

Supporting Information

Nonthermal Microwave Effects Revisited – On the Importance of Internal Temperature Monitoring and Agitation in Microwave Chemistry

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General Experimental Details: ^1H NMR and ^{13}C NMR spectra were recorded on a 360 MHz instrument at 360 and at 90 MHz, respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quadruplet and multiplet. Low resolution mass spectra were obtained on a LC/MS instrument using atmospheric pressure chemical ionization (APCI) in positive or negative mode. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (119×3 mm, particle size 5 mm) or a reversed-phase column (150×4.6 mm, particle size 5 mm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 0.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100 % B in 10 min, hold at 100% solution B for 5 min. GC-MS data were recorded on a Hewlett-Packard GC/MSD, GC-HP 6890 Series with an HP-MSD 5973 detector based on electron impact ionization (70eV) using a HP-5MSI column ($30 \text{ m} \times 0.250 \text{ mm} \times 0.025 \times 0.025$). After 3 min at 50 °C the temperature was increased in 10 °C/min steps up to 300 °C and kept at 300 °C for 10 minutes. The carrier gas was argon and the flow rate 1.0 mL/min. Dry-flash chromatography was performed on silica gel 60 H (< 45 nm particle size). Melting points were obtained on a standard melting point apparatus in open capillary tubes. TLC analyses were performed on pre-coated (silica gel 60 HF₂₅₄) plates. All anhydrous solvents (stored over molecular sieves), and chemicals were obtained from standard commercial vendors and were used without any further purification except where stated otherwise.

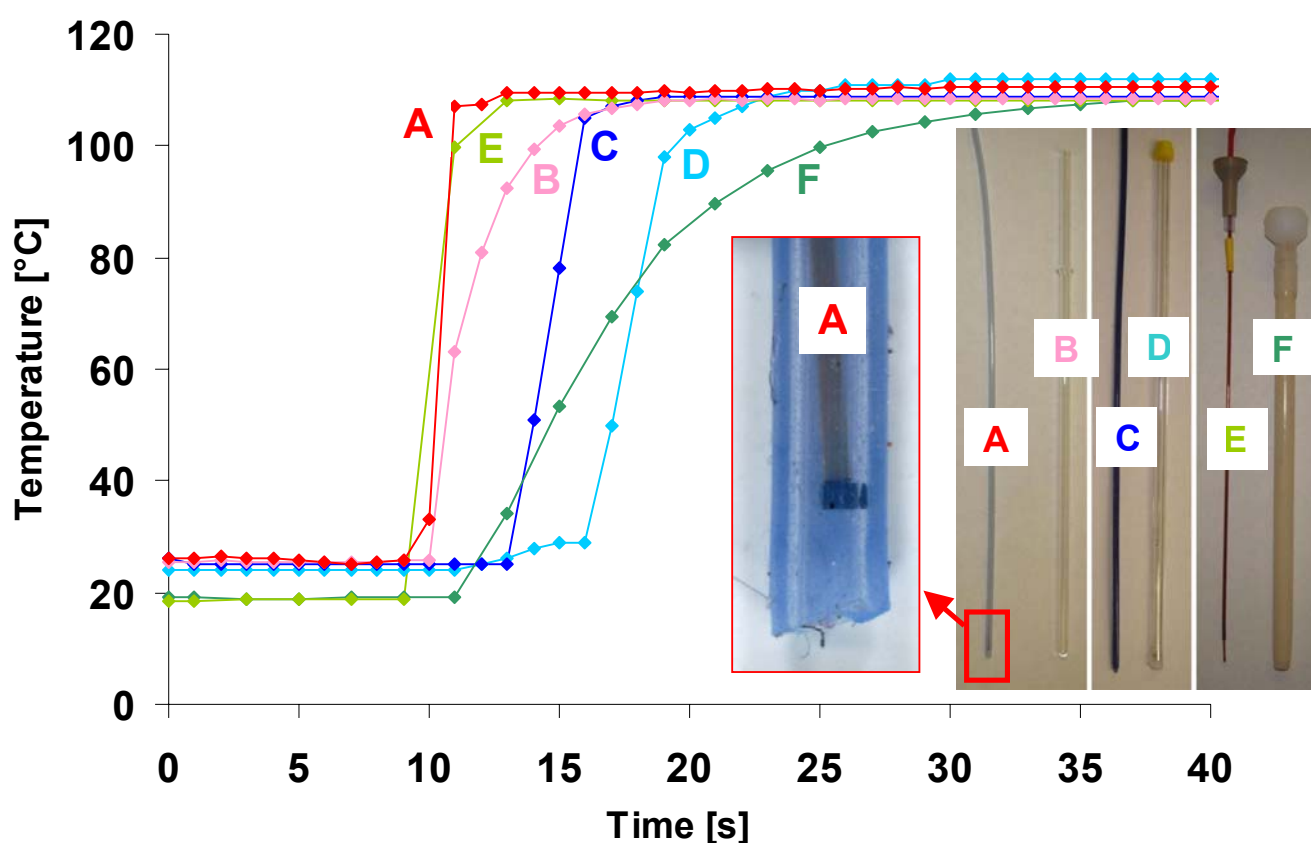


Figure S1. Comparison of response times for three different fiber-optic temperature probes A, C and E (GaAs principle) used with and without their appropriate protective immersion wells B, D and F. The response times were determined by introducing the probes into an ethylene glycol bath preheated/ equilibrated at 110 °C. The fiber optic probes were inserted at the 10 second mark. Data are shown for:

- Opsens fiber-optic sensor OTG-F-62 as used for this work (OPSENS, www.opsens.com): (A) unprotected use; (B) in conjunction with a quartz immersion well.
- FISO fiber-optic sensor FOT-L-BA as used with microwave reactors from CEM (FISO, www.fiso.com): (C) unprotected use; (D) in conjunction with CEM immersion well (Sapphire).
- FOTEMP fiber-optic sensor TS-1 as used with microwave reactors from Milestone (FOTEMP, www.fotemp.com): (E) unprotected use; (F) in conjunction with Milestone immersion well (coated ceramics).

The insert shows graphical representations of the three different probes along with their protective immersion wells. In some fiber-optic probes (for example C) the actual sensor (GaAs crystal) is additionally protected by polymer coating. This increases the lifetime of the probe but slows down the response time. In other, “faster” probes (for example A or E) the GaAs crystal is unprotected and can be seen at the tip of the probe (see magnified view of probe A). In system E/F a very fast probe (E) is used in combination with an inert immersion well which slows down the response time significantly (F).

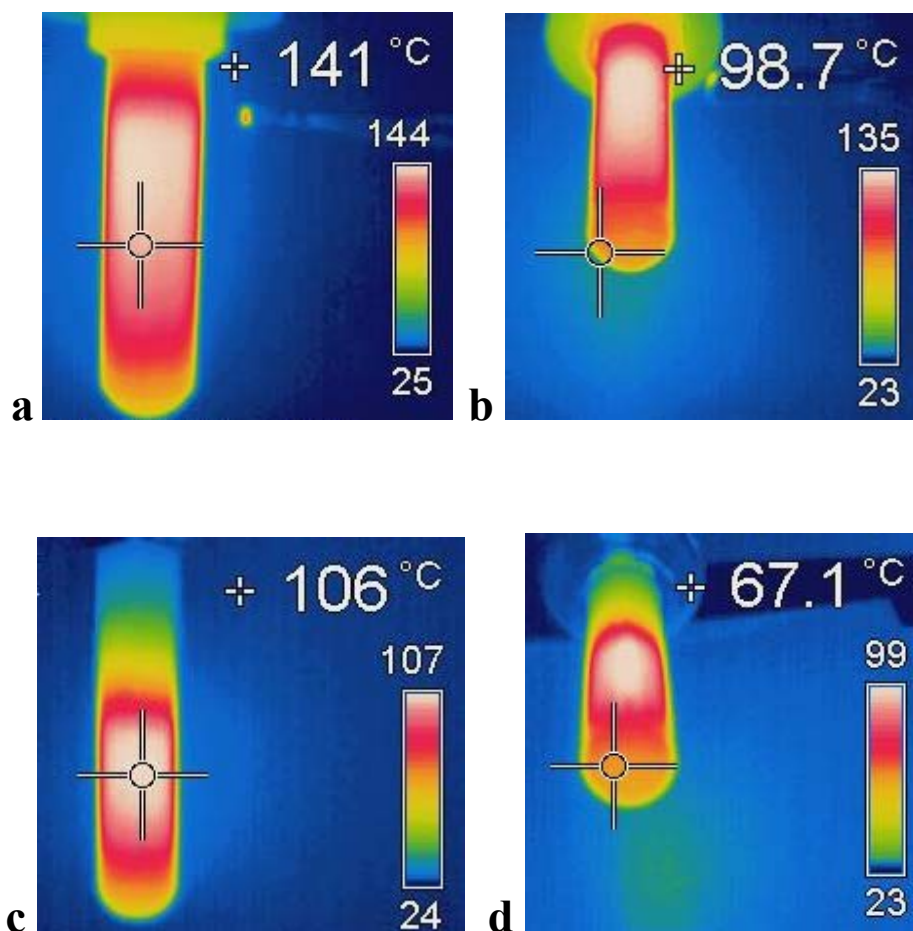


Figure S2. IR thermal images of a sample of 5 mL of NMP contained in a standard 10 mL Pyrex microwave process vial. The vial was irradiated with constant 50 W magnetron output power for 40 min without stirring. The images were taken immediately after irradiation was stopped and the heated vials were removed from the cavity (ca 5-10 seconds). In agreement with the internal temperature measurements (Figure 1) the temperature in the middle of the vial is significantly higher than at the bottom. **a, b:** CEM Discover Labmate, 135 versus 99 °C. **c, d:** Biotage Initiator EXP 2.0, 99 versus 67 °C.

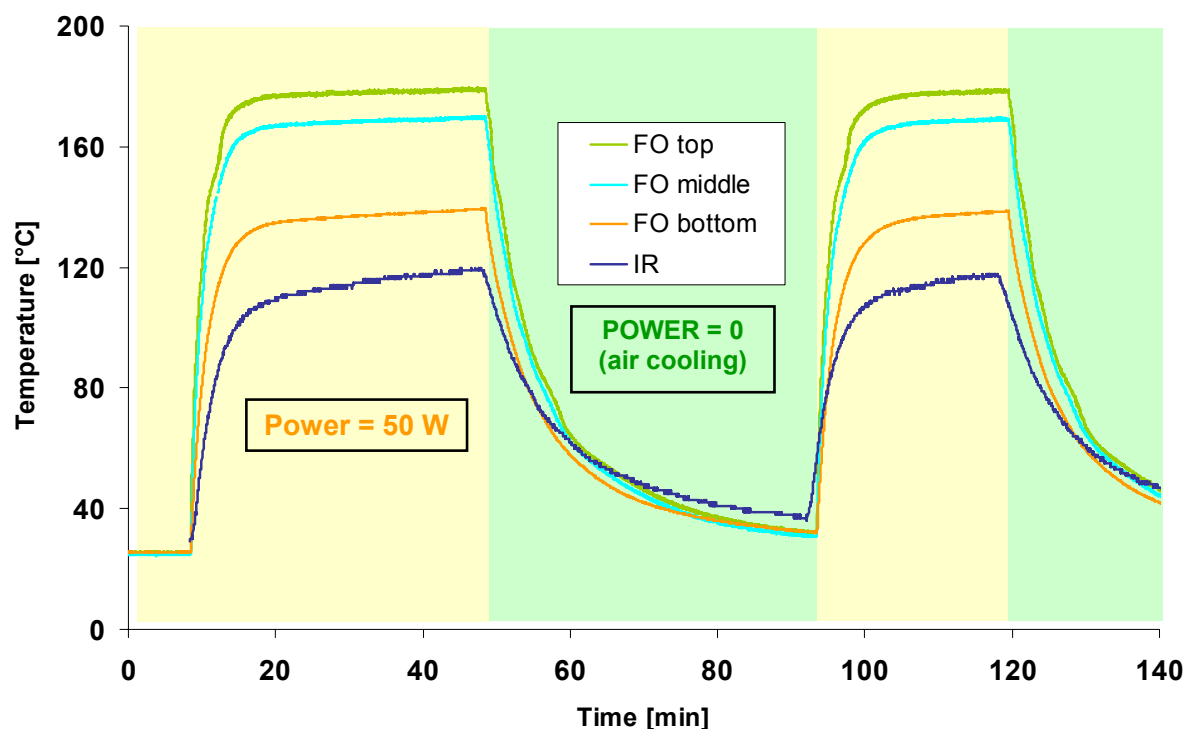


Figure S3. In order to demonstrate the reproducibility of the effect shown in Figure 1a the same heating experiment was performed twice. After ca 10 minutes, the power was set to 50 W and after ca 50 minutes, the power was switched off. When ca 90 minutes later the power was again set to 50 W the exact same temperature gradients across the unstirred mixture could again be observed. Note the persistence of the temperature gradients after the power has been turned off.

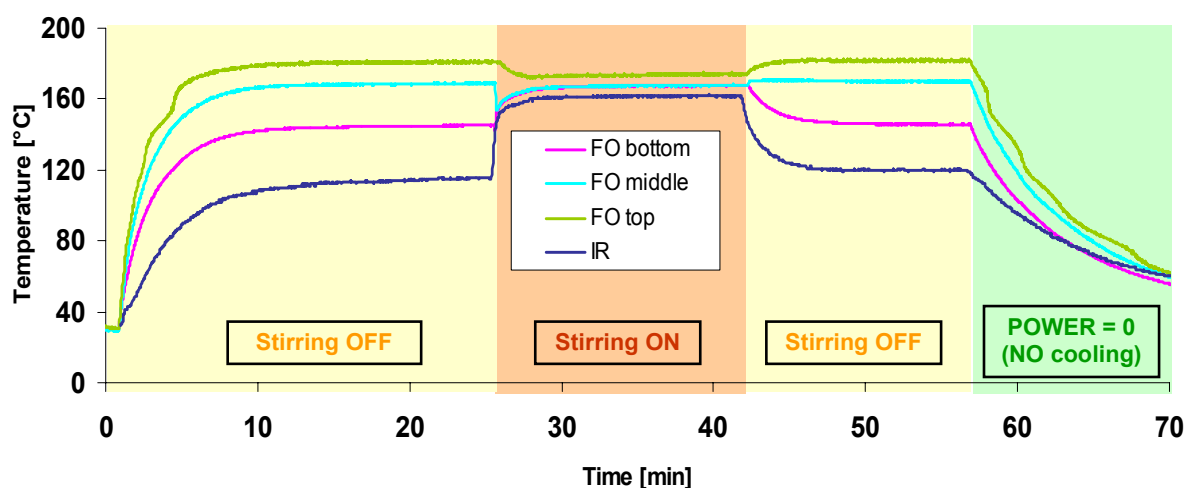


Figure S4. Temperature profiles for a sample of 5 mL of NMP contained in a 10 mL quartz vessel equipped with three internal fiber-optic sensors (Figure 1). The sample was irradiated with constant 50 W magnetron output power for 57 min (CEM Discover). Shown are the profiles for the three internal fiber-optic probes and the external IR sensor. Magnetic stirring reduces the temperature differences between the individual fiber-optic probes from max 36 °C to less than 6 °C.

