CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Development, Scope, and Applications of Titanium(III) Catalyzed Cyclizations to Aminated N-Heterocycles

Authors: Leonardus Hendricus Leijendekker, Jens Weweler, Tobias Martin Leuther, Daniel Kratzert, and Jan Streuff

To be cited as: *Chem. Eur. J.* 10.1002/chem.201805909

Link to VoR: http://dx.doi.org/10.1002/chem.201805909

Supported by
ACES

WILEY-VCH

10.1002/chem.201805909

WILEY-VCH

FULL PAPER

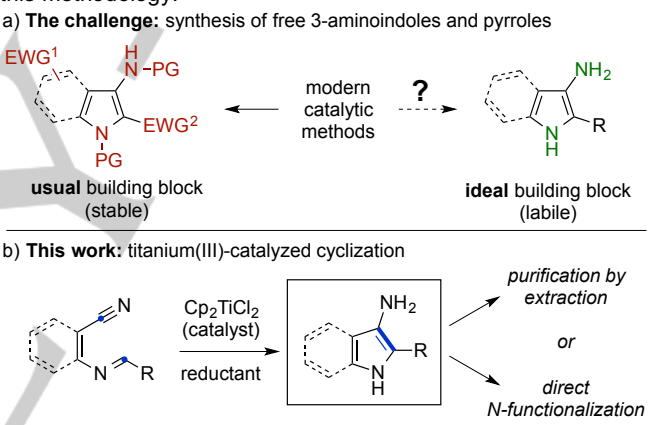
Development, Scope, and Applications of Titanium(III) Catalyzed Cyclizations to Aminated *N*-Heterocycles

Leonardus H. Leijendekker,[a] Jens Weweler,[a] Tobias M. Leuther,[a] Daniel Kratzert,[b] and Jan Streuff*[a]

Abstract: The exceptionally mild conditions of a titanium(III) catalyzed cyclization reaction paired with a convenient acid-base extraction enable the straightforward synthesis, isolation and direct *N*-functionalization of amino heterocycles such as 3-aminoindoles and 3-aminopyrroles. The unprotected heterocycles are ideal building blocks for the installation of aminated indoles or pyrroles into target molecules, but their sensitivity has previously impeded the synthesis by modern catalytic methods. This full paper comprises the development and extended scope of the new cyclization methodology. The transformation of the products into fused bisindoles is demonstrated along with the discovery of an unusual palladium catalyzed reductive biphenyl coupling. The titanium(III) catalyzed cyclization is also applied to the synthesis of substituted 3-iminoindolines, which are of potential interest for applications in natural product synthesis and exhibit tunable blue to green fluorescence properties.

Introduction

Aminated indole and pyrrole heterocycles represent a common structural motif of natural products and synthetic small molecules with striking biological activity. For example, substituted 3-aminoindoles occur in compounds such as cryptospirolepin, a potent anti-malaria agent, or are antimitotic agents, tubulin inhibitors and NMDA receptor antagonists.[1] 3-Aminopyrroles mark the backbone of a number of small DNA cavity binding molecules like netropsin, or have been shown to possess strong anticonvulsant and Lck inhibiting properties.[2] Despite the importance of 3-aminoindole and 3-aminopyrrole containing molecules, the number of methods for a straightforward synthesis and installation of these fragments have remained scarce. One main reason behind the synthetic challenge is the inherent instability of the unprotected, electron-rich 3-aminoindoles or 3-aminopyrroles, which would constitute ideal building blocks (Scheme 1a). These compounds tend to undergo oxidative dimerization or similar decomposition reactions, are sensitive to light and air and cannot be purified by chromatography.[3,4] As a consequence, the major approaches have remained traditional indole nitration and azidation reactions followed by a reduction to the free amine,[3] or ionic cyclization reactions.[1,2,5] Modern catalytic methods, on the other hand, give rise to electron-poor and/or protected derivatives that require deprotection or subsequent functional group interconversion steps.[6] To this end, we have developed a titanium(III) catalyzed imine-nitrile cyclization reaction that provides free aminoindoles and -pyrroles in a direct fashion (Scheme 1b). The mild conditions and a convenient acid-base extraction procedure allow the straightforward isolation and an optional direct *N*-functionalization of the products. Following our initial communication, we herein describe the development, extended scope, and application of this methodology.[7]



Scheme 1. a) Usual and ideal scenarios for the catalytic synthesis of 3-aminoindole and -pyrrole building blocks. b) Envisioned titanium(III)-catalyzed cyclization to the unprotected/electron-rich 3-aminoheterocycles.

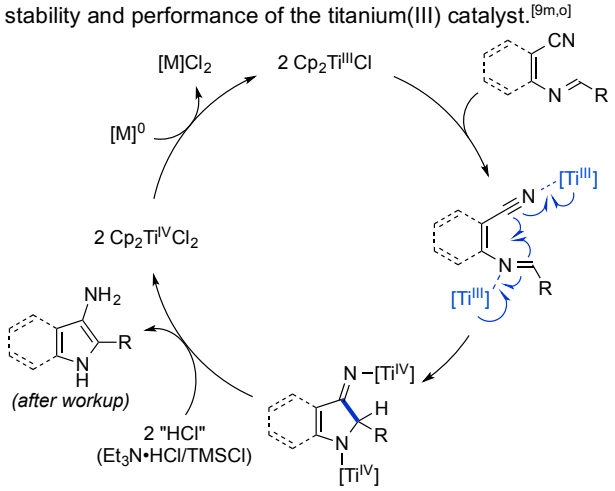
Titanium(III) catalysis allows the reductive construction of carbon-carbon and carbon-heteroatom bonds from readily available functional groups such as epoxides, aziridines, alkyl halides, carbonyls, nitriles, or Michael-acceptors under mild conditions.[8,9] Furthermore, low-valent titanium catalyzed radical reactions can proceed under high catalyst control, leading to chemo-, regio-, stereo-, and even enantioselective transformations.[10,11] Our group has recently developed a number of titanium(III) catalyzed reductive cyclizations and cross-couplings that give rise to 1,2-, 1,4-, or 1,6-difunctionalized compounds, constituting reductive umpolung reactions.[11b,12,13]

Based on these unique features, we contemplated that low-valent titanium catalysis would provide an ideal approach for accessing the elusive aminoindoles and -pyrroles. This was supported by complementary works by Fürstner, who reported low-valent titanium promoted and catalyzed McMurry-type couplings for the synthesis of indoles, pyrroles, or other heterocycles.[14] In agreement with our previous studies,[12,13] we hypothesized that the nitrile and the imine of a cyanoarylated or

[a] L. H. Leijendekker, J. Weweler, T. M. Leuther, Dr. Jan Streuff
Institut für Organische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstr. 21, 79104 Freiburg im Breisgau, Germany
E-mail: jan.streuff@ocbc.uni-freiburg.de
[b] Dr. D. Kratzert
Institut für Anorganische und Analytische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstr. 21, 79104 Freiburg im Breisgau, Germany

Supporting information for this article is given via a link at the end of the document.

cyanoalkenylated imine precursor would each coordinate to an in situ formed titanium(III) catalyst (Scheme 2). This would trigger a radical-radical coupling reaction and the resulting imino heterocycle would then get transformed into the desired product by ensuing Ti-N cleavages and a tautomerization. In theory, this required the addition of two equivalents of HCl, which could be substituted by chlorotrimethylsilane and triethylamine hydrochloride. Moreover, these additives would improve the stability and performance of the titanium(III) catalyst.[9m,o]



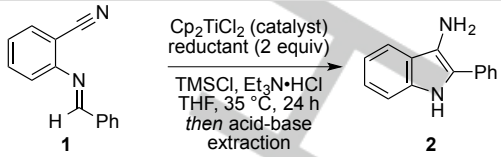
Scheme 2. Simplified catalytic cycle.

