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ARTICLE

Asymmetric Organocatalytic Synthesis of 4,6-Bis(1*H*-indole-3-yl)-piperidine-2 carboxylates

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We developed an asymmetric organocatalytic synthesis of 4,6-bis(1*H*-indole-3-yl)-piperidine-2-carboxylates using 10 mol% of a chiral phosphoric acid. The products, which are novel bisindole-piperidine-amino acid hybrids, can be obtained in one step from 3-vinyl indoles with imino esters in dichloromethane at room temperature after 1 h of reaction time. A variety of these compounds could be synthesized in up to 70% yield and 99% *ee*, and they were experimentally and computationally analyzed regarding their relative and absolute stereochemistry.

Introduction

Bisindole alkaloids can be widely found in nature, exhibiting various interesting biological activities which can be medically important. There are numerous compounds of marine origin bearing two isolated indoles on one heterocycle (Fig. 1), such as nortopsentins (**1a**–**d**)[1,2] and their analogs which exhibit antitumor,[2d,3–8] antiproliferative, antiplasmodial,[9] and antifungal[3] activities. The dragmacidins[10] (e.g. **2a**–**b**) possess antitumor,[11,12] phosphatase inhibitory,[13] and antiviral[14] activities and their derivatives hamacanthins[15] (e.g. **3**) have antitumor,[16] antifungal,[17] and antibacterial[16,18] properties.

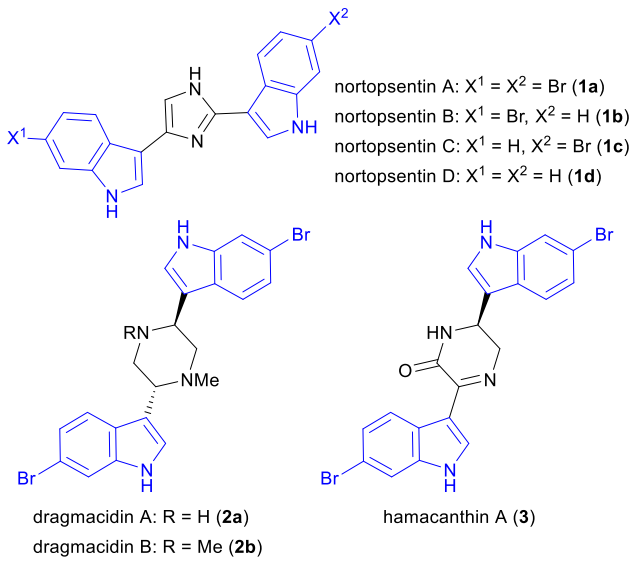


Fig. 1. Structures of some indole alkaloids containing two isolated indole moieties.

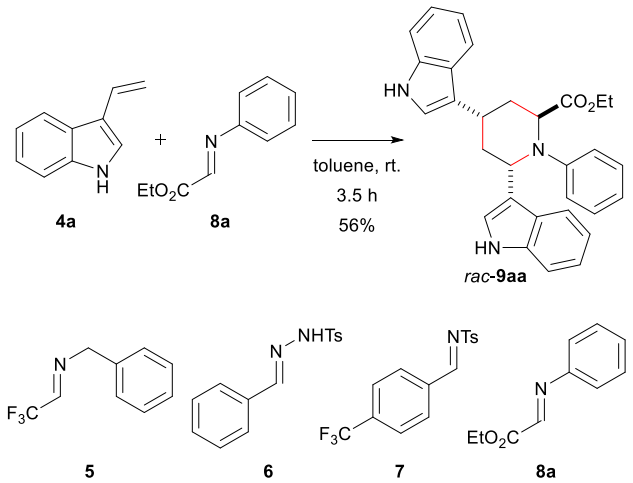
Starting from the late 80s, 3-vinylindole (**4a**) was found to be a versatile building block for the synthesis of heterocycles fused to an indole moiety. This is due to the fact that 3-vinylindole acts as an diene in Diels-Alder reaction with various electron-deficient olefins and aza dienophiles, e.g. nitrosobenzene, DEAD, diethyl mesoxalate, benzoquinone, and maleimides.[19–22] The reactivity of 3-vinylindoles can be utilized in the synthesis of carbazoles.[19,20,23,24] Also reactions with singlet oxygen are reported.[25] In the last years, the first asymmetric organocatalytic Diels-Alder reactions of 3-vinylindoles were reported, including thiourea-catalyzed reactions with maleimides or quinones[26] and indolones.[27] Furthermore, the reactivity of 3-vinylindole can be that of a dienophile, furnishing Povarov-type products when reacted with electron-rich arylimines.[28] In that work, it was proven that the intermediate could be trapped by excess of 3-vinylindole (5 equiv.) leading to an interesting and complex bisindole consisting of two units of vinylindole and one unit of arylimine. However, Ricci's work mainly focused on the asymmetric Povarov reaction and they made no further investigations towards the synthesis and the relative/absolute configuration of the resulting bisindole-piperidine-hybrid.

