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## Accessing Multiple Classes of 2*H*-Indazoles: Mechanistic Implications for the Cadogan and Davis-Beirut Reactions

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### Abstract

The Cadogan cyclization is a robust but harsh method for the synthesis of 2*H*-indazoles, a valuable class of nitrogen heterocycles. Although nitrene generation by exhaustive deoxygenation is widely accepted as the operating mechanism in the reductive cyclization of nitroaromatics, non-nitrene pathways have only been theorized previously. Here, 2*H*-indazole *N*-oxides were synthesized through an interrupted Cadogan/Davis-Beirut reaction and are presented as direct evidence of competent oxygenated intermediates; mechanistic implications for both reactions are discussed. Isolation and characterization of these *N*-oxides enabled a formal Cadogan cyclization at room temperature for 2*H*-indazole synthesis.

### Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13481.

Experimental procedures, characterization data, <sup>1</sup>H and <sup>13</sup>C NMR spectra, crystallographic information, and details of quantum chemical calculations (PDF)

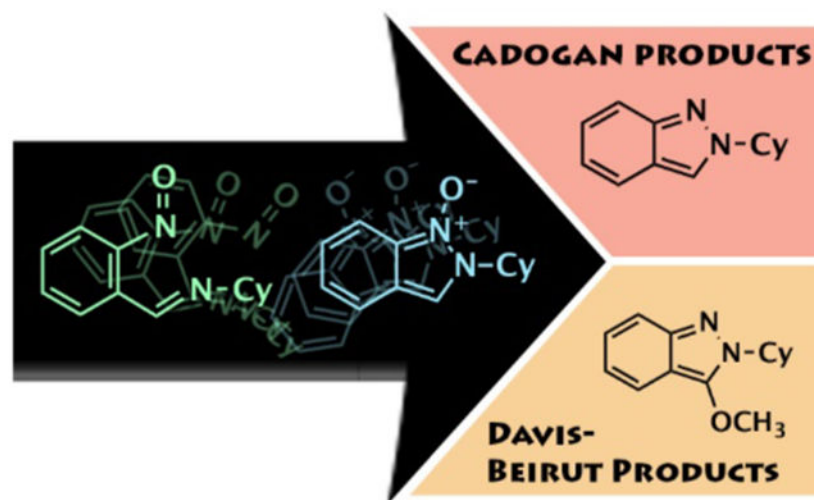
X-ray crystallographic data (CIF)

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The authors declare no competing financial interest.

CCDC 1883187, 1883188, and 1883189 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by e-mailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.



## INTRODUCTION

The synthesis of nitrogen heterocycles is of paramount importance due to their high value in pharmaceutical applications. In particular, *2H*-indazoles and their derivatives have highly desirable therapeutic properties,<sup>1</sup> for example, modulation of PARP,<sup>2</sup> VEGF,<sup>3</sup> GK,<sup>4</sup> and CRAF.<sup>5</sup>

The Cadogan reaction is a classical reductive cyclization method for synthesizing *2H*-indazoles from nitroaromatic compounds.<sup>6</sup> The reaction is generally carried out at high temperatures, i.e., refluxing in excess trialkyl phosphites or trialkyl phosphines (typically at >150 °C). Recent advances made by Genung and co-workers allow the Cadogan reaction to proceed under milder, although not mild, conditions (80 °C).<sup>7</sup> The Cadogan cyclization using a catalytic amount of phosphorus based on a P<sup>III</sup>/P<sup>V</sup> redox cycling strategy has also been recently reported by Radosevich<sup>8</sup> and Nazaré.<sup>9</sup> This reductive heterocyclization is widely accepted to proceed via a nitrene intermediate derived by exhaustive deoxygenation of the nitro group (Scheme 1; **1a** → **2** → **3** → **4**). This mechanistic model is supported by the fact that aromatic azides can also be used to generate the targeted *2H*-indazoles.<sup>10</sup>

On the other hand, studies of the related Sundberg reductive cyclization for indole synthesis have shown that N—O bond-containing indole byproducts can be isolated, an observation that seems incompatible with a nitrene mechanism.<sup>6b</sup> The Sundberg system has since been theoretically studied, and a five-center  $6\pi$  electrocyclization was found to be a viable alternative pathway.<sup>11</sup> Taken together, these results imply that more than one mechanistic pathway may be operational in the reductive cyclization of nitroaromatics. Analogous N—O bond-containing byproducts have not been observed in the Cadogan cyclization, and a non-nitrene pathway has yet to be established.<sup>11</sup> This is perhaps due to the challenges associated with stopping the Cadogan reaction at the *2H*-indazole *N*-oxide stage, because *N*-oxide-containing heterocycles are known to undergo rapid deoxygenation by phosphorus reagents at just 60–70 °C.<sup>12</sup> In contrast, hydroxy indoles are resistant to deoxygenation by triethyl phosphite even at >160 °C.<sup>6b</sup> Therefore, we have explored the chemistry of *o*-nitrosoimine **2**

(Scheme 1) under non-deoxygenating conditions, with the complementary goals of developing synthetically useful reactions and increasing the understanding of the Cadogan and related reactions.