Results and Discussion

3-Aminoindoles. We started the investigation of the cyclization reaction using imine **1**, obtained by condensation of benzaldehyde with 2-aminobenzonitrile. The reaction was carried out in THF in presence of 5 mol% of titanocene dichloride as catalyst, zinc as terminal reducing agent, TMSCl and Et_3N•HCl as additives. The aminoindole **2** was formed and it was discovered that a simple acid-base extraction provided the product in analytical purity and 61% yield (Table 1, entry 1). This rapid way of purification proved to be highly advantageous, since the free aminoindole showed very limited stability in solution and could not be purified by chromatography. In agreement with the original preparation by Fischer,[3c] the product could be crystallized from benzene if desired. It was possible to enhance the yield by replacing zinc with manganese (74%, entry 2). We then tested whether the catalyst amount could be further reduced and confirmed that no background reaction took place (entries 3–5). Afterwards, the amounts of TMSCl and Et_3N•HCl were successively optimized to 1.0 and 2.0 equivalents, respectively (entries 6–11). Using the optimized conditions, the analytically pure product was isolated in 90% yield (entry 7).

In a similar manner, a wide range of free 3-aminoindoles could be accessed in high yield (Scheme 3). The acid-base extraction procedure provided a convenient way for the purification of all products, which could be stored in neat form for 1–5 days at –20 °C under argon in the dark. In detail, various electron-donating, and electron-withdrawing substituents were tolerated in the para- and meta-position of the 2-phenyl group (**3**–**11**).

Table 1. Screening of the reaction conditions for the titanium catalyzed aminoindole cyclization.



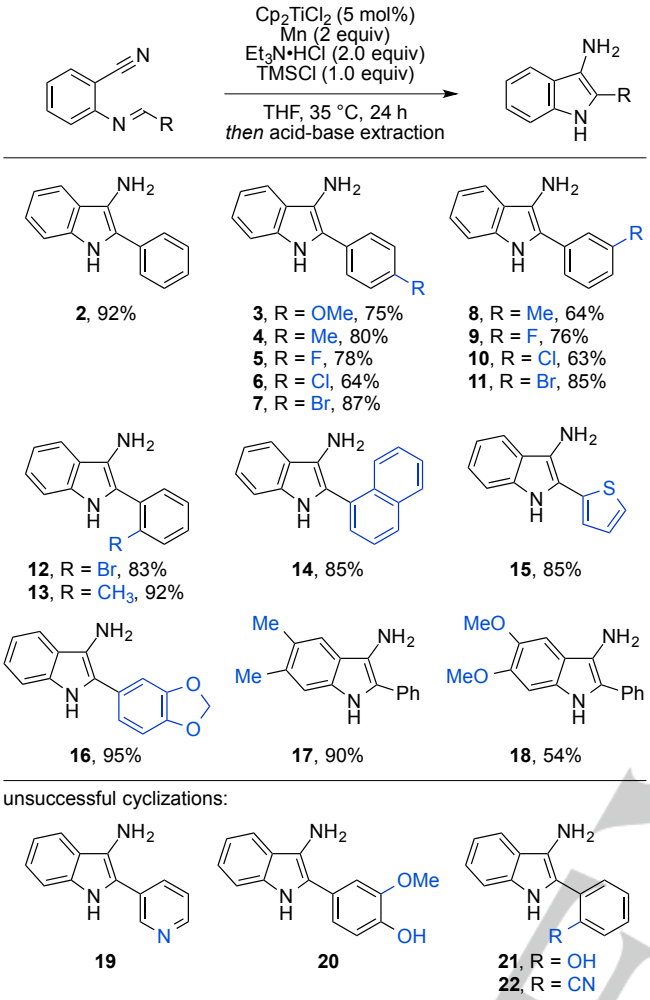
Entry	mol% Cp_2TiCl_2	Reductant	equiv TMSCl	equiv Et_3N•HCl	Yield [%][a]
1	5	Zn	3.0	2.0	61
2	5	Mn	3.0	2.0	74
3	2	Mn	3.0	2.0	42
4	1	Mn	3.0	2.0	29
5	-	Mn	3.0	2.0	0
6	5	Mn	2.0	2.0	87
7	**5**	**Mn**	**1.0**	**2.0**	**90**
8	5	Mn	0.5	2.0	10
9	5	Mn	-	2.0	0
10	5	Mn	1.0	1.0	42
11	5	Mn	1.0	-	6

[a] Yield of isolated product.

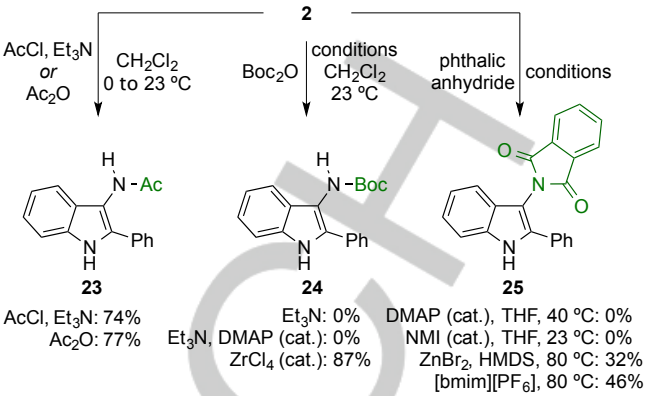
This included chloro or bromo substituents that provide valuable entry points for subsequent cross-coupling reactions. Of particular importance was the fact that *ortho*-bromo and *ortho*-methyl substituted 2-aryl-3-aminoindoles **12** and **13**, or the 1-naphthyl derivative **14** could be prepared in high yield as well (83%–93%). Ortho substitution represented a significant limitation of our previous cyclization and cross-coupling reactions, usually yielding only minor amounts of product.[7b,11b,13d–g] The reaction could also be used to access thiophene and benzodioxole derivatives (**15**,**16**), or products with additional electron-donating substituents such as methyl or methoxy at the indole core (**17**,**18**). Only very electron-poor substituents and free alcohol functions appeared to inhibit the reaction. For example, substrates derived from nicotine aldehyde, vanillin, or salicylic aldehyde as well as a cyanobenzaldimine did not undergo the cyclization (**19**–**22**).

Overall, the titanium(III) catalysis provided for the first time a reliable way for accessing the free 3-aminoindoles in high yield and purity. To demonstrate the synthetic potential of this approach for the installation of such aminoheterocycles into target molecules, we sought to combine the aminoindole synthesis with subsequent *N*-functionalization reactions (Scheme 4). To begin with, we isolated and submitted **2** to acetylation conditions using acetyl chloride. The reaction provided the desired product **23** in 74% yield, but significant double acetylation was observed. The chemoselectivity could be improved by using acetic anhydride,

10.1002/chem.201805909



Scheme 3. Scope of the titanium(III) catalyzed cyclization to free aminoindoles.



Scheme 4. Optimization of the conditions for *N*-acetylation, *N*-Boc and *N*-phthalimide protection reactions.

