Generation of benzyne from benzoic acid using C–H activation†

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Received 13th July 2010, Accepted 30th September 2010
DOI: 10.1039/c0cc02547j

ortho **C–H activation of benzoic acids with Pd(II) generates an oxapalladacycle that can decarboxylate to produce a palladium-associated aryne. The arynes then undergo [2 + 2 + 2] trimerisation to afford triphenylenes.**

Transition-metal (TM) catalysed aryne chemistry has undergone rapid growth in recent years, sparked by the introduction of *O*-triflato silanes **1** as aryne precursors.[1] Activated by fluoride at room temperature, this class of precursor has been applied to a number of innovative TM-catalysed transformations, frequently involving insertion of the aryne moiety into a conventional Pd(0) or Ni(0) cross-coupling (Fig. 1).[2] Despite these successes, use of precursor **1** has economic drawbacks that may hinder more widespread applications. Its doubly functionalised character, containing a triflate group, makes it expensive as a starting material for aromatic chemistry.[3] Analogs are not commercially available and must be synthesised from the appropriate halo-phenol,[4] and the process of aryne generation is poorly atom economic.

We envisaged the possibility of generating arynes from benzoic acids, **3**, *via* Pd-mediated *ortho* C–H bond activation (Fig. 1). Benzoic acids would be superbly versatile aryne precursors, being extremely cheap, commercially available compounds that are easy to handle and functionalise. Furthermore, a Pd-activated benzyne generation step would simplify and even expand the subsequent aryne capture chemistry, as the dual roles of benzyne production and subsequent C–C/C–X bond formation would be handled by a single catalyst.[5]

Ample precedent exists for the first step of the proposed pathway, *ortho*-palladation of benzoic acid. Cyclopalladated complexes **4** have been prepared and characterised,[6] and are likely intermediates in a host of catalytic Pd-catalysed C–H functionalisation transformations discovered in recent years.[7] The second step, by contrast, is far less precedented in the literature. Indeed, it has been reported to fail for both Pd and Pt oxapalladacycles in stoichiometric studies.[6c,8] A single report from Kim and co-workers, however, describes the successful Pd(0)-mediated generation of benzyne from *o*-bromobenzoic acid, implying that decarboxylation of **2** is possible under the right conditions.[9]

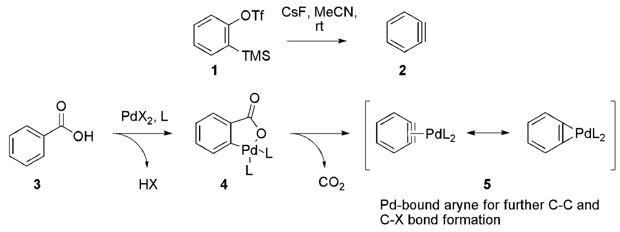


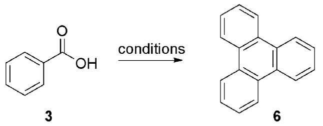
Fig. 1 Generation of benzyne from benzoic acid by C–H activation.

To assess the viability of benzoic acid as a benzyne precursor we chose the TM-mediated trimerisation of benzyne to triphenylene as a model reaction. First described in seminal work from Rees and Gilchrist using platinum catalysis,[8,10] the reaction was applied to precursor **1** using catalytic Pd(0) by Guitian, Perez and co-workers in 1998.[11] This pioneering report marked the beginning of modern TM-catalysed aryne chemistry, and has itself been widely applied to polyphenylene synthesis for use as functional molecules.[12]

Initial screening used Pd(OAc)$_2$ as the catalyst and varied oxidant, solvent and ligand in the presence of K_2HPO_4 as base, a phase transfer catalyst and 4 Å molecular sieves (Table 1).