Our group previously reported the synthesis and applications of *in situ* generated *o*-nitrosobenzaldehyde in connection with the Davis—Beirut synthesis of 3-alkoxy 2*H*-indazoles<sup>1</sup> and indazolones.<sup>13</sup> Throughout these studies, nitrogen nucleophiles were found to react with the nitroso group, leading us to suggest that the imine of **2** can be recruited to react intramolecularly with its nitroso moiety to generate 2*H*-indazole *N*-oxide (Scheme 1; **2** → **5** ↔ **6**). Indeed, many well-known reactions are thought to rely on an imine being nucleophilic at nitrogen, such as the Staudinger reaction for  $\beta$ -lactam synthesis,<sup>14</sup> the Paal–Knorr pyrrole synthesis,<sup>15</sup> the Shaw four-component reaction for  $\gamma$ -lactam synthesis,<sup>16</sup> and the Castagnoli–Cushman reaction for  $\delta$ -lactam synthesis<sup>17</sup> (note: nucleophilic attack by imine intermediates has not been fully demonstrated in all cases).

Biological activities of *N*-oxygenated derivatives of privileged heterocycles have been repeatedly demonstrated,<sup>18</sup> as shown by librium,<sup>19</sup> minoxidil,<sup>20</sup> tirapazamine,<sup>21</sup> and the widespread application of carbadox/olaquinox/cyadox.<sup>22</sup> The relative scarcity of 2*H*-indazole *N*-oxides perhaps accounts for their lack of representation among clinical candidates, although the antiprotozoal activity of 2*H*-indazole *N*-oxides has been reported.<sup>23</sup> Known methods for their construction involve the use of cyanide salts,<sup>23</sup> isocyanides,<sup>24</sup> 1,7-electrocyclizations,<sup>25</sup> 1,3-dipolar cycloadditions,<sup>26</sup> and rearrangements of sulfonyl amides.<sup>27</sup> Here, the development of a new and convenient method for 2*H*-indazole *N*-oxide synthesis is disclosed, with an eye toward empowering future studies on their medicinal potential.

## RESULTS AND DISCUSSION

For the proposed intramolecular cyclization between the nitroso and the imine groups of **2** to occur, several reaction manifolds must be shut down. First, the formation of **2** must not involve external reduction of the nitro group due to the possibility of over-reduction.<sup>28</sup> Second, the solvent for the reaction must not be a primary alcohol due to the possibility of hemiaminal ether formation, which ultimately would lead to the corresponding 3-alkoxy-2*H*-indazole.<sup>1</sup> To address these issues, the following strategies were applied. First, a straightforward base-mediated conversion<sup>29</sup> of **9** → **2** (Table 1) was used rather than external reduction. Second, the reaction solvent employed was <sup>t</sup>PrOH because it is not effective<sup>13</sup> at converting **2** to the corresponding hemiaminal ether or subsequent 3-isopropoxy 2*H*-indazole.<sup>29</sup> In addition, base-mediated *N*-oxide deoxygenation<sup>30</sup> or indazolone formation could compete with the desired cyclization.<sup>13</sup> While base-mediated deoxygenation of the target *N*-oxides was circumvented by lowering the reaction temperature, indazolone formation is known to occur under ambient photochemical conditions.<sup>31</sup> Nonetheless, despite the relative uncertainty regarding whether indazolone formation would outcompete *N*-oxide formation, the outlined conditions were selected as a launch point for this investigation.

The reaction between *o*-nitrobenzyl bromide **9** and *n*-butylamine was performed in <sup>t</sup>PrOH, water, and KOH at room temperature to generate **2** *in situ*. LCMS analysis of the crude

