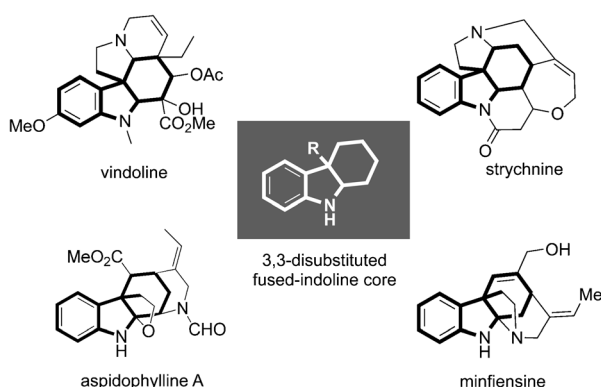


Brønsted Acid Catalysis

Versatile Access to Chiral Indolines by Catalytic Asymmetric Fischer Indolization**

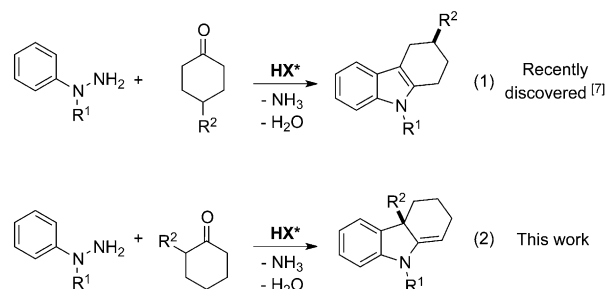
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Dedicated to the Bayer company on the occasion of its 150th anniversary

 3,3-Disubstituted fused indolines are privileged substructures of diverse natural products, and their synthesis has attracted intense attention (Scheme 1).^[1,2] While a number of enantio-


Scheme 1. Examples of natural products containing 3,3-disubstituted fused indoline cores.

 selective approaches to monosubstituted indolines have been reported,^[3] the asymmetric synthesis of challenging 3,3-disubstituted indoline targets has been less developed.^[4] A recent achievement in this field of research has been the work of MacMillan et al., who employed a Diels–Alder–Michael addition cascade to enantioselectively generate precursors for a number of indole alkaloid total syntheses,^[5] illustrating the potential of organocatalysis for natural product synthesis.^[6] Herein we report a complementary strategy to 3,3-disubstituted fused-indolines based on the Fischer indolization, in which the formation of the indole scaffold itself serves as the basis for asymmetric induction.

 Recently, our group developed an organocatalytic asymmetric variant of the Fischer indole synthesis [Scheme 2, Equation (1)].^[7] We speculated that this procedure, originally designed for the synthesis of chiral 3-substituted tetrahydro-


Scheme 2. Potential formation of enantioenriched 3,3-disubstituted fused indolines. HX* = chiral Brønsted acid.

 carbazoles, could potentially have further-reaching applications in organic synthesis, just as the non-asymmetric version has had throughout its long history.^[8] For example, we envisaged that upon condensation of an α -substituted cyclic ketone with a phenylhydrazine, a chiral Brønsted acid catalyzed [3,3]-sigmatropic rearrangement of the higher substituted ene–hydrazine would lead to an enantioenriched fused indoline [Scheme 2, Equation (2)].^[9,10]

 With this plan in mind, we began our studies with commercially available *N*-benzyl-*N*-phenylhydrazine (**1a**) and 2-phenylcyclohexanone (**2a**). In the presence of a range of chiral phosphoric acids and the weakly acidic cation exchange polymer Amberlite CG50, indoline–enamine **3a** could indeed be obtained in promising yields and enantioselectivities (Table 1).^[11]

 Both BINOL-^[12] and SPINOL-derived^[13] phosphoric acids were employed, and it was noticeable that the highest yields were obtained with SPINOL-derived catalysts (Table 1, entries 5–7). Moreover, the hindered SPINOL phosphoric acid STRIP (**5e**), previously introduced by our group,^[13b] was seen to comfortably outperform its BINOL analogue TRIP (**4e**)^[14] in terms of enantioselectivity (Table 1, entries 4 and 7). Thus (*R*)-STRIP became the catalyst of choice for further studies.^[15] The importance of the weakly acidic CG50 polymer was then underlined by running the reaction in its absence (Table 1, entry 8). A poor yield (15%) was obtained, which is thought to be due to the build-up of ammonia, inhibiting protonation of the key ene–hydrazine intermediate and drastically hindering turnover of the acid catalyst (e.g. 93.5:6.5 with or without polymer).^[7]

