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The first intramolecular Heck–Matsuda reaction and its application in the syntheses of benzofurans and indoles

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ABSTRACT

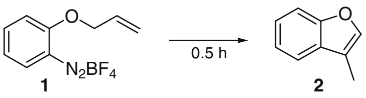
In this Letter, we report, for the first time, the development of an efficient method for the intramolecular Heck reaction of arenediazonium salts in the synthesis of benzofuran and indole derivatives. In addition, this methodology allowed the synthesis of a series of dihydrobenzofuran acetic acid derivatives via a domino Heck–Matsuda coupling–carbonylation reaction.

The Pd-catalysed Heck cyclisation is a versatile strategy for the formation of C–C linkages and the syntheses of carbocycles, heterocycles and complex molecules.[1] As such, the Heck cyclisation has been used as a tool in the synthesis of several complex natural products and biologically active compounds. Hitherto, intramolecular Heck cyclisations have relied on the use of either aryl triflates or aryl halides[2,3] as the agent of the olefin acceptor. Amongst these reports, there are several examples demonstrating their application towards the synthesis of important benzofuran and indole structures.[1–5] To the best of our knowledge, in spite of its methodological potential, the intramolecular Heck cyclisation employing arenediazonium salts (Heck–Matsuda reaction) goes unreported. Presently the intramolecular cyclisation using arenediazonium salts with olefins has been restricted to the Meerwein arylation, employing cooper salts, or with UV-light irradiation in the presence of Bu_3SnH.[6a] Such intramolecular cyclisations of these arenediazonium salts have been reported to proceed via radical-mediated processes.[6] Related radical-mediated cyclisations of arenediazonium salts with olefins but with addition of thiols, nitriles or halides, have also been reported in the literature.[6b,c] The Pd-catalysed coupling of arenediazonium salts to olefins presents some advantages over traditional aryl halide electrophiles.[7] For one thing, coupling reactions employing arenediazonium salts do not require the use of phosphines as ligands and the protocol tolerates aerobic conditions, which makes the reaction more practical and easier to handle. Additionally, the reaction can be performed with or without a base and is often faster than traditional Heck protocols.[8] For these reasons, arenediazonium salts are good alternatives for meeting the demands for more efficient and greener processes than aryl halides or triflates.[9] In this work, we describe, for the first time, a new methodology for the construction of benzofurans, indoles and dihydrobenzofurans via a palladium-catalysed intramolecular Heck–Matsuda coupling reaction.

Initially, the intramolecular cyclisation was evaluated using compound **1** which was easily prepared in four steps from 2-aminophenol. $Pd(OAc)_2$ proved to be a superior catalyst than Pd_2dba_3 and further optimisation studies revealed that running the reaction in methanol at 50 °C provided the best yields (Table 1, entries 1, 4, 5, 6 and 7). Increasing the catalytic loading to 10 mol % of $Pd(OAc)_2$ did not lead to any considerable improvement (entry 2), however lowering the catalytic loading to 2 mol % $Pd(OAc)_2$ resulted in a deterioration in yield (entry 3).

Next, the reaction scope of the intramolecular Heck–Matsuda protocol was extended to substrates bearing electron-donating and/or electron-withdrawing groups at the aromatic position (Table 2). In all cases examined, electron-rich, -poor and -neutral substituents afforded Heck adducts in lower yields, compared to those obtained for an unsubstituted benzofuran **1**. This observation is in agreement with earlier reports that have described the intramolecular Heck coupling of similar substrates (but using aryl iodides).[5] Substrates bearing either *meta*-methoxy or *para*-methyl groups furnished the expected benzofuran products in similar yields (entries 1 and 2). Unexpectedly, the chloro-substituted

Table 1
Cyclisation of the aryl *O*-allylether **1**



Entry	Catalyst (mol %)	Solvent	Temp (°C)	% Yield
1	$Pd(OAc)_2$ (5)	MeOH	50	65
2	$Pd(OAc)_2$ (10)	MeOH	50	67
3	$Pd(OAc)_2$ (2)	MeOH	50	30
4	$Pd(OAc)_2$ (5)	MeOH	rt	30
5	$Pd(OAc)_2$ (5)	CH_3CN	rt	—
6	$Pd_2.dba_3$ (5)	MeOH	rt	54
7	$Pd_2.dba_3$ (5)	CH_3CN	rt	—

