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# Titanocene(III)-Catalyzed Formation of Indolines and Azaindolines

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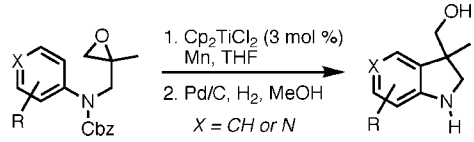
## ABSTRACT




**Reductive cyclization of epoxides tethered to substituted anilines and aminopyridines in the presence of 3 mol % of titanocene dichloride and stoichiometric manganese metal promotes a radical annulation to form 3,3-disubstituted indolines and azaindolines.**

The continued development of new methodology for the construction of indolines[1,2] and azaindolines[3] is well justified by the tremendous therapeutic potential associated with these heterocyclic building blocks.[4] Natural products containing the 3,3-disubstituted indoline motif include the clinically used antitumor agent vinblastine (**1**),[5] the novel marine metabolite diazonamide A (**2**),[6] and the cagelike structures of kopsidarine (**3**),[7] and scholarisine A (**4**)[8] (Figure 1).

Alkyl radical cyclization onto pyridine rings to prepare azaindolines is common;[9] in contrast, methods to construct indolines by alkyl radical cyclization onto the aromatic nucleus without using xanthate transfer are scarce.[2b,c] While the majority of known protocols for indoline synthesis utilize nucleophilic, Lewis acid, and transition-metal cross-coupling techniques, we envisioned a radical process that installs a quaternary carbon simultaneous with pyrrolidine formation from readily available epoxidized allylic amines.[10] The reductive opening of epoxides using either stoichiometric[11] or catalytic[12] titanocene(III) chloride was particularly attractive toward this goal. Nearly two decades after the first reports of using in situ prepared titanocene(III) chloride to

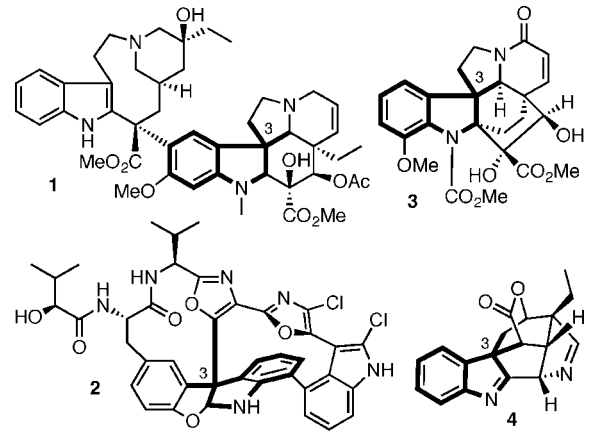



**Figure 1.** Representative natural products with 3,3-disubstituted indoline scaffolds (outlined in bold).

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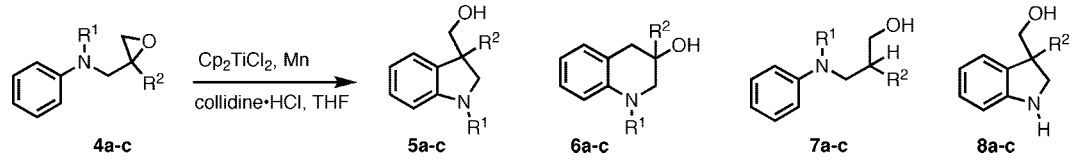
**Table 1.** Optimization of the Titanocene(III) Catalyzed Reductive Cyclization of Anilines[a,b]