reaction mixture after 24 h revealed a mixture of products, including indazolone (Table 1). However, also in this mixture was a compound containing the targeted mass for 2*H*-indazole *N*-oxide **10**, and the mass spectrum of this compound featured a fragment consistent with N—O bond cleavage (see Table 1, mass spectrum at top right). This compound was isolated and the <sup>13</sup>C NMR data were in good agreement with *N*-oxide product **10**; these initial conditions gave **10** in only 15% yield (Table 1; entry 1). Next, a variety of non-alcohol solvents were screened (entries 2–7), and *N*-alkylation dominated in all solvents explored except DMSO (entry 7), which instead gave the *N*-oxide in 22% yield. The amount of water present was critical for the success of the reaction: water exclusion gave a complex mixture (entry 8), while increasing the amount of water to 1 mL resulted in a yield increase to 54% (entry 9). Further increasing the amount of water to 1.5 mL lowered the yield of **10** to 47% (entry 10). The reaction was also sensitive to the equivalents of base used. For example, using 40 equiv of KOH reduced the yield of **10** to 42% (entry 12), while using 10 equiv of KOH resulted in a 78% yield (entry 13). Further decreasing the amount of base to 5 or 2 equiv gave *N*-oxide in 58% yield (entries 14 and 15). As expected, increasing the reaction temperature above 40 °C led to a complex mixture of products, which did not contain the desired *N*-oxide (entries 16–19). Finally, *n*-butylamine equivalents were varied, and the reaction was found to be sensitive to this parameter. Decreasing the amine to 1 equiv resulted in a lower yield (entry 20), but 2 equiv gave similar results to 5 equiv (entries 13 and 21). Increasing to 10 equiv of amine gave the *N*-oxide in 91% yield (entry 22).

The scope of the reaction was explored using both 2 and 10 equiv of amine (Table 2). Consistent with the optimization studies described above, yields generally increased when 10, rather than 2, equiv of amine was used (**16**, **21**, and **22** are the exceptions). Yields of ~90% could be achieved in some cases; for example, compound **11** was synthesized in 92% yield at small scale and a comparable 89% yield at gram scale. Much of the trifluoromethyl-containing *N*-oxide **22** was deoxygenated even at room temperature. Using benzylamine as the starting material did not deliver **23** under basic conditions due to side-reactions leading to 3-phenylquinazoline formation,<sup>13</sup> but when KOH was excluded and the reaction was carried out under photochemical conditions,<sup>31</sup> **23** was obtained in 29% yield. Unfortunately, use of an aryl rather than alkyl amine is incompatible with these reaction conditions; for example, *N*-aryl 2*H*-indazole *N*-oxide **24** was not produced under either basic or photochemical conditions.

When the amine or *o*-nitrobenzyl bromide component of the reaction is either precious or of limited availability, 2*H*-indazole *N*-oxides may alternatively be synthesized using secondary *o*-nitrobenzyl amines (Table 3) by reductive amination of *o*-nitrobenzaldehyde using just **1** equiv of amine. Indeed, **10** was synthesized from the preformed benzylic amine in a yield (72%) comparable to that for the reaction using *o*-nitrobenzyl bromide (74%, Table 2, where 2 equiv of amine was used). Compound **25** could not be synthesized from the amine and benzyl bromide due to *N*-alkylation regioselectivity issues, but reductive amination of *o*-nitrobenzaldehyde followed by treatment with base gives **25** in 66% yield. Disappointingly, the starting material for **26** was difficult to dissolve in the DMSO/water mixture, and consequently, the yield of **26** was only 33%. This was not an issue with **27**, which was

isolated in 62% yield. Attempts to synthesize *N*-aryl products (e.g., **28** and **24**) again were not successful; for example, in targeting **24**, *p*-anisidine was recovered instead in 14% yield.

The isolation of *p*-anisidine from the attempted synthesis of **24** suggests that water/hydroxide-promoted cleavage (akin to deprotection)<sup>29</sup> of the nitroso imine may be operational under the reaction conditions reported here, consistent with *N*-oxide **5/6** being in equilibrium with **2**, its ring-opened form (Scheme 1). This type of ring-opening/ring-closing process is well documented in the literature for *N*-oxide heterocycles.<sup>32</sup> While X-ray crystal structures for compounds **11**, **12**, and **16** (Figure 1) were consistent with the proposed 2*H*-indazole *N*-oxide, it was not possible to rule out that perhaps the ring-closed form is favored only in the solid state. Therefore, we turned to solution NMR and compared experimental <sup>13</sup>C NMR values for our compounds to reported literature values of related compounds<sup>25</sup> and found them to be in good agreement. In addition, we sought an additional layer of reassurance using quantum chemically computed NMR chemical shifts.<sup>33</sup> Thus, the <sup>1</sup>H and <sup>13</sup>C chemical shifts for **11** and its ring-opened form were calculated using the gauge-including atomic orbital (GIAO) method.<sup>34</sup> The geometries of all conformers for each structure were optimized at the B3LYP/6-31+G(d,p) level.<sup>35</sup> NMR calculations were performed on the optimized structures at the mPW1PW91/6-311+G(2d,p) level,<sup>36</sup> using the SMD continuum model for chloroform.<sup>37</sup> A linear scaling approach was used.<sup>33b,38</sup> The calculated chemical shifts of **11** (Table 1 and 2 in the Supporting Information) were consistent with the experimentally observed shifts (mean absolute deviations of only 0.14 and 1.29 ppm for <sup>1</sup>H and <sup>13</sup>C chemical shifts, respectively). In contrast, computed shifts for the ring-opened form, which is predicted to be ~5 kcal/mol higher in energy than **11**, deviate greatly from the experimental shifts. Note that there exists a C—H...O interaction between the O and secondary amine carbon in the lowest energy conformer of **11**;<sup>39</sup> conformers without this interaction have significantly different chemical shifts.

