COMMUNICATION

ChemComm
www.rsc.org/chemcomm

# Microwave-assisted Negishi and Kumada cross-coupling reactions of aryl chlorides†

**Peter Walla and C. Oliver Kappe***

*Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria.*
*E-mail: oliver.kappe@uni-graz.at; Fax: ++43-316-3809840; Tel: ++43-316-3805352*

***Received (in Cambridge, UK) 31st October 2003, Accepted 21st January 2004***
***First published as an Advance Article on the web 30th January 2004***

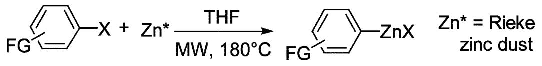
**Rapid Pd or Ni-catalyzed microwave-accelerated Negishi and Kumada cross-coupling reactions of aryl chlorides in solution and on solid phase are reported.**

The biaryl motif is found in a range of pharmaceuticals, natural products, agrochemicals, ligands, conducting polymers, liquid crystals and advanced materials.[1] The Negishi cross-coupling reaction utilizing organozinc reagents represents a powerful method for the synthesis of this privileged structural scaffold.[2] One major disadvantage of Pd or Ni-catalyzed Negishi couplings is the rather long reaction times involving hours or even days. Recent evidence suggests that many transition metal-catalyzed transformations, such as Heck, Suzuki, Sonogashira and Stille couplings, can be significantly accelerated by microwave irradiation.[3] For Negishi cross-coupling reactions only two reports on microwave-enhanced processing have been published in the peer-reviewed literature, both describing examples involving activated aryl halides.[4] Importantly, a general and efficient protocol employing aryl chlorides is not available to date. Recent studies by Fu and coworkers have demonstrated that the proper choice of the ligand is crucial when attempting Pd-catalyzed Negishi (and other) cross-coupling reactions with aryl chlorides.[5] Notably, one of the most active catalytic systems discovered by the Fu group utilizes electron-rich Pd($t$Bu$_3$P)$_2$ complexes.[6] Herein we report rapid microwave-assisted Negishi cross couplings of aryl chlorides with aryl- and alkylzinc halides as coupling partners.

The organozinc reagents for the desired Negishi couplings could be prepared by insertion of activated Rieke zinc into aryl bromides (or iodides). This transformation normally requires several hours under reflux conditions in THF.[7] We have accelerated this process by use of controlled microwave irradiation[8] under sealed vessel conditions to 5–30 min (Table 1).

Our initial experiments in microwave-assisted Negishi couplings involved Ni complexes (5 mol%) as the economically most favorable catalysts. Selected optimization studies involving a variety of ligands, solvent systems and reaction temperatures for one model reaction are shown in Table 2. In general, couplings mediated by NiCl$_2$dppf afforded the highest yield of the desired cross-coupling product. Surprisingly, the catalyst combination Ni(acac)$_2$/$t$Bu$_3$P which efficiently catalyzes Kumada cross-coupling reactions,[9] failed in microwave assisted Negishi reactions (entry 6).

**Table 1** Microwave-accelerated preparation of arylzinc halides by Rieke zinc insertion into aryl halides[a]



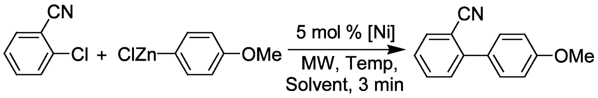
| Entry[a] | FG | X | Zn* (equiv.) | Time (min) |
|---|---|---|---|---|
| 1 | 2-CN | Br | 2 | 10 |
| 2 | 4-CN | Br | 2 | 10 |
| 3 | 3-COOEt | Br | 3 | 30 |
| 4 | 2-COOMe | I | 1.5 | 5 |
| 5 | 4-COOEt | I | 2 | 10 |
| 6 | 3-OMe | I | 2 | 10 |

[a] All transformations showed > 99 % conversion by HPLC-UV or GC-MS.

In all cases of Ni-catalyzed reactions, however, significant amounts of the corresponding homocoupling product derived from the organozinc reagent were also formed. In addition we found that NiCl$_2$dppf-catalyzed Negishi reactions involving electron rich (deactivated) aryl chlorides such as 4-chloroanisole could not be driven to completion even when a higher catalyst loading or excess of the zinc reagent was applied.[10] Moreover, the catalysis with Ni complexes is incompatible with nitro groups.[11]

