Highly enantioselective intramolecular aza-spiroannulation onto indoles using chiral rhodium catalysis: asymmetric entry to the spiro-β-lactam core of chartellines†

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A versatile, highly enantiocontrolled entry to the spiro-β-lactam core of chartellines has been developed by expanding the scope of oxidative nitrogen atom transfer methodology based on chiral Rh-nitrenoid species.

Bryozoans living in the marine environment inspire the synthetic community by presenting secondary metabolites with exquisitely complicated architectures. Chartellines (**1a–c**, Fig. 1),[1] the small group of unique, indole–imidazole alkaloids isolated from *Chartella papyracea* have received considerable attention as targets for total synthesis,[2–5] regardless of there being no reports to suggest their pharmaceutical applicability. Synthetic routes to the chartellines have yet to be achieved, except for the insightful biomimetic approach conducted by Baran and Shenvi, which culminated in the first total synthesis of racemic chartelline C.[4b] Exploring the synthesis of the chartellines should offer ample opportunity for the discovery and development of new chemistry.

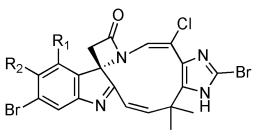
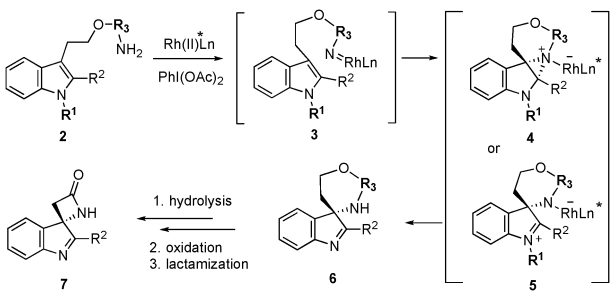


Fig. 1 The structure of chartellines.



Scheme 1 The plan for enantioselective synthesis of the spiro-β-lactam.

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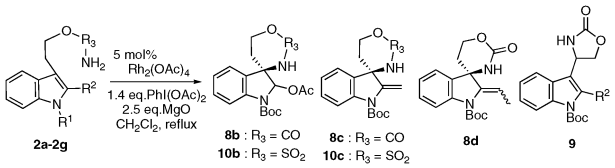
Table 1 Spirocyclization of indolyl carbamates with $Rh_2(OAc)_4$



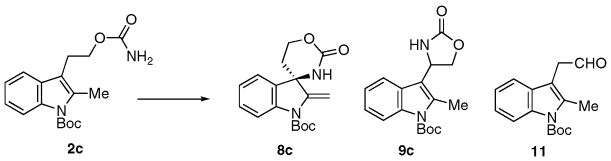
Entry		Substrate R_1	R_2	R_3	Time/h	Yield[a] Spiro-cyclization	C–H insertion
1	**2a**	H	H	CO	2	Complex mixtures	
2	**2b**	Boc	H	CO	10	**8b** (61%)	**9b** (26%)
3	**2c**	Boc	Me	CO	10	**8c** (91%)	ND
4	**2d**	Boc	Et	CO	18	**8d** (85%)[b]	**9d** (10%)
5	**2e**	Boc		CO	24	ND	**9e** (47%)
6	**2f**	Boc		CO	12	ND	ND
7[c]	**2g**	Boc	H	SO_2	2	**10b** (24%)	ND
8[c]	**2h**	Boc	Me	SO_2	2	**10c** (44%)	ND

[a] Yield of isolated product. [b] *E* or *Z* ratio was 1 : 0.9. [c] The reaction was conducted with 2 mol% $Rh_2(OAc)_4$, 1.1 equiv. $PhI(OAc)_2$, and 2.3 equiv. MgO at rt.

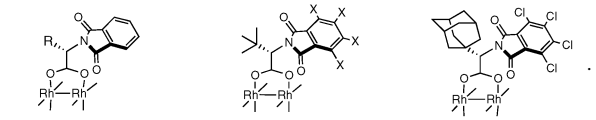
Our synthetic conception, centering on the asymmetric generation of the nitrogen-substituted spirocenter, is depicted in Scheme 1. In light of the continued development of Du Bois's C–H amidation chemistry,[6] we envisioned that a metal nitrenoid **3** tethered with a 3-indolylethyl pendant generated from **2** would produce a spirocycle **6** *via* aziridine **4** or betain **5**.[7–9] The subsequent sequence including hydrolytic detachment of the tether moiety, oxidation, and lactamization would provide the chiral spiro-β-lactam **7**. For this approach to be successful, the discovery of a modular combination of R_1, R_2, tethering R_3 groups, and a chiral ligand that realises a practical level of asymmetric induction as well as an efficient merger with the right-half portion of chartellines is required. We describe herein the first enantiocontrolled entry to the spiro-β-lactam core of chartellines, featuring a highly enantioselective, oxidative intramolecular nitrogen atom transfer to an indole nucleus by chiral rhodium catalysis.

