Pyrroles

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The Organocatalytic Approach to Enantiopure 2*H*- and 3*H*-Pyrroles: Inhibitors of the Hedgehog Signaling Pathway

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Abstract: *A divergent approach to enantioenriched 2H- and 3H-pyrroles catalyzed by a spirocyclic phosphoric acid is reported that makes use of a Fischer-type indolization and a [1,5]-alkyl shift. Catalyzed by the chiral phosphoric acid STRIP, good to excellent yields and enantioselectivities could be obtained. Remarkably, biological evaluation reveals one of these novel 2H-pyrroles to be a potent but nontoxic inhibitor of the Hedgehog signaling pathway by binding to the Smoothened protein.*

2*H*- and 3*H*- pyrroles are core structures of various biologically active compounds, natural products, and pharmaceutical agents.[1] For example, a 2*H*- and a 3*H*-pyrrole are both part of Precorrin-6B, a macrocyclic vitamin B_{12} precursor, whereas 2*H*-pyrroles can be found in alkaloids such as Calyciphylline G and Chamobtusin A (Figure 1).[1h–k] However, while 1*H*-pyrroles are well-explored compounds, biological investigations of the corresponding 2*H*- and 3*H*-pyrroles are still limited. One reason for this might be the lack of synthetic approaches to non-aromatic 2*H*- and 3*H*-pyrroles, especially in an enantioselective fashion. Indeed, there are just a few catalytic asymmetric methods reported, and these are mainly based on transition-metal catalysis.[2] For example, the You research group developed a palladium-catalyzed asymmetric allylic dearomatization of 1*H*-pyrroles to generate enantioenriched 2*H*-pyrroles.[2b,d] In 2015, Zhao and co-workers reported the first enantioselective synthesis of 3*H*-pyrroles by applying a silver-catalyzed [3+2] cyclization of allenoates and activated isocyanides.[2c]

Inspired by our catalytic asymmetric dearomatizing synthesis of 1,4-diketones by an interrupted Fischer indolization,[3] we became interested in exploring whether or not the designed reactivity could also be diverted into an asymmetric pyrrole synthesis. In fact, our previous reaction of hydrazine **1a** and cyclohexanone (**2a**) via ene hydrazine **A** required the addition of water to hydrolyze the diimine intermediate **B** formed in the enantiodetermining [3,3] sigmatropic rearrangement (Scheme 1).[3,4] We hypothesized that performing the reaction in the absence of water would inhibit this hydrolysis and instead provide access to the corresponding enantioenriched 3*H*-pyrrole **4a**, a novel structure that is somewhat reminiscent of an aza steroid.[5] Furthermore, 3*H*-pyrroles can be converted into the corresponding 2*H*-pyrroles by a suprafacial [1,5] sigmatropic alkyl shift,[6] which would give access to both compound classes at once. The interesting and novel structural motifs and potential bioactivities of such enantioenriched 2*H*- and 3*H*-pyrroles encouraged us to carry out this investigation. Herein, we present the fruition of our work in a successful divergent Brønsted acid catalyzed

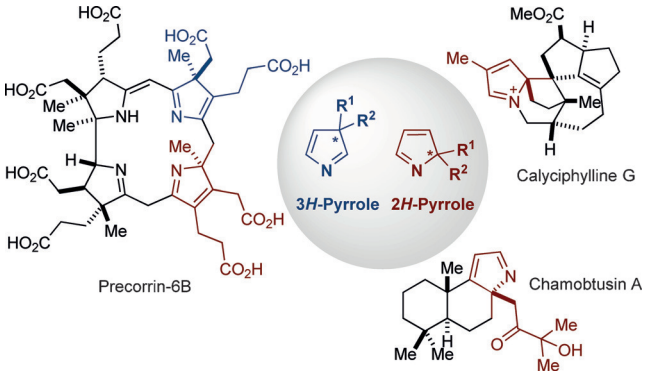
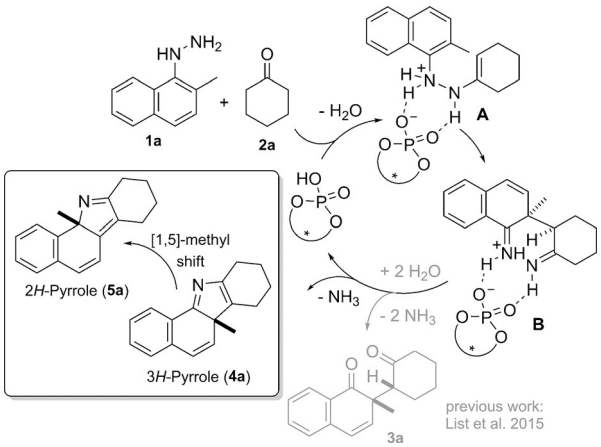


Figure 1. Natural products containing 2*H*- and 3*H*-pyrrole rings.



