Communication

Enantioselective Synthesis of Indole-Annulated Medium-Sized Rings

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Enantioselective Synthesis of Indole-Annulated Medium-Sized Rings

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Supporting Information Placeholder

ABSTRACT: Asymmetric synthesis of indole-annulated medium-sized-ring compounds is developed through an Iridium-catalyzed allylic dearomatization/retro-Mannich/hydrolysis cascade reaction. The reaction features mild conditions and a broad substrate scope. Under the optimal conditions, various seven-, eight-, or nine-membered-ring compounds can be afforded in good to excellent yields and excellent enantioselectivity. The proposed mechanism is supported by capturing the dearomatized intermediate through *in situ* reduction.

Cyclic compounds hold a vital position in modern organic chemistry due to their ubiquity in nature and serve as one class of the most important molecules in both academia and industry. Thus the synthesis of cyclic compounds is extremely significant in organic chemistry. To date, there are a lot of efficient methods available for the synthesis of macrocyclic compounds,[1-5] such as Corey–Nicolaou macrolactonization,[2] Keck macrolactonization,[3] Yamaguchi macrolactonization,[4] and ring-closing metathesis reaction.[5] However, the synthesis of medium-sized rings still remains a challenge because of their unfavorable transannular interactions and entropic factors.[6] Up to now, there are few general methods to synthesize medium-sized rings.[7] Furthermore, the synthesis of medium-sized-ring compounds in an enantioselective manner by catalytic methods is much more challenging. In this regard, there are only limited examples, which mainly focus on the formation of seven-membered rings.[8] Thus, the development of novel strategies for efficient catalytic asymmetric construction of medium-sized-ring compounds is still in great demand.

Indole-annulated medium-sized rings are the constituents of a variety of natural products and pharmaceutical agents (Figure 1),[9] such as ibogamine,[9a] catharanthine,[9b] trigonoliimine,[9c] and conoliferine.[9d] Therefore it is of great significance for the construction of indole-annulated medium-sized-ring skeletons. In recent years, although a few methods for the synthesis of such racemic molecular skeletons have been reported,[10] their asymmetric synthesis is still unknown. Herein we report an efficient catalytic asymmetric synthesis of indole-annulated medium-sized-ring compounds in good to excellent yields and excellent enantioselectivity.

During recent studies on asymmetric dearomatization reaction of indoles,[11,12] we found that spiroindolenine, a dearomatized indole product that bears a methanamine linker is highly reactive and can undergo re-aromatization smoothly.[12d,12p] Based on these findings, we envisioned that indole-annulated seven-membered-ring compound **2a** could be synthesized by an Ir-catalyzed allylic dearomatization/retro-Mannich reaction/hydrolysis cascade reaction from readily available tetrahydro-γ-carboline tethered allylic carbonate **1** (Scheme 1). The nucleophilic attack of the indole C3 position to the π-allyliridium moiety firstly delivers the bridged intermediate **II**. Subsequently, a ring-opening retro-Mannich reaction affords the ring-expansion intermediate **III**, from which the final hydrolysis of the iminium moiety gives the desired product **2a**. The release of ring strain and the re-aromatization of the indole ring serve as the main driving force for the ring-expansion step (**II** to **III**).

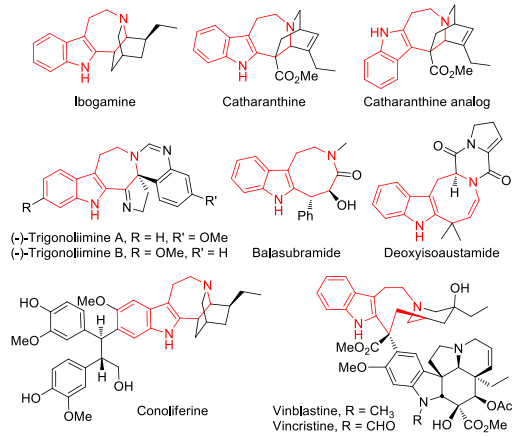
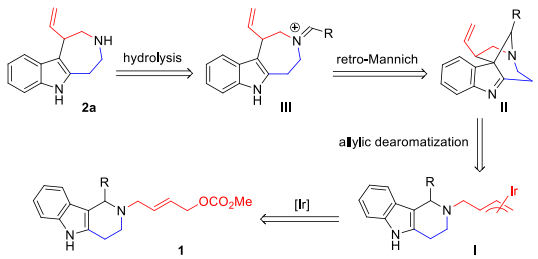