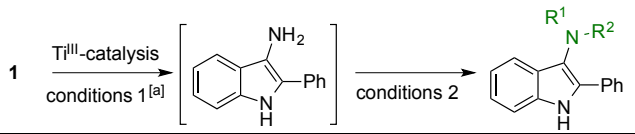
which afforded only the mono-acetylation product **23** in 77% yield. We then tested subsequent *N*-Boc or *N*-phthalimide protections and found that these could be achieved using optimized reaction conditions. For example, the Boc-protection did not occur in the presence of triethylamine or triethylamine-DMAP. But with zirconium tetrachloride (10 mol%) as promoter, the desired product **24** was obtained in 87% yield.[15,16] The phthalimide formation required the use of an additional Lewis-acid ($ZnBr_2$) or an ionic liquid, the latter of which gave the best result (**25**, 46%).[17]

Aiming to take advantage of the purification by acid-base extraction, it was found that the titanium-catalyzed cyclization and the following *N*-functionalization could be even carried out in a single operational sequence. This gave immediate access to a range of *N*-derivatized products (Table 2). In detail, the combination of the titanium(III) catalyzed cyclization and the in-sequence acetylation with Ac_2O gave product **23** in 71% yield (entry 1). The fact that treatment of **2** with acetyl chloride led to double-acetylation was utilized to achieve the formation of the bis-acylated product **26** in 52% yield by employing a five-fold excess of this reagent (entry 2). Using benzoyl chloride, the mono-benzoylated product **27** could be isolated in 76% yield and small amounts (5%) of the corresponding bis-benzoylated aminoindole were formed as well (entry 3). Attempts to enforce a double benzoylation by using an excess of benzoyl chloride, however, were unsuccessful. The *N*-Boc and *N*-phthalimide protected products **24** and **25** were obtained in 79% and 42% yield, respectively (entries 4 and 5). Sequential *N*-tosyl and *N*-Fmoc protections could be carried out giving **28** and **29** in 58% and 82% yield (entries 6 and 7). A direct treatment of **2** with Burgess reagent or tosyl isocyanate gave sulfonamide (**30**) and urea (**31**), albeit in low yields of 25% and 38% (entries 8 and 9). Importantly, our approach could also be applied to the coupling of the crude aminoindole with an amino acid derivative. As shown in entry 10, the direct coupling with Boc-Ala-OH proceeded smoothly in presence of T3P as promoter (73% yield). This result could be of use for the incorporation of such aminoindoles into peptides and other biomolecules.

The cyclization-*N*-functionalization sequence further enabled the preparation of products that were either not stable enough otherwise to be isolated as free aminoindoles or could not be received in analytically pure form (Scheme 5). Since the *N*-functionalization increased the stability, the products could be conveniently purified by flash chromatography afterwards. By applying a combination of the cyclization and the direct Boc-protection, the indoles **33** and **34** containing a valuable bromo- or chloro-substituent were received in 84% and 52% yield. The corresponding 5,6-dimethylated *N*-Boc-aminoindole **35** was prepared in 31% yield and the Boc and Ac protected 2(*ortho*-bromophenyl)-indoles **36** and **37** were produced in analogy (71% and 66% yield, respectively). In addition, we demonstrated that 3-amino-7-azaindoles could be accessed from 2-aminonicotine nitrile derived imines. 7-Azaindoles find wide use in medicinal and biological chemistry as well as materials science and coordination chemistry.[18] Here, the final Boc-protected product **38** was conveniently isolated by simple filtration (72%). Finally, an *N*-acetyl-2-styryl aminoindole (**39**) was synthesized from an imine derived from cinnamaldehyde, showing that alkenyl substituents were tolerated at this position as well. The structure of **39** was

10.1002/chem.201805909

Table 2. Scope of the direct cyclization/*N*-functionalization sequence: variation of the *N*-functionalization.

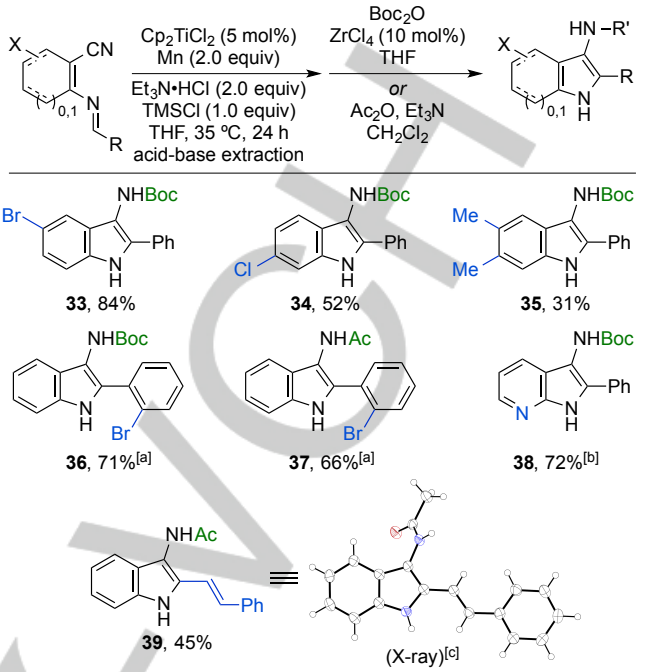


Entry	Conditions 2	Product	Yield [%][b]
1	Ac_2O, Et_3N, CH_2Cl_2, 0 °C → 23 °C	**23**: R^1 = Ac, R^2 = H	71
2	AcCl (5.0 equiv), Et_3N, CH_2Cl_2, 0 °C → 23 °C	**26**: R^1,R^2 = Ac	52
3	BzCl, Et_3N, CH_2Cl_2, 0 °C → 23 °C	**27**: R^1 = Bz, R^2 = H	76[c]
4	Boc_2O, $ZrCl_4$ (10 mol%), THF, 23 °C	**24**: R^1 = Boc, R^2 = H	79
5	Phthalic anhydride, [bmim][PF_6], 80 °C	**25**: R^1 + R^2 = Phthaloyl	42
6	TsCl, Et_3N, CH_2Cl_2, 0 °C → 23 °C	**28**: R^1 = Ts, R^2 = H	58
7	Fmoc-Cl, THF, 23 °C	**29**: R^1 = Fmoc, R^2 = H	82
8	Burgess reagent, CH_2Cl_2, 0 °C → 23 °C	**30**: R^1 = SO_2NHCO_2Me, R^2 = H	25
9	TsNCO, CH_2Cl_2, 0 °C → 23 °C	**31**: R^1 = C(O)NHTs, R^2 = H	38
10	Boc-Ala-OH, T3P, Et_3N, CH_2Cl_2, 0 °C → 23 °C	**32**: R^1 = Boc-Ala, R^2 = H	73

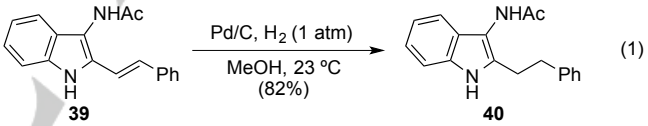
[a] For the titanium(III) catalysis conditions, see Scheme 3. [b] Isolated yield based on **1**. [c] 5% of *N*,*N*-bis-benzoylated product were isolated in addition.

confirmed by X-ray analysis.[7a] Importantly, the cyclization-derivatization sequence could be carried out on gram-scale, as was exemplified for products **36** and **37**.

