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Diazo Compounds

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Selective Synthesis of Six Products from a Single Indolyl α-Diazocarbonyl Precursor

Michael J. James, Peter O'Brien, Richard J. K. Taylor, and William P. Unsworth**

Abstract: *Indolyl α-diazocarbonyls can be selectively cyclized to give six distinct products through the careful choice of catalyst and reaction conditions. A range of catalysts were used, including complexes of Rh^{II}, Pd^{II}, and Cu^{II}, as well as SiO$_2$, to promote diazo decomposition and subsequent cyclization/rearrangement through a range of mechanistic pathways.*

The ability to access structurally diverse compounds is the cornerstone of lead generation in the pharmaceutical and agrochemical industries.[1] In most cases, such compounds are generated using organic synthesis, and over the years, a number of reliable and predictable methods have emerged.[1,2] The importance of such methods cannot be over-stated, but nonetheless, there is also value in the examination of reaction systems which react less predictably.[3] Reactive precursors known to participate in a wide range of synthetic transformations can significantly streamline the synthesis of diverse compounds by allowing multiple products to be generated from a single precursor, provided their reactivity can be controlled.

With this in mind, we initiated the research described herein, focusing on the reactions of indolyl α-diazocarbonyl compounds.[4] The utility of diazo precursors in diversity-orientated synthesis was elegantly demonstrated by Warriner, Nelson and co-worker in 2014,[3] who exploited the unpredictable reactivity of α-diazoamides to generate product mixtures for bioassays. In our research we have taken an alternative approach, using a different reaction system, and focused on controlling the "unpredictable" nature of diazocarbonyl reactivity by catalyst variation. The ability to access several distinct products from a common precursor is synthetically important, and such research can also lead to advances in the study of catalysis and mechanism. With this as motivation, we challenged ourselves to uncover a reaction system capable of delivering as many product scaffolds as possible from a single precursor by varying the catalyst and reaction conditions.[5] Most reported methods of this type allow the selective synthesis of two distinct products,[6] with protocols able to deliver three or more products being much more rare.[7] However, herein we report the catalyst-selective synthesis of six structurally distinct cyclic scaffolds from a single α-diazocarbonyl, of the form **1**, by a series of mild rhodium(II)-, palladium(II)-, copper(II)-, and SiO$_2$-catalyzed processes, as discovered through a mix of careful reaction design and serendipity (Figure 1).

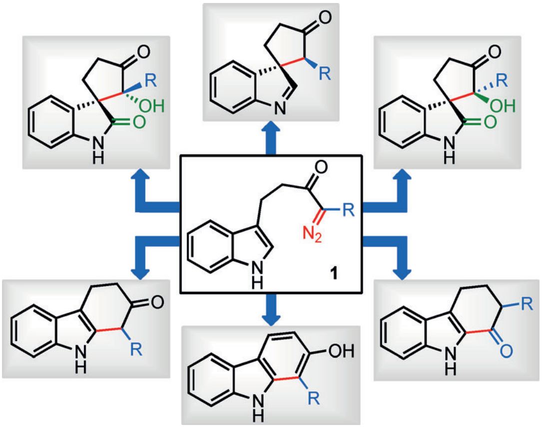

Figure 1. Catalyst-selective synthesis: six scaffolds from one precursor.

Our studies began with the three-step synthesis of the α-diazocarbonyl **1a** from the commercially available acid **2a** (Table 1),[8] which was then treated with a range of potential catalysts (10 mol%) in CH$_2$Cl$_2$ at room temperature for 16 hours. Selected results are given in Table 1 (for full details, see the Supporting Information).

A number of catalysts able to promote diazo decomposition and cyclization were uncovered. Five identifiable products were observed in total, with mechanistically related products grouped to aid the subsequent discussion: the spirocyclic indolenine **3a** and α,β-dicarbonyl **4a** (group A), C2 annulated indole **5a** and carbazole **6a** (group B), and isomeric indole **7a** (group C). As expected, many of the catalysts afforded complex mixtures of products, as exemplified by the reactions of the rhodium(II)- and copper(II)-based catalysts (Table 1, entries 1–4). However, more promising catalysts were also found and they enabled the selective synthesis of group A products **3a** and **4a** [Rh$_2$oct$_4$)], group B redox isomers **5a** and **6a** [Pd(MeCN)$_4$(BF$_4$)$_2$ or Cu(OTf)$_2$], and the rearrangement product **7a** (SiO$_2$), and these catalysts were therefore selected for further optimization.