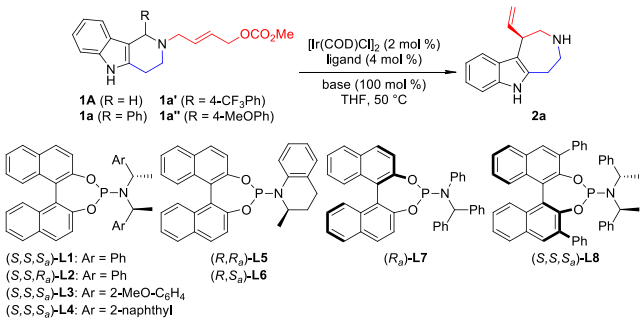
Figure 1. Selected indole-annulated medium-sized-ring natural products



Scheme 1. A proposed strategy for the synthesis of indole-annulated medium-sized-ring compounds

At the outset, we examined the reaction with substrate **1A** (R = H). In the presence of a well-studied Ir-catalyst,[13,14] generated from 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of Feringa ligand (**L1**), and 1.0 equiv of Cs_2CO_3, the reaction of **1A** in THF at 50 °C for 10 hours gave the indole-annulated seven-membered-ring product **2a** in 39% yield and 95% ee (entry 1, Table 1). Interestingly, it was failed to improve the efficiency of the retro-Mannich and/or hydrolysis step by adding various acids (See the Supporting Information for details). Next, a phenyl group was introduced to the tether of **1A**, which would stabilize the intermediate **III** (R = Ph) and promote the retro-Mannich and/or hydrolysis step. Indeed, we were pleased to find that the reaction of **1a** bearing a phenyl group could give product **2a** in 72% yield and 92% ee (entry 2). Encouraged by these preliminary results, various chiral phosphoramidite ligands were investigated. The employment of ligand **L2**, the diastereoisomer of **L1**, resulted in a low yield with 90% ee after 50 hours (entry 3). To our delight, Alexakis ligand **L3** could give promising results (81% yield, 95% ee, entry 4). The reactions with **L4**, **L5** or **L7** afforded the desired product in a slightly lower yield and enantioselectivity (entries 5, 6, 8). When ligand **L6**, the diastereoisomer of **L5**, was used, the yield was reduced to 36% with moderate enantioselectivity (entry 7). With the 3,3'-phenyl substituted ligand **L8**, the starting material **1a** remained almost unchanged and only trace amount of product was observed (entry 9). Next, a survey of various bases revealed that DBU was the optimal base (entries 10-15). Stronger bases gave better results while only a small amount of product was obtained with weak bases (Li_2CO_3, Et_3N) or no base. The electronic nature of the tethered aryl group was also examined. Either a CF_3 or OMe substituent at the para position (**1a'** or **1a''**) did not lead to better outcomes (entry 16-17). As a result, the optimal reaction conditions was established as described in entry 11 for simple phenyl substituted substrate **1a**.

Table 1. Optimization of the reaction conditions[a]

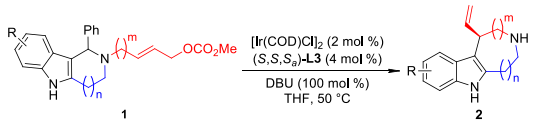


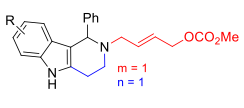
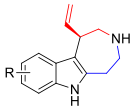
entry	substrate	ligand	base	time (h)	yield (%)[b]	ee (%)[c]
1	**1A**	**L1**	Cs_2CO_3	10	39	95
2	**1a**	**L1**	Cs_2CO_3	3	72	92
3	**1a**	**L2**	Cs_2CO_3	50	14	-90
4	**1a**	**L3**	Cs_2CO_3	1	81	95
5	**1a**	**L4**	Cs_2CO_3	3	77	91
6	**1a**	**L5**	Cs_2CO_3	3	77	90
7	**1a**	**L6**	Cs_2CO_3	38	36	-89
8	**1a**	**L7**	Cs_2CO_3	11	70	84
9	**1a**	**L8**	Cs_2CO_3	46	<5	---
10	**1a**	**L3**	K_3PO_4	3	78	96
11	**1a**	**L3**	DBU	1	86	98
12	**1a**	**L3**	K_2CO_3	3	76	98
13	**1a**	**L3**	Et_3N	42	19	98
14	**1a**	**L3**	Li_2CO_3	42	15	98
15	**1a**	**L3**	---	42	<5	---
16	**1a'**	**L3**	DBU	1	87	98
17	**1a''**	**L3**	DBU	1	61	98

