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Highly Diastereo- and Enantioselective Synthesis of Cyclohepta[b]indoles via Chiral Phosphoric Acid-Catalyzed (4+3)-Cycloaddition

Coralie Gelis,[†] Guillaume Levitre,[†] Jérémy Merad,[†] Pascal Retailleau, Luc Neuville and Géraldine Masson*

Abstract: A highly enantio- and diastereoselective formal (4+3)-cycloaddition of 1,3-diene-1-carbamates with 3-indolylmethanols using a chiral phosphoric acid catalyst is reported. The approach described herein provides efficient access to 6-amino-tetrahydrocyclohepta[b]indoles in good yields with excellent levels of enantioselectivity (>98:2 dr and up to 98% ee) and mostly complete diastereoselectivity. Mild reaction conditions, easy scale-up, and versatile derivatization highlight the practicality of this methodology. The mechanism study suggests that cycloaddition occurs in a stepwise fashion, after formation of an ion pair between the chiral catalytic phosphate and the intermediate carbocation.

Cyclohepta[b]indole unit is present in a large number of natural products, and pharmaceutical drugs.^[1,2] Examples include exotines A and B isolated from *Murraya exotica*,^[2a] actinophyllic acid from the leaves of *Alstonia actinophylla*,^[2b] ervitsine from *Pandacea boiteau*,^[2c] and a synthetic sirtuin 1 inhibitor (Figure 1).^[2d,e] Although their prominence in natural and non-natural bioactive molecules has stimulated considerable synthetic efforts in this area,^[1,2] the construction of cyclohepta[b]indoles in a stereodefined way remains challenging^[3] and very few methods account for the asymmetric formation of such molecules.^[4] Multi-step syntheses have been reported by the groups of Gaich^[4a] and Zheng and You^[4b] in which the cyclohepta[b]indole moiety was delivered by a diastereoselective cyclization of enantioenriched preformed precursor. In 2011, Enders *et al.* reported the first enantioselective synthesis of the corresponding seven-membered ring based on two consecutive Friedel–Crafts reactions catalyzed by a chiral thioamide and Au^I sequentially.^[4c] Even though the enantioselectivity was excellent (up to 99% ee), this elegant approach is mainly limited to the formation of mono-substituted benzocyclohepta[b]indoles. Two years later, Hong *et al.* described an enantioselective organocatalytic one pot, two-step sequential process to synthesize trisubstituted cyclohepta[b]indoles with excellent enantioselectivity, albeit moderate diastereoselectivity.^[4d]

In this context, the development of a straightforward procedure for the synthesis of enantiopure cyclohepta[b]indoles is highly desirable. Among the practicable strategies,^[1,3-7] (4+3)-

cycloadditions^[8] appear as the most efficient, direct, and economical approach. Surprisingly, only one asymmetric version has been disclosed by Sun *et al.* in which Rh-catalyzed dearomative (4+3)-cycloaddition of vinylindoles led to cyclohepta[b]indolines with high ee.^[9] However, the formation of more complex and easily post-functionalizable scaffolds would be particularly useful considering the structural diversity of biologically active cyclohepta[b]indoles. In this way, we wish to report the first highly diastereo- and enantioselective preparation of polysubstituted cyclohepta[b]indoles based on an organocatalyzed (4+3)-cycloaddition process.

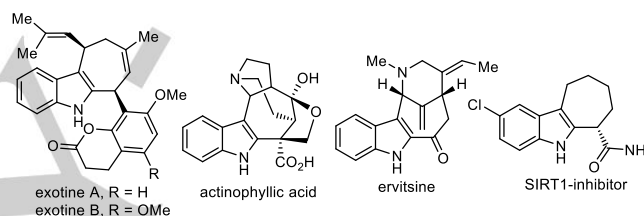


Figure 1. Representative cyclohepta[b]indole compounds.

