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The Catalytic Asymmetric Fischer Indolization

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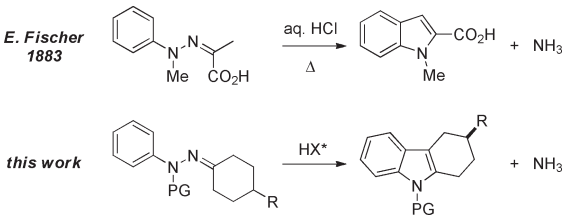
Supporting Information

ABSTRACT: The first catalytic asymmetric Fischer indolization is reported. In the presence of a 5 mol % loading of a novel spirocyclic chiral phosphoric acid, 4-substituted cyclohexanone-derived phenylhydrazones undergo a highly enantioselective indolization. Efficient catalyst turnover was achieved by the addition of a weakly acidic cation exchange resin, which removes the generated ammonia. The reaction can be conducted under mild conditions and gives various 3-substituted tetrahydrocarbazoles in generally high yields.

Indoles are heterocyclic compounds that are widely distributed in nature, and their synthesis has attracted massive attention. Of the numerous methods available for the construction of indoles,[1] the acid-mediated Fischer indolization of phenylhydrazones, first reported over 120 years ago, remains one of the most widely used procedures.[2,3] Remarkably, however, catalytic asymmetric Fischer indolizations have remained elusive to date. Here we report a spirocyclic phosphoric acid-catalyzed enantioselective Fischer indolization of 4-substituted cyclohexanone-derived phenylhydrazones (Scheme 1).

The lack of previous catalytic asymmetric versions of the Fischer indole synthesis may be attributed to a variety of reasons. Typically, rather harsh reaction conditions operating at elevated temperatures and employing at least stoichiometric amounts of acid are required to facilitate the reaction efficiently. In fact, cases in which only catalytic amounts of a promoter are used are rare and limited to isolated examples, mainly employing Lewis acids.[4] An explanation for this may be the stoichiometric formation of ammonia as the byproduct of the reaction, potentially poisoning Brønsted acidic catalysts by salt formation. Furthermore, upon first inspection, the absence of intrinsic chirality at the indole reveals no obvious handle for asymmetric induction. However, the formation of chiral products in the course of the reaction is by no means uncommon. The use of simple α-branched carbonyl compounds, for instance, leads to the formation of indolenines bearing a quaternary stereocenter.[5] In cases where a suitable internal nucleophile or electrophile is tethered to the α-branched carbonyl compound, chiral annulated indolines are obtained.[6] This strategy was elaborated by Nishida et al.[7] who developed a chiral auxiliary-based route to give pyrroloindolines with up to 85:15 dr. More recently, Garg and co-workers applied the same auxiliary to their interrupted Fischer indolization[8] to access an enantiomerically enriched furoindoline.[9] Especially noteworthy are their attempts to utilize chiral phosphoric acid catalysts in this transformation. However, the only reported example involved an excess of a chiral BINOL-derived phosphoric acid (1.2 equiv) and furnished the desired product with low enantioselectivity.

Scheme 1. Fischer Indolizations



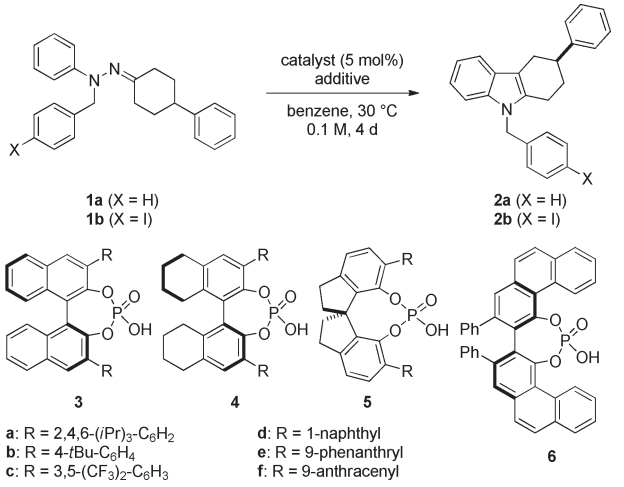
Our own strategy relies on the indolization of 4-substituted cyclohexanone-derived phenylhydrazones to give chiral tetrahydrocarbazoles, a compound class with manifold potent biological activities.[10] The desymmetrization of 4-substituted cyclohexanones is an emerging strategy in asymmetric catalysis;[11] especially noteworthy in this context is the work by Li and Seidel on the catalytic asymmetric Friedländer condensation.[12] To realize the proposed Fischer indolization, we hypothesized that chiral phosphoric acids, which have emerged as powerful organocatalysts within the past few years,[13] may be capable of facilitating this transformation enantioselectively by accelerating the [3,3]-sigmatropic rearrangement.[14] However, to enable the use of a chiral Brønsted acid at substoichiometric loadings, the aforementioned problem of catalyst poisoning by ammonia would have to be addressed.

