Synthetic Methods

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Catalytic Reductive Synthesis and Direct Derivatization of Unprotected Aminoindoles, Aminopyrroles, and Iminoindolines

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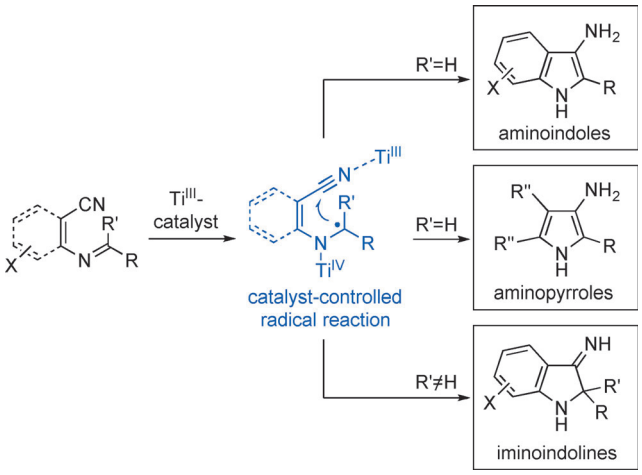
Abstract: *A titanium(III)-catalyzed radical cyclization to unprotected 3-aminoindoles, 3-aminopyrroles, or 3-iminoindolines is reported. The reaction is non-hazardous, scalable, and allows facile isolation of the free products by extraction. The method is demonstrated on a large substrate scope and it further allows the direct installation of various nitrogen protecting groups or the synthesis of building blocks for peptide chemistry in a single sequence. Fused bisindoles can be directly accessed from the cyclization products.*

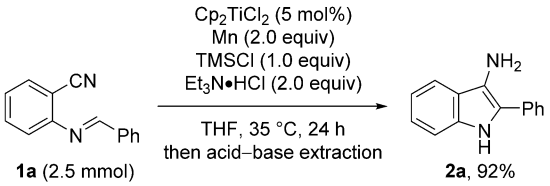
Aminated five-membered heterocycles are important building blocks in organic synthesis and indispensable to medicinal chemistry.[1] In particular, 3-aminoindoles, 3-aminopyrroles, and related heterocycles mark structural motifs of molecules with striking biological activities.[2] Hence, there is a need for efficient approaches to the corresponding synthetic precursors. Modern catalytic methods, however, usually furnish electronically deactivated and N-protected derivatives that lead to undesired functional-group modifications in the ensuing synthetic applications.[3] This problem also applies to conventional anionic cyclizations to nitriles.[4] The development of new synthetic approaches to electron-rich, unprotected aminoindoles and aminopyrroles was impeded by the low stability of the products in solution and in the solid form.[5] As a consequence, nitration-reduction or azidation-reduction sequences that present significant hazards still constitute the main synthetic routes.[5–7] To overcome these issues, we herein report an operationally convenient and broadly applicable titanium(III)-catalyzed synthesis of unprotected 3-aminated indoles, pyrroles, and iminoindoline products, which further allows a facile derivatization.

We contemplated that an in situ formed titanium(III) catalyst would undergo a single-electron transfer to an N-cyanoarylated or N-cyanoalkenylated imine, forming a stabilized aminoalkyl radical (Scheme 1).[8] In accordance with previous reports on Ti^{III}-catalyzed cyclizations to nitriles,[9,10] this would trigger a catalyst-controlled radical attack to the nitrile,[11,12] and depending on the nature of the imine an aminoindole, aminopyrrole, or iminoindoline product is ultimately received. The overall sequence would constitute a catalytic reductive umpolung reaction,[13] that is complementary to Fürstner's low-valent Ti-promoted and catalyzed syntheses of indoles or pyrroles in terms of mechanism, functional-group tolerance, and oxidation-state distribution at the carbon centers involved.[14]



Scheme 1. Concept of a titanium(III)-catalyzed synthesis of unprotected aminated heterocycles.

