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Synthesis of spirocyclopentene-indolines by intramolecular alkylidine insertion reactions

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ABSTRACT

Intramolecular 1,5 CH insertion of unstabilized carbenes into the tertiary carbon of a substituted indoline generates spiro[cyclopent[2]ene-1,2′-indolines] in good yields and excellent enantioselectivities.

Indolines containing chiral quaternary carbons are common architectures in a number of natural products and biologically active compounds. For instance, this chemical motif can be found in natural products such as the antiviral pseudoindoxyl alkaloid **1**[1] or in substances such as the peptidomimetic inhibitor of Hepatitis C **2** (Fig. 1).[2]

Traditionally, these compounds have been synthesized using metal-catalyzed processes,[3] radical-mediated reactions,[1] or direct alkylation strategies.[2] However, many of these methods present limitations, such as the lack of stereocontrol of the newly formed quaternary carbon, and/or the use of toxic reagents.[4] Recently, Hayes and co-workers have reported an innovative approach toward the synthesis of N-bearing quaternary stereocenter structures that resolves the issues of stereocontrol and scalability.[5] The strategy relies on the use of unstabilized carbene intermediates, a field pioneered by Ohira,[6] Gilbert,[7] and Taber,[8] and has been successfully applied to the synthesis of a number of substances such as pyrrolidine **3** (Fig. 2).

In order to expand the scope of this methodology, we decided to investigate the viability of this approach toward the synthesis of chiral spirocycloindolines such as **4**. In an analogous fashion to Hayes' strategy, a 1,5 CH insertion reaction of an unstabilized alkylidine carbene was viewed as the key step in the elaboration of these heterocyclic structures (Scheme 1).

The study started with the synthesis of cyclization precursors **5** and **6**. Thus, oxidation of the enantiomerically pure alcohol **7**[9] to the corresponding aldehyde using Dess–Martin periodinane followed by treatment with acetylmethylene triphenylphosphorane gave enone **8** in 73% overall yield. Catalytic hydrogenation (Pd/C, H_2, EtOAc) of **8** provided ketone **5** in 99% yield. Subsequent Wittig olefination of **5** was carried out using NaHMDS as the base and gave vinyl chloride **6** in 60% yield as a 1:1 mixture of *E*:*Z* isomers.[10] With these precursors in hand, we were in a position to test the key 1,5 CH insertion reaction. Gratifyingly, we found that treatment of chloride derivative **6** with KHMDS in Et_2O at room temperature for 5 h provided spirocycloindoline **4** in 64% yield (Scheme 2).[11] Alternatively, **4** was also obtained in 60% yield when the cyclization was performed with the ketone precursor **5** under Ohira conditions and using THF as the solvent.[6b] The stereochemical integrity of the spirocyclic structure **4** was confirmed by synthesizing a racemic sample of this compound and resolving the mixture by chiral HPLC. Subsequent injection of the indoline **4**[12] showed that its ee was greater than 95%.

The spiroindoline **4** could be transformed into the ring expanded product **10** via oxidative cleavage of **4**, followed by intramolecular aldol reaction of keto aldehyde **9** and subsequent

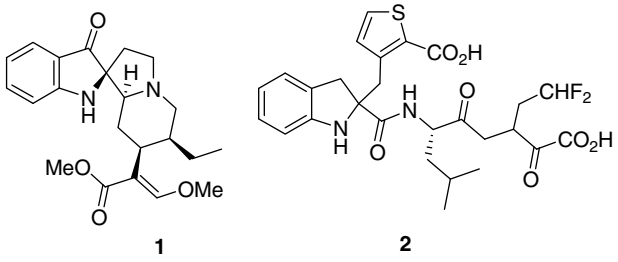

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Figure 1.

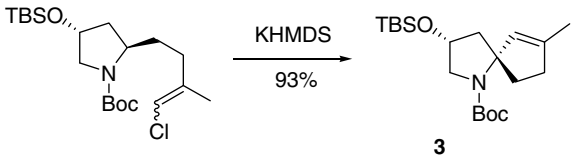

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Figure 2. Hayes' synthesis of enantiomerically enriched pyrrolidines.