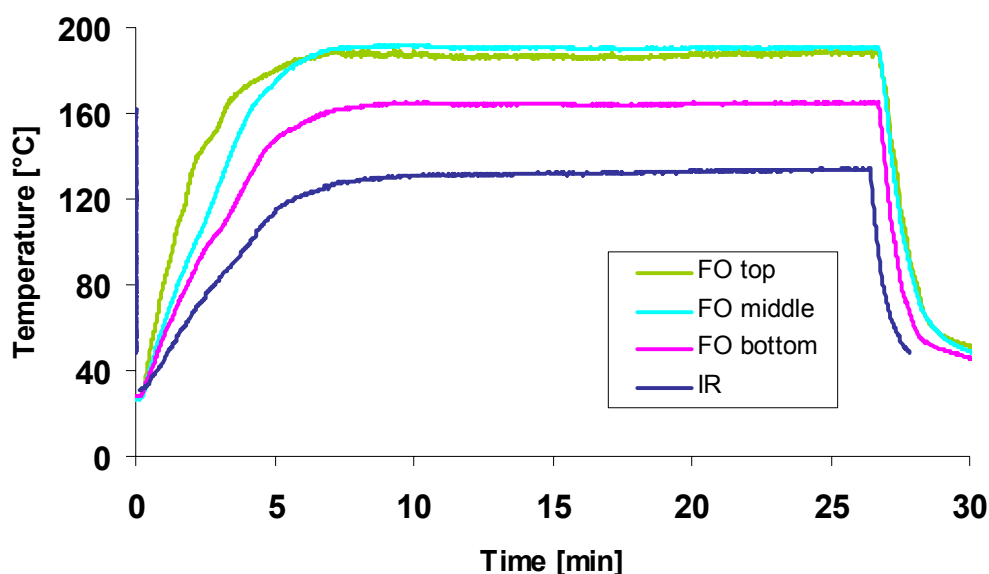


Figure S5. Temperature profiles for a sample of 3.5 g (ca 5 mL filling volume) of Montmorillonite K10 Clay contained in a 10 mL quartz vessel equipped with three internal fiber-optic sensors (Figure 1b). The strongly microwave absorbing sample was irradiated with constant 20 W magnetron output power for 27 min (CEM Discover). Shown are the profiles for the three internal fiber-optic probes and the external IR sensor. Magnetic stirring of the solid sample proves inefficient and does not reduce the temperature differences between the individual fiber-optic probes.

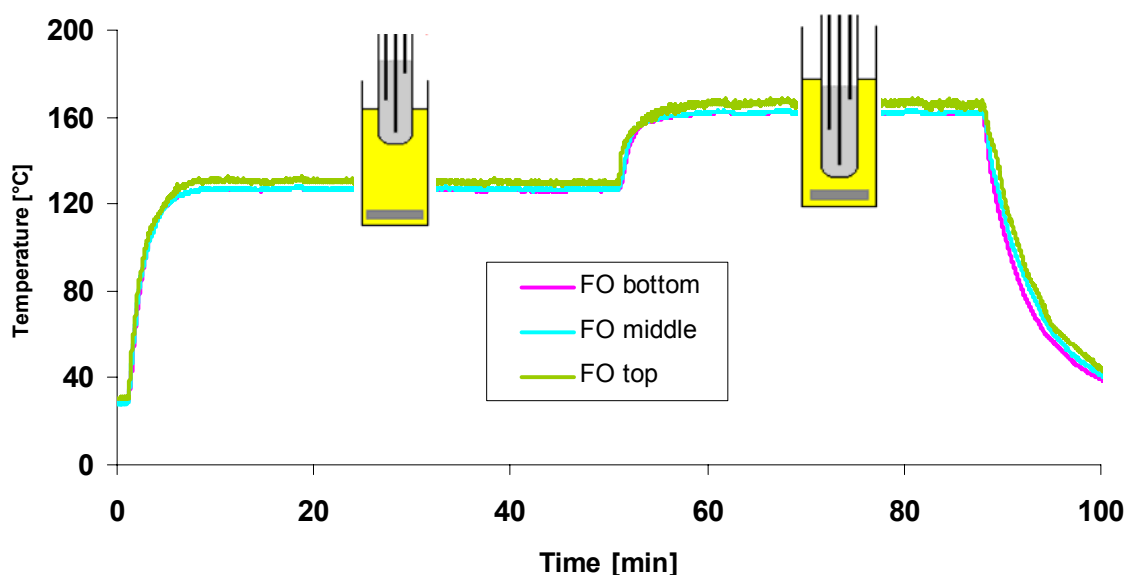


Figure S7. Temperature profiles for a sample of 5 mL of NMP contained in a 10 mL quartz vessel equipped with three internal fiber-optic sensors (Figure 1b). The vessel was initially immersed ca 2 cm into a pre-heated oil-bath at 160 °C. After 50 min the vessel was immersed further (5 cm) so that the fluid level of the reaction mixture was below the fluid level of the preheated oil. Shown are the profiles for the three internal fiber-optic probes. Virtually no temperature gradients could be observed regardless if magnetic stirring was employed or not (data shown are without stirring).

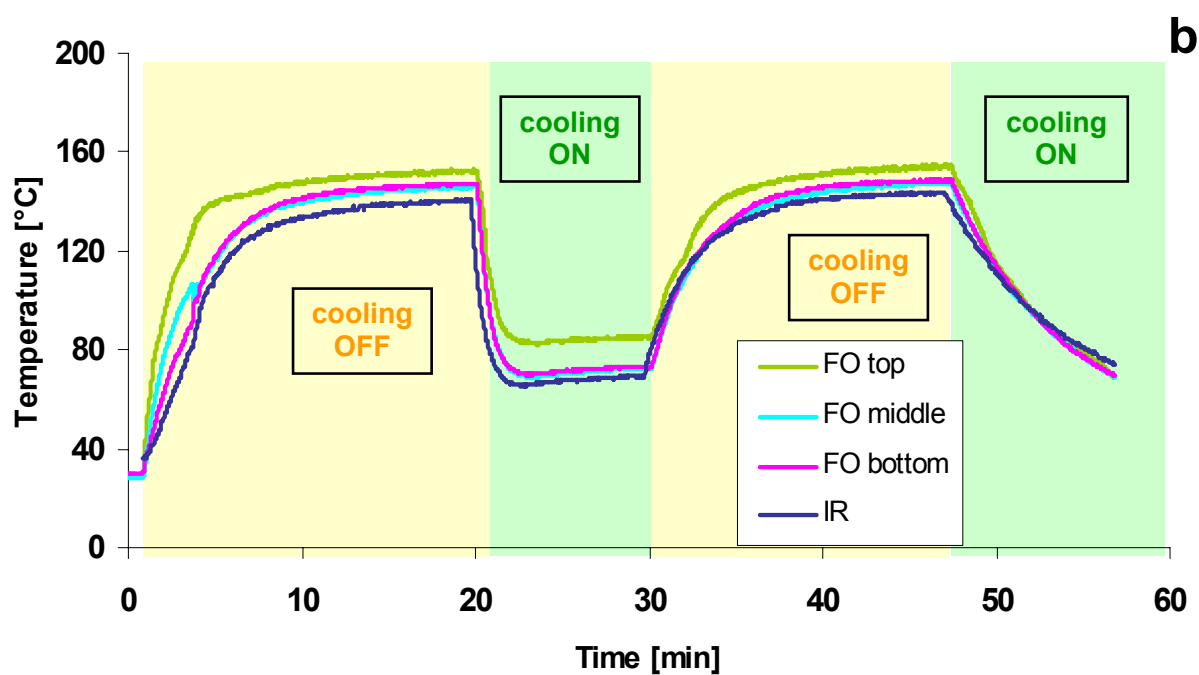
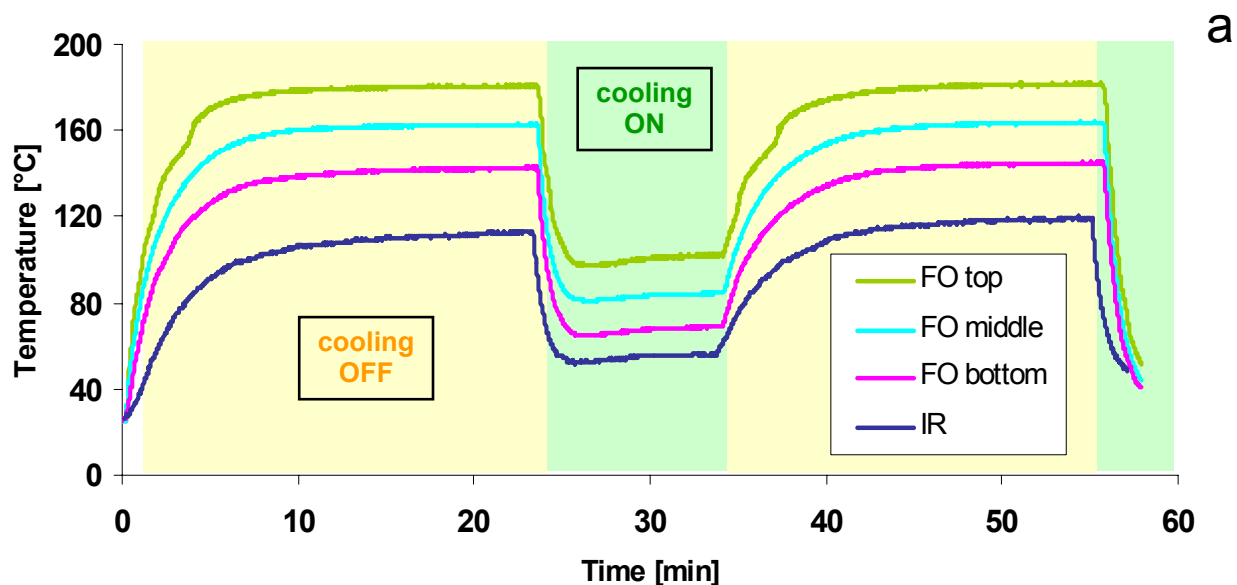


Figure S6. Temperature profiles for a sample of 5 mL of NMP (a: without stirring, b: with stirring) contained in a 10 mL quartz vessel equipped with three internal fiber-optic sensors (Figure 1b). The sample was irradiated with constant 50 W magnetron output power (CEM Discover). Shown are the profiles for the three internal fiber-optic probes and the external IR sensor. After ca 20 min of irradiation, external cooling by compressed air (30 °C, 4 bar) was applied for ca 10 min which reduced both the internally (fiber-optic) and the externally (IR) measured temperatures by ca 70 °C.

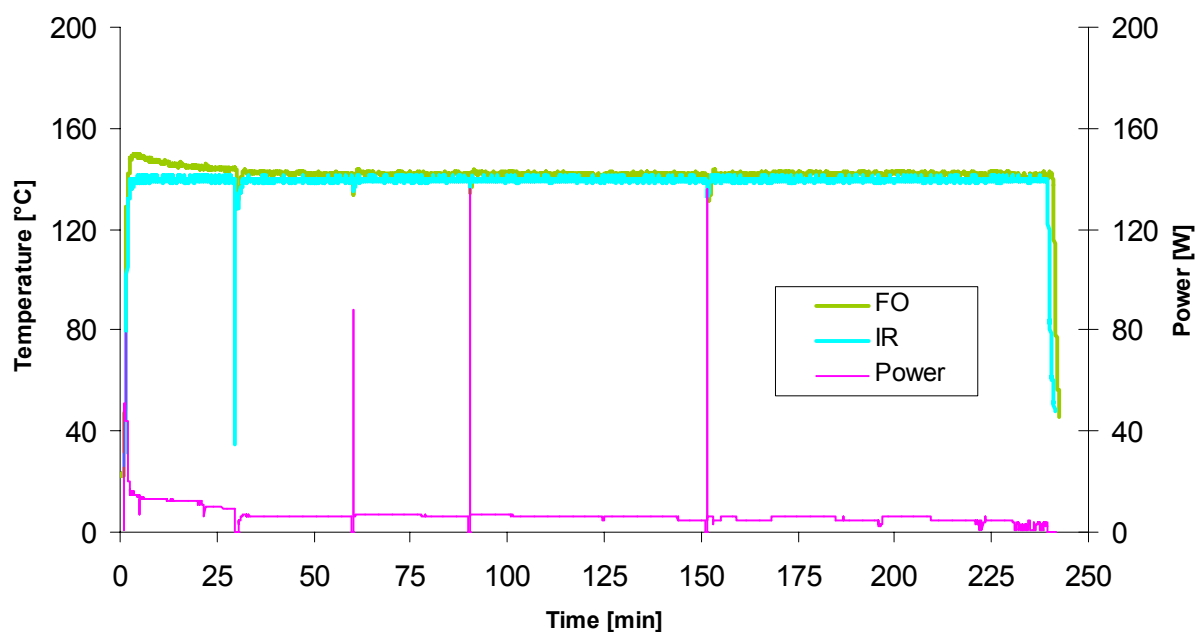


Figure S8. Heating profiles for the Diels-Alder cycloaddition of 5-methoxycarbonyl-2-pyrone and phenylacetylene (Table 1) performed in the microwave reactor (set temperature 140 °C). In order to obtain a kinetic profile of the reaction, samples for ^1H -NMR and HPLC analysis were withdrawn after 30, 60, 90, 150 and 240 min. Shortly before the withdrawal, the power was set to 0 W for a very short time (ca 5-10 seconds).