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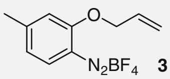
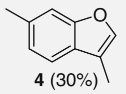
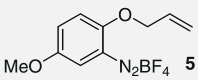
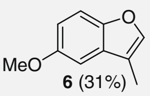
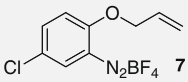
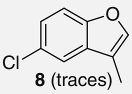
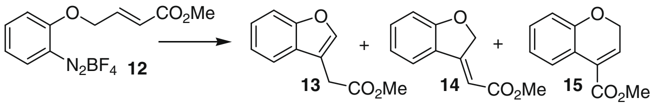
Table 2
Cyclisation of substituted *ortho*-diazo aryl allyl ethers[a]

Entry	Substrate	Product
1	 **3**	 **4** (30%)
2	 **5**	 **6** (31%)
3	 **7**	 **8** (traces)

[a] Reaction conditions: 5 mol % $Pd(OAc)_2$, arenediazonium salt (0.25–0.5 mmol), MeOH (2.3–7.5 mL), 25 °C, 0.5 h.

Table 4
Heck–Matsuda cyclisation of α,β-unsaturated ester **12**



Entry	$Pd(OAc)_2$ (mol %)	Solvent	Temp (°C)	Product (% yield)
1	5	MeOH	50	**13** (12), **4** and **15** (17)
2	5	MeOH	25	**14** and **15** (36)
3	10	MeOH	25	**15** (58)
4[a]	10	MeOH/PhCN	25	**15** (38)
5[a]	10	MeOH/ MeCN	25	**15** (13)

[a] Solvent ratio 1:1.

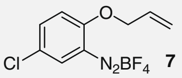
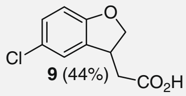
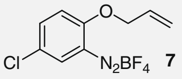
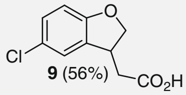
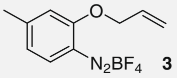
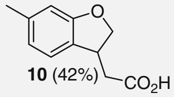
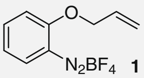
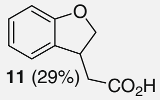
arenediazonium salt **7** provided the corresponding benzofuran **8** in only traces amount (entry 3).

The intermolecular Heck–Matsuda reaction involving electron-poor arenediazonium salts has been reported to proceed smoothly under an atmosphere of carbon monoxide (which generates Pd(0) from Pd(II)).[10] In the hope of improving product yields in the cyclisation of substrate **7**, the reaction was performed in CH_3CN at room temperature and 1 atm CO (Table 3).[11] Interestingly, these conditions afforded the corresponding carboxylic acid **9** instead of the expected benzofuran unit **8** (entry 1). Using $Mo(CO)_6$ as an alternative source of CO in solution, the reaction yield was slightly improved to 56% (entry 2). The methyl-substituted substrate (**3**) similarly furnished Heck adduct **10** in a slightly higher yield than that obtained for product **11**(entries 3 and 4).

During the course of our study using aryl allyl ethers as substrates, we noticed that the intramolecular Heck–Matsuda reaction obeys Baldwin's rules by favoring a 5-*exo*-trig product.[12]

The intramolecular coupling of arenediazonium salts bearing an α,β-unsaturated ester unit (**12**) was found to proceed in a non-selective manner and gave rise to a mixture of products (Table 4, entry 1). The observed formation of three different Heck adducts motivated us to investigate other conditions that would allow greater selectivity. We found that temperature and catalyst loading again showed significant influences. Running the reaction at a lower temperature suppressed the formation of benzofuran **13** but still afforded a mixture of **14** (kinetic product) and 2*H*-chromene **15** (entry 2). Employing a higher catalytic loading (10 mol % $Pd(OAc)_2$) at room temperature, the reaction behaved more selectively and furnished exclusively 2*H*-chromene **15** in 58% yield as the sole product (entry 3). A binary mixture of solvents was also investigated and although selectivity for product **15** was maintained, the yield was disappointingly lower (entries 4 and 5). The formation of 2*H*-chromene **15** from substrate **12** proceeded via a 6-*endo*-trig mode and is in agreement with the literature for substrates possessing an activated Michael type olefinic fragment.[13]

