

Supplemental material for:

**Remarkable Facilitation of Hetero-Cycloisomerizations with Water:  
Metal-Free Synthesis of Indolizines**

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## General

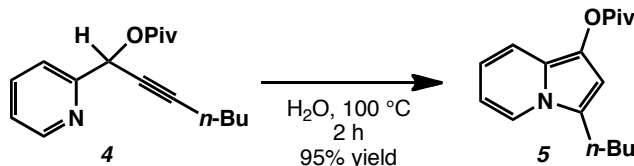
The majority of the compounds reported herein were prepared previously in our laboratory. For detailed procedures describing the synthesis of substrates as well as full characterization data for both starting materials and heterocyclic products, see C. R. Smith, E. M. Bunnelle, A. J. Rhodes, R. Sarpong, *Org. Lett.* **2007**, *9*, 1169-1171.

## Materials and Methods

Unless otherwise stated, reactions were performed in 4 mL glass vials sealed with Teflon® lined caps. The water used in all reactions was deionized and distilled using a Milli-Q® purification system. Reaction temperatures above 23 °C were controlled by an IKA® temperature modulator. Reactions were monitored by thin layer chromatography using Sorbent Technologies silica gel XHL pre-coated plates (0.25 mm), which were visualized using UV irradiation or anisaldehyde stain. SiliCycle Silica-P silica gel (particle size 40-63 µm) was used for flash chromatography. <sup>1</sup>H NMR were recorded on Bruker AVB-400, AV-500 or DRX-500 MHz spectrometers with <sup>13</sup>C operating frequencies of 100, 125 and 125 MHz, respectively, in benzene-*d*<sub>6</sub> at 23 °C.

## Representative Procedures for the Formation of Indolizines

**Scheme S1** The hetero-cycloisomerization of propargylic ester **4** to indolizine **5**.



A heterogeneous mixture of pyridine propargylic ester **4** (54.7 mg, 0.200 mmol) and distilled deionized water (200 µL) were heated at 100 °C for 2 h at which point TLC analysis indicated that the starting material had been consumed. The reaction mixture was cooled to 23 °C and the solvent removed to provide the crude product, indolizine **5** as a brown oil (52.0 mg, 95% yield). The crude product was >90% purity by <sup>1</sup>H NMR. <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.30 (d, J = 9.01 Hz, 1H), 7.04 (d, J = 7.10 Hz, 1H), 6.76 (s,

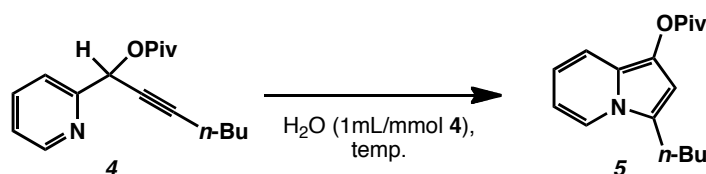
1H), 6.32 (dd, J = 8.99, 6.42 Hz, 1H), 6.06 (t, J = 6.76 Hz, 1H), 2.26 (t, J = 7.65 Hz, 2H), 1.40-1.32 (m, 2H), 1.27 (s, 9H), 1.18-1.10 (m, 2H), 0.74 (t, J = 7.34 Hz, 3H); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 175.7, 127.1, 121.3, 120.9, 120.7, 116.1, 114.0, 109.6, 105.0, 38.9, 29.0, 27.0, 25.2, 22.4, 13.6; IR (film) ν<sub>max</sub> 2958, 2931, 2871, 1749, 1278, 1120, 728 cm<sup>-1</sup>; HRMS (EI) calcd for [C<sub>17</sub>H<sub>23</sub>NO<sub>2</sub>]<sup>+</sup>: m/z 273.1729, found 273.1732.

## Additional Studies

### 1. Temperature studies

In order to maximize product formation on an acceptable time scale (~18 h) using **4**, it was important to heat the reaction mixture to 100 °C (Table S1). No product was detected when **4** was vigorously stirred with water at room temperature (entry 4). However, indolizine product **5** was detected in reactions conducted at both 50 °C and 75 °C (entries 3 and 2, respectively) although these reactions failed to reach completion after 18 h.

**Table S1** Temperature study for the hetero-cycloisomerization of **4**.

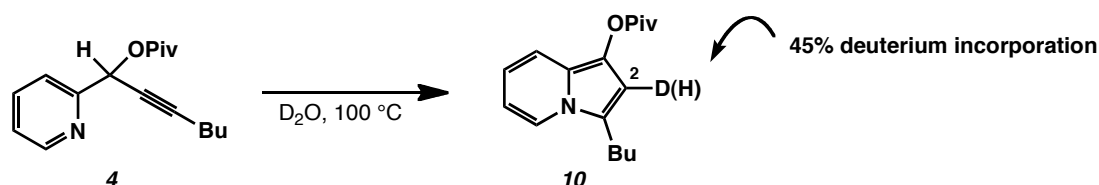


entry	temp (°C)	time (h)	result ( <b>5</b> : <b>4</b> )
1	100	2	>95:5
2	75	18	7:1
3	50	18	1:15
4	23	18	<5:95

## 2. Deuterium incorporation study

When the cycloisomerization of **4** was carried out in D<sub>2</sub>O, deuterium incorporation was observed at the 2 position of the indolizine product (see, **10** in Scheme S2). <sup>1</sup>H NMR clearly indicates 45% deuterium incorporation at C2 (see attached spectrum). In an effort to determine if deuterium incorporation occurs during the cycloisomerization of **4** or after the indolizine product had formed, indolizine **5** (Scheme S3) in D<sub>2</sub>O was heated to 100 °C for 2 h and then worked up according to the representative procedure. No deuterium incorporation was observed as judged by <sup>1</sup>H NMR, suggesting that deuterium incorporation takes place prior to indolizine formation.

**Scheme S2** Hetero-cycloisomerization conducted in D<sub>2</sub>O.



**Scheme S3** Indolizine **5** in D<sub>2</sub>O.