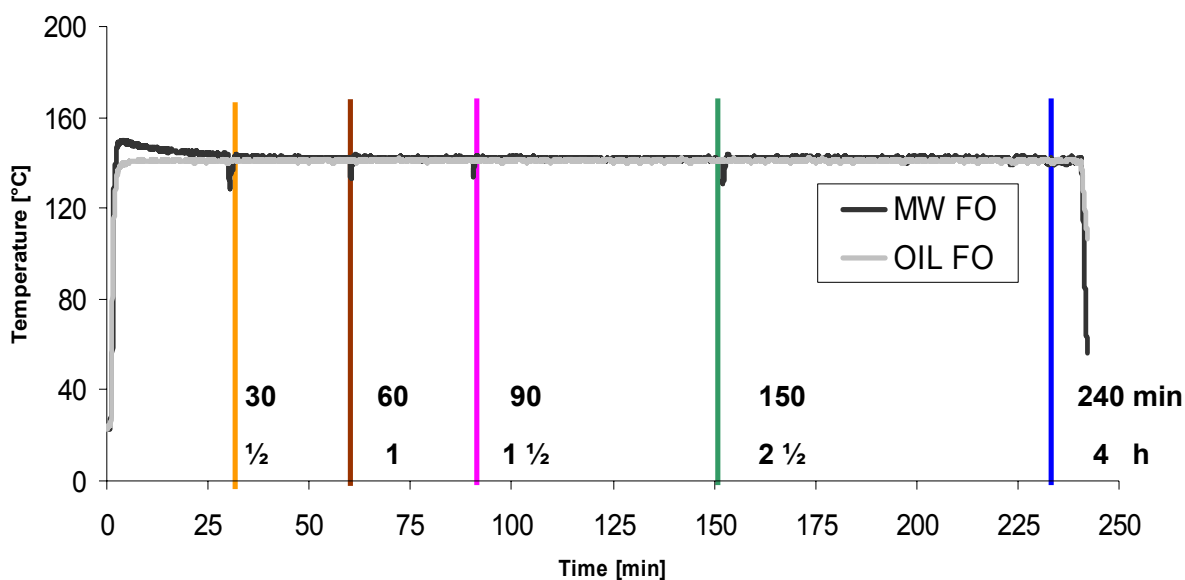


Figure S9. Fiber-optic temperature profiles for the Diels-Alder cycloaddition of 5-methoxycarbonyl-2-pyrone and phenylacetylene performed in the microwave reactor (MW) as well as in a preheated oil bath (OIL) using the reaction vessel shown in Figure 1b. After 30, 60, 90, 150 and 240 minutes, samples were withdrawn in order to measure the ^1H NMR conversions at the specified time. The average reaction temperatures were very similar for the microwave and the oil bath experiment (141.0 °C vs 141.8 °C).



Figure S10: Solidified reaction product **7** attached to the fiber optic immersion tubes after removal from the reaction vessel (10 minutes of microwave irradiation at set temperature of 150 °C, maximum internal temperature 240 °C). The arrow indicates the stirring bar which becomes completely immobilized once a significant amount of product has been formed.

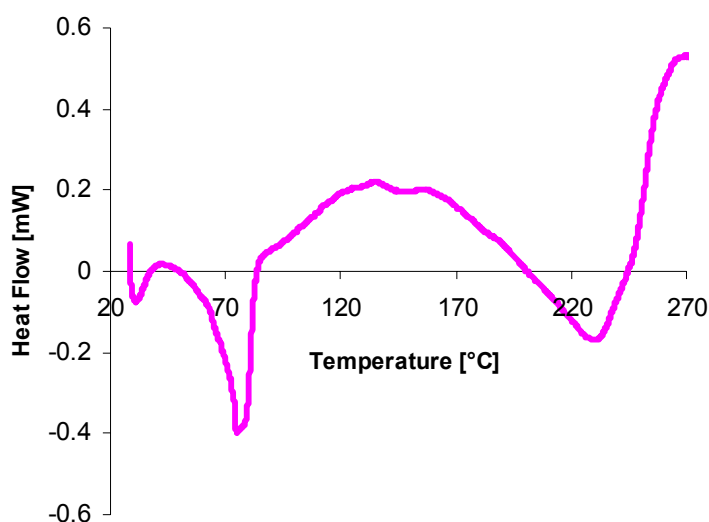


Figure S12: Differential Scanning Calorimetry (DSC) heating profile (10 °C per minute, sealed crucible) of an equimolar mixture of triphenylphosphine and benzyl chloride. Clearly visible is the melting point of triphenylphosphine around 80 °C resulting in a negative heat flow. The optimum reaction temperature for alkylation is around 120 °C where a strongly exothermic reaction takes place (positive heat flow). The second minimum at about 220 °C indicates again melting of the formed product/byproduct and at higher temperature (> 250 °C) decomposition takes place.

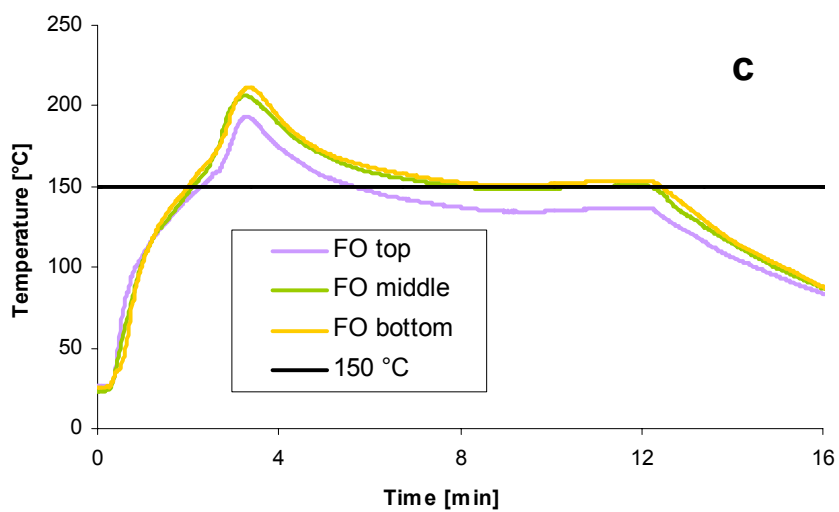
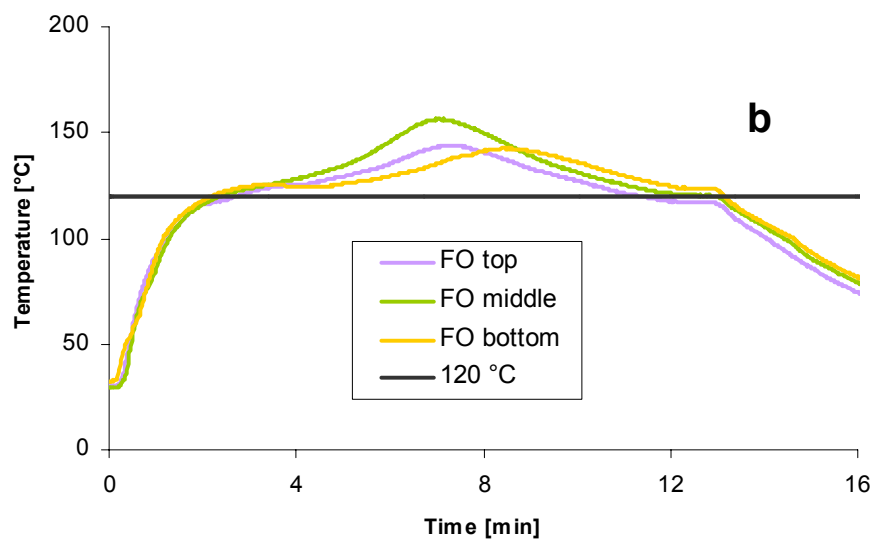
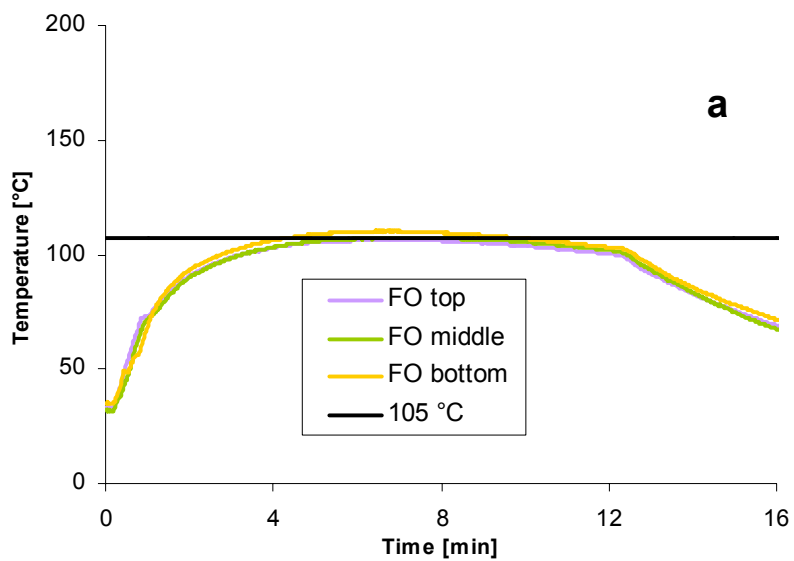


Figure S11: (previous page) Heating profiles for the alkylation of triphenylphosphine with benzyl chloride (Table 2). Reactions were performed on a 10 mmol scale using the reaction vessel shown in Figure 1b utilizing a pre-heated oil bath. Shown are the three internal temperature probes for experiments at an oil bath temperature of (a) 105 °C (b) 120 °C and (c) 150 °C for 10 minutes. While at 105 °C the reaction temperature is more or less constant during the whole experiment, at higher bath temperatures (b and c) thermal runaways were observed leading to significantly higher internal reaction temperatures. Note that in the 150 °C run the top sensor was not properly immersed into the crystallized reaction mixture and therefore did not display a correct temperature.

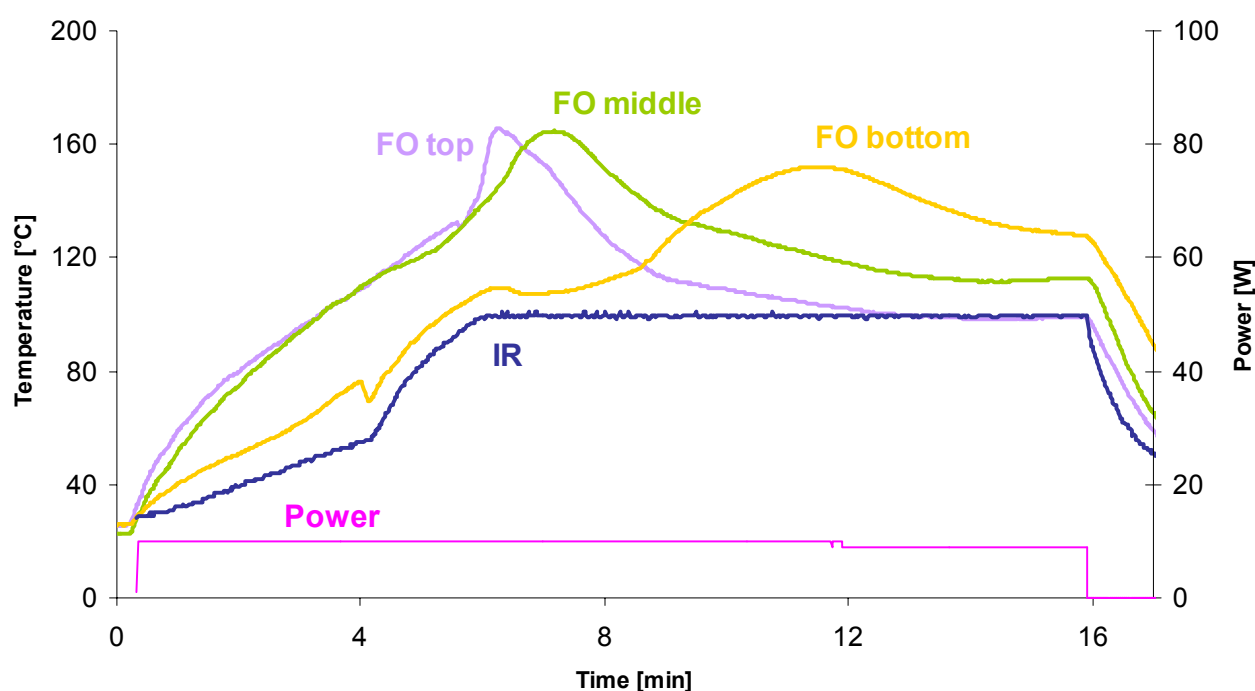
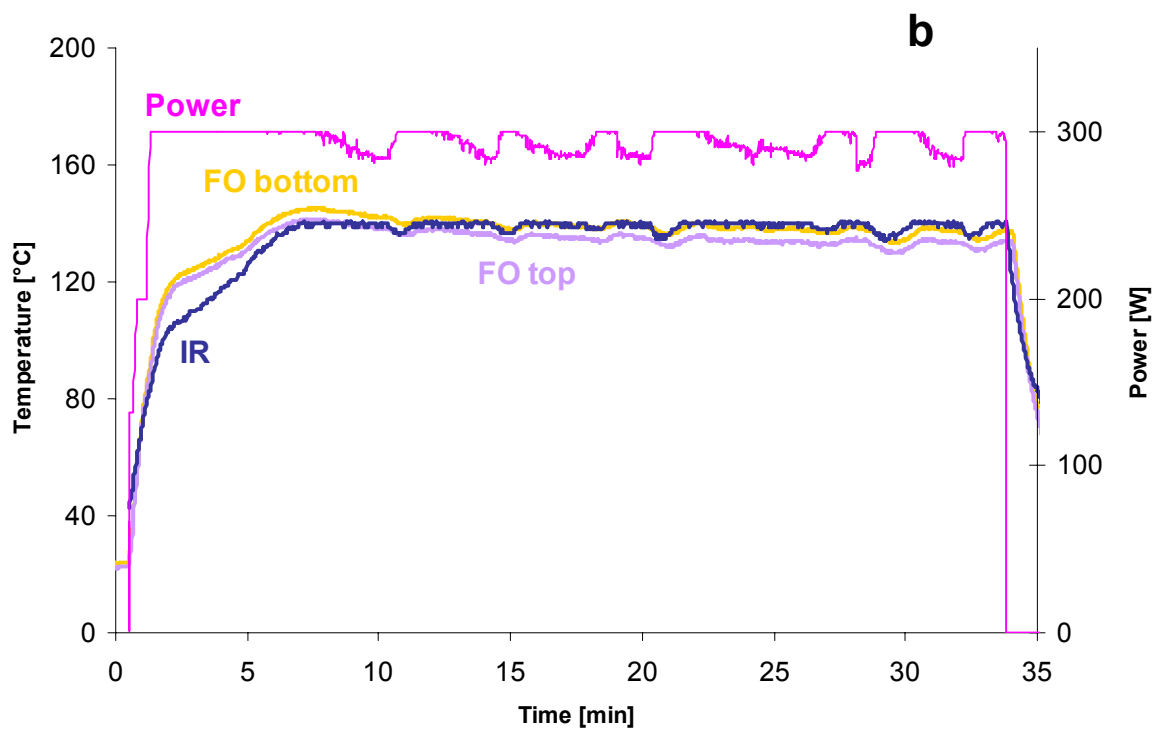
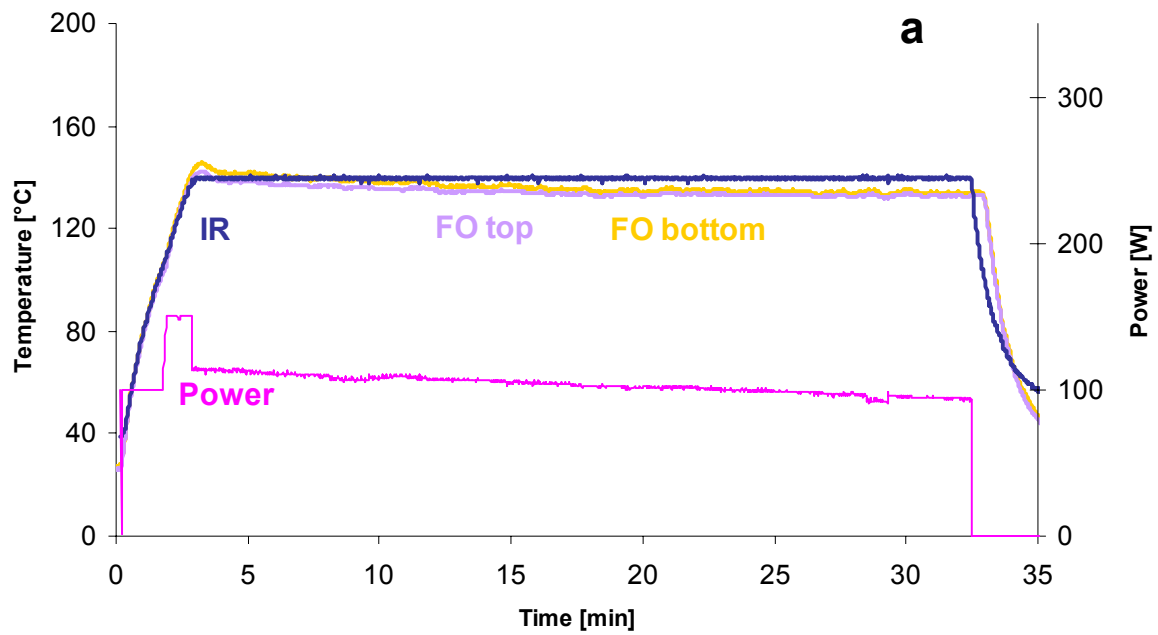


