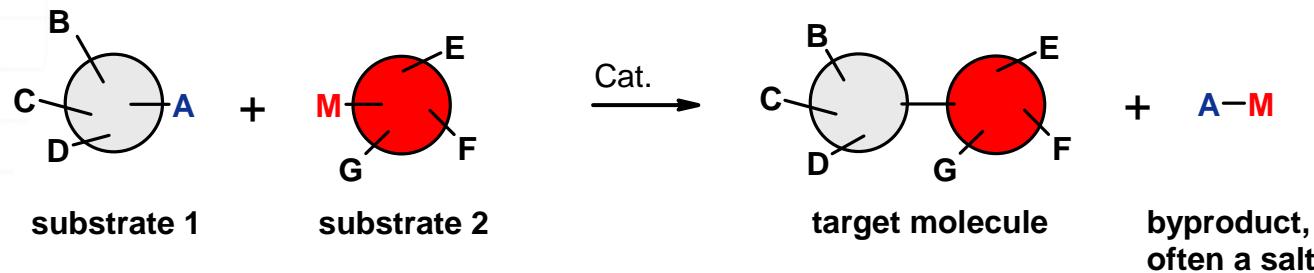


Decarboxylative Cross-Coupling Reactions

A Modern Strategy for C-C-Bond Formation

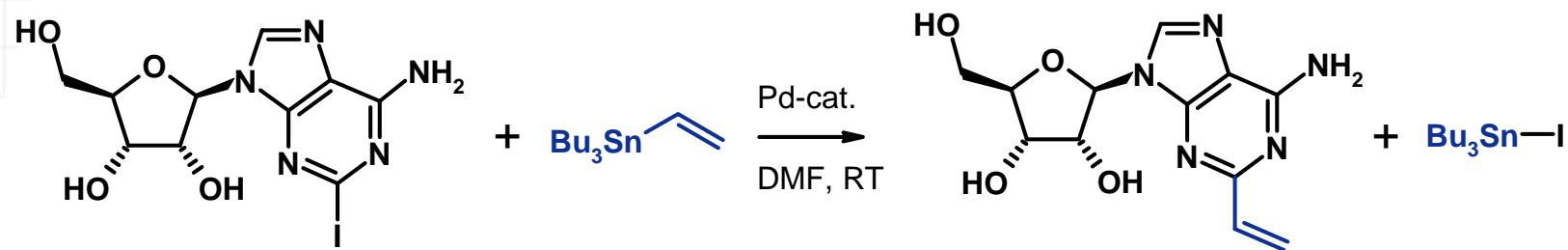
Prof. Dr. Lukas J. Gooßen
Fachbereich Chemie - Organische Chemie
Technische Universität Kaiserslautern

Reactions in which two molecules are connected at positions defined by leaving groups to give a target molecule and a byproduct



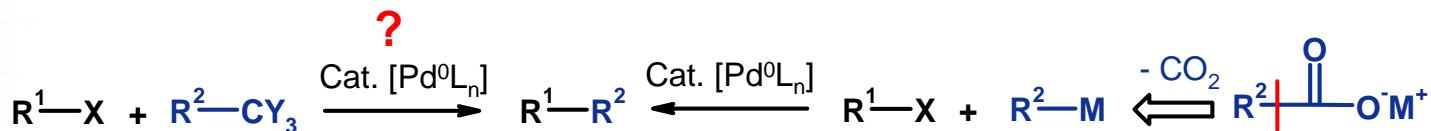
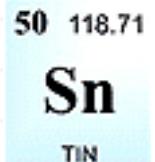
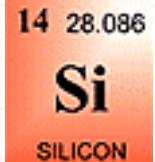
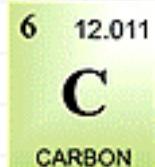
- Selective bond formation at a given position A-M
- No reaction at other functional groups B, C, D...

Cross-coupling reactions are indispensable tools in organic synthesis

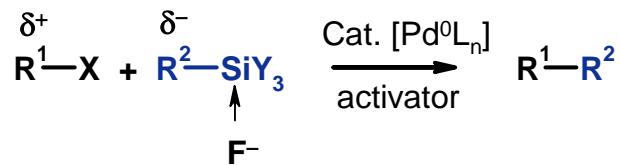


V. Nair et al., *Chem. Commun.* **1989**, 878

C-Nucleophiles in catalytic cross-couplings

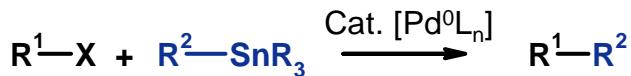


M. Nilsson, *Acta Chem. Scand.* **1966**, 20, 423.



R^1 = alkenyl, aryl, allyl
 R^2 = silyl, alkyl, aryl, alkenyl, alkynyl
 X = Cl, Br, I, OSO_2CF_3 , OCO_2Et
 Y = Me, F, Cl, ...

K. Tamao, M. Kumada, et al., *Organometallics* **1982**, 1, 542; A. Hallberg, et al., *Chem. Lett.* **1982**, 1993; Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, 53, 918; S. E. Denmark, et al., *J. Am. Chem. Soc.* **1999**, 121, 5821.



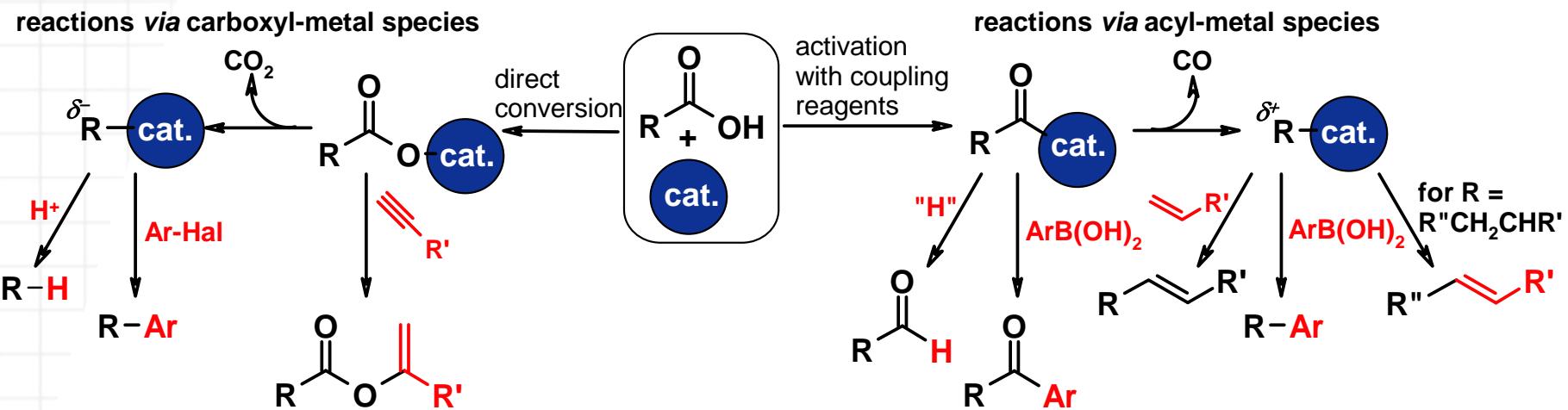
R^1 = alkyl, alkynyl, aryl, vinyl
 R^2 = acyl, alkynyl, aryl, benzyl, vinyl
 X = Br, Cl, I, OAc, $\text{OP}(=\text{O})(\text{OR})_2$, OTf

M. Kosugi, T. Migita, et al., *Chem. Lett.* **1977**, 301; *Chem. Lett.* **1977**, 1423; J. K. Stille, et al., *J. Am. Chem. Soc.* **1978**, 100, 3636; *J. Am. Chem. Soc.* **1979**, 101, 4992.

Excellent availability

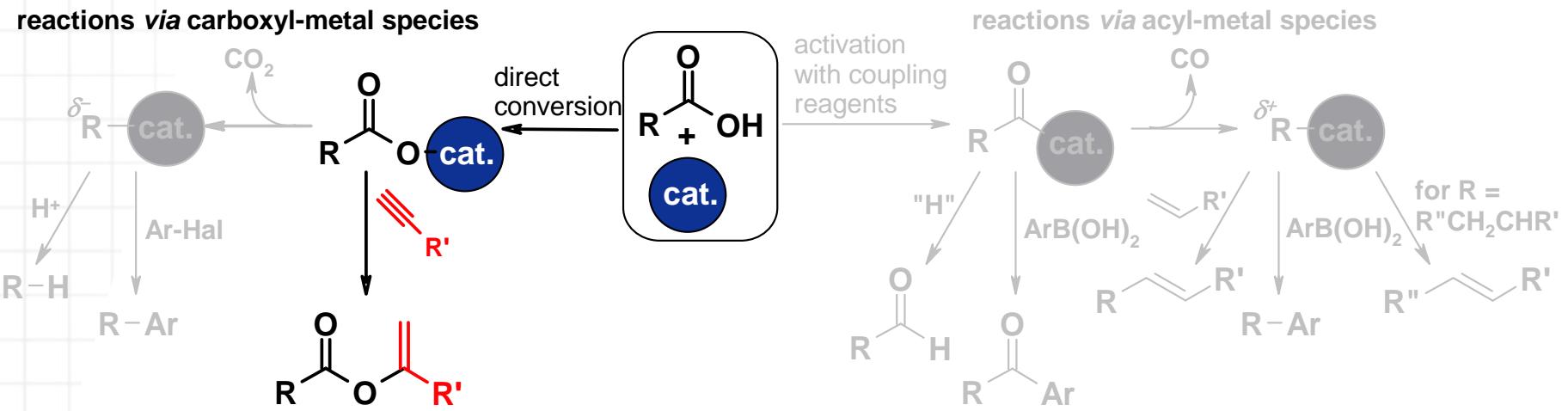
- Huge variety of carboxylic acids are commercially available and cheap
- Many natural products contain acid functionalities
- Environmentally benign syntheses of carboxylic acids by (air) oxidations

At least four reaction modes are conceivable:



Reactions via metal carboxylate species

- Addition of carboxylic acids to multiple bond

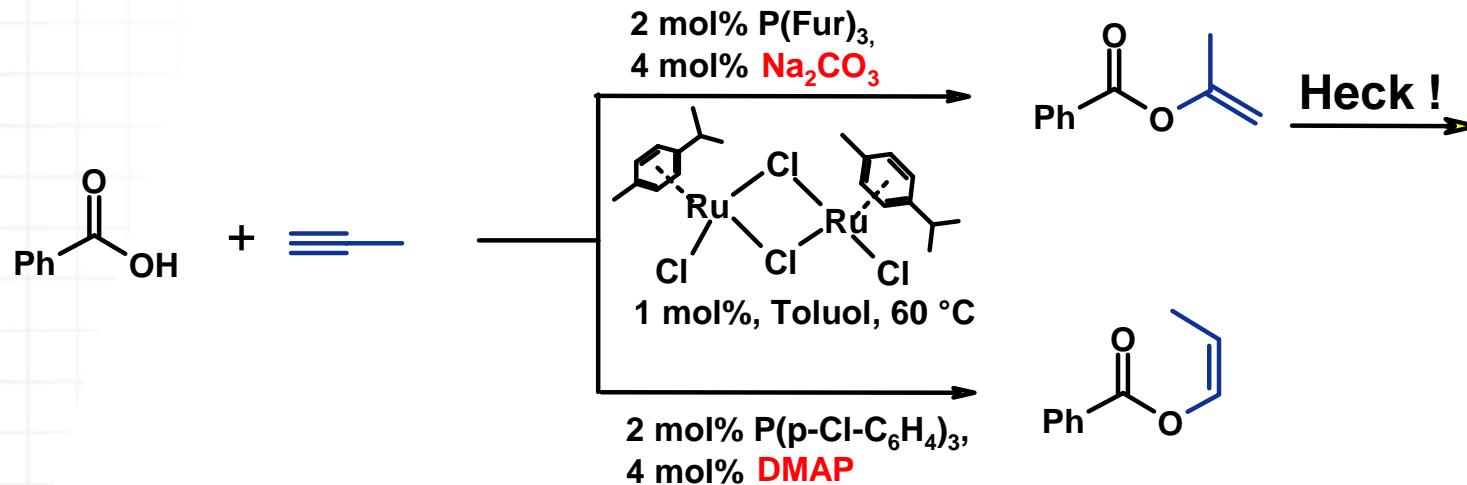


ChemComm 2003, 706
Angew. Chem. 2005, 117, 4110

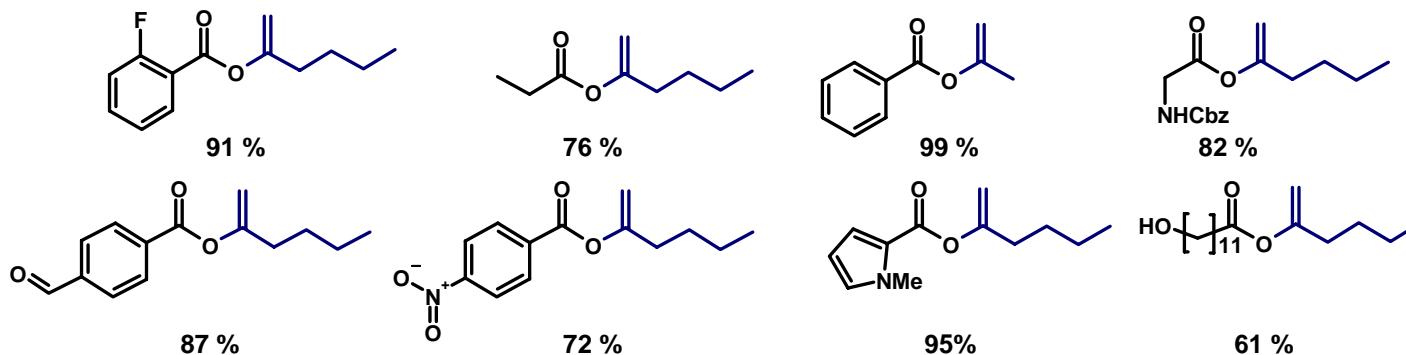
1st Reaction Mode: Additions to Multiple Bonds

Ideal atom economy, extremely mild reaction conditions

- High selectivities for the Markovnikov product (>20:1)



- **DMAP** as the base: **reversal of selectivity!** >40:1 anti-Markovnikov!