The proposed ring-closing mechanism was also subjected to computational scrutiny (Figure 2) using a variety of methods: PCM(DMSO)-B3LYP/6-31+G(d,p),<sup>35,40</sup> PCM(DMSO)-B3LYP-D3(Bj)/6-31+G(d,p),<sup>41</sup> SMD(DMSO)-B3LYP-D3(Bj)/6-31+G(d,p), and PCM(DMSO)-M06-2X/6-31+G(d,p).<sup>42</sup> These methods provide a consistent picture (standard corrections for changing from gas phase to solution were computed, but found not to change the results; see SI for details).

Conversion of **29** to **11** (Figure 2, top) is predicted to be kinetically feasible and exergonic, consistent with experiment. Conversion of **30** to **28** (Figure 2, bottom) is also predicted to be feasible, if slightly less exergonic, despite our inability to isolate **28**, perhaps a result of as-yet unidentified competing reactions.

In that heterocyclization is predicted to be facile for structures such as **29**, it is possible that this type of process also occurs in classic Cadogan reactions, rather than, or in addition to, nitrene formation. We carried out computations on nitrene formation as well, examining both singlet and triplet pathways (see SI for details) and have yet to find a nitrene formation pathway with a lower barrier than cyclization, although we cannot definitively rule out this process as contributing.

On the basis of the results of our calculations, we propose an alternative route to formal Cadogan products in which a phosphine (here,  $\text{PMe}_3$ ) is used to promote deoxygenation. For example, we predict that deoxygenation of **29**, which is in equilibration with **11**, has an activation barrier of less than 20 kcal/mol (relative to **29**), whether nitrogen or oxygen is attacked first, and is greater than 70 kcal/mol downhill in energy overall (Figure 3), consistent with expectations for a reaction making a new  $\text{P}=\text{O}$  bond. Such a process (**1b**  $\rightarrow$  **2**  $\rightarrow$  **4** in Scheme 1) may well occur during Cadogan reactions. Oxygen transfer from N to P is well established in the literature for *N*-oxides (generally requiring temperatures in the 60–70 °C range),<sup>12</sup> but we propose here that 2*H*-indazole *N*-oxide deoxygenation would occur via a ring-opening then deoxygenation/ring-closure process.

Deoxygenation also can be carried out under reductive conditions (Table 4). Unsurprisingly, the reduction of these *N*-oxide-bearing heterocycles occurred rapidly, even at room temperature. Overall, the reported **1b**  $\rightarrow$  **2**  $\rightarrow$  **6**  $\rightarrow$  **4** reaction sequence is formally a Cadogan cyclization carried out under phosphorus-free conditions at ambient temperature, the mildest conditions yet reported for this type of nitroaromatic reductive cyclization.

Finally, prior to the isolation and characterization of the *N*-oxide heterocycles reported here, **2** was the only common intermediate in the Cadogan and Davis–Beirut reactions (Scheme 1). However, it is possible that both reactions also share structure **5**  $\leftrightarrow$  **6**. Indeed, when *N*-oxide **10** was treated with typical Davis–Beirut conditions, 3-alkoxy-2*H*-indazoles were obtained in high yields (Table 4).

## CONCLUSIONS

In summary, we report the design and optimization of a method for controlling highly reactive nitroso imines, using them to produce 2*H*-indazole *N*-oxides. This reaction provides access, under mild conditions, to a synthetically and biologically underutilized class of *N*-oxide heterocycles. The structures of these compounds were determined using X-ray crystallography and computational NMR. Moreover, isolation of these *N*-oxides under ambient conditions has significant implications for mechanistic models of both the Cadogan and Davis–Beirut reactions. For both transformations, *N*-oxides appear to be competent intermediates.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

