

Chemical Synthesis with Inductively Heated Copper Flow Reactors

Sascha Ceylan,^a Tobias Klande,^b Carla Vogt,^b Carsten Friese,^c Andreas Kirschning*^a

^a Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, Schneiderberg 1b, 30167 Hannover, Germany
E-mail: andreas.kirschning@oci.uni-hannover.de

^b Institute of Inorganic and Analytical Chemistry, Leibniz Universität Hannover, Callinstr. 1, 30167 Hannover, Germany

^c PIT – Plasma Induction Technology, Lorettostr. 20, 40219 Düsseldorf, Germany

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Abstract: Inductively heated copper wire inside a flow microreactor can serve as a source for a catalytic copper species that promotes 1,3-dipolar cycloadditions of alkynes with in situ formed azides to yield 1,2,3-triazoles. The same setup was used to carry out decarboxylations of 2-alkynoic acids and for the intramolecular C–O coupling of 2'-bromobiphenyl-2-carboxylic acid.

Key words: click chemistry, copper, heterogeneous catalysis, microreactors, inductive heating

Recently, we introduced the term enabling technologies for organic synthesis. These describe techniques that allow to perform organic synthesis as well as purification more rapidly, more efficiently, and less wasteful.¹ Typical enabling technologies can be new heating devices like microwave assistance,² new or nonclassical solvent systems,³ continuous flow reactors,⁴ and immobilization of chemically active species such as reagents and homogeneous catalysts (Figure 1).⁵ Truly new synthetic technology platforms, however, will not be based on the individual application of these techniques but will require the integration of two or more of these enabling techniques for a given synthetic challenge.

In this context, we developed several flow-reactor devices⁶ and incorporated immobilised reagents⁷ as well as catalysts⁸ and in selected cases encased this fixed bed reactor by a microwave apparatus in order to accelerate continuous-flow transformations and to reduce residence times.⁹

Recently, we disclosed inductive heating of ferromagnetic materials as a new heating technique and demonstrated that it is particularly suitable for being combined as fixed bed material inside flow reactors.¹⁰ As heating media inside flow reactors we chose magnetic Fe₃O₄ nanoparticles that are commonly employed because of their magnetic properties which allows to remove them from a reaction mixture with a magnet.^{11,12} In our case, these Fe₃O₄ nanoparticles are coated with a silica shell. We showed that inductive heating allows to perform many principle endothermic reactions such as transesterifications, condensations, palladium-catalysed cross-coupling reactions and Wittig olefinations under flow conditions.

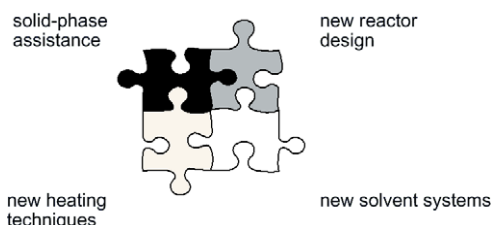


Figure 1 Enabling technologies for organic synthesis

In principal, also conductive metals such as iron, cobalt, nickel, copper, or alloys derived from these should be able to serve as heating media. Copper and copper salts can be a source for several catalytic transformations¹³ including Meldal's¹⁴ and Sharpless'¹⁵ copper-catalysed [3+2] cycloaddition of acetylenic compounds with azides that is founded on Huisgen's pioneering work. Recently, also copper-mediated examples of this cycloaddition under flow conditions were reported by Ley¹⁶ and Sach,¹⁷ respectively. In the present study, we disclose the use of copper metal as an inductively heatable material in mini-flow reactors that at the same time can serve as a catalytic source. This concept was expected to have several charming features such as: a) simple setup, b) only copper is the initial source of heat and it occurs inside the reactor, c) the heated metal is the source of the catalyst which guarantees ideal activation, d) copper can be heated at least above 220 °C, and e) metal leaching is kept to a minimum.