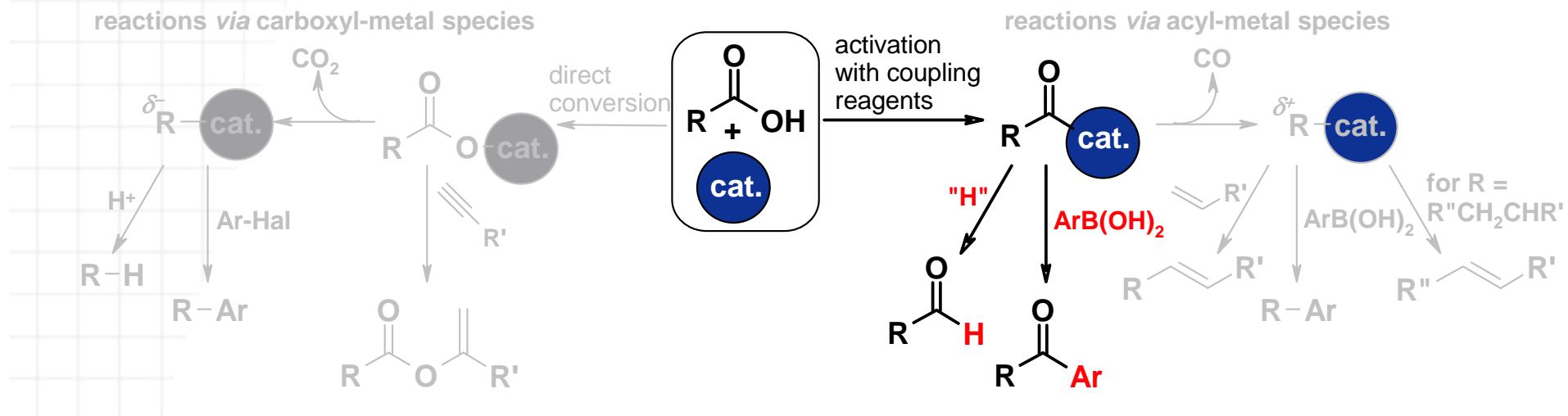


L. Gooßen, J. Paetzold, D. Koley, *Chem. Commun.* **2003**, 706-707

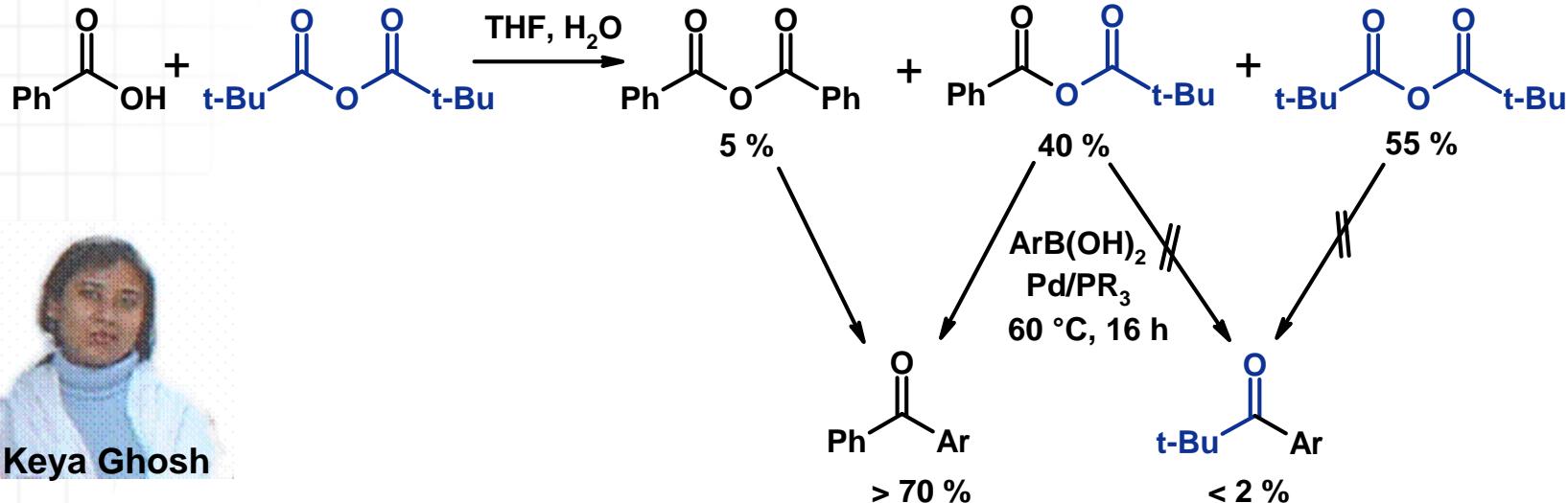
Compare with: T. Mitsudo, Y. Hori, Y. Watanabe, *J. Org. Chem.* **1985**, 50, 1566

Reactions via acyl metalspecies:

- Carboxylic acids as synthetic equivalents of acyl halides

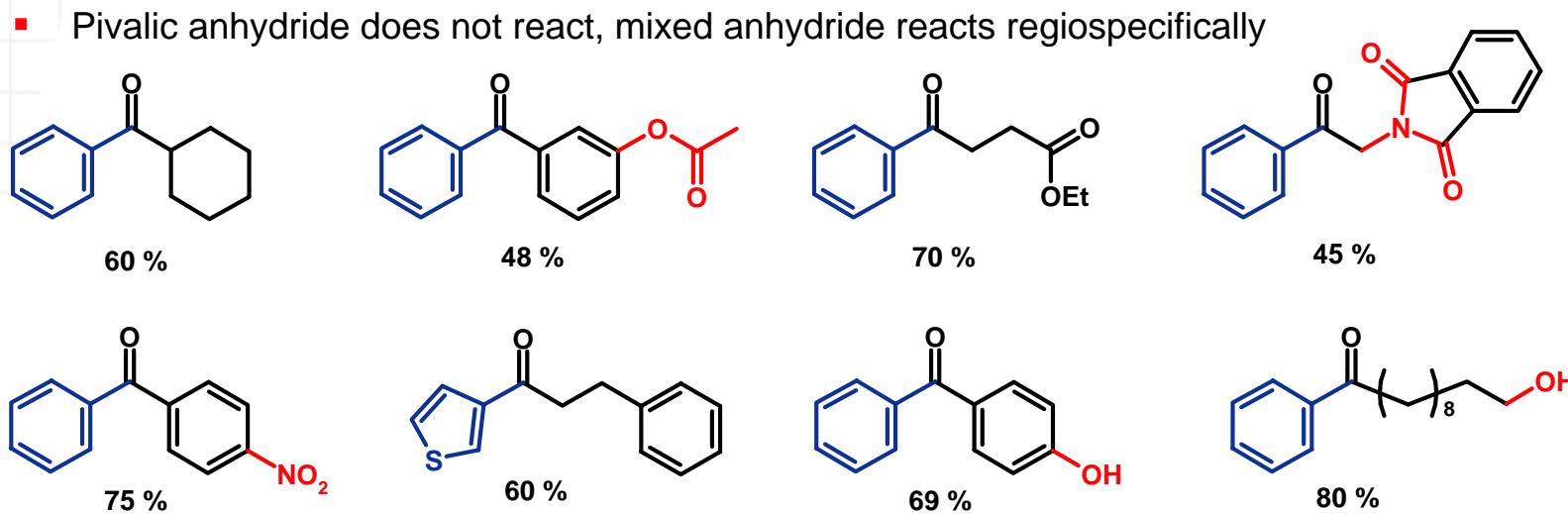


2nd Reaction Mode: Arylation of Carboxylic Acids



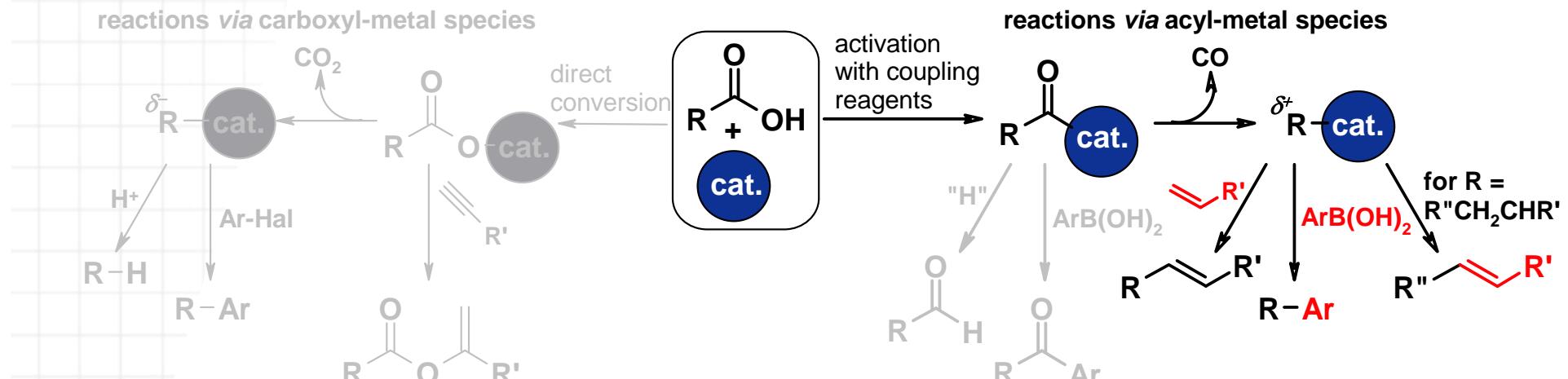
with K. Ghosh, *Angew. Chem.* **2001**, *113*, 3566

- Equilibrium of possible anhydrides forms when mixing carboxylic acids with pivalic anhydride
- Pivalic anhydride does not react, mixed anhydride reacts regiospecifically



Reactions via the decarboxylation of acyl metal species:

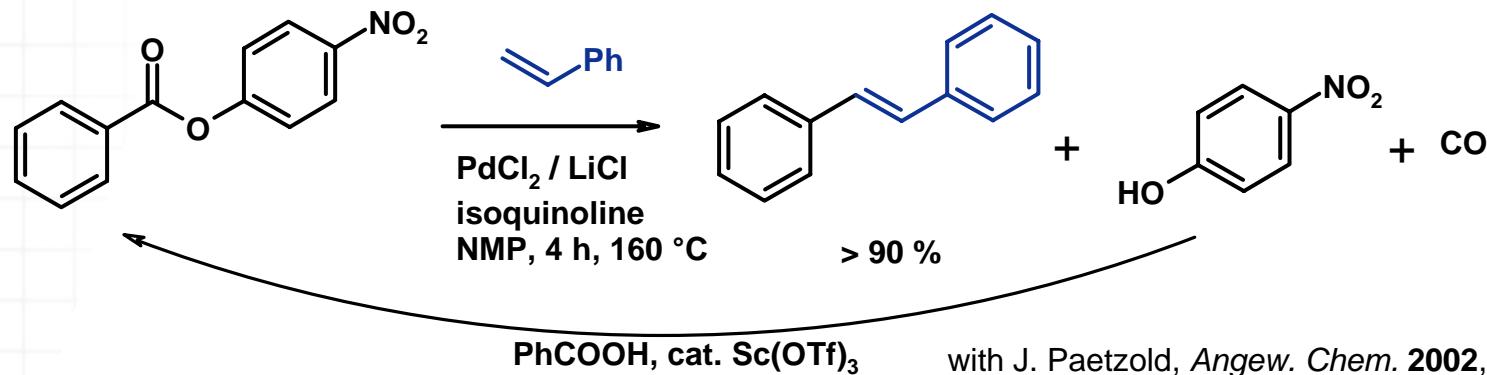
- Carboxylic acids as synthetic equivalents of aryl or alkyl halides



Angew. Chem. **2002**, *114*, 1285
Angew. Chem. **2004**, *116*, 1115

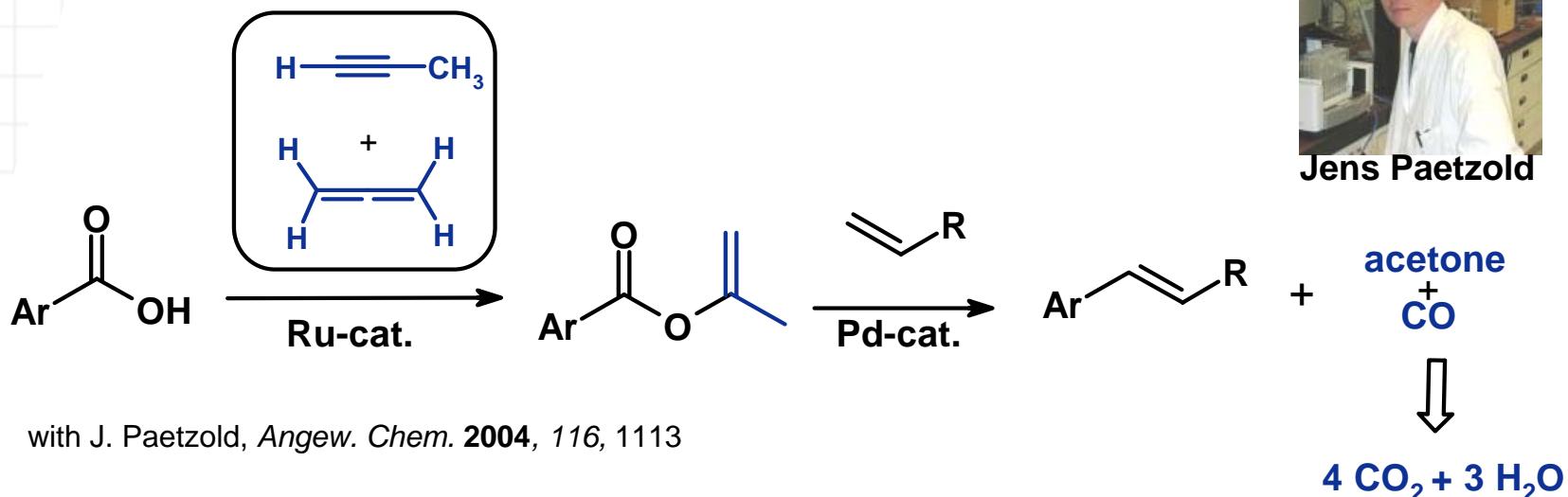
Decarbonylative Heck Reactions

Decarbonylative olefination of *p*-nitrophenyl esters



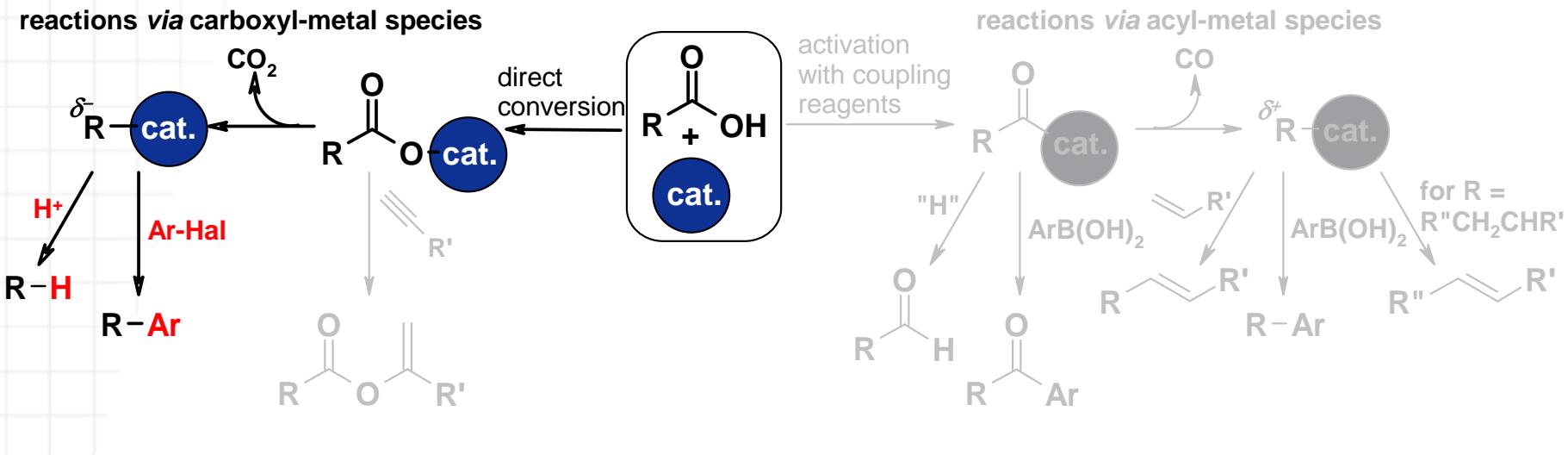
- Catalyst: $\text{PdCl}_2/\text{LiCl}$, No phosphine; isoquinoline stabilizes the Pd
- Nitrophenol ester can be regenerated: Salt-free olefination process is practicable

Alternative: Reaction via enol esters



Reactions via decarboxylation of metal carboxylates

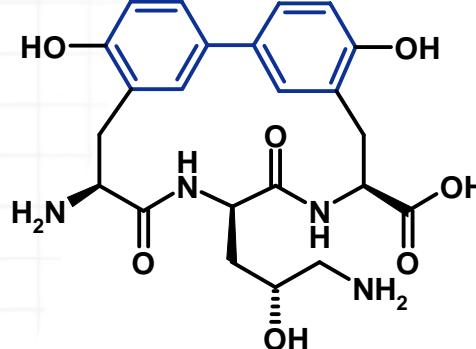
- Carboxylate salts as synthetic equivalents of aryl metal species



