Annulations

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Reaction of Donor-Acceptor Cyclobutanes with Indoles: A General Protocol for the Formal Total Synthesis of (±)-Strychnine and the Total Synthesis of (±)-Akuammicine

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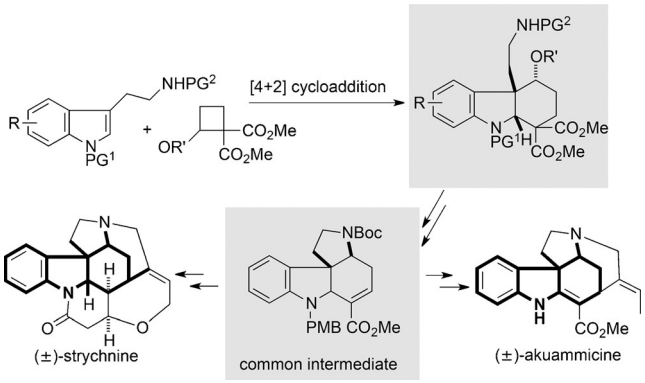
Abstract: *A ligand-promoted catalytic [4+2] annulation reaction using indole derivatives and donor-acceptor (D-A) cyclobutanes is reported, thus providing an efficient and atom-economical access to versatile cyclohexa-fused indolines with excellent levels of diastereoselectivity and a broad substrate scope. In the presence of a chiral SaBOX ligand, excellent enantioselectivity was realized with up to 94% ee. This novel synthetic method is applied as a general protocol for the total synthesis of (±)-akuammicine and the formal total synthesis of (±)-strychnine from the same common-core scaffold.*

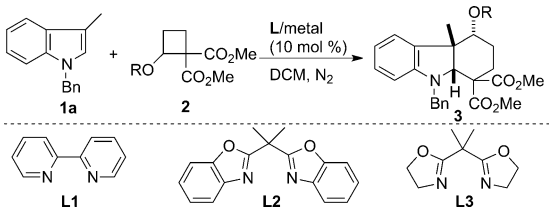
Owing to their synthetic potential of accessing various cyclic compounds by formal [4 + n] cycloadditions, donor-acceptor (D-A) cyclobutanes have attracted increasing attention in recent years.[1,2] In 2013, Matsuo et al. reported an elegant regioselective inter- and intramolecular formal [4+2] cycloaddition of cyclobutanones with indoles in 31–98% yields with moderate to good diastereoselectivities.[2i] In 2016, we demonstrated a highly efficient formal [2+2+2] strategy for the rapid construction of polycyclic spiroindolines.[3] Recently, we found that indole and its derivatives can react with D-A cyclobutanes through an intermolecular [4+2] annulation reaction, which allows facile construction of the cyclohexa-fused indoline motif bearing three contiguous stereogenic centers with excellent levels of diastereoselectivity. Further studies showed that the transformation of the products could provide concise access to the core skeleton of *strychnos* alkaloids.[4] Thus, we developed a short synthesis of (±)-akuammicine and a formal total synthesis of (±)-strychnine (Scheme 1). Herein, we report the preliminary results.

Initially, we chose the indole **1a** (for structure see Table 1) and the BnO-substituted D-A cyclobutane **2a** as model substrates, and tested catalysts[2] reported to perform well in the formal cycloaddition reactions of D-A cyclobutanes with various dipolarophiles. However, these catalysts proved to be unsuitable for this [4+2] annulation reaction. For instance, no [4+2] cycloadduct was detected with $Sc(OTf)_3$ as the catalyst, which was highly efficient in the [4+2] annulation of D-A cyclobutanes with aldehydes as reported by Parsons and Johnson.[2c] When $SnCl_4$, which succeeded in promoting the [4+2] reaction of D-A cyclobutanes with ketones[2g] and enol silanes,[2h] was used, only the Friedel–Crafts alkylation by-product[5] was obtained. Although $Yb(OTf)_3$[2d–f] gave the desired product in 33% yield with a high d.r. value at 0 °C,



Scheme 1. A new route to access *strychnos* alkaloids. PG = protecting group, PMB = *p*-methoxybenzyl.

Table 1: Reaction optimization.[a]



Entry	Metal salt	R	L	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]
1	$Cu(SbF_6)_2$	Bn (**2a**)	**L1**	−20	4	31	78:22
2	$Cu(SbF_6)_2$	Bn (**2a**)	**L2**	−20	4	6	70:30
3	$Cu(SbF_6)_2$	Bn (**2a**)	**L3**	−20	2	42	80:20
4	$Cu(SbF_6)_2$	2,6-dimethyl-benzyl (**2b**)	**L3**	−20	2	42	88:12
5[d]	$Cu(SbF_6)_2$	2,6-dimethyl-benzyl (**2b**)	**L3**	−60	11	90	90:10

[a] Reaction conditions: **1a**/**2** = 1.2:1, **1a** (0.24 mmol), **2** (0.2 mmol), Lewis acid (0.02 mmol), and **L** (0.024 mmol) in DCM (3 mL). [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] **1a**/**2** = 2:1, 4 Å M.S. was added, **2b** was added in two portions with an interval of 8 h. DCM = dichloromethane.

