H(4)…H(12)	1.997	N(1)-C(5)-C(6)-C(7)	12.35		

Calculations

DFT calculations were performed using the program Spartan[5] with the B3LYP functional and the basis set 6-31G*, extended to LACVP for transition metal atoms. Initially, the non-metallated intermediate (2-(1-naphthyl)-pyridino gold trichloride) was optimized as anti-rotamer (Figures 3 and 4) where the gold atom is closer to the C1-carbon atom (leading to γ-substitution).

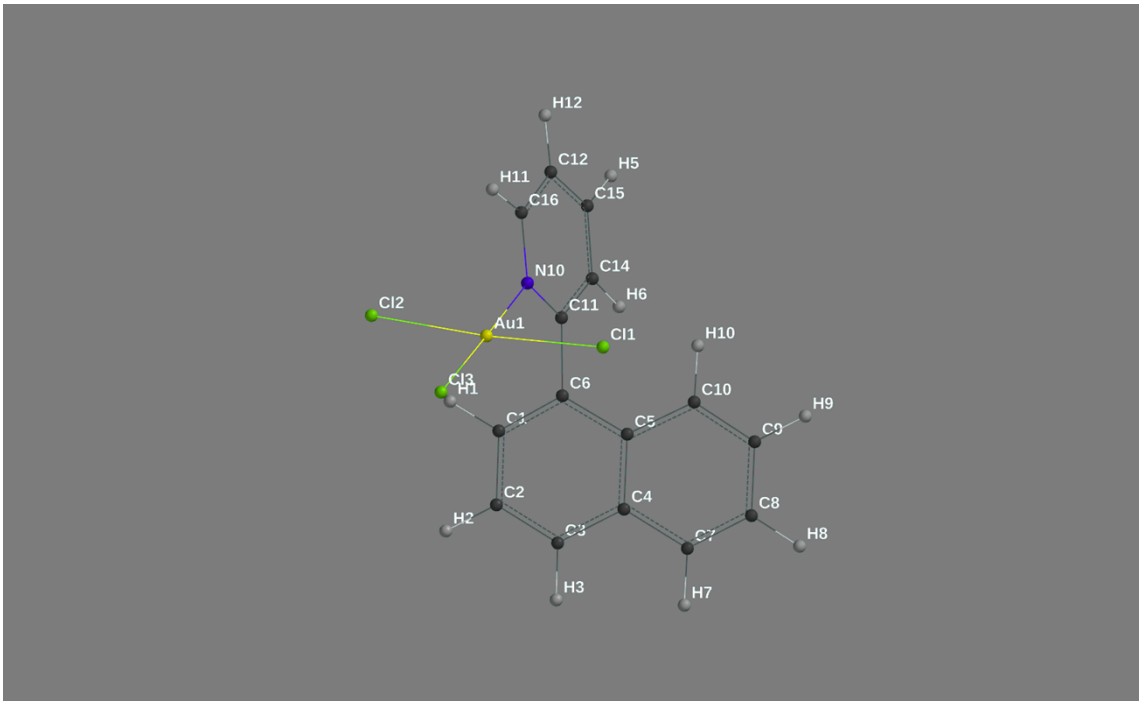


Figure S3. Structure and atom numbering in minimized anti-rotamer of non-metallated Au-intermediate.

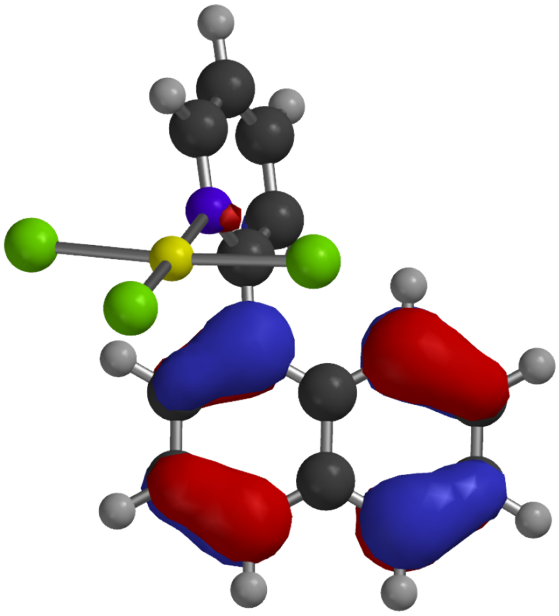


Figure S4. Graphical representation of HOMO in minimized anti-rotamer of non-metallated Au-intermediate.

