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# Chiral 2,3-Disubstituted Indolines from Indoles and Aldehydes by Organocatalyzed Tandem Synthesis Involving Reduction by Trichlorosilane

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**Abstract:** The organocatalytic trichlorosilane reduction system has been successfully utilized to develop a multi-step tandem approach for the easy preparation of chiral 2-methyl-3-alkylindolines starting from simple 2-methylindoles and aldehydes. A broad range of chiral 2-methyl-3-alkylindoline products was obtained with high yields and enantioselectivities and excellent stereoselectivities by this approach.

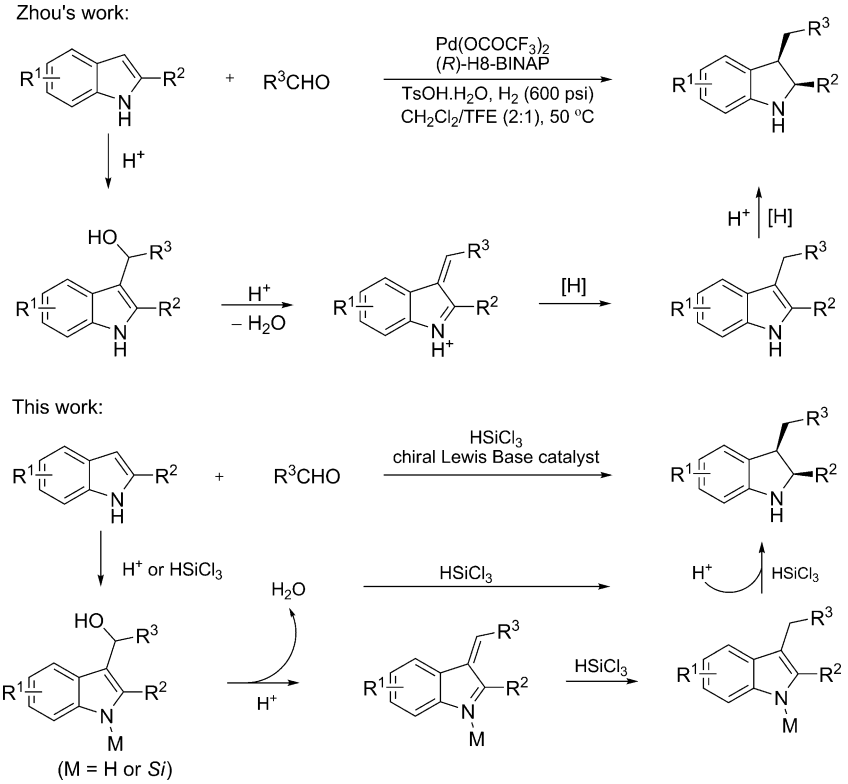
**Keywords:** enantioselectivity; indolines; reduction; tandem reactions; trichlorosilane

Organic synthesis through one-pot tandem reactions is a fascinating synthetic approach, especially to complex molecules with multi-functional groups and/or multi-chiral centers. It simplifies the synthetic operations to a large extent since it runs different reactions in a single operation and avoids the separate work-up, separation and purification of intermediates as is needed in traditional step-by-step synthesis. This is particularly true if multiple steps and intermediates are involved. In recent years, remarkable advances have been made in the development of tandem reactions.[1] In particular, quite a few catalytic asymmetric reaction systems have been successfully incorporated into tandem reactions, resulting in many highly efficient and stereoselective tandem protocols.[2] Nonetheless, so far the catalytic reaction systems that could be applied to tandem reactions are still limited, and the application potentials of the catalytic reaction systems in tandem reactions are far from being fully explored. Therefore, the development of new catalytic tandem reactions remains highly desirable.