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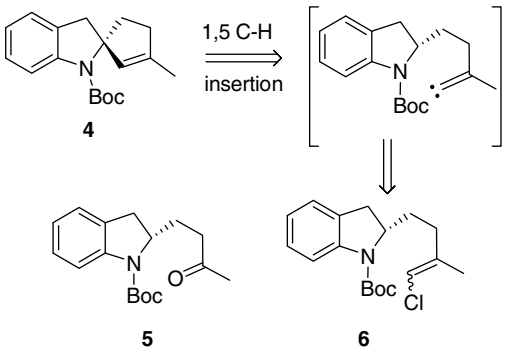
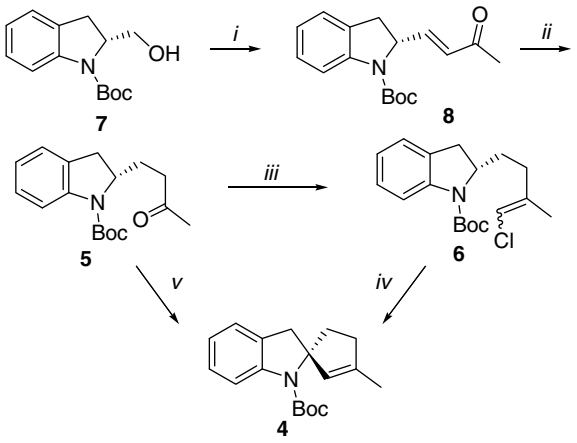


Scheme 1. Proposed alkylidene 1,5 C–H insertion reaction.

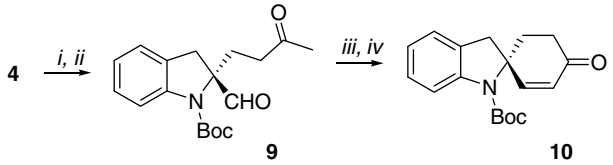


Scheme 2. Reagents and conditions: (i) (a) Dess–Martin periodinane, DCM, $NaHCO_3$; (b) acetylmethylene triphenylphosphorane, 73% from **7**; (ii) H_2, Pd/C, 99%; (iii) (chloromethyl) triphenylphosphonium chloride, NaHMDS, 60%; (iv) KHMDS, rt, Et_2O, 64%; (v) BuLi, $TMSCHN_2$, THF, −78 °C to rt, 60%.

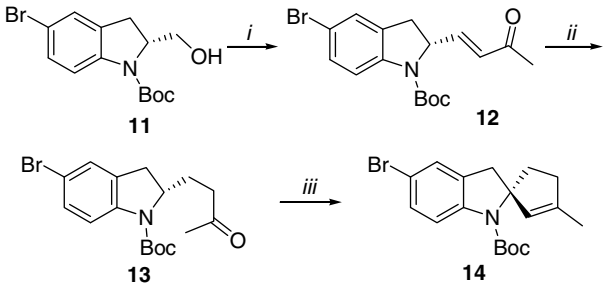
dehydration.[5a] Thus, this method provides a versatile strategy toward the synthesis of enantiomerically enriched indolines that contain quaternary carbons (Scheme 3).

In order to evaluate if the methodology could be used for the synthesis of more functionalized spirocycloindolines, we applied this route to the bromo indoline **11**. Thus, oxidation of alcohol **11**[13] with Dess–Martin periodinane, followed by enone formation and Pd-catalyzed hydrogenation provided precursor **13** in good overall yield. We were pleased to find that when ketone **13** was treated under Ohira cyclization conditions,[6b] it gave the brominated spirocycloindoline **14** in 61% yield (see Scheme 4).

Due to these encouraging results we decided to investigate the 1,5 CH insertion reaction with precursors bearing an alkyl group on the indoline side chain. We first started this study by synthesizing vinyl chloride derivatives **16a** and **16b**, which contain a methyl side chain with different relative stereochemistry. The required cyclization precursors were prepared via 1,4-addition reaction of



Scheme 3. Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$ (3%), NMO, acetone/H_2O (10:1), 91%; (ii) $NaIO_4$, THF/H_2O (2:1), 83%; (iii) EtONa, EtOH, 85%; (iv) MsCl, Et_3N, DCM, 70%.