To the best of our knowledge, the [Rh$_2$oct$_4$]-catalyzed procedure[9] to form **3a** represents the first reported synthesis of a spirocyclic indolenine[10] from a diazocarbonyl precursor, although C3 functionalization of indoles using diazocarbonyl compounds has been reported,[11,12] so this outcome was not wholly unexpected.[13] However, the formation of the oxidized

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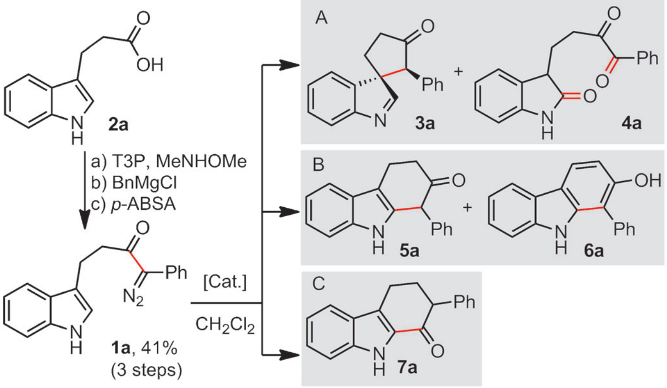
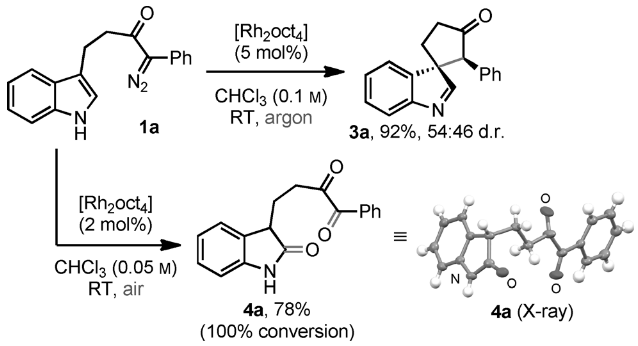
Table 1: Initial catalyst screening.



Entry		Catalyst[a]	Product composition [%][b] 1a	3a	4a	5a	6a	7a
1	mix	$[Rh_2(OAc)_4]$	–	–	50	20	15	15
2		$[Rh_2esp_2]$	–	10	55	15	–	20
3		$Cu(MeCN)_4OTf$	–	20	–	60	20	–
4		$Cu(MeCN)_4PF_6$	15	65	20	–	–	–
5	A	$[Rh_2oct_4]$	–	95	5	–	–	–
6	B	$Pd(MeCN)_4(BF_4)_2$	–	–	–	95	5	–
7		$Cu(OTf)_2$	–	–	–	70	30	–
8	C	SiO_2 (1 g/g)	–	–	–	–	–	>90

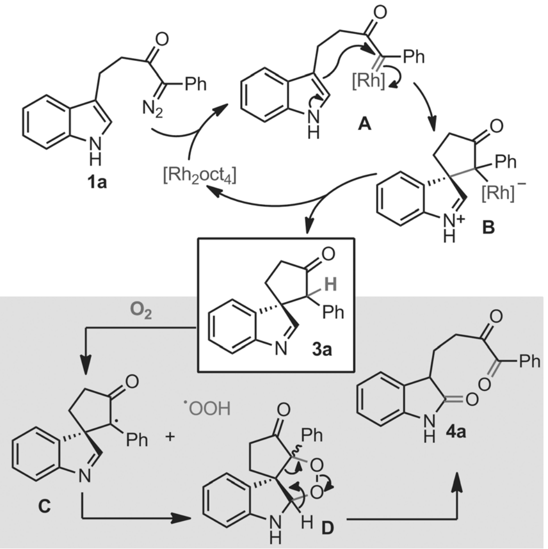
[a] Reactions performed with 0.05 mmol of **2a** and 10 mol% catalyst in CH_2Cl_2 (0.1 M) under argon at RT for 16 h. [b] Calculated using the ^1H NMR spectrum of the unpurified reaction mixture. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate, oct = octanoate, *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, T3P = propane phosphonic acid anhydride, Tf = trifluoromethanesulfonyl.

product **4a** was much more surprising, with the structure of this product confirmed by X-ray crystallography.[14] It was found that the selective synthesis of either product could be achieved, with the reaction outcome being dependent on the presence of air in the reaction. By switching the reaction solvent from CH_2Cl_2 to chloroform, reducing catalyst loading to 5 mol%, and performing the reaction under oxygen-free conditions, **3a** was isolated in 92% yield (Scheme 1). Furthermore, carrying out the same reaction in a flask open to air was sufficient to completely switch the selectivity to efficiently furnish **4a**.