The organic Lewis base/trichlorosilane ($HSiCl_3$) system has proven to be a powerful catalytic reduction system.[3] In recent years, with the development of chiral Lewis base catalysts, the efficiency and the enantioselectivity of this system have reached a fairly high level. Its application scope has also been significantly expanded to the reduction of a wide variety of substrates including various ketones,[4] ketimines,[5] and enamines.[6] Moreover, the environmentally benign nature and the low cost features render this reaction system particularly attractive for practical applications. However, this reduction system has been rarely applied in the development of tandem reactions. So far there have been only two reports in the literature presenting two-step tandem reactions based on the reduction of C=C conjugated ketones using this reduction system.[7] Herein, we wish to report the first design and implementation of multi-step tandem reactions based on the asymmetric reduction of enamines and conjugated imines by the Lewis base/$HSiCl_3$ system.

Chiral 2,3-disubstituted indolines represent an important structural motif and and frequently seen in biologically important molecules such as natural products and pharmaceutically active compounds.[8] Their construction generally goes through multi-step reactions, whereby the stereocontrol relies on stoichiometric chiral starting materials or reagents.[9] Catalytic asymmetric reduction of substituted indole derivatives may be a most straightforward and atom economic means towards chiral 2,3-disubstituted indolines. Recently, Zhou and co-workers reported an efficient method for the highly stereoselective reduction of a broad range of substituted indoles *via* chiral transition metal complex-catalyzed hydrogenation.[10] Later on, we developed an organocatalytic method for the same transformation using the Lewis base/$HSiCl_3$ system, which also afforded high stereoselectivities




**Scheme 1.** The tandem reactions for the production of chiral 2,3-disubstituted indolines.

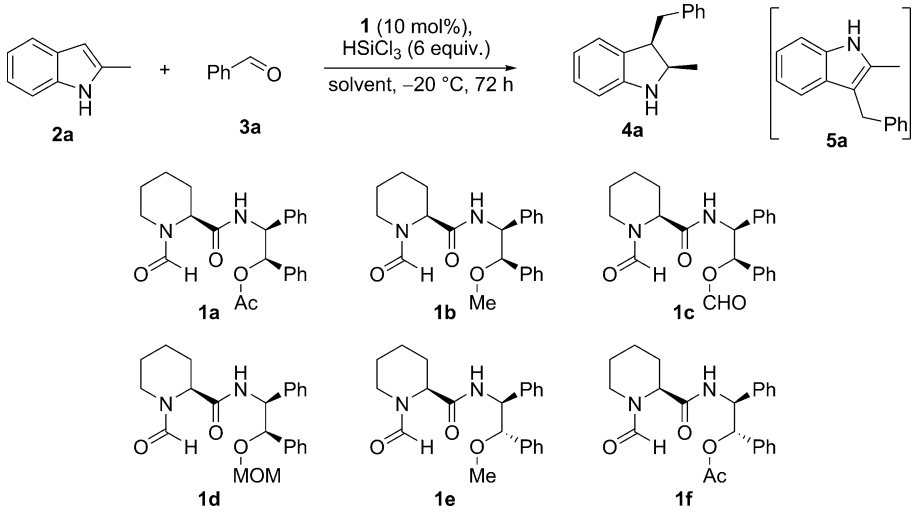
and exhibited good substrate generality.[6e] However, this approach suffers from an apparent drawback that certainly limits its application. All the 2,3-disubstituted indole substrates need to be prepared through complicated and tedious procedures starting from relatively expensive materials, and the yields are generally low to moderate. To address this limitation, Zhou and co-workers recently developed an elegant approach to chiral 2,3-disubstituted indolines starting from easily available and cheap indoles and aldehydes or their adducts through tandem reactions (Scheme 1), which use a relatively complicated catalytic systems containing a Pd(II)/chiral phosphine complex as catalyst and Brønsted acid as stoichiometric activator.[11] Enlightened by this work, we designed an organocatalytic version of this tandem approach using the Lewis base/$HSiCl_3$ reduction system. The main advantages of this design include: (i) the use of expensive transition metal catalysts is avoided; (ii) the Friedel–Crafts reaction can be initiated by either the small amount of hydrochloride contained in $HSiCl_3$ or by the Lewis acidic $HSiCl_3$ itself; (iii) water generated in the dehydration step can be easily consumed by trichlorosilane, which not only forms driving force for the dehydration, but also releases hydrochloride as Brønsted acid activator for the hydrosilylation of the indole intermediate, thus, no external Brønsted acid needs to be introduced.