| entry | epoxide | $Cp_2TiCl_2$ (mol %) | Mn (equiv) | concentration [M] | $R^1$ | $R^2$ | product (s), yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | 10 | 0.80 | 0.03 | Ph | H | **5a**:**6a** (3:1)[c,d] |
| 2 | **4b** | 10 | 0.65 | 0.03 | Ph | $CH_3$ | **5b**, 82[d] |
| 3 | **4b** | 10 | 0.65 | 0.03 | Ph | $CH_3$ | **5b**, 84[e] |
| 4 | **4c** | 10 | 1.5 | 0.1 | Cbz | $CH_3$ | **5c**:**7c** (2:1)[f] |
| 5 | **4c** | 3 | 1.5 | 0.1 | Cbz | $CH_3$ | **8c**, 63[g] |
| 6 | **4b** | 3 | 1.5 | 0.1 | Ph | $CH_3$ | **5b**, 89 |
| 7 | **4a** | 3 | 1.5 | 0.1 | Ph | H | **5a**:**6a** (3.8:1), 87 |
| 8 | **4c** | 3 | 1.5 | 0.1 | Cbz | $CH_3$ | **5c**, 14[h] |
| 9 | **4c** | 3 | 0 | 0.1 | Cbz | $CH_3$ | **5c**, 0 |
| 10 | **4c** | 0 | 1.5 | 0.1 | Cbz | $CH_3$ | **5c**, 0 |

[a] For epoxide preparation, see the Supporting Information. [b] All reactions were performed in degassed THF heated at reflux unless otherwise noted. [c] Yield not determined; product ratio was determined by GC analysis of crude reaction mixtures. [d] Reaction was performed in degassed THF at room temperature using sonication. [e] Reaction was performed in degassed THF at room temperature using magnetic stirring. [f] Yield not determined; product ratios were determined by $^1$H NMR analysis of crude reaction mixtures. [g] Yield was determined over two steps. [h] Starting material **4c** was recovered in 43% yield.

generate reactive radical intermediates from epoxides, novel applications of this reagent continue to emerge.[13]

To test the potential of this methodology in the synthesis of 3,3-disubstituted indoline and azaindoline heterocycles, epoxide **4a**[14] was subjected to 10 mol % of $Cp_2TiCl_2$ at room temperature in degassed THF (0.1 M) in the presence of 2 equiv of zinc dust. However, these conditions gave only traces of the desired indoline and mainly undesired side products. Fortunately, upon lowering the concentration of the substrate to 0.03 M and using 10 mol % of precatalyst in the presence of 0.80 equiv of 20−50 mesh manganese powder under sonication[15] at room temperature, a 3:1 ratio of indoline **5a** and tetrahydroquinoline **6a** was detected by GC analysis of the crude reaction mixture (Table 1, entry 1). Substoichiometric amounts of manganese metal increased the ratio in favor of indoline **5a**; a possible indication of reversible radical pathways.[12c] Addition of a methyl group to the epoxide in substrate **4b** ($R^2 = CH_3$) improved the efficiency of the titanocene(III) chloride catalyzed process and afforded **5b** as a single product in 82% yield (entry 2). With 1,1-disubstituted epoxides, sonication was not essential and conventional magnetic stirring also afforded the product in good yield (entry 3).

Model substrates **4a** and **4b** were designed to facilitate the cyclization by the presence of two symmetrical *N*-phenyl substituents. However, in order to broaden the scope of this reaction, we intended to replace one of them with a suitable nitrogen protective group. For reasons that are not completely clear, the secondary amine ($R^1 = H$) mostly decomposed in the reaction mixture, and only a minor amount of reduced amino alcohol was formed. Alternatively, among protecting groups at this position, including the *p*-toluenesulfonyl, benzyl, trifluoroacetyl, and *tert*-butoxycarbonyl functions, the benzylcarbamate (Cbz) group proved to be the most versatile substituent after we reoptimized the reaction parameters. At room temperature, anilide **4c** afforded a ~2:1 mixture of **5c**:**7c** at 0.1 M concentration in the presence of 10 mol % of titanocene dichloride (Table 1, entry 4). The undesired reduced epoxide **7c** could be suppressed by lowering the precatalyst loading to 3 mol % of $Cp_2TiCl_2$ while increasing the reaction temperature to THF at reflux.[16] Under these conditions, indoline **8c** was isolated in 63% yield over two steps (entry 5). When these optimized conditions were applied to the earlier model system **4b**, indoline **5b** was formed in 89% yield (entry 6). High yields were also obtained for epoxide **4a**, which provided a 3.8:1 mixture of **5a** and **6a** in 87% yield. We also explored the sensitivity of the reaction to air. When the epoxide-opening rearrangement with substrate **4c** was performed in a flask kept open to the atmosphere in nondegassed THF, the reactivity was greatly diminished (entry 8). Additional control experiments using