Inductive heating can be generated in medium or high frequency fields. As the technical setup for the former is simpler than for the latter, we carried out electromagnetic induction of heat in magnetic nanoparticles or other conductive materials by applying a medium frequency field (10–25 kHz). The copper-loaded (24 g) flow reactor was made of glass and encased with an inductor. The dimensions of the reactor were 12 cm length and 8.5 mm internal diameter. The inner volume (for the fluid) of this fixed bed reactor was determined to be 2 mL. In cases when a higher temperature than the boiling point of the solvent was needed a PEEK (polyether ether ketone) reactor with the same inner dimensions and equipped with an in-line back-pressure regulator was applied (Figure 2).

Although the leaching of copper species was envisioned to be low the system was also equipped with a metal scavenger cartridge. This cartridge was charged with commer-

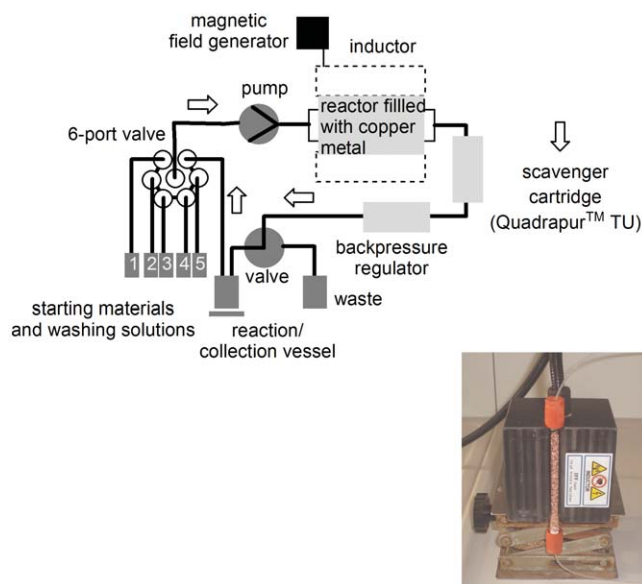


Figure 2 Reactor filled with copper wire and encased with an inductor (bottom) and schematic drawing of experimental setup (up)

cially available Quadrapur TU.¹⁸ The processes can be operated in a circular or a continuous mode. However, we optimised reaction parameters (concentration of reactants, flow rates, induction parameters for heating) to achieve full conversion in a single pass.

