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## Synthesis of phthalazinones *via* palladium(II)-catalysed intramolecular oxidative C–H/C–H cross-coupling of *N*'-methylenebenzohydrazides†

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A palladium(II)-catalysed intramolecular oxidative C–H/C–H crosscoupling of N'-methylenebenzohydrazides to phthalazin-1(2H)ones has been developed. This cyclization is believed to mechanistically proceed *via* electrophilic *ortho*-palladation and subsequent C-arylation of the carbon–nitrogen double bond.

Pyridazin-3(2*H*)-ones and phthalazin-1(2*H*)-ones<sup>1</sup> are important structural motifs that are encountered in many biologically active compounds and thus have found important applications in pharmaceuticals (*e.g.* azelastine, emorfazone) and pesticides (*e.g.* pyridaben, norflurazon). Moreover, phthalazinone-containing polymers exhibit a number of advantageous properties, including high thermo-oxidative stability, mechanical strength, and glass transition temperature.<sup>2</sup>

Significant progress has recently been made in the area of transition-metal-catalysed C-H bond functionalisation reactions,<sup>3,4</sup> which provide a straightforward and atom-economical method for transforming otherwise unreactive C-H bonds into carbon-carbon or carbon-heteroatom bonds. In this context, oxidative C-H/C-H cross-coupling would be an ideal approach for forming C-C bonds free of prefunctionalised coupling partners.<sup>4</sup> Some carbo- and heterocycles have previously been synthesised by Pd(II)-catalysed cyclisation reactions involving intramolecular oxidative C-H/C-H cross-coupling;<sup>5</sup> however, this strategy has never been applied to the construction of a pyridazinone or phthalazinone skeleton. In this paper, we describe a method for the synthesis of phthalazinones by Pd(II)catalysed intramolecular oxidative C-H/C-H cross-coupling of N'-methylenebenzohydrazides, in which the aromatic and methylene C-H bonds are cleaved by electrophilic palladation and β-hydride elimination, respectively.<sup>6</sup>

The *N*-methyl-*N'*-methylene aryl hydrazides **1** were prepared from the corresponding aroyl chlorides in two steps

(Scheme 1): (i) condensation of aroyl chlorides with methylhydrazine (CHCl<sub>3</sub>, rt) and (ii) condensation of the resulting *N*-methyl aryl hydrazides with paraformaldehyde (toluene, reflux). The *N*'-methylene hydrazides thus obtained were stable to air and moisture, which made their utilisation easier.

When treated with 10 mol% Pd(OAc)<sub>2</sub> as a catalyst and 1 equiv. of Ag<sub>2</sub>O as an oxidant at 120 °C in acetic acid under nitrogen, *N'*-methylene-*p*-tolylhydrazide **1a** underwent intra-molecular oxidative C-H/C-H cross-coupling to give phthalazinone **2a** in 55% yield after 7 h (Table 1, entry 1).<sup>7</sup> The use of PdCl<sub>2</sub> led to a lower yield (entry 2), and only traces of the desired product were formed in the absence of Ag<sub>2</sub>O (entry 3). In addition, solvents other than acetic acid were completely ineffective in this reaction.<sup>8</sup> Screening of oxidants revealed that the organic oxidant, benzoquinone (BQ),<sup>9</sup> was the most suitable for the reaction, giving **2a** in good yield (entries 4–6).<sup>10</sup>

The mechanism for this Pd( $\pi$ )-catalysed intramolecular oxidative C–H/C–H cross-coupling reaction can be accounted for by considering a C=N variant of the oxidative Heck-type cyclisation (Scheme 2).<sup>11</sup> Initially, electrophilic *ortho*-palladation of the aryl group of **1** with Pd(OAc)<sub>2</sub> leads to cyclometalated ArPd-( $\pi$ )OAc intermediate **A** (or **A**'),<sup>12</sup> and intramolecular carbopalladation onto the C=N bond in a 6-*endo* fashion generates Pd( $\pi$ ) amide **B**. Subsequent  $\beta$ -hydride elimination releases product 2, and reoxidation of the Pd(0) species with BQ regenerates the catalytically active Pd( $\pi$ ) concomitantly with the formation of hydroquinone (HQ).