We aimed to investigate whether aliphatic imines would lead to 2-alkylated aminoindoles. Previously, we reported that aliphatic ketones smoothly undergo cyclizations to nitriles, and the groups of Hirao and Nicholas demonstrated that titanium-catalyzed pinacol-type couplings proceed smoothly with aliphatic aldehydes.[11b,19] However, the corresponding aliphatic imines could either not be prepared or not be obtained in sufficient purity. For example, the ketimines of acetone, cyclopentanone, or cyclohexanone did not form, even under aza-Wittig conditions.[20] A pivalaldimine could not be obtained in sufficient purity and the material obtained did not undergo the desired cyclization. 2-(Methyleneamino)benzonitrile prepared from formaldehyde led to the re-isolation of 2-aminobenzonitrile. Nevertheless, 2-alkylated aminoindoles were accessible by hydrogenation of the 2-alkenylated products as shown for 2-styryl aminoindole **39** [Eq. (1)].



Scheme 5. Scope of the cyclization/*N*-functionalization sequence: variation of the 3-aminoindole precursor. Isolated overall yields. [a] Gram scale. [b] Isolated by filtration. [c] Solvent molecules have been removed. Thermal ellipsoids are shown at the 50% probability level.

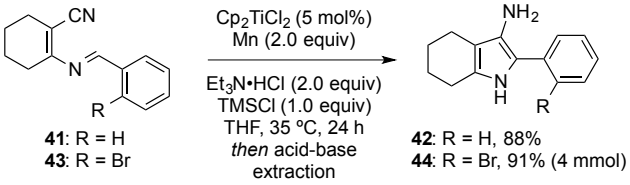


(1)

3-Aminopyrroles. We then probed whether our method could be applied to the preparation of substituted 3-aminopyrrole derivatives. This was considerably more challenging than the synthesis of the 3-aminoindoles, since unprotected 3-aminopyrroles are known to be even less stable. For example, 3-aminopyrrole itself, could only be synthesized and characterized in situ.[3b] 3-Ammoniumpyrrole tautomerizes to the C2-protonated pyrrole in solvents such as acetonitrile or dichloromethane, which underlines the electron-rich nature of these compounds.

We chose imines based on aminocyclohexenyl or aminocyclopentenyl carbonitriles as precursors that contained a fixed (*Z*)-configured enamine moiety. The preparation was conveniently achieved by a Thorpe reaction followed by a standard imine condensation.[21] Afterwards, the titanium(III) catalyzed cyclization was carried out using the benzaldehyde-derived substrate **41** and, gratifyingly, the corresponding 2-phenyl substituted aminopyrrole **42** could be obtained in pure form using identical conditions as before (Scheme 6). The fully substituted aminopyrrole was found to be sufficiently stable for standard characterization purposes. A 2-(*ortho*-bromophenyl) derivative (**44**) could be prepared in a similar fashion. Here, a reaction carried out on 4 mmol scale gave an improved yield in comparison to our previous result.[7a]

10.1002/chem.201805909



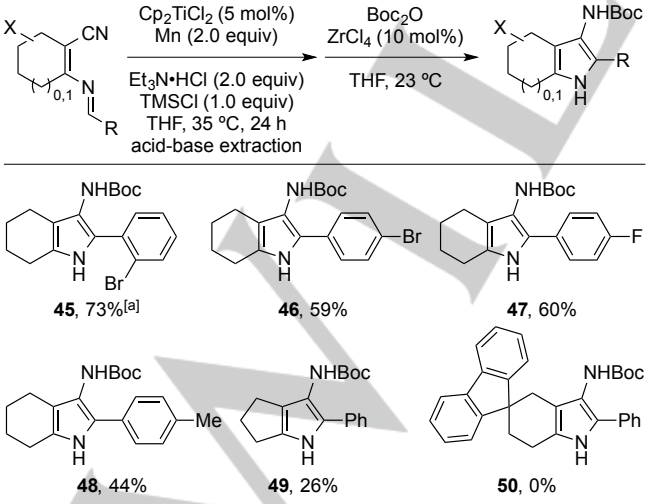
41: R = H
43: R = Br

42: R = H, 88%
44: R = Br, 91% (4 mmol)

Scheme 6. Synthesis of unprotected 3-aminopyrroles **42** and **44**.

When testing other precursors to explore the scope of the aminopyrrole cyclization, it was found that the product material isolated after extraction was not sufficiently pure. Without the possibility of chromatographical purification, we were delighted to find that the direct in-sequence derivatization could be applied as well. Using the in situ Boc protection protocol, *ortho*- and *para*-halogenated, as well as *para*-methylated 2-phenyl-3-aminopyrroles were prepared in 44–73% yield (**45–48**, Scheme 7). Even a cyclopentane-annulated aminopyrrole (**49**) that was significantly more strained than the 6-5 bicycle products could be obtained in 26% yield. We also probed the cyclization to fluorene spirocycle **50**, but no reaction took place. We assumed that the fluorene unit shielded the top and bottom sides of the iminonitrile precursor, preventing a coordination to the titanium catalyst. Still, these results demonstrated the strength of our approach to access such labile heterocycles. It should be noted that all pyrrole syntheses and manipulations of the products were carried out in the dark to avoid a premature decomposition.

To highlight the potential for future applications of the cyclization, we investigated whether the 2-(*ortho*-bromoaryl) substituted amino heterocycles could be cyclized to fused bisindoles and indolopyrroles. Bisindoles have recently gained interest in the field of organic field-effect-transistors (OFETs) as a potential organic semiconductors.[22,23] Using our cyclization it would be possible to gain access to selectively protected, unsymmetric derivatives. And indeed, when submitting the Boc and acetyl protected aminoindoles **36** and **37** to copper-promoted C-N coupling conditions,[24] the cyclizations to the desired

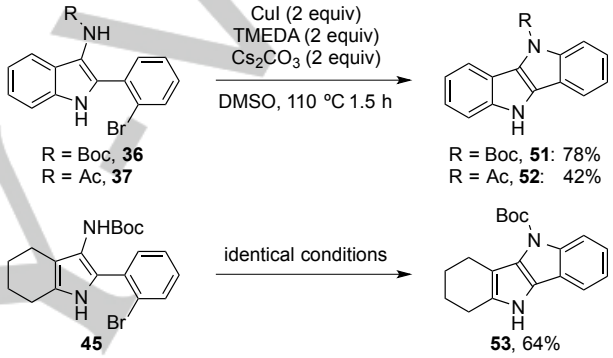


45, 73%[a]
46, 59%
47, 60%
48, 44%
49, 26%
50, 0%

Scheme 7. Application of the cyclization/N-functionalization sequence to *N*-Boc-aminopyrroles, isolated yields. [a] Gram scale.

bisindoles **51** and **52** took place, giving 78% and 42% yield, respectively (Scheme 8). Starting from pyrrole **45**, a corresponding pyrroloindole **53** could be prepared as well (64%).