The cyclization of aldimine **1a** to 3-aminoindole **2a** served as the starting point for the development of the new indole synthesis [Eq. (1)]. Several parameters including the catalyst



(1)

type, reducing agent, and additives were optimized in a series of screening experiments.[15] Importantly, no reaction was observed in the absence of the catalyst. As expected, product **2a** and related unprotected aminoindoles were found to be unstable, which prevented standard chromatographic purification. Crystallization from benzene or toluene–hexanes mixtures under exclusion of light and oxygen was found to be a viable way to enhance the product purity,[5c] but the yield was be diminished. Gratifyingly, an acid–base extraction was found to allow the isolation of **2a**. Using these conditions and only 5 mol% of titanocene dichloride, the desired product was isolated in a yield of 92% from a 2.5 mmol reaction.

A number of unprotected 3-aminoindoles was then synthesized using this method to demonstrate the scope of the titanium(III)-catalyzed cyclization (Scheme 2). Electron-

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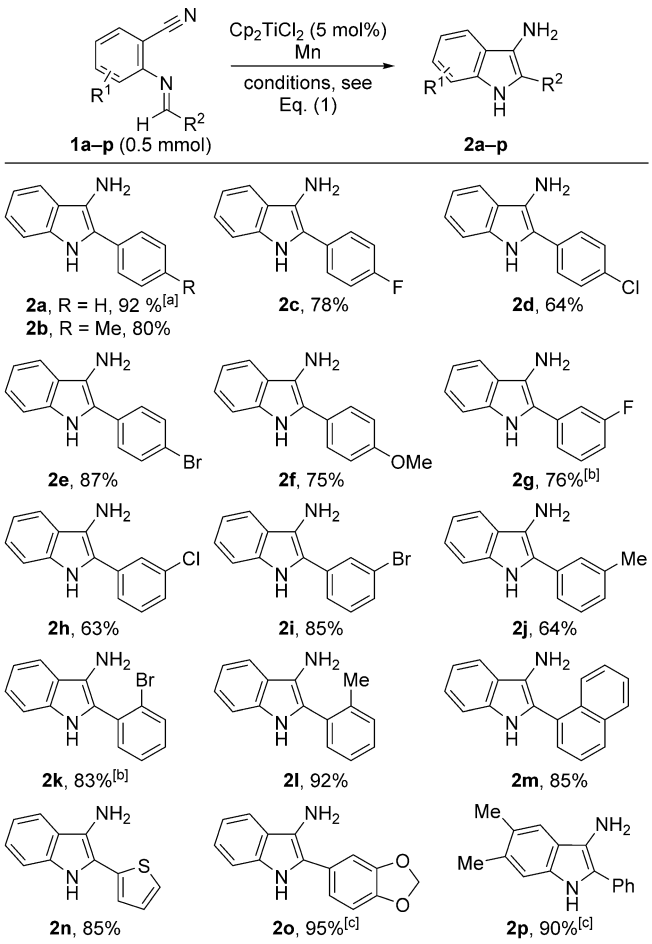
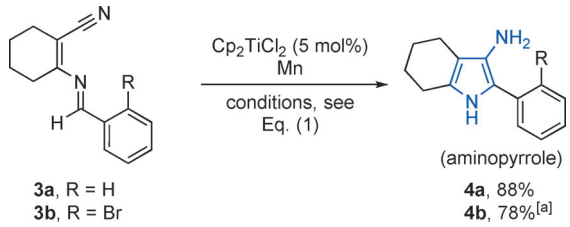


Scheme 2. Scope of the cyclization to unprotected aminoindole products. [a] 2.5 mmol scale, identical to Equation (1). [b] 5 mmol scale. [c] 0.2 mmol scale.

