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Construction of the N1−C3 Linkage Stereogenic Centers by Catalytic Asymmetric Amination Reaction of 3-Bromooxindoles with Indolines

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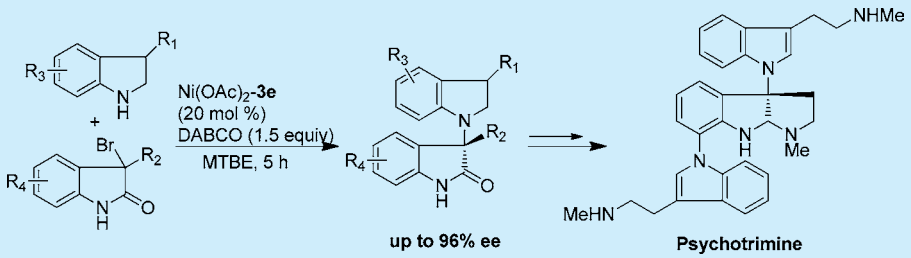
Supporting Information



ABSTRACT: The catalytic asymmetric amination reaction of 3-bromooxindoles with indolines for the construction of the N1−C3 linkage stereogenic centers has been realized for the first time. Moreover, the racemic substrates (3-substituted indolines) were also applicable under the same chiral conditions. The newly developed method conveniently led to a formal synthesis of (+)-psychotrimine.

The indole-derived pyrroloindolines widely exist in a large number of natural products and pharmacologically important compounds.[1,2] However, a small collection of molecules, including chaetomin,[3] kapakahines,[4] psychotrimine,[5] and psychotetramine,[5f] are linked through N1−C3 bonds[7] (Figure 1). These indole alkaloids show unique structures and interesting bioactivity profiles. For example, psychotrimine, a trimeric-tryptamine-related alkaloid, was isolated from the leaves of the plant *Psychotria rostrata* by Takayama and co-workers in 2004[5a] and exhibits potent antitumor activity against colon and lung cancers[5e] and antibacterial activity against Gram-positive bacteria.[6] The unique structure and interesting biological activity of psychotrimine have attracted considerable attention from synthetic chemists worldwide.[5b−f] Takayama et al. employed an asymmetric Ireland−Claisen rearrangement as a key step for the first enantioselective total synthesis of (+)-psychotrimine.[5e] An elegant total synthesis of (+)-psychotrimine was achieved by Baran and co-workers, through the direct aniline−indole coupling of *o*-iodoaniline with 7-bromo-D-tryptophan derivative.[5f]

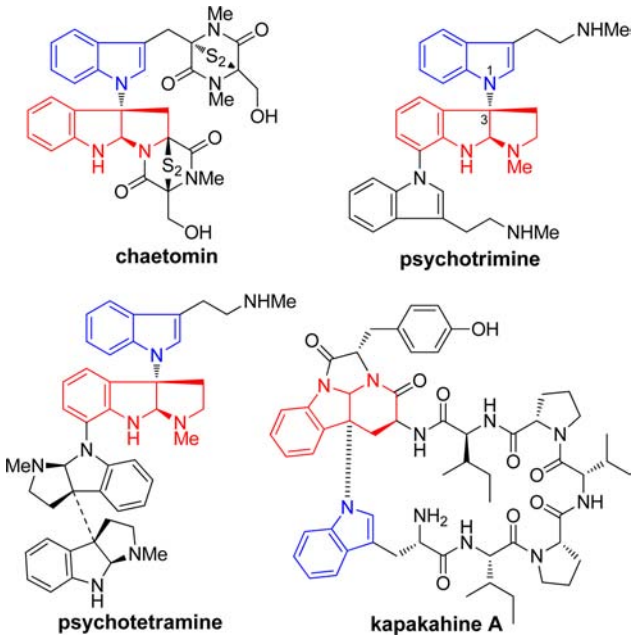


Figure 1. Representative members of the N1−C3 linkage indole alkaloids.