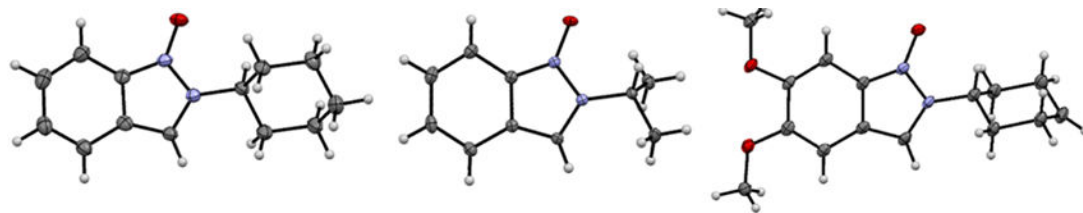
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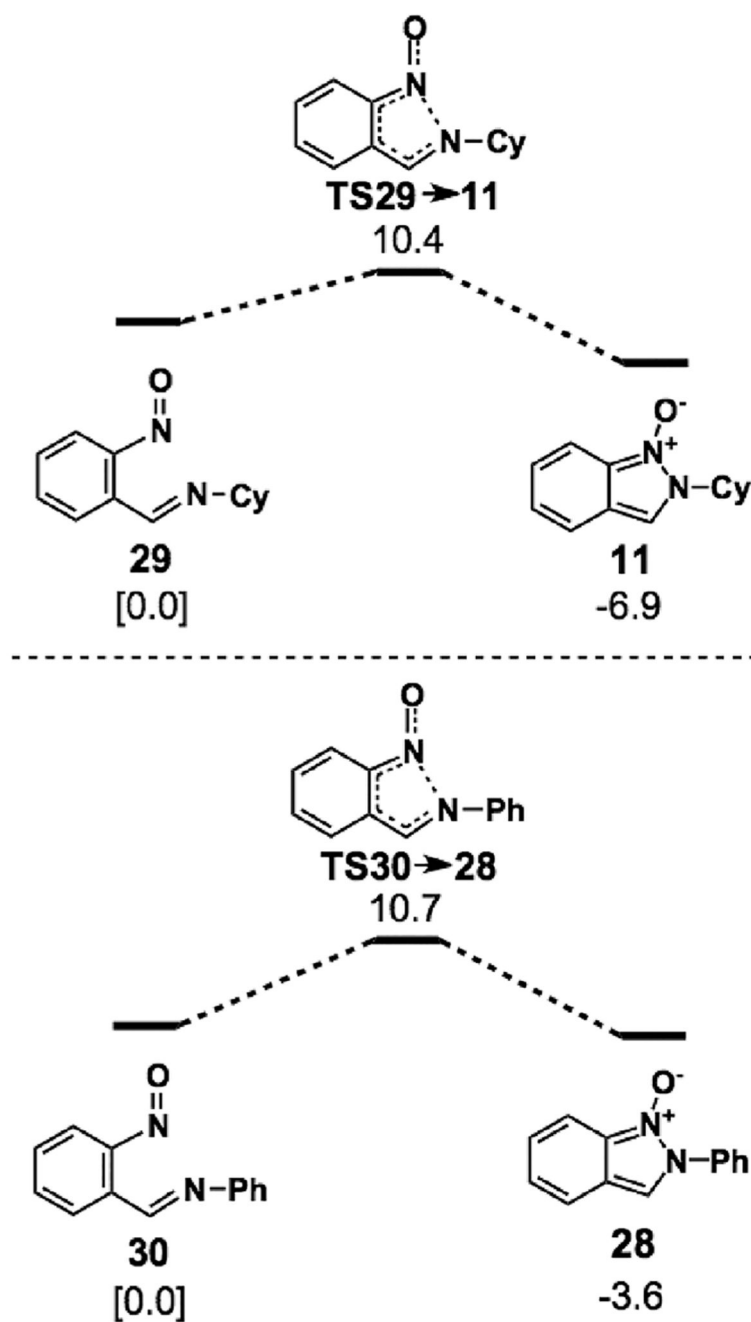
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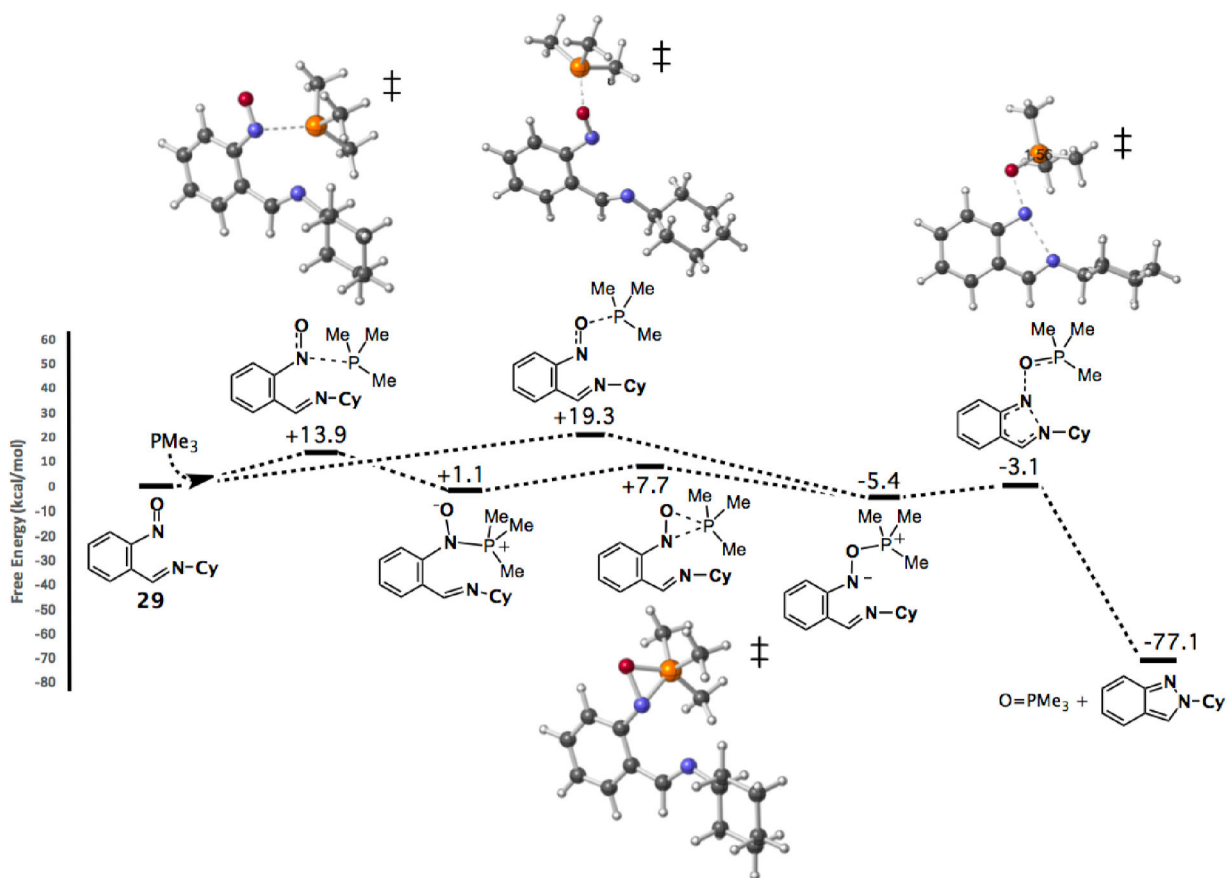