Scheme 1. Design of a new approach to enantiopure pyrroles.

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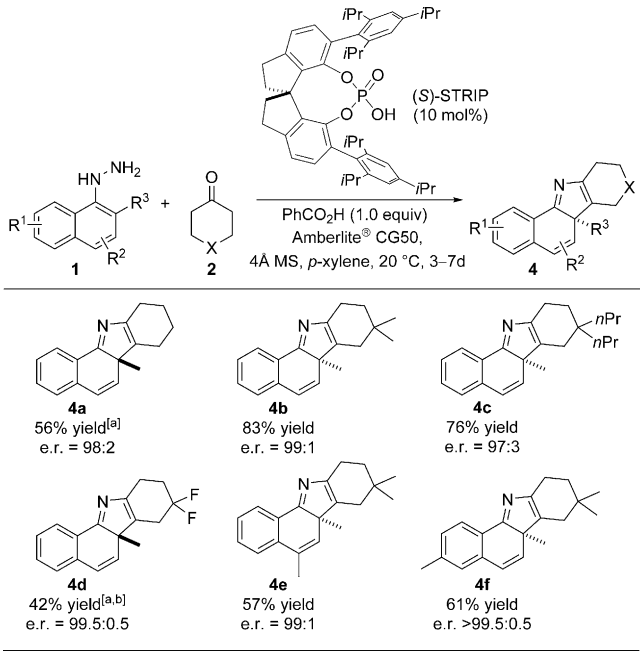
asymmetric synthesis of 2*H*- and 3*H*-pyrroles[7] by applying a dearomatizing Fischer indolization and an in situ [1,5]-alkyl shift.

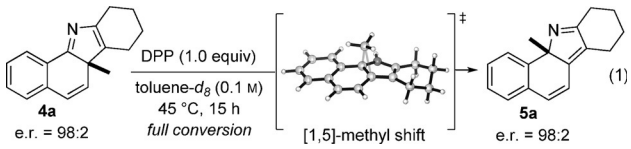
We began our investigations using hydrazine **1a** and cyclohexanone (**2a**) as substrates, with the aim of identifying conditions that would lead to the selective formation of 3*H*-pyrrole **4a** (see the Supporting Information).[8] Indeed, the formation of 1,4-diketone **3a** could be successfully suppressed by performing the reaction under completely dry conditions and adding 4 Å molecular sieves to the reaction mixture. The SPINOL-derived phosphoric acid STRIP (**6a**) was found to be the best catalyst in terms of yield and enantioselectivity.[9] As shown in our previous studies on catalytic asymmetric Fischer indolizations, the addition of Amberlite CG50 proved to be crucial to remove the released ammonia and to regenerate the catalyst.[3,4] The addition of benzoic acid was also found to have a beneficial effect on the reactivity without diminishing the enantioselectivity.[3,10] Decreasing the temperature to 20 °C improved both the yield and the enantioselectivity. Increasing the catalyst loading to 10 mol% and performing the reaction in *p*-xylene (0.1 M) afforded the desired product in 56% yield and an excellent enantiomeric ratio of 98:2 (for the details of the reaction optimization, see the Supporting Information).

With the optimized conditions in hand, we next investigated the scope of the reaction. The use of 10 mol% (*S*)-STRIP as catalyst afforded a variety of 3*H*-pyrroles **4** in good yields and excellent enantioselectivities. Substituents in the 4-position of the ketone are well-tolerated, as shown by the generation of the corresponding 3*H*-pyrrole **4b** in 83% yield and an enantiomeric ratio of 99:1 (Scheme 2). Changing to 4,4-di-*n*-propylcyclohexanone delivered the desired product **4c** in 76% yield and an enantiomeric ratio of 97:3. The use of 4,4-difluorocyclohexanone is also possible and affords 3*H*-pyrrole **4d** with an excellent enantiomeric excess of 99% and a slightly lower yield of 42% if the reaction is conducted at 30 °C. Substituents on the hydrazine moiety were found to have a beneficial effect on the enantioselectivity, furnishing the corresponding products **4e** and **4f** in excellent enantiomeric ratios of 99:1 (**4e**) and > 99.5:0.5 (**4f**).[11]