The HOMO orbital is located at carbon atoms C1-C3 and C6-C10, with the highest coefficient on C10 and the lowest on C1. In order to verify that the values do not change significantly depending on a rotamer, minimization of the syn-rotamer (leading to δ-substitution) was performed.

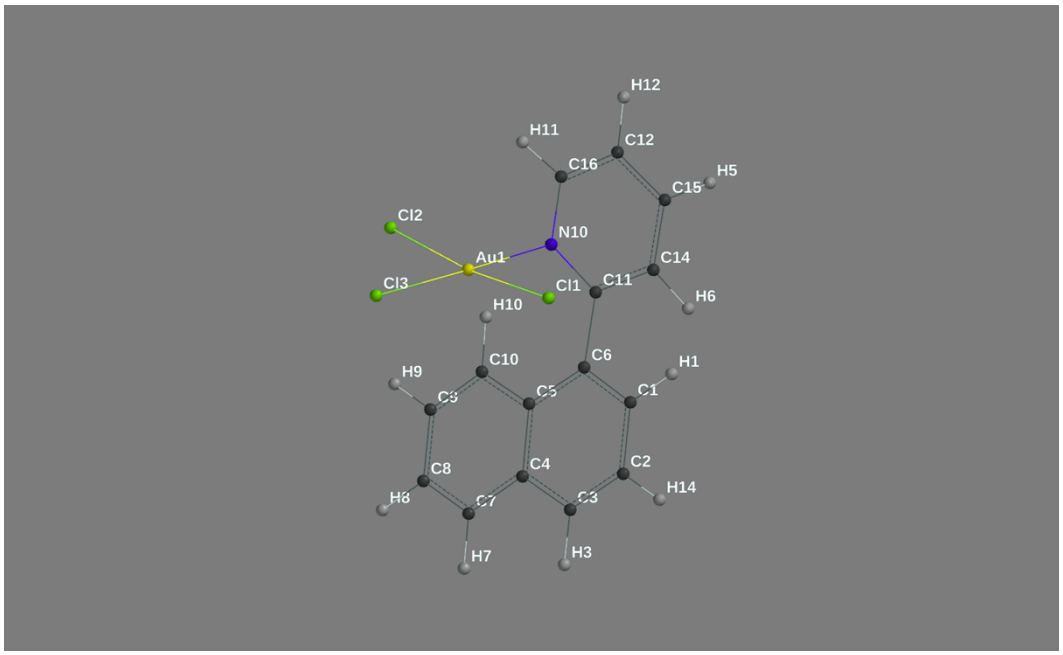


Figure S5. Structure and atom numbering in minimized syn-rotamer of non-metallated Au-intermediate.

Overall, it was found 1.6 kcal/mol higher in energy. The coefficients of atomic orbitals changed slightly, however the relative order remained the same. This indicates that the δ-carbon atom in N-metallated 2-(1-naphthyl)-pyridine is more nucleophilic than γ-carbon atom.

Table S4. The highest inputs into HOMO of non-metallated Au-intermediate

Anti-rotamer (γ-substitution)			Syn-rotamer (δ-substitution)		
Atom label	Orbital	Value	Atom label	Orbital	Value
C1	p_x	**-0.132**	**C1**	p_x	**-0.132**
C2	p_x	0.156	C2	p_x	0.159
C3	p_x	0.213	C3	p_x	0.215
C6	p_x	-0.228	C6	p_x	-0.233
C7	p_x	-0.237	C7	p_x	-0.250
C8	p_x	-0.150	C8	p_x	-0.154
C9	p_x	0.151	C9	p_x	0.158
C10	p_x	**0.242**	**C10**	p_x	**0.256**

The cyclopalladation intermediate (2-(1-naphthyl)-pyridino palladium diacetate) was optimized (Figure 5). The anti-rotamer was found to be more stable by 1.2 kcal/mol.