To implement our design, we first tested the reaction of 2-methylindole **2a** and benzaldehyde **3a** with $HSiCl_3$ in the presence of *N*,*N*-dimethylformamide (DMF) as Lewis base activator. To our delight, the desired 2-methyl-3-benzylindoline product **4a** was obtained in good yield and excellent diastereoselectivity (Table 1, entry 1). Next, various chiral Lewis base catalysts were screened to check if good enantiocontrol could also be achieved. Amide catalysts **1** derived from L-2-pipecolinic acid and chiral 1,2-diphenyl-2-hydroxyethylamine proved to be highly effective. All **1a–f** exhibited good chemical activity and excellent diastereoselectivity, undergoing the tandem reactions in 72 h with 73–92% yields and >99:1 diastereomeric ratios (Table 1, entries 2–7). Catalyst **1d** that was previously shown to exhibit the best efficacy in the reduction of 2,3-disubstituted indoles again gave rise to the best results, affording 92% yield, >99:1 *dr*, and 89% *ee*. Its analogues **1a** and **1c** that bear an acyl group instead of the MOM group on the oxygen terminal both are slightly less active and enantioselective, whilst the analogue **1b** bearing a methyl group at the same position exhibited significantly lowered activity and enantioselectivity.

Next, different reaction conditions were examined to see if the **1d**-catalyzed tandem reactions of **2a** with **3a** could be further optimized. Dichloromethane, 1,2-dichloroethane, and toluene all proved to be effective solvents for the present reaction system, but afforded

**Table 1.** Formation of indoline **4a** *via* Lewis base-catalyzed tandem reactions of **2a** with **3a**.[a]



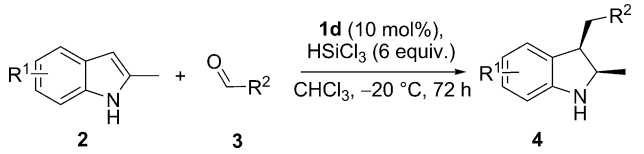

| Entry | Cat. | Solvent | Yield of **4a** [%][a] | *dr* | *ee* [%][c] |
|---|---|---|---|---|---|
| 1[d,g] | DMF | $CHCl_3$ | 90 | >99:1 | – |
| 2 | **1a** | $CHCl_3$ | 85 | >99:1 | 84 |
| 3[e] | **1b** | $CHCl_3$ | 73 | >99:1 | 65 |
| 4 | **1c** | $CHCl_3$ | 90 | >99:1 | 85 |
| 5 | **1d** | **$CHCl_3$** | **92** | **>99:1** | **89** |
| 6 | **1e** | $CHCl_3$ | 81 | >99:1 | 72 |
| 7 | **1f** | $CHCl_3$ | 82 | >99:1 | 82 |
| 8 | **1a** | toluene | 79 | >99:1 | 75 |
| 9[e] | **1a** | MeCN | <5 | – | – |
| 10 | **1a** | DCE | 84 | >99:1 | 83 |
| 11 | **1a** | DCM | 89 | >99:1 | 75 |
| 12[f] | **1a** | $CHCl_3$ | 65 | >99:1 | 91 |
| 13[g] | **1a** | $CHCl_3$ | 92 | >99:1 | 81 |
| 14[e,h] | **1a** | $CHCl_3$ | 42 | >99:1 | 88 |

[a] Unless noted otherwise, reactions were performed with **2a** (0.2 mmol), **3a** (0.2 mmol), catalyst **1** (0.02 mmol), and $HSiCl_3$ (1.2 mmol) in solvent (2.0 mL) at −20 °C for 72 h.
[b] Yield of isolated product **4a**.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] 1 equiv. DMF was used.
[e] The corresponding 2-methyl-3-benzylindole intermediate **5a** is the main product.
[f] The reaction temperature is at −40 °C.
[g] The reaction temperature is at 0 °C.
[h] 5% catalyst was used.