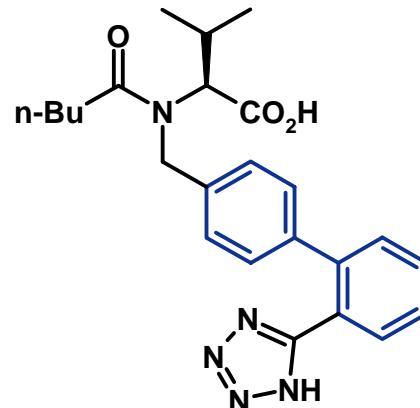
Science 2006, 313, 662
 JACS 2007, 129, 4824

4th Reaction mode: Opportunities

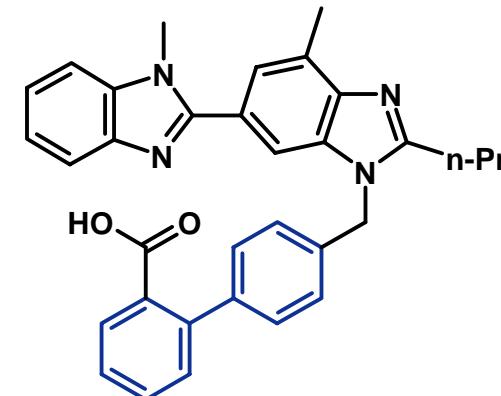
- Biaryls are a privileged motif in pharmaceuticals and functional materials
- Syntheses *via* Suzuki couplings are troublesome in industrial production



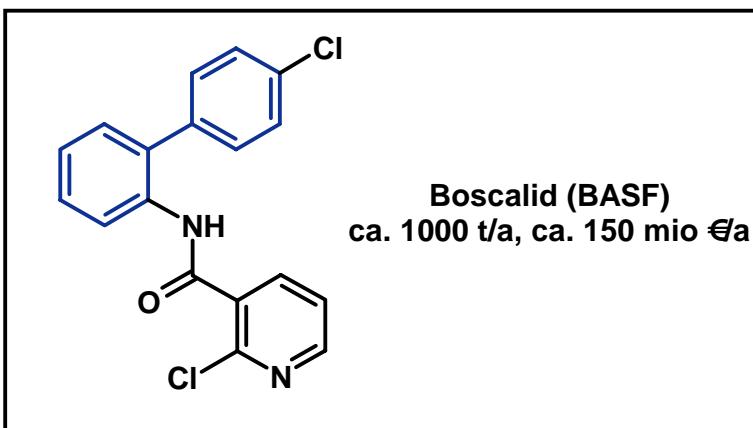
Biphenomycin B



Diovan (Valsartan, Novartis)
2004 sales: 2.6 bn €



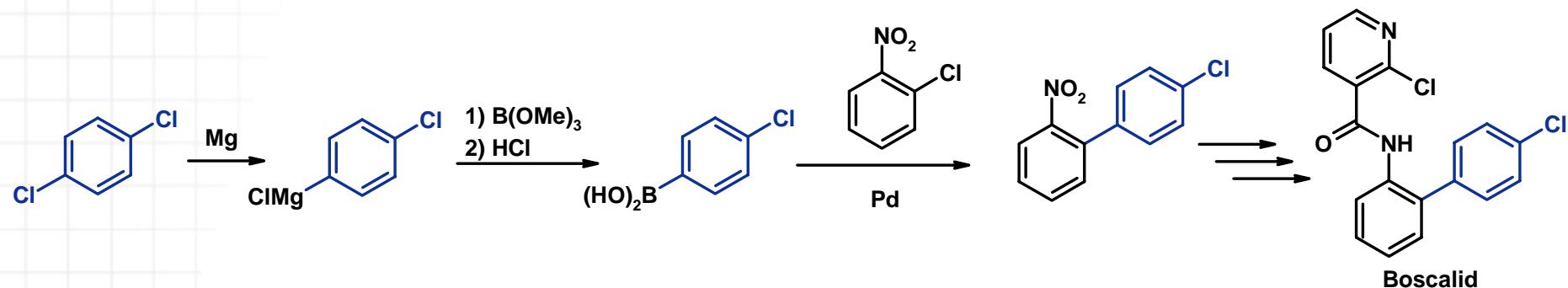
Micardis (Telmisartan, Boehringer)
2004 sales: 789 mio €



Synthesis of Biaryls from Carboxylic Acids

Method of choice for regiospecific arylations: Suzuki reaction

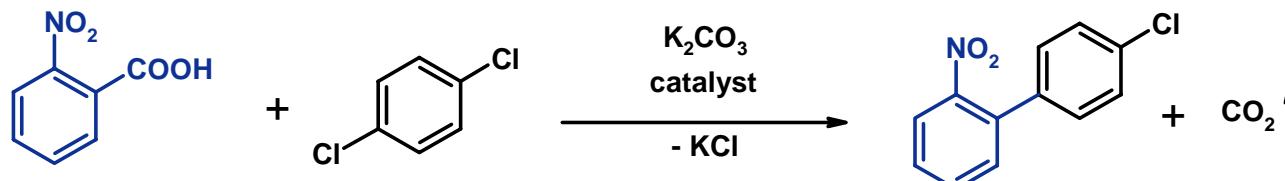
- The problem in cross-couplings is the synthesis of the carbon nucleophiles



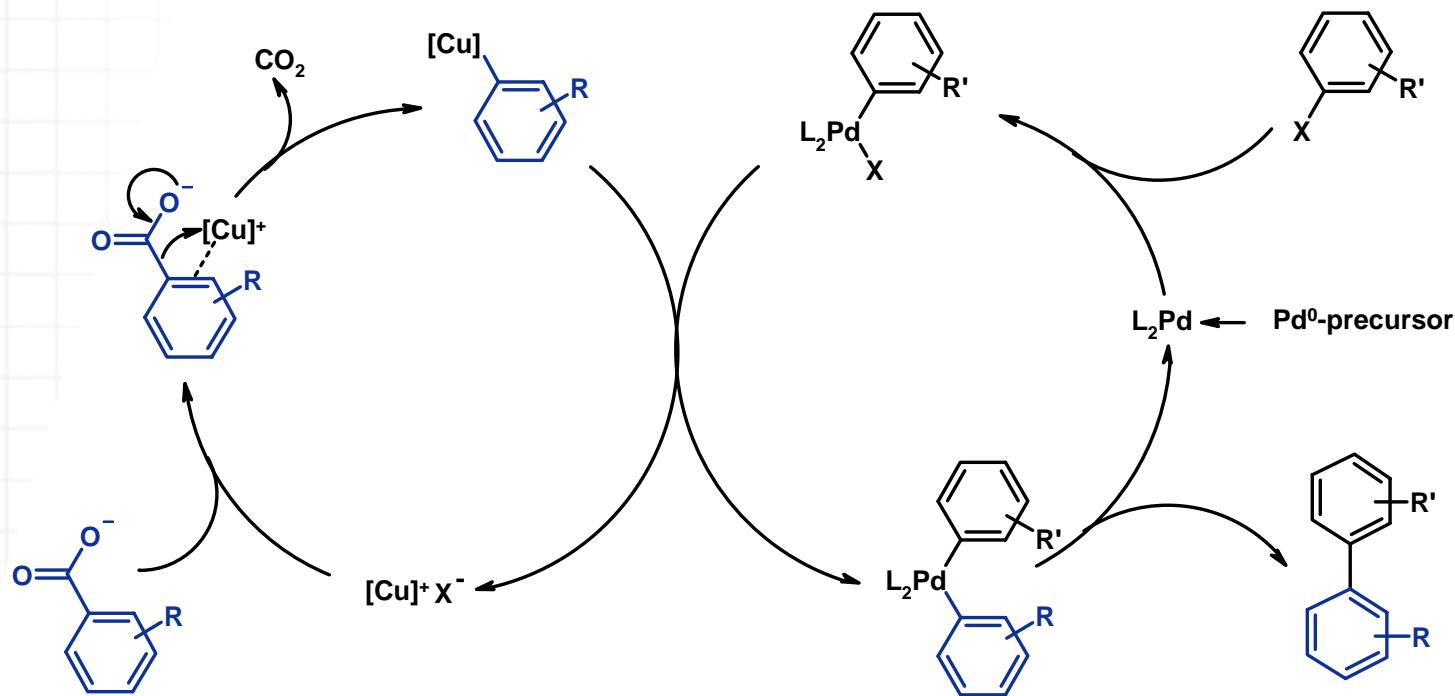
Alternative direct arylations are regioselective not for all arenes

Regiospecific decarboxylative coupling of carboxylates

- Generation of organometallic reagents from simple metal carboxylates
- The carboxylate group predefines the position of C-C-bond formation



Combination of a decarboxylation with a Pd-catalyzed cross-coupling

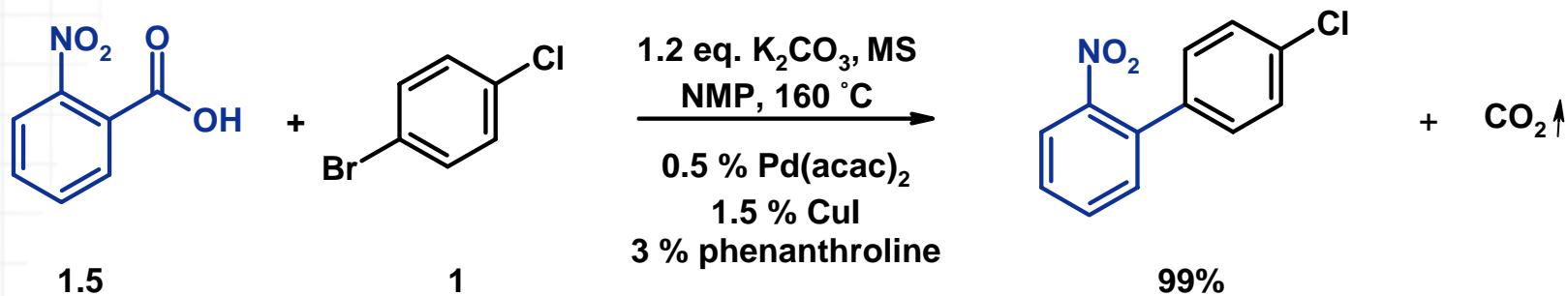


Key step: decarboxylation of a metal carboxylate to an aryl metal species

- Insertion of the metal into the aromatic C-C bond: Ag^+ , Cu^+ , Au^+ ...

1st System: Catalytic in Cu(I), Catalytic in Pd

- Decarboxylation at a Cu(I)-phenanthroline complex
- Removal of the reaction water *via* azeotropic distillation or molecular sieves avoids protodecarboxylation
- Transfer of the aryl group to a phosphine-free palladium co-catalyst



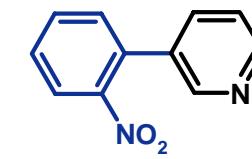
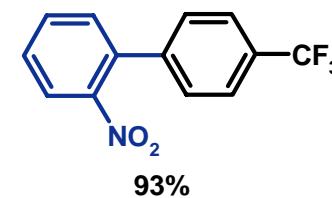
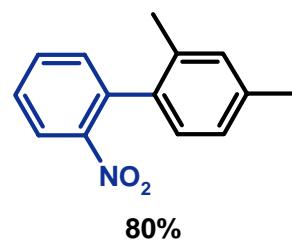
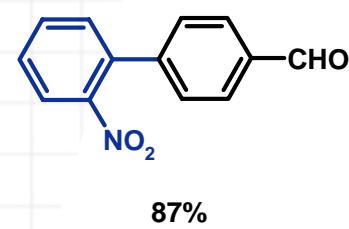
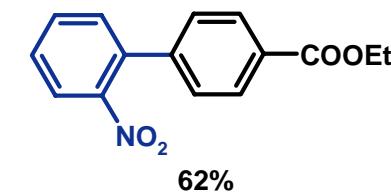
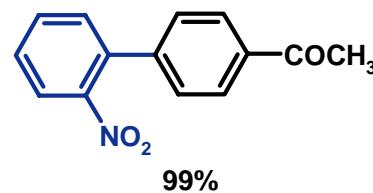
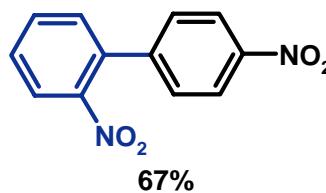
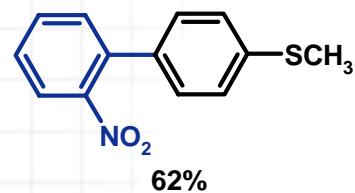
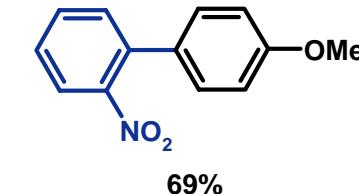
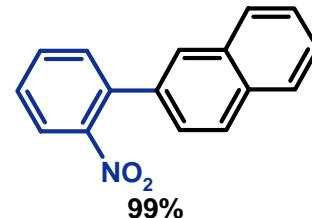
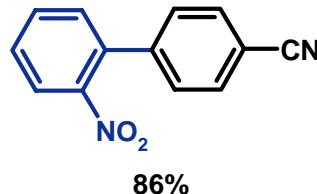
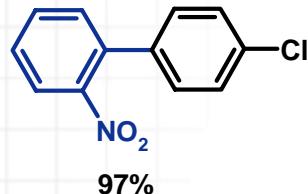
- + catalytic in Pd: 0.5 mol%
- + catalytic in Cu: 1.5 mol%
- + inexpensive bipyridine as ligand



with G. Deng, L. M. Levy, Science **2006**, 313, 662;

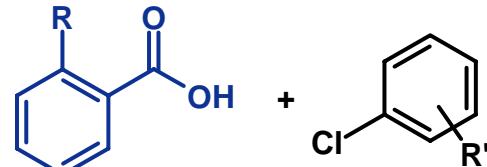
Scope with Regard to the Aryl Halides

Smooth reaction of o-nitrobenzoic with a wealth of aryl bromides...

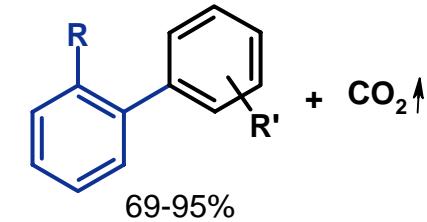


with G. Deng, L. M. Levy, Science **2006**, 313, 662;

...and meanwhile also aryl chlorides!