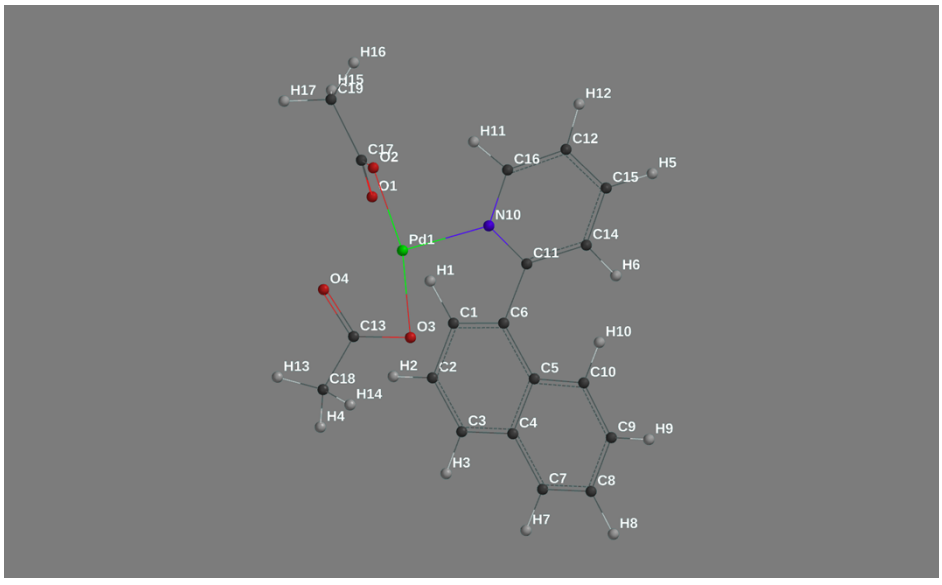


Figure S5. Structure and atom numbering in minimized anti-rotamer of non-metallated Pd-intermediate.

Table S5. The highest inputs into HOMO of the non-metallated Pd-intermediate

Anti-rotamer (γ-substitution)			Syn-rotamer (δ-substitution)		
Atom label	Orbital	Value	Atom label	Orbital	Value
C1	p_x	**0.157**	**C1**	p_x	**-0.122**
C2	p_x	0.159	C2	p_x	0.124
C3	p_x	-0.208	C3	p_x	0.185
C6	p_x	0.236	C6	p_x	-0.194
C7	p_x	-0.250	C7	p_x	-0.220
C8	p_x	0.149	C8	p_x	-0.139
C9	p_x	-0.122	C9	p_x	0.141
C10	p_x	**-0.211**	**C10**	p_x	**0.222**