Figure S13: Temperature and microwave power profiles for the microwave-assisted solvent-free alkylation of triphenylphosphine with benzyl chloride (CEM Discover single-mode reactor, reaction vessel: see Figure 1b, 10 W maximum magnetron output power, temperature control using the built-in IR sensor). Shown are the profiles for the three internal fiber-optic temperature probes, for the external IR sensor located at the bottom of the instrument (IR), for and the magnetron output power (Power). While the IR sensor controlling the magnetron power continuously measures 100 °C corresponding to the correct set temperature, the internal fiber-optic probes reveal the inhomogeneous temperature distribution within the reaction vessel with a maximum recorded temperature of 164 °C.



(contd)

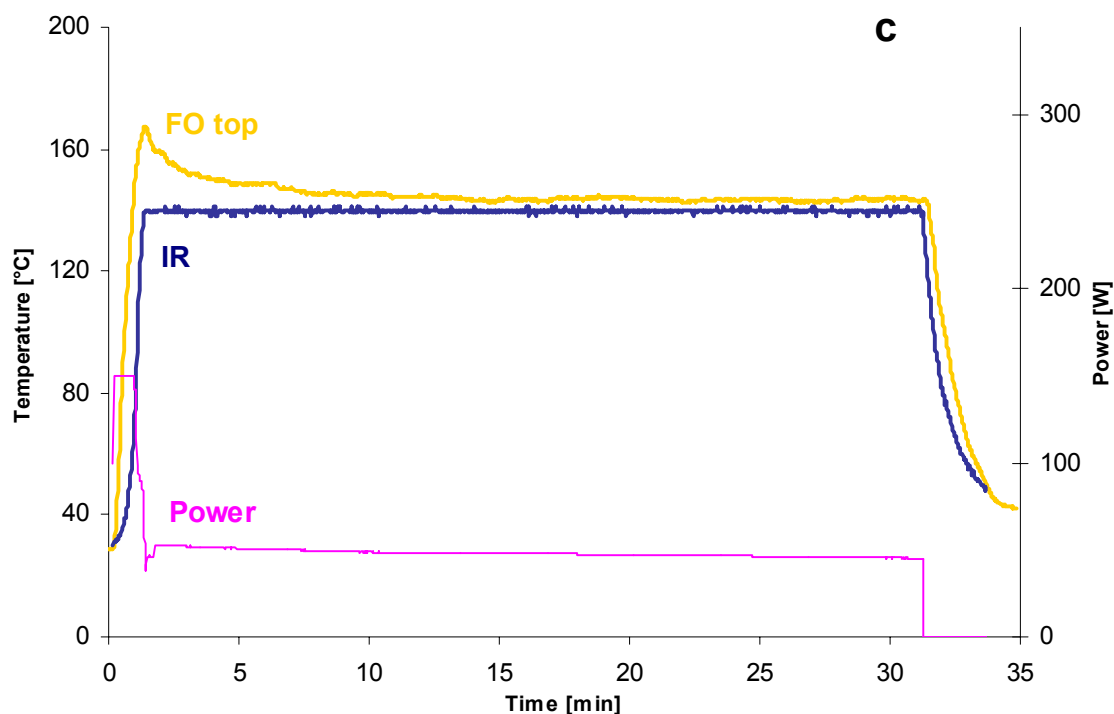


Figure S14: Temperature and microwave power profiles for the microwave-assisted alkylation of triphenylphosphine with benzyl chloride in *p*-xylene at 140 °C for 30 minutes (Table 3, entry 3) (CEM Discover single-mode reactor, reaction vessel: see Figure 1b, temperature control using the built-in IR sensor). Shown are the profiles for the experiments: (a) microwave heating at 105 W average power; (b) with simultaneous cooling consuming an average power of 292 W; and (c) employing a strongly absorbing SiC passive heating element reducing the average power to 51 W. Note that the internal reaction temperature using the SiC heating element in the initial phase of the experiment is significantly higher than the measured IR temperature explaining the slightly higher yield using this technique (18 versus 14%, Table 3, entry 3).

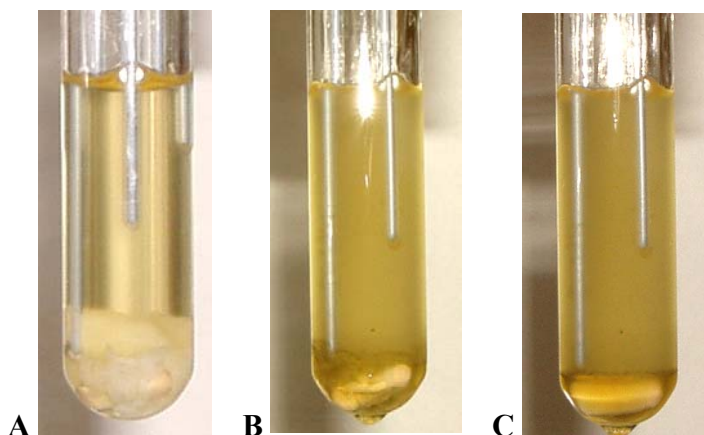


Figure S15: Alkylation of 1,2,4-triazole with 2,2',4'-trichloroacetophenone in *p*-xylene at 140 °C (Scheme 1). The images show two fiber optic probes immersed in a mixture of 5.0 mmol triazole and 5.5 mmol 2,2',4'-trichloroacetophenone dissolved in 3 mL *p*-xylene (top phase). **A:** reaction mixture before the reaction. While 2,2',4'-trichloroacetophenone is soluble in *p*-xylene, 1,2,4-triazole, which is a solid at room temperature, stays undissolved at the bottom of the vessel. **B, C:** Since the melting point of 1,2,4-triazole is lower than the reaction temperature (140 °C) the starting material melts during the reaction. The biphasic reaction mixture can not be efficiently stirred using the magnetic stir bar, thus the molten triazole remains at the bottom of the vessel which can lead to differential heating and erroneous temperature measurement (**B:** stirred case, **C:** unstirred case).