We started our investigations with *N*-benzyl-protected hydrazone **1a**. To elucidate the potential of organic phosphoric acids as catalysts, we first conducted the Fischer indolization in the presence of stoichiometric amounts of achiral diphenyl phosphate (DPP) in benzene at 50 °C. After 4 h the reaction reached complete conversion and gave racemic tetrahydrocarbazole **2a** in 83% yield (Table 1, entry 1). As expected, we observed a dramatic decrease in the reaction rate when a catalytic amount (5 mol %) of the same catalyst was used. After fast initial product formation, the reaction rate decreased dramatically, and after 48 h, a yield of only 9% was observed (entry 2). We believe that this loss of reactivity was indeed due to poisoning of the Brønsted acidic catalyst by basic ammonia as discussed above.

To preserve the catalyst activity over the course of the reaction, we next investigated different reaction parameters. Variations of the solvent, temperature, and concentration were unsuccessful.[15] However, while elaborating the role of additives, we found that the addition of Amberlite CG50, a weakly acidic cation exchange resin, restored the catalyst reactivity and improved the yield to 63% under otherwise identical reaction conditions (entry 3). Although ion exchange resins have previously

Received: August 5, 2011
Published: November 01, 2011

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	additive	X	yield[b]	er[c]
1[d,e]	DPP	-	H	83%	-
2[e,f]	DPP	-	H	9%[g]	-
3[e,f]	DPP	CG50	H	63%	-
4[e,f]	-	CG50	H	<5%[g]	-
5	**3a**	CG50	H	25%	54.5:45.5
6	**3b**	CG50	H	20%	40.5:59.5
7	**3c**	CG50	H	50%	59.5:40.5
8	**3d**	CG50	H	43%	70.5:29.5
9	**3e**	CG50	H	50%	83:17
10	**3f**	CG50	H	75%	85:15
11	**4d**	CG50	H	42%	61.5:38.5
12	**4e**	CG50	H	66%	74:26
13	**5a**	CG50	H	24%	80:20
14	**5b**	CG50	H	11%	43.5:56.5
15	**5c**	CG50	H	98%	48.5:51.5
16	**5f**	CG50	H	98%	93.5:6.5
17	**6**	CG50	H	52%	49.5:50.5
18	**5f**	CG50 + 4Å MS	I	98%	95:5

[a] Reactions were run on a 0.05 mmol scale. Where indicated, Amberlite CG50 (100 mg) and 4 Å MS (25 mg) were added. DPP = diphenyl phosphate; CG50 = Amberlite CG50. [b] Isolated yields unless otherwise stated. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 1 equiv of DPP and a reaction time of 4 h were used. [e] 50 °C. [f] 48 h. [g] Determined by ^{1}H NMR spectroscopy.

been used as catalysts for Fischer indolizations,[16] this resin alone was incapable of catalyzing the reaction, giving only traces of the indolization product at 50 °C (entry 4). Encouraged by these observations, we speculated that with this additive, acceptable catalyst turnover might be achieved at even lower temperatures by removing the ammonia generated and thus continually regenerating the active phosphoric acid catalyst.