10% CuI, 1% PdI₂,
1,10-phenanthroline,
(o-biphenyl)P(*t*Bu)₂
NMP/quin., 160 °C

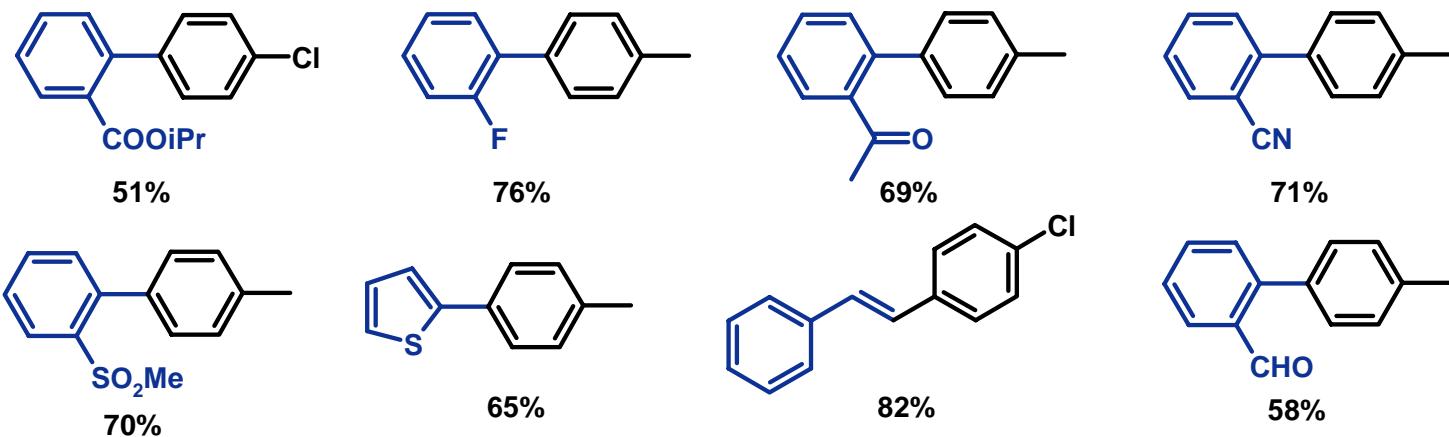


with B. Melzer, T. Knauber, *Angew. Chem.* **2008**, 120,

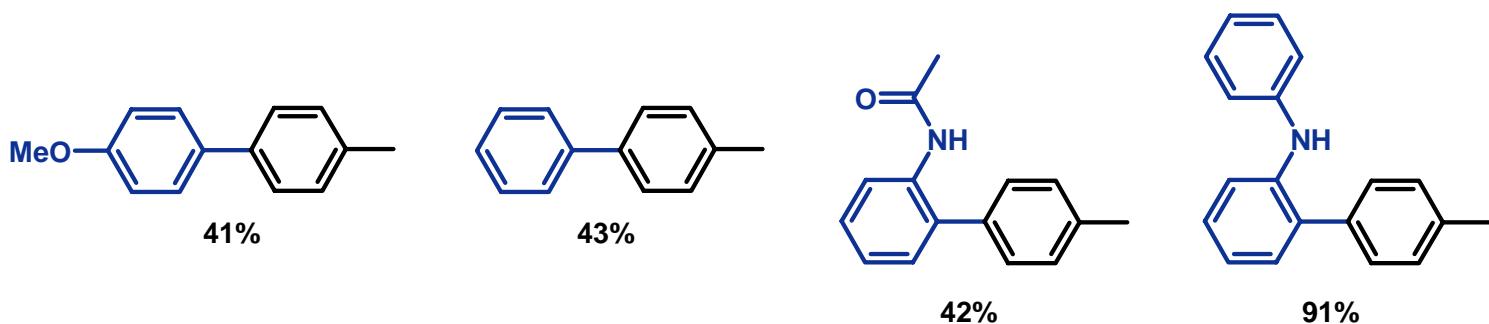
Scope with Regard to the Carboxylic Acids

„Double-catalytic“ protocol already works for many carboxylic acids, particularly when bearing a coordinating *o*-substituent

- Fine tuning of the catalyst is required for every substrate



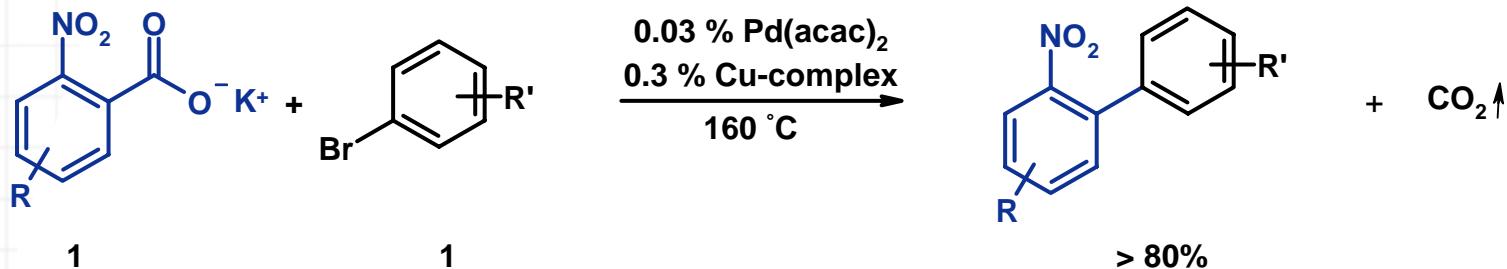
Some other carboxylates also work but still require stoichiometric amounts of Cu



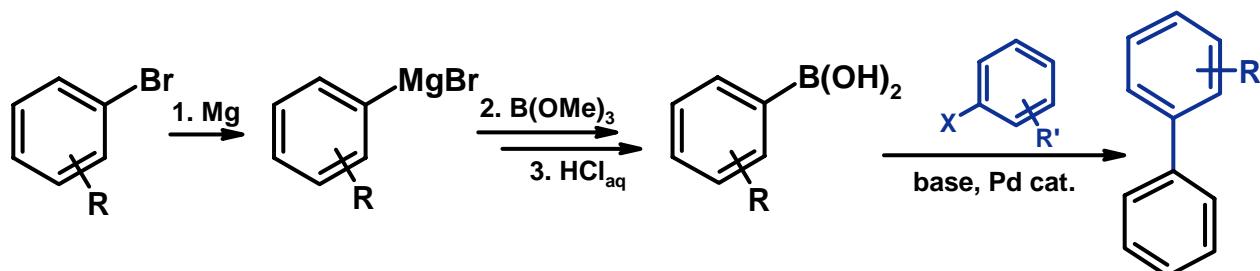
with N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, 129, 4824.

Optimized protocol for a commercial substrate (pilot scale: 100 kg)

- 1:1 substrate ratio, in situ deprotonation with KOH
- Small amount (60%) mesitylene as solvent
- Only 0.03 mol% Pd, 0.3 % Cu
- Simple workup: 80 % yield after crystallization



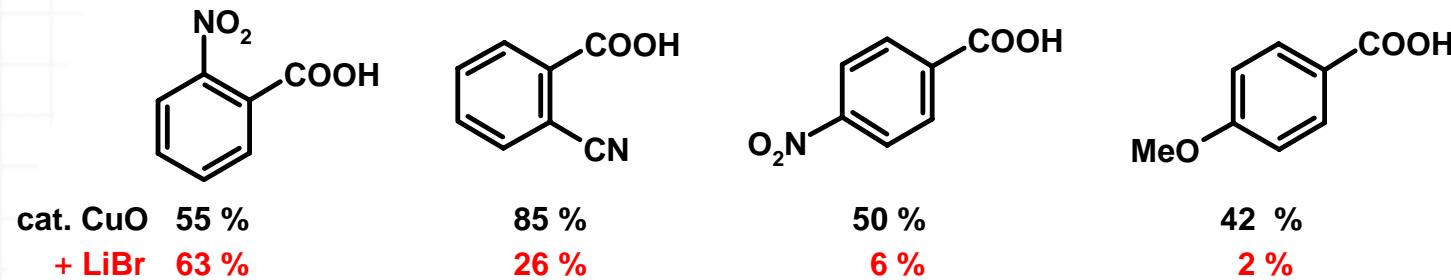
Compare with:



Preparative scale procedures: with N. Rodríguez, C. Linder, B. Melzer, T. Knauber, *Org. Synth.* **2008**, 85, 196-204.

Are there Intrinsic Substrate Limitations ?

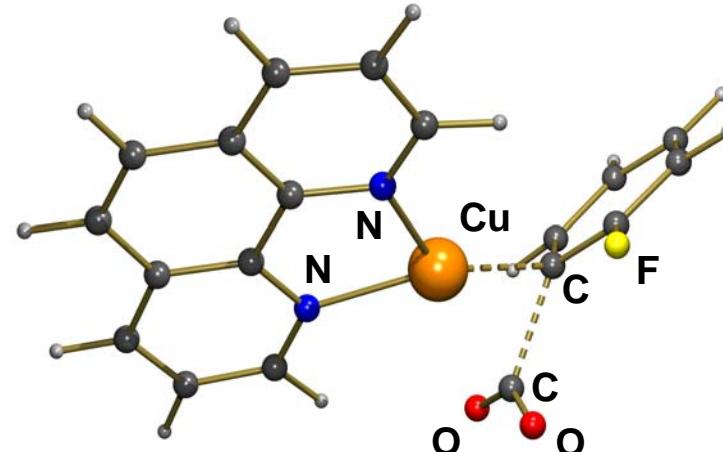
- In the absence of halide salts, a broad variety of substrates decarboxylate
- The presence of halide salts has little influence on the decarboxylation of some benzoates, mostly o-substituted derivatives, while for other benzoates, an excess of halide with regard to Cu inhibits decarboxylation



Conditions: 0.15 mmol CuO, 0.15 mmol 1,10-phenanthroline, 0.15 mmol quinoline, 0.15 mmol K_2CO_3 , 3 mL NMP, 160 °C, 24 h



Andreas Fromm

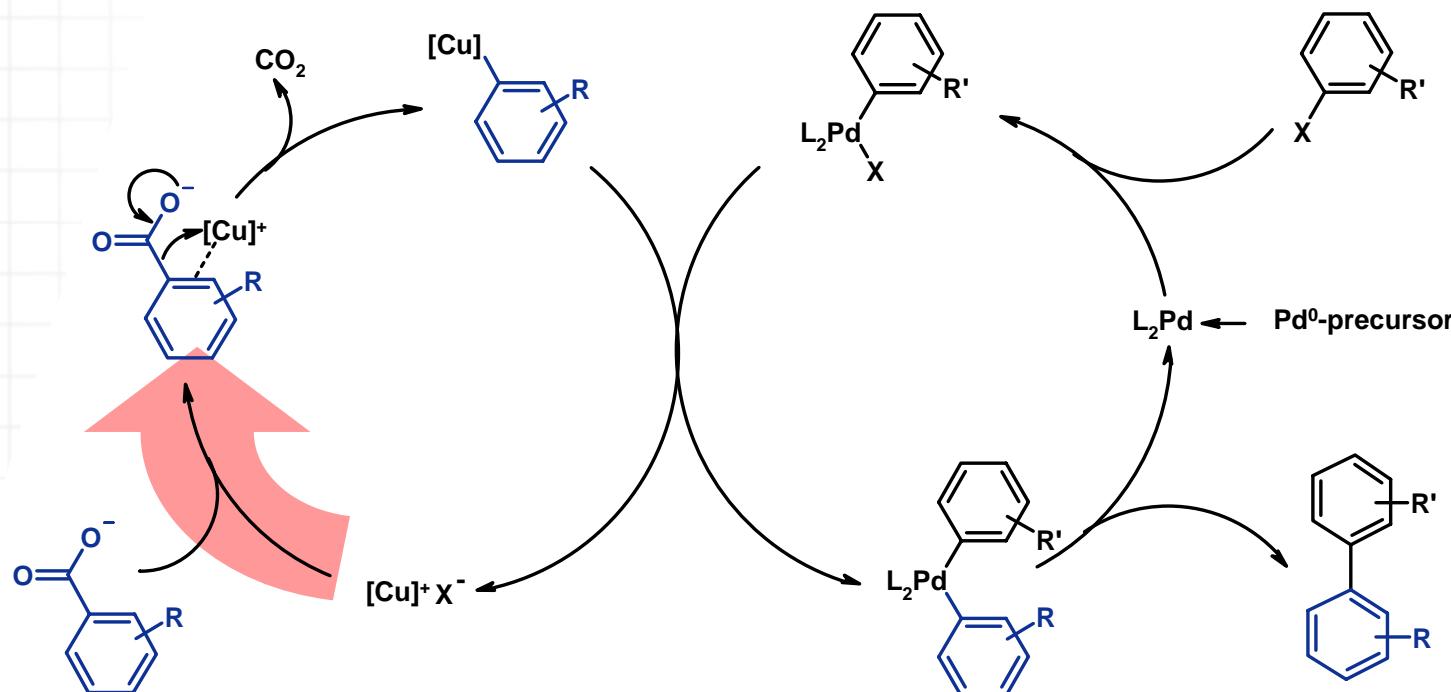


- Modified Cu-catalysts give full conversion for most benzoic acids

L. J. Gooßen, W. R. Thiel, N. Rodríguez, C. Linder, B. Melzer, *Adv. Synth. Catal.* **2007**, 349, 2241-2246

Limiting Step of the “Double-catalytic” Process

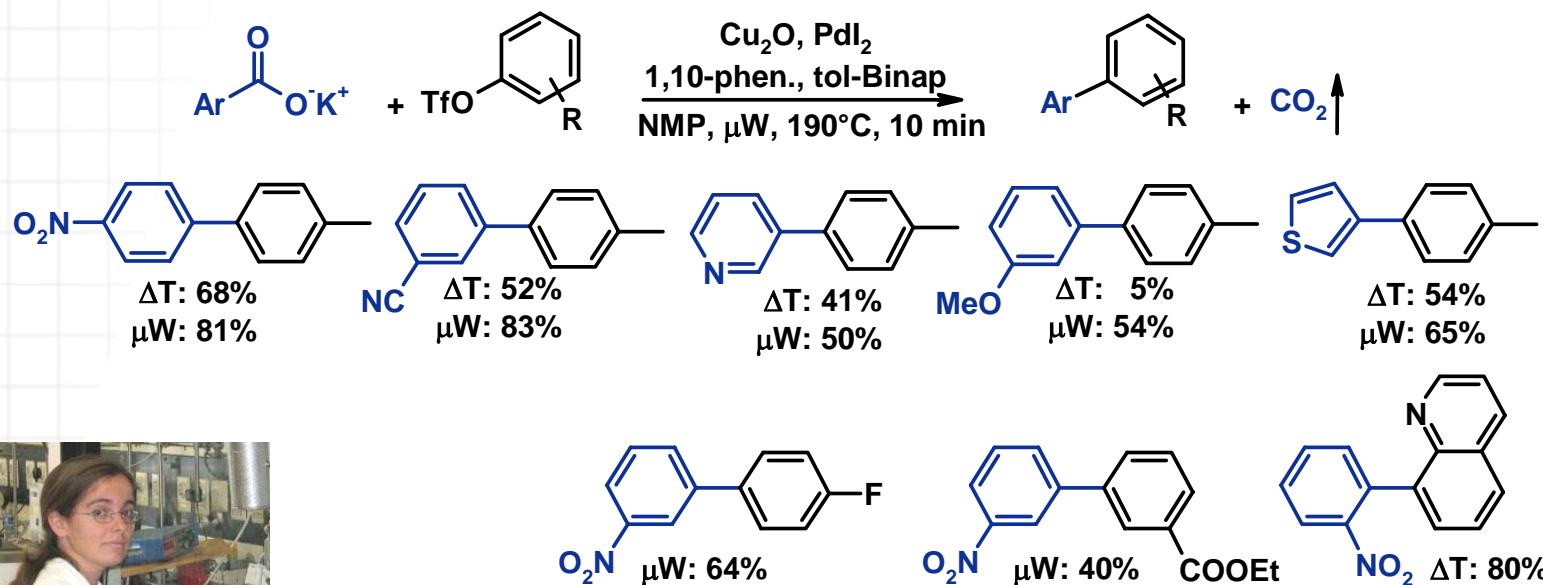
- The ligand exchange between potassium carboxylate and copper halide is apparently more difficult for non-ortho-functionalized arene carboxlates



- Improved Cu-catalyst with a higher preference for carboxylates over halides may lead to general reaction protocols for decarboxylative cross-couplings

Coupling of non-Activated Arenecarboxylates

- Aryl triflates as coupling partners preclude the formation of halide salt
- The most recent systems allow the turnover of less costly tosylates



with N. Rodriguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248-15249;
 L. J. Gooßen, C. Linder, N. Rodríguez, P. P. Lange, *Chem. Eur. J.* **2009**, *15*, 9336-9349.