Table 3
Pd-catalysed cyclisation of substituted aryl allyl ethers in CH_3CN at room temperature in a CO atmosphere[a]

Entry	Substrate	Product
1[b]	 **7**	 **9** (44%)
2	 **7**	 **9** (56%)
3	 **3**	 **10** (42%)
4	 **1**	 **11** (29%)

[a] Reaction conditions: 10 mol % $Pd(OAc)_2$, $Mo(CO)_6$ (1.5 equiv), NaOAc (3 equiv), MeCN (1.5–3.0 mL), 25 °C, 2.5 h.
[b] Reaction performed in the absence of $Mo(CO)_6$.

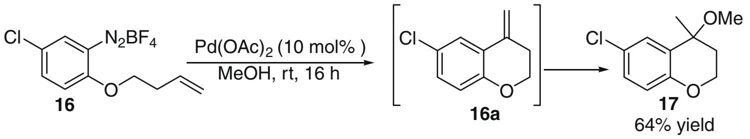
Gratifyingly, we were able to apply this methodology to the intramolecular coupling of an arenediazonium salt to an unactivated alkene (Scheme 1).

Using $Pd(OAc)_2$ as a catalyst, the cyclisation of substrate **16** was achieved at room temperature in methanol yielding chroman **17** in good yield (64%). Surprisingly, the addition of methanol at the benzylic carbon position of **16a** occurred under catalytic conditions. The acidity of the reaction medium increases as the Heck reaction proceeds and therefore **16a** presumably undergoes a hydroalkoxylation reaction with methanol in a sequential manner.

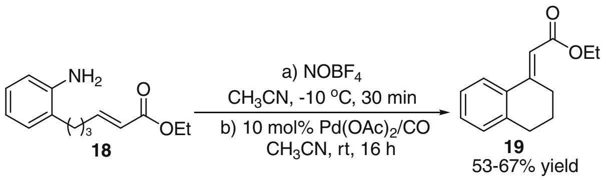
The α,β-unsaturated ester precursor **18** was prepared using a concise three-step procedure starting from commercially available reagents. With the aniline in hand, the preparation of the desired diazonium salt was attempted using our standard methodology.[14] Unfortunately, the diazotisation reaction was not successful and resulted in decomposition of the aniline **18**. Alternatively, $NOBF_4$ was used to generate the required arenediazonium salt in solution under neutral conditions then added directly to the reaction mixture. The cyclisation was carried out in the presence of 10 mol % $Pd(OAc)_2$ under an atmosphere of CO and afforded the six-membered ring **19** in moderate yield (53–67% for three experiments) with exclusive trans selectivity (Scheme 2).[15]

Reactions of aryl allyl methylcarbamates could be performed in either MeOH at 50 °C or MeCN at room temperature (Table 5).

Using substrate **20** as a model compound and employing 5 mol % of catalyst, indole **21** was isolated in only 37% yield. A higher catalytic loading of 10 mol % $Pd(OAc)_2$ was necessary on this occasion and the yield was gratifyingly improved to 85% (entry 1). The same conditions were employed for the cyclisation of more highly substituted arenediazonium salts. In general, the corresponding cyclisation products were obtained in moderate to low yields (entries 2–5) and the catalytic performance was particularly sluggish for the methyl-substituted arenediazonium salts. The product yield for Heck adduct **27** was slightly improved when using acetonitrile as a solvent and performing the reaction under an atmosphere of CO (entry 4). For the electron-rich arenediazoni-

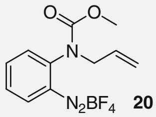
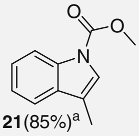
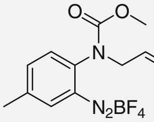
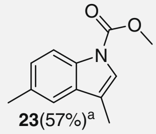
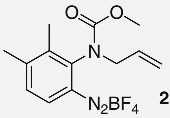
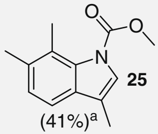
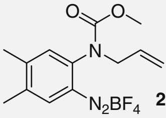
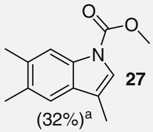
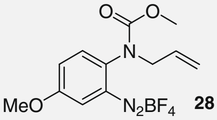
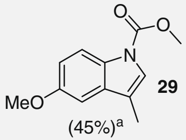


Scheme 1. Pd-catalysed domino Heck–Matsuda-hydroalkoxylation reaction.