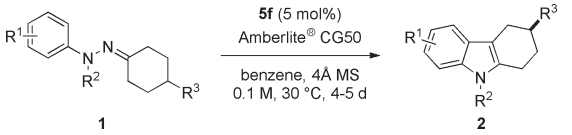
We next investigated the performance of various established chiral acid catalysts,[13] including BINOL-, H_8-BINOL-, VAPOL-, and the more recently introduced SPINOL-derived phosphoric acids.[17] The reactions were run at 30 °C with a catalyst loading of 5 mol % and were stopped after 4 days, irrespective of the conversion. Accordingly, the obtained yields varied significantly between 11% (Table 1, entry 14) and 98% (entries 15 and 16). The novel spirocyclic phosphoric acid **5f** was found to be the optimal catalyst in terms of yield and enantioselectivity, giving the desired product in 98% yield and 93.5:6.5 er (entry 16).[18] Further variations of the nitrogen protecting group [see the Supporting Information (SI)] revealed that bulky substituents at the 4-position of the benzyl group had a beneficial effect on the enantioselectivity. We ultimately opted for the use of the 4-iodobenzyl protecting group, supposing that this entity would be analogous to the parent benzyl group in terms of deprotection while at the same time granting advantageous crystallinic properties of the starting materials and products as well as offering a handle for the synthesis of compound libraries by means of cross-coupling reactions.[19] Finally, we found that when the reaction of hydrazone **1b** was conducted in the presence of molecular sieves (MS) as a supplementary additive, we obtained tetrahydrocarbazole **2b** in 98% yield and 95:5 er (entry 18).

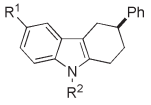
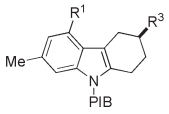
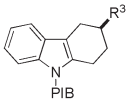
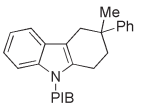
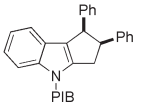
We next investigated the scope of our reaction. The *N*-benzyl-protected hydrazone **1a** and the iodinated analogue **1b** reacted smoothly to give products in 94% and 99% yield and enantiomeric ratios of 94:6 and 95:5, respectively (Table 2, entries 1 and 2). Different para substituents on the hydrazine moiety furnished 6-substituted tetrahydrocarbazoles **2c**−**e** in good yields, regardless of their electronic properties, albeit with slightly reduced enantioselectivity (entries 3−5). Also the 3,5-dimethyl-substituted hydrazone **1f** reacted similarly (entry 6). When 3-methyl-substituted phenylhydrazones **1g** and **1h** were employed, the reaction proceeded with good regiocontrol (6:1), and the corresponding 7-methylcarbazole derivatives **2g** and **2h** were obtained as the major regioisomers with enantiomeric ratios of 96:4 and 93:7 respectively (entries 7 and 8). All of the hydrazones in which R^3 was an aromatic group (**1i**−**o**) were transformed to the tetrahydrocarbazoles in high yields (88−99%) with good enantioselectivites (between 94:6 and 96:4 er), irrespective of the electronic or steric nature of the substituent (entries 9−15). Aliphatic groups in this position were also tolerated (entries 16−18). The desired products **2p**−**r** were obtained in good yields (70−98%), with a notably high enantioselectivity of 95:5 er in the case of the small methyl substituent (entry 16). Switching to more sterically demanding alkyl substituents afforded diminished enantioselectivity (entries 17 and 18). Heteroatom-substituted substrates **1s** and **1t** were well-tolerated and give the desired products **2s** and **2t** in 99% yield (entries 19 and 20). Particularly noteworthy is the high enantioselectivity of 98.5:1.5 er observed in the benzoyloxy-substituted product **2s**. Given the biological relevance of 3-aminotetrahydrocarbazoles,[20] we investigated the possibility of obtaining **2t** in a one-pot procedure from the corresponding phenylhydrazine and 4-*N*-phthalimidocyclohexanone. The results obtained were comparable to those obtained starting from the preformed hydrazone **1t** (cf. entries 20 and 21). The synthesis of tetrahydrocarbazole **2u** bearing a quaternary stereogenic center proved challenging in terms of conversion and enantioselectivity (entry 22). Although cyclopentanone-derived hydrazone **1v** also showed reduced reactivity, conducting the reaction at elevated temperatures and with a prolonged reaction time gave **2v** in 62% yield with 90.5:9.5 er (entry 23).