Initially, it was our goal to achieve these C-N couplings by a Hartwig-Buchwald type coupling in presence of catalytic amounts of Pd_2dba_3 and Xantphos.[25] To our utmost surprise, an unexpected reductive homo coupling took place and biphenyl derivative **54** was isolated in 74% yield (Scheme 9). The identity of **54** was unambiguously established by an X-ray analysis.[26] Since no reducing agent was added, the mechanism of this overall reductive coupling remained unclear. In principle, the substrate itself may have acted as the terminal reductant. As an alternative, 1,4-dioxane could have served as the reducing agent. This was supported by the fact that the reaction took place only in dioxane. Other solvents such as toluene or THF showed no formation of **54**. Such a scenario was further supported by a recent study on solvent-induced reduction of palladium aryl species.[27] However,



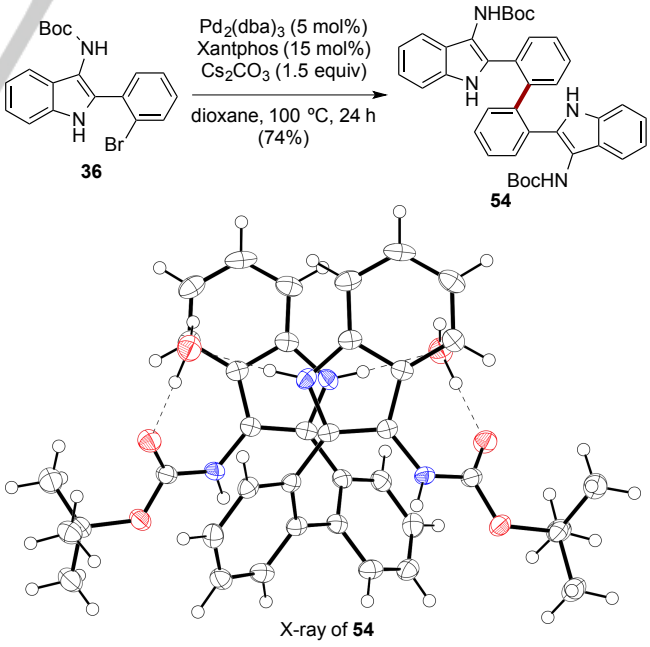
R = Boc, **36**
R = Ac, **37**

R = Boc, **51**: 78%
R = Ac, **52**: 42%

45

53, 64%

Scheme 8. Copper-mediated C-N coupling to bisindoles and pyrroloindoles.



36

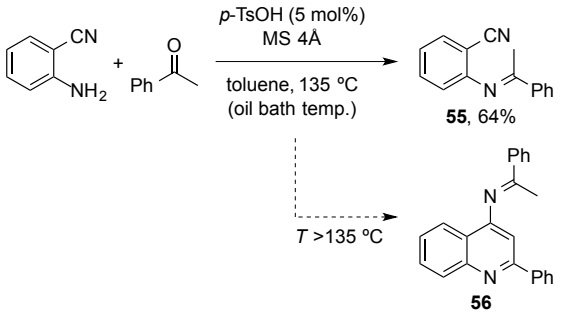
54

X-ray of **54**

Scheme 9. Unexpected reductive homo-coupling of **36** and X-ray structure of **54**. Thermal ellipsoids are shown at the 50% probability level.

no byproducts of a potential oxidation of the substrate or dioxane that could have supported either theory were identified by NMR, GC, or isolation.

3-Iminoindolines. Finally, the transfer of the cyclization reaction to ketimine substrates was explored. The reaction would then lead to iminoindoline products that can in principle be hydrolyzed to 3-indolinones (pseudoindoxyls),[28] a structural motif of several important natural products.[29] It was found that the synthesis of the ketimine precursors required a precise temperature control as exemplified for the formation of **55** in Scheme 10. At oil bath temperatures lower than 120–130 ºC, the condensation would not occur, while at temperatures significantly higher than 135 ºC, undesired quinoline formation set in (**56**).[30]

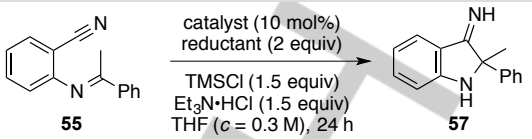


Scheme 10. Formation of ketimine **55** required precise temperature control.

The catalytic cyclization was first attempted under the conditions that were established for the aldimine cyclizations, albeit with a catalyst loading of 10 mol% (Table 3, entry 1). The reaction appeared to be significantly hindered by the additional methyl group and the desired product **57** was formed only in 7% yield. In addition, it was found that a severe decomposition of the substrate to an undefined complex mixture took place even in absence of the catalyst, an issue that was addressed by careful optimization of the reaction conditions. The catalysis was able to outrun the decomposition at an elevated temperature, and at 60 ºC, the desired iminoindoline was formed in 22% yield (entry 2). The background reactions were further reduced by changing the reductant to manganese powder (41% yield, entry 3). We also briefly investigated other catalyst precursors, all of which gave inferior results (entries 4–9). Again, no product could be observed in absence of catalyst (entry 10). Increasing the temperature to 80 ºC and using *rac*-(ebthi)$TiCl_2$ as catalyst under these conditions then led to satisfying 52% yield (entries 11,12). Additional optimization attempts (reaction time, concentration, additive amounts) did not improve the outcome.[7a]

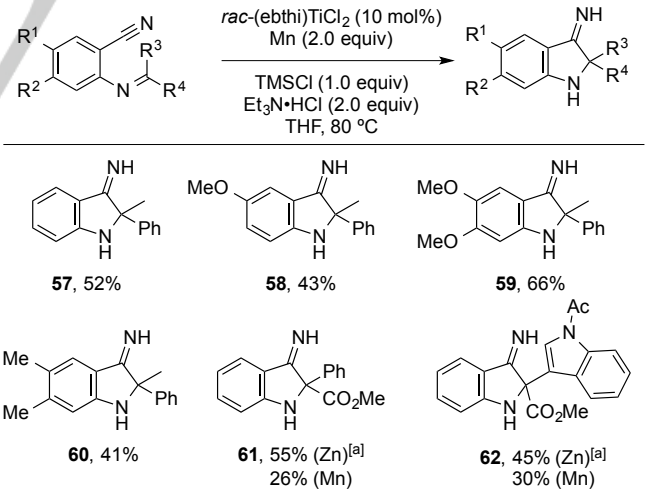
The optimized conditions were then applied to the synthesis of six different iminoindolines (Scheme 11). Substitution at the cyanoaryl moiety with electron-donating methoxy or methyl groups was well-tolerated and the products **58–60** were isolated in moderate to good yield (43–66%). Importantly, ketimines derived from phenyl glyoxylate and from a corresponding indolylglyoxylate also underwent the cyclization reaction, forming the 2-methoxycarbonyl iminoindolines **61** and **62**.[31] For these ester-substituted imines, it was empirically found that zinc gave

Table 3. Optimization of the cyclization to 3-iminoindolines.



Entry	catalyst	reductant	*T* [ºC]	Yield [%][a]
1	Cp_2TiCl_2	Zn	35	7
2	Cp_2TiCl_2	Zn	60	18 (22)[b]
3	Cp_2TiCl_2	Mn	60	37 (41)[b]
4	Cp_2TiBr_2	Mn	60	32
5	(t-BuCp)$_2TiCl_2$	Mn	60	27
6	(EtCp)$_2TiCl_2$	Mn	60	19
7	$Cp_2Ti(OPh)_2$	Mn	60	18
8	(Cp*)$_2TiCl_2$	Mn	60	7
9	*rac*-(ebthi)$TiCl_2$	Mn	60	29
10	-	Mn	60	0
11	Cp_2TiCl_2	Mn	80	47[b]
12	***rac*-(ebthi)$TiCl_2$**	Mn	**80**	**52**[b]

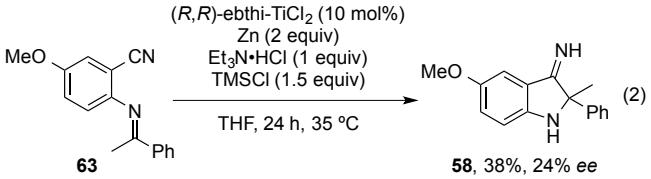
[a] NMR yield determined with 1,2-benzodioxole as internal standard. [b] Yield of isolated product.