References

1. J. Quintin, X. Franck, R.Hocquemiller and B. Figadere, *Tet. Lett.*, 2002, **43,** 3547.

2. J. Yang, S. Liu, J.-F. Zheng and J. Zhou, *Eur. J. Org. Chem.*, 2012, **2012**, 6248.

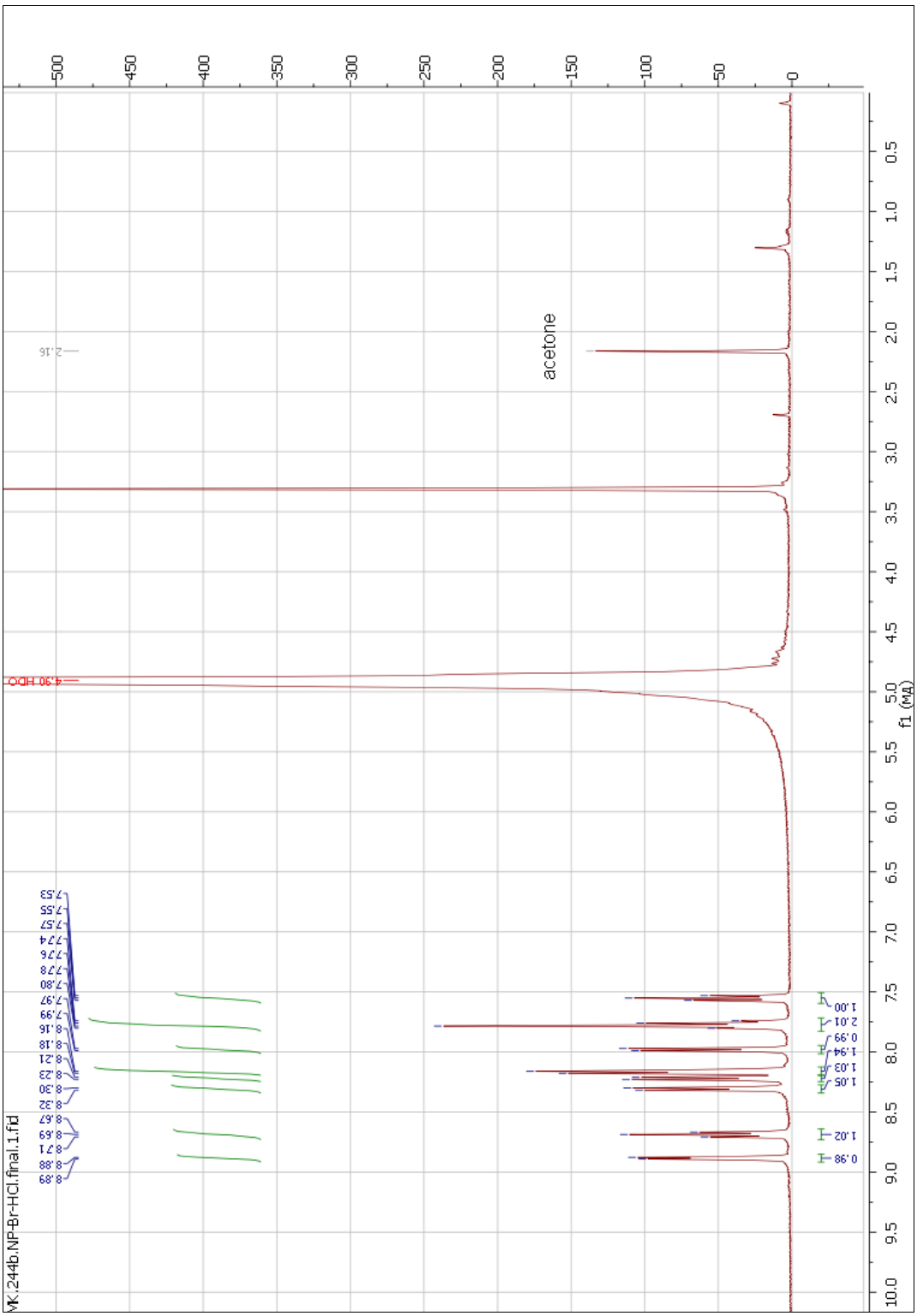
3. Crysalis CCD; Oxford Diffraction Ltd.: Abingdon, Oxfordshire, UK (2005). Crysalis RED; Oxford Diffraction Ltd.: Abingdon, Oxfordshire, UK (2005).

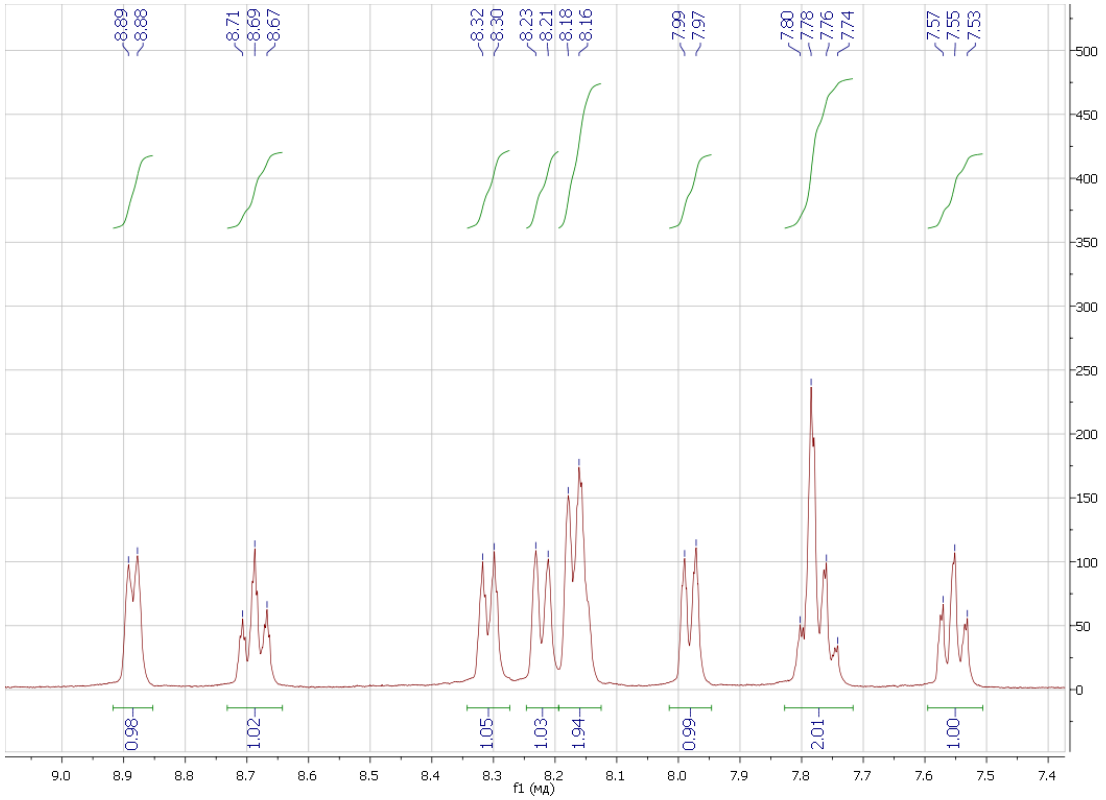
4. G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112–122.