First, we explored the possibilities of catalytic spirocyclization using a panel of 3-indolylethyl carbamates with $Rh_2(OAc)_4$ (Table 1). Although the reaction of indolylethyl carbamate **2a**[10] under Du Bois/Espino conditions[11] using 5 mol% $Rh_2(OAc)_4$ in the presence of $PhI(OAc)_2$ and MgO resulted in complex mixtures due to oxidative decomposition of the indole moiety, the *N*-Boc-protected indole substrate **2b** gave

Table 2 Enantioselective spirocyclization



Entry	Catalyst (5 mol%)[a]	Time/h	Yield[b] (ee)[c] 8c	9c	11[e]
1	**12**	30	93 (10)	ND	ND
2	**13**	22	34 (67)	46	3
3	**14**	19	62 (90)	19	3
4	**15**	27	36 (94)	ND	10
5	**16**	16	35 (94)	ND	11
6[d]	**16**	48	53 (93)	ND	20

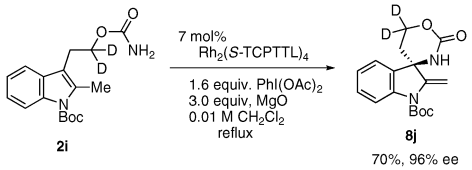


[a] Reactions were conducted using 5 mol% catalyst in the presence of 1.4 equiv. $PhI(OAc)_2$, 2.5 equiv. MgO, in boiling 0.1 M CH_2Cl_2. [b] Isolated yield. [c] Enantiomeric excess was determined after **8c** was transformed to the di-Boc derivative, followed by chiral HPLC analysis using a Chiralpak AD-H column. [d] The reaction was run in 0.01 M CH_2Cl_2. [e] Yields were determined by ^1H NMR integration of the crude mixture.

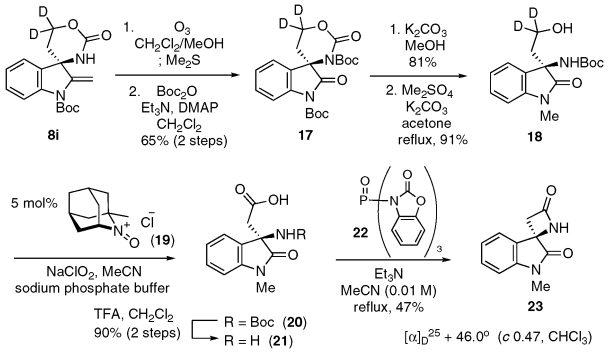
the desired spirocyclization product **8b** in 61% yield along with a considerable amount of the C–H insertion product **9b** in 26% yield (entries 1, 2). Importantly, when the 2-methylindolyl substrate **2c** was employed, the reaction gave the product **8c** exclusively in 91% yield (entry 3). In the case of the 2-ethylindolyl substrate **2d**, similar spirocyclized products were produced in a regioisomeric mixture (*E* or *Z* = 1.0/0.9) in 85% yield accompanied by the C–H insertion product **9d** in 10% yield. Unfortunately, the reaction of the 2-alkynylindolyl carbamate **2e** did not produce the spirocyclization product but gave only the C–H insertion product **9e** in moderate yield (entry 5). The reaction of 2-alkenylindolyl carbamate **2f** gave intractable mixtures of unidentifiable products (entry 6). These results highlighted the role of the 2-alkyl group in donating electron density to the indole moiety to overcome the competing C–H insertion at the benzylic position. We next examined the catalytic spirocyclization of sulfamate esters **2g** and **2h**, both of which resulted in low yields due to accompanying decomposition.

It is interesting to point out that the reaction of (*N*-Boc-2-methylindol-3-yl)acetamide gave *N*-(*N*-Boc-2-methylindol-3-ylmethyl)acetamide[10] quantitatively.