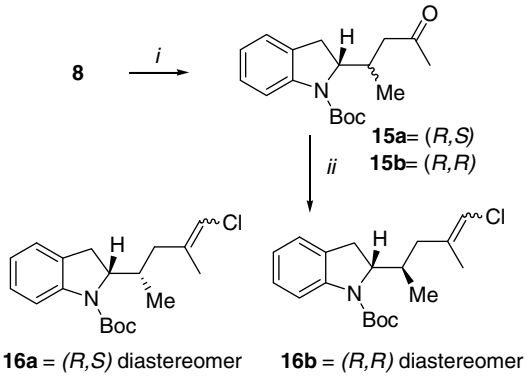


Scheme 4. Reagents and conditions: (i) (a) Dess–Martin periodinane, DCM, $NaHCO_3$; (b) acetylmethylene triphenylphosphorane, 65% from **7**; (ii) H_2, Pd/C, 70%; (iii) BuLi, $TMSCHN_2$, −78 °C to rt, 61%.

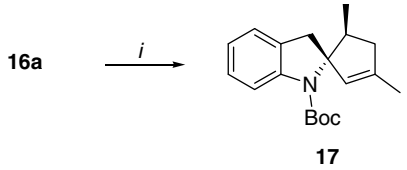
methyl cuprate and enone **8**.[14] This reaction gave a diastereomeric mixture of ketones **15a** and **15b** (in a ratio of 1:7) that were separated by column chromatography. Each diastereomer was treated with (chloromethyl) triphenylphosphonium chloride in the presence of NaHMDS to give the desired compounds **16a** and **16b**, respectively (Scheme 5).[15]

With both precursors in hand the cyclization was attempted under the previous reaction conditions (i.e., KHMDS, Et_2O, rt, 5 h). Aqueous work-up followed by analysis of the crude ^1H NMR of both reaction mixtures, showed that only diastereomer **16a** had proceeded in the expected cyclization mode. Flash chromatography of the crude reaction mixture of **16a** provided the spirocyclic compound **17** in 63% yield as a single diastereomer (Scheme 6).[15] In contrast to **16a**, the cyclization of **16b** resulted in a mixture of unidentified products.[16]

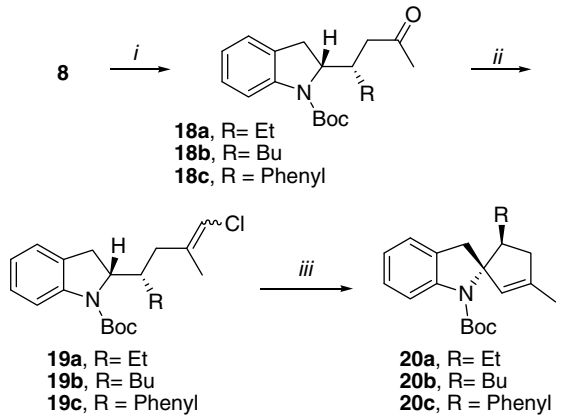
With this limitation in mind, we decided to investigate the scope of this 1,5 CH insertion reaction in other substituted indoline precursors. The synthesis of these compounds was carried out by addition of different alkyl groups into enone **8**. The corresponding (*R,S*) isomers **18**(**a**–**c**) were separated by column chromatography and converted into the vinyl chloride precursors **19(a–c)** (Scheme 7).[17] The results of the cyclization experiments with these precursors are summarized in Table 1.



Scheme 5. Reagents and conditions: (i) MeLi, CuBr, 85%; (ii) (chloromethyl) triphenylphosphonium chloride, NaHMDS (71–83%).



Scheme 6. Reagents and conditions: (i) KHMDS, rt, Et_2O, 63%.



Scheme 7. Reagents and conditions: (i) RLi, CuBr (67–82%); (ii) (chloromethyl) triphenylphosphonium chloride, NaHMDS (55–65%); (iii) KHMDS, rt, Et_2O.

Table 1
Cyclization of precursors **19a–c**

Entry	Precursor	Conditions	Product	Yield[a,b] (%)
1	**19a**	KHMDS, 25 °C, 5 h	**20a**	70
2	**19b**	KHMDS, 25 °C, 5 h	**20b**	68
3	**19c**	KHMDS, 25 °C, 5 h	**20c**	51[c]

[a] Isolated yield after column chromatography over silica gel.
[b] Reactions carried out using Et_2O as the solvent.
[c] Isolated yield after column chromatography over basic alumina.