Results and discussion

Reaction between 3-vinylindole (4a) and glyoxylate imine (8a)

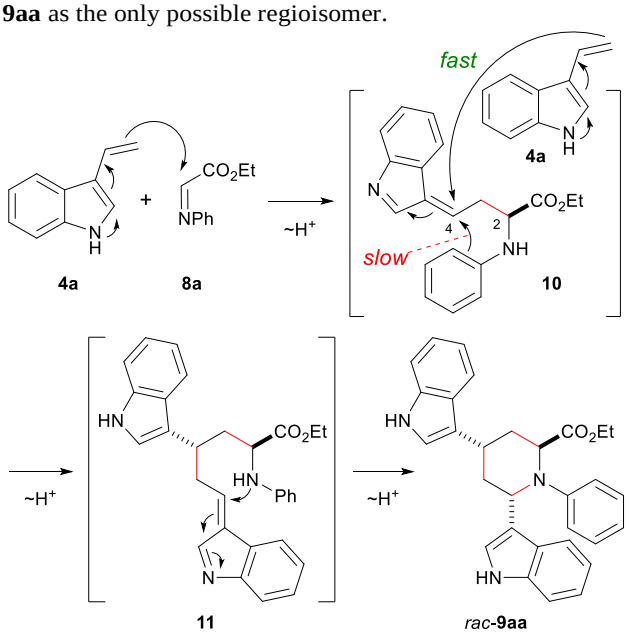
We took on the interesting and dual reactivity of 3-vinylindoles and explored the behaviour towards various types of imines in order to create nitrogen heterocycles bearing new stereocenters. Imines **5**–**8a** were prepared according to established procedures[29–32] and treated with 3-vinylindole (**4a**)[33] in toluene (Scheme 1). Only in the case of ethyl glyoxylate-derived imine **8a** a reaction was observed. It turned out that 3-

vinylindole did not act as a diene in this reaction, but the formed product arised from a multicomponent addition of two equivalents 3-vinylindole (**4a**) and one equivalent of imino ester **8a**. Interestingly, this reaction occurred already at room temperature with short reaction time (3.5 h) without any addition of catalyst. The product is similar to that reported by Ricci *et al.* but has an ethyl ester moiety at the 2-position (therefore being an amino acid derivative) instead of a phenyl substituent and does not need for a large excess of vinylindole.



Scheme 1. Racemic synthesis of bisindole *rac*-**9aa** with imino ester **8a** (see SI for more information) and attempted reactions with other imines **5**–**7**.

A plausible mechanism for this reaction is given in Scheme 2. After a first addition, a second molecule 3-vinylindole (**4a**) is able to attack the stabilized intermediate **10**. This step proceeds considerably faster than a nucleophilic attack of the aromatic phenyl ring at position 4, since only traces of the corresponding Povarov reaction product were found. An intramolecular ring closure of **11** finally gives piperidine-2-carboxylic ester *rac*-**9aa** as the only possible regioisomer.