rich and electron-poor substituents were tolerated in the *para* and *meta* positions of a 2-aryl substituent and the corresponding products **2b–2j** were obtained in good to very good yields (63–87%). Of particular interest were the smooth reactions that were observed with the *ortho*-bromo or *ortho*-methyl benzaldehyde-derived imines **1k** and **1l** (83% and 92% yield, respectively). *Ortho*-substitution was previously found to be problematic for a number of titanium(III)-catalyzed reductive couplings.[10] Along these lines, the cyclization to 1-naphthyl-substituted **2m** proceeded without problems in 85% yield. The method was further applied to the construction of thienyl- and benzodioxole-derived products **2n** and **2o**. Even a free 3-aminoindole containing two mildly electron-donating methyl groups in the backbone (**2p**) could be accessed in a very good yield of 90%.

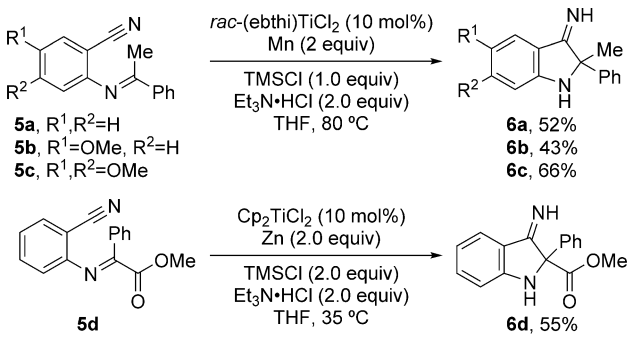
All products shown in Scheme 2 were received after extraction, either in analytically pure form or in > 95% purity as judged by NMR spectroscopy. Analysis had to be carried out quickly because of the rapid decomposition of the free products in solution. A number of the free aminoindoles could be precipitated,[15] and limited storage (1–5 days) of the neat products was possible at −20 °C under argon in the dark.

The titanium(III)-catalyzed cyclization was then tested in the synthesis of 3-aminopyrroles. Corresponding pyrroloamides play a unique role in the molecular recognition of DNA,[2d,e] but the ways of preparing unprotected aminopyrrole building blocks are limited, in particular with regard to fully substituted pyrroles. Only recently was 3-aminopyrrole itself prepared and characterized in solution.[5a] For these reasons, we were delighted to find that the unprotected aminopyrrole **4a** was formed in good yield from readily accessible aldimine **3a** under standard reaction conditions (Scheme 3).[15] The product was isolated in analogy to the aminoindoles **2a–p** by extraction in 88% yield. In a similar fashion but with 10 mol% catalyst and 1.5 equivalents of chlorotrimethylsilane, 2-(*o*-bromophenyl)-substituted **4b** was obtained in 78% yield.[16]

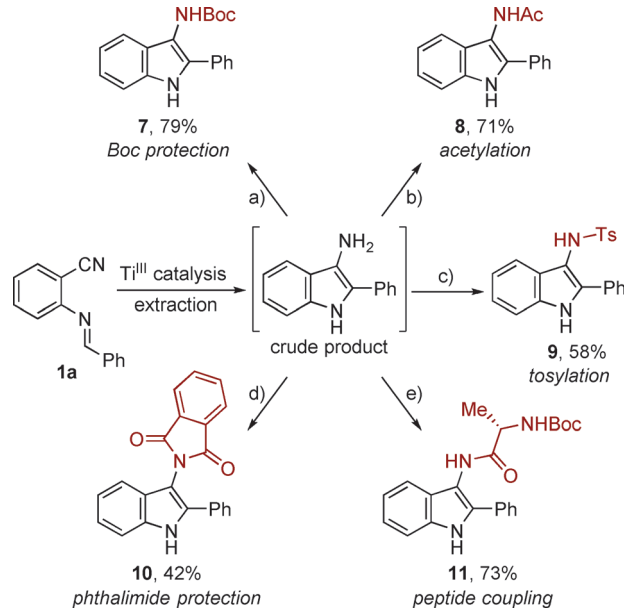


Scheme 3. Catalytic reductive synthesis of unprotected 3-aminopyrroles. [a] Reaction in presence of 10 mol% Cp_2TiCl_2 and 1.5 equiv TMSCl.