With the identified optimal reaction conditions, the scope of the reaction was assessed using a number of different substrates (Table 2). While phenyl and *p*-anisyl derivatives **1b** and **1c** afforded phthalazinones **2b** and **2c** in 73% and 60% yields,



Scheme 1

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 Table 1
 Optimisation of reaction conditions<sup>a</sup>



<sup>*a*</sup> **1a** (0.200 mmol), Pd catalyst (0.020 mmol, 10 mol%), and oxidant were reacted at 120 °C in acetic acid (1.0 mL). <sup>*b*</sup> Isolated yield.



respectively (entries 1 and 2), hydrazide 1d, carrying a strong electron-withdrawing nitro group on the phenyl ring, failed to undergo the cyclisation (entry 3). This result indicated that the reaction outcome was significantly affected by the electronic nature of the aryl substituents. p-Bromobenzohydrazide 1e gave product 2e without deterioration of the C-Br functionality, albeit with diminished yield (entry 4).<sup>13</sup> Steric effects were also seen to play a crucial role in the reactivity. The reaction of m-tolyl hydrazide 1f occurred site-specifically with C-C bond formation at the less hindered C(6) position on the aryl group, affording 7-methylphthalazinone 2f in 85% yield (entry 5). Similarly, the reaction of 3,4-disubstituted arylhydrazides 1g and 1h resulted in the exclusive formation of 6,7-disubstituted products 2g and 2h, respectively (entries 6 and 7). 3,5-Xylyl and o-tolyl hydrazides 1i and 1j were found to be less reactive substrates for the reaction because of steric reasons, giving the corresponding phthalazinones 2i and 2j in low yields (entries 8 and 9). 2-Naphthyl derivative 1k gave benzo[g]phthalazinone 2k in 72% yield via selective cleavage of the C(3)-H bond

**Table 2** Synthesis of phthalazinones **2** by Pd(n)-catalysed intramolecular oxidative C–H/C–H cross-coupling of **1**<sup>a</sup>





 $^a$  1a (0.200 mmol), Pd(OAc)<sub>2</sub> (0.020 mmol, 10 mol%), and BQ (1.2–2 equiv.) were reacted at 120 °C in acetic acid (1.0 mL).  $^b$  Isolated yield.





Scheme 3 Synthesis of 4-substituted phthalazinones via Heck-type cyclisation.

(entry 10), whereas the 1-naphthyl counterpart gave a complex mixture of products. The reaction with hydrazine **1l**, which lacked a carbonyl group, failed to afford the corresponding sixmembered product, showing that the reaction is only applicable to hydrazide substrates (entry 11).

The effect of varying the substituents on the nitrogen atoms was also examined. Unfortunately, neither *N*-phenyl- or *N*-*t*-butyl hydrazides, nor *N'*-benzylidene- or *N'*-ethylidene hydrazides participated in the cyclisation under the present reaction conditions (Fig. 1).

To overcome issues arising from the narrow substrate scope, the Heck-type cyclisation of 2-iodobenzohydrazides **3** was attempted for the synthesis of 4-substituted phthalazinones (Scheme 3). In the presence of 20 mol% Pd(OAc)<sub>2</sub> and 1 equiv. of AcOK at 130 °C in DMF, 2-iodo-*N*-methyl-*N'*-methylenebenzohydrazide **3a** was converted into **2a** (R = H) in 61% yield. The Heck-type cyclisation was applicable to *N'*-benzylidene- and *N'*-ethylidene hydrazides (**3m** and **3n**, respectively), affording the corresponding 4-phenyl- and 4-methylphthalazinones (**2m** and **2n**, respectively), which were inaccessible *via* the oxidative C–H/C–H cross-coupling.

In summary, phthalazin-1(2*H*)-ones were catalytically synthesised by intramolecular oxidative C–H/C–H cross-coupling using readily accessible *N'*-methylenebenzhydrazides **1** and a catalyst system (Pd(OAc)<sub>2</sub>, BQ and acetic acid). The mechanism of the Pd( $\mu$ )-catalysed cyclisation of **1** was accounted for by the relatively uncommon Heck-type cyclisation reactions of carbon–nitrogen double bonds.

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- 9 Sublimed BQ was used.

- 10 Results with several oxidants: Ag<sub>2</sub>CO<sub>3</sub> (25%), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (no reaction), Oxone® (complex mixture), chloranil (40%).
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