Scheme 2. Proposed mechanism for the formation of bisindole *rac*-**9aa**.

For the reaction, a free NH group is necessary on the indole moiety, as in a reaction of N-methylated derivative (1-methyl-3-vinyl-1*H*-indole) with glyoxalate imine **8a**, no product could be isolated. This supports the proposed mechanism for the racemic formation of **9aa** in Scheme 2, which involves several proton transfers of the indole NH. Furthermore, following attempts to protect the indole-NH functionalities in the reaction product **9aa** with trifluoroacetate or tosylate failed.

Asymmetric synthesis of bisindole 9aa and optimization

Next, the asymmetric reaction of **4a** and **8a** was investigated. It was envisioned that chiral thiourea catalysts, such as **12**–**14** (Fig. 2), would be able to interact strongly with imine **8a** *via* H-bond catalysis.[26,27,34–37] However, the results employing these catalysts were not satisfying, giving almost no enantioinduction with 7.5% *ee* at most and often strongly diminished yields (Table 1) compared to those without employing any catalyst. The enantioselectivity could not be improved when the temperature was lowered (entry 2). A considerable improvement of the yield was observed when utilizing catalyst **14** in CH_2Cl_2, however, in this case the product was nearly racemic (entry 4).

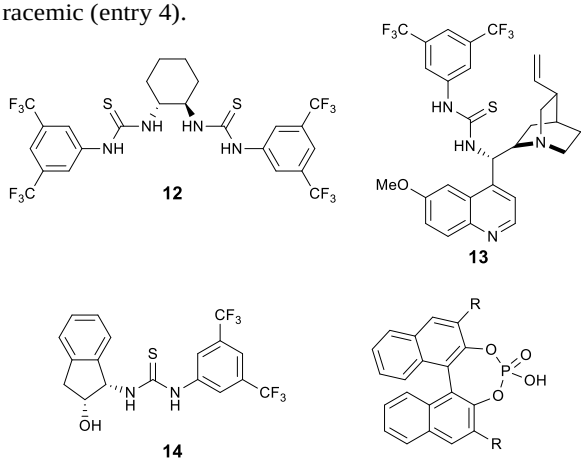


Fig. 2. Screened thiourea und phosphoric acid catalysts.

Chiral phosphoric acids[38] represent another catalyst class widely used in organic chemistry, especially in the strongly related asymmetric (vinylogous) Mannich-type reactions and also employed by Ricci *et al.* in the aforementioned paper.[28] Three phosphoric acid catalysts **15**–**17** (Fig. 2), which are commercially available, and different reaction conditions were screened towards their ability to promote an asymmetric reaction of 3-vinylindole (**4a**) and imine **8a** to substituted piperidine **9aa**.

Table 1. Screening of thiourea catalysts (upper part), phosphoric acid catalysts (middle part), and solvents (lower part).

Entry	Cat. [mol%]	solvent	time	Temp.	Yield[a]	*ee*[b]
1[c]	**12** [20]	*n*hexane/ toluene 2:1	4 h	rt.	22%	3%
2	**12** [20]	CH_2Cl_2	2 h	–78 °C	13%	3%

3[c]	**13** [20]	*n*hexane/ toluene 2:1	18 h	rt.	15%	0%
4	**14** [20]	CH_2Cl_2	16 h	rt.	52%	2%
5	**14** [20]	*n*hexane	16 h	rt.	13%	7.5%
6	**15** [10]	toluene	2 h	rt.	46%	69%
7	**15** [10]	toluene	2.5 h	0 °C	51%	56%
8[d]	**15** [10]	toluene	5 h	0 °C	54%	54%
9	**16** [10]	toluene	2 h	rt.	47%	88%
10	**16** [10]	toluene	5 h	–78 °C	traces	-
11	**16** [10]	toluene	4 h	–40 °C	30%	79%
12[c]	**16** [10]	toluene	1 h	rt.	60%	92%
13[c]	**16** [10]	toluene	20 min	50 °C	69%	91%
14[c]	**17** [10]	toluene	1 h	rt.	43%	72%
15[c]	**16** [10]	THF	4.5 h	rt.	70%	91%
16[c]	**16** [10]	Et_2O	1.17 h	rt.	65%	93%
17[c]	**16** [10]	CH_2Cl_2	1 h	rt.	64%	94%
18[c]	**16** [10]	MeCN	1.5 h	rt.	67%	87%
19[e]	**16** [10]	CH_2Cl_2	1 h	rt.	57%	94%
20[f]	**16** [10]	CH_2Cl_2	1 h	rt.	61%	98%