In these experiments, we observed that when precursors **19**(**a**–**c**) were treated under the standard cyclization conditions (KHMDS, Et_2O, rt, 5 h) the reactions proceeded in good yields with both the alkyl and phenyl substituents (entries 1–3). The resulting spirocycloindoline products from these reactions **20**(**a**–**c**) were obtained as single diastereomers and were purified by column chromatography (Table 1).

In summary, we have expanded the use of 1,5 CH carbene insertion reactions to the synthesis of chiral spirocyloindolines. The methodology provides a new entry into functionalized chiral indoline structures, although the cyclization is dependent on the relative stereochemistry of the precursors.

Acknowledgments

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9. The compound was prepared according to the synthetic procedure described in: Lee, S.; Yi, K. Y.; Kim, S.-K.; Suh, J.; Kim, N. J.; Yoo, S.-e.; Lee, B. H.; Seo, H. W.; Kim, S.-O.; Lim, H. *Eur. J. Med. Chem.* **2003**, *38*, 459.
10. Hayes and co-workers have shown that there is little difference in reactivity between the *E* and *Z* isomers when a related substrate was subjected to the spirocyclization conditions. See: Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett* **2004**, 1443.
11. *Typical procedure for the 1,5 CH insertion reaction:* To a stirred solution of **6** (1.15 g, 3.57 mmol) in Et_2O (30 mL) was added a 0.5 M solution of KHMDS in toluene (14.3 mL, 7.15 mmol). The reaction mixture was stirred for 5 h at room temperature and then it was washed with citric acid and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (gradient of elution 0–3% EtOAc in hexanes) to give 0.65 g (64%) of spirocycloindoline **4**. $[\alpha]_D$ +65.9 (*c* 0.75, CH_2Cl_2). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.68 (d, J = 8.2 Hz, 1H), 7.13–7.09 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 3.06–3.04 (m, 2H), 2.40–2.25 (m, 3H), 2.06–2.02 (m, 1H), 1.73 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 151.8 (C), 142.8 (C), 139.1 (C), 129.5 (CH), 128.6 (C), 127.0 (CH), 124.3 (CH), 121.9 (CH), 114.3 (CH), 79.6 (C), 78.2 (C), 43.1 (CH_2), 37.4 (CH_2), 34.8 (CH_2), 27.9 (CH_3), 16.3 (CH_3).
12. Experiment was carried out with the chiral indoline **4** derived from ketone **5**. HPLC was performed using a chiral AD column and 1% IPA in hexanes as eluant.
13. The compound was prepared according to the synthetic procedure described in: Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Tetrahedron* **2005**, *61*, 2075.
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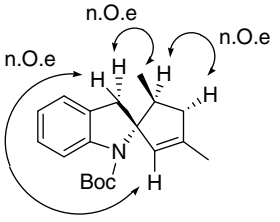
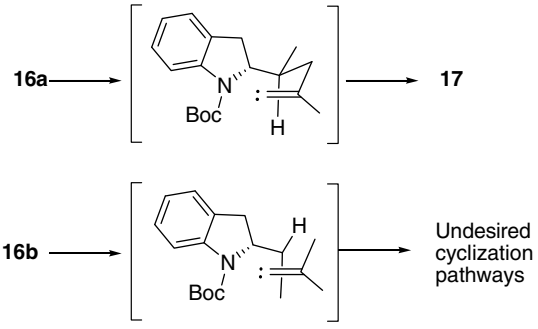
15. The relative stereochemistry of **15a,b** and **16a,b** was assigned based on NOE irradiation experiments on the cyclization product **17**. Thus, in a NOESY experiment we observed the following strong NOE signals, which allowed us to assign the relative stereochemistry of these compounds.



16. The different outcome of these two reactions can be rationalized in terms of the relative energy of their transition states. Thus, the transition state required for spirocyclization is lower in energy for **16a** than for **16b**. This difference in energy can be attributed to the unfavorable steric interaction between the Boc and methyl groups for the transition state of **16b**, and leads this precursor to undergo alternative cyclization pathways.



17. The (*R*,*S*) to (*R*,*R*) ratio of diastereomers for the 1,4-addition reactions were found to be dependent on the alkyl group. Thus, the observed (*R*,*S*) to (*R*,*R*) ratios of products were **18a** (1:3.3), **18b** (1:2.7), and **18c** (1–18). The stereochemistry of these products was assigned based on the ability of substrates **19a–c** (derived from **18a–c**) to undergo the 1,5 CH insertion reaction.