Communication

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Copper-Catalyzed Highly Enantioselective Cyclopentannulation of Indoles with Donor-Acceptor Cyclopropanes

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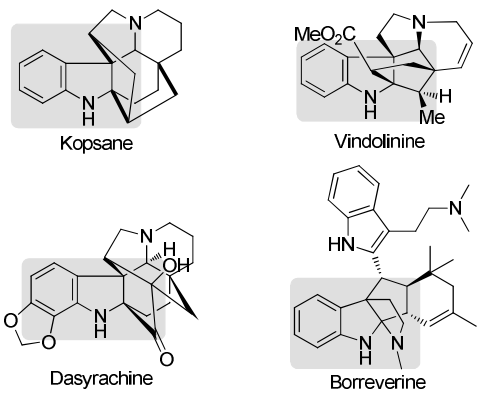
Asymmetric catalysis, [3+2] Annulation, Indoles, Cyclopropanes, Indolines

Supporting Information Placeholder

ABSTRACT: A highly diastereo- and enantio-selective BOX/Cu(II)-catalyzed C2,C3-cyclopentannulation of indoles with donor-acceptor cyclopropanes is developed on the basis of asymmetric formal [3+2] cycloaddition of indoles. This reaction provides a rapid and facile access to a series of enantioenriched cyclopenta-fused indoline products, and can be further extended to the construction of tetracyclic pyrroloindolines. The synthetic potential of the reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

C2,C3-fused indolines are widely present as core structures in a large number of natural products and biologically active molecules, and have been the focus of extensive synthetic efforts for a long time.[1] Recently, catalytic asymmetric transformations of indoles has been emerging as a powerful enantioselective strategy to synthesize these products, featuring the rapid assembly of the multi-cyclic skeletons in a cascade fashion and the readily available indole feedstocks.[2-4] The key step in this transformation is the generation of the chiral electrophilic indoleniminium intermediate which is susceptible to the intramolecular attack of a pendant group to close the ring. Asymmetric organocatalytic Friedel-Crafts reaction is the most studied approach to generate the chiral incipient indoleniminiums,[3] while asymmetric metal-catalyzed reactions such as palladium-catalyzed C3-allylation of indoles,[4a] copper-catalyzed arylation,[4e] and the gold-catalyzed alkenylation[4f] also proved to be effective. Recently, Barluenga and coworkers[4b] reported the use of tungsten Fischer carbenes in the asymmetric C2-C3 annulation reaction of indoles and Davies et al.[4c] established a rhodium-catalyzed version with vinyldiazoacetates. The two works represent the few enantioselective examples for the synthesis of cyclopenta-fused indoline which is a common structure in many natural products[1,7] such as kopsane, vindolinine, and dasyrachine (Figure 1). Within this scenario, we wish to report here a new entry to this arsenal, a highly diastereo- and enantio-selective Lewis acid-catalyzed formal [3+2] cycloaddition[5-6] of indoles with donor-acceptor (D-A) cyclopropanes. In particular, pyrroloindoles can also participate in this annulation reaction, which provides a core structure in borreverines.[7]

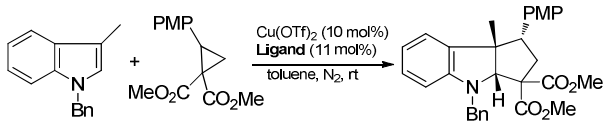
Figure 1. Cyclopenta-Fused Indolines in Natural Products.