Early results were not encouraging, with little if any triphenylene being formed. Surprisingly, only copper(II) acetate was found to have an impact on the reaction with all other oxidants giving no yield of triphenylene (entries 1–4). The only positive result obtained in early runs was a 4% yield of triphenylene using diphenylphosphinobutane (dppb) as ligand and Cu(OAc)$_2$ in DMF at 150 °C (entry 4). Screening for ligands indicated that both 1,10-phenanthroline and

Table 1 Selected optimisation conditions for triphenylene synthesis



Entry	Oxidant	Solvent	Ligand	Yield[a] (%)
1	Air	DMF	dppb	0
2	Ag_2CO_3	DMF	dppb	0
3	Benzoquinone	DMF	dppb	0
4	Cu(OAc)$_2$ (1 equiv.)	DMF	dppb	4
5	Cu(OAc)$_2$ (1 equiv.)	DMF	phen	7
6	Cu(OAc)$_2$ (1 equiv.)	DMF[c]	phen	13
7	Cu(OAc)$_2$ (0.75 equiv.)	DMF[c]	phen	20
8	Cu(OAc)$_2$ (0.5 equiv.)	DMF[c]	phen	17[b]
9	Cu(OAc)$_2$ (0.75 equiv.)	Sulfolane[c]	phen	37
10	Cu(OAc)$_2$ (0.75 equiv.)	Sulfolane[c]	phen	13
11	Cu(OAc)$_2$ (0.75 equiv.)	Sulfolane[d]	phen	47[e]

Reaction conditions: solvent (0.5 mL), Pd(OAc)$_2$ (10 mol %), ligand (10 mol %) and benzoic acid (111 mg, 0.9 mmol) were sonicated together for 1 min. K_2HPO_4 (2 equiv.), TBAB (1 equiv.), 4 Å MS, and oxidant were then added and the reaction was heated to 150 °C for 16 h, open to air. [a] Yields determined by GC with triphenylene as external standard. [b] No sonication. [c] 1.5 mL of solvent used. [d] 2.5 mL of solvent used. [e] Isolated yield; dppb = diphenylphosphinobutane; phen = 1,10-phenanthroline.

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† Electronic supplementary information (ESI) available: Preparation and characterisation of all new compounds. See DOI: 10.1039/c0cc02547j

(2-biphenyl) di-*tert*-butylphosphine lead to slightly improved reaction yield, with the former found to be superior in later screens (entry 5). It was also found that reaction favoured dilute conditions and adding an extra 1 mL of DMF to the reaction resulted in a doubling of the yield (entry 6). The stoichiometry of the copper(II) acetate was also found to be an important parameter: too little and catalyst turnover is harmed, too much and the dibenzopyranone **7** appeared as a side product (entries 7–9), presumably formed *via* insertion of benzyne into palladacycle **4** without decarboxylation (Fig. 2). Compound **7** could be isolated in a 25% yield by increasing the amount of copper(II) acetate to 2 equivalents and using *tert*-butyl XPhos as ligand.

Lastly, screens of solvents with varying dilutions showed a dilute sulfolane solvent system to be the best for the reaction. With DMF as solvent dilutions of greater than 1.5 mL of solvent resulted in diminished yields due to the reaction of DMF decomposition products with the benzoic acid starting materials. This does not occur with the more thermally stable sulfolane, affording a highest isolated yield of 47% of triphenylene from benzoic acid (entry 11).

We applied these reaction conditions to a range of simple benzoic acids to establish substrate scope (Fig 3.). Aryne trimerisation of *para*-substituted benzoic acids can yield a pair of regio-isomeric triphenylene products, **6** and **6′**. Likewise, *ortho*-substituted starting materials can produce **8** and **8′**. In both cases one isomer of each pair is C_3-symmetric (**6′** and **8′**) and the other is unsymmetric (**6** and **8**). For *meta*-substituted benzoic acids, the possibility of regio-isomeric aryne generation exists (**2a** and **2b**), permitting access to all four triphenylene regioisomers. We were pleased to observe very high levels of selectivity in the cyclisation of *para*-substituted benzoic acids, with unsymmetrical triphenylenes **6b–f** being isolated as single isomers, albeit in modest yield. Fluorinated triphenylenes **6d** and **6f** are novel compounds that have not been previously accessed using conventional triphenylene syntheses. This selectivity was replicated for the *meta*-substituted starting materials, such that *m*-toluic acid produced the same 2,6,11-trimethyltriphenylene **6b** in very similar yield as when *p*-toluic acid was used as starting material. Importantly, no trace of triphenylenes **8** could be detected, indicating that aryne generation from *m*-benzoic acids proceeds, as expected, *via* activation of the C–H bond distal from the *meta*-substituent.[7] The identical regioselectivities across *meta* and *para*-substituted starting materials are supporting evidence for an aryne intermediate.