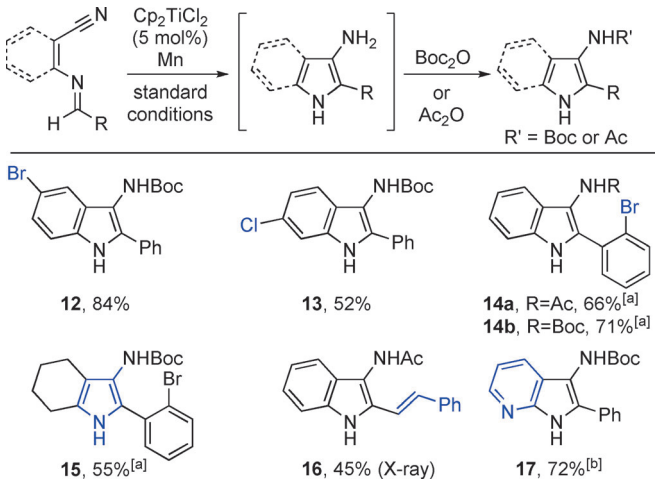
In a parallel series of experiments we sought to investigate whether N-cyanoarylated ketimines could be cyclized in a similar fashion to the corresponding 3-iminoindolines (Scheme 4). This transformation would be of interest, since indoxyls, which can be obtained by hydrolysis of iminoindolines,[17] occur in the skeleton of biologically active natural products, such as brevianamide A or several duocarmycins.[17b,18] Using ketimine **5a**, a brief survey of the cyclization conditions then showed that the reaction can indeed be achieved,[15] and a combination of *rac*-(ebthi)$TiCl_2$ as catalyst and manganese as reductant at 80 °C gave the best results, minimizing the formation of unidentifiable byproducts. Following these conditions, the products **6a–c** were furnished in 43–66% yield. To our delight, even an ester-substituted imine



Scheme 4. Catalytic reductive cyclization to iminoindolines. ebthi = ethylenebis(tetrahydroindenyl).



Scheme 5. Direct sequential N-functionalization. Overall yields are given with respect to **1a**. a) Boc_2O, $ZrCl_4$ (10 mol%), THF, 23 °C, 24 h, 79%; b) Ac_2O, Et_3N, CH_2Cl_2, 0 °C → 23 °C, 14 h, 71%; c) TsCl, Et_3N, CH_2Cl_2, 0 °C → 23 °C, 14 h, 58%; d) Phthalic anhydride, [bmim][PF_6], 80 °C, 24 h, 42%; e) Boc-Ala-OH, T3P (1.43 M in DMF), Et_3N, CH_2Cl_2, 0 °C → 23 °C, 24 h, 73%.

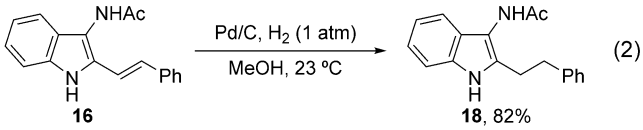


Scheme 6. Expansion of the substrate scope. The overall yield with respect to the imine precursor is reported. [a] Gram scale. [b] Isolated by filtration.