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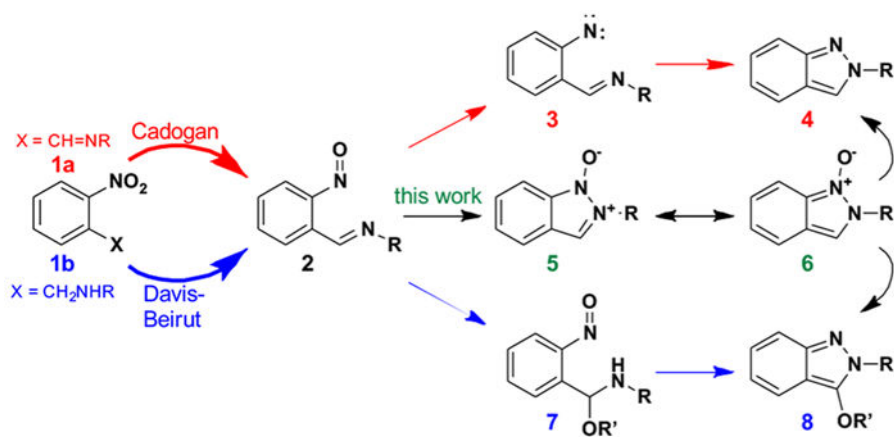
**Figure 1.**  
Crystal structures of **11**, **12**, and **16**, respectively.