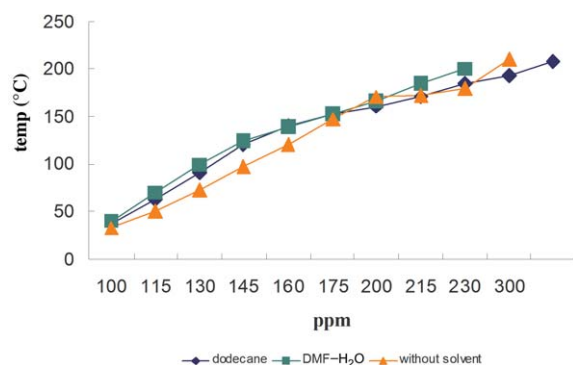


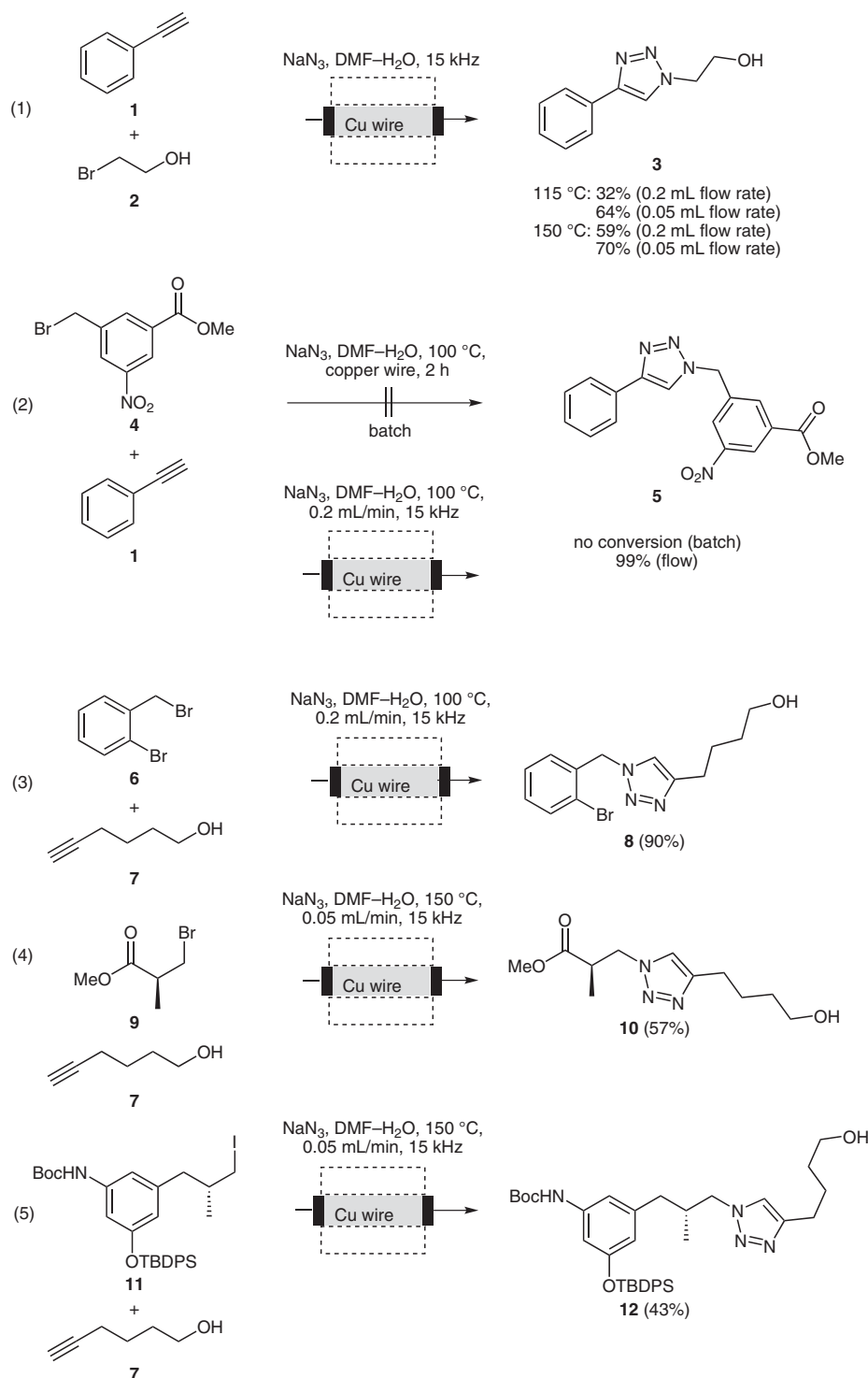
Figure 3 Heating profile of copper wire, measured without solvent, with degassed dodecane, and with degassed DMF-H₂O (5:1), 15 kHz (ppm = parts per million, equals percentage of power input)

First, we studied the effect of an inductive field on the copper wire. A reactor was charged with copper wire (4 mm × 1 mm × 1 mm) and the generated heat in relation to the used power was recorded. We found that copper heats up very rapidly and efficiently to temperatures above 220 °C, irrespective of the solvent employed (the temperature was determined by external application of an IR pyrometer on the surface of the reactor). It should be noted that at temperatures around 180 °C oxidations on the metal surface occurred that we associated to air oxygen (Figure 3) and which is visualised by a plateau in the heating diagram. This means that raising the power does not result in an increase of the temperature. However, this effect can be avoided if oxygen is excluded from the reaction mixture using degassed solvents.