We have therefore focused our attempts on developing rapid, microwave-assisted Negishi couplings utilizing Pd catalysts, in particular applying the recently reported very active $t$Bu$_3$P ligand system.[6] In contrast to the originally described ($t$Bu$_3$P)$_2$Pd catalyst[6] we attempted to utilize a combination of commercially available $t$Bu$_3$P.HBF$_4$ and Pd$_2$(dba)$_3$ in our work.[12] Both of the latter components are air stable and can be kept at ambient temperature, in contrast to ($t$Bu$_3$P)$_2$Pd which must be stored under inert atmosphere at low temperatures. The initial optimization of reaction conditions was performed using 4-chloronitrobenzene and *o*-tolylzinc chloride as coupling partners (Table 3, entry 1). We soon discovered that 175 °C for 10 min proved to be optimal reaction conditions in order to achieve complete conversion for most of the Negishi couplings investigated. The ratio of Pd/$t$Bu$_3$P was 1/2 as reported previously.[6] After optimization of the general reaction parameters the scope of the microwave-assisted Pd-catalyzed Negishi coupling was explored (Table 3). With reactive arylzinc chlorides such as *o*-tolylzinc chloride the reaction proceeds smoothly both with electron-deficient as well as electron-rich aryl chlorides (entries 1–3), in contrast to the Ni-catalyzed reactions described above. When the less reactive arylzinc iodide (entry 4), obtained *via* microwave-assisted Rieke zinc insertion described above (Table 1, entry 6), was employed a 64% conversion was achieved with 5 mol% of Pd catalyst. The Pd-catalyzed Negishi couplings also provided good yields for transformations involving heterocyclic coupling partners (entries 5–7). Using this methodology it was even possible to successfully couple aryl chlorides with alkylzinc reagents such as e.g. *n*-butylzinc chloride (entry 8) in a very rapid manner. Note that all transformations (with the

**Table 2** Optimization of Ni catalyzed cross-coupling



| Entry | [Ni] | Solvent | Temp (°C) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | NiCl$_2$(PPh$_3$)$_2$ | THF | 140 | 62 |
| 2 | NiCl$_2$dppf | THF | 140 | 81 |
| 3 | NiCl$_2$dppf | THF/NMP | 140 | 81 |
| 4 | NiCl$_2$dppf | THF | 160 | 82 |
| 5 | Ni(PPh$_3$)$_2$dppf[b] | THF | 140 | 75 |
| 6 | Ni/ $t$Bu$_3$P[c] | THF | 160 | 17[d] |

[a] Isolated yield. [b] NiCl$_2$dppf/2PPh$_3$/2BuLi. [c] Ni(acac)$_2$/$t$Bu$_3$P.HBF$_4$ (mol ratio 1/2). [d] HPLC conversion.

---

† Electronic supplementary information (ESI) available: Experimental procedures and spectral data. See http://www.rsc.org/suppdata/cc/b3/b313887a/

DOI: 10.1039/b313887a

**Table 3** Microwave-assisted Pd catalyzed Negishi cross-coupling reactions

$$\text{Ar-Cl} + \text{XZn-R} \xrightarrow[\text{MW, Solvent, 175°C, 10 min}]{\text{Pd}_2(\text{dba})_3/\ \text{Bu}_3\text{P.HBF}_4} \text{Ar-R}$$

| Entry | ArCl | Ar–ZnX | Catalyst[a] (mol %) | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 4-Cl–$C_6H_4$–$NO_2$ | *o*-Tol–ZnCl | 1/4 | THF/NMP | 85 |
| 2 | 2-Cl–$C_6H_4$–CN | *p*-Tol–ZnCl | 0.015/0.06 | THF/NMP | 90 |
| 3 | 4-Cl–$C_6H_4$–OMe | *o*-Tol–ZnCl | 1/4 | THF/NMP | 90 |
| 4 | 2-Cl–$C_6H_4$–CN | 3-MeO–$C_6H_4$–ZnI | 2.5/10 | THF | 83[c] |
| 5 | 4-Cl–$C_6H_4$–CN | 2-Py–ZnCl | 1.5/6 | THF | 73 |
| 6 | 4-Cl–$C_6H_4$–$NO_2$ | 2-Py–ZnCl | 1.5/6 | THF | 75 |
| 7 | 4-Cl–Py | 4-MeO–$C_6H_4$–ZnCl | 1.5/6 | THF | 77 |
| 8[d] | 4-Cl–$C_6H_4$–$NO_2$ | Bu–ZnCl | 1/4 | THF | 84 |

[a] $Pd_2(dba)_3$/$^tBu_3P.HBF_4$ (mol ratio 1/4). [b] Isolated yields after chromatography. [c] GC-MS conversion. [d] Run at 120°C for 30 minutes.

exception of entry 4) showed complete conversion after 10 min of microwave irradiation, comparing very favourably with reaction times of 2–24 h observed under conventional conditions.[6,13] We also report here that the use of microwaves facilitates the Grignard reaction as shown in Scheme 1 and the so obtained arylmagnesium bromide can be subjected to subsequent high yielding Kumada cross-coupling[1] with an aryl chloride under the same conditions as used in the Negishi reactions.