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a large amount of by-product was detected and the starting materials were completely consumed. Further optimization of the $Yb(OTf)_3$ system failed to achieve a better result.[6]

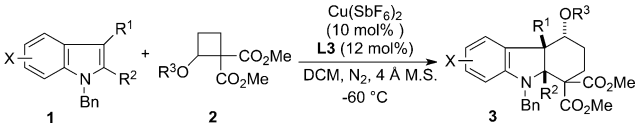
We then employed a variety of ligands aimed at regulating the Lewis acidity of the catalyst. As shown in Table 1, using the bipyridine ligand (**L1**) with $Cu(SbF_6)_2$ only gave the desired product in 31% yield with 78:22 d.r. (entry 1), and was accompanied by a lot of the Friedel–Crafts alkylation by-product.[5] Bisoxazoline (BOX; **L2**) also failed to improve the yield and diastereoselectivity (entry 2). When changing to **L3** as the ligand, the desired product was afforded in 42% yield with 80:20 d.r. (entry 3). It was found that a bulkier R group led to a better d.r. value. When R was changed to 2,6-dimethylbenzyl, 88:12 d.r. was obtained, albeit still with moderate yield (entry 4). Further screening of the reaction conditions[6] showed that the side reactions could be greatly suppressed by using 4 Å M.S. as additives. By a combination of optimal reaction conditions, including temperature, substrates ratio, etc.,[6] finally, 90% yield with 90:10 d.r. was achieved (entry 5).

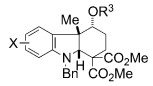
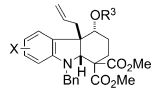
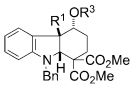
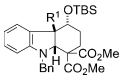
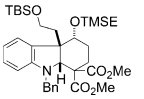
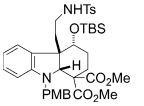
The substrate scope was investigated under the optimized reaction conditions. As shown in Table 2, a variety of indoles, including those containing both electron-rich and electron-poor substituents on the aryl ring, reacted smoothly with **2b** to give the desired products in up to 97% yield with up to 90:10 d.r. (entries 2–8). It is noteworthy that indoles containing various functional groups at the C3-position, like allyl, benzyl, hydroxy, and amino groups, were also tolerated (entries 9–17). Considering the difficulty of removing the 2,6-dimethylbenzyl group, the TBSO-substituted cyclobutane **2c** was employed, thus delivering the products that were suitable for further transformation (entries 18 and 19). Additionally, a tryptophol-derived substrate reacted smoothly, thus affording the product **3t** in 76% yield with 83:17 d.r. (entry 20). Notably, with the PMB-protected tryptamine as a substrate, and $Cu(PF_6)_2$ as a Lewis acid, the desired product **3u** was furnished in 50% yield with >99:1 d.r. (entry 21).

Further studies showed that the asymmetric version of this method can also be realized. Although cyclobutanes with oxygen-donating groups only gave poor enantioselectivity,[6] cyclobutanes with sulfur-donating groups resulted in excellent *ee* values. As shown in Scheme 2, in the presence of a chiral the side-arm-modified BOX (SaBOX) ligand **L4**, a variety of enantiotopic chiral cyclohexa-fused indolines (**4a–e**) were furnished with excellent enanatioselectivity (90–94% *ee*) through the enantioselective [4+2] annulation of indoles with the *p*-MeO-phenylthio-substituted cyclobutane **2d**.[7,8] Many easily transformed functional groups on the indoles were tolerated by the current catalyst system, including an allyl group at the 3-position and halo substituents at the 5- and 6-positions.