We found that heating of the solution proceeds very rapidly once it has entered the reactor. The desired temperature was commonly reached within the first cm of the reactor. In analogy to recent work by Sach et al.¹⁷ we first explored a one-pot click methodology by in situ creating organic azides from their corresponding alkyl halides at high temperatures and immediately reacted them with acetylenes. This approach would reduce the problem of safety when preparing 1,2,3-triazoles. We optimised (residence time, reactor temperature, concentration and equivalents of alkyl azide^{19,20}) the one-pot click methodology using phenyl acetylene (**1**), 2-bromoethanol (**2**), and sodium azide in a DMF–water mixture (Scheme 1). By employing those conditions we reacted selected organobromides with either 5-hexynol (**7**) or phenyl acetylene (**1**). In fact, benzyl bromides were smoothly converted into triazoles in high yields (equations 2 and 3). On the other hand nonbenzylic bromides/iodides provided the products, too, but needed lower flow rates due to their lower nucleophilicity (equations 1, 4, and 5). We also employed more functionalised as well as chiral bromides and smoothly obtained the expected products without loss of any functionality (equations 4 and 5). Under our optimised flow conditions with respect to temperature, concentration, and catalyst no conversion could be achieved in a flask (e.g., equation 2). This observation can be rationalised if one assumes hot-spot effects on the copper surface inside the flow reactor. Induction is expected to create much higher temperatures inside the copper wire than the global temperatures measured. This may result in the generation of active catalytic species on the surface or its release into solution. Under conventional heating conditions (oil bath) in the batch mode this activation will not necessarily occur.

In order to further demonstrate the applicability of our copper flow system we investigated other copper-catalysed reactions. For that purpose we chose the catalytic decarboxylation of 2-alkynoic acids and the C–O coupling (Scheme 2). Thus, alkyneic acids can serve as protecting groups, as anchor groups for resolutions,²¹ or as control elements for improved stereoselectivity.²² In addition, the copper-catalysed C–O coupling has become an established method²³ and was utilised for the synthesis of the isolamellarins.²⁴ Our flow system is ideally suited for the decarboxylation of 2-alkynoic acids **13** and **15** (equations 6 and 7)²⁵ as well as for the formation of benzopyrone **18** via C–O coupling (equation 8).²⁶ In the case of the C–O coupling we found that in the batch mode no conversion occurred. Only when the reaction was run in the presence of equimolar amounts of copper(I) chloride and sodium carbonate full conversion was observed in the flask.

With respect to copper leaching under our flow conditions we found for the ‘click’-type cycloaddition 3.52 ppm copper on average. During the copper-catalysed decarboxylation the degree of copper leaching was even below the ICP-OES sensitivity threshold (<0.01 ppm). In contrast, we encountered significant amount of leaching with 12.65



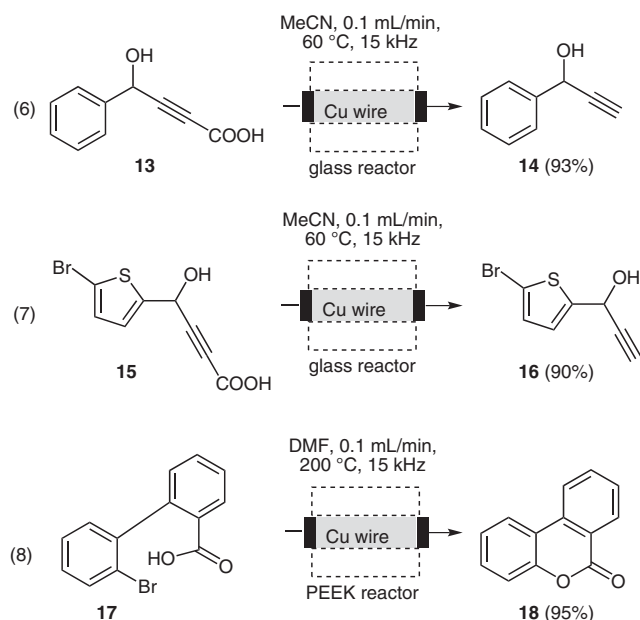
Scheme 1 Continuous (single pass) copper-catalysed Huisgen-‘click’ cycloadditions with inductive heating (full conversion, isolated yields). *Reagents and conditions:* glass reactor, substrates dissolved in DMF–H₂O (10:1, 0.25 M for bromides, 0.125 M for alkynes, 0.25 M for sodium azide), inductive frequency 15 kHz.

ppm on average for the C–O coupling, which can be attributed to elevated temperature (200 °C) employed.