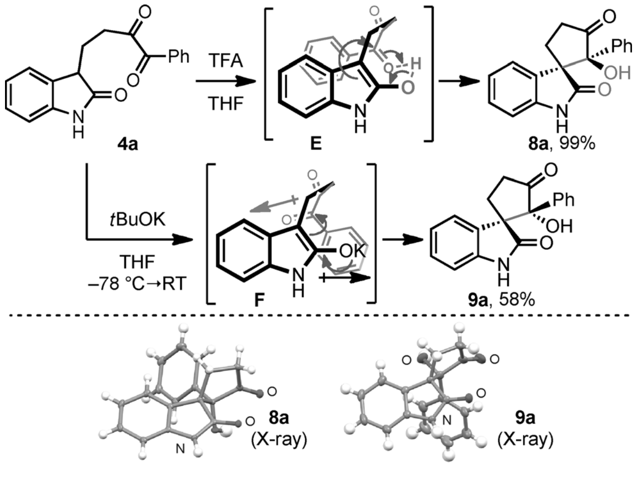
Scheme 1. Selective synthesis of **3a** and **4a**.

We propose that both reactions start with the formation of the rhodium carbenoid **A**,[15] which then reacts with the nucleophilic indole to form the spirocycle **B**, before undergoing protodemetallation to furnish **3a** (Scheme 2). Then, in the presence of oxygen, we propose that **3a** forms the intermediate endoperoxide **D**,[8a] possibly by a radical rebound process (**3a**→**C**→**D**),[16] before fragmenting as shown to afford the product **4a**.[17] Additional evidence for this mechanism (including an X-ray structure for a related endoperoxide) can be found in the Supporting Information.



Scheme 2. Proposed mechanism for the formation of **3a** and **4a**.

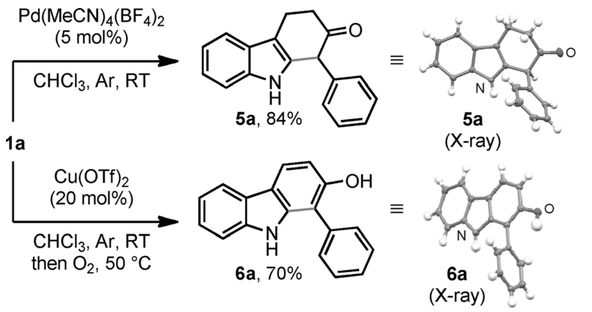
While **4a** could be isolated in good yield, it was found to be relatively short-lived as it degraded during silica gel chromatography and upon storage, but pleasingly, we were able to exploit its high reactivity to deliver two new oxindole scaffolds, **8a** and **9a** (Scheme 3). Thus, two highly diastereoselective intramolecular aldol-type reactions were developed using either Brønsted-acidic or Brønsted-basic conditions.



Scheme 3. Stereoselective formation of **8a** and **9a**.

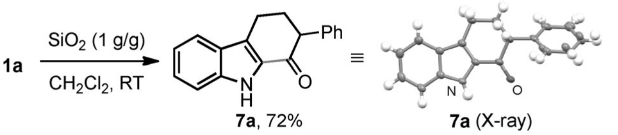
Both reactions were performed in one pot, thus requiring only a solvent switch to THF and the addition of an excess of either TFA or *t*BuOK. Under acidic conditions **4a** was selectively converted into the *syn*-diastereoisomer **8a** in 99% yield, and we propose this to be the result of hydrogen bonding between the oxindole and α,β-dicarbonyl moieties (**E**). Conversely, under basic conditions, the *anti*-diastereoisomer **9a** was formed, and we propose that it results from a reactive conformation of the form **F**, in which the destabilizing steric interactions are lower than those in **E**, and the carbonyl dipoles are opposed. Both product structures were confirmed by X-ray analysis.[14]