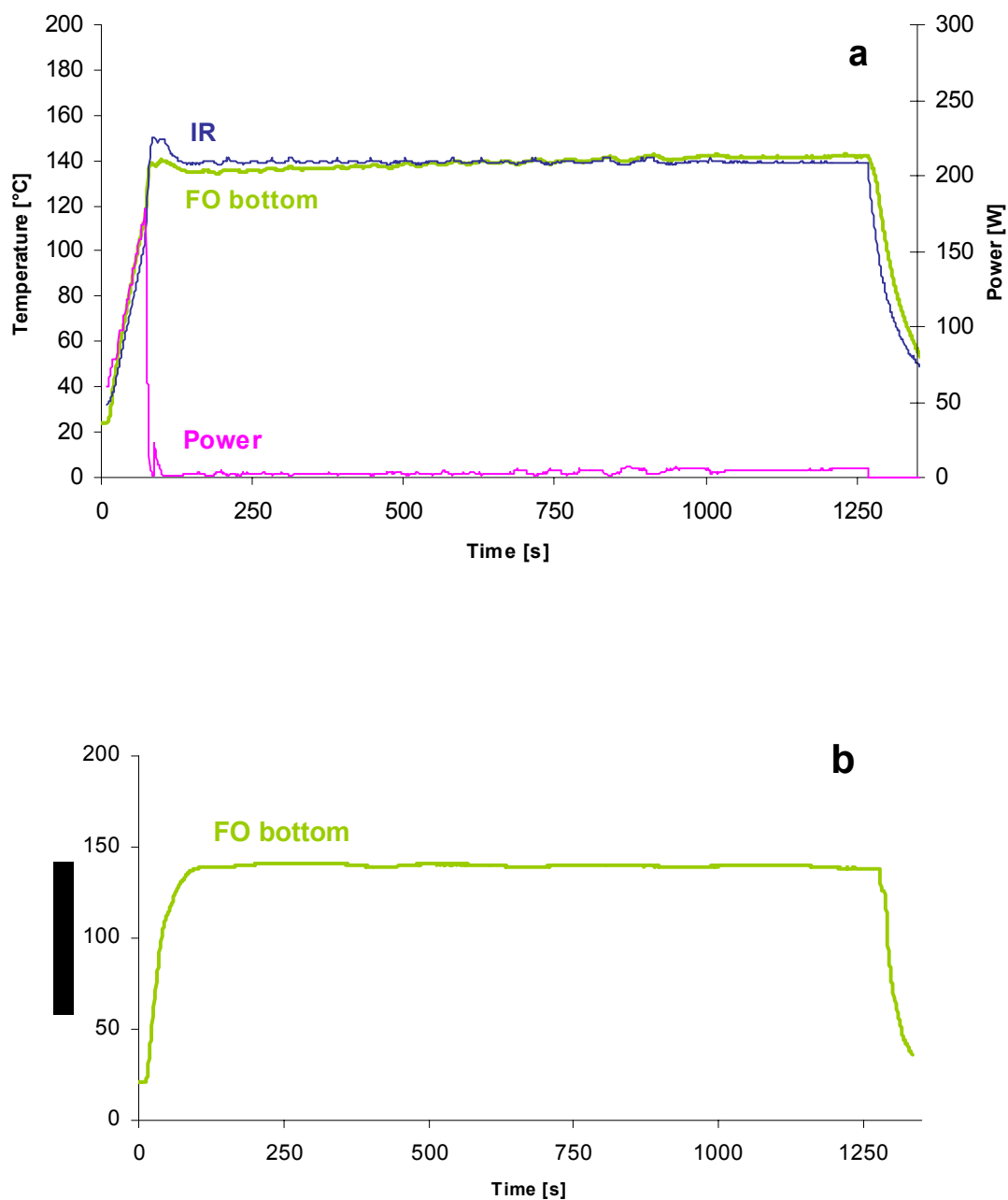
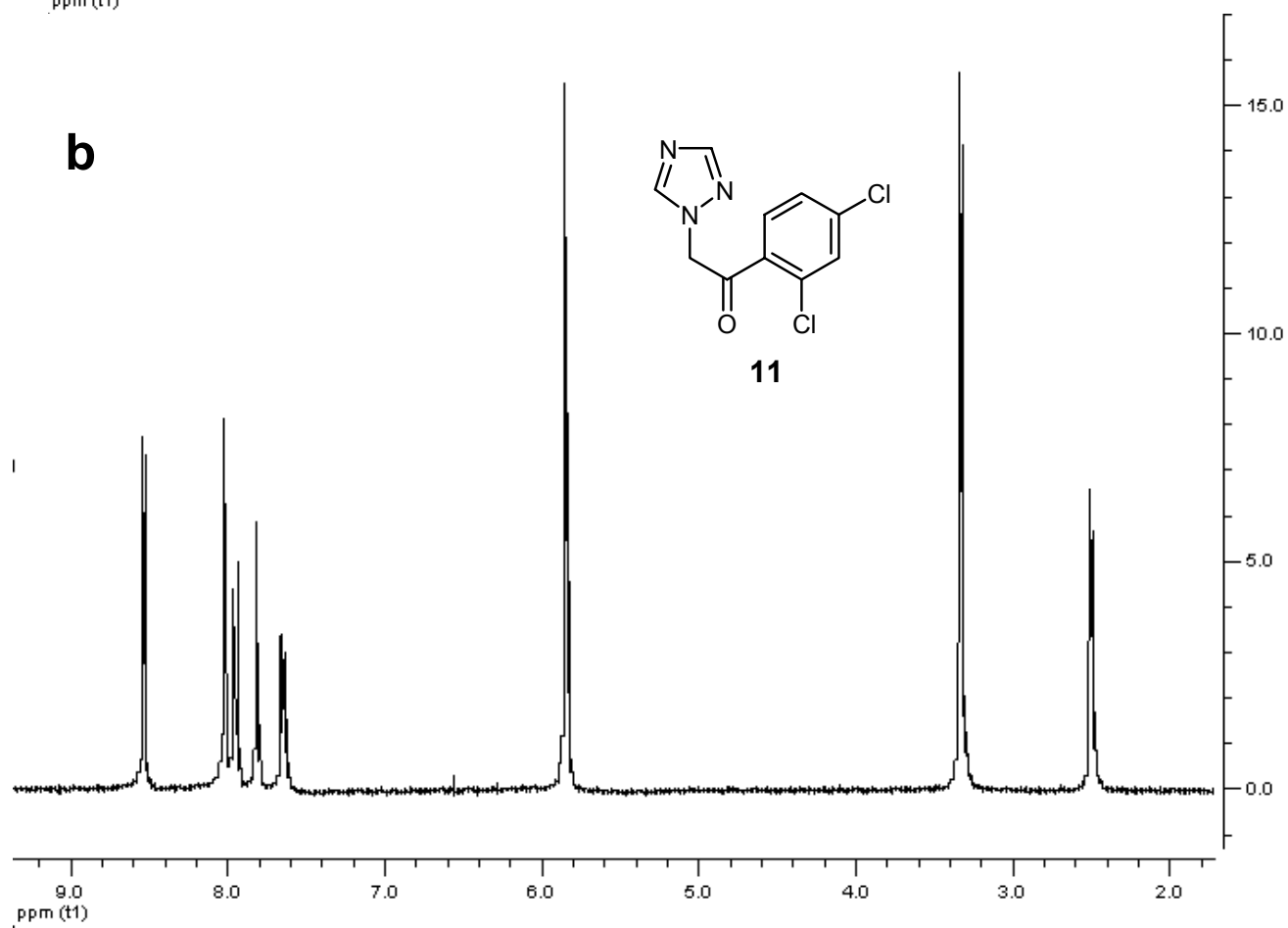
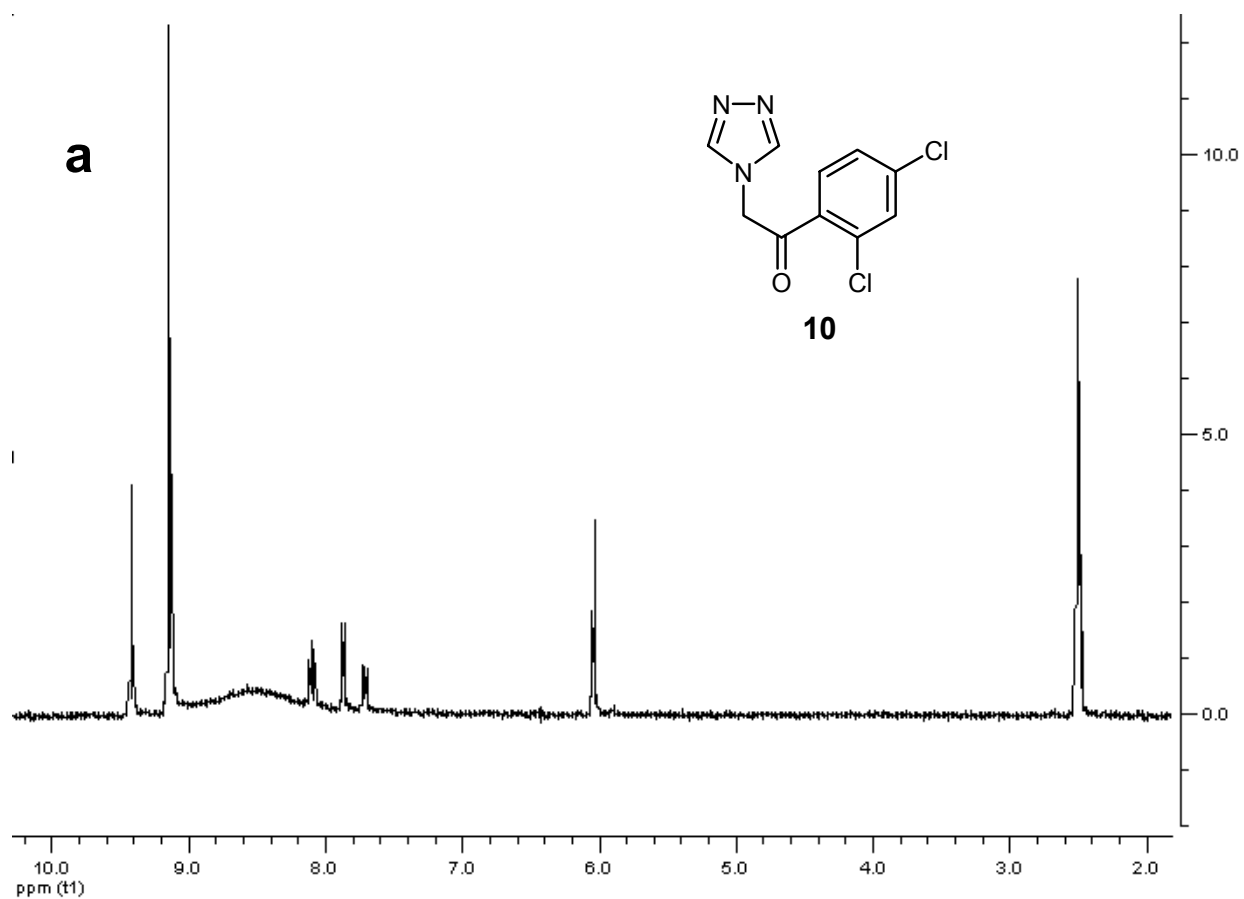
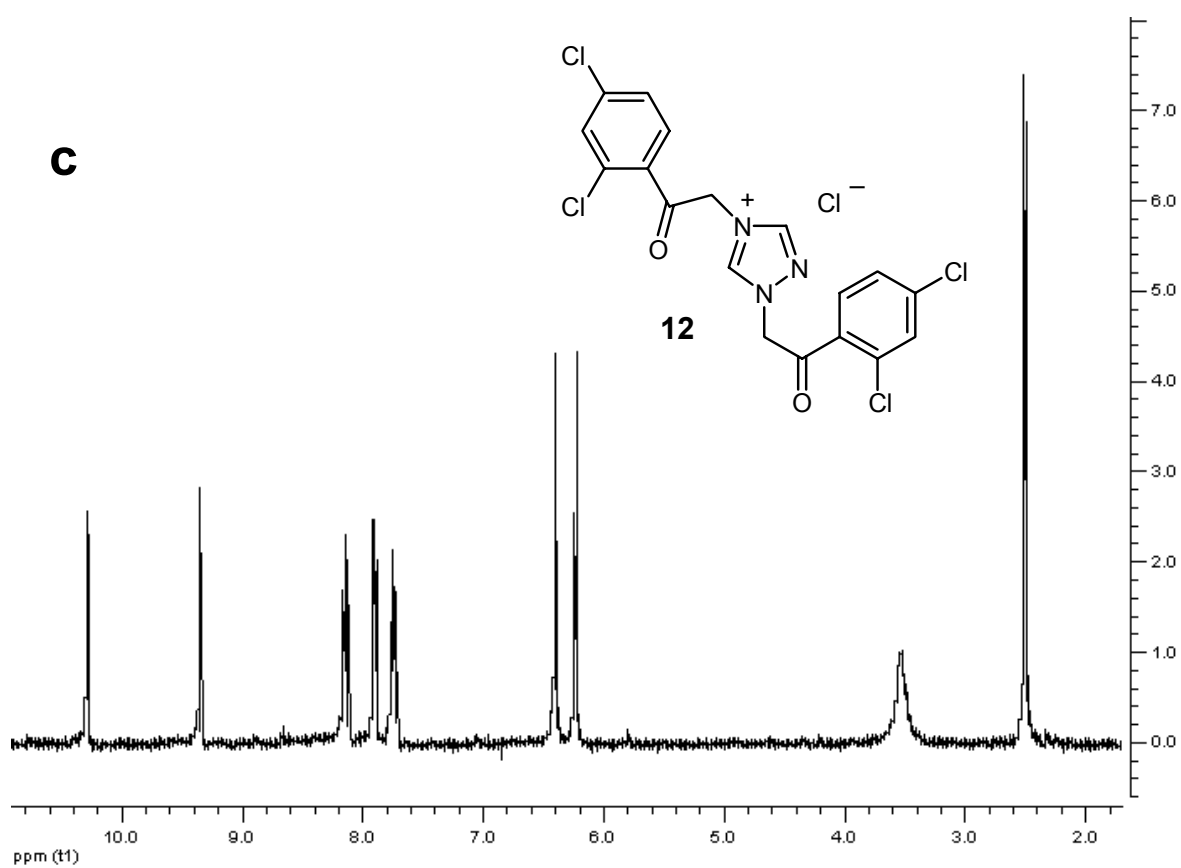


Figure S16: Temperature and microwave power profiles for the microwave-assisted alkylation of 1,2,4-triazole with 2,2',4'-trichloroacetophenone in *p*-xylene at 140 °C for 20 minutes (Scheme 1 and Table 4, 1 mL *p*-xylene) (CEM Discover single-mode reactor, reaction vessel: see Figure 1b, temperature control using the built-in IR sensor and one additional fiber-optic probe). Shown are the profiles for (a) microwave heating, and (b) oil bath heating





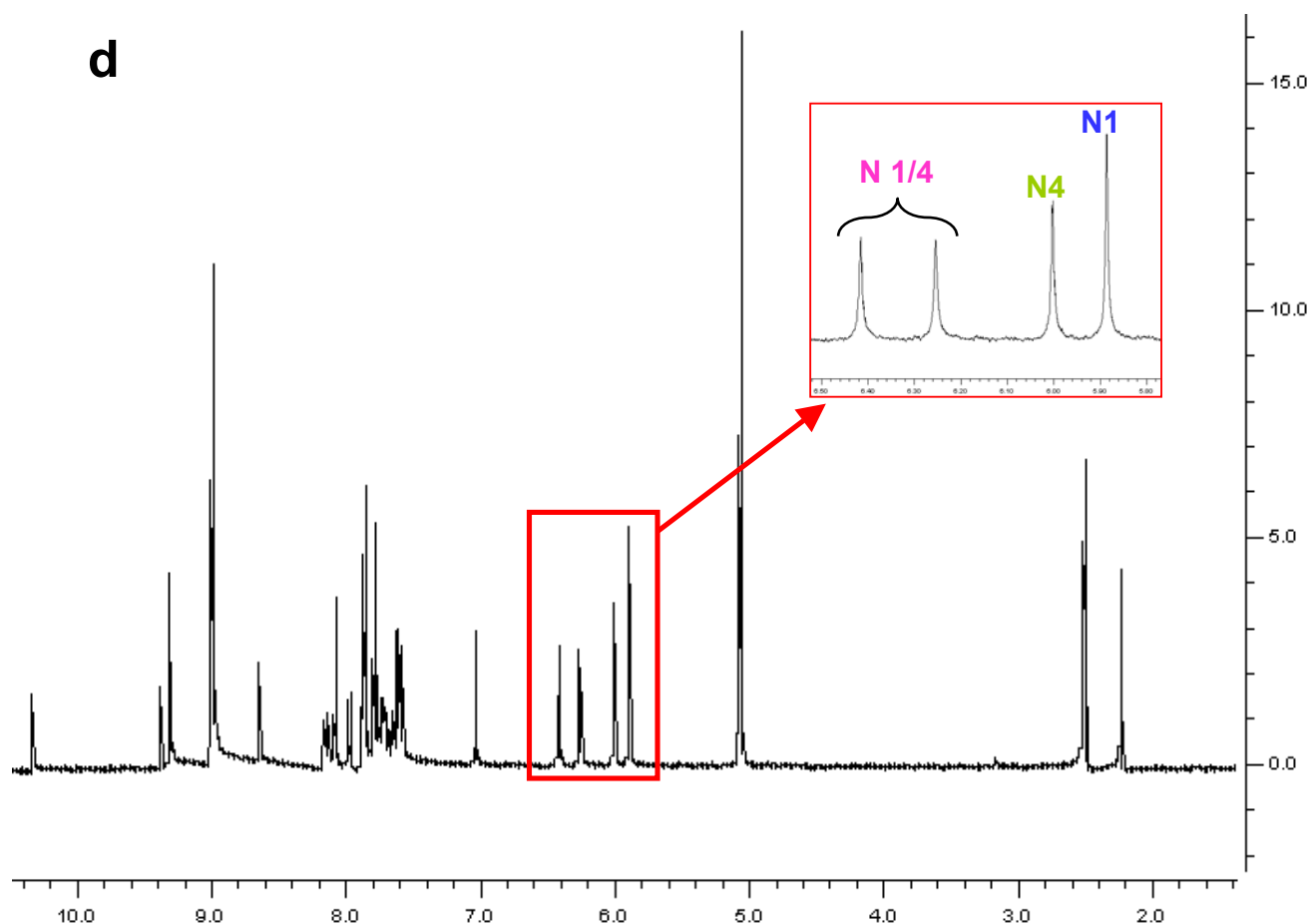


Figure S17. ^1H NMR spectra (360 Mhz) of triazole alkylation products **10-12** (a-c, see Scheme 1) and crude spectrum of product mixture resulting from the oilbath experiment described in Table 4, entry 1 (d). The insert shows the region containing the NCH_2CO signals used for integration purposes. The starting materials **8** and **9** are identified in spectrum d by shifts at 9.00 and 5.06 ppm, respectively For NMR data, see the Experimental Section.

