

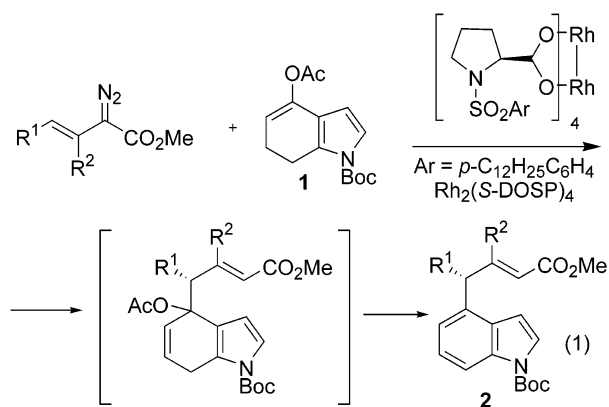
## C–H Activation as a Strategic Reaction: Enantioselective Synthesis of 4-Substituted Indoles

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The indole nucleus has long been of great interest to synthetic chemists owing to its ubiquity in a large number of biologically active alkaloids<sup>1</sup> and pharmaceutical agents.<sup>2</sup> Traditional strategies for the synthesis of functionalized variants of this “privileged” moiety have relied largely upon cyclization of an appropriately substituted precursor,<sup>3</sup> metalation followed by electrophilic trapping of the anion,<sup>4</sup> and cross-coupling reactions.<sup>5</sup> Recently, attention has been focused on the asymmetric functionalization of the indole core.<sup>6</sup> While these examples take advantage of the relatively nucleophilic 3-position of the indole nucleus to add electrophiles via a Friedel–Crafts type reaction, there are comparatively few methods for selective functionalization of the less reactive 4-position. Such methods include a thallation/iodination reaction,<sup>7</sup> directed lithiation of 3-substituted gramine,<sup>4a</sup> and cross-coupling reactions.<sup>8</sup> We herein disclose a novel strategy for the highly enantioselective synthesis of 4-substituted indoles **2** from a 4-acetoxy-6,7-dihydroindole (**1**) via a rhodium(II)-catalyzed combined C–H activation/Cope rearrangement–elimination reaction (eq 1).



The development of catalytic methods for C–H activation is of considerable current interest.<sup>9,10</sup> The combined C–H activation/Cope rearrangement is an impressive example because it proceeds with excellent stereocontrol.<sup>11</sup> The rhodium prolinato catalyst, Rh<sub>2</sub>-(S-DOSP)<sub>4</sub>, is very effective in this chemistry, routinely resulting in very high enantioselectivity. 1,2-Dihydronaphthalenes have been versatile substrates for the C–H activation, leading to the synthesis of formal Michael addition products,<sup>11b</sup> naphthalene derivatives,<sup>11b</sup> double C–H functionalization,<sup>11f</sup> and the synthesis of the natural products, (+)-erogorgiaene,<sup>11e</sup> (–)-colombiasin A,<sup>11g</sup> and (–)-elisapterosin B.<sup>11g</sup> This current study demonstrates that dihydroindoles are also effective substrates for this unusual chemistry.

The Rh<sub>2</sub>(S-DOSP)<sub>4</sub>-catalyzed reaction with 4-acetoxy-6,7-dihydroindole (**1**) is applicable to a range of terminally substituted vinyl diazoacetates **3** as illustrated in Table 1. The standard reaction conditions used 1 mol % of catalyst and 2,2-dimethylbutane (DMB) as solvent. Electron-rich and electron-deficient aryl substituents are compatible with this chemistry (entries 1–5), as well as an

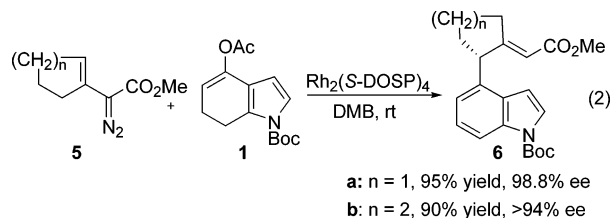
Table 1. Synthesis of 4-Substituted Indoles

entry	compound	R	yield, %	ee, %
1	a		65	98.5
2	b		52	98.0
3	c		53	98.7
4	d		45	98.0
5	e		56	98.0
6	f		64	97.7
7	g		56	99.0
8	h		61	98.6

