

# Supporting Information

## **A Teflon microreactor with integrated piezoelectric actuator to handle solid forming reactions**

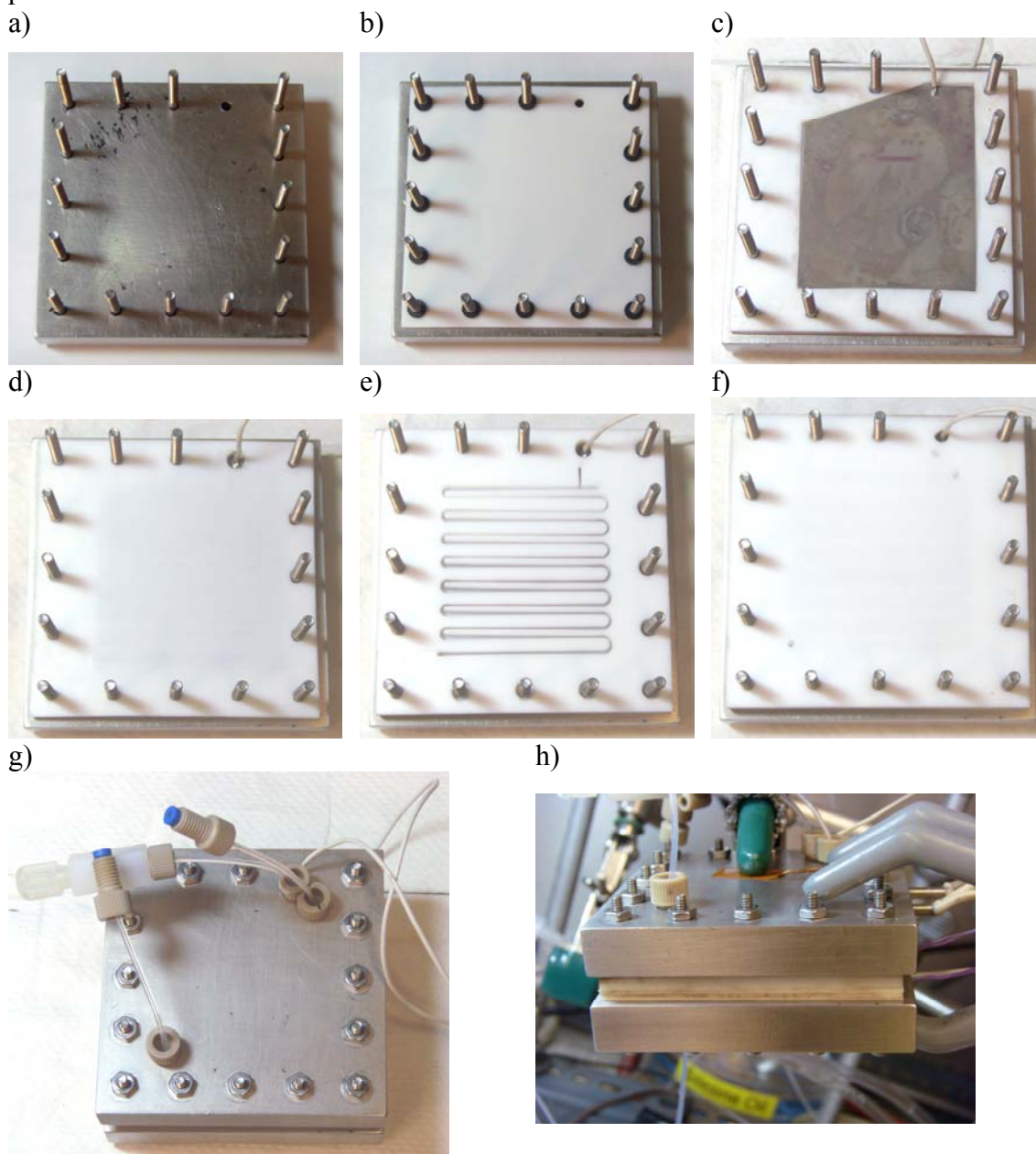
Simon Kuhn,<sup>a</sup> Timothy Noël,<sup>b</sup> Lei Gu,<sup>a</sup> Patrick L. Heider<sup>a</sup>  
and Klavs F. Jensen<sup>a\*</sup>

<sup>a</sup> *Department of Chemical Engineering, Massachusetts Institute of Technology,  
77 Massachusetts Avenue, Cambridge, MA 02139, USA.*

<sup>b</sup> *Department of Chemistry, Massachusetts Institute of Technology,  
77 Massachusetts Avenue, Cambridge, MA 02139, USA.*

### 1. Microreactor assembly

Figure S1 depicts the assembly of the microreactor together with the integration of the piezoelectric actuator.