In agreement with the widely accepted mechanism of the Fischer indolization,[21] we propose that catalyst **5f** accelerates the

dx.doi.org/10.1021/ja2092163 |*J. Am. Chem. Soc.* 2011, 133, 18534–18537

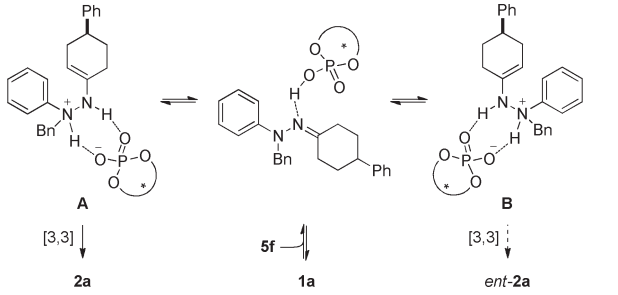
Table 2. Catalytic Asymmetric Fischer Indolization[a]



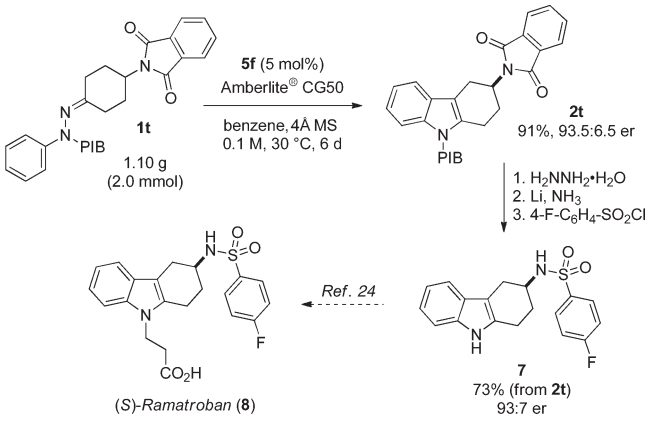
entry		product	yield[b]	er[c]
				
1	**2a**	R^1 = H, R^2 = Bn	94%	94:6
2	**2b**	R^1 = H, R^2 = 4-iodobenzyl (PIB)	99%	95:5
3	**2c**	R^1 = Me, R^2 = PIB	99%	92.5:7.5
4	**2d**	R^1 = OMe, R^2 = PIB	96%	87.5:12.5
5	**2e**	R^1 = Br, R^2 = PIB	82%	87.5:12.5
				
6	**2f**	R^1 = Me, R^3 = C_6H_5	90%	88:12
7	**2g**	R^1 = H, R^3 = C_6H_5	91%[d]	96:4
8	**2h**	R^1 = H, R^3 = 2-naphthyl	90%[d]	93:7
				
9	**2i**	R^3 = 4-*t*Bu-C_6H_4	89%	94.5:5.5
10	**2j**	R^3 = 4-MeO-C_6H_4	94%	96:4
11	**2k**	R^3 = 4-F-C_6H_4	99%	94.5:5.5
12	**2l**	R^3 = 3,5-Me_2-C_6H_3	88%	94:6
13	**2m**	R^3 = 3,5-$(MeO)_2$-C_6H_3	98%	94.5:5.5
14	**2n**	R^3 = 3-Cl-C_6H_4	97%	94:6
15	**2o**	R^3 = 2-naphthyl	99%	94.5:5.5
16	**2p**	R^3 = Me	70%	95:5
17	**2q**	R^3 = cyclohexyl	98%	91.5:8.5
18	**2r**	R^3 = *t*Bu	90%	80:20
19	**2s**	R^3 = OBz	99%	98.5:1.5
20[e]	**2t**	R^3 = NPhthal	99%	93.5:6.5
21[e,f]	**2t**	R^3 = NPhthal	83%	91:9
22	**2u**		11%[g]	80.5:19.5
23[h]	**2v**		62%[g]	90.5:9.5

[a] Reactions were run on a 0.1 mmol scale with Amberlite CG50 (200 mg) and 4 Å MS (50 mg). PIB = 4-iodobenzyl. [b] Isolated yields. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 6:1 mixture of regioisomers (as determined by ^{1}H NMR analysis). [e] 6 days. [f] Starting from the corresponding hydrazine and ketone. [g] Incomplete conversion of starting material. [h] 8 days at 50 °C.

Scheme 2. Proposed Dynamic Kinetic Resolution Pathway



Scheme 3. Formal Synthesis of Ramatroban



hydrazone−enehydrazine tautomerization. We expect that the benzyl group is essential in rendering the anilinic nitrogen sufficiently basic to ensure enehydrazine protonation at this position. This would allow the reaction to proceed via a distinct pathway involving a chiral hydrogen-bond-assisted ion pair for the dual activation of the substrate.[22] We suppose that one of the diastereomeric ion pairs **A** and **B** undergoes the irreversible [3,3]-sigmatropic rearrangement at a higher rate to give product **2a**, along with the ammonium salt of **5f**, by means of a dynamic kinetic resolution (Scheme 2). Alternatively the preferred formation of one enehydrazine enantiomer from the hydrazone and subsequent rearrangement can also be envisioned but seems less likely.[23] Ultimately, the active catalyst **5f** is regenerated by cation exchange with the resin.

