10th Blue Danube Symposium on Heterocyclic Chemistry, September 3 – 6, 2003 Vienna - Austria

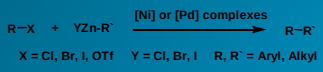
MICROWAVE-PROMOTED HIGH-SPEED NEGISHI CROSS COUPLING REACTION AS A POWERFUL TOOL FOR ORGANIC SYNTHESIS

Peter Walla and C. Oliver Kappe*

Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
email: peter.walla@uni-graz.at website: http://www.maos.net

❶ Introduction

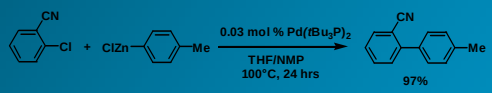
• **The Negishi Cross-Coupling Reaction:**



King, O.; Okukado, N.; Negishi E. *J. Org. Chem.* **1977**, *42*, 1821-1823.

• **Advantages:**
wide functional group compatibility/tolerance of the organozinc reagents (in contrast to Grignard reagents).

• **Disadvantages:**
long reaction times especially for arylchlorides as starting materials, e.g.:

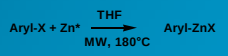


Chaoyang, D.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724.

• Till date, there is only one publication dealing with microwave assisted Negishi cross coupling reactions starting from arylbromides (Westman, J.; Öhberg, L. *Synlett* **2001**, 1893-1896).

Our Aim:
- To develop high speed microwave assisted Negishi cross coupling reaction starting from arylchlorides.
- To extend Fu's catalytic system (Netherton, M. R.; Fu, G. C. *Org. Lett.* 2001, *3*, 4295) $Pd_2(dba)_3$ / $tBu_3P.HBF_4$ to microwave promoted Negishi cross couplings in solution and solid phase employing arylchlorides.

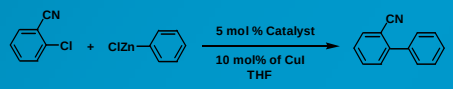
❷ Preparation of Organozinc Reagents by Microwave Accelerated Insertion of Rieke's Zinc Dust



Aryl	Aryl-ZnX	Equiv. Zn*	Time (min)	HPLC Conversion
NC–Br	NC–ZnBr	2	10	>99%
CN, Br	CN, ZnBr	2	10	>99%
EtOOC, Br	EtOOC, ZnBr	3	30	>99%
COOMe, I	COOMe, ZnI	1.5	5	>99%

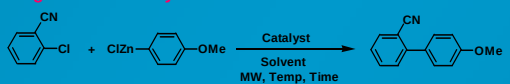
❸ Optimization of Negishi Cross-Coupling Reactions

• **Nickel versus Palladium Catalytic System in Microwave Promoted Negishi Cross Coupling Reactions**



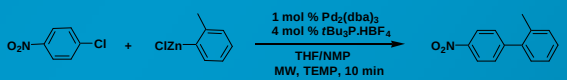
$PdCl_2(PPh_3)_2$	0 %
Pd(PPh3)4	50%
$NiCl_2(PPh_3)_2$	76%

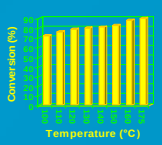
• **Finding the Best Catalyst**



Cat. (mol %)	Solvent	Temp (°C)	Time (min)	Yield (%)
$NiCl_2(PPh_3)_2$ (5)	THF	140	3	62
$NiCl_2$dppf (5)	THF	140	3	81
$NiCl_2$dppf (5)	THF	160	3	82
$NiCl_2$dppf (5)	THF/NMP	140	3	81
$Ni(PPh_3)_2$dppf (5)	THF	140	3	75
$Pd_2(dba)_3$/$tBu_3P.HBF_4$ (1/4)	THF/NMP	175	10	

• **Determining the Optimal Temperature**

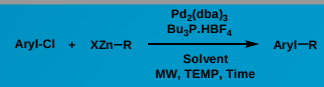




2 Equivalents of 2-Tolylzinciumchloride:
175°C, 10 min, 100 % conversion, 80 % Yield
130°C, 20 min, 100 % conversion, 91 % Yield

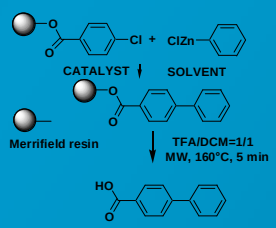
lower yield obtained at higher temperature due to the decomposition of substrate bearing NO_2 group

❹ Application of $Pd_2(dba)_3$/ *t*-$Bu_3P.HBF_4$ to Solution Phase Negishi Cross-Coupling Reactions of Arylchlorides



Aryl-X	Organozinc	Mol % of $Pd_2(dba)_3$ /$tBu_3P.HBF_4$	Solvent	Temp/Time	Yield (%)[a]
CN, Cl	ClZn, Me	0.015/0.06	THF/NMP	175/10	85
NC, Cl	ClZn, N	1.5/6	THF	175/10	73
Cl⊖ H⊕ N, Cl	ClZn, OMe	1.5/6	THF	175/10	77
MeO, Cl	ClZn, Me	2.5/10	THF	175/10	80 % HPLC conversion
O_2N, Cl	ClZn-Bu	1/4	THF	120/30	84

❺ Application of $Pd_2(dba)_3$/ $tBu_3P.HBF_4$ Catalytic System to Solid Phase Negishi Cross-Coupling Reactions



Cat. (mol %)	Solvent	Temp	Time	Yield
$Pd_2(dba)_3$/$tBu_3P.HBF_4$ (2.5/10)	THF/NMP	175 °C	10 min	90 %
$NiCl_2(PPh_3)_2$ (8)	THF	160 °C	10 min	81 %

Scope and Limitations

- Microwave enhanced high-speed Aryl-Aryl and Aryl-Alkyl Negishi cross couplings of arylchlorides utilizing $Pd_2(dba)_3$/$tBu_3P.HBF_4$ as catalytic system is limited to activated arylchlorides
- Microwave promoted Negishi Aryl-Aryl cross coupling catalysed by Nickel complexes allows activated as well as deactivated aryl chlorides
- Catalysis by Nickel-phosphine complexes is not compatible with NO_2 groups

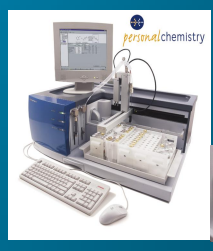
Conclusion

- We developed high-speed microwave-assisted Negishi cross coupling reaction applied to arylchlorides (reaction times 1-20 minutes)
- We extended the air stable $Pd_2(dba)_3$/*t*-$Bu_3P.HBF_4$ catalyst system to microwave enhanced Negishi cross-coupling of arylchlorides in solution as well as solid phase

Acknowledgement

This work was supported by the Austrian Science Fund (FWF, P-15582)

We thank *PersonalChemistry AB* (Uppsala, Sweden) for providing the Emrys Synthesiser instrument (www.personalchemistry.com)



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