**Figure S1:** Assembly of the microreactor layers. a) bottom stainless steel chuck. b) PTFE plate for electrical insulation of the piezoelectric actuator. c) piezoelectric actuator with PTFE housing. d) bottom layer of the microreactor. e) middle layer of the microreactor with the channel structure. f) top layer of the reactor with the inlet and outlet holes. g) microfluidic connections. h) sideview of the assembly.

## 2. General reagent information

All reactions were carried out using reagent grade solvents, and all solutions were prepared under an argon atmosphere. 4-chloroanisole, 4-bromoveratrole, aniline, 4-*tert*-butylaniline, sodium *tert*-butoxide and dioxane (anhydrous, Sure-Seal bottle) were purchased from Sigma-Aldrich chemical company and were used as received. XPhos **1** was purchased from Strem Chemicals. XPhos precatalyst **2**<sup>[1]</sup> was prepared according to a literature procedure. Sodium *tert*-butoxide (NaOtBu) was stored in a nitrogen-filled glovebox and was taken out in small quantities and stored in a dessicator for up to two weeks. Reaction solutions were prepared in screw-cap, oven-dried volumetric flasks. For the continuous-flow experiments, two solutions were prepared. The first solution contained aryl halide, aniline, XPhos precatalyst **2**, and biphenyl in dioxane or THF. The second solution contained NaOtBu and dioxane or THF and was filtered through a syringe filter (PTFE membrane, 25 mm disk, 0.45 μm pores) prior to use. Solid reagents were added to the volumetric flasks and were then evacuated and refilled with argon. This process was repeated a total of 3 times. Liquid reagents were added by syringe and the solutions were made up to the desired volume with dioxane or THF. These solutions were loaded into syringes and attached to syringe pumps.

## 3. General analytical information

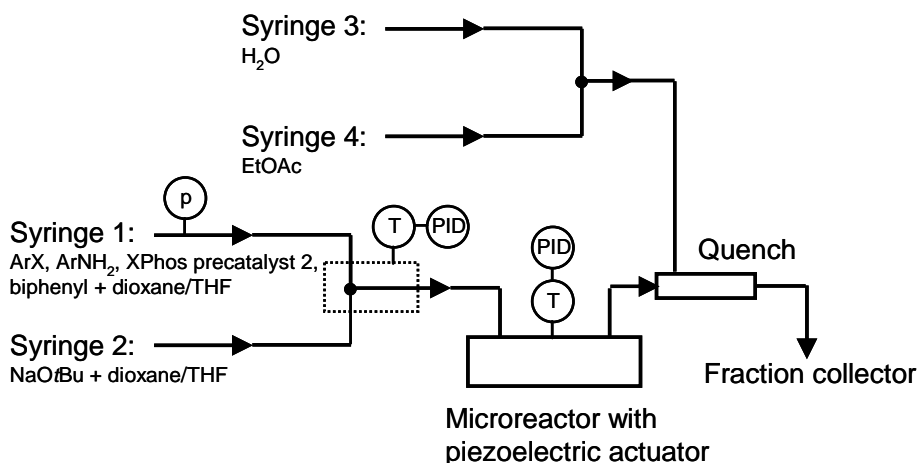
All compounds were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectroscopy. Copies of the <sup>1</sup>H and <sup>13</sup>C spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. All <sup>1</sup>H NMR are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All <sup>13</sup>C NMR are reported in ppm relative to deuteriochloroform (77.23 ppm), unless otherwise stated, and all were obtained with 1H decoupling. All IR spectra were taken on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm ID). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

## 4. Workup and yields

Samples were collected in test tubes and were diluted with equal amounts of ethyl acetate and water and vigorously mixed. An aliquot of the organic phase was filtered through a short plug of silica gel and analyzed by GC. In certain cases, the phases were separated and the water phase was extracted in total 3 times with ethyl acetate. The organic phases were combined and concentrated *in vacuo*. The crude material was purified by column chromatography.