The N1−C3 linkage stereogenic center is the pronounced feature in these natural products. From a synthetic point of view, several members of the indole alkaloids contain the N1−C3 linkage stereogenic center that could potentially be accessed via 3-aminooxindole[8] **4** (Scheme 1). Therefore, the catalytic asymmetric construction of the N1−C3 linkage stereogenic center in **4** would be the critical element in the divergent synthesis of these indole alkaloids. Unsurprisingly, the methods to construct this type of C−N bond directly in an asymmetric and catalytic fashion are rare.[9−11] Recently, we disclosed an asymmetric alkylation reaction of 3-bromooxindoles with 3-substituted indoles with high diatereoselectivity and excellent enantioselectivity by using a nickel(II) catalyst. We found that the enantioselectivity was controlled by the chiral electrophile

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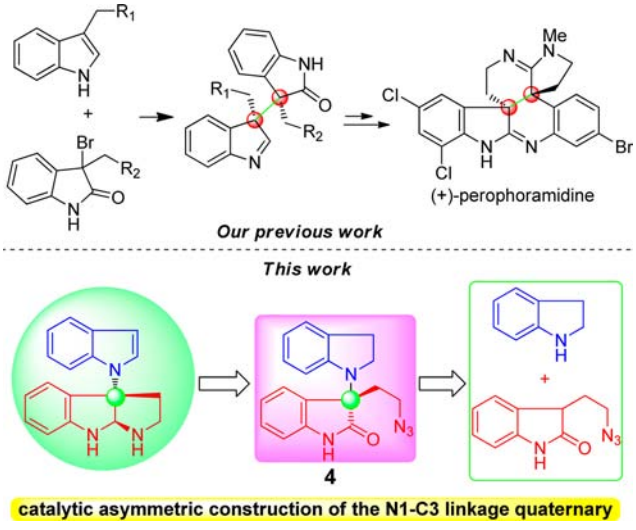
Scheme 1. Strategically Diversity-Oriented Retrosynthetic Analysis

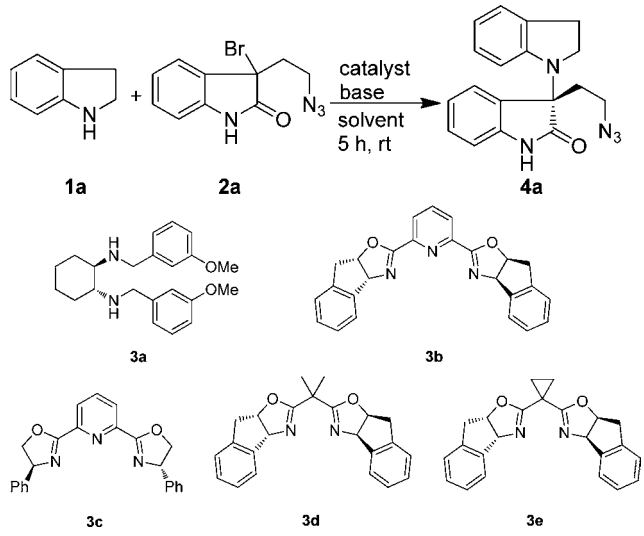


(indol-2-one) complex induced by a chiral nickel(II) catalyst.[12] Herein, we developed an efficient catalytic asymmetric amination reaction of 3-bromooxindoles[13] with indolines for the construction of the N1−C3 linkage stereogenic centers. This method also could be convenient for the synthesis of (+)-psychotrimine.

In our initial experiments, we investigated an examination of the reaction between 3-bromooxindole **2a** and indoline **1a** in the presence of chiral nickel(II) catalysts. As shown in Table 1, the 1:1 Ni(OAc)$_2$−**3a** complex (20 mol %, THF, rt, 5 h) combined with K_3PO_4, which we have been developing in a previous study,[12] afforded the desired product **4a** in excellent yield, but with low enantioselectivity (Table 1, entry 1). However, the replacement of **3a** with other ligands, such as **3b**, **3c**, **3d**, or **3e**, gave no significant improvement to the enantioselectivity (Table 1, entries 2−5). Then, several bases were surveyed. To our great delight, when DABCO was used as a base, the enantioselectivity was enhanced (75% ee, Table 1, entry 9). Subsequent screening of solvents revealed that MTBE appeared to be the most suitable reaction media for high enantioselectivity (up to 87% ee; Table 1, entries 14). Finally, we found that lowering the amount of base results in a slightly enhanced enantioselectivity at 90% ee (Table 1, entry 15).

