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High-Speed Transition Metal-Catalyzed Chemistry Promoted by Microwave Irradiation

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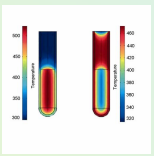
❶ Introduction

When using traditional heating under reflux conditions many transition metal-catalyzed C-C and C-X bond forming reactions typically need hours or days to reach completion. Fast and reliable microwave protocols are therefore very much needed for speeding up transformations in the field of homogeneous catalysis, taking into account the advantages of microwave heating – rapid transfer of energy and inverted temperature gradients,[1] by increasing the lifetime of the catalyst, i.e. eliminating the wall effects seen in convetional heating methods.

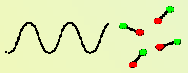
Direct "*In Core*" Heating by Single-Mode Microwave Irradiation



inverted temperature gradients

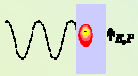
Dielectric Microwave Heating Mechanisms

Dipolar Polarization Mechanism



Dipolar molecules try to align to an oscillating field by rotation thus generating heat by friction

Conduction Mechanism

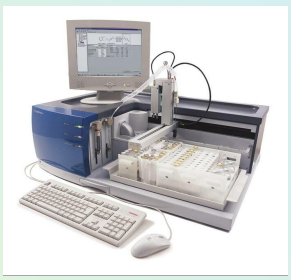


Ions in solution will move by the applied electric field

[1] a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.*, **2002**, *35*, 717; b) Kappe, C.O. *Angew.Chem.Int.Ed.* **2004**,43, *in press*

❷ Automated Synthesis in Microwave Reactors

Microwave Synthesis was performed using a single-mode reactor (sealed vessels) with possibilities for automated dispensing of reaction components and automated vessel transfer



Emrys™ Synthesizer

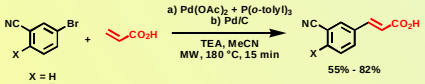
+ sample robot
+ up to 120 reactions
+ magnetic stirring
+ 12-15 reactions per hour
+ 0-300 W
+ 60-250 °C, 0-20 bar

❸ Homogeneous Metal-Catalyzed Chemistry in the Kappe Lab

Here we present a summary of recent examples of rapid microwave-assisted transition metal-catalyzed chemistries, studied in our laboratories, involving Pd-catalyzed Heck,[2] Suzuki, Sonogashira,[3] aminocarbonylation, Negishi,[4] Liebeskind-Srogl,[5] and C-P bond forming reactions.[6] In addition, examples of microwave–assisted Cu(I)-catalyzed Goldberg N-arylations, terminal alkyne-azide ligations („Click chemistry") and Ru-catalyzed ring closing methathesis[7] are illustrated.

• Heck Reaction

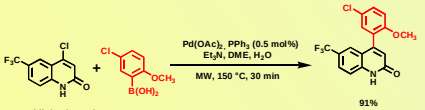
In a scalability study, the Heck arylation of acrylic acid was performed in a 2-20mmol scale going from a monomode to a multimode microwave reactor, using both homogeneous and heterogeneous Pd-catalyst, showing close agreement in yields in small and larger scale.



[2] Stadler, A.; Yousefi, B.H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C.O. *Org.Process Res.Dev.* **2003**, 7, 707

• Suzuki Coupling

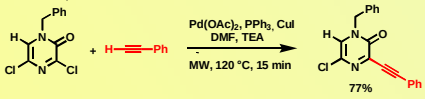
The Suzuki arylation was used as part of a multi-step microwave synthesis of a 3,4,6-substituted *2H*-quinolone as potential K^+-channel opener for treatment of erectile disfunction, involving catalytic amount of Pd(0)-catalyst formed „*in situ*".



unpublished results

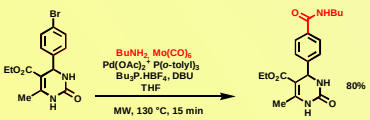
• Sonogashira Reactions

Sonogashira reaction, as well as Stille, Suzuki and Heck C-C couplings, have been demonstrated as useful tools for decorating the 2(1*H*)-pyrazinone scaffold as a building block for the synthesis of biologically active compounds.