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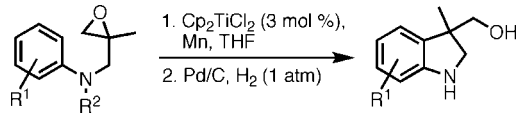
(15) Sonication was used to increase reagent solubility.

**Table 2.** Indolines Prepared Using Titanocene(III) Catalysis



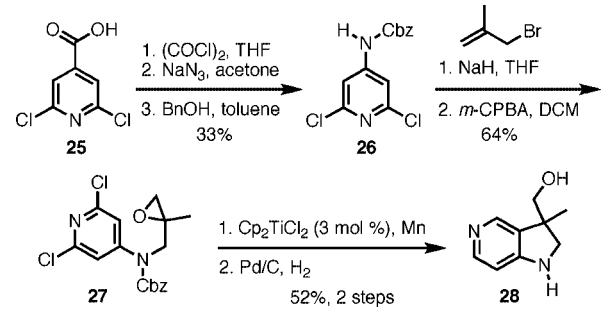

| entry | epoxide | indoline | yield |
|---|---|---|---|
| 1 | **9** | **10** | 65% |
| 2 | **11** | **12** | 62%[a] |
| 3 | **13** | **14** | 35%[a] |
| 4 | **15** | **16** | 69%[a] |
| 5 | **17** | **18** | 21%[a] |
| 6 | **19** | **20** | 56%[a] |
| 7 | **21** | **22** | 41% |
| 8 | **23** | **24** | - |

[a] Yields determined over two steps.

either solely the precatalyst (entry 9) or the manganese metal (entry 10) under otherwise identical reaction conditions failed to afford indoline products.

The general scope of indoline formation was further illustrated by the conversions summarized in Table 2. Alkyl-substituted substrates, including tetrahydroquinoline **15** afforded the corresponding indolines in modest to good yields (entries 2−4). The electron-rich 5-methoxyindoline **18** was isolated in low yield (21% over two steps). Electron-deficient substrates underwent the epoxide-opening rearrangement to afford substituted indolines in good yields (entries 6 and 7). However, an attempt to prepare the tricyclic pyrroloindole

**Scheme 1.** Preparation of 5-Azaindoline **28**




**24** from epoxide **23** did not yield any of the cyclized product (entry 8). *Meta*-substituted anilines generally led to 1:1 mixtures of regioisomeric indolines (data not shown).

Azaindoles are attractive bioisosteres of indoles in pharmaceutical research.[17] We therefore investigated the possibility of applying this methodology toward the formation of azaindolines, using aminopyridines in place of anilines. Chemoselective epoxidation of alkenes in the presence of a pyridine ring is precedented; however, attempts to efficiently prepare the epoxide on an unsubstituted aminopyridine substrate were unsuccessful. This was primarily due to the reactivity of the nucleophilic pyridine nitrogen toward either *m*-CPBA or DMDO.[18] In contrast, an *o*-chlorine substitution[19] proved to be sufficient to attenuate the nucleophilic character of the pyridine nitrogen. Curtius rearrangement of the known carboxylic acid **25**[20] and trapping of the intermediate isocyanate with benzyl alcohol afforded aminopyridine **26** (Scheme 1). Subsequent methallylation of the Cbz-protected amine and epoxidation with *m*-CPBA led to epoxide **27**. Under the optimized titanocene(III) chloride conditions, cyclization provided an intermediate 4,6-dichloro-5-azaindoline, which was concurrently deprotected and dechlorinated with Pd/C under an atmosphere of $H_2$ to give azaindoline **28** in 52% yield over two steps.