As part of a program directed toward the stereoselective synthesis of heterocycles,^[10] we recently described an efficient enantioselective synthesis of trisubstituted cyclopenta[b]indoles^[10c] via a chiral phosphoric acid-catalyzed (3+2)-cycloaddition between alkylideneindolenium ions generated *in situ* from indolylarylmethanols^[11] and enecarbamates as dienophiles.^[12,13] We also reported that chiral phosphoric catalysts were able to efficiently catalyze asymmetric nitroso-Diels–Alder reactions with 1,3-diene-1-carbamates.^[10b,14] Since (4+3)-cycloadditions have already been established starting from indolylarylmethanols,^[1,6h-m] we reasoned that dienecarbamates could suit well as partners to develop the first catalytic enantioselective (4+3) cycloadditions in the presence of a chiral phosphoric acid. To validate this assumption, we initially attempted to conduct the reaction of indolyl(phenyl)methanol derivative **1a** with benzyl (penta-1,3-dien-1-yl)carbamate **2a** with and 5 mol% of (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid **4** in CH₂Cl₂ in the presence of 4 Å molecular sieves. Gratefully, the reaction proceeded smoothly to afford the corresponding 6-aminotetrahydrocyclohepta[b]indole **3a** in 78% yield with 91% ee as a single all-*cis* diastereomer (entry 1). Toluene was found to be a better solvent furnishing **3a** in slightly better yield with 97% ee (entry 2). Lowering the reaction temperature markedly decreased the yield of **3a** and did not have a significant effect on the enantioselectivity (entry 3). Performing the same reaction in the absence of 4 Å MS led to a lower yield, indicating the deleterious effect of water on the overall process (entry 4). Other drying agents were evaluated, but 4 Å MS provided the best results in terms of both yield and

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enantioselectivity (entries 3 vs 5-8). Diversely substituted carbamates can react with **1a** but the best results were obtained with Cbz-protected dienamines (entries 3 vs 9 – 12).

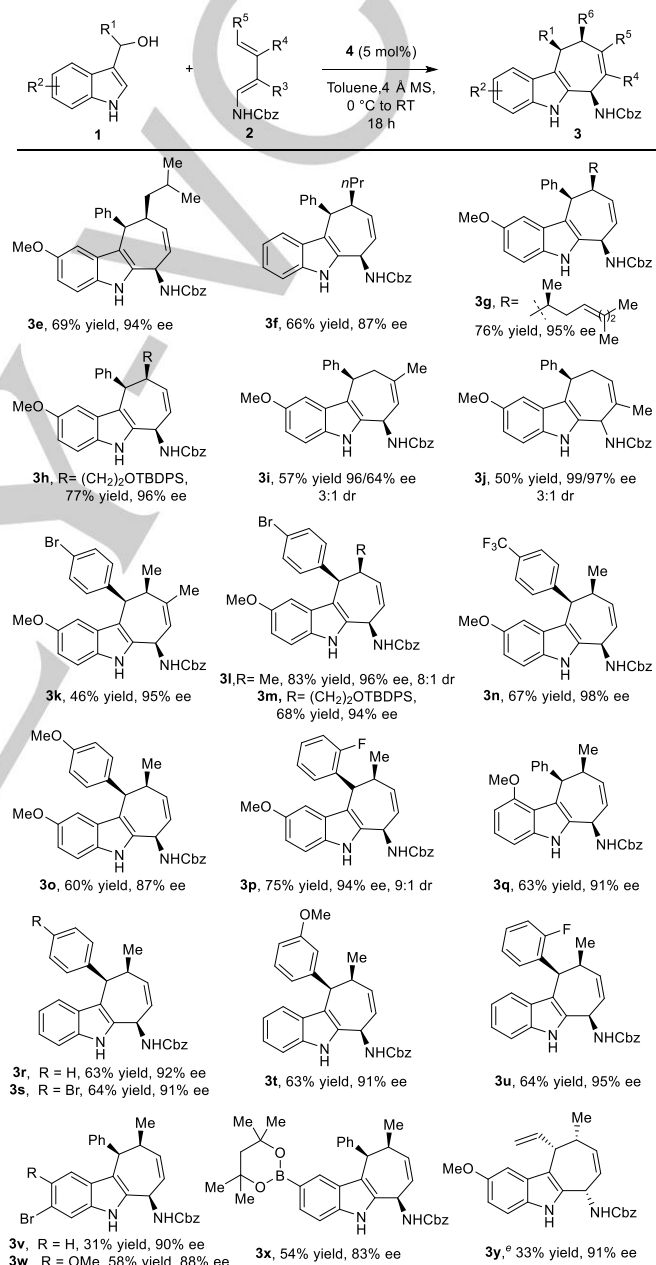
Table 1. Survey of Reaction Conditions for Enantioselective (4+3)-Cycloaddition^[a]

