# JOC*Note*

Synthesis of Oxindoles by Tandem Heck-Reduction-Cyclization (HRC) from a Single Bifunctional, in Situ Generated Pd/C Catalyst

François-Xavier Felpin,* Oier Ibarguren,
Luma Nassar-Hardy, and Eric Fouquet

Université de Bordeaux, CNRS, Institut des Sciences Moléculaires, 351 Cours de la Libération, 33405 Talence Cedex, France

fx.felpin@ism.u-bordeaux1.fr

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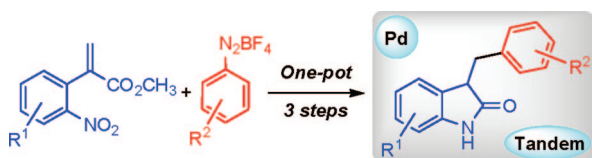
A tandem sequence involving palladium-catalyzed sequential Heck-reduction-cyclization transformations in mild conditions has been developed for the synthesis of oxindoles. The protocol involves inexpensive reagents and does not require any additives such as base or ligands.

In recent years, the development of rapid and practical routes for the production of libraries of small organic molecules in drug discovery has attracted much attention from the synthetic community.[1] To this end, multiple transformations performed in a one-pot process, called domino, tandem, or cascade reactions,[2] have become an important area of research in organic chemistry.[3,4] Preparative protocols in which at least two consecutive transformations are carried out in the same reaction vessel offer a number of advantages to the organic chemist. For instance, they allow the elaboration of complex structures from relatively simple starting materials in a reduced number of technical operations, and syntheses using such reactions

become more economically advantageous (time and resource management benefits) and environmentally friendly (waste reduction). The unrivalled diversity of transition-metal-catalyzed reactions available has made them important mediators for the elaboration of tandem processes.[3,4] Among them, palladium has been intensively studied for tandem transformations of two or more mechanistically related reactions. However, the use of palladium complexes for the catalysis of at least two fundamentally different reactions is quite unusual[5] because of the high specificity of the catalyst, and these challenging tandem reactions remain essentially described with other metals such as rhodium, ruthenium, and copper.[6]

Palladium metal has been widely used for a century as a hydrogenation, hydrogenolysis, and hydrodechlorination catalyst essentially under a heterogeneous form. On the other hand, the use of homogeneous palladium complexes as catalysts for carbon−carbon bond formation is more recent with the discovery of Heck,[7] Suzuki,[8] Stille,[9] Sonogashira,[10] and other related reactions[11] in the 1970s.

Processes based on the exploitation of the dual reactivity of palladium catalysts (C−C bond formation and hydrogenation) have, quite surprisingly, rarely been developed in the context of one-pot reactions.[12] In this paper, we report our results related to the synthesis of C3 benzylated oxindoles by a sequential tandem Heck-reduction-cyclization (HRC)[13] using aryl diazonium salts as "super" electrophiles.

Oxindole-containing heterocycles, particularly those substituted at the C3 position, are commonly encountered in natural products[14] and pharmaceutical compounds[15] (Figure 1). They display a wide range of biological properties including antiarthritis,[16] antitumoral,[17] and antiviral activities.[18] As a

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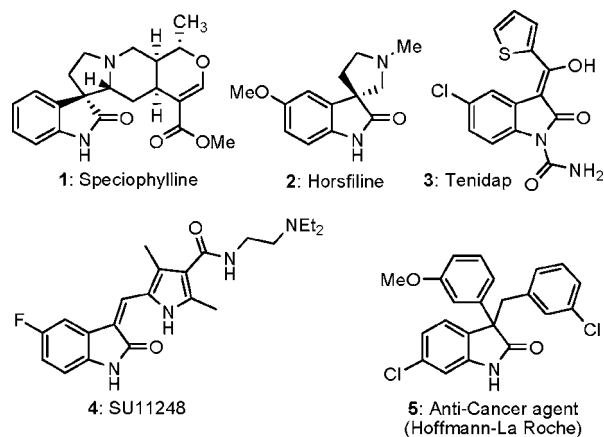
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FIGURE 1. Representative oxindole-containing natural products (**1** and **2**) and drugs (**3**–**5**).