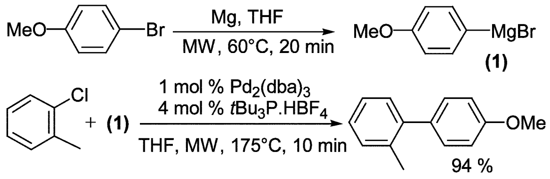
It has to be noted, however, that typically a higher amount of homocoupling product is formed using microwave irradiation as compared with ultrasound-promoted Grignard reactions performed at ambient temperature.

Finally we wish to report that microwave-assisted Negishi cross-coupling reactions can also be carried out employing a resin-bound aryl chloride (Table 4).

Applying the optimized $Pd_2(dba)_3$/*t*$Bu_3P.HBF_4$ catalyst system a solid-phase protocol was realized, applying microwave-assisted reactions in all three steps of the synthesis.[14] For two model arylzinc halides (Table 4), complete conversions were achieved within 10 minutes employing 5 mol% of the Pd catalyst, providing the desired biaryl carboxylic acids in high yield and high purity. These are the first reported transition metal-catalyzed C–C coupling reactions on solid-phase involving aryl chlorides.[15]

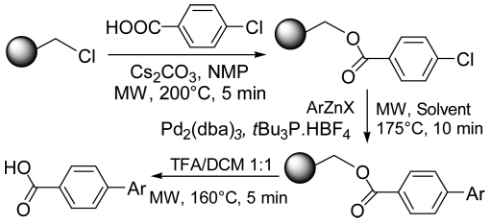
In conclusion, we have developed a general and efficient protocol for high-speed microwave-assisted Negishi cross-coupling reactions in solution- and solid-phase applied to aryl chlorides. Similarly, Grignard, Kumada and Rieke zinc insertion reactions could be easily conducted under microwave conditions in sealed vessels without the need for inert atmosphere.

This work was supported by the Austrian Science Fund (FWF, P-15582). We thank Personal Chemistry AB (Uppsala) for providing single-mode microwave technology.



**Scheme 1** Microawave-assisted Grignard and Kumada reactions.

**Table 4** Microwave assisted Negishi cross-coupling reaction of arylchloride bound to Merrifield resin



| Entry | Ar–ZnX | Solvent | Yield (%) | Purity[a] |
|---|---|---|---|---|
| 1 | Ph–ZnCl | THF/NMP | 90 | 96 |
| 2 | 3-MeO–$C_6H_4$–ZnI[b] | THF | 87 | 90 |

[a] HPLC purity [b] prepared by Rieke zinc insertion (Table 1, entry 6)

## Notes and references

1 For reviews see: V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263; J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.

2 For a review, see: E.-I. Negishi, in *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich, P. J. Stang, Wiley-VCH, New York, 1998.

3 M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717.

4 (*a*) L. Öhberg and J. Westman, *Synlett*, 2001, 1893; (*b*) P. Stanetty, M. Schnürch and M. D. Mihovilovic, *Synlett*, 2003, 1862; (*c*) See also: B. Hayes, *Microwave Synthesis. Chemistry at the Speed of Light*, CEM Publishing, Matthews, 2002.

5 For an excellent review, see: A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4176.

6 C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 2719.

7 (*a*) L. Zhu, R. M. Wehmeyer and R. D. Rieke, *J. Org. Chem.*, 1991, **56**, 1445; (*b*) L. Zhu, K. H. Shaughnessy and R. D. Rieke, *Synth. Commun.*, 1993, **23**, 525; (*c*) R. D. Rieke, M. V. Hanson and J. D. Brown, *J. Org. Chem.*, 1996, **61**, 2726.

8 (*a*) P. Lidström, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225; (*b*) A. Stadler and C. O. Kappe, *J. Comb. Chem.*, 2001, **3**, 624; (*c*) For online resources on microwave-assisted organic synthesis, see: www.maos.net.

9 V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr and W. A. Herrmann, *Angew. Chem. Int. Ed.*, 2000, **39**, 1602.

10 D. Zim and A. L. Monteiro, *Tetrahedron Lett.*, 2002, **43**, 4009 and references therein.

11 S. Saito, S. Oh-tani and N. Miyaura, *J. Org. Chem.*, 1997, **62**, 8024 and references therein.

12 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.

13 Note that here the use of microwave irradiation provides very high turnover frequencies for Pd-catalyzed C–C cross-coupling reactions of aryl chlorides (TOF 270 h$^{-1}$, Table 3, entry 3), for Pd-catalyzed cross-couplings of aryl chlorides in general ($36 \times 10^4$ h$^{-1}$, entry 2) and for Ni-catalyzed cross-couplings (328 h$^{-1}$, Table 2, entry 4). For comparison, see: B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2002, **124**, 14127.

14 For literature precedent regarding the microwave-assisted coupling and cleavage of arylcarboxylic acids to Merrifield resins, see: A. Stadler and C. O. Kappe, *Eur. J. Org. Chem.*, 2001, 919.

15 J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359 see in particular p. 1429.