Entry	Solvent	Additive	Product	Yield [%] ^[b]	ee [%] ^[c,d]
1	CH ₂ Cl ₂	4 Å MS	3a	78	91
2	Toluene	4 Å MS	3a	81	97
3 ^[e]	Toluene	4 Å MS	3a	67	97
4	Toluene	–	3a	63	86
5	Toluene	3 Å MS	3a	64	96
6	Toluene	5 Å MS	3a	74	96
7	Toluene	MgSO ₄	3a	59	89
8	Toluene	Na ₂ SO ₄	3a	69	86
9 ^[f]	Toluene	4 Å MS	3a	83	97
10	Toluene	4 Å MS	<i>ent</i> - 3b ^[g]	63	94
11	Toluene	4 Å MS	3c	57	87
12	Toluene	4 Å MS	<i>ent</i> - 3d ^[g]	79	95

[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.11 mmol) and **4** (0.005 mmol) in 2.0 mL of solvent for 18 h at RT. [b] Yields refer to chromatographically pure all *cis*-isomer **3** determined to be higher than 98/2 by ¹H NMR. [c] ee values were determined by HPLC with a chiral stationary phase. [d] All *cis*-configuration was determined by X-ray single crystal structure analysis of racemate (+)-**3w** and the absolute configuration (6*R*,9*S*,10*R*) was assigned by X-ray single crystal structure analysis of enantioenriched **9** (see Supporting Information). [e] Performed at 0°C. [f] With 1.0 mmol scale of **1a**. [g] Performed with *ent*-**4** as a catalyst.

Having optimized the reaction conditions for the synthesis of the tetrahydrocyclohepta[*b*]indol-6-yl)carbamate **3a**, we investigated the scope of **4**-catalyzed diastereo- and enantioselective (4+3)-cycloaddition reactions of **1a** with a variety of dienes **2**. In general, the reaction proceeded smoothly with excellent diastereo- and enantioselectivity. For instance, the diene carbamates bearing branched or linear alkyl chains at the C₄ position led to corresponding cycloadducts (**3e–3f**) in good yields. Chiral dienecarbamate derived from (*R*)-citronellol gave **3g** with an excellent enantiomeric excess. Additionally, silyl ethers (**3h**) are compatible functional groups in this process. The diastereoselectivity was substantially affected when non terminal substituted dienes were used. Nevertheless, appreciable level of selectivity remained as observed for compounds **3i** and **3j** (3:1 dr) with excellent enantioselectivity for the major isomer (96% and 97% ee respectively). On the other hand, substituents at the C₃ position of dienes does not affect the selectivity (**3k**). Next,

the scope of the reaction was successfully extended to other 3-indolylmethanols **1** under similar conditions. Dipole precursors **1** bearing either electron-rich or electron-deficient aryl groups at 1' position worked well providing the corresponding cyclohepta[*b*]indoles **3i–3o** in generally high enantioselectivities (87–98%). Challenging *ortho*-substituted aryl groups were also tolerated in the cycloaddition, forming **3p** in respectable yield and high enantioselectivity. The displacement of the methoxy group onto the indole C₅-position also provides good results in term of yields and selectivity (**3q**). Finally, we observed that the electronic property of the substituents on the indole did not