Next, the palladium(II)- and copper(II)-catalyzed reactions were optimized, thus allowing selective formation of the C2-annulated product **5a** and carbazole **6a** using $Pd(MeCN)_4(BF_4)_2$ (5 mol%) and $Cu(OTf)_2$ (20 mol%), respectively (Scheme 4).[18,19] A key difference between these reactions is that it is necessary to perform the carbazole-forming reaction under oxygen at 50°C. It is difficult to unambiguously determine whether these reactions proceed by direct nucleophilic attack from the indole C2 or by initial C3 attack followed by a 1,2-migration. Based on related precedent,[20] and the observation that **3a** can be converted into a mixture of **5a** and **6a** upon reaction with $Cu(OTf)_2$, the latter appears more likely.



Scheme 4. Selective formation of **5a** and **6a**. TFA = trifluoroacetic acid, THF = tetrahydrofuran.

The silica-promoted C2-annulation reaction required minimal deviation from the initial screen. The compound **7a** was prepared in good yield by reacting **1a** with an equivalent weight of SiO_2 in CH_2Cl_2 (Scheme 5). The reaction likely proceeds by a Wolff rearrangement, induced by the mildly acidic silica,[21] and trapping by the nucleophilic indole (either by direct C2 attack or by an initial C3 attack followed by a 1,2-migration). To the best of our knowledge, only one other example of a C2-annulation reaction of this type has been reported.[22]



Scheme 5. Synthesis of **7a**.

Finally, the scope of all six procedures was tested on five diazocarbonyl substrates (**1a**–**e**), thus delivering 30 discrete products in total (Scheme 6). The spirocycles **3a**–**e** were each formed in good yield, with variable diastereomeric ratios, and is likely due to epimerization of the α-keto stereocenter during chromatography. The other five procedures were all well tolerated by the same precursor set. The spirocyclic oxindoles **8a**–**e** and **9a**–**e**, as well C2 annulation products **5a**–**e**, **6a**–**e**, and **7a**–**e** were formed in generally good yields, and is pleasing given that no additional optimization was performed for any of these reactions.[23]

In summary, we report a novel catalyst-controlled approach to form six structurally diverse products from a single α-diazocarbonyl precursor. While other catalyst-selective synthesis systems are known,[5–8] we know of no other capable of delivering the level of scaffold diversity by simply varying the catalyst and reaction conditions. Given the importance and diversity of the compound classes accessible, the methods are expected to be of much synthetic interest,[24,25] while the novel reactivity and mechanistic information uncovered is likely to be useful to researchers studying catalysis. These discoveries (some of which were serendipitous) were made as a result of challenging the methodology in terms of the number of products which could be selectively formed. Much as natural product synthesis has long been used to inspire the invention of new synthetic processes,[26] we believe that the same principles apply in catalyst-selective synthesis.

Acknowledgments

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Keywords: cyclizations · diazo compounds · indoles · spirocycles · synthetic methods