In conclusion, we demonstrated the use of copper metal as a material that can rapidly be heated up to 220 °C in an inductive field and simultaneously be employed as a source for a catalytic species that enables to carry out several transformations under flow conditions.

Acknowledgment

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Scheme 2 Continuous (single pass) copper-catalysed decarboxylation of propargylic acids (full conversion, isolated yields). *Reagents and conditions:* substrates dissolved in MeCN (0.1 M), inductive frequency 15 kHz; yields in batch for **14** (quant, 3 h), **16** (96%, 3 h); continuous (single pass) copper-catalysed C–O coupling (full conversion, isolated yield). *Reagents and conditions:* substrate dissolved in DMF (0.04 M), inductive frequency 15 kHz; yields in batch for **18** [77%, 2.5 h, CuCl as Cu(I) source].

References and Notes

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- (18) Quadrapure TU is commercially available from Sigma-Aldrich.
- (19) Hazard warning: Aliphatic azides are regarded to be potentially explosive. Not for all azides that can occur as byproducts in the 'click' chemistry reactions data are available in the literature. We never encountered any hazards during these studies. However, this observation does not exclude the possibility of explosions.
- (20) **Typical Procedure for Triazole Syntheses**
A glass reactor (12 cm length and 8.5 mm internal diameter) was filled with copper wire (ca. 24 g) and incased with the inductor. The reactor (void volume: 2 mL) was connected to the pump and at the outlet side to a scavenger cartridge which was filled with Quadrapure™ TU. The collection vial was placed behind the scavenger cartridge. The system was flushed with a DMF–H₂O mixture (5:1), and the temperature was adjusted to 100 °C. After the flow (flow rate 0.2 mL/min) and temperature values reached a steady state a solution of bromide **4** (0.25 M), phenylacetylene (**1**, 0.125), and sodium azide (0.25 M, higher concentrations led to blockage of the system due to precipitation) in DMF–H₂O was pumped through the system (residence time approx. 10 min). After collection of the crude product, the mixture was diluted with H₂O, extracted with EtOAc, and dried (MgSO₄). After evaporation of the solvent the crude product was purified by flash chromatography on silica gel to yield compound **5** in quantitative yield as a slightly yellow solid.
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- (25) **Typical Procedure for the Catalytic Decarboxylation**
A glass reactor (12 cm length and 8.5 mm internal diameter) was filled with copper wire (ca. 24 g) and incased with the inductor. The reactor (void volume: 2 mL) was connected to the pump and at the outlet side to a scavenger cartridge which was filled with Quadrapure™ TU. The collection vial was placed behind the scavenger cartridge. The system was flushed with MeCN, and the temperature was adjusted to 60 °C. After the flow (flow rate 0.1 mL/min) and temperature values reached a steady state a solution of 2-alkynoic acid **13** (0.1 M) in MeCN was pumped through the system (residence time approx. 20 min). After collection of the crude product, the solvent was evaporated in vacuo, and the crude material was purified by flash chromatography on silica gel to yield compound **14** in 93% yield as a yellow oil.
- (26) **Synthesis of Benozopyranone 18**
A PEEK reactor (12 cm length and 8.5 mm internal diameter) was filled with copper wire (ca. 24 g) and incased with the inductor. The reactor (void volume: 2 mL) was connected to the pump and on the outlet side to a back pressure device (6.9 bar) which led to a scavenger cartridge which was filled with Quadrapure™ TU. Behind the scavenger cartridge the collection vial was placed. The system was flushed with DMF, and the temperature was adjusted to 200 °C. After the flow (flow rate 0.1 mL/min) and temperature values reached a steady state a solution of bromo acid **17** (0.04 M) in DMF was pumped through the system (residence time approx. 20 min). After collection of the crude product, the mixture was diluted with H₂O, extracted with EtOAc, and dried (MgSO₄). After evaporation of the solvent in vacuo the crude product was purified by flushing through a short pad of silica to yield compound **18** in 95% yield as a pale brownish solid.