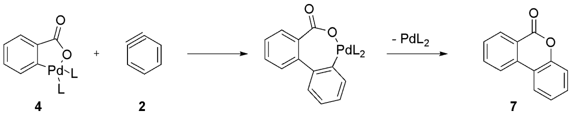

Fig. 2 Dibenzopyranone formation from complex **4**.

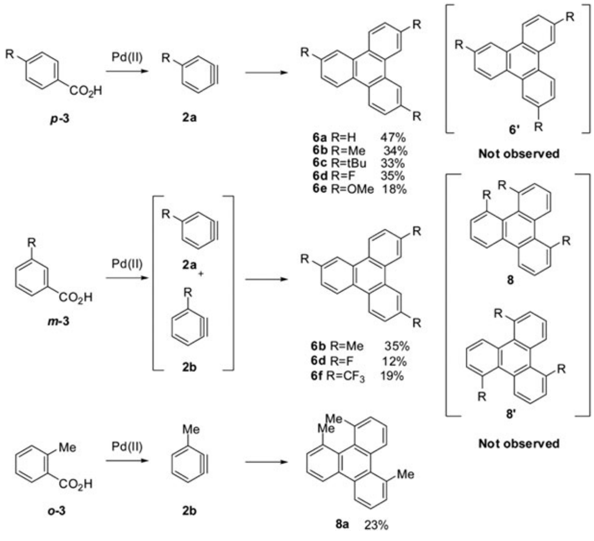

Fig. 3 Monosubstituted benzoic acid trimerisation. Conditions as in Table 1.

Aryne intermediacy is further indicated by the observed triphenylene regioisomers matching those formed from Pt and Pd-catalysed trimerisations of conventional aryne precursors.[9,10,12] *ortho*-Substituted benzoic acids were generally ineffective in the reaction, with only *o*-toluic acid affording a 23% yield of the unsymmetrical isomer **8a**.[11]

We investigated the effect of adding a ground state alkyne into the reaction mixture, as mixed aryne/alkyne trimerisations are well known to afford phenanthrene and naphthalene products.[13,14] Using diphenylacetylene, we were pleased to observe the controlled formation of either phenanthrene **9** or naphthalene **10**, depending on the reaction stoichiometry. Excess benzoic acid produced **9** (48% yield) containing two benzyne derived aromatic rings, whereas excess alkyne at the slightly lower reaction temperature of 120 °C afforded a good yield of the naphthalene **10** (Fig. 4).

In conclusion, a novel method of generating benzyne from cheap and readily available benzoic acids has been developed. The method was used to make various tri and bi-cyclic aromatic compounds along with arene fused lactones. Benzoic acid is over 1000 times cheaper than *O*-triflato silane **1**,[15] making it an attractive starting material for simple triphenylene synthesis. Whilst the yields of substituted triphenylenes are generally low, a one step transformation of cheap and readily available substituted benzoic acids is competitive with the multi-step routes required for substituted aryne precursor synthesis and subsequent trimerisation. More importantly, we have demonstrated for the first time that arynes may be generated from simple benzoic acid through C–H activation and decarboxylation. Optimisation of this process will be the subject of future work in our laboratory.

We thank Sally-Ann Fancy for technical assistance in setting up the GC-MS screen and the EPSRC mass spectrometry service at the University of Swansea. We thank Pfizer, CRUK, and the University of Edinburgh for funding (A.A.C) and the EPSRC for the award of a Leadership Fellowship to M.F.G.

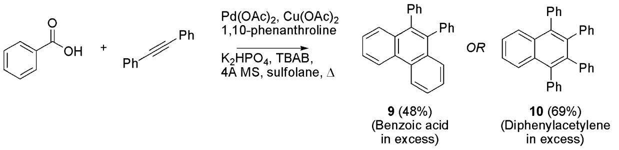

Fig. 4 Naphthalene and phenanthrene synthesis from benzoic acid.

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