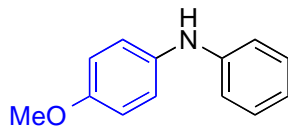
### 5. Typical procedure to obtain isolated yields

An oven-dried screw-top volumetric flask (10.00 mL) that was fitted with a Teflon screw-cap, was charged with XPhos precatalyst **2** (14.8 mg, 0.02 mmol) and biphenyl (61.6 mg, 0.4 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times). Next, the aryl halide (2 mmol) and aniline (2.4 mmol) were added via syringe and dioxane or THF was added to make the solution volume 10 mL. A second oven-dried screw-top volumetric flask (10.00 mL) that was fitted with a Teflon screw-cap, was charged with NaOtBu (288.4 mg, 3 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and dioxane or THF was added to make the solution volume 10 mL. These two solutions were loaded into Normject plastic syringes and fitted to a single syringe pump. The different solutions were flowed through the reactor, as described in Figure S2, with the appropriate flow rates to give the different residence times. When exiting the reactor, the reaction was quenched with ethyl acetate and water. The flow rate of the ethyl acetate stream and water stream are equal to the flow rate of the reaction stream. Typically, each experiment is preceded by a flush in order to ensure steady-state data collection. Next, a sample was collected in order to obtain exactly 1 mmol of product. The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated *in vacuo* and purified by column chromatography *via* Biotage SP4 (silica-packed 25 g snap column; eluting with hexanes and 0-20% ethyl acetate).

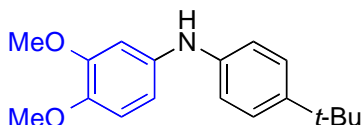


**Figure S2:** Experimental setup for the cross-coupling of aryl halides with nitrogen nucleophiles.

## 6. Experimental procedures



**4-methoxy-N-phenylaniline.**<sup>[2]</sup> Following the typical procedure, a first syringe (10 mL solution) was loaded with 4-chloroanisole (245  $\mu$ L, 2 mmol), aniline (219  $\mu$ L, 2.4 mmol), XPhos precatalyst **2** (14.8 mg, 0.02 mmol) and biphenyl (63.2 mg, 0.4 mmol) dissolved in dioxane. A second syringe (10 mL solution) was loaded with NaOtBu (288.4 mg, 3 mmol) dissolved in dioxane. These syringes were fitted to a single syringe pump as described in Figure S2. The reagents were flowed through the reactor with the appropriate flow rates (90 seconds residence time, 0.667 ml/min total flow rate). A sample was collected for 7.5 minutes (1 mmol). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated *in vacuo* and purified by column chromatography (silica gel, eluting with hexanes and 0-10% ethyl acetate) to give the title compound as an off-white solid (188.4 mg, 95 %), mp = 104-106 °C (lit. 104-106 °C)<sup>[2]</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.20 (t,  $J$  = 8.0 Hz, 2H), 7.07 (d,  $J$  = 8.0 Hz, 2H), 6.93-6.82 (m, 5H), 5.50 (br s, 1H), 3.79 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 155.4, 145.3, 135.9, 129.5, 122.4, 119.7, 115.8, 114.8, 55.7 ppm. IR (neat, cm<sup>-1</sup>): 3395, 1597, 1505, 1321, 1298, 1248, 1236, 1031, 741, 1031.

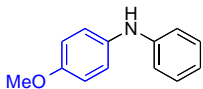


**N-(4-(tert-butyl)phenyl)-3,4-dimethoxyaniline.** Following the typical procedure, a first syringe (10 mL solution) was loaded with 4-bromoveratrole (289  $\mu$ L, 2 mmol), 4-tert-butylaniline (379  $\mu$ L, 2.4 mmol), XPhos precatalyst **2** (14.8 mg, 0.02 mmol) and biphenyl (63.2 mg, 0.4 mmol) dissolved in THF. A second syringe (10 mL solution) was loaded with NaOtBu (288.4 mg, 3 mmol) dissolved in THF. These syringes were fitted to a single syringe pump as described in Figure S2. The reagents were flowed through the reactor with the appropriate flow rates (60 seconds residence time, 1 ml/min total flow rate). A sample was collected for 5 minutes (1 mmol). The organic layer was separated and the aqueous layer was extracted 3 more times with ethyl acetate. The combined organic layers were concentrated *in vacuo* and purified by column chromatography (silica gel, eluting with hexanes and 0-20% ethylacetate) to give the title compound as brown oil (283.5 mg, 99 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.24 (td,  $J$  = 2.0, 8.8 Hz, 2H), 6.89 (td,  $J$  = 2.0, 8.8 Hz, 2H), 6.77 (d,  $J$  = 8.5 Hz, 1H), 6.68 (d,  $J$  = 7.5 Hz, 1H), 6.63-6.59 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 1.28 (s, 9H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 149.8, 144.4, 143.1, 142.3, 137.1, 126.3, 126.2, 116.3, 115.1, 112.4, 111.5, 104.9, 56.5, 56.1, 34.2, 31.7 ppm. IR (neat, cm<sup>-1</sup>): 3372, 2959, 1607, 1512, 1463, 1257, 1232, 1200, 1027, 827.

