ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 3628–3630

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Decarboxylative biaryl synthesis in a continuous flow reactor†

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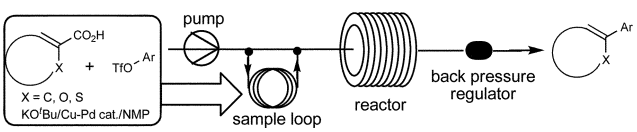
Received 21st December 2010, Accepted 13th January 2011
DOI: 10.1039/c0cc05708h

A practical protocol was developed that allows performing decarboxylative cross-coupling reactions in continuous flow reactors. Various biaryls were thus synthesized from aromatic carboxylic acids and aryl triflates using a Cu/Pd-catalyst system.

The formation of biaryl substructures is a key step in the synthesis of many biologically active compounds. Established synthetic methods include transition metal-catalysed cross-couplings[1] and C–H-activation reactions.[2] Recently, decarboxylative cross-couplings have evolved as an advantageous alternative. In this regiospecific C–C-bond forming reaction, carboxylate salts replace organometallic reagents as sources of carbon nucleophiles.[3] The decarboxylation step leads to the generation of an organometallic aryl nucleophile and is mediated by a Cu-,[4] Ag-,[5] Pd-,[6] or Rh-species.[7] The cross-coupling step with aryl halides[8] or sulfonates[9] has been achieved with Pd-[10] and Cu-catalysts.[11] Over the last years a steadily increasing number of decarboxylative reactions have been reported, and have established this concept as a widely applicable synthetic methodology.[12]

In order to further increase the attractiveness of decarboxylative couplings for industrial applications, it is essential to adapt them to state-of-the-art-reaction technologies such as microwave heating[10a,13,14] or continuous flow processes.[15] The key advantages of reactions performed in flow reactors (Scheme 1) over traditional batch reactions are the superior heat and mass transfer, the increased process safety, the ease of scale-up, and the possibility to include automated product purification and solvent recycling technologies. This technology should be of particular assistance for decarboxylative cross-couplings, as



Scheme 1 Reactor setup for decarboxylative cross-couplings.

they require high temperatures that are hard to reach and safely control in larger batch reactors.

In the development of a flow-based protocol for decarboxylative couplings, a major obstacle had to be overcome. Using established protocols, the reaction mixtures are slurries with large amounts of suspended solids that arise from the low solubility of the carboxylate salts and copper precursors in *N*-methylpyrrolidinone (NMP). Reactions in suspension require especially modified flow-through equipment that is unavailable in most laboratories.[16]

Our initial investigations thus focussed on identifying a way to fully dissolve all reaction components at room temperature in a minimal amount of solvent. Preformed potassium 2-nitrobenzoate did not fully dissolve in NMP. However, we discovered that upon mixing our model substrate 2-nitrobenzoic acid with an equivalent amount of the soluble base KO^{t}Bu, the deprotonation took place reliably, and clear 0.2 M solutions in NMP were obtained. We attributed this to an additional solubilising effect of the ^{t}BuOH released. Of all the copper precursors tested, only commercial $CuNO_3(phen)(PPh_3)_2$ had a sufficient solubility in NMP. A range of Pd sources including $Pd(acac)_2$ were found to be reasonably soluble.

The appropriate choice of the electrophilic coupling partner is also crucial. In the coupling of aryl halides, potassium halides are formed, which precipitate during the reaction. In contrast, the coupling of aryl triflates generates NMP-soluble potassium triflate. The added benefit of using aryl triflates as electrophiles is that they can be coupled with a wider range of carboxylic acids.[9a,b]

Based on the results of these initial investigations, we prepared a 0.2 M solution of 2-nitrobenzoic acid, KO^{t}Bu and 4-tolyl triflate in NMP and added catalytic amounts of $CuNO_3(phen)(PPh_3)_2$ and $Pd(acac)_2$. When this solution was passed through a stainless steel coil (10 mL) on a Vapourtec R2 + /R4 reactor[17] heated to 140 °C at a rate of 0.33 mL min^{-1} (30 min residence time), the desired biaryl **3aa** was formed in an encouraging 14% yield (Table 1, entry 1).

Increasing the residence time to 60 min and the reactor temperature to 160 °C improved the yield to 57% (entry 2). The same results were obtained without added PPh_3 demonstrating that the phosphine released from the Cu-catalyst suffices to stabilize the Pd catalyst (entry 3). Further lowering the flow rate did not have an extra benefit.

