**Synthetic Methods**

**Palladium-Catalyzed Direct C–H Functionalization of Benzoquinone**

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**Abstract:** A direct Pd-catalyzed C–H functionalization of benzoquinone (BQ) can be controlled to give either mono- or disubstituted BQ, including the installation of two different groups in a one-pot procedure. BQ can now be directly functionalized with aryl, heteroaryl, cycloalkyl, and cycloalkene groups and, moreover, the reaction is conducted in environmentally benign water or acetone as solvents.

Benzoquinone (BQ, 1)** and its derivatives are ubiquitous in organic chemistry as they are useful in many fields, such as oxidation chemistry,[3] molecular electronics,[4] medicinal chemistry,[5] natural products,[6] dyes,[7] and as ligands.[8] Despite the prevalence of Pd**-catalyzed cross-couplings for the formation of C–C bonds, a method for the direct Pd-catalyzed Heck coupling with BQ has so far eluded synthetic chemists. This reflects its electronic properties: BQ and its derivatives will often act as an oxidant[3] or ligand[8a–c] rather than a substrate in Pd catalysis.[9,10] As a result, for decades, the controlled Pd-catalyzed cross-coupling of BQ has relied on first installing a Br, I, or OTf group (substrate 2), followed by a Stille or Suzuki coupling (2–3, Scheme 1).[11,12] This procedure involves additional steps but may also suffer from chemo- and regioselectivity issues during halogenations.[13] The direct C–H functionalization of BQ would clearly expedite the synthesis of BQ-containing targets, but to date, an efficient Pd-catalyzed monofunctionalization has proven elusive.[10,14]

Current methods for the direct functionalization of BQ are based on the Meerwein arylation.[15] This approach, however, utilizes potentially explosive diazonium salt precursors, proceeds through a radical mechanism, and is limited to arylations. Baran et al. have recently reported a Ag-catalyzed C–H monofunctionalization of BQs using boronic acids,[16] and a strong co-oxidant (K₂S₂O₈), which is also thought to proceed through a radical mechanism.[17] However, strong oxidants preclude the use of attractive cross-coupling partners with readily oxidizable (e.g. benzylic) positions.[10b] Furthermore, no examples of functionalizations with heterocycles or alkenes are known and the radical methods are so far mainly useful only for monofunctionalizations. A mild and practical Pd-catalyzed method, capable of either mono- or difunctionalization, is therefore highly desirable.[18]

Initial attempts at Pd-catalyzed C–H arylation of BQ with the Pd(OTf)₂ system used in our previous work[19] gave either irreproducible results or complex mixtures of mono- and various diarylated products. After extensive optimization, we found that the less active catalyst Pd(OAc)₂, G. M. Rosair and the EPSRC UK National Crystallography Service at the University of Southampton for the collection of crystallographic data.[19] Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

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**Scheme 1.** Pd-catalyzed methods for the functionalization of BQ.

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**References:**

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incompatible with existing Ag-catalyzed radical methods[16b]). Suitable substrates (complement each other. Heterocyclic boronic acids are also others fared better in water; the two solvents seeming to

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Table 1: C–H monofunctionalization of BQ,\(^\text{H}\)

| Entry | R \(\text{Yield}^\text{[a]}\) | Yield 5 [%]\(^\text{[b]}\) | Yield 4 [%]\(^\text{[c]}\) |
|-------|------------------|-----------------|-----------------|
| 1     | \(p\)-HO-C\(_6\)H\(_4\) | 71 (5a)         | < 5 (4a)        |
| 2     | \(m\)-MeO-p-HO-C\(_6\)H\(_4\) | 73 (5b)         | trace           |
| 3     | \(m, p\)-(MeO)\(_2\)C\(_6\)H\(_4\) | 58 (5c)         | n.d.            |
| 4     | \(m\)-toly | 53 (5d)         | 28 (4d)         |
| 5     | Ph             | 29 (5e)         | 44 (4e)         |
| 6\(^\text{[d]}\) | \(p\)-F\(_3\)C-C\(_6\)H\(_4\) | —               | 51 (4f)         |
| 7\(^\text{[e]}\) | \(p\)-EtO\(_2\)C-C\(_6\)H\(_4\) | —               | 25 (4g)         |
| 8     | \(o\)-Me-p-HO-C\(_6\)H\(_4\) | 41\(^\text{[f]}\) (5h/4h = 1:1) | —               |
| 9     | \(o\)-MeO-C\(_6\)H\(_4\) | 25 (5j)         | 28 (4l)         |

[a] Yields of isolated products are given. For yields in italics, acetonitrile was used as solvent; for yields in bold, water was used as solvent. If only one yield is given, the reaction in the other solvent proceeded with poor conversion and the product was not isolated. [b] At 35 °C. [c] Additional 2,6-DCBQ, catalyst, and boronic acid added, treated with FeCl\(_3\) at the end of reaction. [d] Product only moderately stable. [e] Isomers not fully separable. n.d. = not determined.

