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Construction of Vicinal All-Carbon Quaternary Stereocenters by Catalytic Asymmetric Alkylation Reaction of 3-Bromooxindoles with 3-Substituted Indoles: Total Synthesis of (+)-Perophoramidine

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Supporting Information

ABSTRACT: Highly congested vicinal all-carbon quaternary stereocenters were generated via catalytic asymmetric alkylation reaction of 3-bromooxindoles with 3-substituted indoles. These catalytic reactions proceeded in excellent yields with a broad scope on either reaction partner, and with outstanding diastereo- and enantiocontrol. The newly developed method led to the total synthesis of (+)-perophoramidine in a highly efficient manner.

(−)-Communesins[1] and (+)-perophoramidine[2] are two architecturally intriguing natural products, which contain a complex multiring system with two crucial vicinal all-carbon quaternary stereocenters (Figure 1). To date, a number of

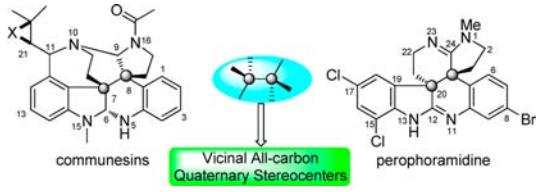


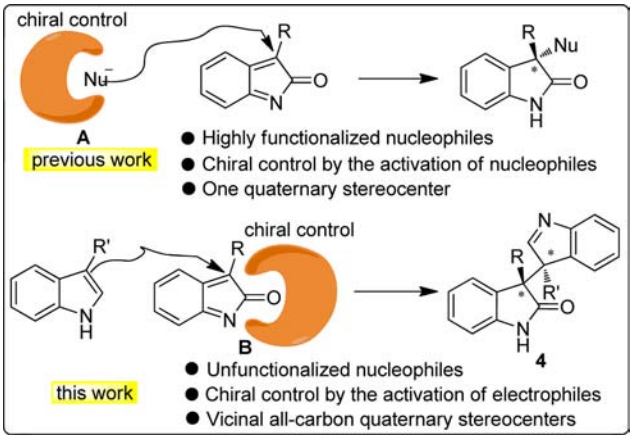
Figure 1. Structures of communesins and perophoramidine.

elegant protocols for assembling these indole alkaloids have been developed.[3−5] In the case of perophoramidine, Funk et al.[6c] and Rainier et al.[6b] reported the total synthesis of (±)-(dehalo)perophoramidine. Subsequently, Qin et al. achieved the asymmetric total synthesis of (+)-perophoramidine by a chiral auxiliary-induced strategy.[6a] However, the catalytic asymmetric synthesis of (+)-perophoramidine has never been reported, probably due to the challenge of catalytic asymmetric construction of the sterically congested vicinal all-carbon quaternary stereocenters.

In fact, the asymmetric assembly, especially in a catalytic fashion, of chiral all-carbon quaternary stereogenic centers is one of the most challenging and dynamic research areas in modern organic synthesis.[7] Hence the catalytic asymmetric construction of *two vicinal all-carbon quaternary centers* with high diastereoselectivity and enantioselectivity in one step remains a truly sterically demanding event.[8]

Indol-2-ones,[9] generated from 3-halooxindoles, could be used as electrophiles in the construction of enantioenriched 3,3-disubstituted oxindoles, in which the enantioselectivity was controlled by the chiral nucleophile complex (**A**) induced by chiral ligand or catalyst.[10] We present herein an enantioselective synthesis of indolenines **4** containing two vicinal all-carbon quaternary stereocenters, in which it was the electrophilic indol-2-one that was activated by the chiral Lewis acid (Scheme 1). The presumed chiral electrophile complex (**B**) of

Scheme 1. Comparison of Two Types of Activation



chiral Lewis acid with indol-2-one was characterized by a base peak at *m*/*z* 857.2210 (for details, see the Supporting Information). By this strategy, the enantioselective total synthesis of (+)-perophoramidine could be easily achieved.

In our initial experiments, we found that exposure of racemic bromooxindole **2a** to K_2CO_3 and 3-substituted indole **1a** in the absence of a Lewis acid did not result in any formation of adduct **4a** (Table 1, entry 1). After a variety of Lewis acid has been surveyed, we found that nickel acetate (entry 5) could efficiently facilitate the reaction. Encouraged by this promising lead, we then examined various complexes of nickel acetate with chiral diamine ligands **3a**−**3g**. Among them, the 1:1 $Ni(OAc)_2$-**3g** complex was found to be the most effective catalyst, delivering the adduct **4a** in 87% yield with 86% ee (entry 11).[11] Afterward, screening of bases showed that the use of 2.0 equiv of K_3PO_4 was an optimum parameter for the reaction. Ultimate optimization of the reaction conditions revealed that the addition of 5 Å sieves could result in a slightly enhanced enantioselectivity of 92% ee (entry 14).

