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Synthesis of indanones by sequential Heck-reduction–cyclization–alkylation (HRCA) reactions

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ABSTRACT

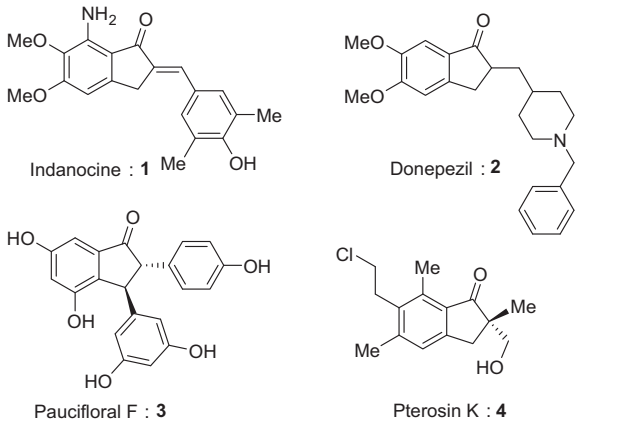
A simple and efficient synthesis of indanones, bearing a quaternary carbon centre, has been developed. The method features, in a one-pot process, the use of a multi-task palladium catalyst for the sequential Heck-reduction reactions, followed by a base-mediated cyclization–alkylation sequence. This methodology, called Heck-reduction–cyclization–alkylation (HRCA), is carried out under mild and simple experimental conditions with the use of inexpensive reagents. The mild conditions have been made possible by the use of diazonium salts that allow Heck couplings at moderate temperature (40 °C) under ligand-free conditions.

The indanone skeleton is an important structure in medicinal chemistry that has been incorporated in many biologically active compounds having anti-cancer[1] (Indanocine **1**) or anti-neurodegenerative activities.

For instance, the marketed drug Donepezil **2** is a potent acetylcholine esterase inhibitor prescribed for the treatment of Alzheimer's disease (Scheme 1).[2] Indanone moieties are also frequently encountered in biologically active natural products such as Paucifloral F **3**[3] and Pterosin K **4**.[4]

We have recently reported the use of a palladium multi-task catalyst for the synthesis of various heterocycles including oxindole,[5] 2-quinolone[6] and 1,2-dihydroisoquinolin-3-ones[7] through Heck-reduction–cyclization (HRC) sequences (Scheme 2, Eqs. 1–4). Our concept allowed four transformations in the same pot with one C–C bond formation, two reductions and one cyclization. The use of aryl diazonium salts as 'super-electrophiles' was a key to the success of our strategy. Indeed, due to their high reactivity we were able to work with simple and mild experimental conditions.[5–7] Moreover, aryl diazonium salts were easily accessed by diazotation of inexpensive anilines with sodium nitrite or *t*-butylnitrite and can be stored at −20 °C for several years. In this Letter we wish to extend this concept to non-heterocyclic substrates with the synthesis of indanones bearing a quaternary carbon centre (Scheme 2, Eq. 5).

The general approach for the synthesis of indanones was related to our recently reported HRC sequences and was based on Heck cross-coupling of a 2-carboxymethyl aryl diazonium tetrafluoroborate **A** with the methyl vinyl ketone **5** (Scheme 3).[8,9] A subsequent Pd-catalysed hydrogenation of the olefin **B** would give the corresponding ketoester **C**, which should cyclize under base-mediated conditions. The generated diketo-anion **D** could be then trapped



Scheme 1. Structure of Indanicine **1**, Donepezil **2**, Paucifloral F **3** and Pterosin K **4**.