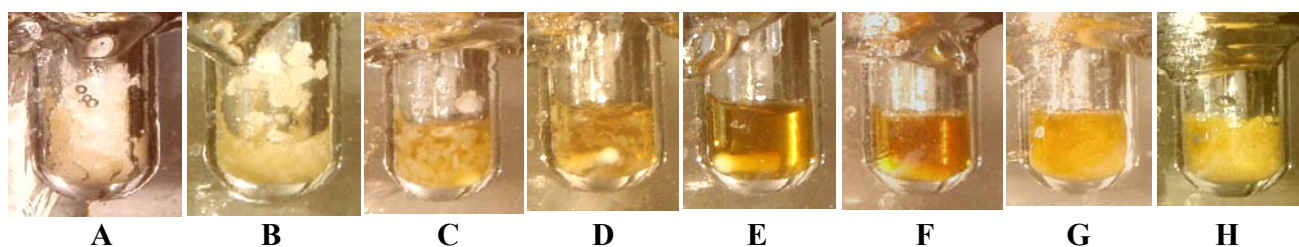


Figure S18. Solvent free alkylation of 1,2,4-triazole with 2,2',4'-trichloroacetophenone at 140 °C bath temperature (Scheme 1). The alkylation reaction was performed on a 5.0 mmol scale (10% excess of alkyl chloride) using the reaction vessel shown in Figure 1b utilizing a pre-heated oil bath. At a bath temperature of 140 °C a thermal runaway was observed leading to significantly higher internal reaction temperatures (199 °C) as monitored by a fiber-optic probe (Figure S19). Shown are images of the reaction mixture (**A-H**) within the initial 5 minutes of the reaction. During the first 2 minutes the starting materials are partly solid (**A-C**). Once the reaction mixture has melted (>120 °C), it is a homogeneous liquid (**D-F**) until the solid products are formed (**G-H**). At that time (**H**) stirring is not efficient.

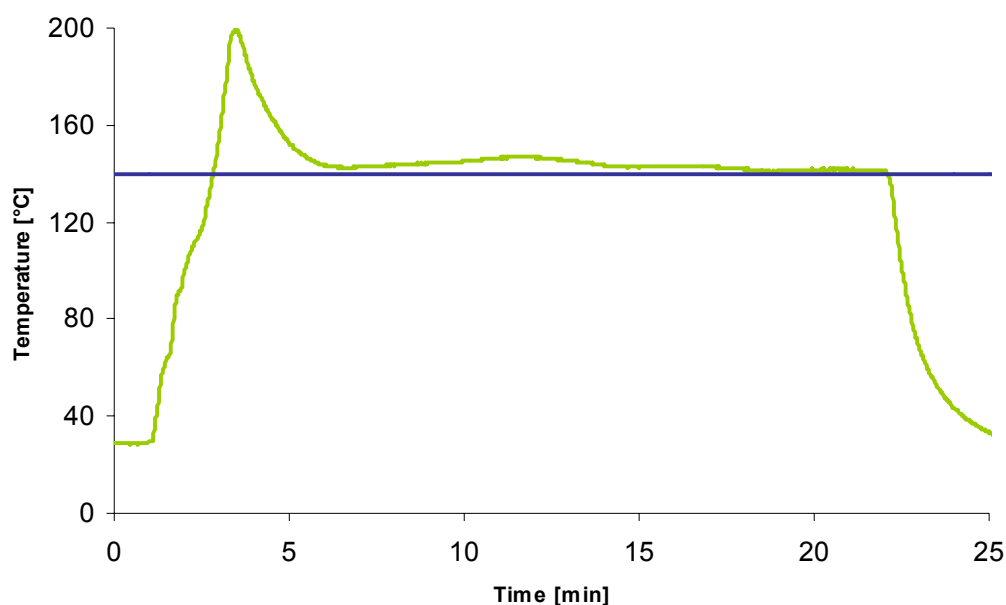


Figure S19: Heating profile for the solvent-free alkylation of 1,2,4-triazole with 2,2',4'-trichloroacetophenone under conventional conditions (Scheme 1). The reaction was performed on a 5.0 mmol scale (10% excess of alkyl chloride) using the reaction vessel shown in Figure 1b utilizing a pre-heated oil bath. At a bath temperature of 140 °C a thermal runaway was observed leading to significantly higher internal reaction temperatures (199 °C) as monitored by a fiber-optic probe.

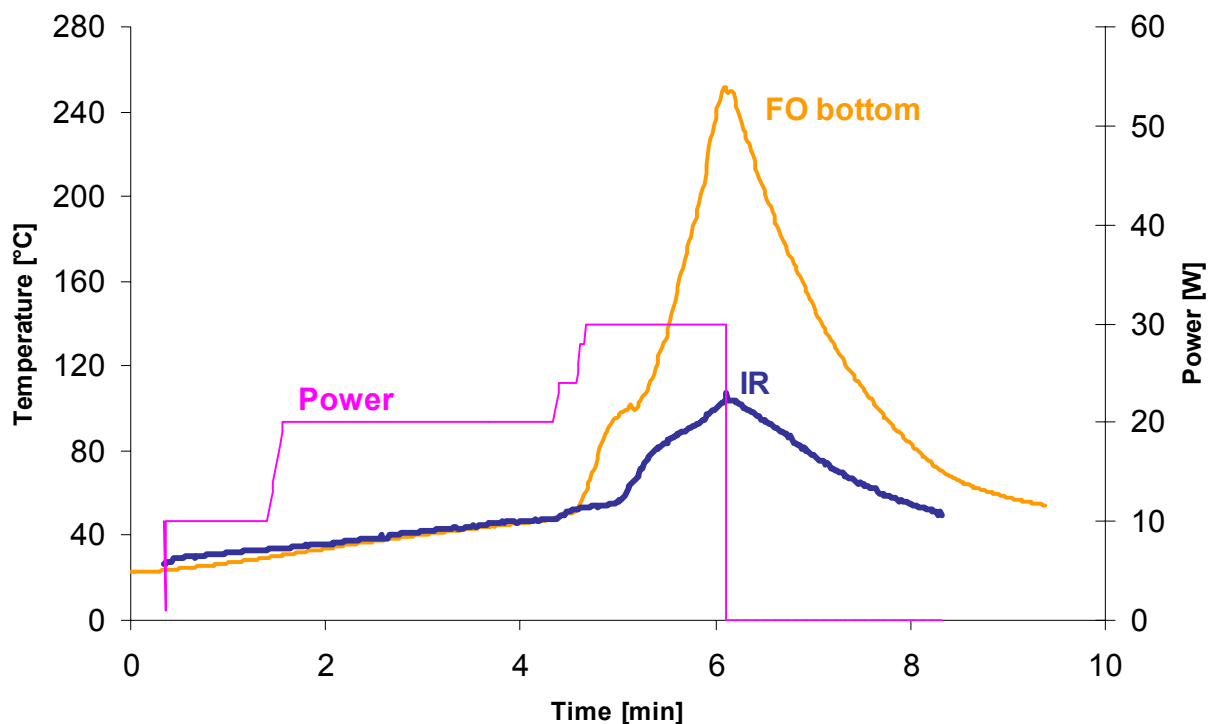


Figure S20: Temperature and microwave power profiles for the microwave-assisted solvent-free alkylation of 1,2,4-triazole with 2,2',4'-trichloroacetophenone (Scheme 1) (CEM Discover single-mode reactor, reaction vessel: see Figure 1b, 30 W maximum magnetron output power, temperature control using the built-in IR sensor, set temperature 140 °C). Shown are the profiles for one internal fiber-optic temperature probe, for the external IR sensor located at the bottom of the instrument (IR), and for the magnetron output power (P). While the IR sensor controlling the magnetron power displayed a maximum temperature of only 100 °C, the internal fiber-optic probe showed the reaction temperature to be > 250 °C at which point the experiment had to be aborted for safety reasons. Note that the reaction starts after the 2,2',4'-trichloroacetophenone melted after ca 4.5 min (mp 52-55 °C). At this point the exothermic alkylation process starts which due to the strongly microwave absorbing properties of the reaction mixture leads immediately to a run away. Cooling by compressed air after abortion of the experiment after 6 min is able bring down the reaction temperature to ambient within 2-3 min.

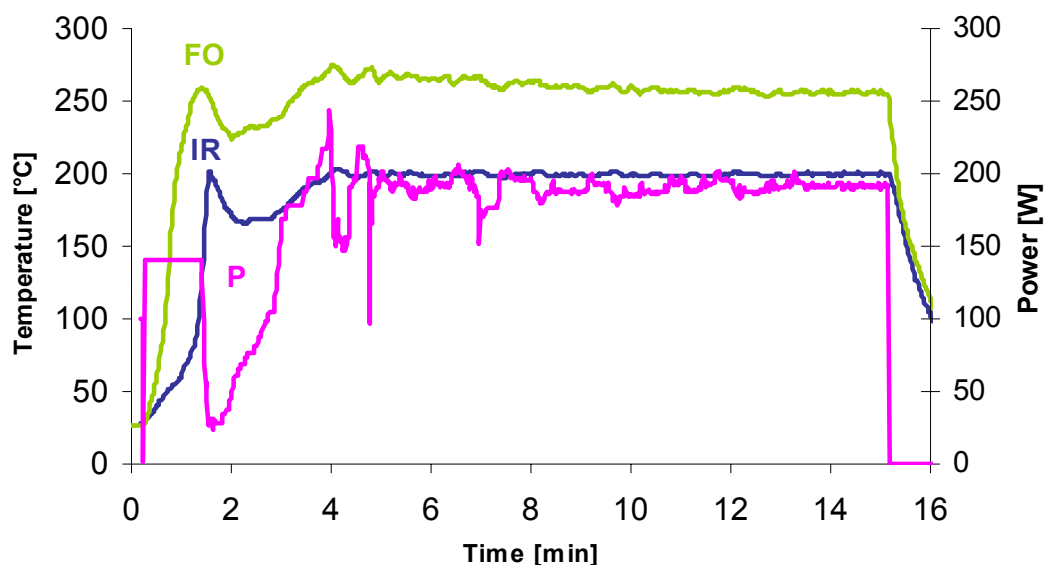


Figure S21. Temperature and microwave power profiles for the microwave-assisted amidation of methacrylic acid with (*R*)-1-phenyl-ethylamine (Scheme 2). CEM Discover single-mode reactor, reaction vessel: see Figure 1b, dual temperature monitoring using IR and one fiber-optic sensor. A constant 140 W microwave output power was initially applied until the IR-temperature reached 200 °C. Subsequently, the constant cooling by compressed nitrogen (rt, 6 bar) was started and the maximum output power was simultaneously raised to 300 W. While the IR sensor (IR) shows constant 200 °C (temperature control) the average temperature measured by an internal fiber-optic sensor (FO) is ca 55-65 °C higher, showing a maximum temperature of 274 °C after ca 4 min, dropping to 255 °C at the end of the experiment (average temperature 257 °C). The average magnetron output power in this experiment is 173 W.

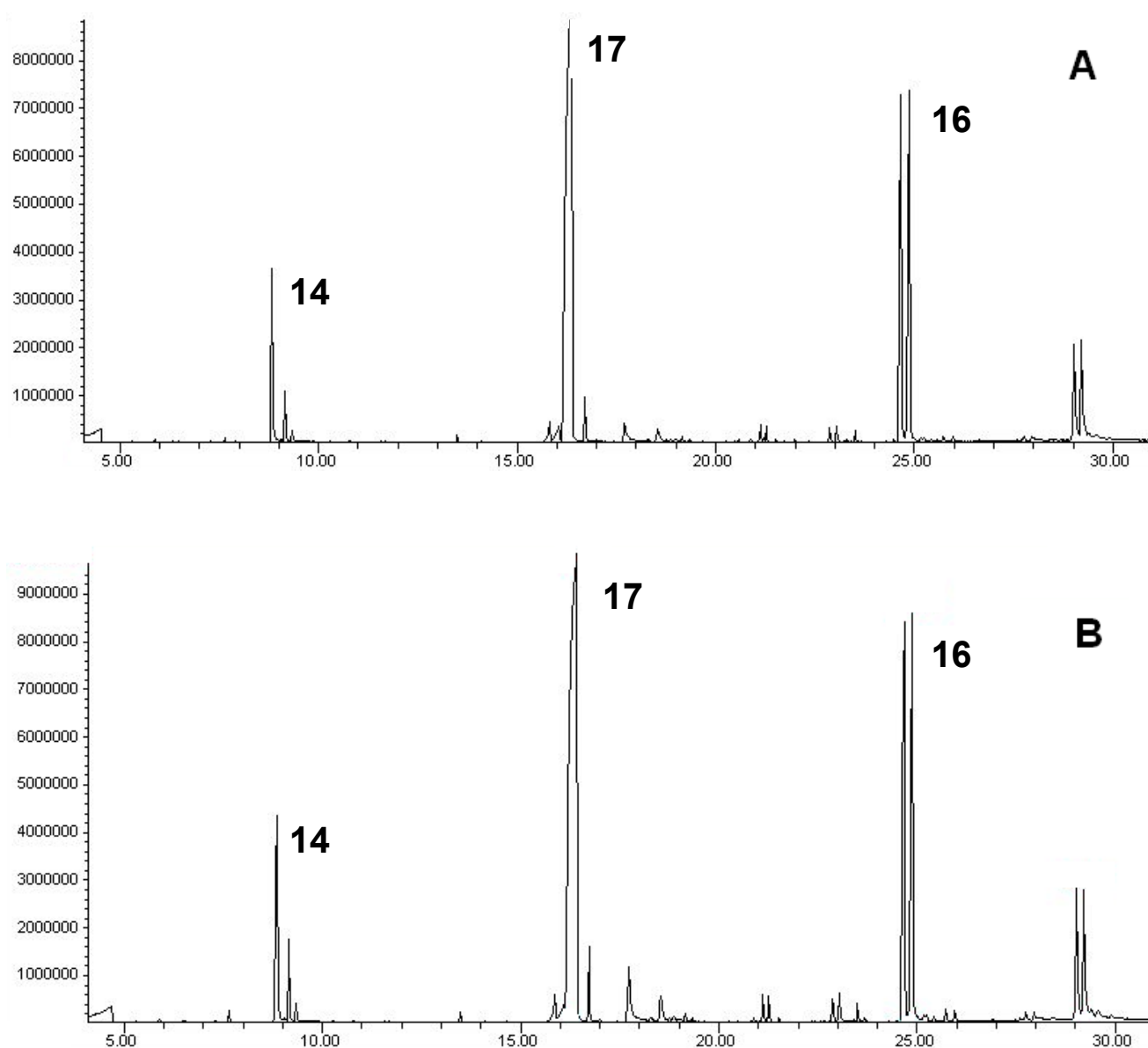


Figure S22. GC-MS trace comparison for the direct amidation of methacrylic acid with (*R*)-1-phenylethylamine (Scheme 2) under both microwave and oil bath conditions at ca 260 °C (Table 5). GC-MS spectra have been recorded directly from the crude reaction mixture dissolved in methanol from experiments performed in a preheated metal bath (**A**, Table 5, entry 2) and in a microwave reactor (**B**, Table 5, entry 3). The corresponding temperature profiles are shown in Figure S23. In both spectra the major desired product (**17**, *m/z*: 189) is present in ca 60 % (area percentage) as compared to amide **16** (*m/z*: 310, ca 25%, double peak). The peaks at ca 29 min likely correspond to decomposition products of methacrylamide **17** as control experiments have confirmed that this material is formed from pure **17** upon prolonged heating at 260 °C (ca 15 min).