Under the optimized reaction conditions, we investigated the generalities for both reaction components. The results are

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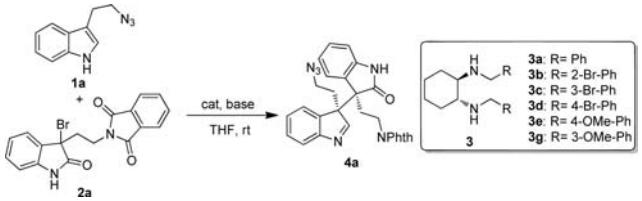
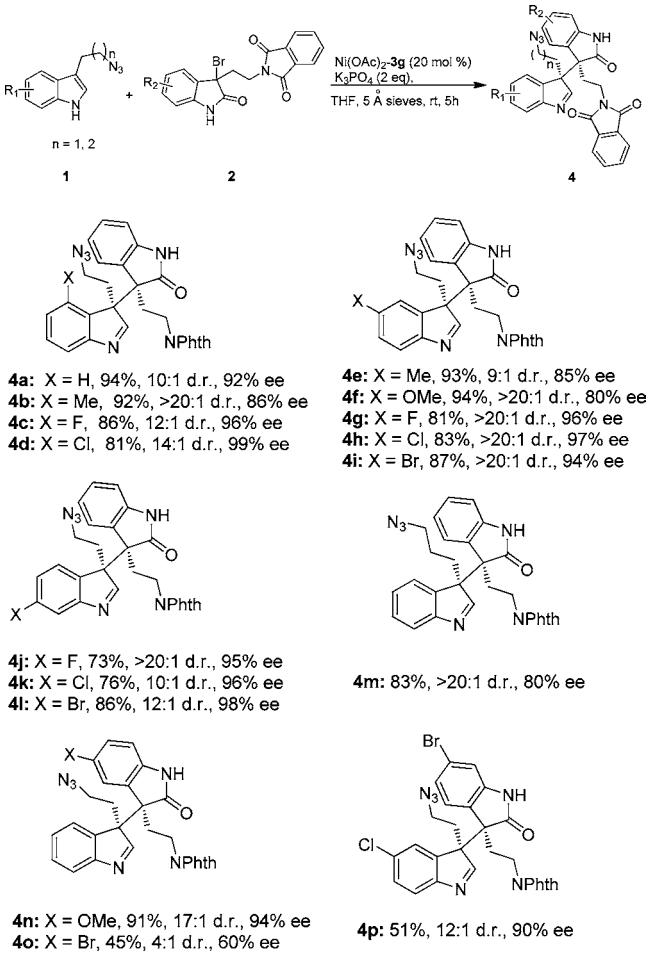
Table 1. Optimization of the Reaction[a]



entry	catalyst (20 mol%)	base	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	–	K_2CO_3	48	–	–	–
2	$Cu(OAc)_2$	K_2CO_3	48	trace	–	–
3	$La(OTf)_3$	K_2CO_3	48	–	–	–
4	$NiCl_2$	K_2CO_3	48	45	7:1	–
5	$Ni(OAc)_2{\cdot}H_2O$	K_2CO_3	48	75	9:1	–
6	$Ni(OAc)_2$-**3a**	K_2CO_3	48	81	10:1	40
7	$Ni(OAc)_2$-**3b**	K_2CO_3	48	79	10:1	37
8	$Ni(OAc)_2$-**3c**	K_2CO_3	48	81	10:1	68
9	$Ni(OAc)_2$-**3d**	K_2CO_3	48	77	10:1	67
10	$Ni(OAc)_2$-**3e**	K_2CO_3	48	75	10:1	83
11	$Ni(OAc)_2$-**3g**	K_2CO_3	48	87	10:1	86
12	$Ni(OAc)_2$-**3g**	K_3PO_4	5	91	10:1	89
13	$Ni(OAc)_2$-**3g**	Cs_2CO_3	2	88	10:1	83
14	$Ni(OAc)_2$-**3g**	K_3PO_4	5	94	10:1	92[e]

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.11 mmol) and **2a** (0.1 mmol) in the presence of catalyst (0.02 mmol) and solvent (1.0 mL). [b]Isolated yield. [c]Diastereoselectivity determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC on a Chiralpak AD-H column. [e]5 Å sieves were added. Phth = Phthaloyl.

Scheme 2. Substrate Scopes[a]



[a]Reaction for **4p** was carried out on a 1 mmol scale.

summarized in Scheme 2. In general, the reaction proceeded well to afford the desired products in high yields and selectivities. We first investigated the generality of the reaction by varying the 3-substituted indoles **1**. When electron-withdrawing groups at C4-, C5-, or C6-position of the indoles **1** were employed, the reaction worked well to give the desired adducts in high yield with excellent enantioselectivity and diastereoselectivity, whereas the indole with electron-donating substituents showed slightly decreased enantioselectivity (**4b**, **4e**, **4f**). Furthermore, a longer chained indole **1** could participate in the reaction, although slightly lower ee was observed (**4m**). We then examined the scope of the reaction with respect to the 3-bromooxindoles **2**. Substitution of the bromooxindole core at C5 with an electron-donating group (5-OMe) gave the desired product in high yield with excellent diastereoselectivity and enantioselectivity (**4n**). Only moderate yield and selectivities were observed when the bromooxindole core with an electron-withdrawing group (5-Br) was used (**4o**). However, to our delight, the presence of substituents on both the indole (5-Cl) and bromooxindole (6-Br) moieties was suitable for the reaction, giving the product **4p** with high levels of stereochemical control, which could be used for the further asymmetric total synthesis of (+)-perophoramidine.