If not stated otherwise, the catalyst, then 3-vinylindole (**4a**, 0.1 mmol) were added to a solution of imine **8a** (0.05 mmol) in absolute solvent (1 mL). After consumption of the starting material the crude mixture was purified via preparative TLC (PE/EtOAc 3:1). [a] Isolated yield; [b] determined by HPLC; [c] reaction was carried out with 0.1 mmol of **4a** and 0.1 mmol of **8a**; [d] imine **8a** was prepared in situ from ethyl glyoxylate and aniline; [e] reaction was performed on a gram scale (14 mmol of **4a** and 7 mmol of **8a**). [f] reaction was carried out with 0.3 mmol of **4a** and 0.1 mmol of **8a**.

The following conclusions can be made considering the results in Table 1: i) All of the screened chiral phosphoric acid catalysts give good enantiomeric excesses; ii) Good yields could be obtained while only using 1 equivalent of each reactant; iii) In some cases, employing a catalyst leads to a considerable improvement of chemical yield to 60% or more (entries 12 and 13) compared to the reaction without any catalyst; iv) The best catalyst in terms of yield and *ee* (> 90%) is catalyst **16** (entries 12 and 13). At 50 °C, the reaction is complete after only 20 min with a yield close to 70% and an *ee* of 91% (entry 13); v) Lowering the temperature did not improve the results, it even gave diminished yields and *ee*s (entries 10 and 11); vi) Preparing imine **8a** in situ from ethyl glyoxylate and aniline gives product **9aa**, too, but with no significant change of yield and *ee* (entry 8), nevertheless this shows that even a four component reaction to form **9aa** is feasible. Also, in the catalyzed reaction, the formation of Povarov products was completely surpressed.

Having found an efficient catalyst **16**, several solvents were screened in order to improve the enantiomeric excess. The yields in any solvent remained quite stable (57–70%, entries 15–20). The enantiomeric excess was optimized in dichloromethane (up to 98%, entry 20). Acetonitrile caused the *ee* value to drop (entry 18).

Relative and absolute configuration of 9aa

The relative configuration was identified through NOE correlations (Fig. 3). In the proposed conformer structure, both indole-3-yl groups are standing in equatorial position, thus minimizing steric interactions between one another, and the ethyl ester is standing axially, possibly to avoid interaction with the *N*-phenyl group. In addition, crystals of **9aa** could be obtained by recrystallization from *i*PrOH. The absolute configuration was unequivocally proven by X-Ray crystallography using the effects of anomalous dispersion (Fig. 3). Thus a (2*S*,4*S*,6*S*) configuration could be confirmed (see also SI and CCDC-977608).

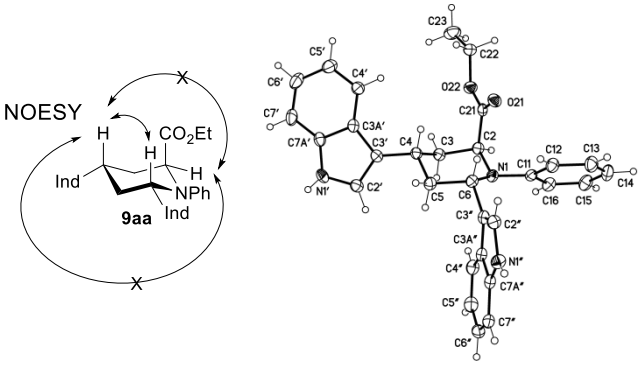


Fig. 3. Structure of bisindole **9aa**, left: experimentally determined NOE correlations; right: molecular structure of **9aa** (displacement parameters are drawn at 50% probability level, CCDC-977608).