slightly lower yields and enantioselectivities than chloroform (Table 1, entries 8, 10, and 11). In contrast, acetonitrile was found not to be suitable at all (entry 9). No desired product **4a** was detected when this solvent was used, 2-methyl-3-benzylindole **5a**, the conjugate reduction intermediate, was observed as the major product instead. When the reaction temperature was lowered from −20 to −40 °C, the *ee* value was slightly increased, but the yield was substantially diminished (Table 1, entry 12). If the catalyst loading was reduced from 10 to 5 mol%, the reaction was significantly slowed down, albeit with unaffected stereoselectivities (Table 1, entry 14).

To explore the application scope and limitation of the present tandem reaction system, various indoles **1** and aldehydes **2** were examined as substrates in the presence of 10 mol% catalyst **1d**. The results are summarized in Table 2. Aromatic aldehydes including benzaldehydes bearing either electron-donating or electron-withdrawing substituents and naphthyl-2-carbaldehyde all are good substrates, affording the desired *cis* indoline products **4a**–**p** in 68–95% yield and 77–90% *ee* (Table 2, entries 1–16). Cinamaldehyde with a conjugated C=C bond could also be applied, giving rise to the 3-allylic *cis*-indoline product in good yield, and 81% *ee* (entry 24). Indoles bearing different substituents at the 5-position were also found to be

**Table 2. 1d**-catalyzed tandem reactions of various indoles **2** and aldehydes **3**.[a]




**2** **3** **4**

| Entry | $R^1$ | $R^2$ | **4** | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | H | Ph | **4a** | 93 | 89 |
| 2 | H | 4-$ClC_6H_4$ | **4b** | 95 | 89 |
| 3 | H | 4-$BrC_6H_4$ | **4c** | 92 | 90 |
| 4 | H | 4-$MeC_6H_4$ | **4d** | 82 | 87 |
| 5 | H | 4-$MeOC_6H_4$ | **4e** | 88 | 87 |
| 6 | H | 4-$NO_2C_6H_4$ | **4f** | 87 | 87 |
| 7 | H | 4-$CNC_6H_4$ | **4g** | 83 | 77 |
| 8 | H | 4-$CF_3C_6H_4$ | **4h** | 68 | 85 |
| 9 | H | 4-*i*-$PrC_6H_4$ | **4i** | 88 | 89 |
| 10 | H | 3-$ClC_6H_4$ | **4j** | 82 | 84 |
| 11 | H | 3-$BrC_6H_4$ | **4k** | 88 | 87 |
| 12 | H | 3-$MeC_6H_4$ | **4l** | 85 | 85 |
| 13 | H | 3-$MeOC_6H_4$ | **4m** | 88 | 89 |
| 14 | H | 3-Br-4-$MeOC_6H_3$ | **4n** | 89 | 90 |
| 15 | H | 2,4,5-$(MeO)_3C_6H_2$ | **4o** | 89 | 89 |
| 16 | H | 2-naphthyl | **4p** | 88 | 87 |
| 17 | 5-Cl | Ph | **4q** | 78 | 81 |
| 18 | 5-Me | Ph | **4r** | 85 | 90 |
| 19 | 5-MeO | Ph | **4s** | 83 | 89 |
| 20 | 7-Me | Ph | **4t** | 88 | 59 |
| 21 | 7-MeO | Ph | **4u** | 82 | 52 |
| 22 | 7-Cl | Ph | | <5 | – |
| 23 | 7-Br | Ph | | <5 | – |
| 24 | H | CH=CH–Ph | **4v** | 85 | 81 |
| 25 | H | *c*-Hex | **4w** | 45 | 72 |
| 26[d] | H | *c*-Hex | **4w** | 79 | 77 |
| 27[d] | H | *i*-Pr | **4x** | 74 | 84 |
| 28[d] | H | $CH_2(CH_2)_4CH_3$ | **4y** | 75 | 81 |

[a] Unless noted otherwise, reactions were performed in a one-pot and one-operation fashion with **2** (0.2 mmol), **3** (0.22 mmol), catalyst **1d** (0.02 mmol), and $HSiCl_3$ (1.2 mmol) in $CHCl_3$ (2.0 mL) at −20 °C for 72 h.