**Figure 2.** Computed energetics (PCM(DMSO)-B3LYP-D3(Bj)/6-31+G(d,p), free energies, kcal/mol; see SI for results from other methods) for ring-closure reactions to form **11** and **28**.



**Figure 3.** Computed reaction pathways for the **29**  $\rightarrow$  **32** conversion. Relative free energies (kcal/mol; PCM(DMSO)-B3LYP-D3(BJ)/6-31+G(d,p)) are shown; see SI for results from other levels of theory and data for other, higher energy, pathways.

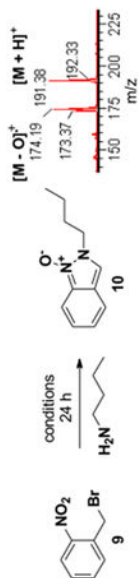



**Scheme 1.**  
Previously Proposed Mechanism of the Cadogan and Davis–Beirut Reactions: Concept of This Work

Table 1.


Reaction Optimization<sup>a</sup>

| entry | base                         | amine   | solvent                | water  | heat   | yield             |
|-------|------------------------------|---------|------------------------|--------|--------|-------------------|
| 1     | 20 equiv KOH                 | 5 equiv | 6 mL <i>t</i> -PrOH    | 0.5 mL | rt     | 15%               |
| 2     | 20 equiv KOH                 | 5 equiv | 6 mL 1,4-dioxane       | 0.5 mL | rt     | N.D. <sup>b</sup> |
| 3     | 20 equiv KOH                 | 5 equiv | 6 mL THF               | 0.5 mL | rt     | N.D. <sup>b</sup> |
| 4     | 20 equiv KOH                 | 5 equiv | 6 mL MeCN              | 0.5 mL | rt     | N.D. <sup>b</sup> |
| 5     | 20 equiv KOH                 | 5 equiv | 6 mL DCM               | 0.5 mL | rt     | N.D. <sup>b</sup> |
| 6     | 20 equiv KOH                 | 5 equiv | 6 mL CHCl <sub>3</sub> | 0.5 mL | rt     | N.D. <sup>b</sup> |
| 7     | 20 equiv KOH                 | 5 equiv | 6 mL DMSO              | 0.5 mL | rt     | 22%               |
| 8     | 20 equiv KOH                 | 5 equiv | 6.5 mL DMSO            | 0 mL   | rt     | N.D. <sup>c</sup> |
| 9     | 20 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 54%               |
| 10    | 20 equiv KOH                 | 5 equiv | 5 mL DMSO              | 1.5 mL | rt     | 47%               |
| 11    | 20 equiv NaO <sup>t</sup> Bu | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 35%               |
| 12    | 40 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 42%               |
| 13    | 10 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 78%               |
| 14    | 5 equiv KOH                  | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 58%               |
| 15    | 2 equiv KOH                  | 5 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 58%               |
| 16    | 10 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | 40 °C  | 55%               |
| 17    | 10 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | 60 °C  | N.D. <sup>c</sup> |
| 18    | 10 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | 80 °C  | N.D. <sup>c</sup> |
| 19    | 10 equiv KOH                 | 5 equiv | 5.5 mL DMSO            | 1 mL   | 100 °C | 0% <sup>d</sup>   |
| 20    | 10 equiv KOH                 | 1 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 32%               |
| 21    | 10 equiv KOH                 | 2 equiv | 5.5 mL DMSO            | 1 mL   | rt     | 74%               |



| entry | base         | amine  | solvent     | water | heat | yield |
|-------|--------------|--|-------------|-------|------|-------|
| 22    | 10 equiv KOH | 10 equiv  | 5.5 mL DMSO | 1 mL  | rt   | 91%   |

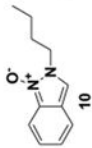
  



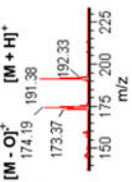
9

conditions  
24 h

$\xrightarrow{\text{H}_2\text{N}}$



10



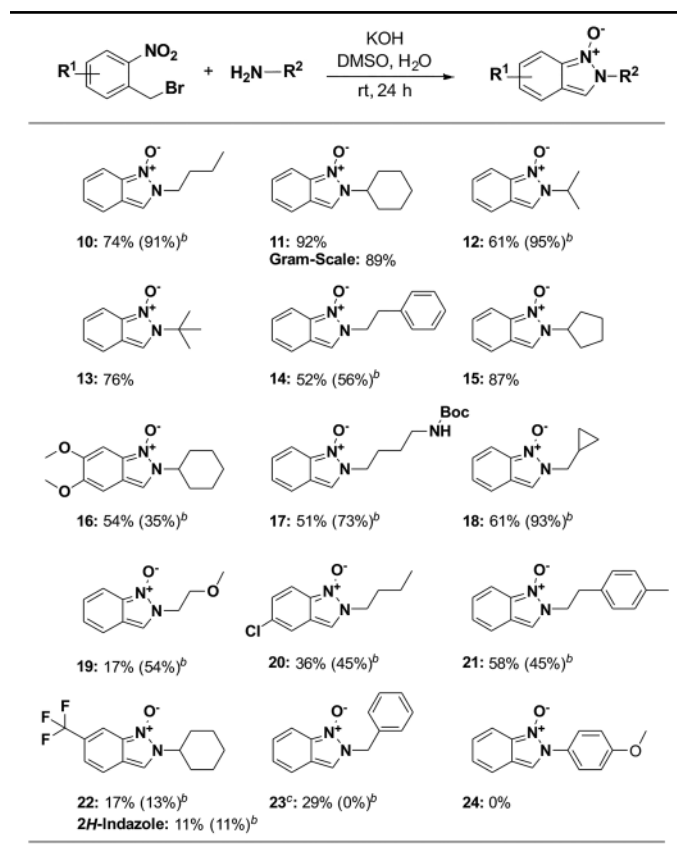
<sup>a</sup>Reaction conducted on a 0.5 mmol scale. Isolated yields are reported.