 We next turned our attention to assessing the substrate scope of the reaction (Scheme 3). It was found that indoline **3a** could be quantitatively furnished in 24 h at 45 °C and with an enantiomeric ratio (e.r.) of 94.5:5.5.^[16] Varying the aryl

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Table 1: Catalyst optimization.^[a]

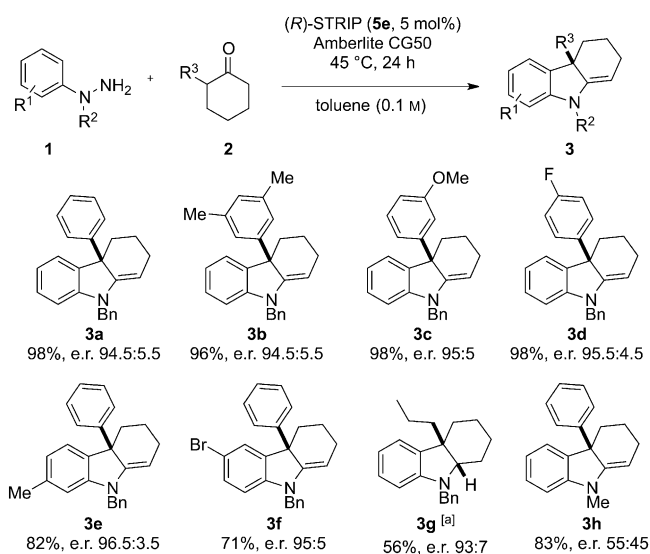
Reaction scheme: 1a + 2a $\xrightarrow[\text{toluene (0.1 M), 60 }^\circ\text{C, 20 h}]{\text{catalyst (5 mol\%), Amberlite CG50}}$ 3a

Catalysts:

a: R = SiPh₃
 b: R = 9-anthracenyl
 c: R = 3,5-(CF₃)₂C₆H₃
 d: R = 1-naphthyl
 e: R = 2,4,6-(iPr)₃C₆H₂

Entry	Catalyst	Yield [%] ^[b]	e.r. ^[c]
1	4a	81	60:40
2	4c	84	68:32
3	4d	81	71.5:28.5
4	4e	82	59:41
5	5b	99	87:13
6	5c	97	64:36
7	5e	99	93.5:6.5
8 ^[d]	5e	15	93.5:6.5

[a] Reactions were run on a 0.05 mmol scale with 50 mg of Amberlite CG50. Bn = benzyl. [b] Determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Amberlite CG50 omitted from the reaction mixture.



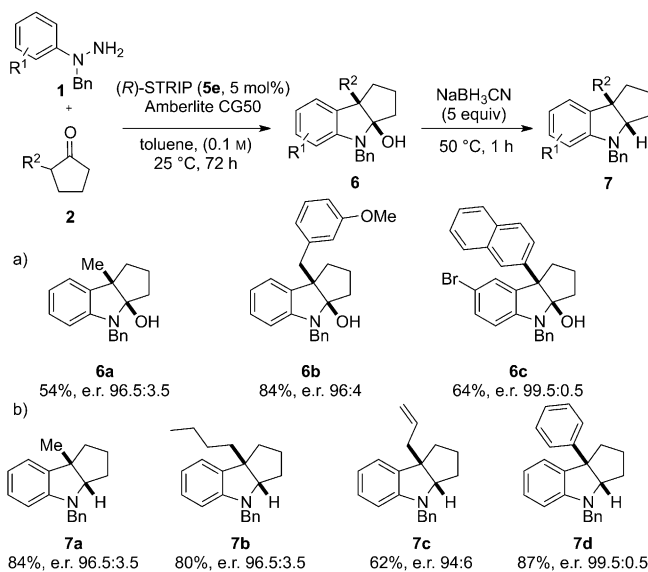
Scheme 3. Substrate scope for the synthesis of indoline derivatives. [a] After in situ reduction of the unstable enamine with NaBH₃CN.

substituent R³ had little effect on either yield or e.r. (3a–d), while more marked effects were revealed when varying the starting hydrazine. First, the introduction of a methyl group in the 3-position of the hydrazine gave a single regioisomeric product 3e with improved enantioselectivity compared to the unsubstituted analogue. A bromo substituent was well tolerated (3f, e.r. 95:5). 2-Alkylcyclohexanones proved to be less reactive (the reaction was carried out at 50 °C for 36 h). One example was the isolation of the *n*-propylindoline derivative 3g in moderate yield as a mixture of diastereoisom-

ers (d.r. 8.5:1) after in situ reduction of the corresponding unstable enamine with NaBH₃CN. NOE-NMR studies showed that the major diastereoisomer was the *cis*-fused system with an e.r. of 93:7.