Screening of a chiral ligand was conducted concurrently with the aforementioned studies (Table 2). Treatment of carbamate **2c** with 5 mol% Rh_2(*S*-PTPA)$_4$ **12**[12] in the presence of $PhI(OAc)_2$ and MgO gave **8c** in 93% yield but in 10% ee (Table 2, entry 1). Use of 5 mol% Rh_2(*S*-PTTL)$_4$ **13**[13] gave **8c** with 67% ee, but the chemical yield was decreased to 34%, and the C–H insertion product **9c** was produced in 46% yield (entry 2). It was found that Rh_2(*S*-TFPTTL)$_4$ **14** and Rh_2(*S*-TCPTTL)$_4$ **16**[14] afforded high levels of enantioselectivity



Scheme 2 Optimization of the enantioselective spirocyclization.



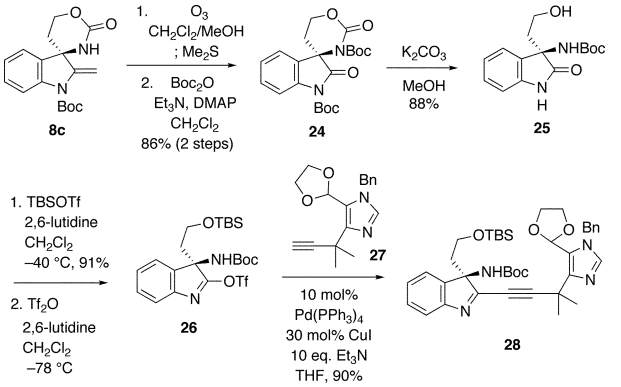
Scheme 3 Synthesis of chiral spiro-β-lactam **23**.

reaching to 90% ee and 94% ee, respectively, although chemical yields were low (entries 3, 4).

The use of Rh_2(*S*-TCPTAD)$_4$ **15**[15] resulted in similar yields of products and enantioselectivity as with Rh_2(*S*-TCPTTL)$_4$ (entry 5). An important clue was obtained from the high dilution reaction (0.01 M) using **16**: the yield was improved to 53% accompanied by 20% yield of aldehyde **11** as a by-product, indicating possible hydrogen abstraction at the α-position of the carbamoyloxy group in **2c**.[16] To suppress this non productive pathway to 11,[17] we synthesized the deuterated substrate **2i**.[10] The reaction of **2i** with 7 mol% Rh_2(*S*-TCPTTL)$_4$ afforded **8i** in 70% yield with complete suppression of the formation of **11** (Scheme 2). The absolute configuration of **8i** was determined to be *R* by its conversion to the known compound AG-041R[18] and the subsequent comparison of its optical rotation with the reported value.[19]

Having identified appropriate conditions for the highly enantioselective aza-spiroannulation onto the indole ring, we attempted transformation of the carbamate **8i** into the spiro-β-lactam of the chartellines **23**, which the Nishikawa/Isobe team had synthesized in the racemic form[3a] (Scheme 3). The exo-methylene moiety of **8i** was cleaved *via* ozonolysis, and *N*-Boc protection led to the bis-Boc carbamate **17**. **17** was treated with K_2CO_3 in methanol to afford the β-amino alcohol, which was *N*-methylated with Me_2SO_4 to give **18**. Oxidation of the primary alcohol **18** to the corresponding carboxylic acid **20** was achieved in a one-pot manner employing a catalytic ammount of 1-MeAZADO$^+$Cl$^-$ (**19**) in the presence of $NaClO_2$ in MeCN and sodium phosphate buffer.[20] The resulting product **20** was deprotected to give the β-amino acid **21**. Upon treatment with tris(2-oxo-3-benzoxazolinyl)phosphine oxide (**22**),[21] **21** furnished the chiral spiro-β-lactam **23** in 47% yield.

The versatility of the spiro-carbamate **8** was confirmed by its conversion to the indolenine–imidazole merger **28** *via* an efficient Sonogashira coupling (Scheme 4). Thus, the alcohol **25**, prepared from **8c** *via* the same sequence as depicted in Scheme 3, was protected as the TBS ether, and the lactam



Scheme 4 Synthesis of indolenine–imidazole merger **28**.

moiety was triflated to give **26**. Upon treatment with 10 mol% $Pd(PPh_3)_4$ and 30 mol% CuI in the presence of 10 equiv of Et_3N in THF, the coupling reaction between **26** and the alkyne **27** proceeded smoothly to furnish the indolenine **28** in 90% yield.

In summary, we have described a highly enantioselective nitrogen atom transfer reaction of 2-(*N*-Boc-2-alkylindol-3-yl)-ethyl carbamates based on rhodium nitrenoid chemistry that provides a reliable platform for enantiocontrolled synthesis of the spiro-β-lactam core of chartellines. Several novel aspects disclosed in this study will stimulate further development of metal nitrenoid chemisty. Efforts toward the synthesis of chartelline alkaloids are now ongoing.

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