Scheme 11. Scope of the titanium(III) catalyzed cyclization to 3-iminoindolines. [a] Reaction carried out with Cp_2TiCl_2 (10 mol%) and Zn dust (2 equiv).

better results (55% and 45%) than manganese (26% and 30%). The products **61** and **62** are of particular intererest, because the imine hydrolysis gives 2-carboxylated indoxyls, which are present in natural products such as duocarmycin family

members and isatisine A, for example.[28b,32] We also attempted the asymmetric cyclization of **63**. But as in our previous efforts towards enantioselective imine-nitrile cyclizations, product **58** was formed only with low enantioselectivity (24% *ee*) together with a slightly reduced yield (38%) [Eq. (2)].[7b]



63 **58**, 38%, 24% *ee* (2)

In agreement with the literature, all 3-iminoindoline products were found to be strongly fluorescent.[28a,c,33] The emission occurred in the blue-green region with compounds **57** and **61** showing a blue fluorescence, a striking property that was also observed for related pseudoindoxyls.[34] It may be rationalized by an equilibrium with the respective 2*H*-indole tautomer, which leads to the fluorescence these compounds [Eq. (3)].

3-iminoindoline 3-amino-2*H*-indole (3)

To investigate the influence of the substitution pattern on the fluorescence properties, absorption-emission spectra were recorded for **57**, the methoxy derivatives **58, 59** and the ester-substituted product **61** (Figure 1). Increasing the number of electron-donating methoxy substituents shifted the absorption maximum for the first electron excitation to higher energies (Table 4, entries 1–3). The corresponding emission maxima of the observed fluorescence spectra were considerably shifted to larger wavelengths, resulting in an increase of the Stokes-shift. The installation of an electron-withdrawing group at the 2-position also increased the absorption energy, while the emission maximum remained almost unchanged (entry 4). The results demonstrate that the absorption and emission properties can be independently adjusted by installing substituents either at the aryl moiety or the 2-position. Hence, these small organic dyes could be of potential interest for applications as fluorescence probes or as blue-green emitters for organic functional materials research.

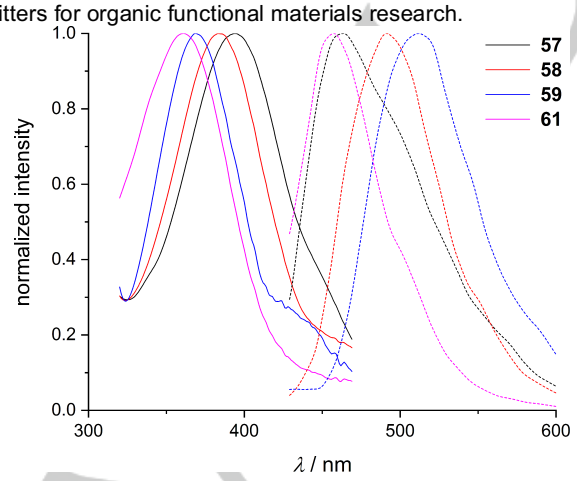


Figure 1. Excerpts of the absorption (—) and emission (---) spectra of compounds **57**–**59** and **61** in chloroform.

Table 4. Selected photophysical properties of compounds **57**–**59** and **61** in chloroform.

Compound	Absorption	Emission		Stokes shift
	$\lambda_{(max)}$ [nm]	$\lambda_{(exc)}$ [nm]	$\lambda_{(em)}$ [nm]	$\Delta\lambda$ [nm]
57	394	394	463	69
58	383	384	491	108
59	369	370	512	143
61	361	360	457	96

Conclusions

In summary, a mild and broadly applicable titanium(III)-catalyzed imine-nitrile cyclization has been developed that gives access to unprotected 3-aminoindoles and 3-aminopyrroles as well as 3-iminoindolines. This addresses a longstanding challenge in the synthesis of these otherwise elusive, electron-rich heterocycles. The isolation of the free products can be conveniently achieved by an acid-base extraction. As an alternative, the direct functionalization at the amino group to produce *N*-derivatized building blocks can be carried out in a single sequence. Transformations of the products into unsymmetrical and selectively protected bisindoles and pyrroloindoles further highlight the synthetic utility of the approach. Overall, this particularly mild synthetic method together with the facile isolation protocol and the demonstrated broad application range may be of greater value for future applications in areas such as organic, medicinal, or material chemistry.

Acknowledgements

This work was funded by the Deutsche Forschungsgemeinschaft (DFG) – project 240508776. The Fonds der Chemischen Industrie (FCI) is gratefully acknowledged for financial support.

Keywords: catalysis • heterocycles • reduction • titanium • umpolung

[1] a) J. Saurí, W. Bermel, A. V. Buevich, E. C. Sherer, L. A. Joyce, M. H. M. Sharaf, P. L. Schiff Jr., T. Parella, R. T. Williamson, G. E. Martin, *Angew. Chem. Int. Ed.* **2015**, *54*, 10160–10164; *Angew. Chem.* **2015**, *127*, 10298–10302; b) R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. Lopez Cara, O. Cruz-Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, N. Zonta, J. Balzarini, A. Brancale, H.-P. Hsieh, E. Hamel, *J. Med. Chem.* **2008**, *51*, 1464–1468; c) A. N. Tackie, G. L. Boye, M. H. M. Sharaf, P. L. Schiff Jr., R. C. Crouch, T. D. Spitzer, R. L. Johnson, J. Dunn, D. Minick, G. E. Martin, *J. Nat. Prod.* **1993**, *56*, 653–670; d) F. G. Salituro, R. C. Tomlinson, B. M. Baron, D. A. Demeter, H. J. R. Weintraub, I. A. McDonald, *Bioorg. Med. Chem. Lett.* **1991**, *1*, 455–460.

[2] a) S. Neidle, *Nat. Prod. Rep.* **2001**, *18*, 291–309; b) P. B. Dervan, *Bioorg. Med. Chem.* **2001**, *9*, 2215–2235; c) S. Lautru, L. Song, L. Demange, T. Lombès, H. Galons, G. L. Challis, J.-L. Pernodet, *Angew. Chem. Int. Ed.* **2012**, *51*, 7454–7458; *Angew. Chem.* **2012**, *124*, 7572–7576; d) T. Takayama, H. Umemiya, H. Amada, T. Yabuuchi, F. Shiozawa, H. Katakai, A. Takaoka, A. Yamaguchi, M. Endo, M. Sato, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 108–111; e) K. Unverferth, J. Engel, N. Höfgen, A. Rostock, R. Günther, H.-J. Lankau, M. Menzer, A. Rolfs, J. Liebscher, B. Müller, H.-J. Hofmann, *J. Med. Chem.* **1998**, *41*, 63–73; f) G. Tarzia, G. Panzone (Gruppo Lepetit S.p.A.), US 4140696, **1979**.

[3] a) P. K. Prasad, R. G. Kalshetti, R. N. Reddi, S. P. Kamble, A. Sudalai, *Org. Biomol. Chem.* **2016**, *14*, 3027–303.; b) M. De Rosa, D. Arnold, *J. Org. Chem.* **2013**, *78*, 1107; c) E. Fischer, T. Schmitt, *Ber. dtsch. Chem. Ges.* **1888**, *21*, 1071.

[4] V. Dave, E. W. Warnhoff, *Can. J. Chem.* **1976**, *54*, 1020.