Among all Pd sources tested, only $Pd(OAc)_2$ was found to be superior to $Pd(acac)_2$ whereas most preformed Pd

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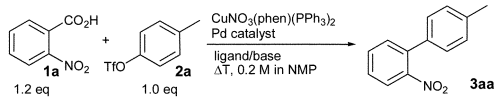
† Electronic supplementary information (ESI) available: Experimental data and procedures for all compounds. See DOI: 10.1039/c0cc05708h

Table 1 Optimisation of reaction conditions[a]

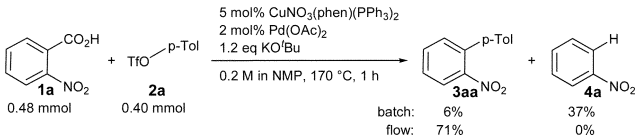


Entry	Cu-cat	Pd-cat	Ligand/Base	T/°C	**3aa**(%)
1[b]	5%	2% $Pd(acac)_2$	4% PPh_3, KO^{t}Bu	140	14
2	"	"	"	160	57
3	"	"	KO^{t}Bu	"	60
4	"	2% $Pd(OAc)_2$	"	"	62
5	"	2% $PdCl_2$(dppf)	"	"	3
6	"	2% $PdCl_2(PCy_3)_2$	"	"	0
7	"	2% $PdCl_2$(dtbf)	"	"	17
8	"	2% $Pd(OAc)_2$	"	170	71[c]
9	"	"	"	200	73
10	"	"	"	220	14
11	"	4% $Pd(OAc)_2$	"	170	45
12	10%	2% $Pd(OAc)_2$	"	"	66
13	"	4% $Pd(OAc)_2$	"	"	65
14	3%	2% $Pd(OAc)_2$	"	"	5

[a] Reaction conditions: 0.48 mmol 2-nitrobenzoic acid, 0.4 mmol 4-tolyl triflate, Pd-catalyst, ligand/base, 2 mL NMP, flow rate 0.167 mL min^{-1} (60 min). Conversions were determined by GC analysis using *n*-tetradecane as the internal standard. [b] Flow-rate: 0.33 mL min^{-1} (30 min). [c] Isolated yield. dppf: 1,1′-bis(diphenylphosphino)ferrocene, dtbf: 1,1′-bis(di-*tert*-butylphosphino)ferrocene.

complexes were ineffective (entries 5–7). At a higher temperature (170 °C) even better results were achieved (entry 8). However, above this temperature, the selectivity dropped, and considerable amounts of homocoupling products were formed.

An optimal balance between decarboxylation and cross-coupling was achieved using 5 mol% of $CuNO_3$(phen)$(PPh_3)_2$ and 2 mol% of $Pd(OAc)_2$ (entries 11–14). At lower catalyst loadings, the yields dropped (entry 14). Under optimised conditions (5 mol% $CuNO_3$(phen)$(PPh_3)_2$, 2 mol% $Pd(OAc)_2$, KO^{t}Bu, 170 °C, 1 h) a 75% conversion based on the aryl triflate was achieved. The desired biaryl was formed almost exclusively, side products arising from protodecarboxylation or homocoupling were detected only in trace amounts. This level of selectivity is unprecedented in batch procedures and its origin is still unclear. When performing a comparative batch reaction under identical conditions, low yields were obtained and protodecarboxylation became the main reaction pathway (Scheme 2).

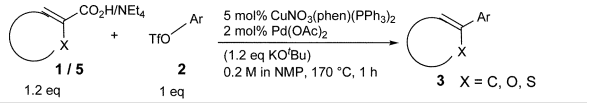


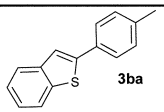
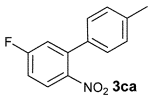
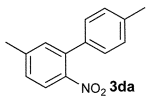
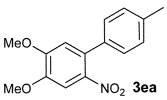
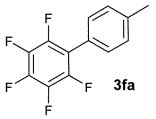
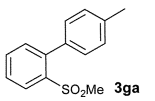
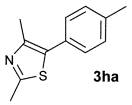
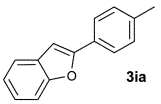
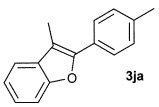
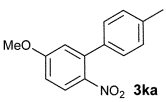
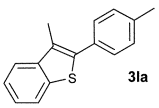
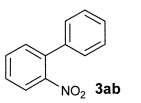
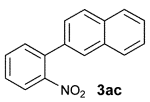
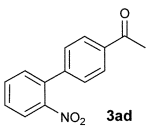
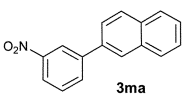
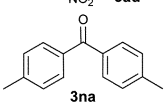
Scheme 2 Comparison between batch and flow.

This illustrates that the protocol is effective only for flow-through conditions, whereas in batch reactions, the presence of ^{t}BuOH inevitably leads to protodecarboxylation.