Nuria Rodriguez

⇒ The biaryl synthesis is not intrinsically limited to o-substituted benzoates

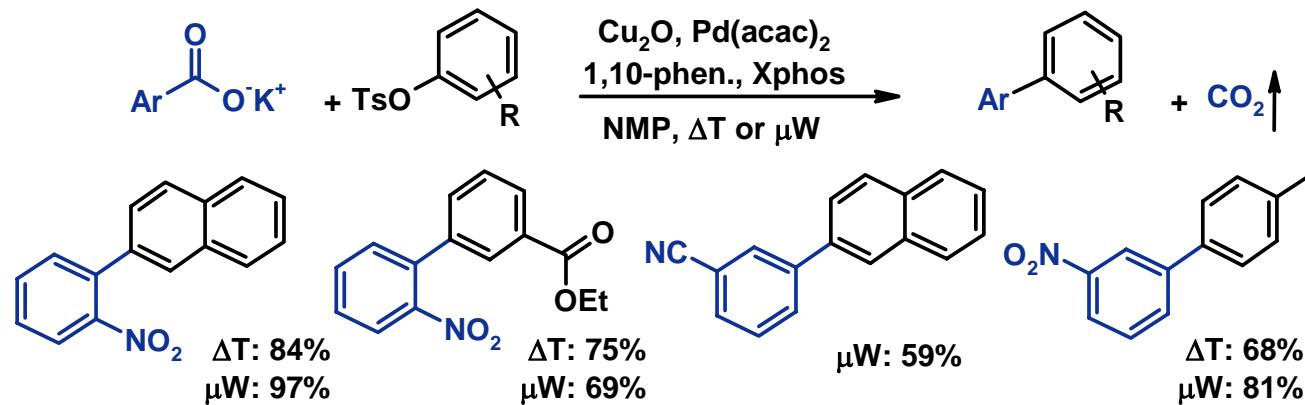
Microwave irradiation shortens reaction time to five minutes

- Sealed vessels, 1 mmol scale, 1 ml solvent, 50W (190°C), 5 min
- Reduces thermal strain, simplifies reaction layout, ideal for parallel synthesis
- Advantageous for all substrate combinations

with B. Zimmermann, C. Linder, N. Rodríguez, P. P. Lange, J. Hartung, *Adv. Synth. Catal.* **2009**, 351, 2667

Coupling of non-activated benzoates with tosylates

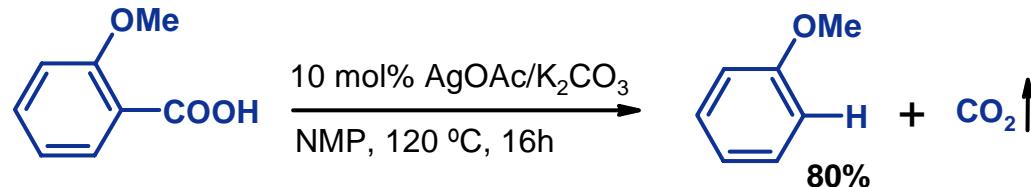
- Use of microwave irradiation effectively suppresses side reactions



with N. Rodríguez, P. P. Lange, C. Linder, *Angew. Chem.* **2010**, 122, 1129

Development of low-temperature catalysts guided by DFT calculations

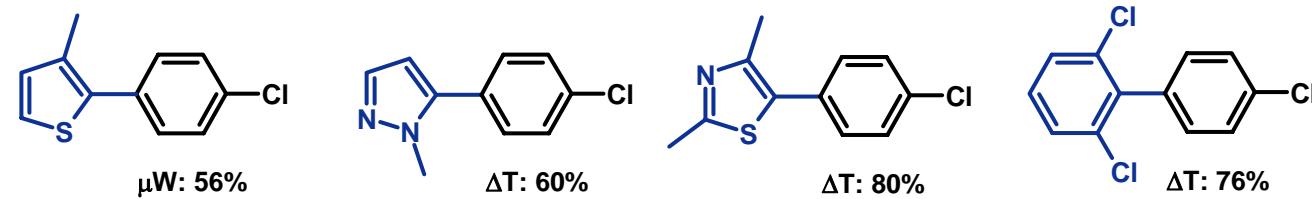
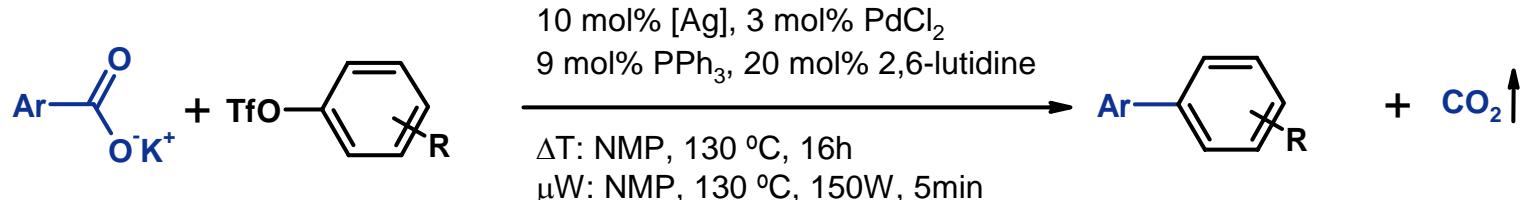
- Modifications at the N-N-ligand will have only limited effect on the Cu-catalyst
- decarboxylations with silver or gold catalysts should be much faster



with C. Linder, N. Rodríguez, P. P. Lange, A. Fromm, *Chem. Comm.* **2009**, 7173.

Low-temperature Pd/Ag-catalyzed decarboxylative cross-coupling

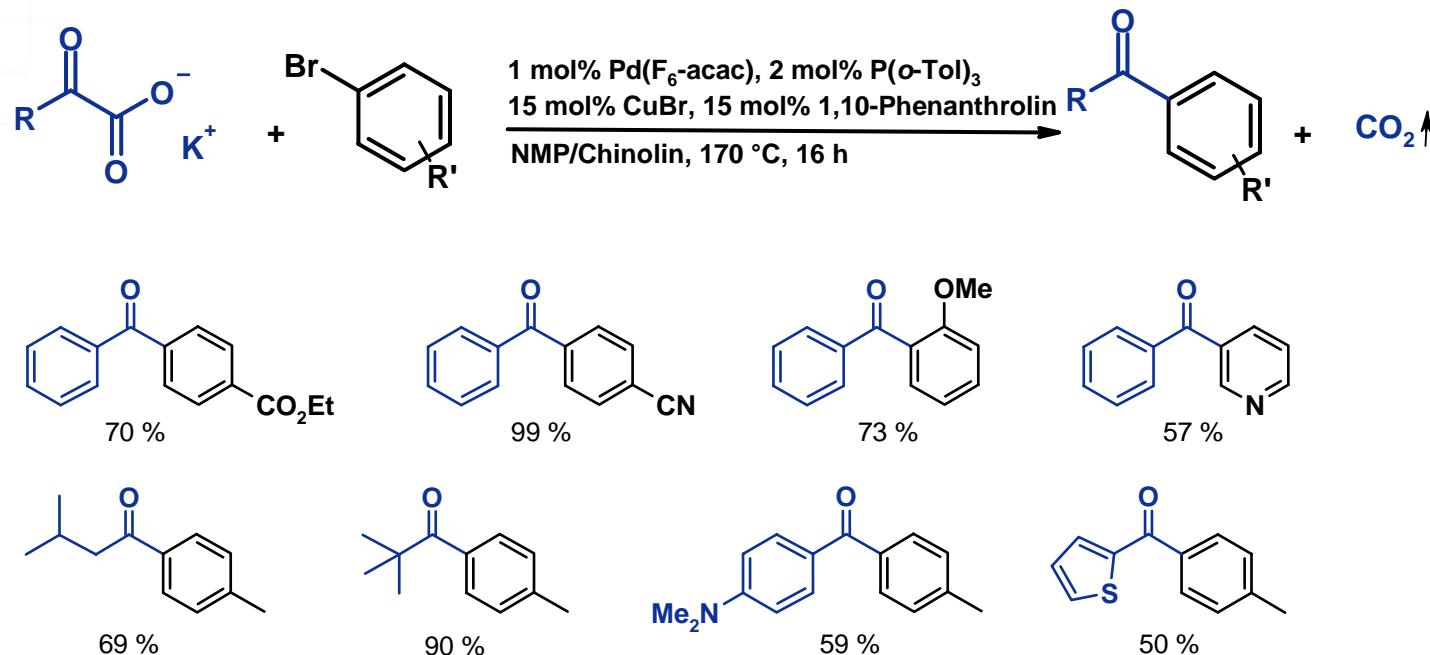
- The new protodecarboxylation catalysts are also effective as co-catalysts



with P. P. Lange, N. Rodríguez, C. Linder, A. Fromm, *Chem. Eur. J.* **2010**, 16, 3906.

Extension to New Substrate Classes

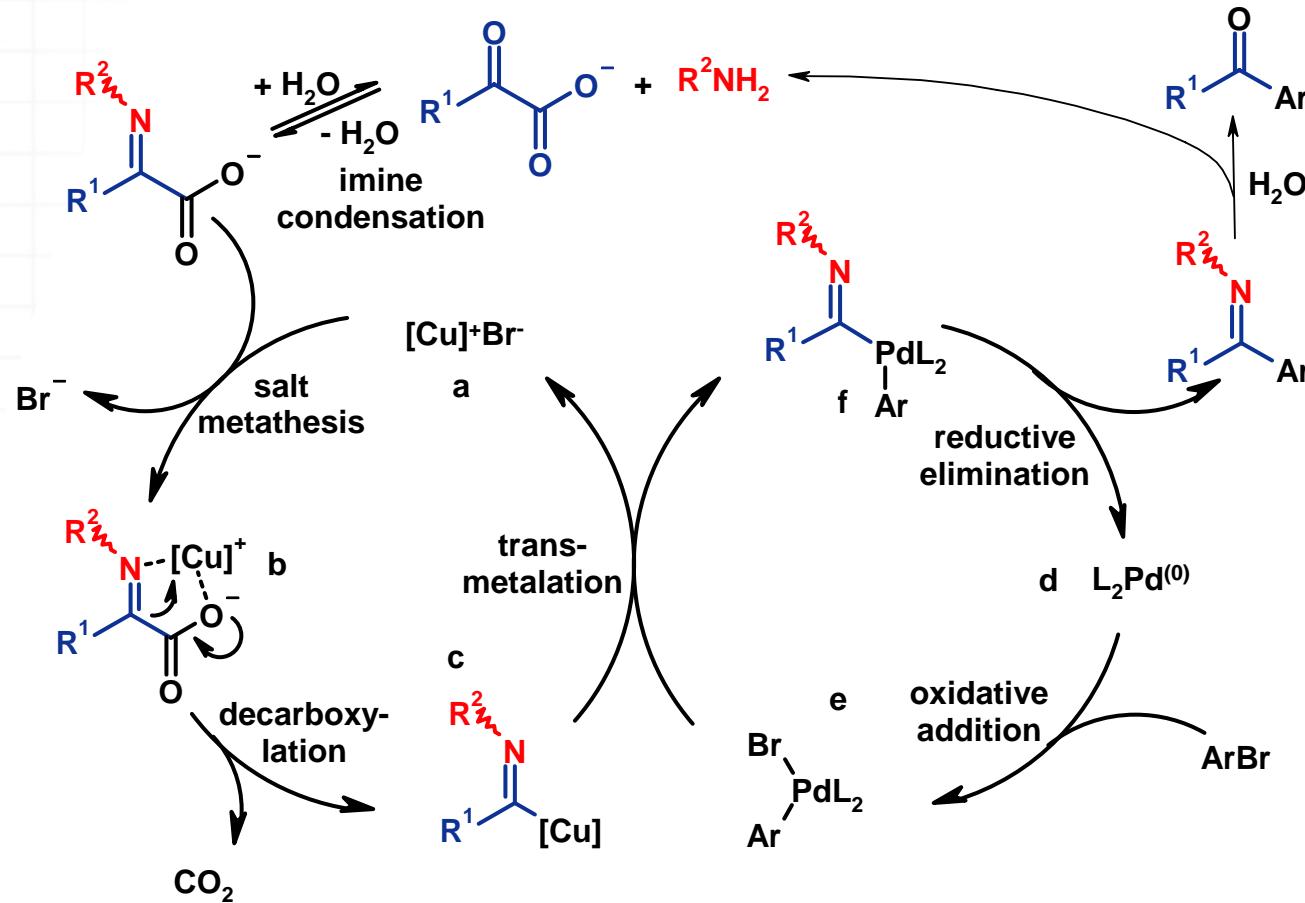
- Synthesis of arylketones via decarboxylative coupling of α -ketocarboxylates
 - In situ generation of „acyl anions“ by decarboxylation and coupling with aryl halides



with F. Rudolphi, C. Oppel, N. Rodriguez, *Angew. Chem.* **2008**, *120*, 3085-3088.

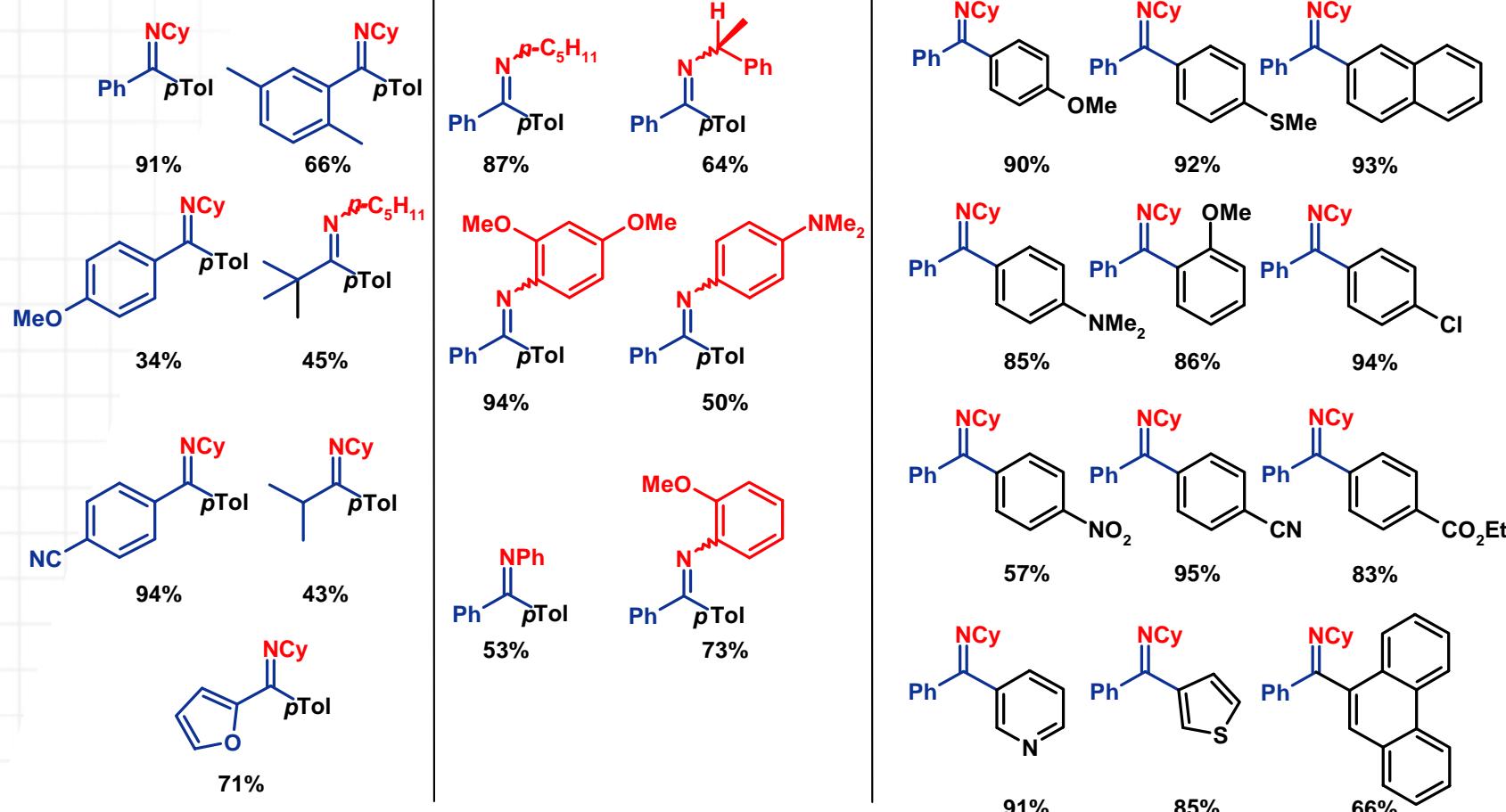
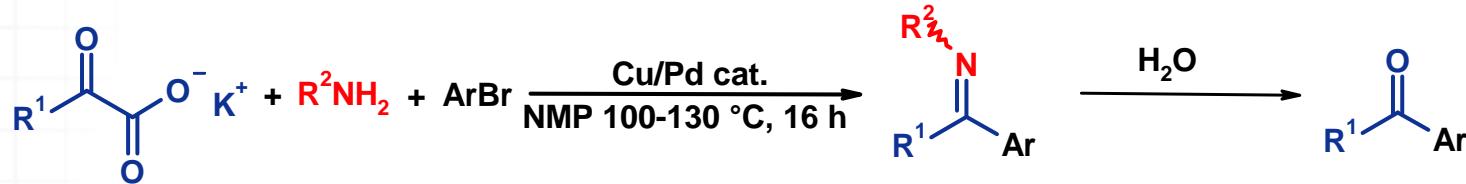