consequence, the selective monofunctionalization at C3 by alkyl, alkenyl, or benzyl groups of N-unsubstituted oxindoles has been a longstanding issue.[19,20] Indeed, base-mediated C3 alkylation generaly gives a mixture of C- and N-alkylated products as a consequence of the close acidity of the protons in C3 and N1 positions.[21] Thereby, a less direct method is generally preferred involving the reduction of 3-alkyl or 3-arylideneoxindoles, prepared by the condensation of unsubstituted oxindoles with aldehydes or ketones.[22] Considering the need for a more straightforward pathway, we designed a novel approach where the oxindole core and the C3 functionalization are executed in the same reaction vessel.

Optimization of Reaction Conditions. Our strategy, outlined in Scheme 1, is based on a Heck cross-coupling of a 2-(2-nitrophenyl)acrylate **A** with an aryl diazonium tetrafluoroborate salt **B**. We[23] and others[24] have reported the practical use of diazonium salts, easily prepared from inexpensive anilines,[25] for Heck reactions without any external additive (base or ligand),

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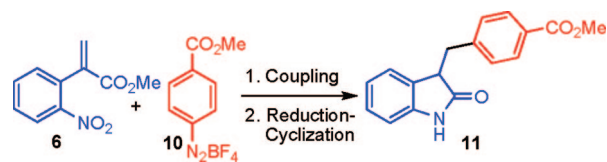
SCHEME 1. Overall HRC Strategy
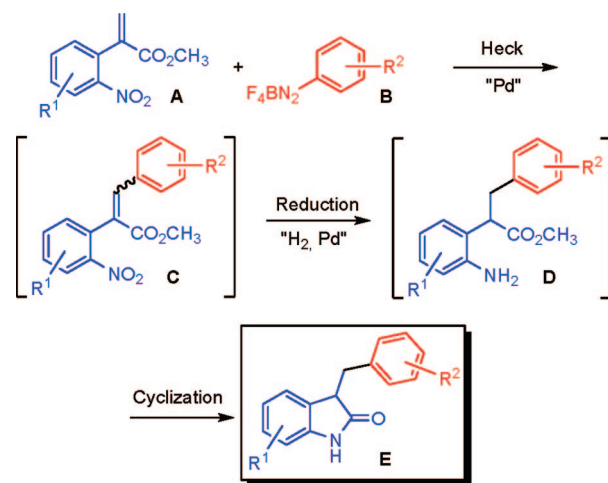
TABLE 1. Preparation of 2-(2-Nitrophenyl)acrylates
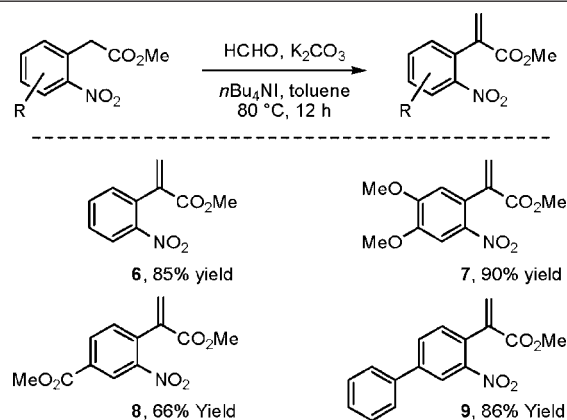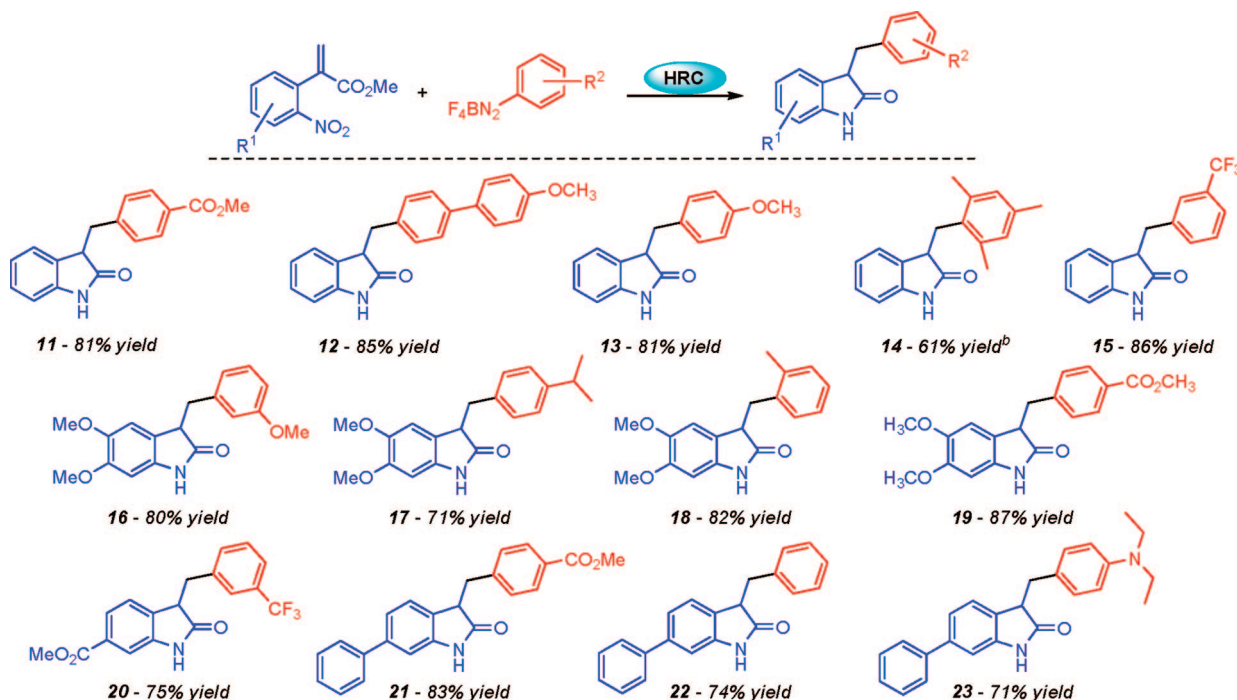