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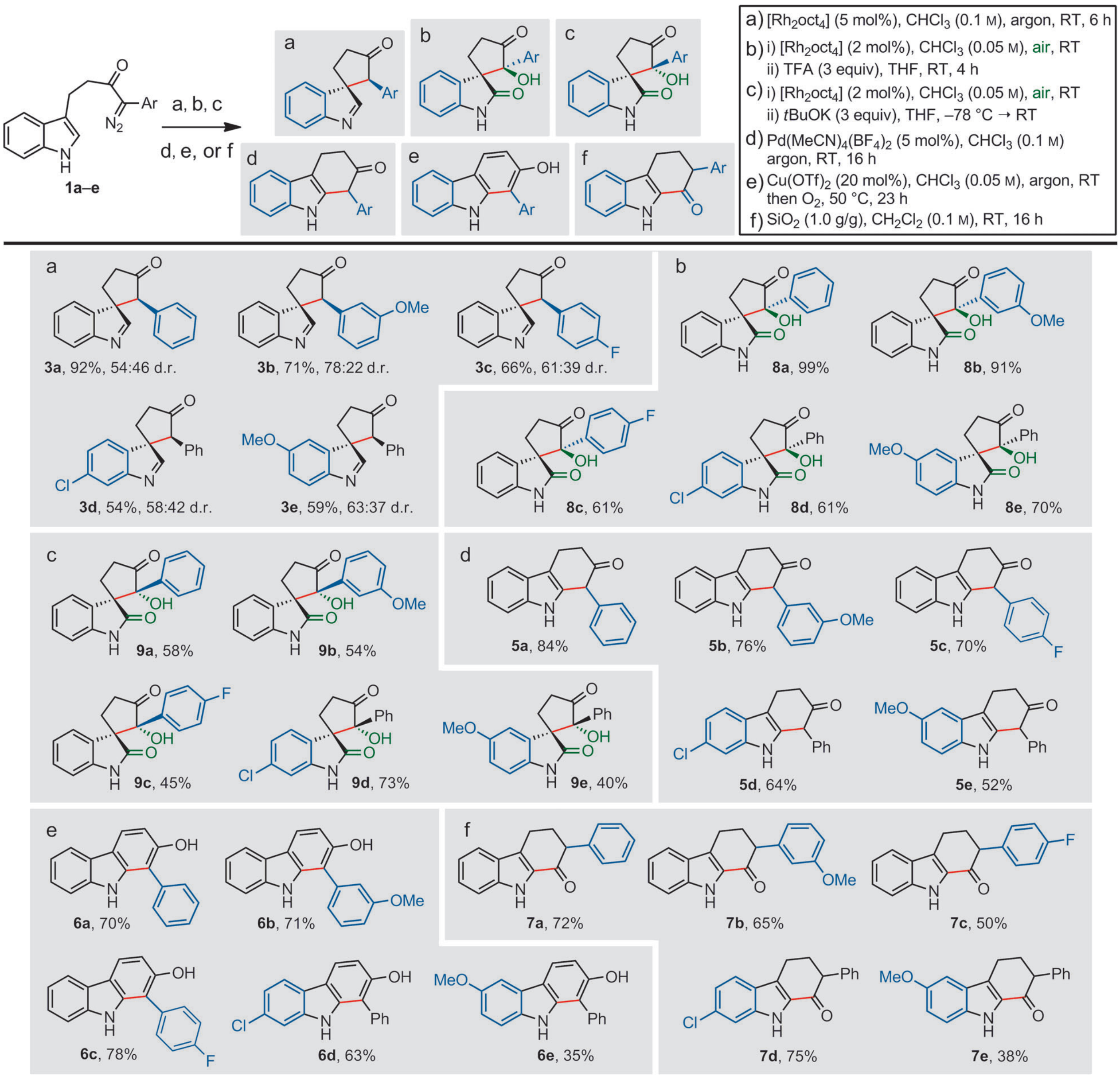

Scheme 6. Catalyst-selective synthesis of six products from a single indolyl α-diazocarbonyl precursor (yields are those of products isolated after column chromatography).

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[9] We are unable to account for the difference in product ratio of the three rhodium(II)-catalyzed reactions in Table 1 (entries 1, 2, and 5). Subtle differences in the solubility, coordination chemistry, and redox potential of the catalysts/intermediates can all influence the reaction outcome. It is noteworthy that all of these reactions had a distinct dark red/burgundy color, which is often indicative of Rh^{II,III} dimer formation.

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[17] Purified **3a** slowly converts into **4a** when stored in solution open to air, thus confirming that the rhodium catalyst is not essential for oxidation.

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[19] For related carbazole syntheses, see: K. S. Rathore, B. S. Lad, H. Chennamsetti, S. Katukojvala, *Chem. Commun.* **2016**, *52*, 5812.

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[25] Efforts to extend these methods to other heteroarenes are ongoing.

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Communications

Diazo Compounds

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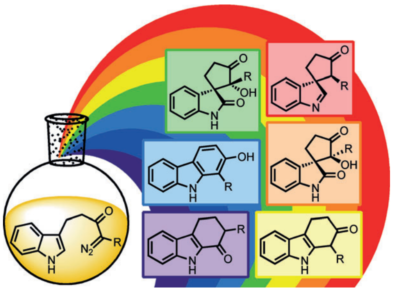
Selective Synthesis of Six Products from a Single Indolyl α-Diazocarbonyl Precursor



Pick a catalyst: Indolyl α-diazocarbonyls can be selectively cyclized to give six distinct products through the careful choice of the catalyst and reaction conditions. A range of catalysts were used, including complexes of Rh^{II}, Pd^{II}, and Cu^{II} as well as SiO_2, to promote diazo decomposition and subsequent cyclization/rearrangement through a range of mechanistic pathways.