5. Spartan 10, Wavefunction Inc.

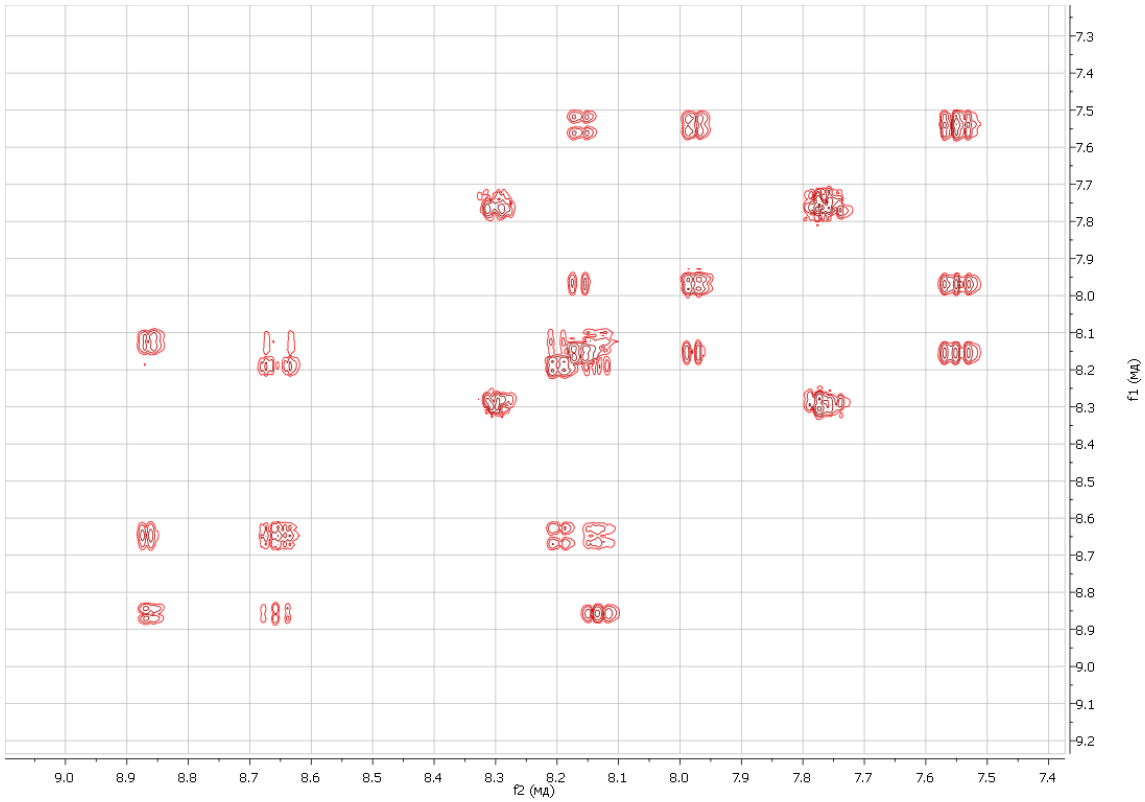
NMR spectra of 4*HCl

^{1}H NMR

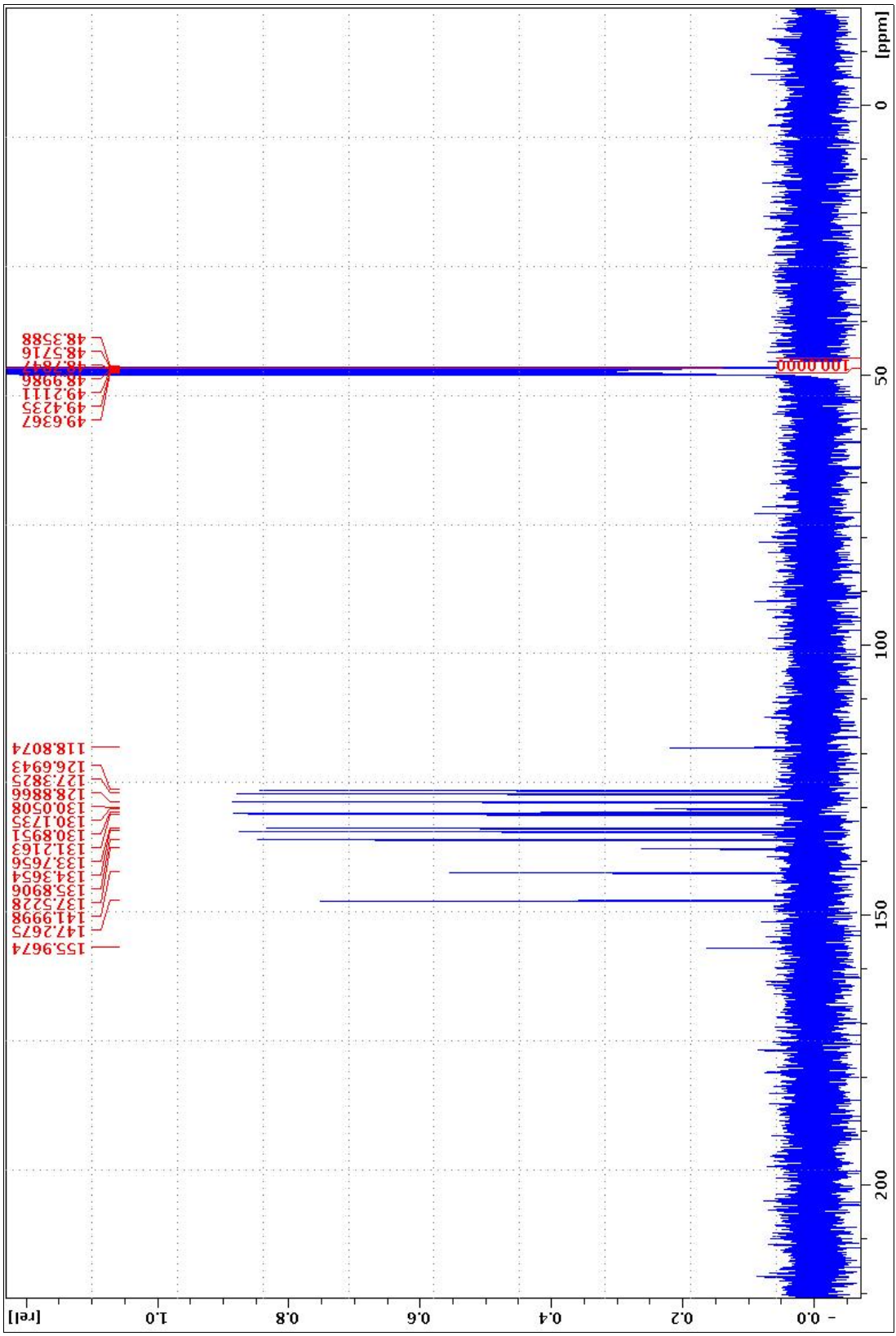



8.89
8.88
8.71
8.69
8.67
8.32
8.30
8.23
8.21
8.18
8.16
7.99
7.97
7.80
7.78
7.76
7.74
7.57
7.55
7.53
0.98
1.02
1.05
1.03
1.94
0.99
2.01
1.00
f1 (мд)

gCOSY NMR



^{13}C NMR


[ppm]
0
50
100
150
200
[rel]
0.0
0.2
0.4
0.6
0.8
1.0
100.0000
48.3588
48.5716
48.7847
48.9986
49.2111
49.4235
49.6367
118.8074
126.6943
127.3825
128.8866
130.0508
130.1735
130.8951
131.2163
133.7656
134.3654
135.8906
137.5228
141.9998
147.2675
155.9674