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Asymmetric organocatalytic synthesis of 4,6-bis-(1H-indole-3-yl)-piperidine-2-carboxylates†

Sabilla Zhong, a,b Martin Nieger, c Angela Bihlmeier, d Min Shi,*a and Stefan Bräse*b,e

We developed an asymmetric organocatalytic synthesis of 4,6-bis(1H-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 medicinally important. There are numerous compounds of marine origin bearing two isolated indoles on one heterocycle (Fig. 1), such as nortopsentsins (1a–d)1,2 and their analogs which exhibit antitumor,2d–8 antiproliferative, antiplasmodial,9 and antifungal3 activities. The dragmacidins10 (e.g. 2a–b) possess antitumor,11,12 phosphatase inhibitory,13 and antiviral14 activities and their derivatives hamacanthins15 (e.g. 3) have antitumor,16 antifungal,17 and antibacterial16,18 properties.

In 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 a diene in the Diels–Alder reaction with various electron-deficient olefins and aza dienophiles, e.g. nitrosobenzene, DEAD, diethyl mesoxalate, benzoquinones, 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 few years, the first asymmetric organocatalytic Diels–Alder reactions of 3-vinylindoles were reported, including thiourea-catalyzed reactions with maleimides or quinones26 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 an 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, the work of Ricci et al. 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 their behaviour towards various types of imines in order to create nitrogen heterocycles bearing new stereocenters. Imines 5–8a were prepared according to established procedures and treated with 3-vinylindole (4a) 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 arose from a multicomponent addition of two equivalents of 3-vinylindole (4a) and one equivalent of imino ester 8a. Interestingly, this reaction occurred at room temperature with a short reaction time (3.5 h) without any addition of the 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 require a large excess of vinylindole.

A plausible mechanism for this reaction is given in Scheme 2. After the first addition, the second molecule 3-vinylindole (4a) is able to attack the stabilized intermediate 10. This step proceeds considerably faster than the 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 regiosomer.

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-1H-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. However, the results employing these catalysts were not satisfying, giving almost no enantioinduction with 7.5% ee at most and often strongly diminished
Table 1 Screening of thiourea catalysts (upper part), phosphoric acid catalysts (middle part), and solvents (lower part)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. [mol%]</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp.</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12&lt;sup&gt;[20]&lt;/sup&gt;</td>
<td>n-Hexane-toluene 2:1</td>
<td>4 h</td>
<td>rt.</td>
<td>22%</td>
<td>3%</td>
</tr>
<tr>
<td>2</td>
<td>12&lt;sup&gt;[20]&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2 h</td>
<td>–78 °C</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>13&lt;sup&gt;[20]&lt;/sup&gt;</td>
<td>n-Hexane-toluene 2:1</td>
<td>18 h</td>
<td>rt.</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>14&lt;sup&gt;[20]&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>16 h</td>
<td>rt.</td>
<td>52%</td>
<td>2%</td>
</tr>
<tr>
<td>5</td>
<td>14&lt;sup&gt;[20]&lt;/sup&gt;</td>
<td>n-Hexane</td>
<td>16 h</td>
<td>rt.</td>
<td>82%</td>
<td>7.5%</td>
</tr>
<tr>
<td>6</td>
<td>15&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>2 h</td>
<td>rt.</td>
<td>46%</td>
<td>69%</td>
</tr>
<tr>
<td>7</td>
<td>15&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>2.5 h</td>
<td>0 °C</td>
<td>51%</td>
<td>56%</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>5 h</td>
<td>0 °C</td>
<td>54%</td>
<td>54%</td>
</tr>
<tr>
<td>9</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>2 h</td>
<td>rt.</td>
<td>47%</td>
<td>88%</td>
</tr>
<tr>
<td>10</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>5 h</td>
<td>–78 °C</td>
<td>Traces</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>4 h</td>
<td>–40 °C</td>
<td>30%</td>
<td>79%</td>
</tr>
<tr>
<td>12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>1 h</td>
<td>rt.</td>
<td>60%</td>
<td>92%</td>
</tr>
<tr>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>20 min</td>
<td>50 °C</td>
<td>69%</td>
<td>91%</td>
</tr>
<tr>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Toluene</td>
<td>1 h</td>
<td>rt.</td>
<td>43%</td>
<td>72%</td>
</tr>
<tr>
<td>15&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>THF</td>
<td>4.5 h</td>
<td>rt.</td>
<td>70%</td>
<td>91%</td>
</tr>
<tr>
<td>16&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>1.17 h</td>
<td>rt.</td>
<td>65%</td>
<td>93%</td>
</tr>
<tr>
<td>17&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1 h</td>
<td>rt.</td>
<td>64%</td>
<td>94%</td>
</tr>
<tr>
<td>18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>MeCN</td>
<td>1.5 h</td>
<td>rt.</td>
<td>67%</td>
<td>87%</td>
</tr>
<tr>
<td>19&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>1 h</td>
<td>rt.</td>
<td>57%</td>
<td>94%</td>
</tr>
<tr>
<td>20&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1 h</td>
<td>rt.</td>
<td>61%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Unless stated otherwise, the catalyst and 3-vinylindole (4a, 0.1 mmol) were added to a solution of imine 8a (0.05 mmol) in an absolute solvent (1 mL). After consumption of the starting material the crude mixture was purified via preparative TLC or column chromatography (PE-EtOAc 3:1).<sup>c</sup> Isolated yield.<sup>c</sup> Determined by HPLC.<sup>c</sup> Reaction was carried out with 0.1 mmol of 4a and 0.1 mmol of 8a. Imine 8a was prepared in situ from ethyl glyoxylate and aniline. Reaction was performed on a gram scale (14 mmol of 4a and 7 mmol of 8a).<sup>c</sup> Reaction was carried out with 0.3 mmol of 4a and 0.1 mmol of 8a.