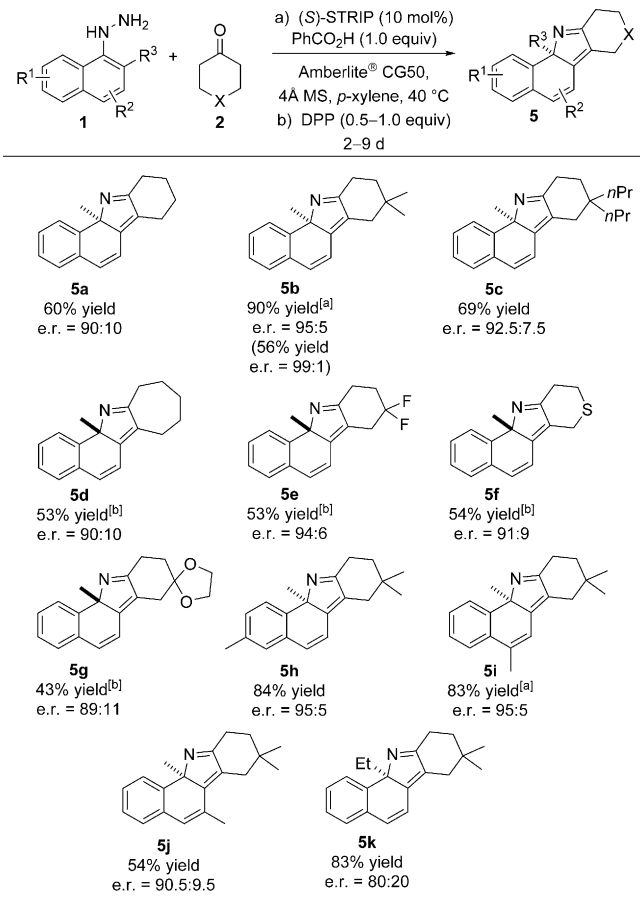


Scheme 2. Substrate scope of 3*H*-pyrroles **4**. a) (*R*)-STRIP was used as the catalyst. b) Reaction conducted at 30 °C.

It has previously been shown that it is possible to convert 3*H*-pyrroles into 2*H*-pyrroles by a stoichiometric acid mediated or thermally induced [1,5]-alkyl shift.[6] Applying this method to products **4** should provide access to the corresponding 2*H*-pyrroles **5**. Such [1,5] shifts are sigmatropic rearrangements that occur suprafacially in the ground state. Accordingly, preservation of enantiopurity can be expected. However, while it has previously been demonstrated that this is actually the case in the corresponding [1,5]-H shifts,[12] the stereospecificity of [1,5]-alkyl shifts has to our knowledge never been confirmed. DFT calculations suggest a concerted suprafacial [1,5]-methyl shift of 3*H*-pyrrole **4a** to 2*H*-pyrrole **5a** and indicate that acid catalysis would lead to a significant lowering of the activation barrier by about 10 kcal mol^{-1} (see the Supporting Information). Indeed, treating 3*H*-pyrrole **4a** with a stoichiometric amount of diphenyl phosphate (DPP) led to a full conversion into the 2*H*-pyrrole **5a** after 15 h and without loss of enantiopurity [Eq. (1)]. Thus, the conversion of enantioenriched 3*H*-pyrroles **4** into enantioenriched 2*H*-pyrroles **5** should be possible by adding diphenyl phosphate to the reaction mixture after full conversion of the hydrazone.