TABLE 2. Optimization Studies of the HRC Sequence

entry	Heck coupling	reduction-cyclization	yield[a] (%)
1	5 mol % Pd(II)/C, MeOH, 40 °C, 0.25 h	H₂, 24 h	b
2	5 mol % Pd(II)/C, dioxane, 40 °C, 2 h	H₂, 48 h	b
3	5 mol % Pd(0)/BaCO₃, MeOH, 40 °C, 2 h	H₂, 24 h	b
4	5 mol % Pd(0)/BaCO₃, dioxane, 40 °C, 2 h	H₂, 48 h	b
5	5 mol % Pd(OAc)₂, charcoal, MeOH, 40 °C, 0.5 h	H₂, 24 h	81
6	5 mol % Pd(OAc)₂, MeOH, 40 °C, 0.5 h	H₂, 48 h	62
7	5 mol % PdCl₂, charcoal, MeOH, 40 °C, 2 h	H₂, 24 h	b
8	5 mol % Pd₂dba₃, charcoal, MeOH, 40 °C, 1 h	H₂, 24 h	<50

a Isolated yield. *b* Complex mixture of products.

making it ideal for tandem transformations. The cross-coupling could be followed by Pd-mediated reductions of the double bond and the nitro group, giving the corresponding aniline **D**, which

**TABLE 3. Preparation of Variously Substituted Oxindoles by the HRC Strategy**

11 - 81% yield   *12 - 85% yield*   *13 - 81% yield*   *14 - 61% yield[b]*   *15 - 86% yield*

16 - 80% yield   *17 - 71% yield*   *18 - 82% yield*   *19 - 87% yield*

20 - 75% yield   *21 - 83% yield*   *22 - 74% yield*   *23 - 71% yield*

[a] Reaction conditions: acrylates (1 mmol), aryldiazonium salt (1.2 mmol), Pd(OAc)$_2$ (5 mol %), charcoal (45 mg), MeOH (5 mL), 40 °C, 15−90 min; then H$_2$, 40 °C, 24 h. Yields are an average of at least two runs. [b] 2 equiv of diazonium salt was used.

should spontaneously cyclize to give variously substituted oxindoles **E**.