As a mechanism for the titanocene(III) chloride catalyzed epoxide-opening annulation, we propose that the formation of the $\beta$-titanoxy radical **30**[11,12] is followed by a reversible

(16) **Typical Procedure:** To a flame-dried two-neck flask was added 129 mg (0.43 mmol) of **4c**, 3.2 mg (0.01 mmol) of $Cp_2TiCl_2$, 102 mg (0.64 mmol) of collidine hydrochloride, and 35.6 mg (0.64 mmol) of $Mn^0$. The vessel was fitted with a reflux condenser and purged three times with Ar. After addition of 4.3 mL of deoxygenated THF (0.1 M), the reaction mixture was placed in a preheated oil bath and heated at reflux for 3 h. The color of the solution gradually changed from light pink to a dark violet. The mixture was cooled to room temperature, quenched with satd $NH_4Cl$, extracted with 3 × 10 mL of $Et_2O$, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was redissolved in 5 mL of MeOH and treated with 30 mg (25% w/w, 0.01 mmol) of Pd/C. The mixture was stirred at room tempearture under 1 atm of $H_2$, and the disappearance of starting material was monitored by TLC (hexanes/EtOAc, 1:1). The solution was then quenched with Celite, filtered, and purified by chromatography on $SiO_2$ (hexanes/EtOAc, 1:2) to afford 44 mg (0.26 mmol, 63%, two steps) of **8c** as a yellow oil.

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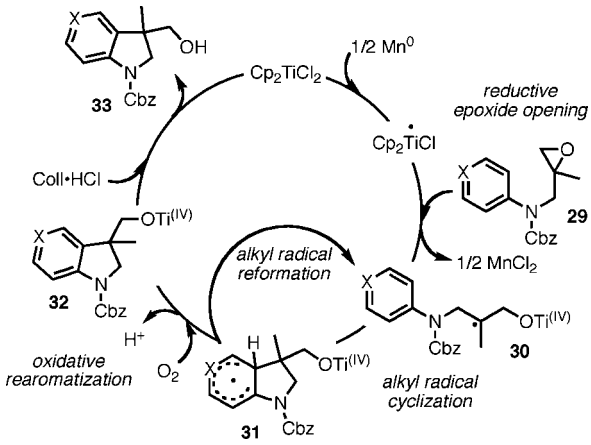


**Figure 2.** Proposed catalytic cycle for the titanocene(III) chloride catalyzed epoxide-opening annulation.

cyclization onto the aromatic ring, forming the cyclohexadienyl radical intermediate **31** (Figure 2).[21] Oxidation of the dienyl radical by trace amounts of dioxygen and proton loss affords the indoline **32**.[22] Furthermore, protodemetalation by collidinium hydrochloride leads to product **33**, and presumably regenerates the precatalyst $Cp_2TiCl_2$.[23]

The titanocene(III) chloride catalyst or the manganese byproducts may also serve as a Lewis acid to promote an epoxide-opening Friedel−Crafts alkylation. However, 5-membered ring benzene annulations by epoxide openings under Friedel−Crafts conditions are quite inefficient,[24] and a stoichiometric amount of reducing agent is required to drive the titanocene(III) chloride catalyzed process to completion.[23] Furthermore, it has previously been shown that the $MnCl_2$ produced in the reaction is not Lewis-acidic enough to promote epoxide-opening reactions.[12a]

In summary, we have developed a novel titanocene(III) chloride catalyzed epoxide-opening arene annulation that affords 3,3-disubstituted indolines and tolerates a range of substituents on the aromatic ring. This methodology can be extended toward other five-membered heterocycles, as demonstrated by the preparation of a 3,3-disubstituted 5-azaindoline.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds, including copies of $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Performing the reaction with epoxide **4c** using 3 mol % of $Cp_2TiCl_2$ and 15 mol % of $Mn^0$, the desired Cbz-protected indoline was isolated in only 35% yield.

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