Having established the optimal reaction conditions, the scope of substrates for the catalytic asymmetric amination reaction of 3-bromooxindoles with indolines was then studied (Scheme 2). On the whole, it was found that a broad range of 3-bromooxindoles and indolines could readily participate in this reaction. We first investigated a variety of indolines under the optimal reaction conditions. Indolines with electron-withdrawing groups gave adducts with high enantioselectivity (88−96% ee) and high yield (71−88%), but indolines with electron-donating groups experienced lower enantioselectivity (**4c**, 74% ee; **4d**, 61% ee). Furthermore, the scope of 3-bromooxindoles was surveyed. Substitution of the bromooxindole with a methoxy group at C5 produced the indoline amination product with good results (**4k**). In contrast, only moderate selectivity and yield were observed with substrate **2l**, which contains an electron-withdrawing C5−Cl on the bromooxindole core. In addition, bromooxindoles bearing different 3-substitution/alkyl chains could participate in this

Table 1. Optimization of the Reaction[a]



entry	catalyst	base	solvent	yield[b] (%)	ee[c] (%)
1	Ni(OAc)$_2$-**3a**	K_3PO_4	THF	94	3
2	Ni(OAc)$_2$-**3b**	K_3PO_4	THF	92	17
3	Ni(OAc)$_2$-**3c**	K_3PO_4	THF	95	13
4	Ni(OAc)$_2$-**3d**	K_3PO_4	THF	91	15
5	Ni(OAc)$_2$-**3e**	K_3PO_4	THF	90	21
6	Ni(OAc)$_2$-**3e**	DBU	THF	83	33
7	Ni(OAc)$_2$-**3e**	Et_3N	THF	84	55
8	Ni(OAc)$_2$-**3e**	*N*,*N*-DIPEA	THF	87	70
9	Ni(OAc)$_2$-**3e**	DABCO	THF	88	75
10	Ni(OAc)$_2$-**3e**	DABCO	Et_2O	64	65
11	Ni(OAc)$_2$-**3e**	DABCO	DME	83	67
12	Ni(OAc)$_2$-**3e**	DABCO	CPME	87	79
13	Ni(OAc)$_2$-**3e**	DABCO	dioxane	84	75
14	Ni(OAc)$_2$-**3e**	DABCO	*t*-MTBE	88	87
15[d]	Ni(OAc)$_2$-**3e**	DABCO	*t*-MTBE	87	90

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), and base (0.2 mmol) in the presence of catalyst (0.02 mmol) and solvent (1.5 mL). [b]Isolated yield. [c]Determined by chiral HPLC on a Chiralpak OD column. [d]DABCO (0.15 mmol) was added. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, DABCO = triethylenediamine, DME = 1,2-dimethoxyethane, CPME = cyclopentyl methyl ether, MTB E= methyl *tert*-butyl ether.

reaction (**4m−o**). To our delight, in addition to indolines, the tetrahydroquinoline was also suitable for the reaction to give the respective adduct with excellent results (**4p**).

On the basis of our recent research,[12] we surmised that racemic 3-substituted indolines could aminate 3-bromooxindoles stereoselectively. As shown in Scheme 3, several 3-substituted indolines can participate in the process to give the desired amination adducts **4** with moderate yield. The ee value was determined by the conversion of indoline **4** into indole **5** with DDQ oxidation. Notably, the product **5d** was obtained in moderate yield with excellent stereoselectivity when the tryptophan-derived indoline was employed. The potential utility of this reaction was supported by the relationship between Chaetomin's skeleton and **5d**.

The synthetic utility of this strategy was demonstrated by the aminated product **4a**,[5e] which has been achieved in 12 chemical steps by Takayama et al., as a key intermediate in the enantioselective synthesis of (+)-psychotrimine (Scheme 4).