[5] Selected references: a) K. Atmakur, N. R. Emmadi, S. Balasubramanian, *J. Heterocyclic Chem.* **2013**, *50*, 513–518; b) A. Pews-Davtyan, M. Beller, *Org. Biomol. Chem.* **2011**, *9*, 6331–6334; c) Y. M. Kim, K. H. Kim, S. Park, J. N. Kim, *Tetrahedron Lett.* **2011**, *52*, 1378–1382; d) A. Pews-Davtyan, A. Tillack, A.-C. Schmöle, S. Ortinau, M. J. Frech, A. Rolfs, M. Beller, *Org. Biomol. Chem*. **2010**, *8*, 1149–1153; e) S. S. Michaelidou, P. A. Koutentis, *Tetrahedron* **2010**, *66*, 685–688; f) J. S. Schneekloth Jr., J. Kim, E. J. Sorensen, *Tetrahedron* **2009**, *65*, 3096–3101; g) N. Chen, Y. Lu, K. Gadamasetti, C. R. Hurt, M. H. Norman, C. Fotsch, *J. Org. Chem.* **2000**, *65*, 2603–2605; h) B. Erdmann, A. Knoll, J. Liebscher, *J. Prakt. Chem.* **1988**, *330*, 1015–1021; i) G. Tarzia, G. Panzone, *Ann. Chim.* **1974**, 64, 807–824.

[6] Selected examples: a) Z. Hu, X. Tong, G. Liu, *Org. Lett.* **2016**, *18*, 2058–2061; b) B. Yao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 5170–5174; *Angew. Chem.* **2012**, *124*, 5260–5264; c) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2012**, *77*, 617–625. d) D. Chernyak, N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2010**, *352*, 961–966.

[7] a) L. H. Leijendekker, J. Weweler, T. M. Leuther, J. Streuff, *Angew. Chem. Int. Ed.* **2017**, *56*, 6103–6106; *Angew. Chem.* **2017**, *129*, 6199–6202. See also: b) G. Frey, H.-T. Luu, P. Bichovski, M. Feurer, J. Streuff, *Angew. Chem. Int. Ed.* **2013**, *52*, 7131–7134; *Angew. Chem.* **2013**, *125*, 7271–7274.

[8] Selected reviews: a) M. C. Rodríguez, I. Rodríguez García, R. N. Rodríguez Maecker, L. Pozo Morales, J. E. Oltra, A. Rosales Martínez, *Org. Proc. Res. Dev.* **2017**, *21*, 911–923. b) N. Funken, Y.-Q. Zhang, A. Gansäuer, *Chem. Eur. J.* **2017**, *23*, 19–32; c) A. Rosales, I. Rodríguez-García, J. Muñoz-Bascón, E. Roldan-Molina, N. M. Padial, L. Pozo Morales, M. García-Ocaña, J. E. Oltra, *Eur. J. Org. Chem.* **2015**, 4567–4591; d) S. P. Morcillo, D. Miguel, A. G. Campaña, L. Álvarez de Cienfuegos, J. Justicia, J. M. Cuerva, *Org. Chem. Front.* **2014**, *1*, 15–33; e) A. Gansäuer, J. Justicia, C.-A. Fan, D. Worgull, F. Piestert, *Top. Curr. Chem.* **2007**, *279*, 25–52.

[9] Selected references: a) T. Liedtke, P. Spannring, L. Riccardi, A. Gansäuer, *Angew. Chem. Int. Ed.* **2018**, *57*, 5006–5010; *Angew. Chem.* **2018**, *130*, 5100–5104; b) R. B. Richrath, T. Olyschläger, S. Hildebrandt, D. G. Enny, G. D. Fianu, R. A. Flowers II, A. Gansäuer, *Chem. Eur. J.* **2018**, *24*, 6371–6379; c) V. K. Chenniappan, S. Silwal, R. J. Rahaim, *ACS Catal.* **2018**, *8*, 4539–4544; d) J. Xuan, Z. Liu, A. Zhu, P. Rao, L. Yu, H. Ding, *Angew. Chem. Int. Ed.* **2017**, *56*, 8898–8901; *Angew. Chem.* **2017**, *129*, 9024–9027; e) Y.-Q. Zhang, E. Vogelsang, Z.-W. Qu, S. Grimme, A. Gansäuer, *Angew. Chem. Int. Ed.* **2017**, *56*, 12654–12657; *Angew. Chem.* **2017**, *129*, 12828–12831; f) W. Hao, X. Wu, J. Z. Sun, J. C. Siu, S. N. MacMillan, S. Lin, *J. Am. Chem. Soc.* **2017**, *139*, 12141–12144; g) F. Daiba, E. Gómez-Bengoa, J. M. Cuerva, J. Bonjoch, J. Justicia, *RSC Adv.* **2016**, *6*, 55360–55365; h) S. Hildebrandt, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 9719–9722; *Angew. Chem.* **2016**, *128*, 9871–9874; i) Y.-Q. Zhang, V. Jakoby, K. Stainer, A. Schmer, S. Klare, M. Bauer, S. Grimme, J. M. Cuerva, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 1523–1526; *Angew. Chem.* **2015**, *128*, 1546–1550; j) X. Zheng, J. He, H.-H. Li, A. Wang, X.-J. Dai, A.-E Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 13739–13742; *Angew. Chem.* **2015**, *127*, 13943–13946; k) K. T. Tarantino, D. C. Miller, T. A. Callon, R. R. Knowles, *J. Am. Chem. Soc.* **2015**, *137*, 6440–6443; l) S. P. Morcillo, D. Miguel, S. Resa, A. Martín-Lasanta, A. Millán, D. Choquesillo-Lazarte, J. M. García-Ruiz, A. J. Mota, J. Justicia, J. M. Cuerva, *J. Am. Chem. Soc.* **2014**, *136*, 6943–6951; m) A. Gansäuer, C. Kube, K. Daasbjerg, R. Sure, S. Grimme, G. D. Fianu, D. V. Sadasivam, R. A. Flowers II, *J. Am. Chem. Soc.* **2014**, *136*, 1663–1671; n) J. Muñoz-Bascón, C. Hernández-Cervantes, N. M. Padial, M. Álvarez-Corral, A. Rosales, I. Rodríguez-García, J. E. Oltra, *Chem. Eur. J.* **2014**, *20*, 801–810; o) A. Gansäuer, M. Behlendorf, D. von Laufenberg, A. Fleckhaus, C. Kube, D. V. Sadasivam, R. A. Flowers II, *Angew. Chem. Int. Ed.* **2012**, *51*, 4739–4742; *Angew. Chem.* **2012**, *124*, 4819–4823; p) A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem. Int. Ed.* **1998**, *37*, 101–103; *Angew. Chem.* **1998** *110*, 107–109; q) A. Gansäuer, *Chem. Commun.* **1997**, 457–458.

[10] a) J. Streuff, A. Gansäuer, *Angew. Chem. Int. Ed.* **2015**, *54*, 14232–14242; *Angew. Chem.* **2015**, *127*, 14438–14448; b) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788.

[11] For selected examples, see: a) N. Funken, F. Mühlhaus, A. Gansäuer, *Angew. Chem. Int. Ed.* **2016**, *55*, 12030–12034; *Angew. Chem.* **2016**, *128*, 12209–12213; b) J. Streuff, M. Feurer, P. Bichovski, G. Frey, U. Gellrich, *Angew. Chem. Int. Ed.* **2012**, *51*, 8661–8664; *Angew. Chem.* **2012**, *124*, 8789–8792; c) A. Gansäuer, L. Shi, M. Otte, *J. Am. Chem. Soc.* **2010**, *132*, 11858–11859; d) A. Gansäuer, C.-A. Fan, F. Keller, J. Keil, *J. Am. Chem. Soc.* **2007**, *129*, 3484–3485; e) Y.-G. Li, Q.-S. Tian, J. Zhao, Y. Feng, M-.J. Li, T.-P. You, *Tetrahedron: Asymmetry* **2004**, *15*, 1707–1710; f) A. Gansäuer, T. Lauterbach, H. Bluhm, M. Noltemeyer, *Angew. Chem. Int. Ed.* **1999**, *38*, 2909–2910; *Angew. Chem.* **1999**, *111*, 3112–3114.