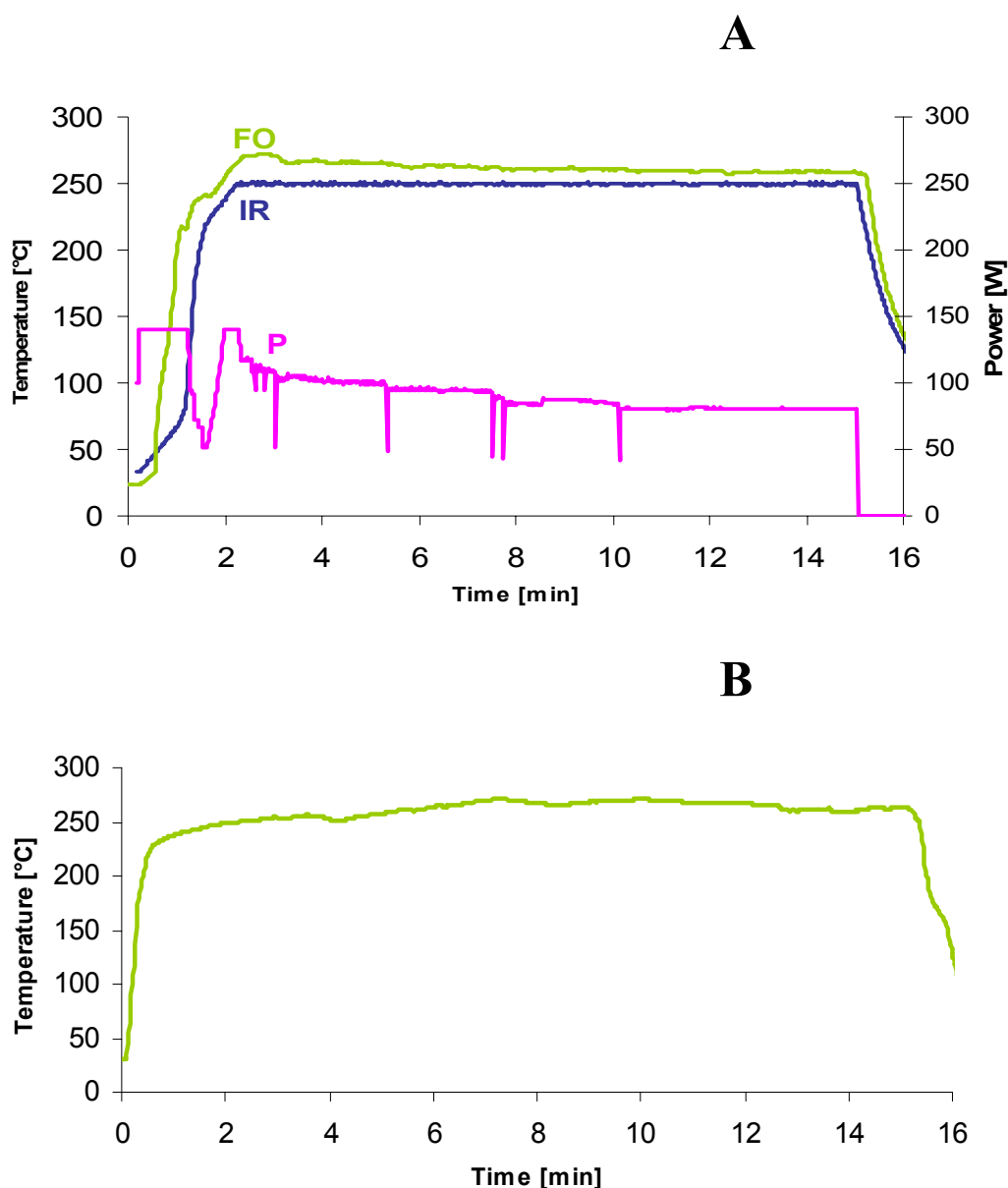


Figure S23. Heating profiles for the amidation of methacrylic acid with (*R*)-1-phenyl-ethylamine (Scheme 2) at a 7.0 mmol scale at ca 260 °C reaction temperature in a microwave reactor (**A**, CEM Discover single-mode reactor, reaction vessel: see Figure 1b, temperature control using the built-in IR sensor and one additional fiber-optic probe) and in a preheated metal bath (**B**). **A**: Although the IR-sensor (IR) shows constant 250 °C, the internal temperature (FO) reveals that the real average temperature was slightly higher (262 °C). **B**: The average internal temperature in the metal bath experiment was 263 °C (bath temperature 258-268 °C). Note that significantly less microwave power is used (average 94 W) as in the experiment involving simultaneous cooling (173 W, Figure S21).

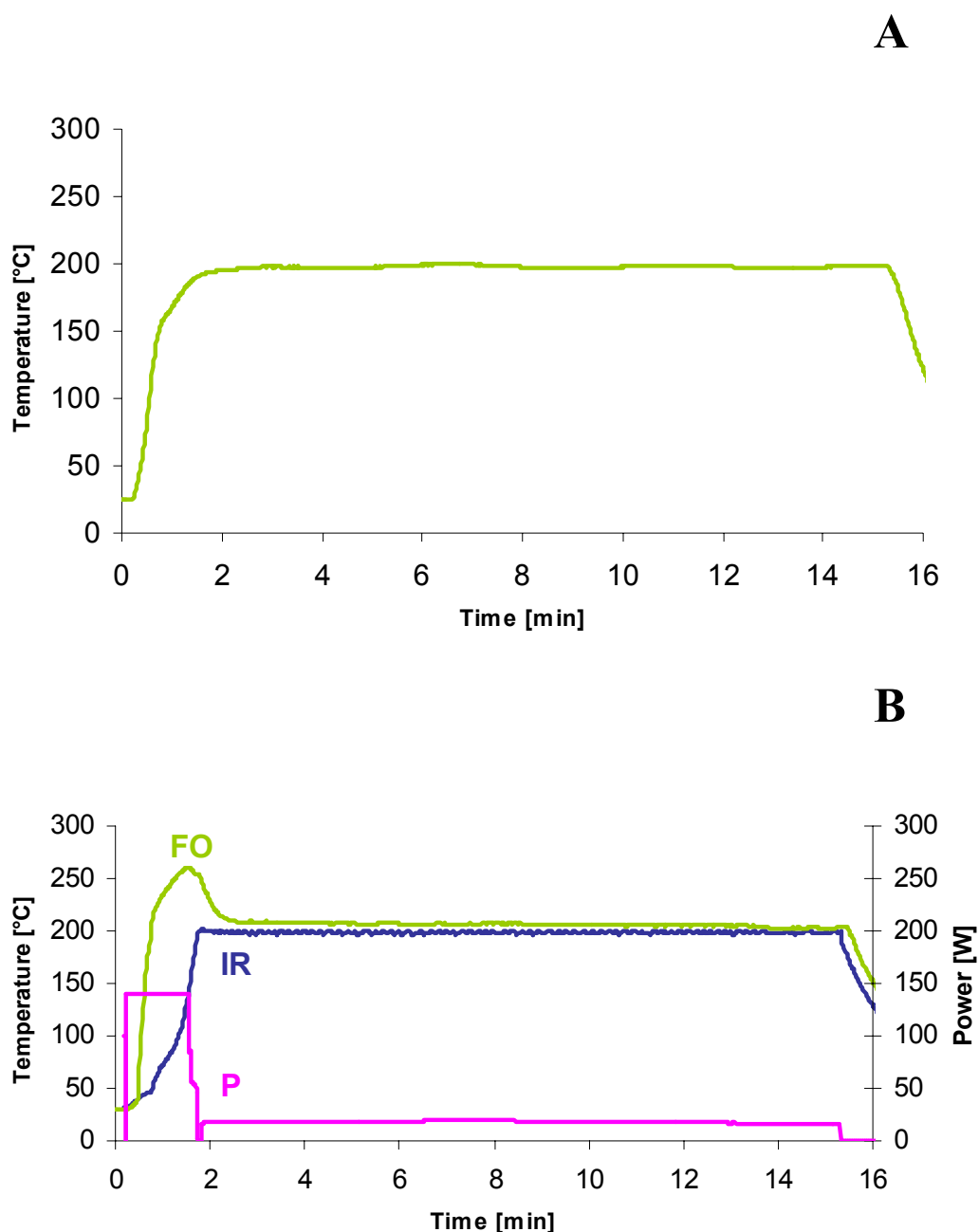


Figure S24. Heating profiles for the amidation of methacrylic acid with (*R*)-1-phenyl-ethylamine (Scheme 2) at a 7 mmol scale at 200 °C in a preheated oilbath (**A**) and in a microwave reactor (**B**, CEM Discover single-mode reactor, reaction vessel: see Figure 1b, temperature control using the built-in IR sensor and one additional fiber-optic probe). The fiber-optic probe (FO) reveals that the maximum internal temperature within the first 2 minutes was 267 °C. Consequently the yield for the microwave experiment was slightly higher compared to the oil bath experiment (Table 5, entry 4 and 5).

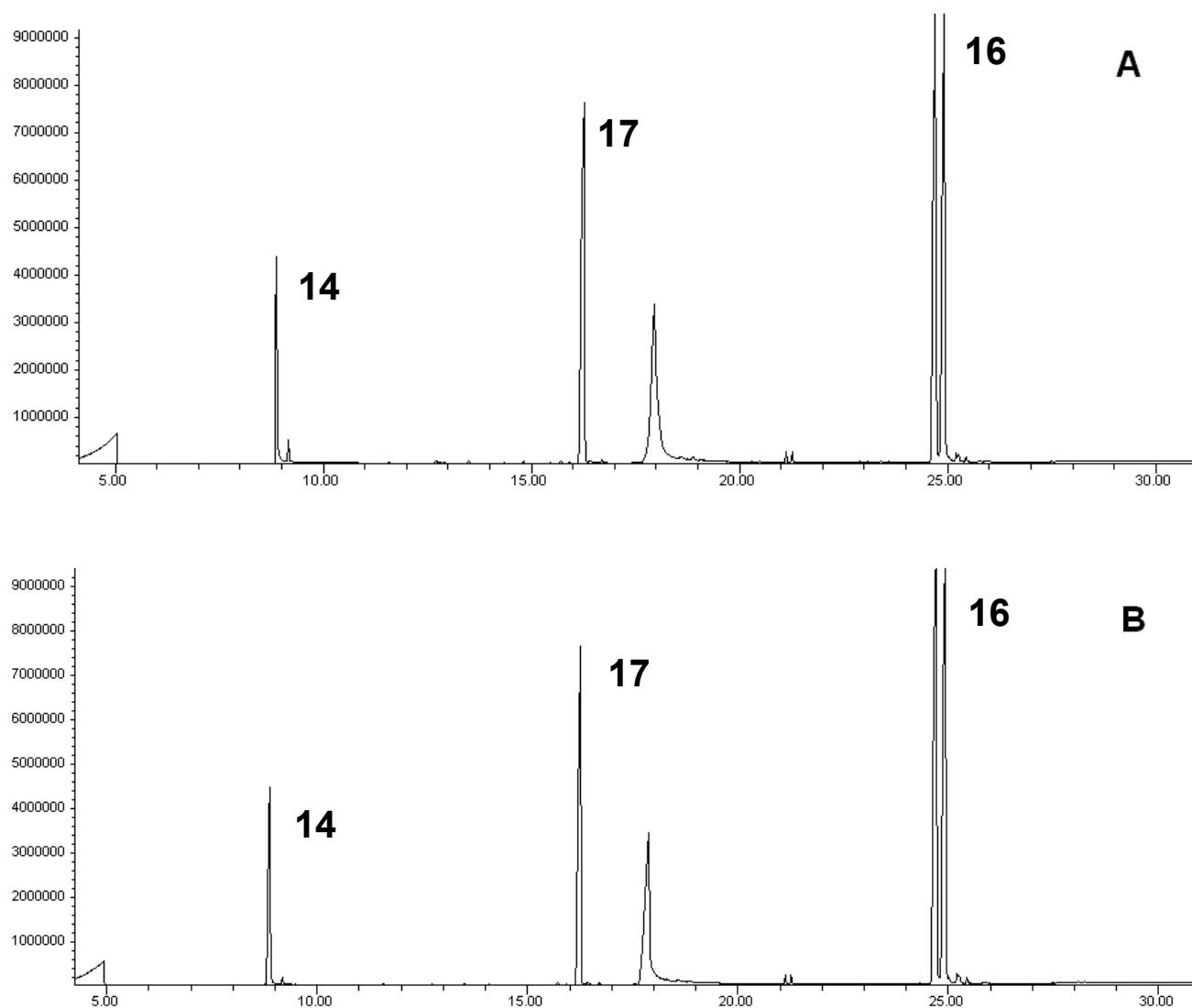


Figure S25. GC-MS trace comparison for the direct amidation of methacrylic acid with (*R*)-1-phenylethylamine (Scheme 2) under both microwave and oil bath conditions at 200 °C (Table 5). GC-MS spectra have been recorded directly from the crude reaction mixture dissolved in methanol from experiments performed in a microwave reactor (**A**, Table 5, entry 4) and in a preheated oil bath (**B**, Table 5, entry 5). The corresponding temperature profiles are shown in Figure S24. In both spectra the product distribution is similar. The unassigned broad peak at ca 18 min is likely due to the initially formed Michael adduct **18**. Analysis of the crude ^1H NMR spectra also indicated incomplete conversion and the presence of significant amounts of the initially formed salt **15** in the reaction mixture.