[b] Yield of isolated product.

[c] Determined by HPLC analysis on a chiral stationary phase; *dr* > 99:1 by $^1H$ NMR analysis (where applicable).

[d] The reaction was conducted in a one-pot but two-operation fashion. The two operations are: indole **2** was reacted with **3** in the presence of 1.0 equiv. $HSiCl_3$ at 0 °C for 3 h first; the reaction mixture was then treated with catalyst **1d** and 5.0 equiv. $HSiCl_3$ at −20 °C for 72 h.

tolerated. The 5-chloro-, 5-methyl-, and 5-methoxyindoles all underwent smooth reactions to furnish the corresponding *cis*-indoline products with good yields (78–83%) and enantioselectivities (81–90% *ee*) (Table 2, entries 17–19). But interestingly, when the substitution is at the 7-position, (Table 2, entries 20–23), a quite different scenario was observed. The electron-donating groups (Me and MeO) at this position had only marginal effects on the reactivity, but caused significant decreases in enantioselectivity, whereas halogen groups (Cl and Br) at the same position resulted in no formation of the desired product at all.

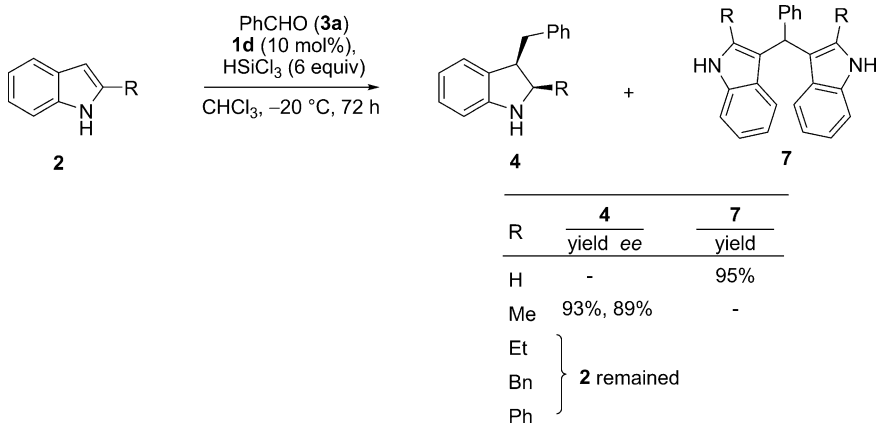
Notably, when aliphatic aldehydes such as cyclohexanecarbaldehyde were utilized as substrate, the yield of the desired *cis*-indoline product tended to be low if the one-pot and one-operation procedure was followed (Table 2, entry 25). The direct reduction product **6** of indole **2** and the intermediate **5** were observed as the major products (see Scheme 3 for the structures of **5** and **6**). However, if a one-pot but two-operation procedure was followed, that is, the aldehyde was reacted with indole **2** in the presence of $HSiCl_3$ and in the absence of catalyst for 3 h first, and then, without work-up, the catalyst and the rest amount of $HSiCl_3$ were introduced to the mixture, the desired *cis*-indoline product could still be achieved with good yield and enantioselectivity (Table 2, entries 26–28).

It should also be noted that variation of the 2-methyl substitution of the indole substrate seems to be hardly tolerated in the present reaction system. If there is no substitution at this position, no desired *cis*-indoline product **4** was detected, and the intermediate **7** was obtained as the only product instead (Scheme 2). On the other hand, when the 2-methyl group was replaced with either ethyl, benzyl or phenyl, no reactions occurred at all, not even the formation of intermediate **7**. Since the formation of **7** is well known to be fairly easy and could be effectively catalyzed by many Brønsted acids and Lewis acids, it seems to be unusual that the large amount of Lewis acidic $HSiCl_3$ plus the unavoidable small amount of HCl in the present reaction system could not make this reaction happen at all.