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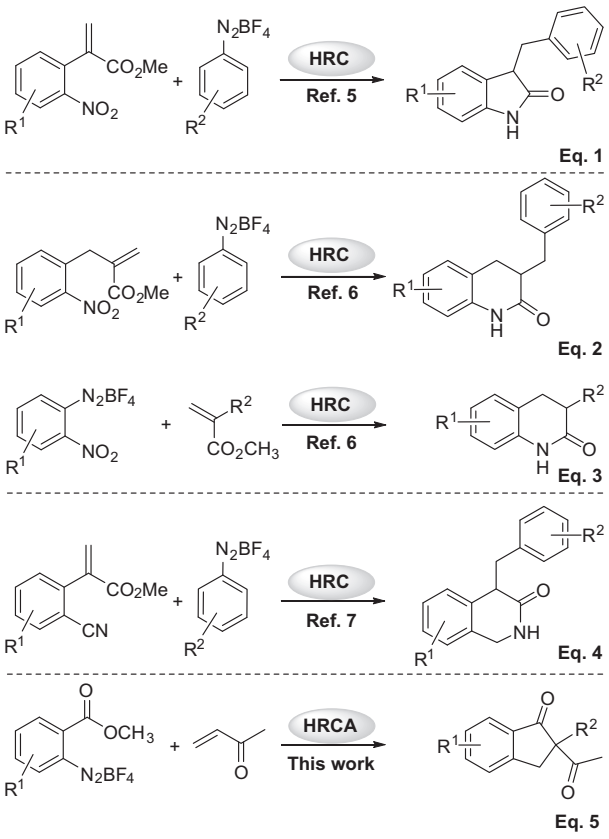
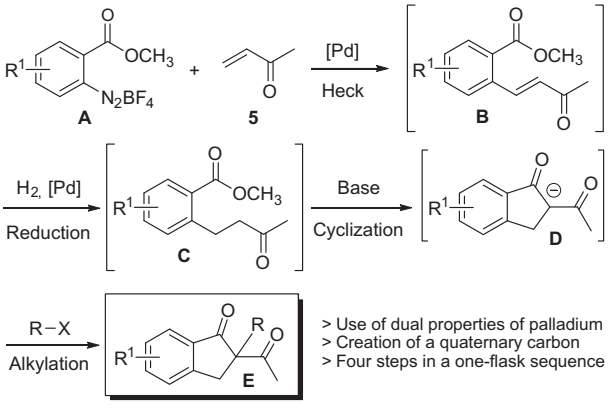


Scheme 2. Variations in the HRC strategy.

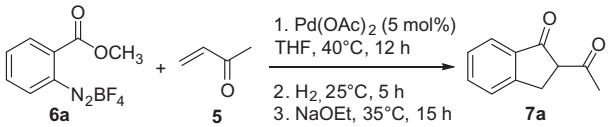


Scheme 3. General strategy for accessing indanones **E**.

with an electrophile to give the corresponding indanones **E**. This sequence allows four different steps in the same flask with a Heck reaction, a hydrogenation, a base-mediated cyclization and an alkylation (HRCA). Our HRCA method aims to exploit, in a one flask sequence, the dual properties of a palladium catalyst (C–C bond formation and hydrogenation) which have been mostly overlooked for the preparation of elaborated compounds.[10]

We started our studies with the optimization of the Heck-reduction–cyclization sequence on a model reaction involving the coupling of 2-carboxymethyl diazonium tetrafluoroborate **6a**[11] with methyl vinyl ketone **5** (Table 1). We found that the corresponding indanone **7a** could be obtained when THF was selected as the reaction solvent and NaOEt as a base in a promising yield over the three steps (56%). In MeOH, while the Heck-reduction

Table 1
Optimization studies for the HRC sequence



Entry[a]	Variation from the 'standard' conditions	Yield[b] (%)
1	None	56
2	MeOH instead of THF	0
3	12 h instead of 5 h for step 2	42
4	NaH instead of NaOEt	25
5	NaOMe instead of NaOEt	0
6	*t*-BuOK instead of NaOEt	45

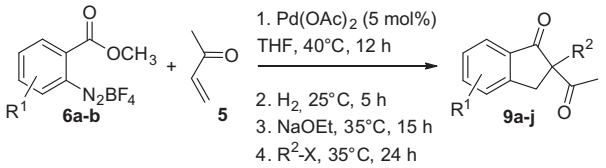
[a] Reaction conditions: methyl vinyl ketone (2 mmol), diazonium salt (1 mmol), $Pd(OAc)_2$ (5 mol %) in THF at 40 °C for 12 h, then H_2 for 5 h at 25 °C, then NaOEt (10 mmol) for 15 h at 35 °C.
[b] Yields of isolated products.