Scheme 2. Intramolecular Heck–Matsuda of a α,β-unsaturated ester.

Table 5
Cyclisation of aryl allyl methylcarbamates[a]

Entry	Substrate	Product
1	 **20**	 **21**(85%)[a]
2	 **22**	 **23**(57%)[a]
3	 **24**	 **25** (41%)[a] (19%)[b]
4	 **26**	 **27** (32%)[a] (41%)[b]
5	 **28**	 **29** (45%)[a] (77%)[b]

[a] Reaction conditions: 10 mol % $Pd(OAc)_2$, NaOAc (3 equiv), MeOH, 50 °C, 0.5 h.

[b] 5 mol % $Pd(OAc)_2$, $Mo(CO)_6$ (1.5 equiv), NaOAc (3 equiv), MeCN, 25 °C, 2.5 h.

um salt **28**, changing the reactions' conditions in a similar way had a more drastic effect in significantly improving yield (entry 5).

A plausible mechanism is proposed and depicted in Figure 1. Starting from Pd(0) **I**, an arylazopalladium complex **III** would initially form via oxidative addition but rapidly extrude nitrogen and generate cationic complex **IV**. Next, olefin insertion takes place and affords alkyl metal complex **V** with subsequent palladium beta-hydride elimination to give Heck adduct **VI** and hydridopalladium(II) complex **VIII**. Finally, heterocycle **VI** isomerises to the lower energy isomer **VII**. The tetrafluoroborate counteranion is replaced by an acetate anion, and Pd(0) complex **I** is reconstituted.

In summary, using either $Pd(OAc)_2$ in an atmosphere of CO or Pd_2dba_3 as a catalyst, the intramolecular cyclisation of arenediazonium salts with olefins can be achieved. The intramolecular Heck–Matsuda reaction provided benzofuran derivatives which, depending on the reaction conditions employed, could be further transformed into carboxylic acid derivatives via a carbonylation process. The scope of this methodology was also successfully expanded to include the synthesis of indole, tetrahydronaphthalene, chromene and chroman derivatives. Further studies are underway, including reaction optimisation and studies towards discerning the reaction mechanism and these will be reported in due course.

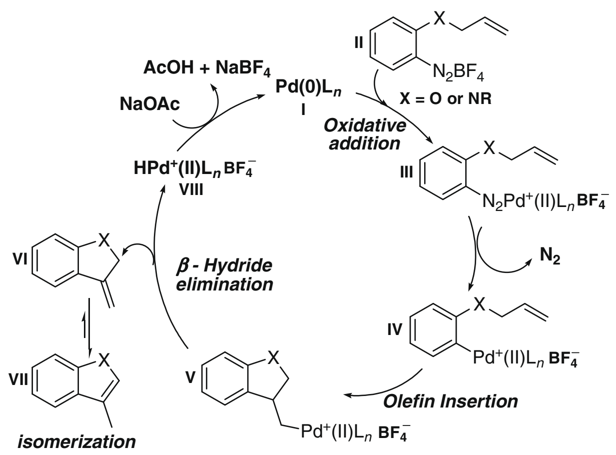


Figure 1. Postulated catalytic cycle for the intramolecular Heck–Matsuda reaction.

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Supplementary data

Supplementary data (experimental procedures and selected NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.011.

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14. A standard diazotisation methodology can be found in the Supplementary data: refer to arenediazonium salts **1**, **5** and **7**.
15. Confirmed by nuclear Overhauser enhancement (nOe) of the aromatic resonance when the olefinic proton was irradiated, that being the only resonance so affected.