The presence of a benzyl group on the nitrogen atom was found to be essential for the enantioselectivity of the reaction. This is illustrated by the synthesis of product 3h bearing an *N*-methyl group, with a poor e.r. of 55:45. It should be noted that all of the reactions were regioselective, with rearrangement taking place at the most substituted α -position of the starting ketone. The possible 1-substituted tetrahydrocarbazoles were not observed in any case.^[9]

Encouraged by these results with cyclohexanones, we were compelled to pursue opportunities with 2-substituted cyclopentanone substrates (Scheme 4). Such substrates have



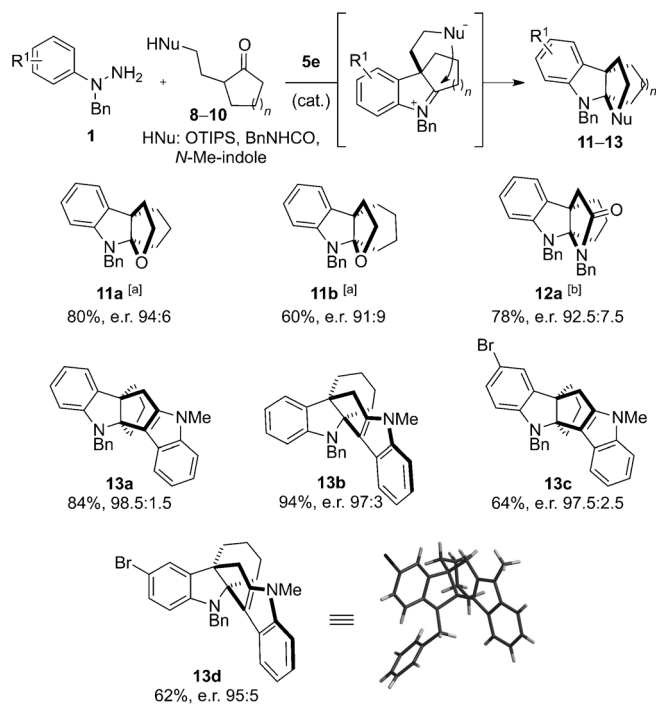
Scheme 4. Synthesis of a) 2-hydroxyindolines 6 and b) indolines 7 after in situ reduction with NaBH₃CN post-indolization.

previously been put forward as challenging for the Fischer indolization, with the products apparently showing instability to the usual rather harsh conditions of the reaction.^[17] We hoped that under our mild conditions, synthetically useful yields would be obtained. Interestingly, we were able to isolate 2-hydroxyindolines of type 6, rather than the corresponding indoline–enamines. Alkyl and benzyl substituents were well-tolerated (6a,b), and incorporation of a naphthyl substituent led to indoline product 6c with remarkably high enantioselectivity of 99.5:0.5.

The moderate yield obtained for methyl-substituted indoline 6a (54%) is due to its instability to chromatographic purification methods. We supposed that the yield of the process could be improved by incorporating a reductive step to the reaction sequence. Indeed, adding NaBH₃CN to the reaction mixture once indolization was judged to be complete resulted in an improved yield of 84% of reduced indoline 7a. Methyl-substituted products 6a and 7a were obtained with identical e.r. of 96.5:3.5. In a similar fashion, reduced indoline products 7b,c could also be obtained in good yields and high

enantioselectivity. Once again, the presence of an aryl group in the substrate led to the indoline product with outstanding enantioselectivity (e.r. 99.5:0.5 for **7d** with $R^2 = \text{Ph}$).

After confirming that our catalytic system could successfully form enantioenriched 3,3-disubstituted fused indolines, we intended to apply this method for the synthesis of more complex molecules. We envisaged that by appropriate design of the starting ketone, the Fischer indolization pathway could be interrupted by the attack of an appropriate tethered nucleophile on the iminium functionality, which is formed upon the loss of ammonia (Scheme 5). This could give rapid



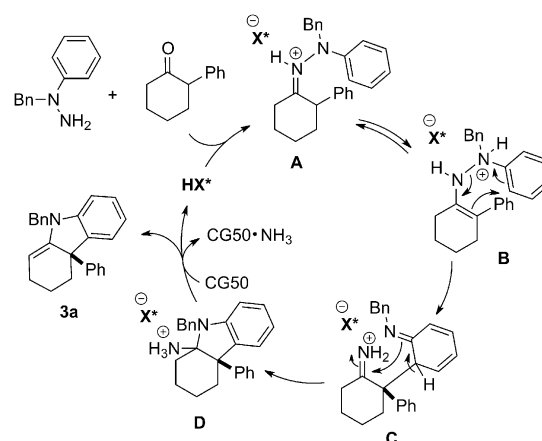
Scheme 5. Catalytic asymmetric interrupted Fischer indolization furnishing enantioenriched (hetero)propellanes. [a] TBAF addition; [b] 70 °C for 3 h after indolization. Nu = nucleophile, TIPS = triisopropylsilyl.