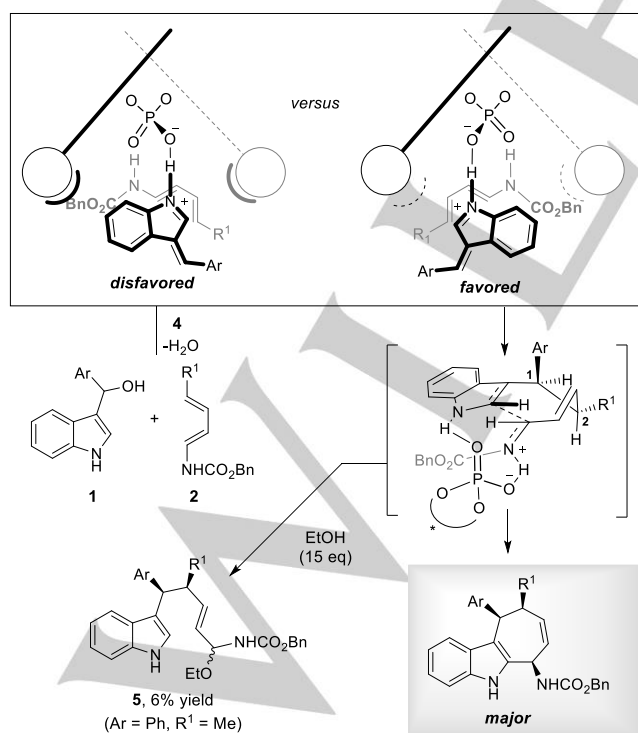
Scheme 1. Scope of the enantioselective (4+3)-cycloaddition.^[a,b,c,d] [a] General reaction conditions: **1** (0.10 mmol), **2** (0.10 mmol), and **4** (0.005 mmol) in 2.0 mL of toluene at 0°C to RT for 18 h with 4 Å MS. [b] Yield of isolated pure product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] If unspecified, dr >98/2, determined by ¹H NMR. [e] Synthesized using *ent*-**4** catalyst (10 mol%).

influence much on the enantioselectivity, but strongly affected the reaction yield. For instance, unsubstituted indoles (**3r-3u**) led to the desired products in good yields whereas the presence of electron poor substituents decreased the yield considerably (**3v**). To our delight, indole bearing both an electron-poor and an electron-rich aromatic moiety was successfully used to form **3w** in a respectable yield. More remarkably, the pinacol boronic ester was tolerated allowing further functionalizations of **3x** using cross-coupling reactions. To finish, new opportunities in terms of scaffold diversity and potential post-transformations were offered by the synthesis of **3y** in lower yields but high enantioselectivity.

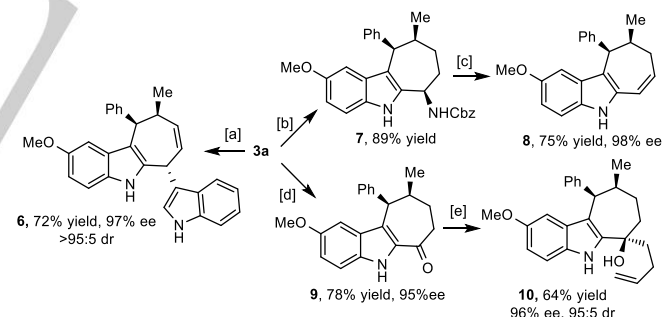
The mechanism of the cycloaddition is assumed to initially involve of H₂O from **1** to generate an ion pair between the new-formed indolium and chiral phosphate. In the meantime, hydrogen bonding between the dienecarbamate NH and the Lewis basic phosphoryl oxygen ensures a highly organized transition state in the enantio-determining step (Scheme 3). Based on the model proposed by Goodman,^[15] the facial selectivity (*Re* face of the indole and *Si* face of the diene) can be rationalized by the chiral environment provided by the tethering phosphoric acid as proposed on scheme 3. Taking into account the reported conformations of cyclohepta-1,4-dienes^[16] and the one of natural products exotines (solution and solid state conformation),^[2a] we can hypothesize that a bent boat-like conformation would be operative in the ring-closing step to afford the all-*cis* product as the major isomer. In the absence of R¹ group (**3f** and **3g**), an easy rotation around the C₁-C₂ bond would bring the aromatic substituent in a more favorable equatorial position leading to a lower diastereoselectivity (see supporting information). The stepwise representation of this reaction is consistent with our previous work on the (3+2)-cycloaddition,^[10a] as well as other reports.^[12, 13a-f] Moreover, the trapped iminium intermediate **5** was isolated in 6% yield when

the reaction between **1g** and **2a** was performed in the presence of EtOH (15 eq).