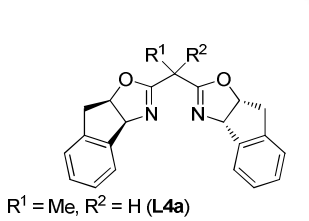


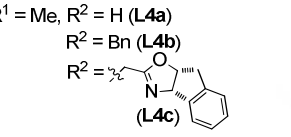
We initiated our study with the ligand screening, using indole **1a** and cyclopropane **2a** as the model substrates and $Cu(OTf)_2$ as the copper source. Tridentate ligands Ph-DBFOX and -PyBOX which have shown good selectivity in the cycloadditions of cyclopropanes with nitrones and aldehydes or imines, [6a,6c,d] did not show any activity in the current reaction (entries 1 and 2). Indane-BOX ligand **L4a** gave the desired cyclopenta-nnulation product **3a** in 86% yield with a promising ee (55%, entry 3). To our delight, modification on the bridging carbon by introducing a benzyl group not only increased the catalytic activity but also significantly improved the enantioselectivity to 80% ee (**L4b**, entry 4). However, a coordinating oxazoline sidearm group[8] retarded the reaction rate and decreased the enantioselectivity by 12%, which may result from the weakened Lewis acidity by the ligation of the additional oxazoline to copper (entry 5). Further elaboration of the ligands was thus focused on the benzyl sidearm group. Unfortunately, both steric and electronic alternations on the benzene ring failed to provide an obvious improvement in enantioselectivity.[9] Recently, we found that a type of cage-like BOX ligands **L5a-5b** containing two aryl sidearm groups can significantly improve the enantioselectivity in the cyclopropanation reaction of alkenes, when comparing to the ligands with only one aryl sidearm group or without this sidearm modification.[10] Though initial replacement of **L4b** with ligand **L5a** led to a significant drop in selectivity (entry 6), introduction of a *tert*-butyl group at the *para* or the two *meta* positions of the

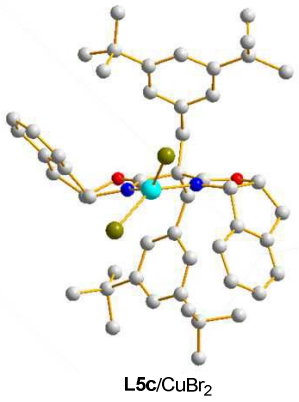
pendant phenyl group improved both the diastereo- and enantio-selectivity (entries 7 & 8), and the new ligand **L5c** was identified as the best (the crystal structure of **L5c** /$CuBr_2$ is shown in Table 1).[9] Varying the substrate ratio and lowering the temperature to 0 °C further improved the stereoselectivity to a decent level (20/1 dr and 91% ee, entry 9).

Table 1. Reaction Optimization.[a]







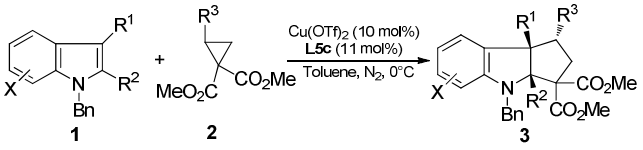


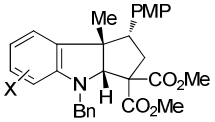
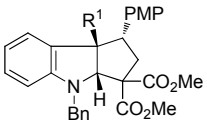
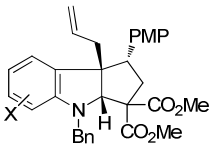
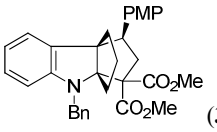
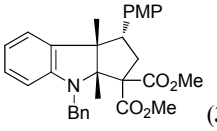
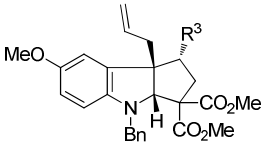
Entry	Ligand	t (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**Ph-DBFOX**	24	NR	-	-
2	**Ph-PyBOX**	24	NR	-	-
3	**L4a**	24	86	7.5/1	55
4	**L4b**	2	93	10/1	80
5	**L4c**	30	76	7/1	68
6	**L5a**	2	88	7/1	63
7	**L5b**	2	94	10/1	86
8	**L5c**	2	93	14/1	88
9[e]	**L5c**	5	95	20/1	91

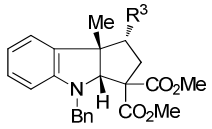
[a] **1a**/**2a** = 1.2/1, [**2a**] = 0.3 mmol in toluene (3 mL), N_2. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC. [e] **1a**/**2a** = 1/1.5, [**2a**] = 0.3 mmol in toluene (3 mL), at 0℃.