As our sample of **9aa** had an enantiomeric purity of *ee* = 94%, it is generally possible that the single crystal used for X-Ray diffraction study consisted of the minor enantiomer. To exclude this eventuality, we measured the electronic circular dichroism (CD) spectrum, which is a property of the bulk compound, in methanol at 20 °C. Furthermore, using the TURBOMOLE program package,[39] the spectrum was calculated with time-dependent density functional theory methods[40] (along with the C-4 epimer of **9aa**, which was clearly ruled out as a possible product, see also SI). Because of good agreement of the calculated spectrum of **9aa** with the experimental spectrum, we can assure the proposed (2*S*,4*S*,6*S*) configuration (Fig. 4).

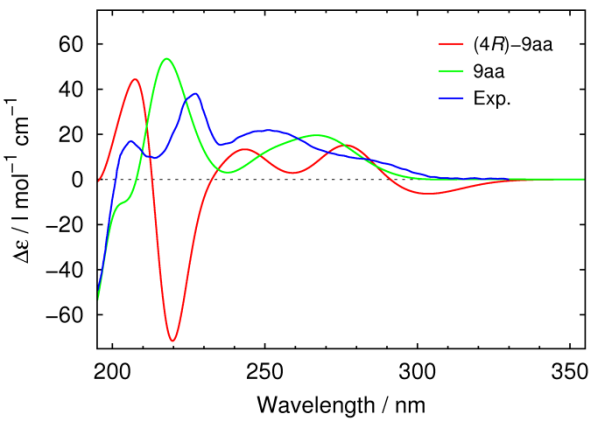


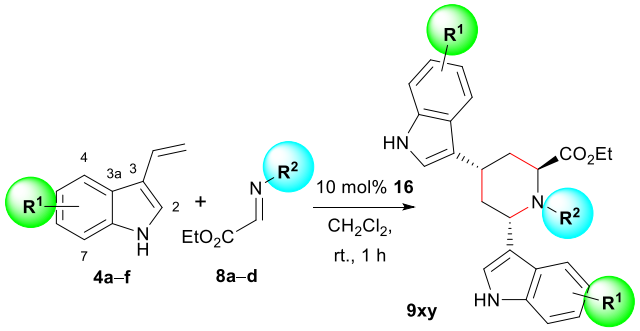
Fig. 4. Experimental CD spectrum (blue curve, 94% *ee*) and calculated CD spectra of **9aa** (green curve) and its C-4 epimer (red curve); conditions: c = 0.05 mg/mL, MeOH, 20 °C.

Scope of the reaction

As the reaction conditions were optimized, the scope of the reaction was explored by using differently substituted 3-vinylindoles **4a**–**f** and glyoxalate imines **8a**–**e**. The reactions were carried out on a 0.1 mmol scale with catalyst **16** in dichloromethane. In all cases, high *ee*s were achieved, while depending on the substitution pattern and varying stability of the different vinylindoles the yields where sometimes

considerably lower than for the unsubstituted substrate **4a** (Table 2). We believe that in the case of vinylindoles **4d** and **4e** (entries 7 and 8), the low yields are due to the fast decomposition of the starting material. Derivatives **4d** and **4e** must be used immediately after preparation and even when stored in the freezer at –20 °C, they decomposed within few days. Furthermore, we discovered that the reaction proceeded diastereoselectively, leading to one main product. Apart from the shown isomers, we observed, in most cases, traces of one or two other diastereomers which could not completely be separated from the main product. In the ^{1}H NMR spectra, their signals can be seen and distinguished especially in the range of 4.5–5.5 ppm adjacent to the main product signals (see SI).