[3] Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. *Mol.Diversity* **2003**, 7, 125

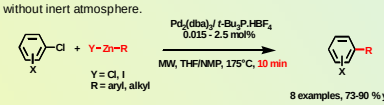
• Aminocarbonylation



unpublished results: M. Larhed, J. Wannberg (Uppsala)

• Negishi Couplings of Aryl Chlorides

A microwave induced protocol for Negishi C-C coupling was developed, involving aryl chlorides and arylzinc halides as coupling partners.The reaction proceeded in a short time under sealed-vessel conditions and without inert atmosphere.

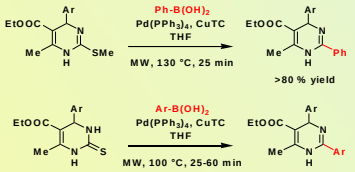


also applicable to resin-bound aryl chlorides (solid-phase synthesis)

[4] Walla, P.; Kappe, C.O. *Chemmun.* **2004**, 564

• Liebeskind-Srogl C-C Bond Formation

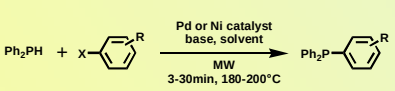
In the context of our ongoing research devoted to the generation of biologically active dihydropyrimidine scaffolds, we applied a thioether-boronic acid coupling strategy toward an efficient synthesis of combinatorial libraries of 2-aryl-1,4-dihydropyrimidines.



[5] Lengar, A.; Kappe, C.O. *Org.Lett.* **2004**, 6, 771

• Carbon-Phosphorous Bond Formation

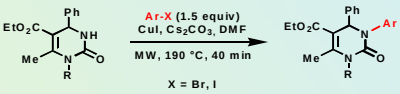
A transition metal-catalyzed direct C-P(III) bond forming reaction was performed for the synthesis of triarylphosphines, employing diphenylphosphine and aryl halides/triflates as substrates.



[6] Stadler, A.; Kappe,C.O. *Org.Lett.* **2002**, 564

• Goldberg reaction

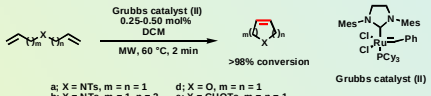
A copper-catalyzed Goldberg reaction was studied, involving dihydropyrimidones as cyclic amides. Arylation at the N3-position occured in good to moderate yields.



unpublished results

• Metathesis (RCM) with Grubbs II Catalyst

The RCM reaction of six standard diene substrates, leading to five-,six- or seven membered carbo- or heterocycles was investigated under controlled microwave irradiation as attractive ring-closure method. Very rapid conversions were achived utilizing 0.5 mol% Grubbs II catalyst in neat and ionic liquid-doped methylene chloride.

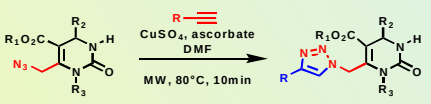


a; X = NTs, m = n = 1
b; X = NTs, m = 1, n = 2
c; X = NTs, m = n = 2
d; X = O, m = n = 1
e; X = CHOTs, m = n = 1
f; X = $C(CO_2Et)_2$, m = n = 1

[7] Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C.O. *J.Org.Chem.* **2003**, 68, 9136

• "Click" Chemistry (Azide-Acetylene Cycloaddition)

A combination of „Click"-chemistry and multicomponent reactions for generating a scaffold wtih two N-heterocyclic pharmacophores, having four points of diversity, was carried out.



unpublished results

❹ Conclusion

Advantages of Microwave Synthesis:

× dramatic rate-enhancements for transition metal-catalyzed reactions
× higher yields, cleaner reaction profiles
× better reproducibility

Acknowledgement:

This studies were supported by the Austrian Science Fund (FWF, P15582). We wish to thank *Biotage AB* for the provision of the Emrys™ Synthesizer.