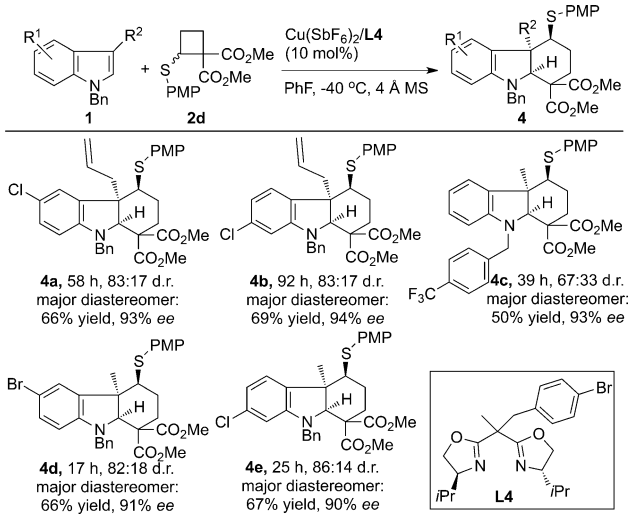
The [3+2] annulation reactions of D-A cyclopropanes have been successfully applied in the total synthesis of many natural products.[9,10] Although the reactions of D-A cyclobutanes have been well studied, few of them were employed in the total synthesis of complex molecules. Inspired by the synthetic efficiency of forming cyclohexa-fused indolines with the current method, we tried to employ it to construct the basic skeletons of some well-known members of the *strychnos, aspidosperma,* and *kopsia* alkaloids.[4,11] As shown in Scheme 3, the [4+2] annulation reaction of PMB-protected tryptamine with D-A cyclobutane was applied as the key step to construct **3u** with excellent diastereoselectivity. The compound **3u** was then deprotected, followed by an intramolecular Mitsunobu reaction, thus affording the cyclization product **6** in excellent yield. The compound **6** was then treated with LiCl to give the decarboxylated product **7** in 92% yield. However, trials on converting **7** into the unsaturated ester by a $PhSeBr/H_2O_2$ oxidation failed. Thus, we treated **7** with Na/naphthalene to give the deprotection product, which was in turn converted into the Boc-protected product **8**, a compound

Table 2: Reaction scope.[a]

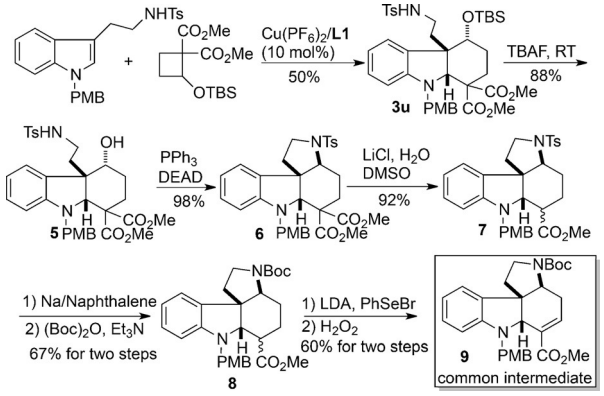


Entry	Product		t [h]	Yield [%][b]	d.r.[c]
1		X = H (**3a**)	11	90	90:10
2		X = 5-Me (**3b**)	18	97	88:12
3		X = 5-F (**3c**)	17	85	83:17
4		X = 5-Cl (**3d**)	18	92	88:12
5		X = 5-Br (**3e**)	18	90	90:10
6		X = 6-Me (**3f**)	17	79	88:12
7	R^3 = 2,6-dimethylbenzyl	X = 7-Me (**3g**)	17	87	88:12
8		X = 7-MeO (**3h**)	18	57	83:17
9[e]		X = H (**3i**)	17	71	91:9
10[e]		X = 5-Me (**3j**)	20	81	88:12
11[e]		X = 5-MeO (**3k**)	20	61	91:9
12[e]		X = H (**3a**)	17	80	91:9
13[e]	R^3 = 2,6-dimethylbenzyl	X = 5-F (**3l**)	21	74	91:9
14[e]		R^1 = Bn (**3n**)	18	82	92:8
15[e]		R^1 =  (**3o**)	19	53	>99:1[d]
16[e]		R^1 =  (**3p**)	25	72	90:10
17[e]	R^3 = 2,6-dimethylbenzyl	R^1 =  (**3q**)	27	64	93:7
18[e]		R^1 = Me (**3r**)	18	54	84:16
19[e]		R^1 =  (**3s**)	42	46	89:11
20[e]		(**3t**)	6	77	86:14
21[f]		(**3u**)	32	50	>99:1

[a] Reaction conditions: **1**/**2** = 2:1, **1** (0.4 mmol), **2** (0.2 mmol), $AgSbF_6$ (0.04 mmol), $CuBr_2$ (0.02 mmol), and **L3** (0.024 mmol) in DCM (3 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture unless otherwise noted. [d] The d.r. value was determined by ^1H NMR analysis of the isolated products. [e] At −40 °C. [f] **L3**/$Cu(PF_6)_2$ was used, at −50 °C. R^3 = 2,6-dimethylbenzyl; Bs = benzenesulfonyl, M.S. = molecular sieves, Ns = 4-nitrobenzenesulfonyl, TBS = *t*-butyldimethylsilyl, TMSE = 2-(trimethylsilyl)ethyl, Ts = 4-methylbenzenesulfonyl.



