Organocatalysis

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Direct Asymmetric Hydrosilylation of Indoles: Combined Lewis Base and Brønsted Acid Activation**

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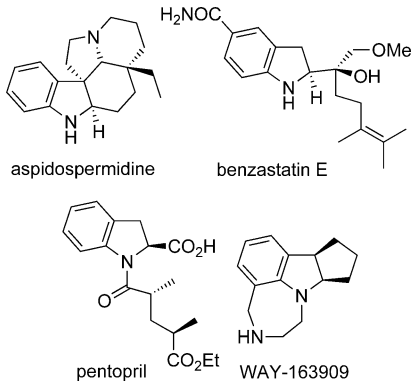
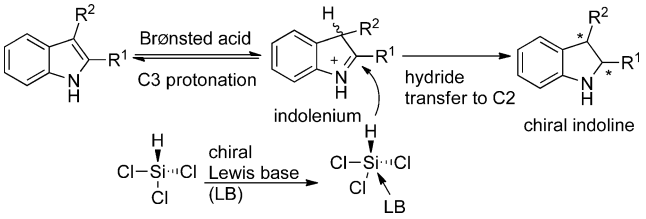
In light of their occurrence in a broad spectrum of natural alkaloids and several important pharmaceutically active compounds,[1] such as those outlined in Scheme 1, enantioenriched indolines have triggered increasing attention in both the synthetic and medicinal chemistry communities.[2]



Scheme 1. Representative chiral indoline derivatives.

While a variety of protocols, including traditional enzymatic or non-enzymatic kinetic resolutions,[3] and organic-molecule- or metal-mediated asymmetric transformations[4] have been described, the direct asymmetric reduction of prochiral indole precursors would be one of the most straightforward ways to make chiral indolines.[5] Thus, a few transition metal/chiral phosphine complexes, including Rh, Ru, and Ir, have been applied by the groups of Kuwano, Feringa, Pfaltz, and others to the asymmetric hydrogenation of indoles, but the methods usually suffer from a limited substrate scope and relatively harsh reaction conditions.[6] A noteworthy breakthrough was made by Zhou, Zhang, and coworkers who reported an elegant palladium-catalyzed enantioselective hydrogenation of unprotected indoles activated by Brønsted acids.[7] In contrast, Rueping et al. presented the chiral Brønsted acid catalyzed transfer hydrogenation of 3*H*-indoles with Hantzsch dihydropyridine as the hydrogen source.[8] Nevertheless, to the best of our knowledge, there is no successful precedent on the direct asymmetric reduction of 1*H*-indoles to access chiral indolines under metal-free conditions despite the fantastic progress of organocatalysis over the past decade.[9]

Recently we discovered a highly diastereoselective intramolecular direct imino-ene reaction of indoles tethered to an olefinic side chain at C3, in which a Lewis acid promoted enamine–imine isomerization of the indole through C3 protonation was key to its success.[10] We also recognized that, for unprotected indoles, a similar C3 protonation would occur in the presence of suitable Brønsted acids, which would destroy the aromaticity of indoles and result in the formation of electrophilic indolenium ions.[11] We envisioned that the asymmetric reduction of indoles might be realized by utilizing a chiral organocatalytic system that is compatible with a Brønsted acid activation process. Herein we report our endeavors on the first direct enantioselective hydrosilylation of prochiral 1*H*-indoles by combined Brønsted acid/Lewis base activation (Scheme 2).[12]



Scheme 2. Proposed direct asymmetric hydrosilylation of indoles through both Lewis base and Brønsted acid activations.

The initial investigation in the direct hydrosilylation of 2-methylindole (**2a**) with excess $HSiCl_3$ was conducted by employing *N*,*N*-dimethylformamide (**1a**; DMF) as the Lewis base catalyst at 0 °C. One equivalent of H_2O was added to react with $HSiCl_3$ to generate a strong Brønsted acid, HCl.[13] The reaction was quite inspiring, and the desired indoline product **3a** was cleanly obtained in high yield after 24 hours

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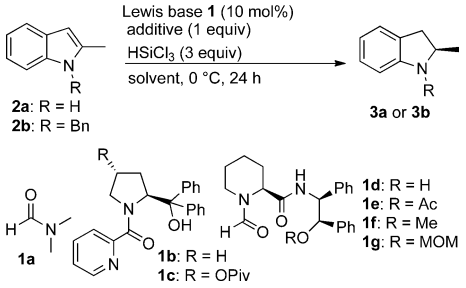
Table 1: Screening studies for the direct hydrosilylation of 2-methylindole (**2a**).[a]