Under the optimized conditions, reaction scope was examined and the results were tabulated in Table 2. The reaction worked well with a range of indoles. Comparing with 5-methyl substituted indole **1b**, the reactions of 5-Br and 5-Cl indole (**1c** and **1d**) were slower, but the electronic effect on the enantioselectivity is negligible (entries 2,5 vs. 3,4). 4-Methyl substituted indoles were converted with a slightly higher diastereo- and enantio-selectivity (>50/1 dr and 95% ee, entry 6) than other substitution patterns (5-, 6-, 7-, entries 2, 7 and 9). It is noteworthy that indole C3-substituents rather than methyl[4b,c] are also compatible in the current reaction and additional functionalities like hydroxy, amino, allyl groups can be introduced into the final products (entries 10-14). In the case of **1k**, the pendant carbamate group may also act as a competing nucleophile to

Table 2. Reaction Scope.[a]



Entry	Product	t	Yield (%)[b]	dr[c]	ee (%)[d]
					
1	X = H (**3aa**)	5h	95	20/1	91
2	5-Me (**3ba**)	5h	95	19/1	90
3	5-Br (**3ca**)	28h	96	>20/1	90
4	5-Cl (**3da**)	25h	96	>20/1	91.5
5	5-OMe (**3ea**)	3h	96	>20/1	93
6	4-Me (**3fa**)	5h	95	>50/1	95
7	7-Me (**3ga**)	5h	94	>20/1	90
8	7-Br (**3ha**)	36h	91	>30/1	94
9	6-Me (**3ia**)	5h	95	>20/1	90
					
10	R^1 =  (**3ja**)	5h	95	19/1	93
11	 (**3ka**)	36h	85	>20/1	86
					
12	X = H (**3la**)	30h	90	>20/1	95
13	5-Me (**3ma**)	24h	97	>20/1	93
14	5-OMe (**3na**)	8h	92	>30/1	95
15	 (**3oa**)	5h	98	3.3/1	80 /94[e]
16	 (**3pa**)	42h	77	>50/1	96[f]
					
17	R^3 = 4-(TBSO)-C_6H_4 (**3nb**)	36h	88	>30/1	94
18	2-furyl (**3nc**)	8h	94	12/1	86
19	2-thienyl (**3nd**)	12h	94	20/1	92
20	3,4,5-	7d	83	>20/1	89

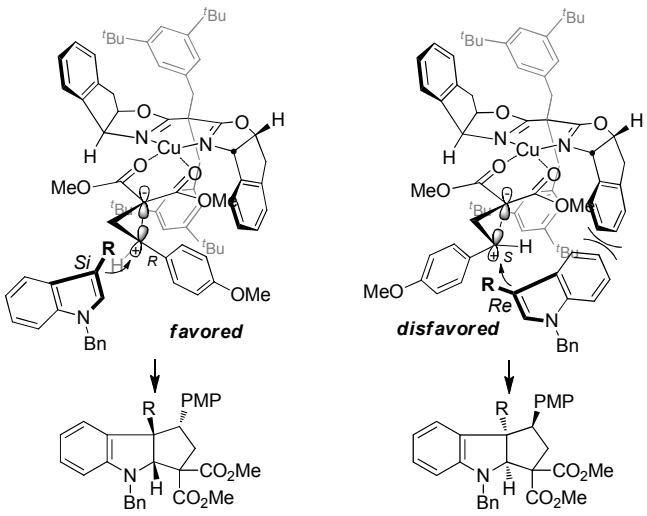
	$(MeO)_3C_6H_2$(**3ne**)				
21	CH=CHPh (**3nf**)	12h	83	12/1	90
					