Under our optimized conditions, the selectivity for 2,6 disubstitution (5) or 2,5 disubstitution (4) appears to be controlled by the electronic nature of the substituent that is introduced (R). For example, strongly electron-donating substituents provide the 2,6 isomers 5a–c, selectively (Table 2, entries 1–3). A weakly electron-donating substituent (meta-tolyl) reduces the selectivity, but 5d is still the major product (Table 2, entry 4), whereas an electron-neutral substituent (phenyl) gives a poor 1:1.5 ratio of 5e/4e (entry 5).\(^\text{[26]}\)

Electron-withdrawing substituents reverse the preference, with 4f and 4g formed selectively (Table 2, entries 6 and 7).

Such products seem relatively unstable compared to their counterparts with electron-donating groups and this may contribute to the lower yields of isolated products in these cases.\(^\text{[27]}\) Finally, \(o\)-tolyl substituents on the aryl ring are detrimental for selectivity (Table 2, compare entry 8 with entry 1), presumably because of steric factors (entries 8 and 9).

With the selectivity and trends for the homo-difunctionalizations in hand, we addressed the more challenging issue of C–H hetero-difunctionalization, in which two different R groups are introduced. Controlled and selective hetero-difunctionalizations are not feasible with traditional methods (see before). Initially, a stepwise procedure utilizing the monofunctionalized BQs (Table 1) was investigated, with the second substituent (R') being introduced using modified conditions from our homo-difunctionalization reactions.

The same selectivity trends seen for 2,5 or 2,6 homodifunctionalizations also apply to hetero-difunctionalizations (Table 3). With two electron-donating substituents, the 2,6 isomers 5j–l are the major products, with higher selectivities observed for more electron-donating substituents (Table 3, entries 1–3). An \(o\)-tolyl substituent causes a drop in selectivity (5m/4m = 5:4, Table 3, entry 4). A combination of electron-donating and electron-poor groups leads, unsurprisingly, to a lower selectivity, independent of the installation order (Table 3, entries 5 and 6). Two different electron-poor sub-
One-pot C–H hetero-functionalization of BQ.

Table 3: C–H hetero-functionalization of BQ.

| Entry | R′ | Yield 5 [%] | Yield 4 [%] |
|-------|----|-------------|-------------|
| 1     | p-MeO-C6H4 | 73 (5j)     | <5 (4j)     |
| 2     | m,p-(MeO)2-C6H4 | 71 (5k)   | 10 (4k)     |
| 3     | p-MeO-C6H4 | 65 (5l)     | 21 (4l)     |
| 4     | o-HO-C6H4 | o-MeO-C6H4 | 50 (5m)     | 41 (4m)     |
| 5     | m,p-(MeO)2-C6H4 | 44 (5n)   | 26 (4n)     |
| 6     | p-ETo2C-C6H4 | p-MeO-(MeO)2-C6H4 | 48 (5n) | 16 (4n) |
| 7     | p-ETo2C-C6H4 | p-F-C6H4 | <5 (5o)     | 47 (4o)     |
| 8     | N-Boc-4-pyrrole-2 | 3- thiophene | trace      | 74 (4p)     |
| 9     | m,p-N-O2-C6H4 | 3- thiophene | trace      | 42 (4q)     |
| 10    | p-ETo2C-C6H4 | 3-thiophene | trace      | 34 (4r)     |
| 11    | m,p-(MeO)2-C6H4 | cyclohexyl | –           | –           |

[a] Yields of isolated products. [b] 2.5 equiv of boronic acid used. [c] Treated with FeCl3 at the end of reaction. [d] Product only moderately stable. [e] Complex mixture of products.

Keywords: benzoquinone · C–H functionalization · palladium · synthetic methods · water

In conclusion, we have developed the first efficient Pd-catalyzed direct C–H monofunctionalization of benzoquinone. Furthermore, an additional C–H functionalization to give difunctionalized products has been achieved, including the controlled installation of two different groups in a one-pot procedure, which is a major advancement in the field. Regioselectivities were found to be dependent on electronics on the aryl ring, and good selectivities were obtained for electron-rich and electron-deficient substrates. We believe that this new Pd-catalyzed method will allow rapid access to difunctionalized BQs that were previously difficult to synthesize.