As a brief demonstration of the utility of the developed method, we targeted a formal synthesis of the thromboxane receptor antagonist ramatroban (**8**).[20a,24] Indolization of hydrazone **1t** on a 2.0 mmol scale proceeded without compromising the yield or enantioselectivity and allowed 55% recovery of the catalyst **5f**. Starting from tetrahydrocarbazole **2t**, deprotection of the phthalimide followed by debenzylation under Birch conditions and subsequent sulfonylation gave the literature-known intermediate **7** in good overall yield without erosion of the initial enantiomeric ratio (Scheme 3). Comparison of the optical rotation of sulfonamide **7** with literature data revealed it to have the *S* configuration.[24] This is in accordance with the absolute configuration of **2b** as determined by X-ray structure analysis (see the SI).

In conclusion, we have presented a general, mild, and efficient method for accessing enantiomerically enriched 3-substituted

tetrahydrocarbazoles by utilizing the first catalytic asymmetric Fischer indolization. Key features of this process are the introduction of the new and powerful chiral phosphoric acid catalyst **5f** as well as the identification of a cation exchange resin for the efficient removal of ammonia from the reaction mixture. This combination allows the reaction to be performed at low temperature and with only substoichiometric quantities of a chiral Brønsted acid. We expect these findings to be of great value for improved syntheses of indole derivatives as well as for new developments in the field of chiral Brønsted acid catalysis. Further exploration of the potential of our spirocyclic phosphoric acids and studies of related transformations are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization, NMR spectra, HPLC traces, and X-ray data for **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We gratefully acknowledge generous support from the Max Planck Society and the Fonds der Chemischen Indutrie (fellowship for S.M.). We also thank Jens Truckenbrodt, Matthias Miosga, and our HPLC and X-ray departments for their support.

■ REFERENCES

(1) For reviews of indole syntheses, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (d) Gribble, G. W. *Contemp. Org. Synth.* **1994**, *1*, 145.

(2) (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.

(3) For reviews, see: (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

(4) For selected examples utilizing catalytic amounts of Lewis acids, see: (a) $ZnCl_2$: Lipińska, T. M.; Czarnocki, S. J. *Org. Lett.* **2006**, *8*, 367. (b) $Sb_2(SO_4)_3$: Srinivasa, A.; Mahadevan, K. M.; Varma, P. P.; Sudhakara, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009**, *184*, 1843. (c) $Bi(NO_3)_3 \cdot 5H_2O$: Sudhakara, A.; Jayadevappa, H.; Kumar, H. N. H.; Mahadevan, K. M. *Lett. Org. Chem.* **2009**, *6*, 159. (d) CAN: Varma, P. P.; Sherigara, B. S.; Mahadevan, K. M.; Hulikal, V. *Synth. Commun.* **2009**, *39*, 158.

(5) For selected recent examples of indolenine syntheses using the Fischer indolization, see: (a) Sajjadifar, S.; Vahedi, H.; Massoudi, A.; Louie, O. *Molecules* **2010**, *15*, 2491. (b) Liu, K. G.; Robichaud, A. J. *Tetrahedron Lett.* **2007**, *48*, 461. (c) Liu, K. G.; Robichaud, A. J.; Lo, J. R.; Mattes, J. F.; Cai, Y. *Org. Lett.* **2006**, *8*, 5769. For an elegant application in total synthesis, see:(d) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

(6) For representative examples, see: (a) Tsuji, R.; Nakagawa, M.; Nishida, A. *Heterocycles* **2002**, *58*, 587. (b) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109. (c) Rosenmund, P.; Sadri, E. *Liebigs Ann. Chem.* **1979**, 927. (d) Britten, A. Z.; Bardsley, W. G.; Hill, C. M. *Tetrahedron* **1971**, *27*, 5631. (e) Grandberg, I. I.; Zuyanova, T. I.; Afonina, N. I.; Ivanova, T. A. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 583.

(7) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181.

(8) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458.

(9) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687.

(10) For a review, see: Knölker, H.-J.; Reddy, K. R. *Alkaloids (San Diego)* **2008**, *65*, 181.