We investigated the scope of the new protocol in the coupling of various carboxylic acids and aryl triflates (Table 2). 2-Nitrosubstituted benzoic acids, thiazole, 2-benzofuran and 2-thiophene substrates were coupled in good yields. Unfortunately, some other potassium carboxylates precipitated during the

Table 2 Scope of the transformation[a]



Product	Yield [%]	Product	Yield [%]
 **3ba**	70[c]	 **3ca**	46[b]
 **3da**	72[b]	 **3ea**	65[c]
 **3fa**	42[b]	 **3ga**	40[c]
 **3ha**	60[c]	 **3ia**	60[c]
 **3ja**	67[b]	 **3ka**	71[b]
 **3la**	82[b]	 **3ab**	62[b]
 **3ac**	73[b]	 **3ad**	54[b]
 **3ma**	<5[b,d]	 **3na**	15[c]

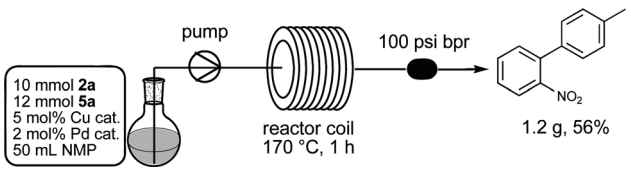
[a] Reaction conditions: 0.40 mmol aryl triflate, 5 mol% $CuNO_3$(phen)-$(PPh_3)_2$, 2 mol% $Pd(OAc)_2$, 2 mL NMP, 170 °C, flow-rate: 0.167 mL min^{-1} (60 min). Isolated yields. [b] 0.48 mmol carboxylic acid, 0.48 mmol KO^{t}Bu. [c] 0.48 mmol tetraethylammonium carboxylate. [d] GC yield.

deprotonation step, precluding their use following the standard procedure. For these compounds, an alternative method was developed, which involves their conversion into tetraethylammonium salts. After deprotonation with tetraethylammonium hydroxide, the carboxylates were precipitated from methanol by the addition of ethyl acetate and redissolved in the NMP reaction solution. This modification extended the scope with regard to the carboxylic acid coupling partner.

In comparison to batch reactions[9b] comparable yields were obtained in shorter reaction time (*e.g.* **3aa**: 91% *vs.* 71%, **3da**: 72% *vs.* 72% in 1 h rather than 16 h). Under microwave conditions[9b] the reaction gives comparable yields within 5 min (**3aa**: 84% *vs.* 71%, **3da**: 73% *vs.* 72%), but only on sub-millimolar scales. The successful coupling of the electron-deficient, sensitive triflate **2d** in a record yield demonstrates that the flow conditions are milder than those of batch reactions. Even under microwave conditions biaryl **3ad** had been obtained in only 23% yield along with considerable amounts of transesterification.[9b]

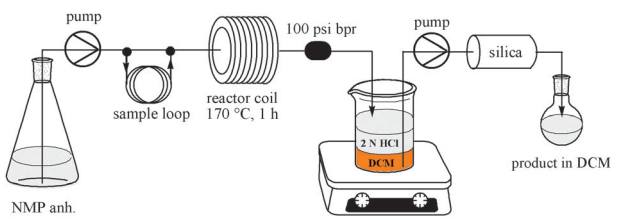
At this stage, there are still limitations with regard to the substrate scope which we hope to overcome with new catalyst generations and optimized flow reactor setups. For example, *meta*-substituted and α-oxo-carboxylic acids were only coupled in low yields.

In order to demonstrate how easily this flow protocol can be scaled up, we adjusted the setup and operated the reactor in a continuous flow mode by aspirating material from a 50 mL stock solution under otherwise unchanged conditions. Within 6 h, we thus synthesized 1.2 g (56%) of 2-nitro-4′-methyl-biphenyl (Scheme 3).



Scheme 3 Biaryl synthesis using continuous flow.

With the long-term aim of a fully automated process for decarboxylative cross-coupling reactions, we probed into the development of an in-line purification unit (Scheme 4). In order to separate the product from unreacted substrates and the NMP solvent, the flow system was supplemented with a vessel filled with HCl and dichloromethane (DCM). This allowed a solvent switch from NMP to volatile DCM. Subsequent in-line filtration of the organic layer through a silica cartridge afforded the desired biaryl in 71% yield as a 7 : 1 mixture with remaining NMP.



Scheme 4 Complete flow setup including in-line purification.

In conclusion, a catalyst system and a reactor layout were developed that for the first time allows performing decarboxylative cross-coupling reactions in a continuous flow reactor. This is an important milestone towards implementing this modern C–C-bond forming strategy as a standard tool in academic and industrial laboratories.

We thank David Fox for helpful discussion, and NanoKat and the Deutsche Forschungsgemeinschaft for funding.

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