- Inverse approach to traditional ketone syntheses



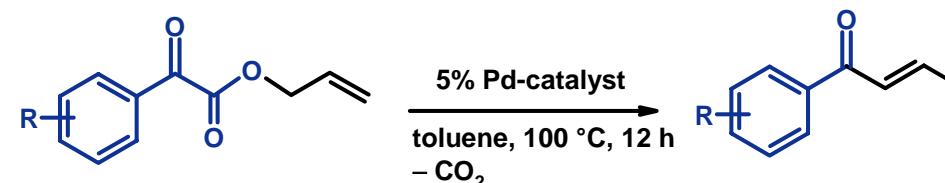
- imine condensation directly of the carboxylate salt
- decarboxylative cross-coupling
- Optional: hydrolysis of the imine after the reaction is complete

One-Pot Three Component Azomethine Synthesis



Synthesis of α,β -Unsaturated Ketones

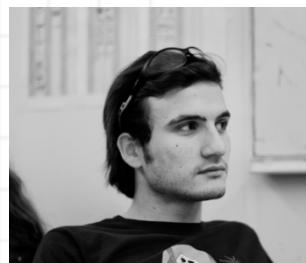
Optimized decarboxylative/isomerization tandem reaction:



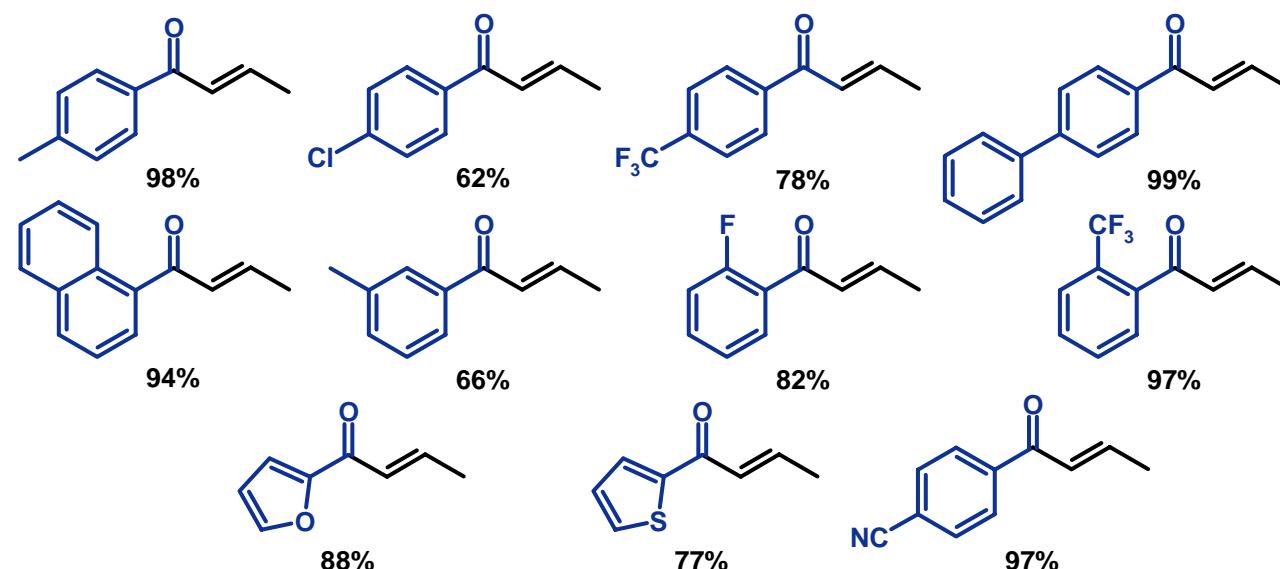
- neutral conditions, no organometallic reagents
- alternatively: in-situ generation of esters from carboxylate salts



M. F. Grünberg



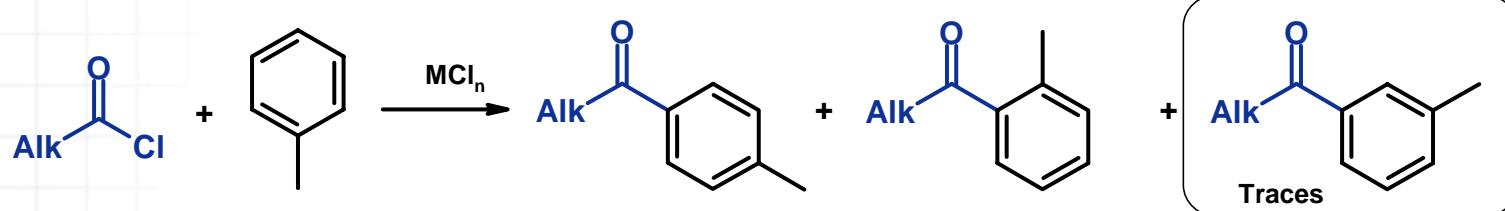
F. Manjolinho



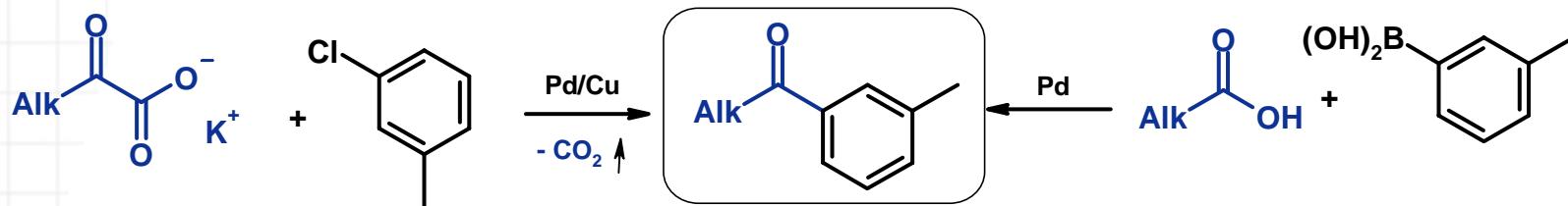
with N. Rodriguez, F. Manjolinho, M. F. Grünberg, 2011, manuscript in preparation.

Alternatives to Friedel-Crafts Reactions

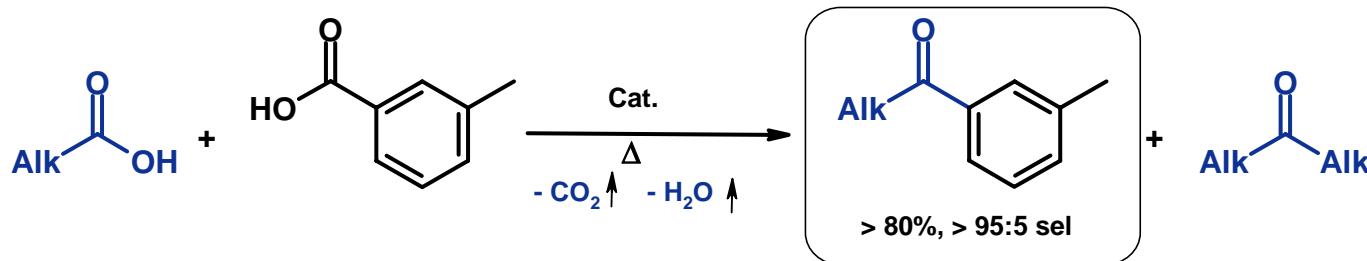
- Friedel-Crafts chemistry is established but unselective and waste intensive
 - Acid chloride substrates, 4 equiv. waste salt, some isomers are inaccessible



- Our Pd-catalyzed reactions are convenient but expensive for bulk chemicals

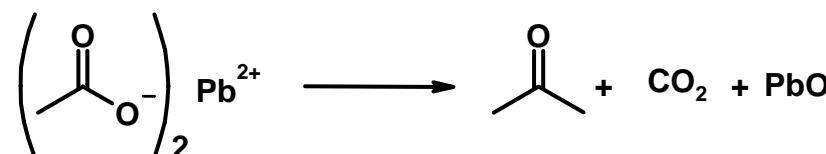


- New discovery: high-temperature decarboxylative cross-ketonization

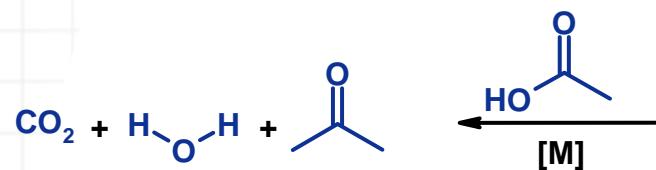


Decarboxylative Ketonizations

Pioneer work: pyrolysis of lead or calcium carboxylates

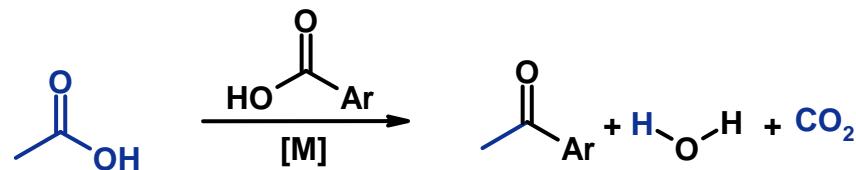


Homo-ketonization (Librarius, 1606)



„Kalksalzsynthese“, T = 270 – 430 °C
 [M] : Ca, Pb, Zr, Mg, K, Ba

Cross-ketonization (Friedel, 1858)



T : 250 – 340 °C
 [M] : Mn, Co, Fe

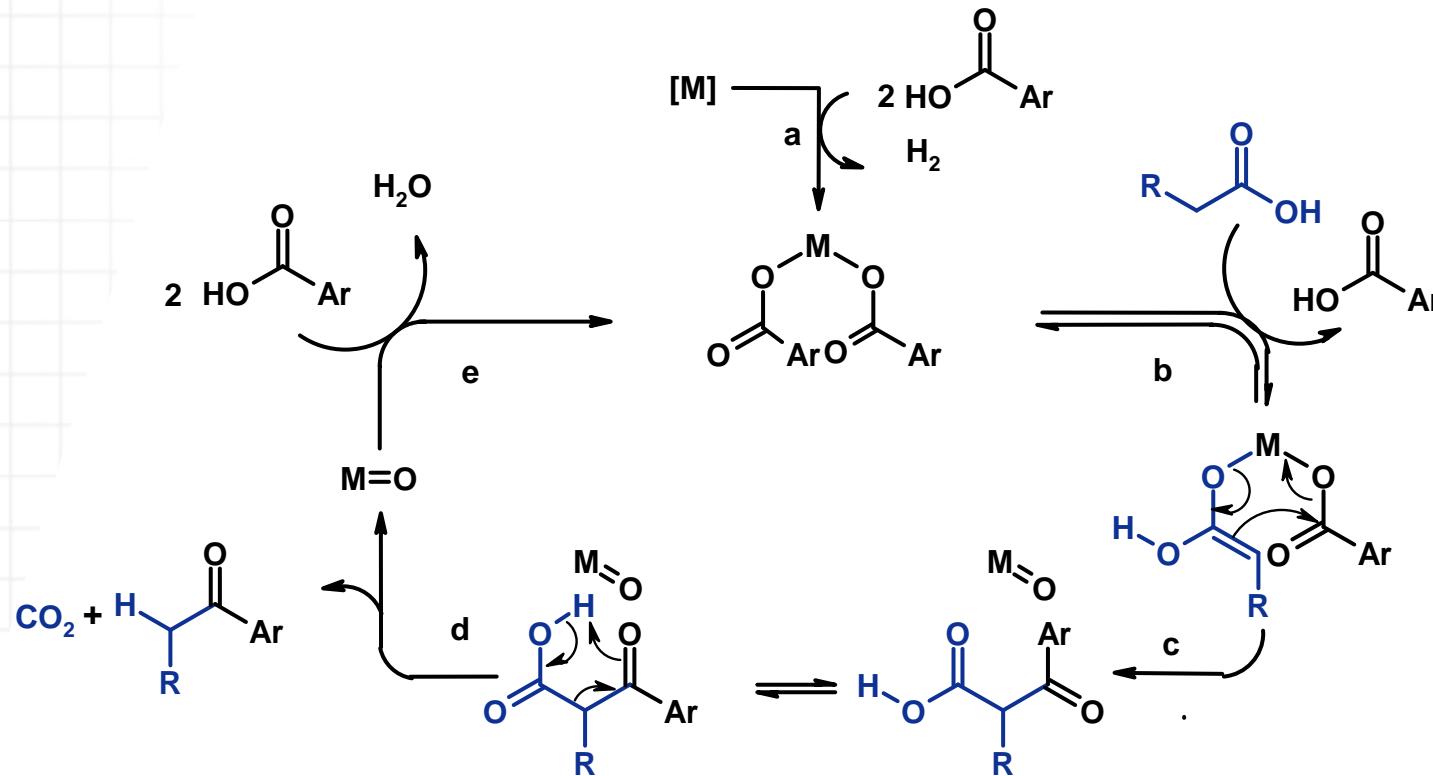
- stoichiometric processes, high temperatures, low yields and selectivity

- a) T. H. Easterfield, C. M. Taylor, *J. Chem. Soc.* **1911**, 99, 2298; b) D. M. Cowan, G. H. Jeffrey, A. I. Vogel, *J. Chem. Soc.* **1940**, 171; c) R. Davis, H. P. Schultz, *J. Org. Chem.* **1962**, 27, 854; C. Granito, H. P. Schultz, *J. Org. Chem.* **1963**, 28, 879; S. Gerchakov, H. P. Schultz, *J. Org. Chem.* **1967**, 32, 1656; d) E. Müller-Erlwein, *Chem. Ing. Tech.* **1990**, 62, 416; e) M. Renz, A. Corma, *Eur. J. Org. Chem.* **2004**, 2036.