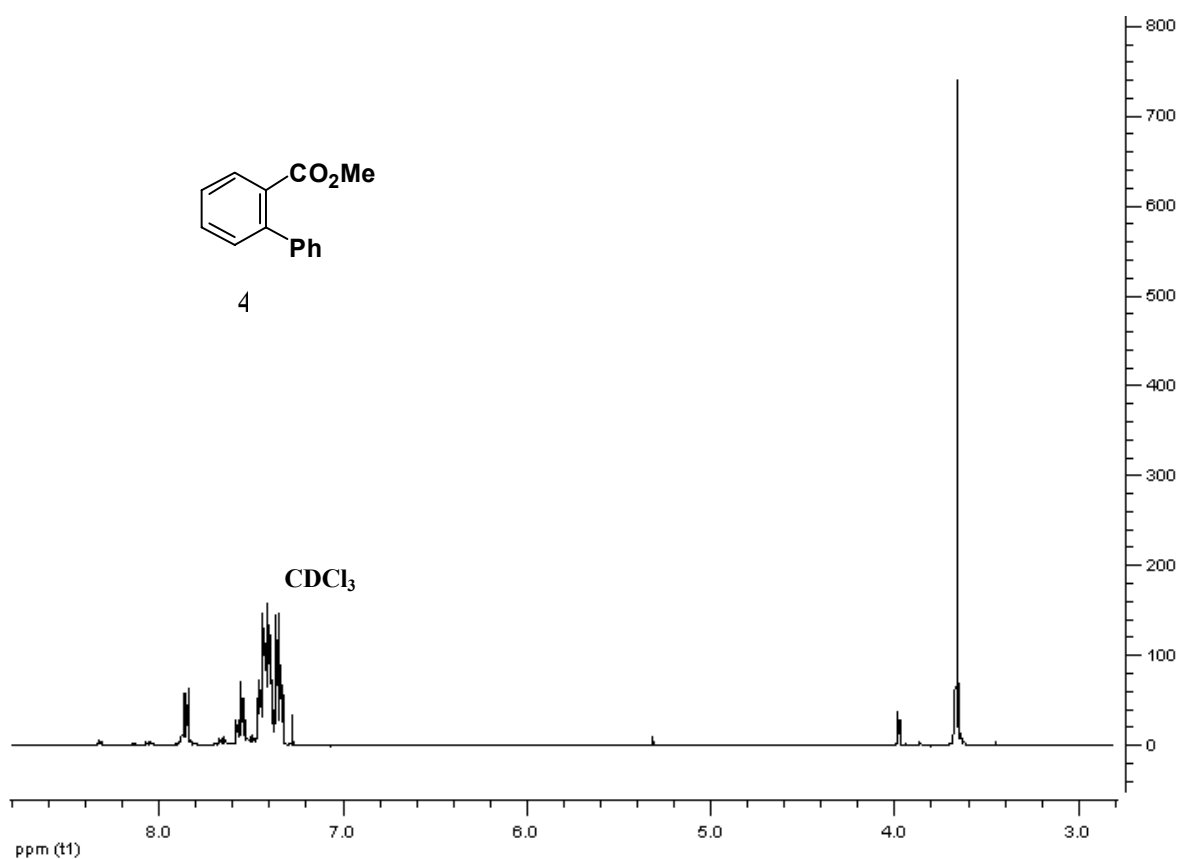


Figure S26. ¹H NMR spectrum (360 MHz) of cycloaddition product **4**.

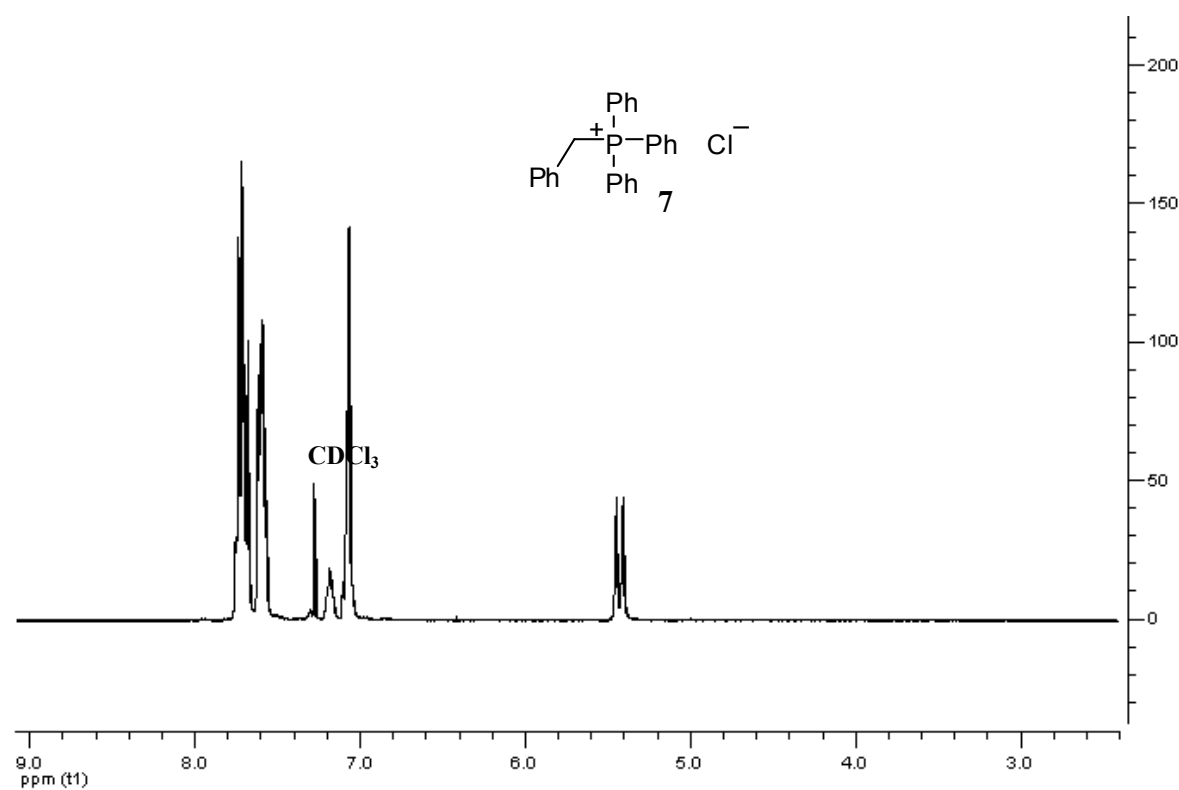


Figure S27. ¹H NMR spectrum (360 MHz) of phosphonium salt **7**.

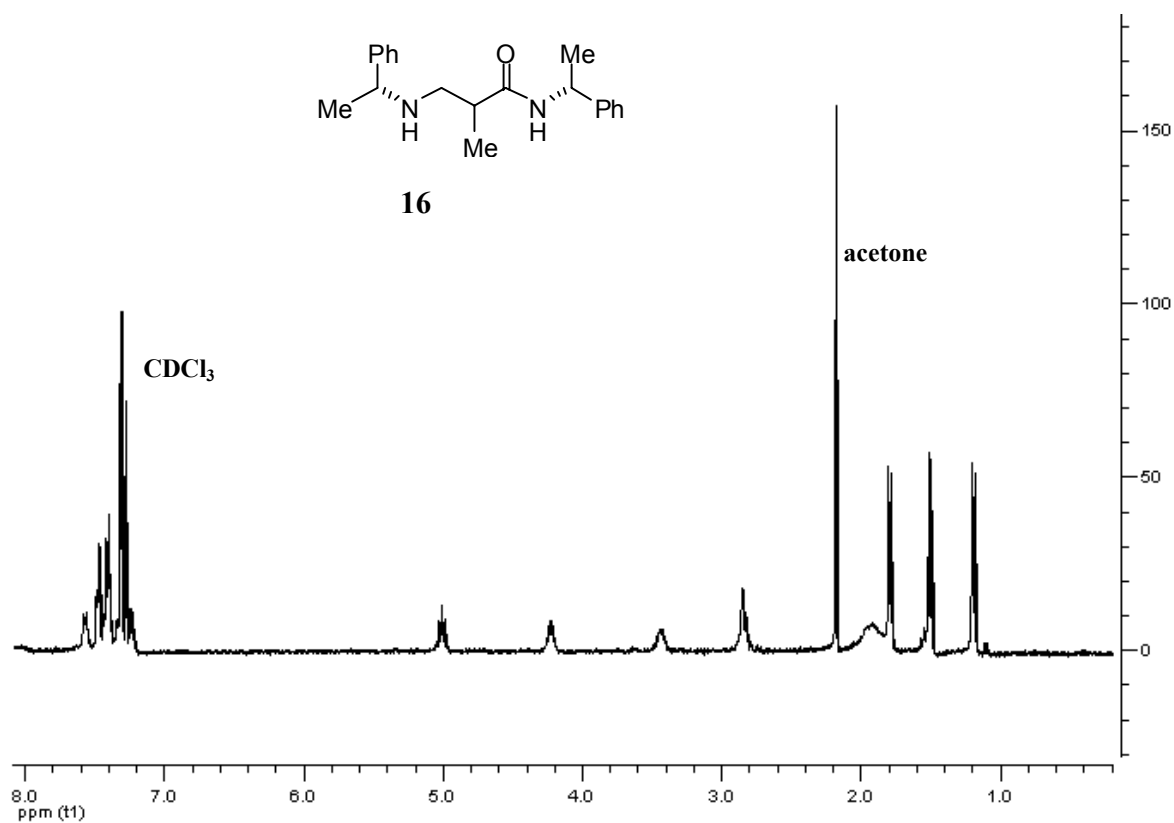


Figure S28. ¹H NMR spectrum (360 MHz) of amide **16**.

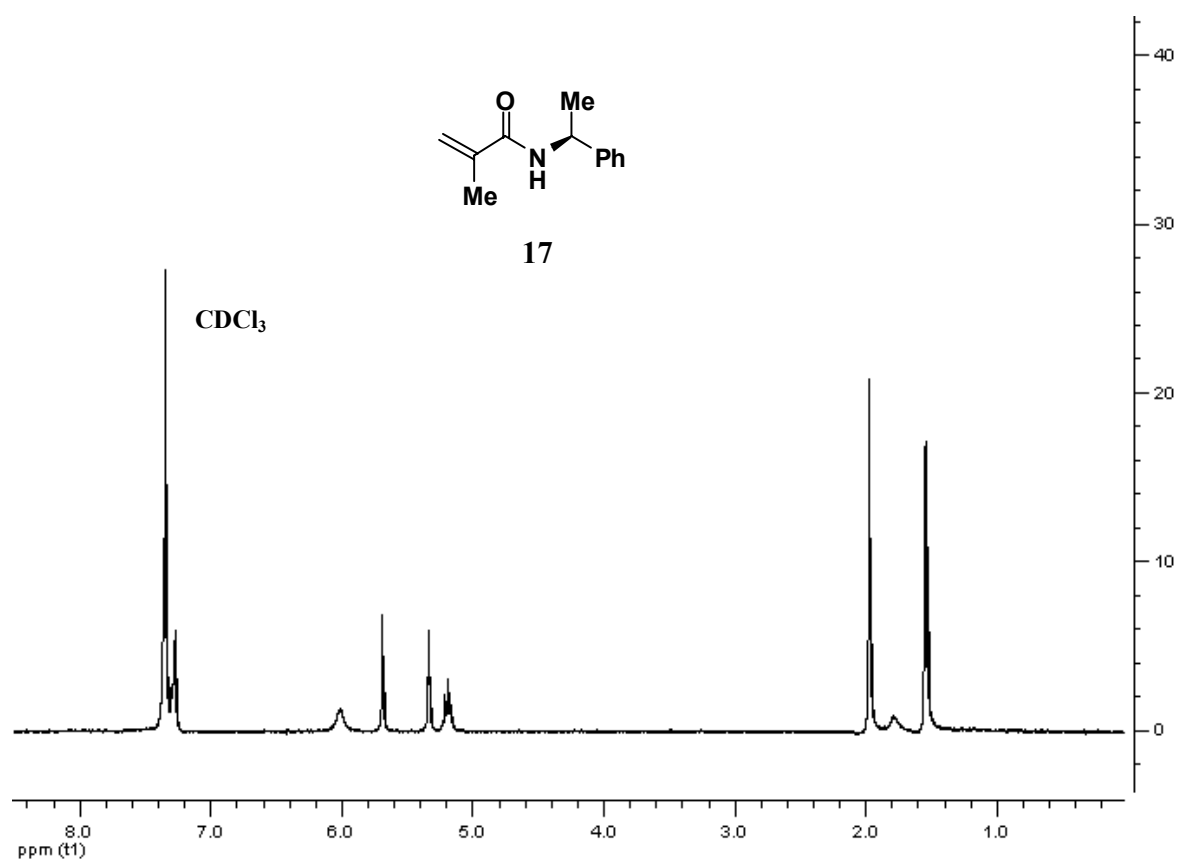


Figure S29. ¹H NMR spectrum (360 MHz) of methacrylamide **17**.