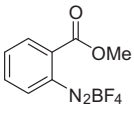
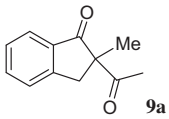
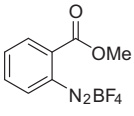
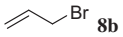
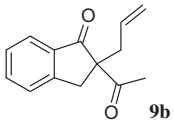
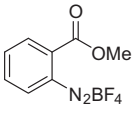
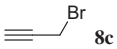
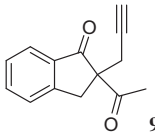
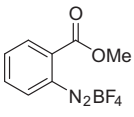
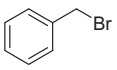
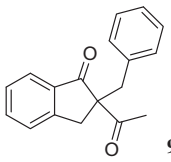
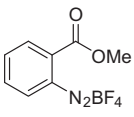
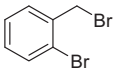
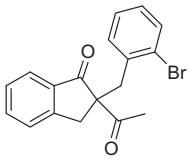
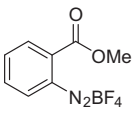
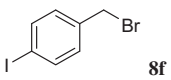
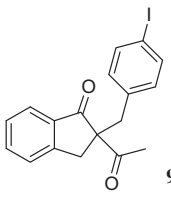
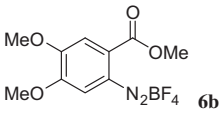
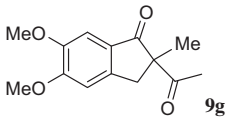
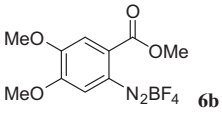
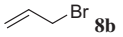
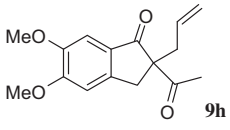
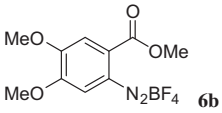
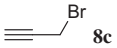
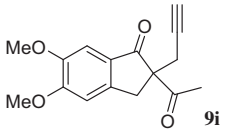
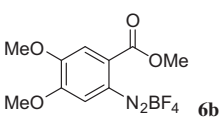
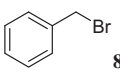
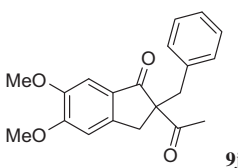
sequence worked well, the cyclization did not proceed whatever the base used (entry 2). The hydrogenation time also proved to be crucial for the success of the sequence (entry 3). Indeed, under a prolonged reaction time, a significant amount of methyl-2-butylbenzoate, resulting from the over reduction of the ketone function, was observed, likely due to the presence of HBF_4 in the solution. After extensive experimentations we found that the reduction was best achieved in 5 h, limiting the formation of methyl-2-butylbenzoate (<10%) and achieving full conversion of the coupling product. Surprisingly, the cyclization step was strongly dependant on the structure and the quality of the base (entries 4–6). With old batches of bases, we observed significant diminished yields, likely due to the presence of hydroxide ions. For some reason we were unable to achieve the cyclization with NaOMe as a base. While this result remains unclear at this time, we believe that the high hygroscopy of NaOMe could prevent sodium hydroxide-free conditions.

Having optimized the reaction conditions for the first three steps, we explored the opportunity of telescoping the diketo-anion **D** with an electrophile to get highly functionalized indanones bearing a quaternary carbon centre. Towards this end, we screened a variety of alkyl, allyl, propargyl and benzyl halides as depicted in the Table 2. We obtained indanones with very practical yields, typically in the range of 40–50%.[12] While these yields could be considered as rather modest, as it should be kept in mind that four different steps are carried out in the same flask. Thereby, a better indicator of the efficiency of the methodology can be found with the average yield per step over the whole process. As reported in Table 2 (see yields in brackets), calculated yields per step are in the range of 75–85%. For such simple experimental conditions, this efficiency is quite relevant. The introduction of allyl (entries 2 and 8) or propargyl (entries 3 and 9) functions as well as halogenated aryls (entries 5 and 6) opened the way for further transformations by standard synthetic chemistry of metal-mediated cross-couplings.

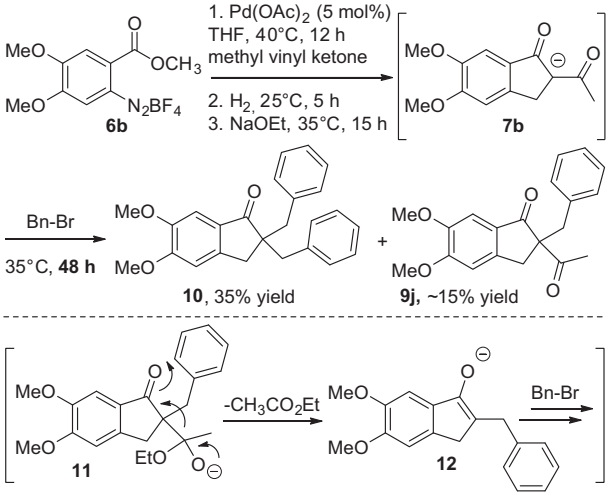
The reaction time of the alkylation step has been carefully optimized through in situ ^1H NMR analyses on a model reaction (Scheme 4). Indeed, the alkylation step proved to be a rather slow process, requiring usually 20–24 h of stirring for a complete conversion. However, under prolonged reaction time (48 h), we observed the formation of a substantial amount of the unexpected product **10** arising from a double alkylation at carbon 2 (Scheme 4). This by-product was likely formed through alkylation of enolate **12** arising from a retro-type claisen fragmentation of **11**.