(11) For selected examples, see: (a) Baeyer−Villiger oxidations: Reetz, M. T.; Brunner, B.; Schneider, T.; Schulz, F.; Clouthier, C. M.; Kayser, M. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4075. *Angew. Chem.* **2004**, *116*, 4167. (b) Aldol reactions: Jiang, J.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *Chem. Commun.* **2007**, 736. (c) Michael additions: Sanzhong, L.; Zhang, L.; Mi, X.; Qiao, Y.; Cheng, J.-P. *J. Org. Chem.* **2007**, *72*, 9350. (d) Ring expansions with diazoacetates: Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834.

(12) Li, L.; Seidel, D. *Org. Lett.* **2010**, *12*, 5064. See also: Ren, L.; Lei, T.; Gong, L.-Z. *Chem. Commun.* **2011**, *47*, 11683.

(13) For reviews of chiral phosphoric acid catalysis, see: (a) Terada, M. *Synthesis* **2010**, 1929. (b) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

(14) For examples of enantioselective [3,3]-sigmatropic rearrangements catalyzed by chiral Brønsted acids, see: (a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228. (b) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 10090. *Angew. Chem.* **2008**, *120*, 10244. (c) Uyeda, C.; Rötheli, A. R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 9753. *Angew. Chem.* **2010**, *122*, 9947. (d) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062.

(15) When the reaction was conducted under reflux conditions and a slight argon stream, full conversion was achieved with a 10 mol % loading of a Brønsted acidic catalyst. However, we failed to obtain useful enantioselectivities under these reaction conditions.

(16) For selected examples, see: (a) Yamada, S.; Chibata, I.; Tsurui, R. *Pharm. Bull.* **1953**, *1*, 14. (b) Wahab, B.; Ellames, G.; Passey, S.; Watts, P. *Tetrahedron* **2010**, *66*, 3861. (c) For a review of heterogeneous catalysis of the Fischer indole synthesis, see: Downing, R. S.; Kunkeler, P. J. In *Fine Chemicals through Heterogeneous Catalysis*; Sheldon, R. A., Bekkum, H., Eds.; Wiley-VCH: New York, 2001; pp 178−183.

(17) SPINOL-derived phosphoric acids were independently introduced by three research groups. See: (a) Xu, F.; Huang, D.; Han, C.; Shen, W.; Lin, X.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 8677. (b) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536. (c) Xing, C.-H.; Liao, Y.-X.; Ng, J.; Hu, Q.-S. *J. Org. Chem.* **2011**, *76*, 4125.

(18) Other acidic additives such as acetic acid or benzoic acids had detrimental effects on the stereochemical outcome of the reaction (also see the SI).

(19) For an example of a study showing how varying *N*-benzyl groups in tetrahydrocarbazoles affects the biological activity, see: Li, L.; Beaulieu, C.; Carriere, M.-C.; Denis, D.; Greig, G.; Guay, D.; O'Neill, G.; Zamboni, R.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7462.

(20) For examples of biologically active 3-aminotetrahydrocarbazoles, see: (a) Böshagen, H.; Rosentreter, U.; Lieb, F.; Oediger, H.; Seuter, F.; Perzborn, E.; Fiedler, V.-B. Cycloalkano[1,2-*b*]indole-sulfonamides. EP 0242518, 1987. (b) Wood, P. L.; McQuade, P. S. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1984**, *8*, 773. (d) King, F. D.; Gaster, L. M.; Kaumann, A. J.; Young, R. C. Use of tetrahydrocarbazone derivatives as $5HT_1$ receptor agonists. WO 9300086, 1993.

(21) The mechanism was originally proposed by Robinson. See: Robinson, G. M.; Robinson, R. *J. Chem. Soc., Trans.* **1924**, *125*, 827.

(22) Garg and Houk have recently shown that in certain Fischer indolizations, hydrazones without a protecting group can be protonated at either of the two nitrogen atoms, resulting in two different reaction pathways. See: Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752.

(23) For a discussion of the dependence of the rate-determining step on the acidity of the medium in Fischer indolizations, see: Hughes, D. L. *J. Phys. Org. Chem.* **1994**, *7*, 625.

(24) Rosentreter, U.; Böshagen, H.; Seuter, F.; Perzborn, E.; Fiedler, V. B. *Arzneim. Forsch.* **1989**, *39*, 1519.