## 7. References

- [1] M. R. Biscoe; B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687.
- [2] T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287-290.

### 8. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra:

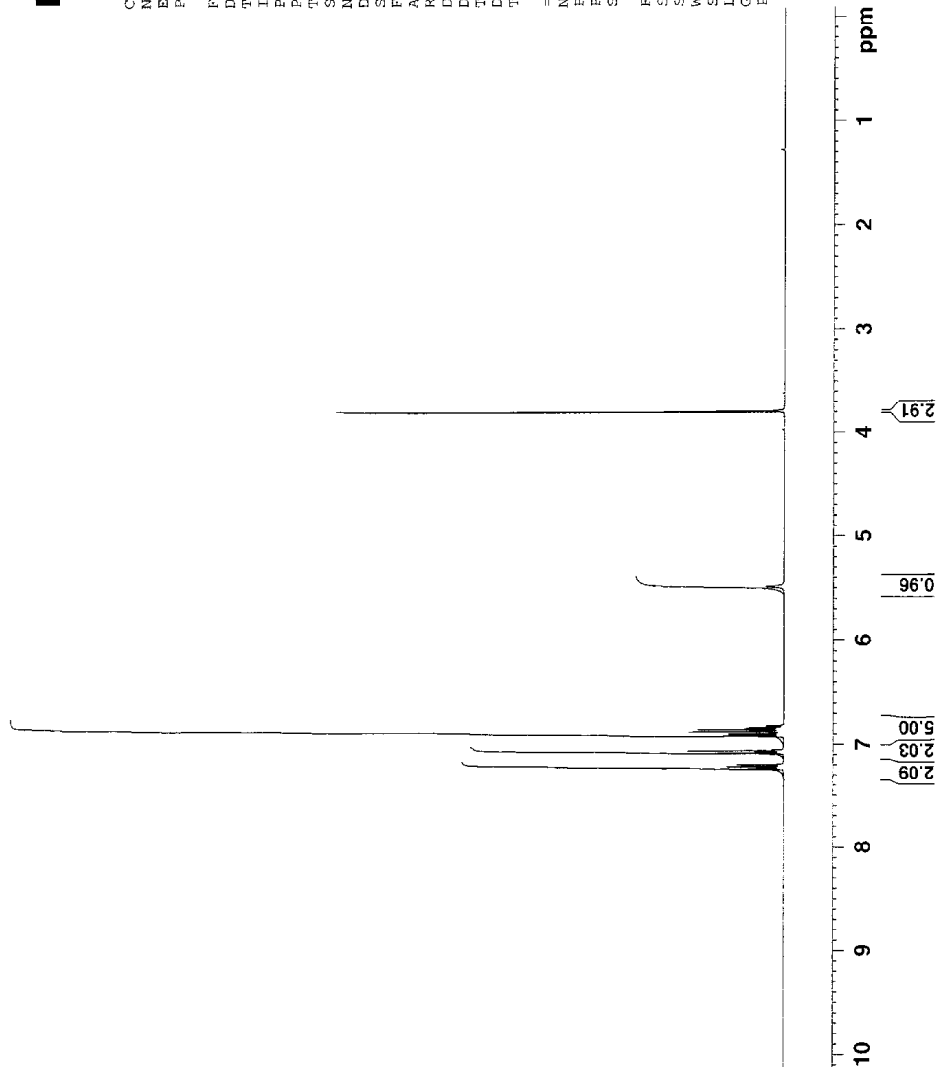


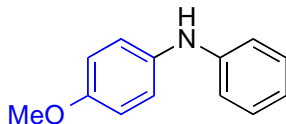
Current Data Parameters  
NAME TN2-075  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20110224  
Time 10.10  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
MS 8  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.12431 Hz  
AQ 3.958423 sec  
RG 128  
KW 60.400 usec  
DE 6.00 usec  
TE 295.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 14.00 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 65536  
SF 400.1300220 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00