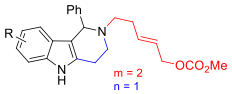
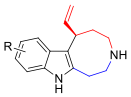
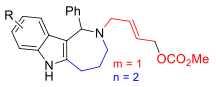
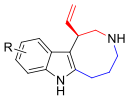
[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of ligand, 0.4 mmol of **1** and 0.4 mmol of base in THF (4.0 mL). Catalyst was prepared by *n*-$PrNH_2$ activation.[14d] [b] Isolated yield. [c] Determined by HPLC analysis.

The substrate scope of the reaction was then investigated and the results are summarized in Table 2. It was found that a wide range of seven- or eight-membered rings could be constructed smoothly in good to excellent yields and excellent enantioselectivity (47-89% yields, 93-99% ee). Indole-annulated seven-membered rings from the six-membered-ring substrates (**2a-2i**, m = 1, n = 1, entries 1-9) were obtained all in excellent ee values. Various 4-, 5- and 6-substitutents on the indole ring could be well tolerated, respectively, regardless of the electronic properties of the substituent group. However, the yields were slightly reduced when the R group was strongly electron-withdrawing, such as 5-F (**2f**, 64% yield, entry 6) or 4,6-Cl_2 (**2i**, 47% yield, entry 9). By adding one more methylene in the linker (m = 2, n = 1), the reaction could give indole-annulated eight-membered rings in reasonable yields and excellent enantioselectivity (**2j-2m**, 57-64% yields, 93-98% ee, entries 10-13). Eight-membered-ring products bearing the NH linker at a different position (m = 1, n = 2) could also be easily constructed in good yields and excellent enantioselectivity (**2n-2q**, 75-84% yields, 98-99% ee, entries 14-17) from the corresponding seven-membered-ring substrates under the standard conditions.

Table 2. Asymmetric synthesis of indole-annulated seven- or eight-membered-ring products[a]

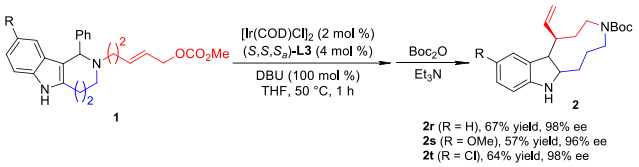


entry	**1**	**2**	yield (%)[b]	ee (%)[c]
				
1	**1a** (R = H)	**2a**	86	98
2	**1b** (R = 4-OMe)	**2b**	82	98
3	**1c** (R = 5-OMe)	**2c**	74	97
4	**1d** (R = 5-Me)	**2d**	72	97

5	**1e** (R = 5-Cl)	**2e**	76	97
6	**1f** (R = 5-F)	**2f**	64	96
7	**1g** (R = 6-OMe)	**2g**	79	98
8	**1h** (R = 6-Cl)	**2h**	89	98
9	**1i** (R = 4,6-Cl_2)	**2i**	47	98
				
10	**1j** (R = H)	**2j**	57	94
11	**1k** (R = 5-Me)	**2k**	59	97
12	**1l** (R = 5-Cl)	**2l**	64	93
13	**1m** (R = 6-Cl)	**2m**	64	98
				
14	**1n** (R = H)	**2n**	75	98
15	**1o** (R = 5-Me)	**2o**	84	98
16	**1p** (R = 5-Cl)	**2p**	80	98
17	**1q** (R = 6-Cl)	**2q**	83	99

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **L3**, 0.4 mmol of **1** and 0.4 mmol of DBU in THF (4.0 mL) at 50 °C. Catalyst was prepared by *n*-$PrNH_2$ activation. [b] Isolated yield. [c] Determined by HPLC analysis.

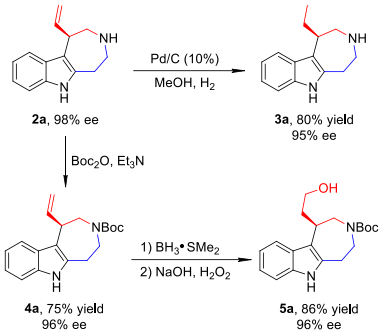
Nine-membered rings can also be assembled in this manner. Notably, the free N–H compounds in these cases are difficult to be purified by silica gel or Al_2O_3 column chromatography. Instead, the corresponding N–Boc protected products **2r**-**2t** were isolated (57-67% yield, 96-98% ee, Scheme 2).