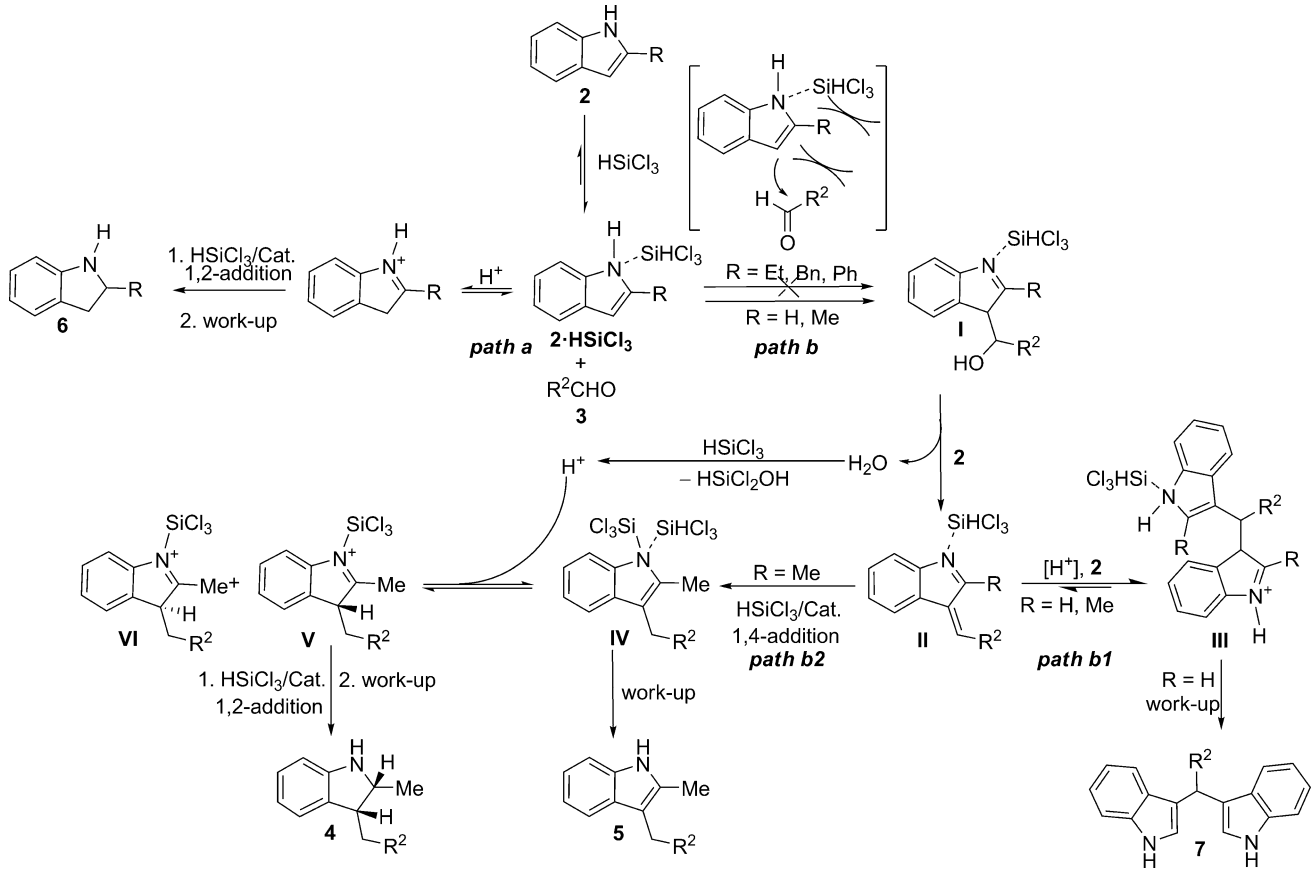
To rationalize the different results achieved with different substrates in the present tandem reaction system, possible pathways were proposed as shown in Scheme 3. The indole **2** is readily able to form a complex (**2**·$HSiCl_3$) with trichlorosilane. This complex can be reduced to generate product **6** in the presence of the Lewis base catalyst and stoichiometric amount of Brønsted acid (*path a*). It can also undergo a Friedel–Crafts aldol reaction with aldehyde **3** to form intermediate **I** following *path b*. Intermediate **I** then undergoes water elimination to give intermediate **II**, which can follow the traditional Friedel–Crafts Michael addition *path b1* to afford intermediate **III** and product **7** upon work-up. If 1,4-addition of $HSiCl_3$ to intermediate **II** occurs following *path b2*, intermediate **IV** is generated, which gives rise to product **5** upon work-up, and can also undergo further tautomerization and 1,2-reduction to furnish product **4** if a stoichiometric amount of Brønsted acid is present.[12]