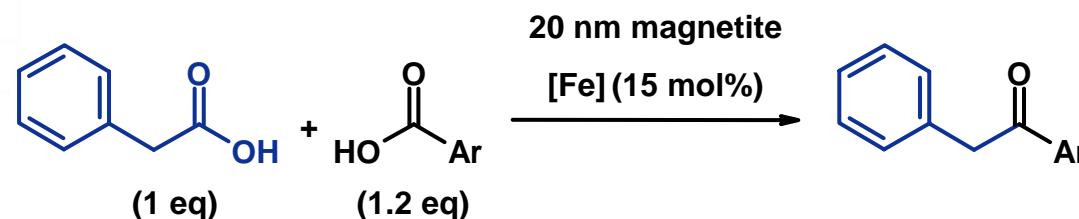
Decarboxylative Cross-Ketonization

How could one achieve selectivity for the aryl alkyl ketone?

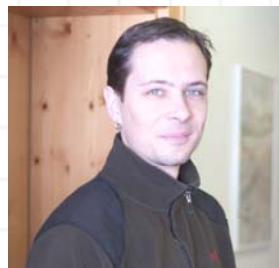
- Aromatic carboxylic acids are more acidic and thus bind preferentially
- Attack at β -position is possible only after exchange with alkyl derivatives



First Catalytic Protocol for Cross-Ketonizations



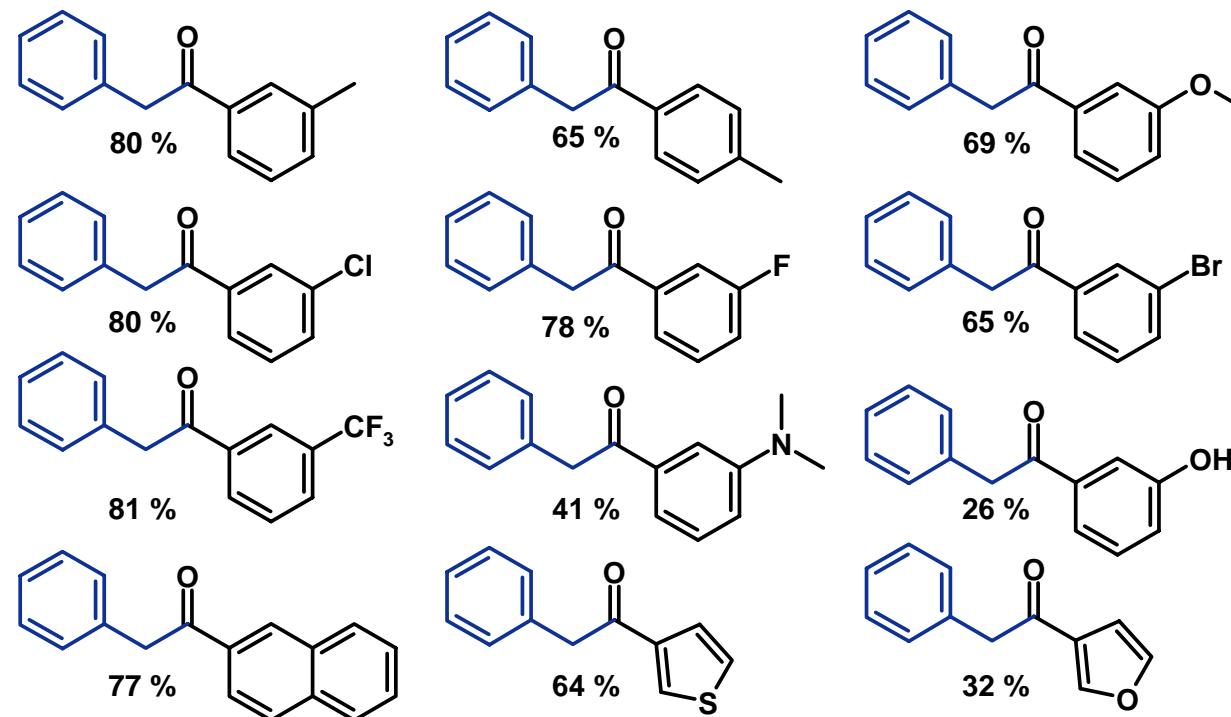
- Selectivity for aryl alkyl ketones is observed with Fe, Co, Mn
- Fe is uniquely reactive, allows catalytic turnover at 250 °C



C. Oppel

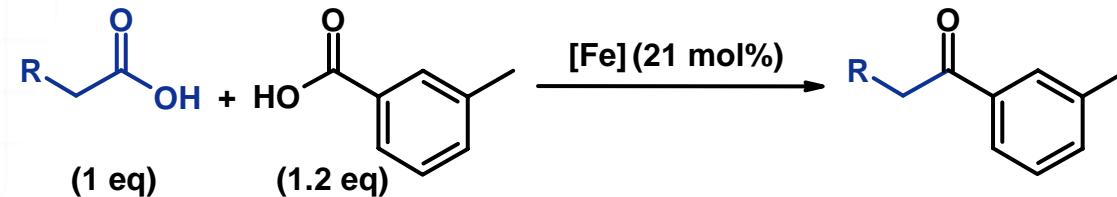


P. Mamone

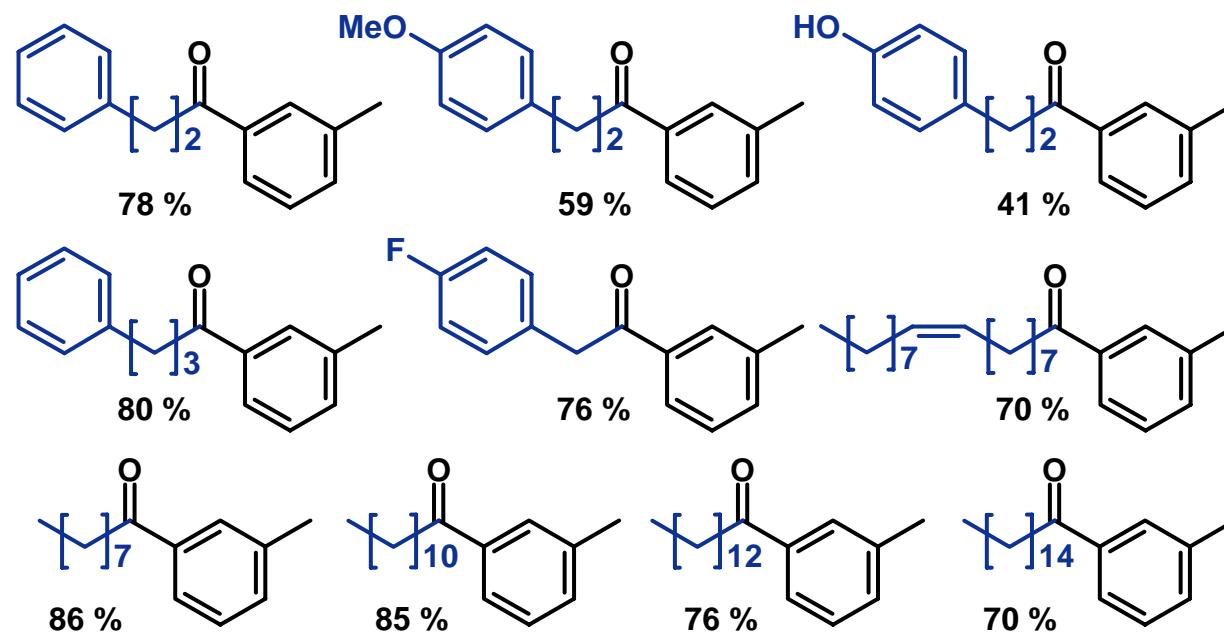


with P. Mamone, C. Oppel, *Adv. Synth. Catal.* **2010**, 353, 57

Scope Regarding Aliphatic Carboxylic Acids

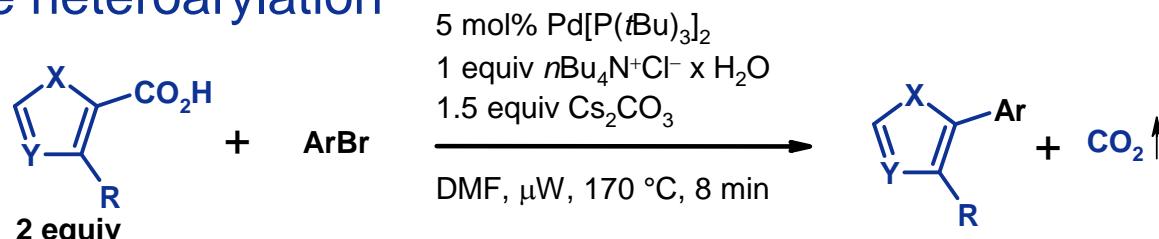


- Various aryl alkyl ketones were synthesized in good yields, many of them inaccessible via Friedel-Crafts-type chemistry :



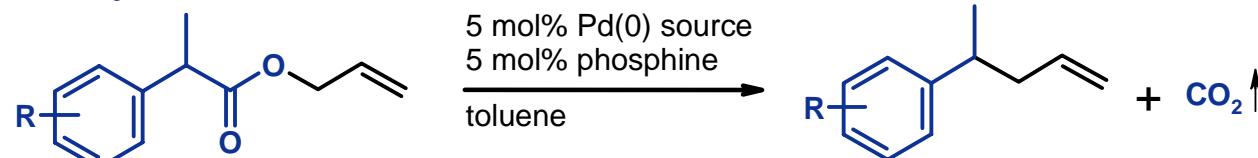
- Many decarboxylative couplings are being disclosed by a rapidly growing number of scientists, e.g., Myers, Steglich, Toste, Stoltz, Crabtree, Forgione, Becht, Liu, Kanai, Moon, Larrosa, Glorius

Decarboxylative heteroarylation



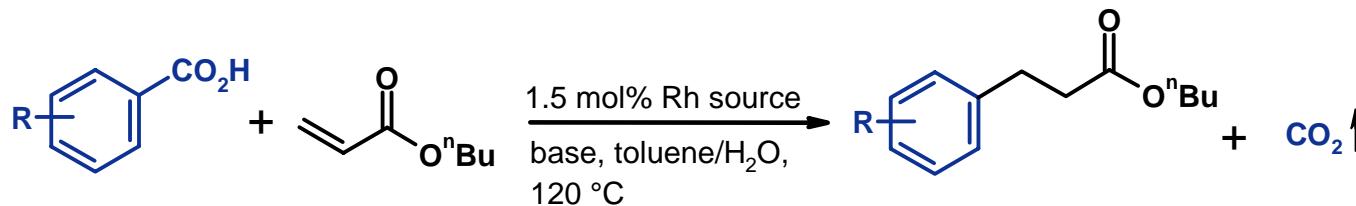
P. Forgione, F. Bilodeau, et al., *J. Am. Chem. Soc.* **2006**, 128, 11350.

Decarboxylative allylations



J. A. Tunge, et al., *J. Am. Chem. Soc.* **2005**, 127, 13510.

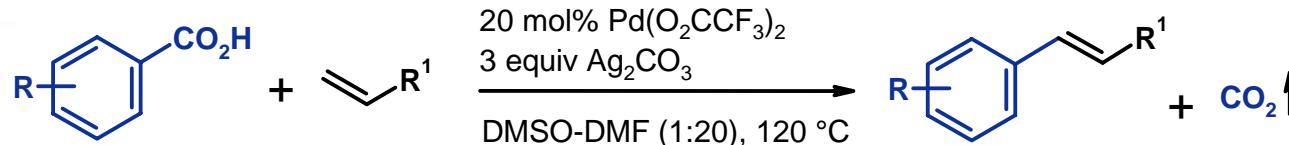
Decarboxylative 1,4-additions



P. Zhao, et al., *Angew. Chem. Int. Ed.* **2009**, 121, 6854.

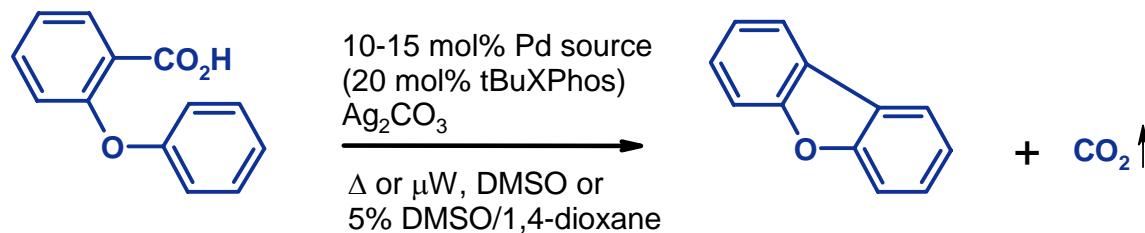
Oxidative Decarboxylative Couplings

Heck-Reactions



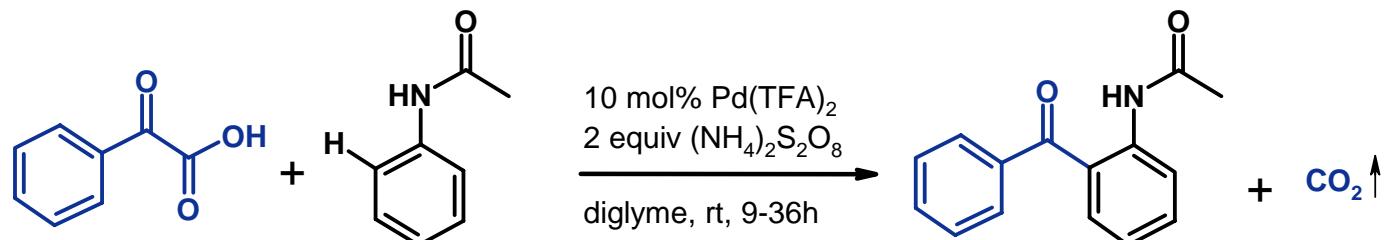
A. G. Myers, et al., J. Am. Chem. Soc. **2002**, 124, 11250.

Biaryl syntheses under C-H activation



R. H. Crabtree, et al., Chem. Commun., **2008**, 6312;
F. Glorius, et al., J. Am. Chem. Soc. **2009**, 131, 4194.

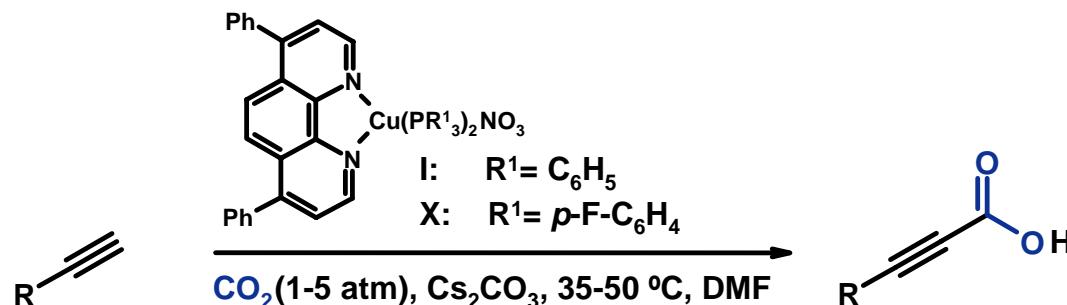
Directed ortho-acylations



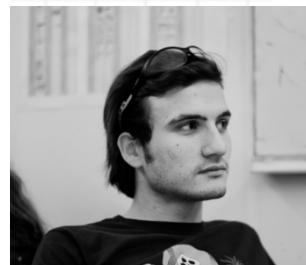
P. Fang, M. Li, H. Ge, J. Am. Chem. Soc. **2010**, 132, 11898.