To demonstrate the practicality and scalability of this procedure, we conducted the reaction on a larger scale (1.0 mmol) under standard conditions, which furnished the pure cyclohepta[*b*]indole product **3a** (83% yield and 97% ee) without any loss of efficiency and selectivity (Table 1, entry 9). Pleasingly, **3a** can be readily transformed into other interesting derivatives owing to the presence of functional groups. For instance, indole addition to **3a** using 5 mol% of Bi(OTf)₃ as Lewis acid^[17] to trigger the formation of benzyl cation intermediate resulted in 72% yield of **6** as a single diastereomer providing efficient access to natural related biologically active products.^[18] Moreover, using PtO₂, the endocyclic olefin was chemoselectively hydrogenated in good yield without affecting the *N*-benzyl group. The carbamate functional group is ideally placed and can also serve as an anchorage point for selective transformations. As illustration, the treatment of **3a** with TsOH.H₂O afforded **8** in respectable yield with no change of enantioselectivity. Finally, subjecting of **1a** to aqueous basic conditions did not lead to the anticipated Cbz deprotection. Instead, unexpected ketone **9** was isolated as the sole product in 78% yield without racemization. Its structure was unambiguously identified through an X-ray crystal structure determination (see supporting information). Transition metal-free allylic isomerization of alcohols leading to ketone have already been reported. Depending on the base used, they involve a deprotonation/reprotonation or a radical pathway. Accordingly, a plausible mechanism could follow a base-mediated allylic isomerization leading to an enamide that would next be hydrolyzed under the conditions.^[19] Then, addition of allylmagnesium chloride to **9** resulted in the formation of **10** in 78% yield with high diastereoselectivity (95:5).



Scheme 3. Activation model via a putative transition state.



Scheme 3. Scale-Up and synthetic transformation of **3a**. Reaction conditions [a] Indole (1 eq), Bi(OTf)₃ (5.0 mol%), toluene/EtOAc (2/1), RT; [b] PtO₂ (5 mol%), H₂ (1 atm), EtOAc, RT. [c] TsOH.H₂O (5.0 eq), THF, RT. [d] LiOH (20 eq), dioxane/H₂O (1.25:1), reflux, 12 h. [e] AllylMgCl (3.0 eq), THF, 0 °C to RT, 3 h.

We reported the first catalytic enantioselective formal (4+3)-cycloaddition of 1,3-diene-1-carbamates with 3-indolylmethanols to furnish 6-amino-tetrahydrocyclohepta[*b*]indoles containing 2 to 3 stereogenic centers in good yields with excellent diastereo- and enantioselectivities (up to 99% ee). The trapping experiments provided sound evidence that the present reaction proceeded via a stepwise mechanism. The excellent yields, enantioselectivities, and operational simplicity make this methodology attractive for the synthesis of natural cyclohepta[*b*]indole products.

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Keywords: (4+3)-cycloaddition • chiral phosphoric acid • cyclohepta[b]indoles • heterocycle • hydrogen bonding

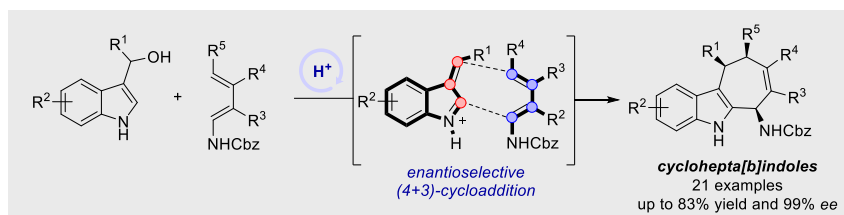
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How chiral protons make large rings: The first chiral phosphoric acid-catalyzed formal (4+3)-cycloaddition between dienecarbamates and 3-indolylmethanols is reported. Various functionalities at different ends of both substrates offer rapid access to optically active 6-amino-tetrahydrocyclohepta[b]indoles bearing three stereogenic centers in one pot. The salient features of this reaction include mild conditions, good yields, good to excellent diastereo- and enantioselectivity, ease of scale-up, and post- transformations.

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