The substituted 2-(2-nitrophenyl)acrylates **6**−**9** employed in this study were easily accessed by methylenation of the corresponding methyl 2-(2-nitrophenyl)acetates in good yields (Table 1). Acrylates **6**−**9** proved to be stable for months when stored in the freezer, rendering their use quite easy.

We selected methyl 2-(2-nitrophenyl)acrylate **6** and 4-(methoxycarbonyl)benzenediazonium tetrafluoroborate **10** as coupling partners in our model system (Table 2). Unfortunately, commercially available supported catalysts such as Pd(II)/C[23] and Pd(0)/BaCO$_3$[12f] were poorly effective, leading to a mixture of inseparable products (entries 1 and 3). Close inspection of the crude reaction mixture after the coupling step showed a large amount of methyl benzoate (formed by dediazoniation). This issue could not be addressed with a nonprotic solvent (entries 2 and 4). Considering that the nature of the Pd source could be crucial for the success of the tandem process, we examined the possibility of forming, in situ, the heterogeneous catalyst by mixing a well-defined homogeneous Pd complex with charcoal. To our delight, 5 mol % Pd(OAc)$_2$ smoothly promoted the HRC sequence (entry 5), while PdCl$_2$ and Pd$_2$dba$_3$ were less efficient for the cross-coupling step (entries 7 and 8). To our knowledge, this work is the first example of a catalytically active heterogeneous palladium complex prepared in the same reaction vessel as the cross-coupling. This unusual approach opens the door for the development of dramatically simplified protocols. From a synthetic point of view, it should be noted that after the 2-(2-nitrophenyl)acrylate **6** has been consumed, as indicated by nitrogen evolution (∼30 min), the reaction mixture was stirred under an H$_2$ atmosphere for 24 h, leading to **11** with a good yield (81%). Importantly, at the end of the reaction, a simple filtration of the charcoal left the solvent and the product almost

**SCHEME 2. Synthesis of Bis-oxindole 25 by the HRC Strategy**

2 C-C and 2 C-N bonds have been created one-pot
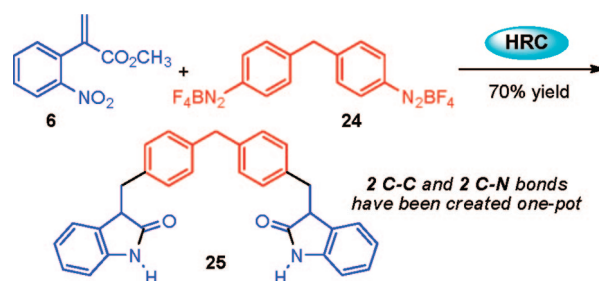
free of palladium residues as indicated by ICP-MS analyses (<50 ppb).[26] This result indicated that virtually all palladium species remained on the charcoal (>99.9%), rendering the purification step easier. As indicated in entry 6, it is interesting to note that when the charcoal was omitted, the hydrogenation step never reached full a conversion even under extended time (>48 h). This observation contrasts with literature precedents[12d,e] in which coupling-hydrogenation sequences without charcoal were described through the in situ formation of palladium nanoparticles.

Scope of the Reaction. Having successfully optimized the HRC protocol on a model sequence, we next explored its scope with various coupling partners (Table 3). A variety of diazonium salts were engaged in our newly designed tandem protocol. Pleasingly, the HRC sequence smoothly furnished the required oxindoles with homogeneous yields (70−80%) whatever the structure of the coupling partners. We learned from these studies a number of interesting features. For instance, the electronic

(26) Other cross-couplings studied in this work showed metal leaching to a similar extent.