[12] a) J. Streuff, *Chem. Rec.* **2014**, *14*, 1100–1113; b) J. Streuff, *Synthesis* **2013**, *45*, 281–307.

[13] a) J. Streuff, D. Himmel, S. Younas, *Dalton Trans.* **2018**, *47*, 5072–5082; b) P. Bichovski, T. M. Haas, M. Keller, J. Streuff, *Org. Biomol. Chem.* **2016**, *14*, 5673–5682; c) J. Streuff, M. Feurer, G. Frey, A. Steffani, S. Kacprzak, J. Weweler, L. H. Leijendekker, D. Kratzert, D. A. Plattner, *J. Am. Chem. Soc.* **2015**, *137*, 14396–14405; d) H.-T. Luu, S. Wiesler, G. Frey, J. Streuff, *Org. Lett.* **2015**, *17*, 2478–2481; e) P. Bichovski, T. M. Haas, D. Kratzert, J. Streuff, *Chem. Eur. J.* **2015**, *21*, 2339–2342; f) G. Frey, J. N. Hausmann, J. Streuff, *Chem. Eur. J.* **2015**, *21*, 5693–5696; g) M. Feurer, G. Frey, H.-T. Luu, D. Kratzert, J. Streuff, *Chem. Commun.* **2014**, *50*, 5370–5372.

[14] a) A. Fürstner, H. Weintritt, A. Hupperts, *J. Org. Chem.* **1995**, *60*, 6637–6641; b) A. Fürstner, A. Hupperts, *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475; c) A. Fürstner, D. N. Jumbam, *Tetrahedron* **1992**, *48*, 5991–6010; d) A. Fürstner, D. N. Jumbam, H. Weidmann, *Tetrahedron Lett.* **1991**, *32*, 6695–6696.

[15] G. V. M. Sharma, J. J. Reddy, P. S. Lakshmi, P. R. Krishna, *Tetrahedron Lett.* **2004**, *45*, 6963–6965.

[16] For comparison, the in situ Boc protection of N1-sulfonylated 3-aminoindoles has been reported with Boc_2O, see: P. Z. Mannes, E. O. Onyango, G. W. Gribble, *J. Org. Chem.* **2016**, *81*, 12478–12481

[17] a) P. Y. Reddy, S. Kondo, T. Toru, Y. Ueno, *J. Org. Chem.* **1997**, *62*, 2652–2654; b) M.-Y. Zhou, Y.-Q. Li, X.-M. Xu, *Synth. Commun.* **2003**, *33*, 3777–3780.

[18] a) S.-B. Zhao, S. Wang, *Chem. Soc. Rev.* **2010**, *39*, 3142–3156; b) F. Popowycz, S. Routier, B. Joseph, J.-Y. Mérour, *Tetrahedron* **2007**, *63*, 1031–1064.

[19] a) M. S. Dunlap, K. M. Nicholas, *Synth. Commun.* **1999**, *29*, 1097–1106; b) T. Hirao, B. Hatano, M. Asahara, Y. Muguruma, A. Ogawa, *Tetrahedron Lett.* **1998**, *39*, 5247–5248.

[20] F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, *Tetrahedron* **2007**, *63*, 523–575.

[21] J. C. Thorpe, *J. Chem. Soc., Trans.* **1909**, *95*, 1901–1903.

[22] I. Cho, S. K. Park, B. Kang, J. W. Chung, J. H. Kim, K. Cho, S. Y. Park, *Adv. Funct. Mater.* **2016**, *26*, 2966–2973.

[23] For selected syntheses, see: a) M. V. Karkhelikar, V. V. Rao, S. S. Shinde, P. R. Likhar, *Tetrahedron Lett.* **2016**, *57*, 4803–4806; b) M. A. Truong, K. Nakano, *J. Org. Chem.* **2015**, *80*, 11566–11572; c) L. Qiu, C. Yu, N. Zhao, W. Chen, Y. Guo, X. Wan, R. Yang, Y. Liu, *Chem. Commun.* **2012**, *48*, 12225–12227; e) K. Muñiz, *J. Am. Chem. Soc.* **2007**, *129*, 14542–14543.

[24] T. Noji, K. Okano, T. Fukuyama, H. Tokuyama, *Org. Synth.* **2011**, *88*, 388–397.

[25] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.

[26] CCDC 1850258 (**54**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[27] J. A. Molina de la Torre, P. Espinet, A. C. Albéniz, *Organometallics* **2013**, *32*, 5428–5434.

[28] a) R. Sulsky, J. Z. Gougoutas, J. DiMarco, S. A. Biller, *J. Org. Chem.* **1999**, *64*, 5504–5510; b) D. L. Boger, J. A. McKie, T. Nishi, T. Ogiku, *J. Am. Chem. Soc.* **1996**, *118*, 2301–2302; c) A. S. Baily, R. Scattergood, W. A. Warr, *J. Chem. Soc., C* **1971**, 2479–2491.

[29] a) D. L. Boger, D. S. Johnson, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1438–1474; *Angew. Chem.* **1996**, *108*, 1542–1580; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127–139.

[30] L. Strekowski, S.-B. Kong, M. T. Cegla, D. B. Harden, *Heterocycles* **1989**, *29*, 539–545.

[31] See also: M. Shimizu, Y. Takao, H. Katsurayama, I. Mizota, *Asian J. Org. Chem.* **2013**, *2*, 130–134.

[32] J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang, Y.-B. Ma, *Org. Lett.* **2007**, *9*, 4127–4129.

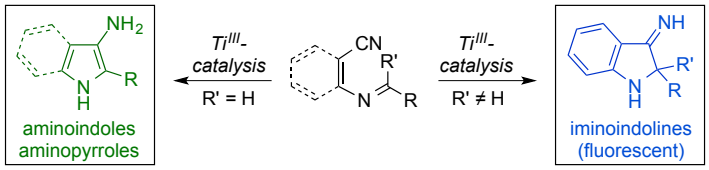
[33] See also: S. G. P. Plant, R. Robinson, *Nature* **1950**, *165*, 36–37.

[34] a) S. Lerch, L.-N. Unkel, M. Brasholz, *Angew. Chem. Int. Ed.* **2014**, *53*, 6558–6562; *Angew. Chem.* **2014**, *126*, 6676–6680; b) Y. Goriya, C. V. Ramana, *Chem. Commun.* **2013**, *49*, 6376–6378; c) S. Matsumoto, D. Samata, M. Akazome, K. Ogura, *Tetrahedron Lett.* **2009**, *50*, 111–114.

10.1002/chem.201805909

Entry for the Table of Contents

FULL PAPER



*Leonardus H. Leijendekker, Jens Weweler, Tobias M. Leuther, Daniel Kratzert, Jan Streuff**

Page No. – Page No.

Development, Scope, and Applications of Titanium(III) Catalyzed Cyclizations to Aminated *N*-Heterocycles

A titanium(III) catalyzed imine-nitrile cyclization gives rise to free aminoindoles, pyrroles, and iminoindolines that are ideal, but fragile building blocks for the installation of such motifs into target molecules. Herein, the development, extended scope, and application of this reaction are described. Moreover, the fluorescence properties of the iminoindoline products are briefly investigated.