22[g]	R^3 = vinyl (**3ag**)	72h	45	3.5/1	84
23[h,i]	Ph (**3ah**)	168h	88	10/1	89
24[h,j]	4-I-C_6H_4 (**3ai**)	106h	90	9/1	86

[a] **1** (0.2 mmol), **2** (0.3 mmol), $Cu(OTf)_2$ (0.02 mmol), **L5c** (0.022 mmol) in toluene (3 mL). [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC using a chiral stationary phase. [e] With 2.0 equiv of **2a**, at -30 °C. [f] With 3.5 equiv of **2a**, at -30 °C. [g] At 40 °C, 3.0 equiv of **2g**. [h] Kinetic resolution, at 40 °C, with 2.0 equiv of cyclopropane. [i] 49% conv., recovered (*S*)-**2h**: 90% ee, S = 94. [j] 51% conv., recovered (*S*)-**2i**: 89% ee, S =38.

give pyrroloindoline as a side product, but it was not observed by proton NMR analysis of the crude product (entry 11). Remarkably, the reaction of penta-fused indole **1o** also proceeded smoothly under this condition, delivering the [3,3,3,0]-tetracyclic indoline **3oa** which contains two quaternary bridging carbons in high yield and good stereoselectivities (entry 15). And the reaction of 2,3-dimethyindole **1p** also proceeded well at -30 °C (96% ee, entry 16). It is worth mentioning that indoles without a C3 substituent normally only gave the C3-Friedel-Crafts alkylation product with high ee rather than the [3+2] annulation product.[11] On the other hand, heteroaryls such as 2-furyl and 2-thienyl substituted as well as alkenyl substituted cyclopropanes all participated in the annulation reaction with high enantioselectivity (entries 18-19 and 21). To our delight, vinyl cyclopropane **3g** also reacted well with a good enantioselectivity, affording a vinyl group for further modifications (entry 22), while alkyl cyclopropanes (R^3 = H or Me) are inert under the current reaction conditions and no product formed even at 50 °C after two days. In general, except for **1o** and **2g**, all reactions proceeded with excellent diastereocontrol (from 12/1 to >50/1 dr). The absolute configuration of **3ha** was assigned by X-ray crystallography,[12] while the configurations of other products were assigned by analogy. For less reactive cyclopropanes, the present reactions could proceed with a concurrent kinetic resolution of the cyclopropanes, though the reactions are normally slower. At ca. 50% conversion, both the [3+2] annulation products and the recovered (*S*)-cyclopropanes **2h-i** can be obtained in high yields with high enantioselectivities (entries 23 & 24).

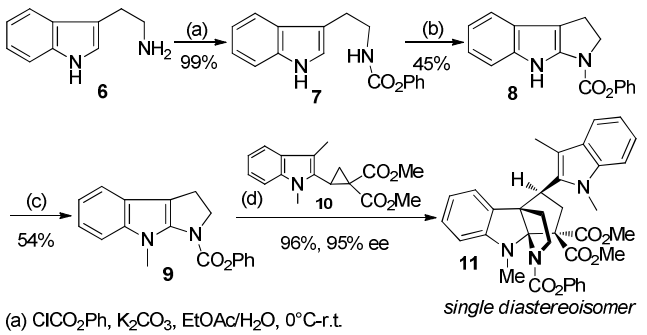
On the basis of crystal structure of **L5c**/$CuBr_2$ complex, the square planar geometry of Box/Cu^{2+}/dicarbonyl complexes,[13] together with the step-wise annulation mechanism[5], a work model (Figure 2) was tentatively proposed to reason the enantioselection in the present reaction. Considering the steric demand in the nucleophilic attack of C3-substituted indoles to a sp^3 carbon and the donor group stabilization effect, the C2 carbon in cyclopropanes must have a significant carbenium ion character.[6a,14] The approach of the *Si* face of indole to the transient (*R*)-cyclopropane (left) should be more favored, which experiences less steric interactions with the ligand indanyl substituent. The preference for (*R*)-cyclopropane is in line with the kinetic resolution results (entries 23 & 24, Table 2), in which (*S*)-configured cyclopropanes were recovered.