<sup>b</sup>Major product is simple *N*-alkylation.

<sup>c</sup>Complex mixture.

<sup>d</sup>16% deoxygenation product *2H*-indazole was isolated.

Table 2.

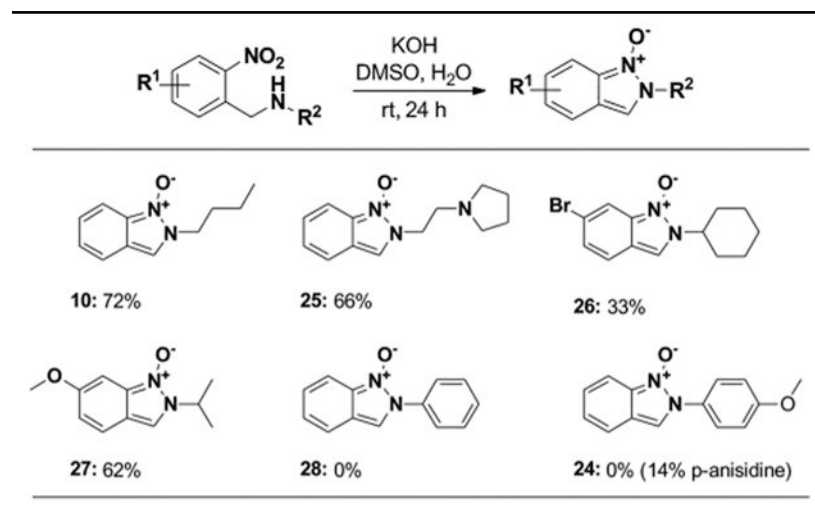
Base-Mediated 2*H*-Indazole *N*-Oxide Synthesis<sup>a</sup>

<sup>a</sup>Reaction conditions: *o*-nitrobenzyl bromide (0.5 mmol), amine (1 mmol), KOH (5 mmol), DMSO (5.5 mL), water (1 mL), room temperature, 24 h reaction time. Isolated yields are reported.

<sup>b</sup>Yield when 5 mmol of amine was used.

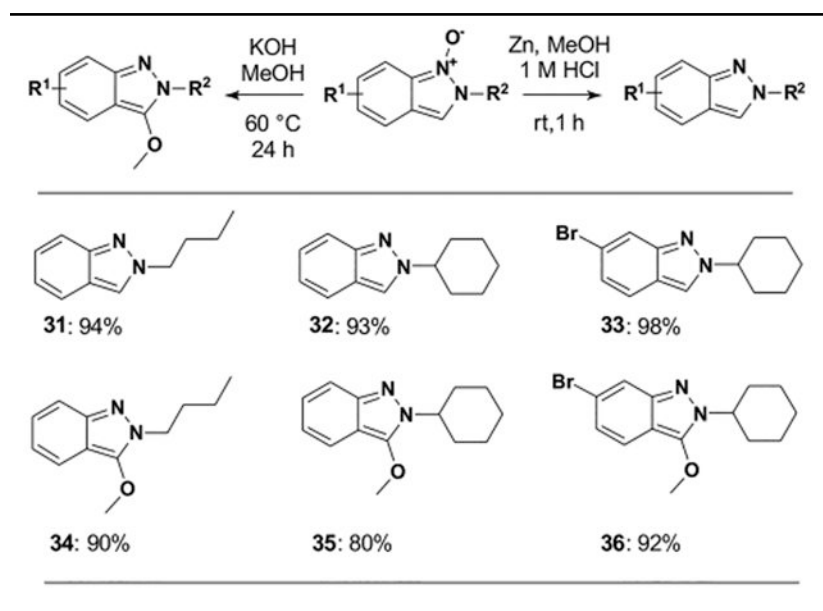
<sup>c</sup>Under photochemical conditions.

Table 3.

Base-Mediated 2*H*-Indazole *N*-Oxide Synthesis<sup>a</sup>

<sup>a</sup>Reaction conditions: *o*-nitrobenzyl amine (0.5 mmol), KOH (5 mmol), DMSO (5.5 mL), water (1 mL), room temperature, 24 h reaction time. Isolated yields are reported.

Table 4.

Derivatization of 2*H*-Indazole *N*-Oxides<sup>a</sup><sup>a</sup> Isolated yields are reported