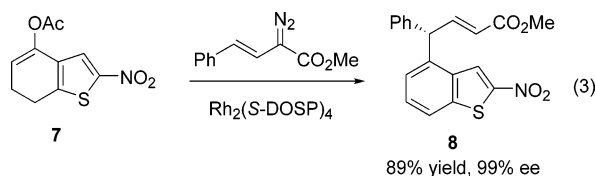
indolylvinyl diazoacetate (entry 6). A dienyldiazoacetate is equally effective (entry 7), and even an alkyl substituent can be accommodated (entry 8). In all instances the new stereogenic centers in the 4-substituted indoles **4** are formed in >97% ee. The absolute configuration of the bromophenyl derivative **4c** (entry 3) was determined by X-ray crystallography of the reduced analogue,<sup>12</sup> while the others are tentatively assigned by assuming an analogous enantioinduction. The yields in these reactions ranged from 45 to 65% because there was some competing reaction initiated at the pyrrole ring.<sup>13</sup>

4-Substituted indoles can also be formed in the reaction of cyclic vinyl diazoacetates **5** as illustrated in eq 2. In these cases, competing reactions on the pyrrole ring were not observed and the 4-substituted

indoles **6** were formed in 90–95% yields. Once again, the enantioselectivities in these reactions were very high.



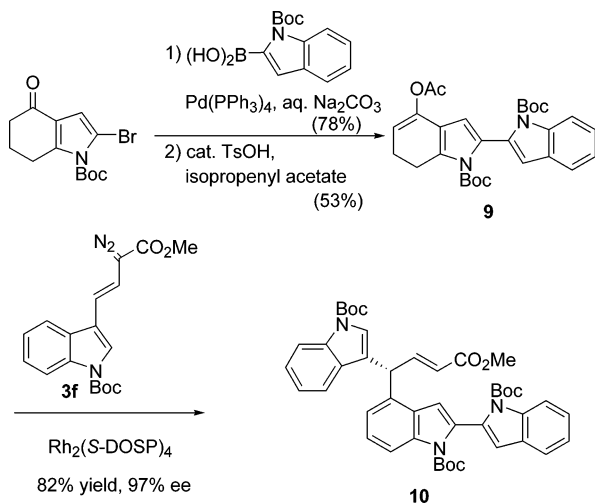
The C–H activation can be extended to a 4-substituted 6,7-dihydrobenzothiophene **7** as illustrated in eq 3. Thiophenes are common reaction partners with rhodium carbenoids,<sup>14</sup> but in this case the C–H activation is the dominant reaction, generating the 4-substituted benzothiophene **8** in 89% yield and 99% ee.



The C–H activation strategy to prepare 4-substituted indoles compliments some of the more conventional methods for indole synthesis as illustrated in Scheme 1. Palladium-catalyzed coupling<sup>15</sup> followed by acylation<sup>16</sup> readily forms the 2-indole derivative **9**.  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed reaction of **9** with the 3-indolylvinyl diazoacetate **3f** generates the trisindole derivative **10** in 82% yield and 97% ee. In **10**, one indole is 2-substituted, another is 3-substituted, and the third is 2,4-disubstituted. The successful outcome of this reaction underscores the facility of the combined C–H activation/Cope rearrangement because indoles have often been shown to be reactive partners in carbenoid chemistry.<sup>17</sup>

In conclusion, we have reported a novel methodology for the asymmetric synthesis of 4-substituted and 2,4-disubstituted indoles

#### Scheme 1



from the  $\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed decomposition of vinyl diazoacetates in the presence of a 4-acetoxy-6,7-dihydroindole precursor. The reaction proceeds via a combined C–H activation/Cope rearrangement–elimination mechanism, resulting in good yields and very high asymmetric induction. The further application of this chemistry to the synthesis of novel pharmaceutical targets is currently in progress.

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**Supporting Information Available:** Full experimental data for the compounds described in this paper; X-ray crystallographic files in CIF format.

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