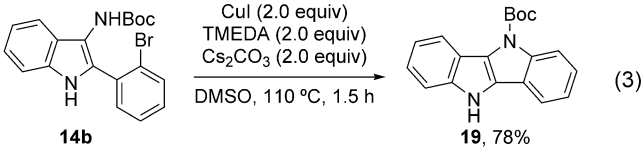
5d that was prepared from methyl phenylglyoxylate underwent the cyclization to iminoindoline **6d** in 55% yield.[19]

Then, it was probed whether the cyclization products **2** could be directly submitted after the extraction to sequential modifications and couplings. Starting from imine **1a**, a direct Boc-protection of the 3-amino group of the crude cyclization product was conveniently achieved with catalytic amounts of $ZrCl_4$ in 79% overall yield (**7**, Scheme 5).[20] In a similar manner, an N-acetylation with Ac_2O, a tosylation with tosyl chloride, and a phthalimide formation using phthalic anhydride were achieved in good yields in a single reaction sequence (**8**–**10**). The strategy could also be applied to a peptide coupling with Boc-Ala-OH and T3P (**11**). The reaction proceeded smoothly and the 3-(2-phenyl)indolyl-protected amino acid derivative was isolated in 73% yield. This could become particularly useful for the introduction of indoles into peptides.

With a direct cyclization-functionalization strategy at hand, the scope of the titanium(III)-catalysis was further expanded (Scheme 6). 3-Aminoindoles having a bromo- or chloro-substituted backbone (**12**, **13**) were isolated after a sequential Boc protection in 84% and 52% overall yield. *N*-Acyl and *N*-Boc 2-(*o*-bromophenyl)-3-aminoindoles **14a** and **14b** and a corresponding *N*-Boc pyrrole **15** were prepared in analogy on gram scale. The sequence also enabled the isolation of aminoheterocycles that were difficult to isolate otherwise, such as 2-styryl derivative **16**, of which the structure was confirmed by X-ray analysis.[21] 7-azaindoles, which represent important structural motifs in medicinal chemistry,[22] could be accessed as well if imines derived from 2-aminonicotinnitrile were employed (**17**, 72%). The product could be conveniently isolated by filtration. The synthesis of 2-alkylated products currently represents a limitation of the method, but 2-alkylated aminoindoles, such as **18**, can be conveniently obtained by hydrogenation of the corresponding 2-alkenyl derivative [Eq. (2)].



To show the value of our approach to other fields, we applied it to the synthesis of fused bisindoles, which are a family of organic semiconductors with increasing application in the development of novel organic field-effect transistors (OFETs).[23] The access to such compounds, in particular to unsymmetric ones, has been very limited until recently. To this end, product **14b** was submitted to copper-promoted coupling conditions and the corresponding selectively monoprotected building block **19** was received in 78% yield [Eq. (3)].



In conclusion, an expedient titanium-catalyzed synthesis of unprotected 3-aminoindoles, 3-aminopyrroles, and 3-iminoindolines was developed that excels in functional-group compatibility and synthetic practicality. It further enables the direct derivatization of the crude 3-aminoheterocycles, which makes the overall sequence a valuable transformation for medicinal chemistry, peptide chemistry, or organic functional-

material synthesis. A further extension of this cyclization approach will be reported in due course.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: heterocycles · homogeneous catalysis · radicals · reductive coupling · titanium

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[15] See Supporting Information.

[16] Using the conditions of Equation (1) (5 mol% Cp_2TiCl_2, 1.0 equiv TMSCl), **4b** was still isolated in 60% yield.

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Communications

Synthetic Methods

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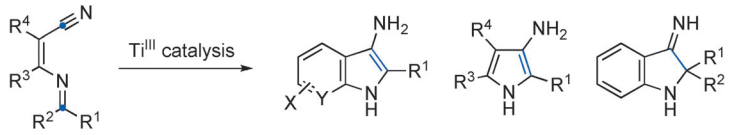

Catalytic Reductive Synthesis and Direct Derivatization of Unprotected Aminoindoles, Aminopyrroles, and Iminoindolines

Free at last: A titanium(III)-catalyzed reductive cyclization allows the safe and convenient synthesis of unprotected aminoindoles, aminopyrroles, and other aminated heterocycles. The novel cyclization approach further enables the direct functionalization at the nitrogen atom via various coupling methods in a single sequence.