On the basis of the success of our methods, we started our catalytic asymmetric total synthesis of (+)-perophoramidine from **4p**. As shown in Scheme 3, the lactam **4p** was converted into the corresponding Ns-imide derivative, which then underwent a cascade transamidation and closure of the resulting carbamate sequence upon romoval of the phthaloyl protecting group to deliver the aminal **7**. Chlorination of **7** with NCS in AcOH, followed by denosylation with PhSH, uneventfully afforded **9**. Next, the nosylation of lactam **9** and the second transamidation by the reduction of the azido functionality, followed by a chemoselective methylation of the newly generated *p*-nosylamide, afforded the pentacyclic compound **12**. However, treatment of the pentacyclic compound with Meerwein's reagent not only resulted in the convertion of the amide bond to an imidate bond but also led to the methylation of the N-11. Consequently, in order to avoid the excessive methylation, the aminal group was first oxidized with PCC and subsequently protected with Boc_2O to give the carbamate **15**. Reduction of the amidine group of **15** with $LiAlH_4$ result in the removal of the Boc protecting group, providing **16** in moderate yield, whose ^{1}H and ^{13}C spectral characteristics were identical to those previously published.[6c] Conversion of the amide into the corresponding methyl imidate with trimethyloxonium tetrafluoroborate then furnished the targeted cyclization precursor **17**. As anticipated, the desired C24 amidine was generated by the attack of the methylamine on the imidate during the deprotection of nosylamide **17**. Finally, the removal of the Boc and a further one-pot oxidation of the aminal group furnished the final (+)-perophoramidine, whose NMR spectroscopic data and specific rotation are consistent with the reported values.[2,6a]

In summary, we have developed a successful strategy for the construction of indolenines containing two vicinal all-carbon quaternary stereocenters with high diastereoselectivity and excellent enantioselectivity by using a nickel(II)-catalyzed

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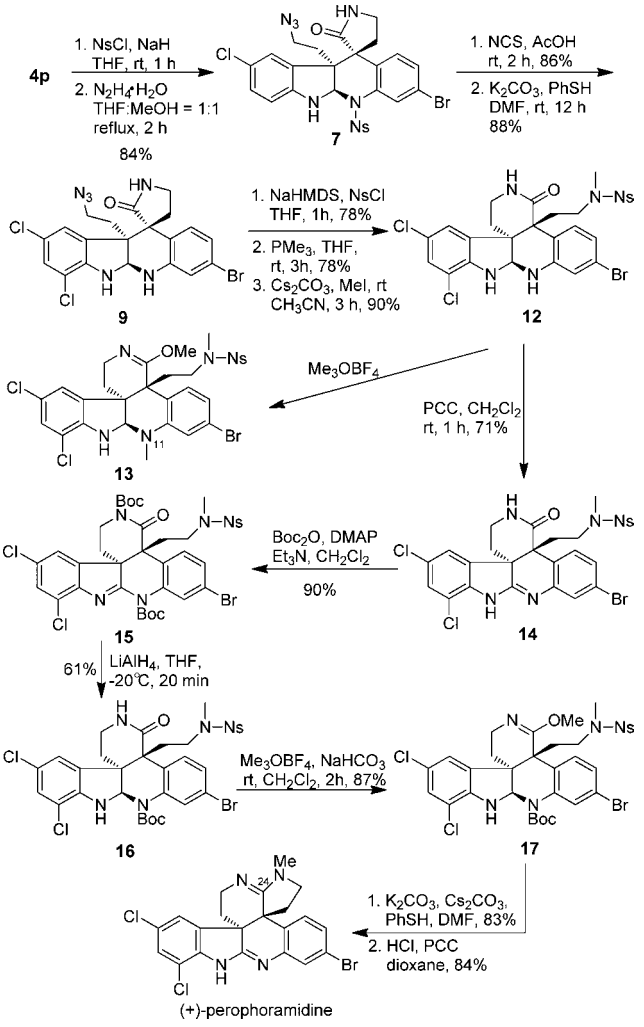
Scheme 3. Total Synthesis of (+)-Perophoramidine[a]



[a]Ns = 4-nitrobenzenesulfonyl, NCS = *N*-chlorosuccinimide, PCC = pyridinium chlorochromate.

asymmetric alkylation reaction of 3-bromooxindoles with 3-substituted indoles. This methodology facilitated the first catalytic asymmetric total synthesis of the cytotoxic agent (+)-perophoramidine. Additional applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization of new compounds, and NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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†H.Z. and L.H. contributed equally.

Notes

The authors declare no competing financial interest.

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