Table 2
Scope of the HRCA process



Entry[a]	Diazonium	R^2–X	Indanone	Yield[b] (%)
1	 **6a**	 **8a**	 **9a**	52 (85)
2	 **6a**	 **8b**	 **9b**	43 (81)
3	 **6a**	 **8c**	 **9c**	47 (83)
4	 **6a**	 **8d**	 **9d**	56 (86)
5	 **6a**	 **8e**	 **9e**	31 (75)
6	 **6a**	 **8f**	 **9f**	50 (84)
7	 **6b**	 **8a**	 **9g**	40 (80)
8	 **6b**	 **8b**	 **9h**	33 (76)
9	 **6b**	 **8c**	 **9i**	31 (75)
10	 **6b**	 **8d**	 **9j**	47 (83)

[a] Reagents and conditions: methyl vinyl ketone (2 mmol), diazonium salt (1 mmol), $Pd(OAc)_2$ (5 mol %) in THF at 40 °C for 12 h, then H_2 for 5 h at 25 °C, then NaOEt (10 mmol) for 15 h at 35 °C, then R^2–X (3 mmol) at 35 °C for 24 h.
[b] Yields of isolated product. Yields in bracket are the average yields per step. All compounds gave satisfactory spectroscopic data.



Scheme 4. Formation of a dialkylated by-product.

In summary, we have disclosed a novel approach for the synthesis of indanones bearing a quaternary carbon centre by the mean of a HRCA sequence. We exploited the high reactivity of diazonium salts under palladium catalysis for developing simple experimental conditions compatible with the four different steps carried out in the same flask. We anticipate that such an approach could be useful for synthetic and medicinal chemists involved in the preparation of indanone-based targets. Alternatively, we believe that this concept could also be extended to other elaborated structures of interest. We are currently working on an asymmetric version of the HRCA strategy. These new exciting developments will be reported in due course.

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11. Diazonium salts **6a** and **6b** were prepared following a published procedure: (a) Hanson, P.; Rowell, S. C.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1126–1134; (b) Hanson, P.; Jones, J. R.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1135–1150.
12. *For a representative procedure*: To a solution of methyl vinyl ketone **5** (166 μL, 2 mmol) in dry THF (8 mL) was added the diazonium salt **6a** (250 mg, 1 mmol) and $Pd(OAc)_2$ (5 mol %) and stirred for 12 h at 40 °C. The resulting mixture was then cooled to 25 °C and stirred under an atmosphere of H_2 for 5 h. Then, a solution of EtONa (680 mg, 10 mmol) in THF (8 mL) was added to the reaction mixture. After 15 h of stirring at 36 °C, methyl iodide (187 μL, 3 mmol) was added and the mixture was stirred for 24 h at 36 °C. The cooled mixture was quenched with water, extracted with CH_2Cl_2 (three times), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc–petroleum ether) gave the desired indanone **9a** (52% yield) as a yellow oil. IR (KBr) ν 1589, 1607, 1699, 1723, 2931, 2974, 3035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.53 (s, 3H), 2.21 (s, 3H), 2.82 (d, 1H, J = 17.4 Hz), 3.82 (d, 1H, J = 17.6 Hz), 7.35–7.40 (m, 1H), 7.47 (dt, 1H, J = 7.6 Hz), 7.58–7.64 (m, 1H), 7.73 (d, 1H, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.5, 25.9, 37.6, 64.0, 124.7, 126.5, 127.8, 134.8, 135.5, 152.9, 204.1, 204.6. HRMS (electrospray) Calcd For $C_{12}H_{12}O_2Na$ $[M+Na]^+$ 211.0729, found: 211.0727.