access to polycyclic cores, which are present in a number of natural products. The so-called interrupted Fischer indolization has been widely studied, most recently by the group of Garg.^[18,19] However, approaches to render the process asymmetric have so far been limited to a single example, employing an excess of a chiral phosphoric acid and inducing moderate enantioselectivity.^[18b] We wished to harness the power of our Fischer indolization process to deliver a catalytic asymmetric variant of this complexity-generating reaction. With this idea in mind, we prepared a range of 5- and 6-membered cyclic ketones bearing oxygen, nitrogen, and carbon nucleophiles at the appropriate positions, which were then subjected to our optimized catalytic system in the presence of different phenyl hydrazines (Scheme 5).

Ketones containing a γ -silyl ether on the side chain reacted smoothly with hydrazine **1a** and, after in situ treatment with TBAF, the corresponding [3.3.3]- and [3.3.4]-oxapropellane furoidolines **11a,b** were obtained in good

yields and enantioselectivities. Protection of the hydroxy group with a silyl group is crucial to achieve a high e.r.^[20] In the case of amide-containing ketones, the temperature had to be increased upon completion of the indolization to accelerate the ring closure by nucleophilic attack of the amide nitrogen atom. Thus indoline **12a** was obtained in moderate yield and good enantioselectivity. Finally, to study ketones bearing a carbon nucleophile, we incorporated an electron-rich *N*-methylindole into its side chain. To the best of our knowledge, there had been no prior examples of an interrupted Fischer indolization featuring a carbon-based nucleophile. The investigated ketone substrates reacted efficiently with hydrazines **1a** and **1c** to give the polycyclic indolines **13a–d** bearing two vicinal quaternary stereocenters in good yields and enantioselectivities.^[21] In both cases yields obtained for the hydrazine **1c**, bearing bromine in the aromatic ring, were lower owing to the slower reaction rate relative to the unsubstituted hydrazine **1a**. The absolute configuration of the indolo-indoline **13d** was unambiguously assigned by X-ray structural analysis (see the Supporting Information).

Scheme 6 shows the proposed catalytic cycle, which is in agreement with the accepted mechanism of the Fischer indolization.^[22] We suggest that chiral phosphoric acid **5e**



Scheme 6. Plausible catalytic cycle of formation of **3a**.

catalyzes the formation of protonated hydrazone **A**, followed by tautomerization to the thermodynamically more stable cationic enehydrazine isomer **B**. The enantioselectivity-determining key step would then be the irreversible [3,3]-sigmatropic rearrangement of intermediate **B**, directed by the chiral phosphate counteranion, affording ion pair **C**. Upon ring closure, iminal **D** eliminates one equivalent of ammonia to give the final product **3a**. Ammonia is trapped by the cation-exchange polymer Amberlite CG50, allowing the turnover of the catalytic system.

In summary, we wish to emphasize the potential power of the catalytic asymmetric Fischer indole synthesis to rapidly access highly diverse indoline scaffolds, often displaying considerable structural complexity, in a single step from simple starting materials. The process has been developed to

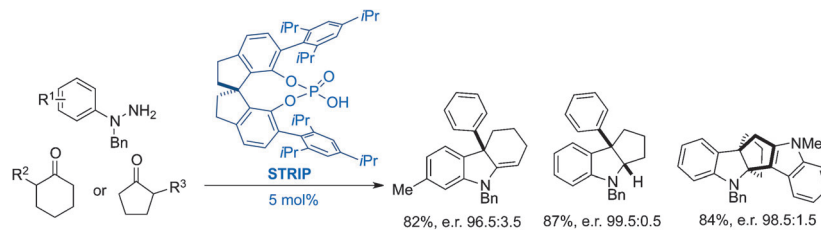
Communications



Brønsted Acid Catalysis

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Versatile Access to Chiral Indolines by
 Catalytic Asymmetric Fischer Indolization



“Fishing” for complexity: The chiral Brønsted acid (*R*)-STRIP catalyzes the asymmetric Fischer indolization of a range of monosubstituted cyclopentanones and cyclohexanones to give chiral fused indolines bearing a quaternary stereogenic center at the 3-position. The

method has been extended to include substrates bearing a tethered nucleophile, thus allowing for enantioselective indolization/ring-closing cascades to complex propellanes featuring two vicinal quaternary stereocenters.