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[1] S. J. Coles, P. A. Gale, Chem. Sci. 2012, 3, 683–689.
[2] I. Abraham, R. Joshi, P. Pardasani, R. T. Pardasani, J. Braz. Chem. Soc. 2011, 22, 385–421.
[3] N. Decharin, S. S. Stahl, J. Am. Chem. Soc. 2011, 133, 5732–5735.
[4] a) P. Petrangolini, A. Alessandrini, P. Facci, J. Phys. Chem. C 2013, 117, 17451–17461; b) J. E. Klare, G. S. Tulevski, K. Sugo, A. de Piicciotto, K. A. White, C. Nuckolls, J. Am. Chem. Soc. 2003, 125, 6030–6031.
[5] P. R. Dandawate, A. C. Vyas, S. B. Padhye, M. W. Singh, J. B. Baruah, Mini-Rev. Med. Chem. 2010, 10, 436–454.
[6] R. H. Thomson, Naturally Occurring Quinones IV, Blackie Academic & Professional, London, 1997.
[7] T. Bechtold, Handbook of Natural Colorants, Wiley, Hoboken, 2009, pp. 151–182.
[8] For example: a) K. Itami, A. Palmgren, A. Thorarensen, J.-E. Backvall, J. Org. Chem. 1998, 63, 6466–6471; b) T. W. Lyons, K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2011, 133, 4455–4464; c) A. Palmgren, A. Thorarensen, J.-E. Backvall, J. Org. Chem. 1998, 63, 3764–3768; d) T. Y. Ura, Y. Sato, M. Shiotzuki, T. Suzuki, K. Wada, T. Kondo, T.-A. Mitsudo, Organometallics 2003, 22, 77–82.
[9] In contrast, Pd-catalyzed arylation of 1,4-naphthoquinines and 1,4-anthraquinones are more straightforward. See: a) S. Zhang, F. Song, D. Zhao, J. You, Chem. Commun. 2013, 49, 4558–4560; b) M. T. Molina, C. Navarro, A. Moreno, A. G. Csáky, Org. Lett. 2009, 11, 4938–4941.
[10] For Pd oxidative Heck reactions, see: O. M. Demchuk, K. M. Pietrusiewicz, Synlett 2009, 1149–1153.
[11] For example: a) M. L. N. Rao, S. Giri, RSC Adv. 2012, 2, 12739–12750; b) A. M. Echavarren, O. de Frutos, N. Tamayo, P. Noheda, P. Calle, J. Org. Chem. 1997, 62, 4524–4527; c) X. Gan, W. Jiang, W. Wang, L. Hu, Org. Lett. 2009, 11, 589–592.
[12] For a stoichiometric Pd0 oxidative coupling, see: T. Itahara, J. Org. Chem. 1983, 50, 5546–5550.
For example, see: a) K. W. Stagliano, A. Emadi, Z. Lu, H. C. Malinakova, B. Twenter, M. Yu, L. E. Holland, A. M. Rom, J. S. Harwood, R. Amin, A. A. Johnson, Y. Pommier, Bioorg. Med. Chem. 2006, 14, 5651–5665; b) G. Viault, D. Grée, S. Das, J. S. Yadav, R. Grée, Eur. J. Org. Chem. 2011, 1233–1241; c) D. Yu, D. L. Mattern, Synth. Commun. 1999, 29, 821–825.

Decarboxylative arylation produced low to moderate yields and was restricted to electron-rich aryl compounds with ortho substituents: Y. Zhao, Y. Zhang, J. Wang, H. Li, L. Wu, Z. Liu, Synlett 2010, 2352–2356.

For example, see: a) A. Honraedt, F. Le Callonnec, E. Le Grognec, V. Fernandez, F.-X. Felpin, J. Org. Chem. 2013, 78, 4604–4609.

a) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. Del Bel, P. S. Baran, J. Am. Chem. Soc. 2011, 133, 3292–3295; b) J. W. Lockner, D. D. Dixon, R. Risgaard, P. S. Baran, Org. Lett. 2011, 13, 5628–5631.

For similar radical methods including the use of Fe, see: a) A. Ilangovan, S. Saravanakumar, S. Malayappasamy, Org. Lett. 2013, 15, 4968–4971; b) P. P. Singh, S. K. Aithagani, M. Yadav, V. P. Singh, R. A. Vishwakarma, J. Org. Chem. 2013, 78, 2639–2648; c) J. Wang, S. Wang, G. Wang, J. Zhang, X.-Q. Yu, Chem. Commun. 2012, 48, 11769–11771.

Recent attempts to utilize Pd II catalysis have either been unsuccessful[24] or gave mixtures of bis-, but no mono-arylated products,[24] limiting its applications in synthesis.

Recent attempts to utilize Pd II catalysis have either been unsuccessful[10] or gave mixtures of bis-, but no mono-arylated products,[24] limiting its applications in synthesis.

[18] a) J. A. Jordan-Hore, J. N. Sanderson, A.-L. Lee, Org. Lett. 2012, 14, 2508–2511; b) S. E. Walker, J. Boehnke, P. E. Glen, S. Levey, L. Patrick, J. A. Jordan-Hore, A.-L. Lee, Org. Lett. 2013, 15, 1886–1889.

[19] a) J. A. Jordan-Hore, J. N. Sanderson, A.-L. Lee, Org. Lett. 2012, 14, 2508–2511; b) S. E. Walker, J. Boehnke, P. E. Glen, S. Levey, L. Patrick, J. A. Jordan-Hore, A.-L. Lee, Org. Lett. 2013, 15, 1886–1889.