Indeed, we found that, upon addition of diphenyl phosphate to the reaction mixture, all the 3*H*-pyrrole **4** was fully converted into the corresponding 2*H*-pyrrole **5**. To enhance the reactivity and to obtain full conversion of the hydrazone, the reaction was conducted at an increased temperature of 40 °C. We further investigated the scope of our reaction by applying this reaction sequence (Scheme 3). Hydrazine **1a** reacted smoothly with a variety of cyclohexanones, thereby generating the desired products in good yields and, probably because of the higher temperature, slightly lower enantioselectivities. Substitution in the 4-position of the cyclohexanone was found to have a beneficial effect on both the reactivity and enantioselectivity. 2*H*-Pyrrole **5b** could be isolated in 90% yield and an enantiomeric ratio of 95:5 when the reaction temperature was decreased to 30 °C. Remarkably, a high enantiomeric ratio of 99:1 can be achieved, when performing the reaction in a two-step procedure at 20 °C and isolating compound **4b** prior to treating it with diphenyl phosphate. Extension to an *n*-propyl-substituted ketone was also possible, and furnished the desired product **5c** in 69% yield and an enantiomeric ratio of 92.5:7.5. Fluoro-substituted ketones can also be used, generating the desired 2*H*-pyrrole **5e** in an enantiomeric ratio of 94:6. A seven-membered ring could be applied as well,

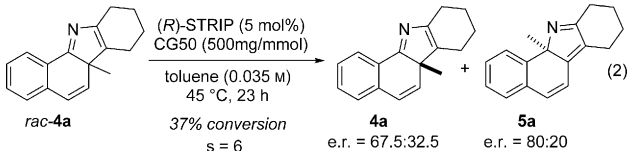


Scheme 3. Substrate scope of 2*H*-pyrroles **5** by an in situ [1,5]-methyl shift. In brackets: Addition of DPP to isolated 2*H*-pyrrole **4b**, yield over 2 steps. [a] Reaction conducted at 30 °C. [b] (*R*)-STRIP was used as the catalyst.

furnishing compound **5d** in 53 % yield and an enantiomeric ratio of 90:10, although a longer reaction time was necessary to obtain full conversion of the hydrazone. The use of sulfur-containing ketone **2f** was also possible, although the desired product **5f** was obtained in a slightly diminished enantioselectivity of 91:9. Substituents on the hydrazine part were generally well-tolerated, generating 2*H*-pyrrole **5h** generated, in 84 % yield and an enantiomeric ratio of 95:5. Decreasing the temperature to 30 °C afforded compound **5i** in 83 % yield and 95:5 e.r.[11b] The use of an ethyl-substituted hydrazine was also possible, generating the corresponding 2*H*-pyrrole **5k** in 83 % yield and 80:20 e.r.

The acid-mediated transformation of 3*H*-pyrroles **4** to 2*H*-pyrroles **5** encouraged us to investigate a kinetic resolution of 2*H*- and 3*H*-pyrroles through a [1,5]-alkyl shift. Remarkably, treating racemic 3*H*-pyrrole **4a** with 5 mol % (*R*)-STRIP (**6a**) in the presence of CG50 in toluene at 45 °C enabled a kinetic resolution of pyrroles **4a** and **5a** with an s factor of 6 under unoptimized reaction conditions [Eq. (2)].[13]

The absolute configuration of pyrroles **4b** and **5b** was assigned by CD spectroscopy, by comparing the experimental CD spectra with TD-B3LYP-D3/TZVP-calculated CD spectra (see the Supporting Information).[14] The CD characteristics of the calculated spectra (blue line) were in good



agreement with the experimental spectra (red line), thus allowing the assignment of the absolute configuration of pyrroles **4b** and **5b**, which were found to be *S* configured, using the *R* enantiomer of the catalyst (Figure 2). This result strongly indicates that the [1,5]-methyl shift is stereospecific and occurs in a suprafacial mode.

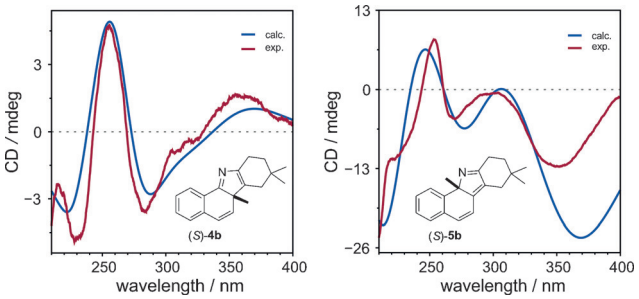
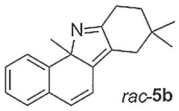


Figure 2. Calculated (blue line) and experimental (red line) CD spectra of pyrroles **4b** (left) and **5b** (right).