When the 2-substitutent R in indole **2** is bigger than methyl, the coordination of $HSiCl_3$ pushes this




**Scheme 2.** The limitation of 2-subsitution on indoles **2**.

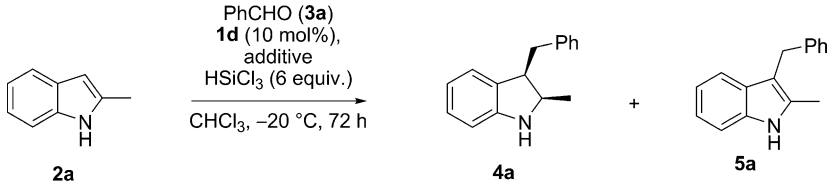



**Scheme 3.** Possible pathways for different substrates.

substituent towards the 3-position. This causes serious steric hindrance for the nucleophilic attack of indole **2** to aldehyde **3**, and thus blocks the Friedel–Crafts aldol reaction and *path b*. In this scenario, *path a* is also forbidden since there is a lack of a stoichiometric amount of Brønsted acid that has proven to be indispensable for such reduction.[6e] This explains why indoles bearing a relatively big 2-R group remain intact in the present reaction system.

When active aldehydes such as **3a**–**u** were used as substrates, the formations of intermediates **I** and **II** should be fairly fast. If the 2-R of indole **2** is hydrogen, the Friedel–Crafts Michael addition (*path b1*) is well-known to be an easy reaction, which explains why **7** was obtained as the exclusive product in this case (*vice supra*). But when the 2-R of indole **2** is a methyl group, the steric congestion caused by this group renders *path b1* unfavorable, whereas *path b2*




| | 4a | 5a |
|---|---|---|
| additive | yield, *ee* | yield |
| 4 Å MS | <5%, - | >90% |
| $Na_2SO_4$ | <5%, - | >90% |
| $MgSO_4$ | <5%, - | >90% |
| $Et_3N$ | 88%, 35% | ND |

**Scheme 4.** Additive effects as evidence for the proposed mechanism.

becomes much more preferable, thus affording **4** as the predominant product.

When relatively less active aldehydes were used as substrates, the formation of intermediates **I** and **II** becomes relatively slow. The **2**·$HSiCl_3$ complex that is not consumed yet can compete for protons with intermediate **IV**, thus both of them can be reduced and both products **6** and **4** can be formed, meanwhile product **5** can also be obtained due to incomplete reduction of **IV**. This perfectly explains the experimental observations that the yield of **4** is low and **5** and **6** are the major by-products when aliphatic aldehydes **3v–x** were used as substrates and the one-pot and one-operation procedures were followed. The reason why this problem could be addressed by following the one-pot and two-operation procedures is that the separated first operation ensures complete conversion of **2**·$HSiCl_3$ to intermediate **II** and **III**, thus the competition of the reduction of **2**·$HSiCl_3$ is avoided.