Figure 2. Proposed work model for the stereoselection.



Inspired by the beneficial electronic effect of the electron-donating groups and good enantioselectivity in the reaction of penta-fused indole **1o**, a synthetic route for the synthesis of the tricyclic core of borreverine[7e] was designed based on the cyclopentannulation of pyrroloindole **9** (Scheme 1). Gratifyingly, the [3+2] annulation of **9** with **10** can even be carried out at -40 ºC, and only a single diastereoisomer was observed with high enantioselectivity (95% ee). The four-step synthesis starting from tryptamine **6** gave the desired product **11** in 23% overall yield. The success with the pyrroloindole-type substrates provides a novel and rapid access to the tetracyclic pyrroloindoline structures.

Scheme 1. Synthesis of the Core of Borreverine.



In summary, a highly diastereo- and enantio-selective cyclopenta-annulation reaction of indoles with cyclopropanes has been successfully developed. The reaction performed well over a series of indoles and D-A cyclopropanes under mild conditions, giving penta-fused indoline products in excellent diastereoselectivities (up to >50/1 dr) and enantioselectivities (up to 95% ee). The application of this reaction to pyrroloindoles established an unprecedented approach to tetracyclic pyrroloindoline compounds. The synthetic potential of the current reaction was demonstrated in a four-step synthesis of the core structure of borreverine.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, characterizations and analytical data of ee values of products, cif files for compounds **11**, **3ha**, **3oa**, and **L5c**/$CuBr_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Note

The authors declare no competing financial interest.

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(9) For more details, see the Supporting Information.

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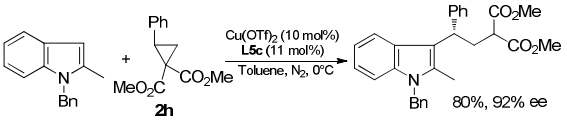
(11) In the reactions of *N*-benzyl-2-methylindole, only Friedel-Crafts alkylation products were isolated, and with 2.0 equiv of cyclopropane **2h**, a good enantioselectivity (92% ee) can also be achieved.



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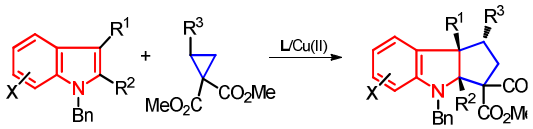

C2,C3-Annulation of Indoles to Cyclopenta-Fused Indolines

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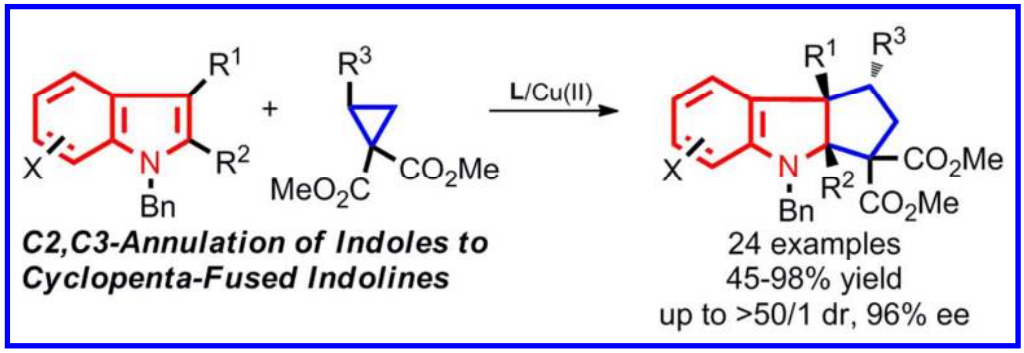

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