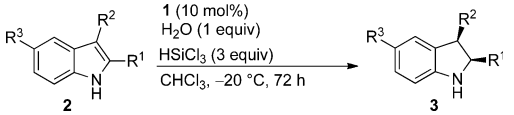
Entry	1	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**1a**	CH_2Cl_2	H_2O	81	–
2	**1b**	CH_2Cl_2	H_2O	85	−60
3	**1d**	CH_2Cl_2	H_2O	85	67
4	**1d**	CH_2Cl_2	MeOH	81	43
5	**1d**	CH_2Cl_2	*t*BuOH	82	66
6	**1d**	CH_2Cl_2	(*S*)-binol	82	67
7	**1d**	CH_2Cl_2	$PhCO_2H$	90	66
8	**1d**	CH_2Cl_2	Tf_2NH	<10	–
9	**1e**	CH_2Cl_2	H_2O	77	47
10	**1f**	CH_2Cl_2	H_2O	85	70
11	**1g**	CH_2Cl_2	H_2O	86	74
12	**1g**	toluene	H_2O	65	39
13	**1g**	$CHCl_3$	H_2O	85	80
14	**1c**	$CHCl_3$	H_2O	86	−70
15[d,e]	**1g**	$CHCl_3$	H_2O	87	85
16[d,f]	**1g**	**$CHCl_3$**	**H_2O**	**86**	**90**
17[d,f,g]	**1g**	$CHCl_3$	H_2O	82	70

[a] Unless noted otherwise, reactions were performed with **2a** (0.2 mmol), additive (0.2 mmol), catalyst **1** (0.02 mmol), and $HSiCl_3$ (0.6 mmol) in solvent (1.0 mL) at 0°C for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] For 72 h. [e] At −10°C. [f] At −20°C. [g] The indole **2b** was used. binol = 2,2′-dihydroxy-1,1′-binaphthyl, MOM = methoxymethyl, Tf_2NH = trifluoromethanesulfonimide.

(Table 1, entry 1). It should be addressed that the reduction did not take place in the absence of either H_2O or **1a**, thus indicating that both the Brønsted acid and Lewis base activations were necessary. Subsequently, a variety of chiral Lewis base organocatalysts, which have been effectively utilized in several asymmetric hydrosilylation reactions with $HSiCl_3$ over the past years,[14] were extensively screened to induce chirality in the product.[15] Pleasingly, both chiral picolinoylpyrrolidine[16] (**1b**) and *N*-formyl L-pipecolinamide[17] (**1d**) exhibited high catalytic activity, and more importantly, promising enantioselectivity (Table 1, entries 2 and 3). We next explored the effects of an array of proton additives with catalyst **1d** (Table 1, entries 4–8). Though the *ee* value was significantly diminished when H_2O was replaced by MeOH (Table 1, entry 4), similar data was generally obtained, even when a chiral (*S*)-binol was used (Table 1, entry 6). It seems that the acid additive just supplies a proton, and might not be involved in the key asymmetric reduction step.[18] Nevertheless, almost no reaction occurred in the presence of Tf_2NH (Table 1, entry 8). In addition, the modified catalysts **1e**–**1g** that are based on **1d** were tested (Table 1, entries 9–11); **1g**, having an MOM ether moiety delivered better enantiocontrol (Table 1, entry 11). Solvent had obvious effects on the enantioselectivity. Whereas a dramatically decreased *ee* value was observed in toluene (Table 1, entry 12), the results could be significantly improved in chloroform (Table 1, entry 13). The O-pivaloyl picolinoylpyrrolidine catalyst **1c**,[19] which was reported by Zhang and co-workers, was also tested in chloroform, but afforded inferior results (Table 1, entry 14). It was found that the enantioselectivity could be improved at lower temperature by using the catalyst **1g**, but a longer reaction was required to guarantee complete conversion (Table 1, entries 15 and 16); however, almost no reaction occurred at −40°C. Interestingly, the *N*-benzyl indole **2b** also showed high reactivity, but a lower enantioselectivity was obtained under the optimal reaction conditions (Table 1, entry 17).

Consequently, the substrate scope and limitations for indole compounds were examined. The reactions were generally conducted with the Lewis base catalyst **1g** at −20°C for 72 hours. The results are summarized in Table 2. For 2-methyl-substituted indole derivatives, the electron-donating or electron-withdrawing substitution on the aromatic ring has marginal effects, and good data were obtained (Table 2, entries 2 and 3). Gratifyingly, 2-methylindoles bearing a variety of alkyl groups at C3 could be smoothly applied, thus exclusively giving *cis* indolines with high enantioselec-

Table 2: Substrate scope in the direct asymmetric hydrosilylation of indoles **2**.[a]