To further support the mechanisms we proposed, some experiments were also conducted. Firstly, the $^1$H NMR experiments revealed that **2** (R = Me and Et) is easy to form complex with $HSiCl_3$ (see spectra in the Supporting Information). Secondly, when the reaction was carried out in deuturated chloroform and monitored by $^1$H NMR, the key intermediates **II** and **IV** were detected. Thirdly, when drying agents including molecular sieves, magnesium sulfate and sodium sulfate were added to the reaction of **2a** with **3a**, **5a** was observed as the predominant product (Scheme 4), demonstrating that water is crucial for the transformation of **IV** to the final product. On the other hand, if triethylamine was added, the desired product **4a** was obtained in 88% yield, but with much lower diastereoselectivity and enantioselectivity. This should due to the coordination of triethylamine with $HSiCl_3$, which can also promote the hydrosilylation and thus interfere with the catalyst.

In conclusion, we have developed a tandem protocol using the organocatalytic trichlorosilane reduction system for the preparation of chiral 2-methyl-3-alkylindolines from inexpensive commercially available substituted 2-methylindoles and aldehydes. Amide catalyst **1** derived from L-2-pipecolinic acid and chiral 1,2-diphenyl-2-hydroxyethylamine proved to be highly effective in this tandem protocol, promoting the efficient production of a wide variety of chiral 2-methyl-3-alkylindolines with high yields and enantioselectivity and excellent diasteroselectivity. The outstanding feature of this tandem reaction system is that water as by-product in the Friedel–Crafts alkylation step provides a promoter for the main reduction step, meanwhile the latter step also provides promotions for the former step, not only by forming the driving force through consumption of the by-product, but also by providing an advantageous acidic environment. In other words, the main reactions incorporated in this tandem protocol are not just compatible or one-way favorable, but provide mutual promotions.

## Experimental Section

All starting materials were of the highest commercially available grade and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use.

### Typical Procedure for the Catalyzed Asymmetric Synthesis of 2,3-Disubstituted Indoline 4

A solution of aromatic aldehyde **3b** (0.22 mmol, 1.1 equiv.) in 0.4 mL $CHCl_3$ was added dropwise to a solution of indole **2a** (0.2 mmol) and catalyst **1d** (0.02 mmol, 0.1 equiv.) in 0.4 mL $CHCl_3$ at −20 °C, and then trichlorosilane (0.12 mL, 1.2 mmol, 6.0 equiv.) in 1.2 mL of $CHCl_3$ was added dropwise into the solution. The solution was stirred at −20 °C for 72 h. The reaction was then quenched with saturated aqueous solution of $NaHCO_3$ (2 mL) and basified with $NaHCO_3$ powder, the mixture was extracted with EtOAc (10 mL) three times. The combined extracts were washed with brine and dried over anhydrous $Na_2SO_4$. The combined solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum

ether/EtOAc) to afford pure indoline **4b**. The *ee* values were determined by HPLC with chiral stationary phases.

**(2*R*,3*R*)-3-(4-Chlorobenzyl)-2-methylindoline (4b):** Obtained as a yellow semi-solid after flash chromatography; yield: 95%; the enantiomeric excess was determined to be 89% by HPLC analysis [Chiralpak OD-H column, 10% 2-propanol/*n*-hexane, 1 mL min$^{-1}$]: $t_{major}$ = 16.26 min, $t_{minor}$ = 9.77 min; $[\alpha]_D^{20}$: −70.3 (*c* 0.31 in $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.27 (d, $J$ = 6.5 Hz, 3H), 2.79–2.86 (m, 1H), 2.93–3.00 (m, 1H), 3.43–3.51 (m, 2H), 3.99–4.06 (m, 1H), 6.54–6.68 (m, 3H), 7.03–7.17(m, 3H), 7.29 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 16.4, 33.8, 46.0, 58.5, 109.5, 118.4, 125.0, 127.7, 128.4, 130.6, 131.7, 131.8, 138.9, 150.5; ESI HR-MS: $m/z$ = 258.1056, calcd. for $C_{16}H_{16}ClN + H^+$: 258.1044.

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