SCHEME 3. Recycling Tests
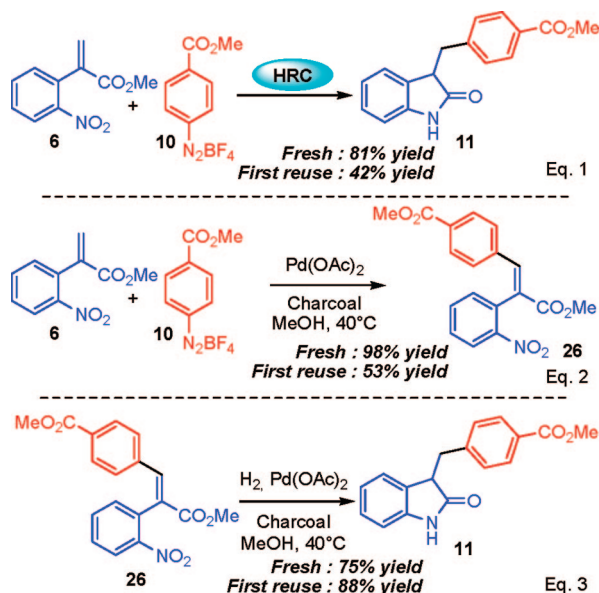
effects of the substituents on the diazonium salts only have a minor impact on the tandem process. Indeed, diazonium salts having electron-withdrawing substituents (compounds **11**, **15**, **19**, **20**, and **21**) react faster with the corresponding acrylate in the Heck cross-coupling than those having electron-donating ones (compounds **14**, **16**, **17**, **18**, and **23**). However, we did not observe any considerable influence of these electronic effects on the yields of the reduction-cyclization sequence. On the other hand, the nature of the acrylates has also a low influence on both kinetics and yields. The compatibility of the method with a biphenyl group (compound **12**) and hindered diazonium salts (compounds **14** and **18**) is noteworthy.

Interestingly, the protocol could be extended to the preparation of even more elaborated substrates (Scheme 2). For instance, the reaction of acrylates **6** with the bis-diazonium salt **24** allows the creation of four chemical bonds in only one reaction vessel (i.e., two C−C and two C−N) with 70% yield.

Recycling Tests. Since the catalyst could be easily separated from the reaction mixture by simple filtration, leaving the solvent and the product almost free of palladium residues, we examined its recyclability with a set of key experiments (Scheme 3). Unfortunately, after the first run, the reused catalyst showed a strong deactivation leading to lower yield of oxindole **11** (eq 1). Additional experiments unambiguously showed that the reused catalyst was less active for the Heck reaction (eq 2) but remained still and even more active for the reduction-cyclization steps (eq 3). It is likely that the reduced form (Pd(0)/C) of the reused catalyst is detrimental for the success of the Heck reaction for which a Pd(II) precatalyst is preferred. On the other hand, the reduction-cyclization sequence requires preferably a palladium with a low degree of oxidation. We are currently working to solve this issue.

In summary, we have reported an efficient synthesis of C3 benzylated oxindoles by a novel tandem HRC process. This work represents one of the few applications in heterocyclic chemistry of tandem reactions catalyzed by a single heterogeneous catalyst.[27] We demonstrated, for the first time, that the preparation of an active heterogeneous catalyst and the tandem process could be carried out in one pot. The experimental simplicity associated with the extremely mild conditions render the method highly competitive over existing procedures. We believe that such a simple method could be of broad interest for synthetic and medicinal chemists.

Experimental Section

General Procedure for the Tandem Heck-Reduction-Cyclization Sequence. To a solution of diazonium salt (1.2 mmol) in MeOH (5 mL) were added acrylate (1 mmol), charcoal (45 mg), and Pd(OAc)$_2$ (5 mol %). The reaction was stirred for 15−90 min at 40 °C and then stirred under H$_2$ for 24 h at 40 °C. After filtration, the crude material was purified by flash chromatography to give the corresponding oxindole.

Supporting Information Available: Detailed experimental procedures, characterization data, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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