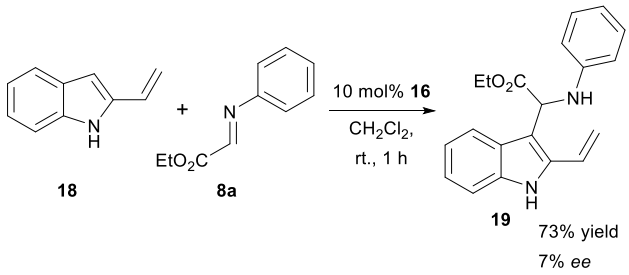
Table 2. Synthesis of bisindole derivatives **9xy**.



Entry	equiv. (**4x**:**8y**)	R^1 (**4x**)	R^2 (**8y**)	yield[a] of **9xy**	*ee*[b]
1	1:1	H (**4a**)	Ph (**8a**)	64% **9aa**	94%
2	1:1	5-Br (**4b**)	Ph (**8a**)	51% **9ba**	90%
3	2:1	7-Me (**4c**)	Ph (**8a**)	43% **9ca**	>99%
4	2:1	5-Br (**4b**)	3,5-Me_2-C_6H_3 (**8b**)	58% **9bb**	94%
5	2:1	H (**4a**)	4-OMe-C_6H_4 (**8c**)	56% **9ac**	97%
6	2:1	H (**4a**)	4-Br-C_6H_4 (**8d**)	28% **9ad**	93%
7	2:1	5-OMe (**4d**)	Ph (**8a**)	21% **9da**	87%
8	2:1	5-Br-7-Me (**4e**)	Ph (**8a**)	25% **9ea**	75%
9	2:1	6-F (**4f**)	Ph (**8a**)	34% **9fa**	89%
10	2:1	6-F (**4f**)	4-OMe-C_6H_4 (**8c**)	48% **9fc**	n.d.

Catalyst **16** (10 mol%), then 3-vinylindole derivative **4**, were added to a solution of imine **8** in CH_2Cl_2 (1–2 mL). After stirring for 1 h at rt., the crude mixture was purified *via* preparative TLC. [a] Isolated yield after column chromatography or preparative TLC; [b] determined by HPLC; n.d. = not determined (no separation of enantiomers achieved).

We also found that this kind of reactivity in a three-component reaction is only possible with 3-vinylindoles and not the isomeric 2-vinylindole (**18**), which certainly supports the necessity of a free electron pair on the nitrogen in conjugation to the vinyl group. Under the same reaction conditions with catalyst **16**, we observed the typical reactivity of unsubstituted indoles with electrophiles, which is that of a spontaneous Friedel-Crafts addition,[41,42] giving amino acid derivative **19** with only poor enantioselectivity (Scheme 3).



Scheme 3. Synthesis of amino acid derivative **19**.

Having proven the generality of the reaction by applying the conditions on various substrates, we explored if an up-scaling of the reaction was possible. Upscaling (2 g scale) the reaction of bisindole **9aa** still gave a comparable yield of 57% with an unchanged *ee* of 94%. Furthermore, we exemplarily showed that the catalyst **16** was recyclable (see SI for more information).

Conclusions

In conclusion, we developed a powerful three-component, enantioselective, and organocatalytic synthesis of 4,6-bis(1*H*-indole-3-yl)piperidine 2-carboxylates **9xy** utilizing easily accessible 3-vinylindoles and imino esters and a chiral phosphoric acid. The reaction proceeds fast (1 h) and diastereoselective at room temperature, building three new bonds and three new stereogenic centers in one step, and furnishes the products in yields up to 70% and *ee*s up to 99%. The reaction can be conducted on a gram scale and the catalyst is recyclable, furthermore, it is also possible to run it as a four-component reaction. The products are highly functionalized, as they are bisindole-piperidine-amino acid hybrids, and they resemble medically interesting natural products. Their activity towards various test organisms is currently under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, analytic data (including NMR spectra, HPLC traces), details of CD spectra calculations, and crystallographic data for **9aa**.
For crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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