As already mentioned, various 2*H*-[1a–c] and 3*H*-pyrroles[1d–f] are known to possess interesting biological properties, which encouraged us to investigate potential bioactivities of our new structural motifs. We were particularly interested in the potential antitumor activities of this novel compound class, focusing on inhibitors of the Hedgehog (Hh) signaling pathway at the outset of our studies.[15] The Hh signaling pathway is of high importance for the regulation of differentiation and proliferation during embryonic development. A deregulation or mutation, such as an abnormal activation of the signaling pathway, can contribute to different types of cancer or promote tumor growth. Thus, therapeutic strategies inhibiting the Hh pathway are currently in high demand.[16] To identify a novel compound class of Hh pathway inhibitors, we subjected some selected 3*H*- (**4**) and 2*H*-pyrroles (**5**) to cell-based assays, monitoring the signal transduction pathways.[17] Remarkably, *rac*-2*H*-pyrrole **5b** showed an inhibition of the Hh signaling pathway with a half-maximal inhibitory concentration (IC_{50}) of 5.06 ± 0.67 μM without being cytotoxic (IC_{50} viability inactive), thus representing a completely new class of Hh signaling inhibitors (Figure 3a). We assessed the ability of *rac*-**5b** to bind to the seven transmembrane receptor Smoothened (Smo) by means of competition experiments with BODIPY-cyclopamine in HEK293T cells ectopically expressing Smo. To our delight, microscopy analysis revealed *rac*-**5b** to be a Smo binder (Figure 3b). Biological evaluations of further 3*H*- and 2*H*-pyrroles (**4**/**5**) and more detailed investigations on the mode of action of these novel compounds are still ongoing.[18]

In conclusion, we have developed a divergent organocatalytic approach towards enantioenriched 2*H*- and 3*H*-

a

Compound	mean IC_{50} [μM]†	IC_{50} [μM] ‡ (viability)
 *rac*-**5b**	5.06 ± 0.67	Inactive

b

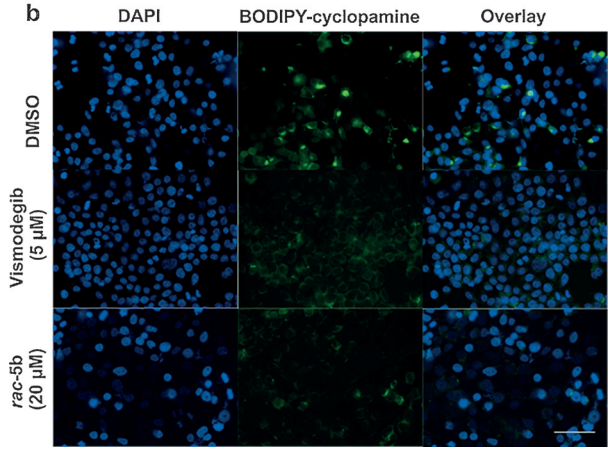


Figure 3. a) Biological evaluation of 2*H*-pyrrole *rac*-**5b** in the Hh pathway inhibition. b) 2*H*-Pyrrole *rac*-**5b** displaces BODIPY-cyclopamine from Smo. HEK293T cells were transiently transfected with Smo expressing plasmid or empty vector. After 48 h, the cells were fixed and treated with BODIPY-cyclopamine (5 nM, green) followed by the addition of *rac*-**5b** (20 μM) or vismodegib (5 μM) and DMSO as controls. Cells were stained with DAPI to visualize the nuclei (blue). †: Mean IC_{50} values ± standard deviation ($n \geq 3$) for inhibition of the Hedgehog signaling pathway as determined in an osteogenesis assay. ‡: Influence on the viability of C3H10T1/2 cells, using the CellTiter-Glo assay. Scale bar: 50 μm.

pyrroles by applying a catalytic asymmetric Fischer indolization and a subsequent [1,5]-alkyl shift. The SPINOL-derived phosphoric acid STRIP afforded the desired products in good to excellent yields and enantioselectivities. Remarkably, 2*H*-pyrrole **5b** was found to inhibit the Hedgehog signaling pathway with an IC_{50} value of 5.06 ± 0.67 μM, thus disclosing a completely new class of Hedgehog inhibitors which bind to the Smoothened protein.

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Keywords: [1,5]-alkyl shifts · 2*H*-pyrroles · 3*H*-pyrroles · Brønsted acid catalysis · Hedgehog signaling inhibitors

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