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<sub>2</sub>Cl<sub>2</sub>; however, in this case the product was nearly racemic (entry 4).

Chiral phosphoric acids<sup>c</sup> represent another catalyst class widely used in organic chemistry, especially in the strongly related asymmetric (vinyllogous) Mannich-type reactions and also employed by Ricci et al. in the aforementioned paper.<sup>28</sup> 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 yield the substituted piperidine 9aa.

The following conclusions can be drawn 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 using 1 equivalent of each reactant; (iii) in some cases, employing a catalyst leads to a considerable improvement of the 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 ees (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 suppressed.

Having found an efficient catalyst 16, several solvents were screened in order to improve the enantioemic 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 the equatorial position, thus minimizing steric interactions between one another, and the ethyl ester is standing axially, possibly to avoid the interaction with the N-phenyl group. In addition, crystals of 9aa could be obtained by recrystallization from iPrOH. The absolute configuration was unequivocally proven by X-ray crystallography using the effects of anomalous dispersion (Fig. 3). Thus a (2S,4S,6S) configuration could be confirmed (see also ESI† and CCDC 977608).

As our sample of 9aa had an enantiomeric purity of ee = 94%, it is generally possible that the single crystal used for the 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,<sup>39</sup> the spectrum was calculated with time-dependent density functional theory methods<sup>40</sup> (along with the C-4 epimer of 9aa, which was clearly ruled out as a possible product, see also ESI†). Because of good agreement of the calculated spectrum of 9aa with the experimental spectrum, we can ensure the proposed (2S,4S,6S) configuration (Fig. 4).

Scope of the reaction

As the reaction conditions were optimized, the scope of the reaction was explored by using differently substituted 3-vinyl-
indoles 4a–f and glyoxalate imines 8a–d. The reactions were
carried out on a 0.1 mmol scale with catalyst 16 in dichloromethane. In all cases, high ees were achieved, while depending
on the substitution pattern and varying stability of the
different vinylindoles the yields were 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 decompose within a 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 diaster-
omers which could not completely be separated from the
main product. In the 1H 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 ESI†).

We also found that this kind of reactivity in a three-com-
ponent 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).

Having proven the generality of the reaction by applying the
conditions on various substrates, we explored whether 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 catalyst 16 was recyclable (see ESI† for more information).

### Table 2 Synthesis of bisindole derivatives 9xy

<table>
<thead>
<tr>
<th>Entry</th>
<th>R′</th>
<th>R″</th>
<th>Yield † ( % ) of 9xy</th>
<th>ee ‡</th>
<th>Equiv. ( (4x : 8y) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>64 † 9aa 94 †</td>
<td></td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>5-Br</td>
<td>Ph</td>
<td>51 † 9ba 90 †</td>
<td></td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>7-Me</td>
<td>Ph</td>
<td>43 † 9ca &gt;99 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>4</td>
<td>5-Br</td>
<td>3,5-Me,C₆H₄</td>
<td>58 † 9bb 94 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-OMe-C₆H₄</td>
<td>56 † 9ac 97 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-Br-C₆H₄</td>
<td>28 † 9ad 93 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>7</td>
<td>5-OMe</td>
<td>Ph</td>
<td>21 † 9da 87 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>8</td>
<td>5-Br-7-Me</td>
<td>Ph</td>
<td>25 † 9ca 75 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>9</td>
<td>6-F</td>
<td>Ph</td>
<td>34 † 9fa 89 †</td>
<td></td>
<td>2 : 1</td>
</tr>
<tr>
<td>10</td>
<td>6-F</td>
<td>4-OMe-C₆H₄</td>
<td>48 † 9fc n.d.</td>
<td></td>
<td>2 : 1</td>
</tr>
</tbody>
</table>

Catalyst 16 (10 mol%) and 3-vinylindole derivative 4 were added to a
solution of imine 8 in CH₂Cl₂ (1–2 mL). After stirring for 1 h at rt., the
crude mixture was purified via preparative TLC. *Isolated yield after column chromatography or preparative TLC. †Determined by HPLC; n.d. = not determined (no separation of enantiomers achieved).

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

In conclusion, we developed a powerful three-component,
enantioselective, and organocatalytic synthesis of 4,6-bis(1H-
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 diastereoselectively
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 ees up to 99%. The reaction can be con-
ducted on a gram scale and the catalyst is recyclable; fur-
thermore, 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
medicinally interesting natural products. Their activity towards
various test organisms is currently under investigation.
Acknowledgements

We thank Dr. Jochen Bürck for CD spectral measurements, De Wang for helpful discussions, and Angela Wandler for experimental assistance. Financial support was realized by the Deutsche Telekom Stiftung, the Karlsruhe House of Young Scientists (KHYS) (fellowships to S. Zhong), the Deutsche Forschungsgemeinschaft (CFN, project C3.3), and the Sino-German collaboration program GZ417.

Notes and references


29 Imine 8a was synthesized similar to: E. Borrione, M. Prato, G. Scorrano, M. Stivanello and V. Lucchini, J. Heterocycl. Chem., 1988, 25, 1831.


33 Synthesis of 4a: this compound was synthesized with a slightly modified procedure according to ref. 26a, see also ESI.†