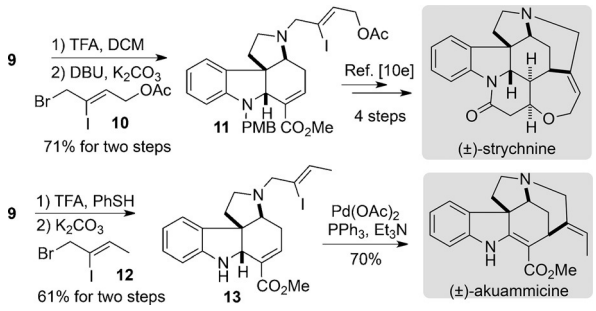
Scheme 2. Strategies to approach a common precursor of natural products. Reaction conditions: **1**/**2d** = 1:2, **1** (0.2 mmol), **2d** (0.4 mmol), $AgSbF_6$ (0.04 mmol), $CuBr_2$ (0.02 mmol), and **L4** (0.024 mmol) in DCM (3 mL). Yield of isolated product. The d.r. value was determined by ^1H NMR analysis of the crude reaction mixture. PMP = *p*-methoxyphenyl.



Scheme 3. Pathway to approach a common precursor of natural products. Boc = *tert*-buoxycarbonyl, DEAD = diethylazodicarboxylate, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, TBAF = tetra-*n*-butylammonium fluoride.

which was feasible for the construction of unsaturated ester **9** through a two-step process comprising a $PhSeBr/H_2O_2$ oxidation sequence. This result suggested that the choice of protecting group on the secondary amine of the newly built five-membered ring is very critical for the reaction outcome.

Having established the common-core structure, we pursued the synthesis of (±)-strychnine and (±)-akuammicine. As shown in Scheme 4, **9** was converted into **11** through a two-step protocol involving deprotection and allylation with the substituted allyl bromide **10**[9e] in 71% overall yield. Then **11** could be converted into (±)-strychnine in four steps according to a known procedure.[11e] The total synthesis of (±)-akuammicine was also achieved from the same key intermediate **9**. Treatment of **9** with trifluoroacetic acid and thiophenol resulted in the deprotection product, which was further functionalized with the allyl bromide **12**,[12] thus



Scheme 4. Formal total synthesis of (±)-strychnine and total synthesis of (±)-akuammicine. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid.

delivering the vinyl iodide **13** over two-steps in 61% yield. A Heck cyclization completed the total synthesis of (±)-akuammicine in 70% yield.[13]

In conclusion, we have developed a ligand-promoted catalytic [4+2] annulation reaction of indole derivatives with D-A cyclobutanes, thus opening a unique pathway to versatile multifunctionalized cyclohexa-fused indolines with good to excellent levels of diastereoselectivity and a broad substrate scope. In the presence of a chiral SaBOX ligand, excellent enantioselectivity was realized with up to 94% *ee*. This novel synthetic method was applied as a general protocol for constructing the common-core scaffold of strychnos alkaloids. By employing the transformation, the total synthesis of (±)-akuammicine and the formal total synthesis of (±)-strychnine were accomplished, and serve as the first example of using the reaction of D-A cyclobutanes in the total synthesis of natural products. This efficient protocol provides alternative, concise, and facile access to such natural alkaloids from simple starting materials. Further application of this approach to other natural and bioactive products is underway in our laboratory.

Experimental Section

A mixture of $CuBr_2$ (0.02 mmol), $AgSbF_6$ (0.04 mmol) and **L3** (0.024 mmol) in DCM (1 mL), with activated 4 Å M.S. (150 mg), was stirred at room temperature for 4 h under N_2. The system was cooled to −60 °C, and **1a** (0.4 mmol) in DCM (1 mL) and **2b** (0.1 mmol) in DCM (1 mL) were added to the catalyst mixture by syringe. When the cyclobutane was completely consumed (monitored by thin-layer chromatography), another potion of **2b** (0.1 mmol) was added. The resulting suspension was allowed to stir at −60 °C for 11 h. The reaction mixture was filtered through a glass funnel with a thin layer (20 mm) of silica gel (100–200 mesh) with DCM (approx. 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the desired product **3a** (90% yield, 90:10 d.r.).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: annulations · cyclobutanes · diastereoselectivity · heterocycles · natural products

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Angew. Chem. **2017**, *129*, 3101 – 3104

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[6] For details, see the Supporting Information.

[7] The relative configuration of **3a** and the absolute configuration of **4b** were determined by X-ray crystallography. CCDC 1439415 and 1517876 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[8] The minor diastereomer of the products **4a**–**e** were difficult to isolate and purify by chromatography because of their similar R_f value with the starting material **2c**.

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