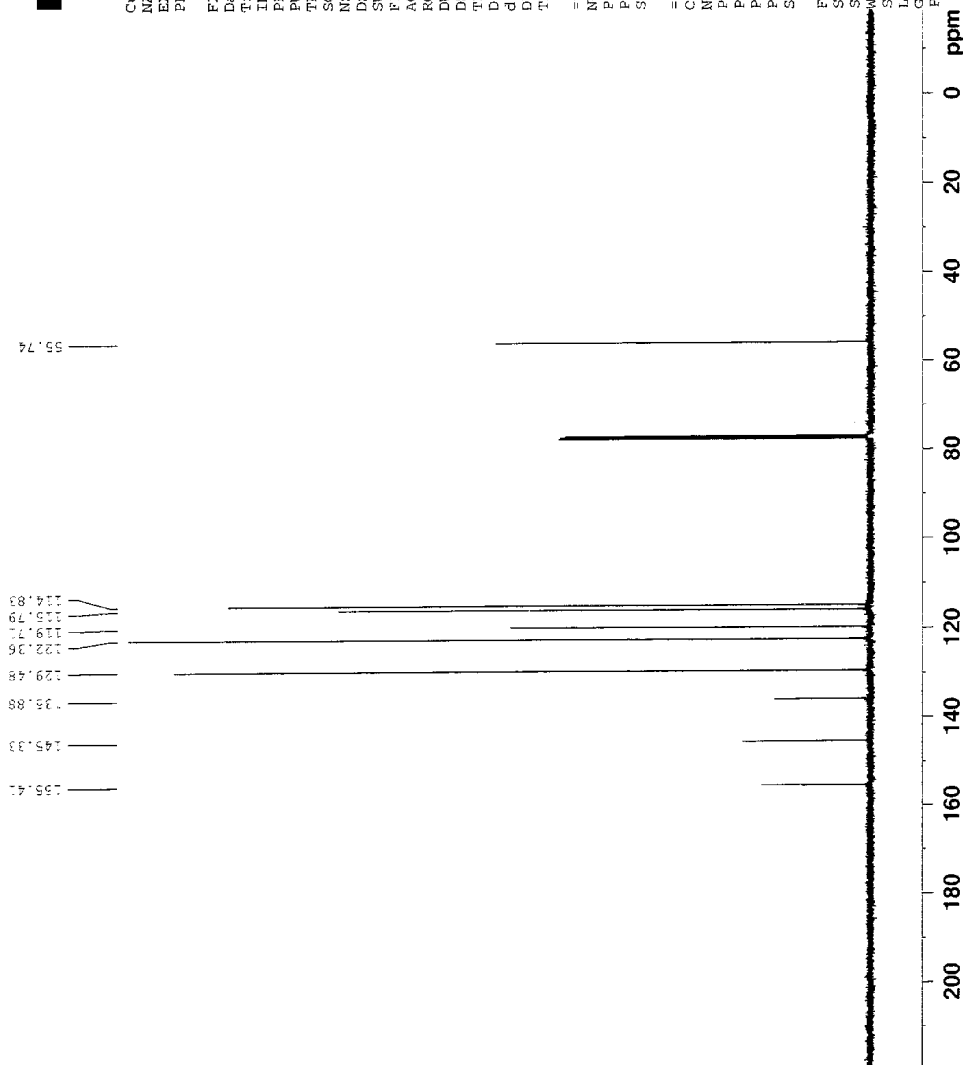
Current Data Parameters  
NAME TN2-075-13CNER  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20110224  
Time 10.17  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 200  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 5792.6  
DM 20.850 usec  
DE 5.00 usec  
TE 295.2 K  
D1 2.0000000 sec  
d11 0.0300000 sec  
DELTA 1.8999998 sec  
TDO 1

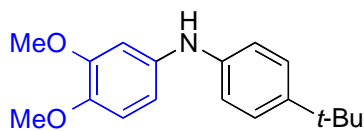
===== CHANNEL f1 =====  
NUC1 13C  
PI 9.38 usec  
PL1 0.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCHD2 90.00 usec  
PL2 0.00 dB  
PL12 16.10 dB  
PL13 19.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6132573 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40