The Reversal of Protodecarboxylations

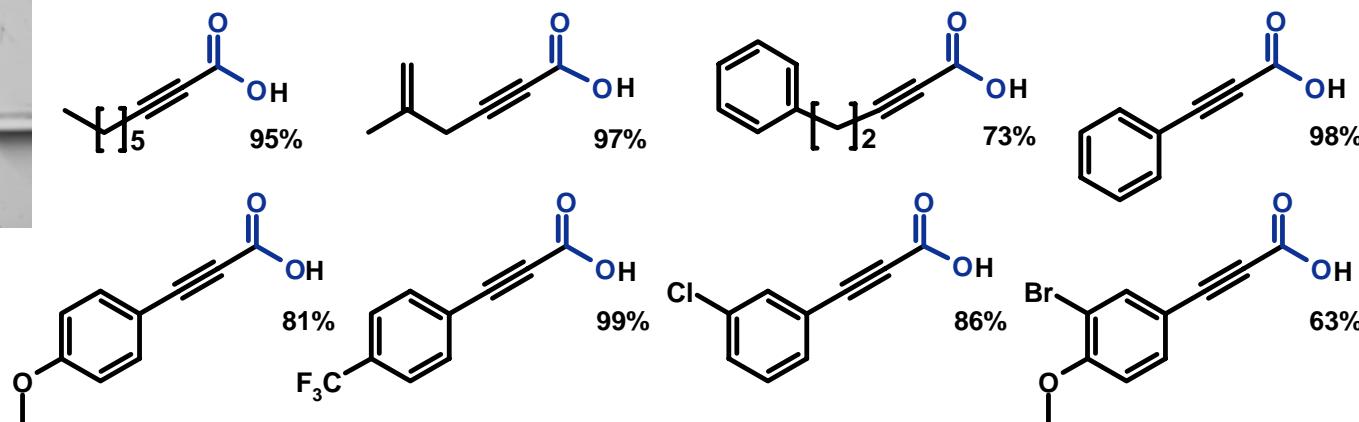
- Copper-Catalyzed Insertion of CO₂ into the C–H Bond of Terminal Alkynes



- Mild conditions: equilibrium on the side of the carboxylated products



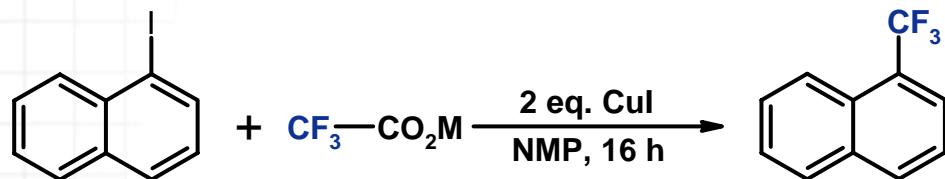
F. Manjolinho



with N. Rodriguez, F. Manjolinho, P. P. Lange, *Adv. Synth. Catal.* **2010**, 352, 2913

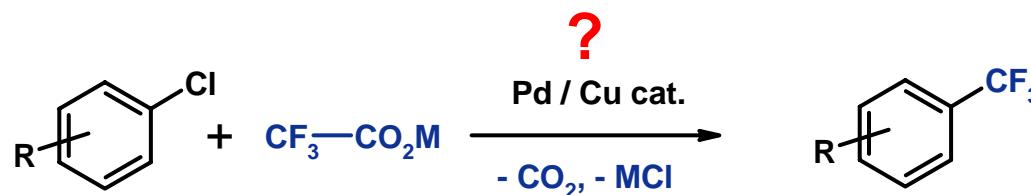
Stoichiometric reactions are known:

- Cu-mediated decarboxylative trifluoromethylation by Chambers et al.
 - Large amounts of copper, varying yields, expensive aryl iodides



G. E. Carr, R. D. Chambers, T. F. Holmes, D. G. Parker, *J. Chem. Soc. Perkin Trans. 1988*, 921

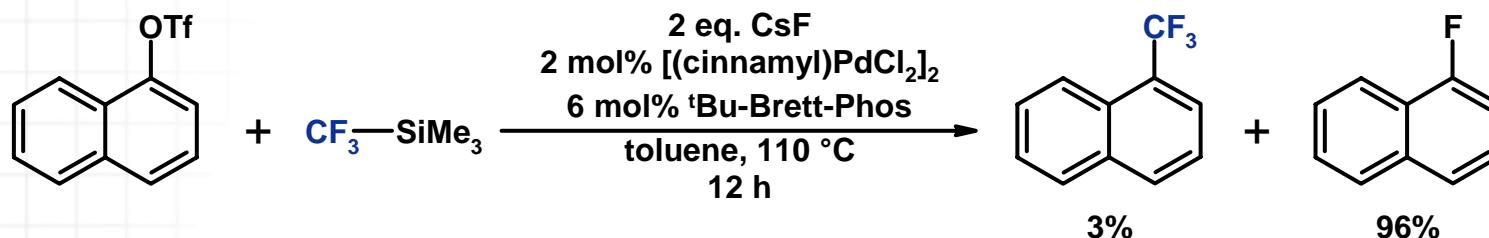
Dream Reaction: Pd/Cu catalyzed decarboxylative Trifluoromethylation



Key issues:

- generate CF_3^- using only catalytic amounts of metal
- Transfer the CF_3 -group to a cross-coupling catalyst (Pd)
- Find a way to reductively eliminate aryl- CF_3 from Pd catalysts

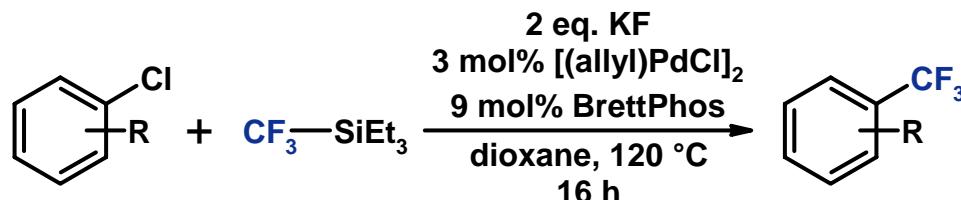
Successful spot-checks using Ruppert's reagent Jan. 2010



- Fluoride free, more stable CF_3 -source required
 - Decarboxylations also involve fluoride additives
 - Idea: Potassium (trifluoromethyl)trimethoxyborate $\text{K}^+[\text{CF}_3\text{BOR}_3]^-$

Break-through by Buchwald et al.

- CF_3SiEt_3 as the reagent, aryl chlorides rather than triflates



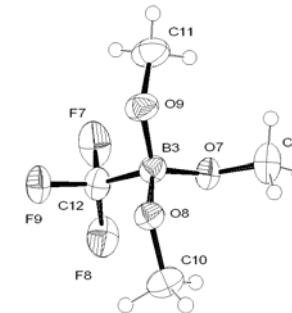
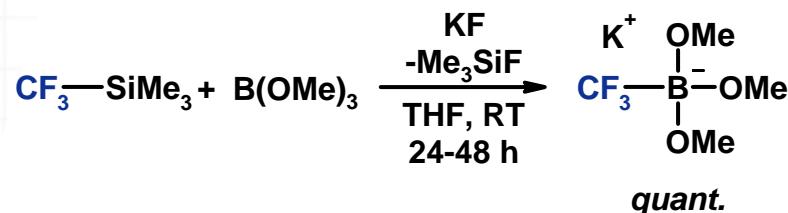
$\text{R} = 4\text{-nBu}$ 80%, 3-CO₂Hex 83%, 4-CN 72%,
4-Ph 84%, 3-OBn 88%,

reductive elimination of CF_3 -groups from Pd-complexes works!

E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, 328, 1679.

Transformation of volatile CF_3SiMe_3 into a crystalline salt

- Collaboration with G.-V. Röschenthaler, 2003:



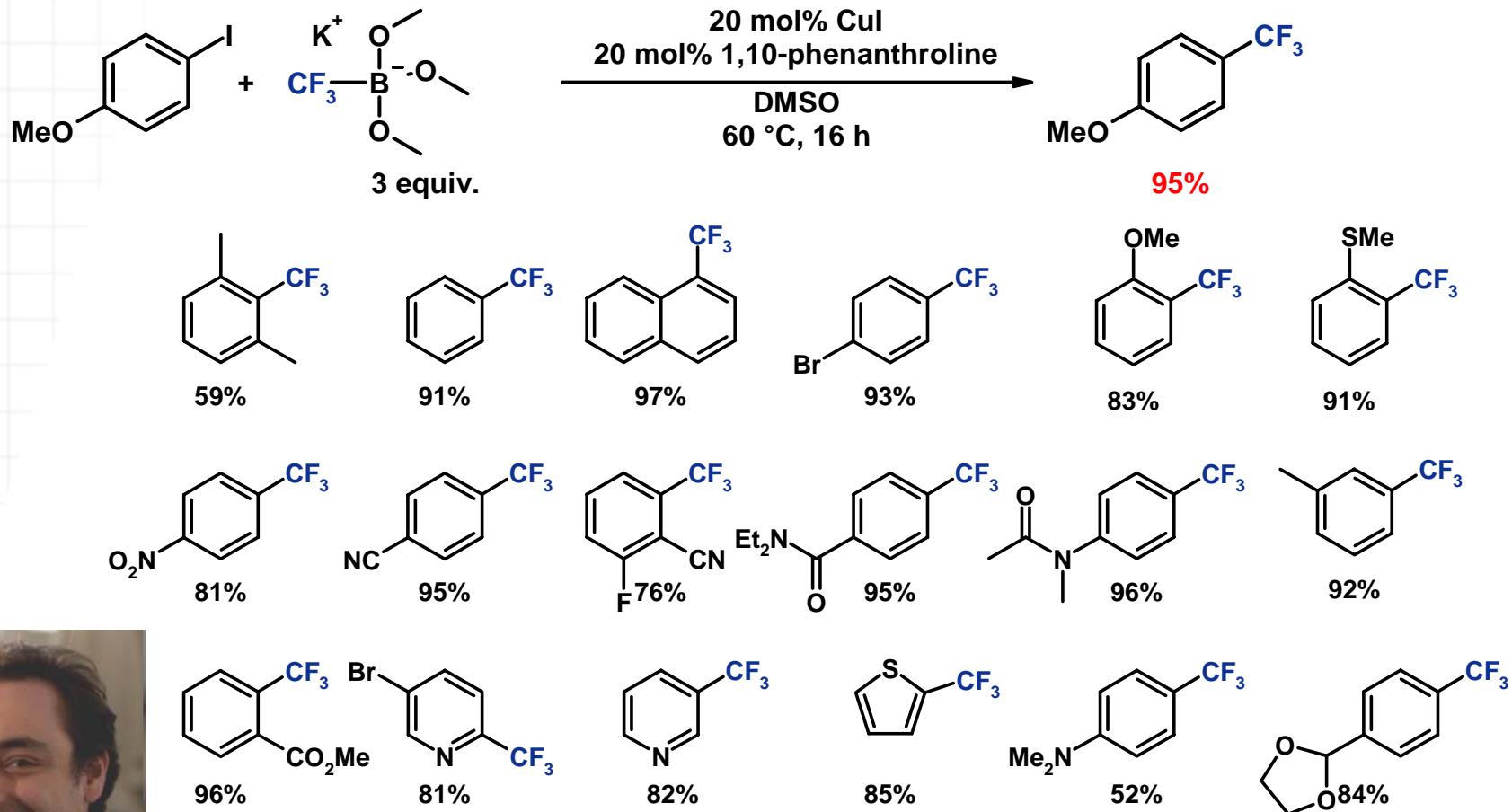
Molecular structure of the anion

- Access to multigram quantities, potentially accessible via direct fluorination
- Easy-to-handle, crystalline solid
- Shelf-stable, mp. 116-118°C (decomposition)
- Stable in aprotic polar solvents (e.g. DMF) up to 80°C
- Meanwhile commercially available, ca 300 € / 100g

A. A. Kolomeitsev, A. A. Kadyrov, J. Szczepkowska-Sztolcman, M. Milewska, H. Koroniak, G. Bissky, J. A. Bartene, G.-V. Röschenthaler, *Tetrahedron Lett.* **2003**, 44, 8273. Single crystal structure: thermal ellipsoids at 50% probability level. Selected bond lengths [\AA] and angles [$^\circ$]: B3-O7 1.488(6), B3-O8 1.1.473(6), B3-O9 1.455(6), B3-C12 1.646(7); O7-B3-O8 115.1(4), O7-B3-O9 116.4(4), O9-B3-O8 101.2(4), O7-B3-C12 103.7(4), O8-B3-C12 110.0(4), O9-B3-C12 110.6(4).

Development of a Cu-catalyzed protocol:

- chelating nitrogen containing ligands, DMSO as the solvent

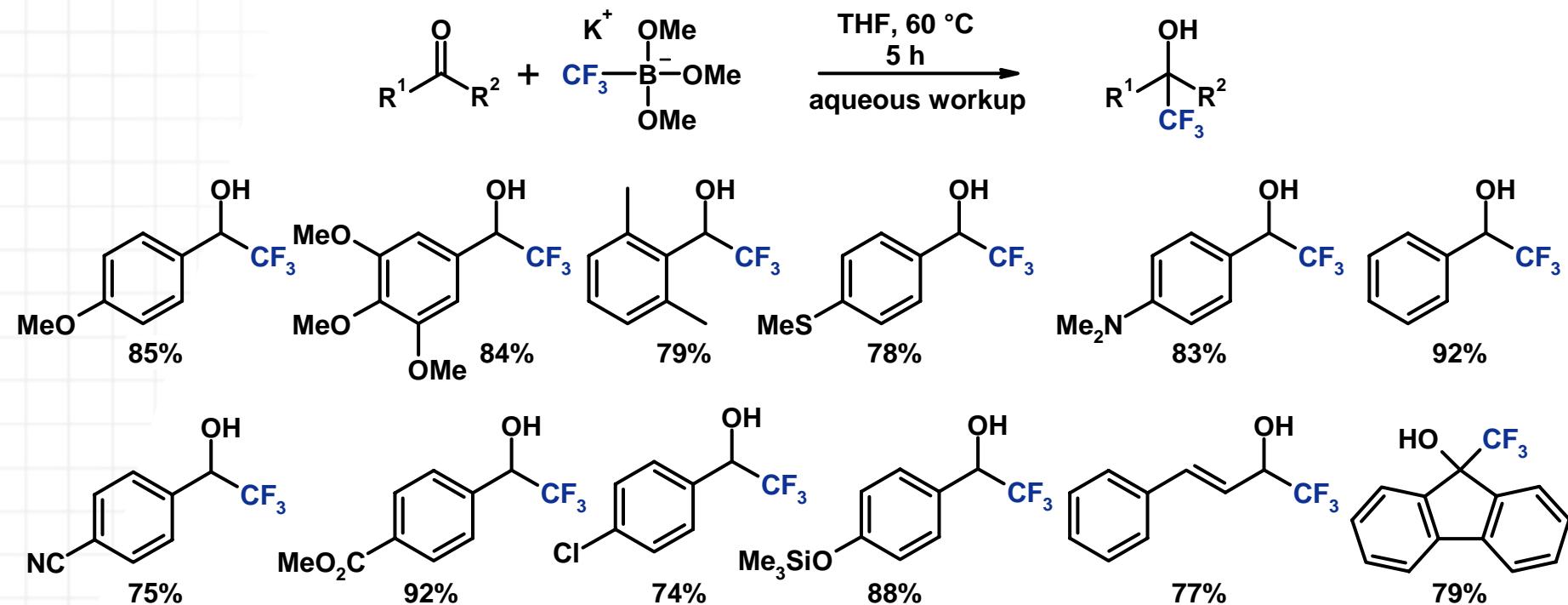


with T. Knauber, F Arikan, G.-V. Röschenthaler, *Chem. Eur. J.* **2011**, *17*, 2689

Trifluoromethylation of Carbonyl Compounds

Conversion of carbonyl compounds into trifluoromethylated alcohols

- Base-free conditions, good yields, easy workup



Research perspective: Use trifluoroacetate as source of CF_3 -groups

Acknowledgements

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