Entry	1	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
1	**1g**	Me	H	H	**3a**: 86	90[d]
2	**1g**	Me	H	Me	**3c**: 89	90
3	**1g**	Me	H	Br	**3d**: 83	85
4	**1g**	Me	Me	H	**3e**: 88	90[d]
5	**1g**	Me	Me	Cl	**3f**: 85	86
6	**1g**	Me	Et	H	**3g**: 92	93
7	**1g**	Me	*n*Bu	H	**3h**: 87	86
8	**1g**	Me	Bn	H	**3i**: 87	88
9[e]	**1g**	Me	*i*Pr	H	**3j**: 82	85
10[e]	**1g**	Me	$CH_2CH_2CO_2Me$	H	**3k**: 82	88
11[e,f]	**1g**	Me	$CH{=}CHCO_2Me$	H	**3k**: 80	87
12[g]	**1g**	$-(CH_2)_4-$		H	**3l**: 87	84
13[g]	**1g**	$-(CH_2)_3-$		H	**3m**: 91	70
14	**1g**	H	Bn	H	**3n**: 80	55
15[e]	**1g**	H	$CH_2CH_2CO_2Et$	H	**3o**: 81	46
16	**1g**	*n*Bu	H	H	**3p**: 78	23
17[e,h]	**1c**	*n*Bu	H	H	**3p**: 87	−76
18[e,h]	**1c**	Bn	H	H	**3q**: 82	−75
19[e]	**1c**	Et	Me	H	**3r**: 82	−90
20[e]	**1c**	*n*Pr	Me	H	**3s**: 80	−88
21[e]	**1c**	*n*Pr	Et	H	**3t**: 78	−88

[a] Unless noted otherwise, reactions were performed with **2** (0.2 mmol), H_2O (0.2 mmol), catalyst **1** (0.02 mmol), and $HSiCl_3$ (0.6 mmol) in $CHCl_3$ (1.0 mL) at −20°C for 72 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; d.r. > 99:1 by ^1H NMR analysis (where applicable). [d] The absolute configuration was determined by comparison of the specific optical rotations with those reported in the literature. The other products were assigned by analogy. [e] At 0°C. [f] $HSiCl_3$ (0.8 mmol) was used. [g] At −30°C. [h] For 24 h.

tivities and yields (isolated; Table 2, entries 4–9). Apparently, a dynamic kinetic resolution was involved in the asymmetric hydrosilylation of the resulting indolenium intermediates.[7a,15] It was notable that an indole substrate carrying a carboxylate group was compatible with the current catalytic system, and good results were attained (Table 2, entry 10). Importantly, a conjugated C=C bond was found to be simultaneously reduced (Table 2, entry 11). A good *ee* value was delivered for cyclohexyl[*b*]indole (Table 2, entry 12), whilst lower enantiocontrol was attained for cyclopentyl[*b*]indole even at −30 °C (Table 2, entry 13). The dynamic kinetic reduction of 3-substituted indoles could be realized, albeit with modest *ee* values (Table 2, entries 14 and 15).[20,15] Unfortunately, the **1g**-based catalytic system was not suitable for indoles having a larger 2-alkyl group, and very low enantioselectivity was obtained for 2-*n*butylindole (Table 2, entry 16).

Subsequently, we re-screened various Lewis base catalysts, hoping to find a preferable catalytic system for the enantioselective hydrosilylation of indoles having a larger 2-alkyl group. To our gratification, the chiral picolinamide catalyst **1c** afforded a much better *ee* value in the reduction of 2-*n*butylindole (Table 2, entry 17).[15] Thus, more indole substrates were explored using the catalyst **1c**. A similar moderate enantioselectivity was obtained for 2-benzylindole (Table 2, entry 18). Fortunately, high *ee* values with excellent diastereoselectivity could be attained by introducing another alkyl group to C3, eventhough the reaction time had to be extended (Table 2, entries 19–21).[21]

In conclusion, we have developed the first organocatalytic direct asymmetric reduction of unprotected 1*H*-indoles to access chiral indoline scaffolds. The reaction proceeds through the generation of electrophilic indolenium ions by C3 protonation with the in situ formed HCl acid, and subsequent chiral Lewis base mediated enantioselective hydrosilylation with $HSiCl_3$. A variety of chiral indolines were efficiently obtained in moderate to excellent enantioselectivity (up to 93% *ee*), and remarkably, the exclusive diastereocontrol was observed for 2,3-disubstituted ones. We hope that this study will help to open an avenue for the direct asymmetric reduction of indoles under metal-free reaction conditions. Currently more applications using the reported catalytic strategy are under investigation in this laboratory.

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[21] Indoles carrying a phenyl or carboxylate group at either C2 or C3 showed no reactivity under current catalytic conditions; this is probably due to the failure of the C3-protonation process.