Scheme 2. Asymmetric synthesis of indole-annulated nine-membered-ring products

The stereochemistry of **2a** was identified as (*R*) by VCD and IR experiments. The absolute configuration of other products was assigned by analogy. To be noted, the chirality of the products was solely determined by chirality of the ligand, because almost the same stereochemical outcomes were achieved when either enantiomerically pure or racemic substrate was utilized (See the Supporting Information for details).

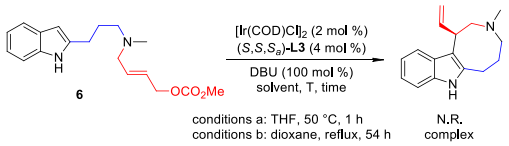
To test the practicality of this methodology, we carried out the reaction with substrate **1a** on a 5.7 mmol scale under standard conditions. The reaction proceeded smoothly to give product **2a** in 87% yield (1.06 g) and 98% ee (See the Supporting Information for details). The transformation of **2a** was also executed (Scheme 3). Subjecting **2a** to a Pd/C-catalyzed hydrogenation reaction afforded product **3a** in 80% yield and 95% ee. The corresponding alcohol **5a** was obtained smoothly after Boc protection of the amino group of **2a** and the following hydroboration oxidation reaction.



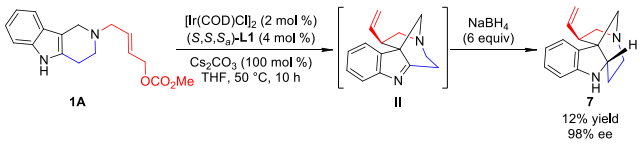
Scheme 3. Transformation of the product

The current method provides a novel route to enantioselective synthesis of indole-annulated medium-sized-ring products, which are highly challenging to be accessed by direct intramolecular reaction. This was confirmed by the facts that either no reaction or complex mixture was observed when substrate **6** was subjected to the standard reaction conditions (Scheme 4). We believe that the substrates **1** are pre-organized by six- or seven-membered rings to reduce energetically unfavorable transannular and torsional strain in the Ir-catalyzed allylic dearomatization reaction, which represents the key advantage of our reaction design.

To further shed light on the mechanism of the reaction, the isolation of intermediate **II** (n = 1, m = 1) was attempted. Unfortunately, **II** could not be isolated by silica gel or Al_2O_3 column chromatography, probably owing to its instability. However, after reduction of **II** by 6 equiv of $NaBH_4$, the corresponding product **7** could be obtained in 12% yield and 98% ee (Scheme 5). The isolation of **7** supports the proposed pathway depicted in Scheme 1.



Scheme 4. Attempt to construct eight-membered ring via direct Ir-catalyzed allylic alkylation reaction



Scheme 5. Capture of the bridged intermediate by *in situ* reduction

In summary, we have developed a general strategy for enantioselective synthesis of indole-annulated medium-sized-ring compounds by an Ir-catalyzed allylic dearomatization/retro-Mannich/hydrolysis cascade reaction. Under mild reaction conditions, various seven-, eight-, or nine-membered rings can be formed smoothly in good to excellent yields and excellent enantioselectivity. The catalytic system tolerates a broad substrate scope. Our proposed mechanism is supported by *in situ* reduction of the bridged cyclic intermediate. This novel synthetic strategy opens a window for asymmetric synthesis of medium-sized rings, which are challenging to be

accessed by other methods. Further expanding this strategy of enantioselective construction of medium-sized ring structures is in progress in our lab.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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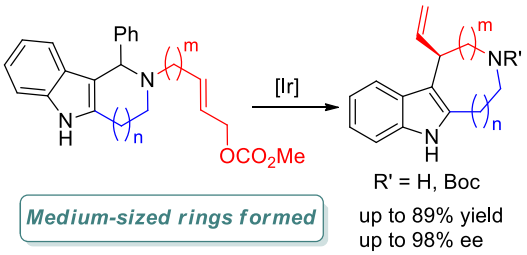
Ph
N
m
N
H
n
OCO2Me
[Ir]
m
NR'
N
H
n
R' = H, Boc
Medium-sized rings formed
up to 89% yield
up to 98% ee