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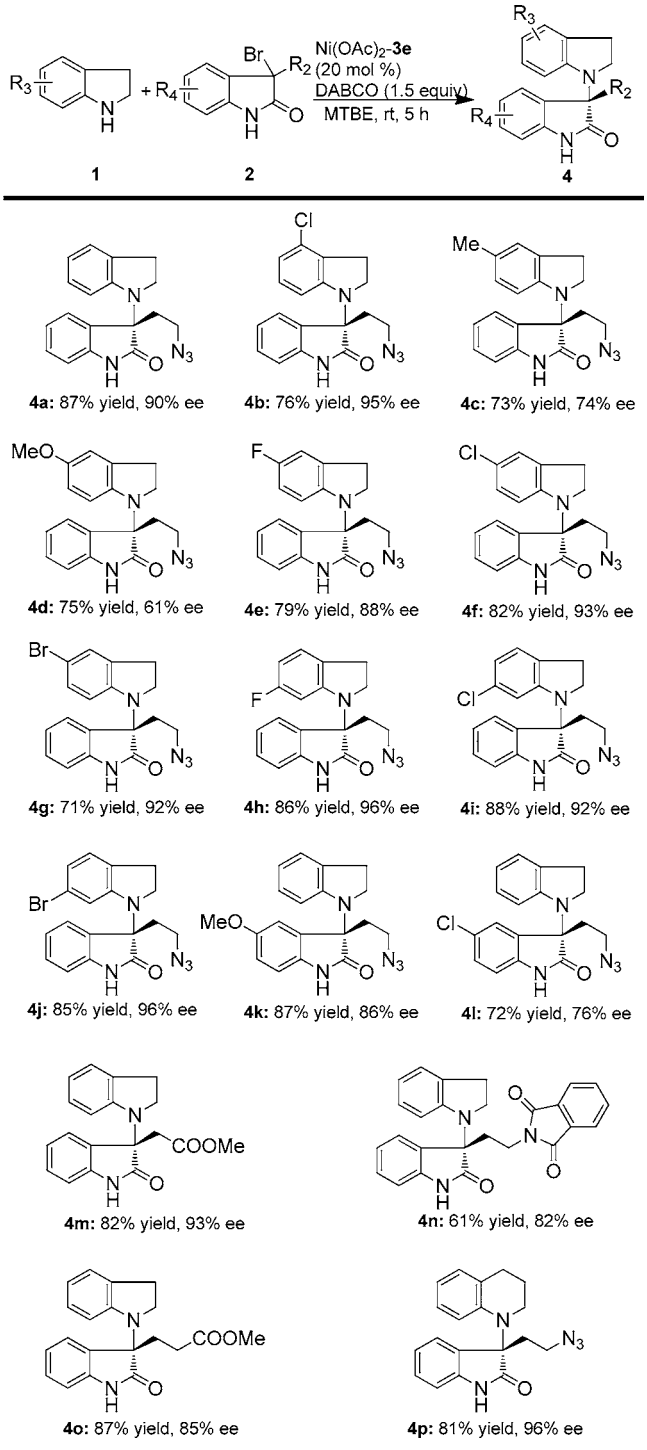
Scheme 2. Scope of the Reaction[a]

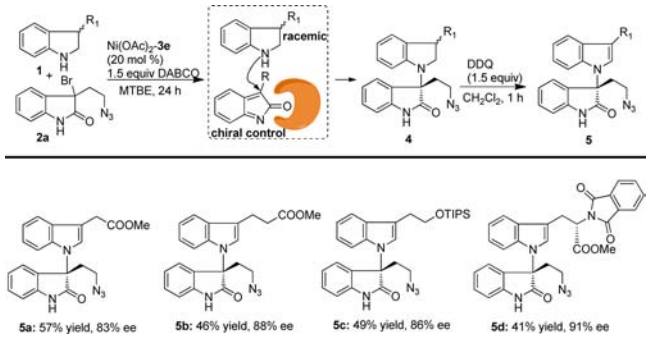


[a]Unless otherwise specified, the reaction was carried out with **1** (0.12 mmol), **2** (0.1 mmol), and base (0.15 mmol) in the presence of a catalyst (0.02 mmol) and solvent (1.5 mL). Isolated yield. The ee values were determined by HPLC on a chiral phase (Chiralcel column).

Here, we could expediently obtain a series of **4a** analogues by the direct catalytic asymmetric amination reaction of 3-bromooxindoles with indolines, and the chemical diversity of (+)-psychotrimine may be accessed via this method.

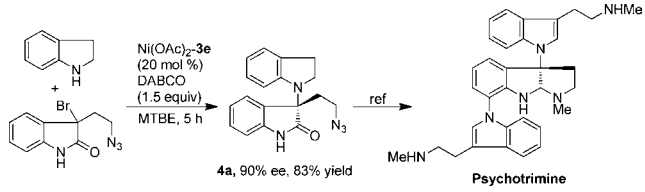
In conclusion, we have developed a mild enantioselective nickel(II)-catalyzed amination reaction of 3-bromooxindoles with indolines for the construction of the N1−C3 linkage quaternary stereogenic centers. Notably, the racemic substrates (3-substituted indolines) could also participate in the reaction with high stereoselectivity. Furthermore, this method facilitated access to cytotoxic (+)-psychotrimine. Further application of this method to this class of alkaloids is underway.

Scheme 3. Scope of the Racemic 3-Substituted Indolines[a]



[a]The reaction was performed on 0.1 mmol scale with **1** (1.2 equiv) and **2a** (1.0 equiv). DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

Scheme 4. Formal Synthesis of Psychotrimine



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, experimental and HPLC data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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References 5e−g contained errors in the version published ASAP April 11, 2014; the correct version reposted April 18, 2014.