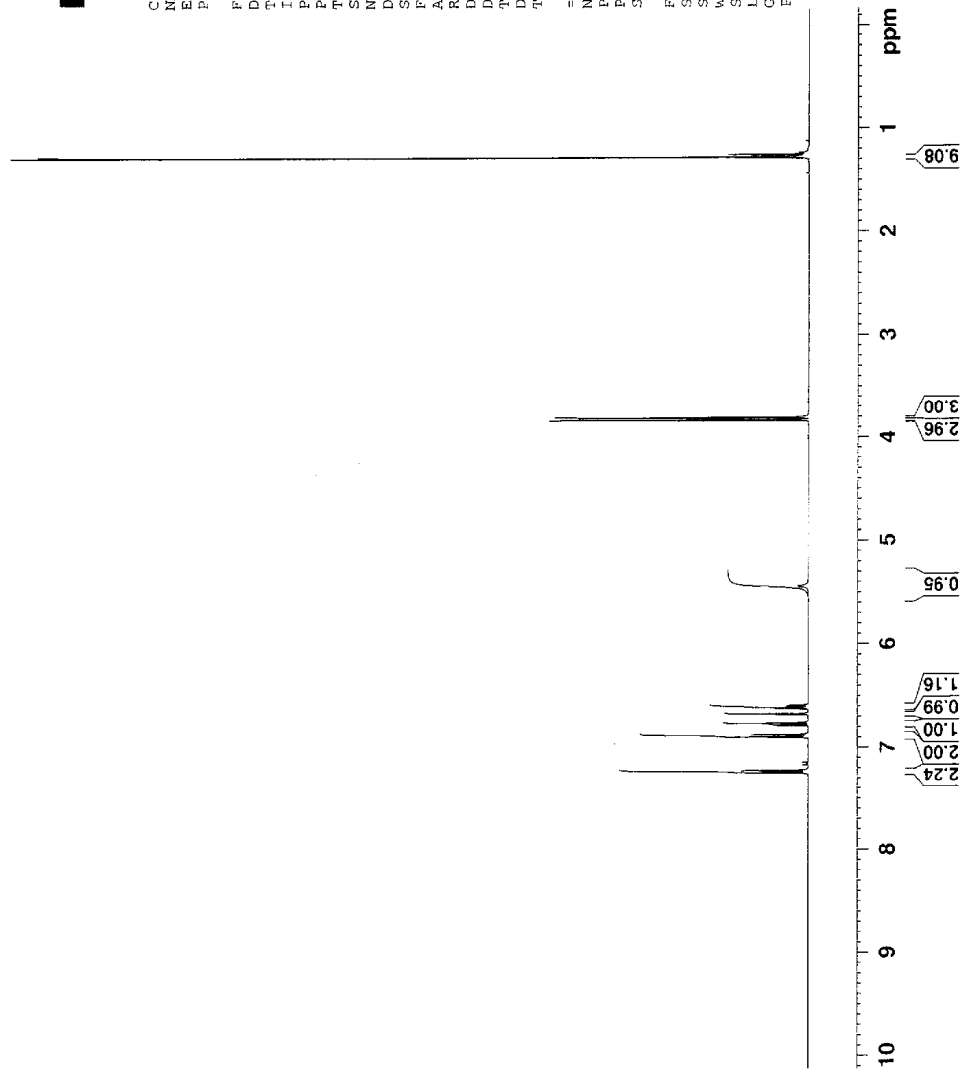


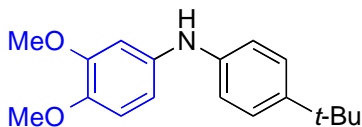
Current Data Parameters  
NAME Tm2-082  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20110226  
Time 19.07  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 2  
DS 8  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.95684243 sec  
RG 256  
RW 60.400 usec  
DE 6.00 usec  
TE 296.2 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 14.00 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 65536  
SF 400.1300220 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00





Current Data Parameters  
 NAME TN2-062-13CNMR  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20110224  
 Time 10.40  
 INSTRUM spect  
 PROBHD 5 mm QNP 1H/13  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 95  
 DS 4  
 SWH 23980.814 Hz  
 FIDRES 0.365918 Hz  
 AQ 1.3664756 sec  
 RG 1625.5  
 DW 20.850 usec  
 DE 6.00 usec  
 TE 295.2 K  
 D1 2.0000000 sec  
 d11 0.0300000 sec  
 DELTA 1.8999998 sec  
 TDO 1

==== CHANNEL F1 =====  
 NUC1 13C  
 P1 9.38 usec  
 PL1 0.00 dB  
 SFOL 100.6228298 MHz

==== CHANNEL F2 =====  
 CPDPRG2 waltz16  
 NUC2 1H  
 P2 90.00 usec  
 PL2 0.00 dB  
 PL12 16.10 dB  
 PL13 19.00 dB  
 SFO2 400.1316005 MHz

F2 - Processing parameters  
 SI 32768  
 SF 100.6127542 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

