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A Titanium(III)-Catalyzed Reductive Umpolung Reaction for the Synthesis of 1,1-Disubstituted Tetrahydroisoquinolines

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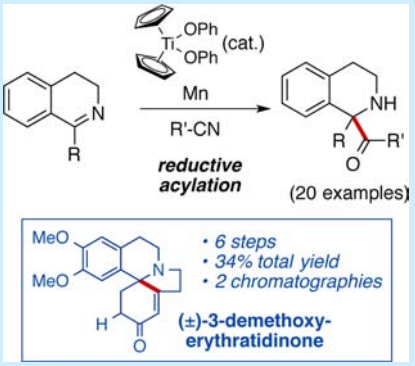
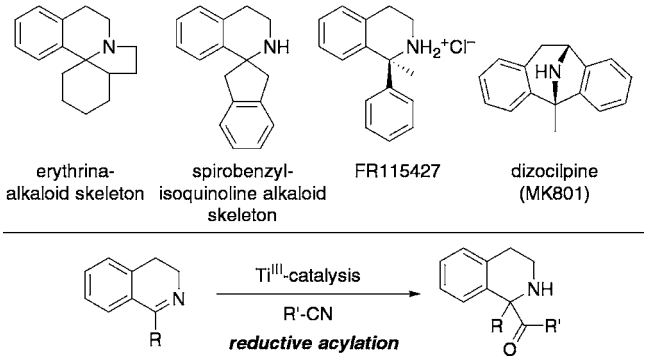
Supporting Information

ABSTRACT: A catalytic reductive C1-acylation of 3,4-dihydroisoquinolines is presented that gives direct access to 1,1-disubstituted tetrahydroisoquinolines. The reaction is a titanium(III)-catalyzed reductive umpolung process in which nitriles act as effective acylation agents. The method is highly chemo- and regioselective and is demonstrated in 20 examples. It is well-suited for the large-scale synthesis of functionalized tetrahydroisoquinoline products, which is exemplified in the form of a six-step synthesis of (±)-3-demethoxyerythratidinone.



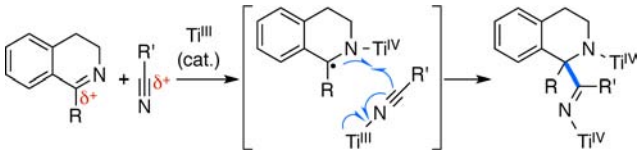
Tetrahydroisoquinolines represent an important class of compounds in organic and medicinal chemistry.[1] They find application in the form of C1-monosubstituted derivatives, and therefore numerous procedures have been developed for their synthesis.[2] 1,1-Disubstituted tetrahydroisoquinolines possess remarkable biologic properties too, but are a considerably bigger challenge to organic synthesis. Noteworthy families are the erythrina and spirobenzylisoquinoline alkaloids,[3] as well as synthetic agents such as the anticonvulsants MK-801 and FR115427 (Scheme 1).[4] The methods for the preparation of such 1,1-disubstituted frameworks showed strong limitations regarding the substrate scope and required several steps or the installation of N-protecting or N-activating groups.[5,6] To this end, we herein report a novel and unconventional approach to 1,1-difunctionalized tetrahydroisoquinolines in the form of a direct and broadly applicable titanium(III)-catalyzed reductive radical acylation of 3,4-dihydroisoquinolines. This approach closes a methodological gap in modern organic synthesis.

Scheme 1. 1,1-Disubstituted Tetrahydroisoquinolines and Access via a Titanium(III)-Catalyzed C1-Acylation



Recently, titanium(III)-catalysis found application as a versatile tool for reductive coupling reactions,[7] and we anticipated that a titanium(III)-catalyst could perform a single-electron transfer to a dihydroisoquinoline (Scheme 2).

Scheme 2. Mechanistic Concept



Afterward, the resulting benzyl-aminyl radical would attack the desired nitrile and as a result lead to a C−C connection in the form of a reductive umpolung reaction.[8] This scenario was supported by our earlier reported carbonyl-nitrile couplings,[9] as well as works by other groups dealing with titanocene-catalyzed pinacol couplings and epoxide-opening induced radical additions to nitriles.[7,10,11] In this context, an additional activation of the nitrile by a second titanium(III)-species has been postulated.[9a−d,11b,c,12]

We chose the reductive acylation of 1-methyl-3,4-dihydroisoquinoline (**1a**) with benzyl cyanide (**2a**, 5 equiv) in the presence of titanocene dichloride (**4a**) as the catalyst (10 mol %) as the starting point for our investigations (Table 1). A 72% conversion to the desired 1,1-difunctionalized tetrahydroiso-

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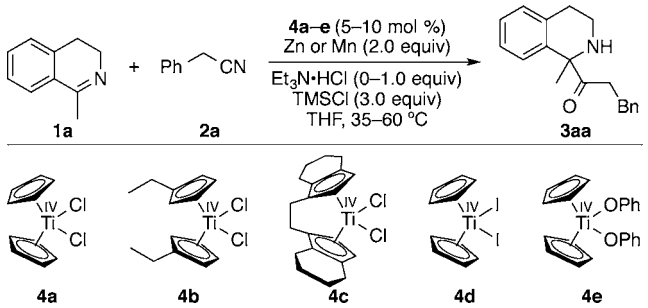
Table 1. Optimization of the Titanium(III)-Catalyzed Reductive Coupling of 1a with 2a[a]



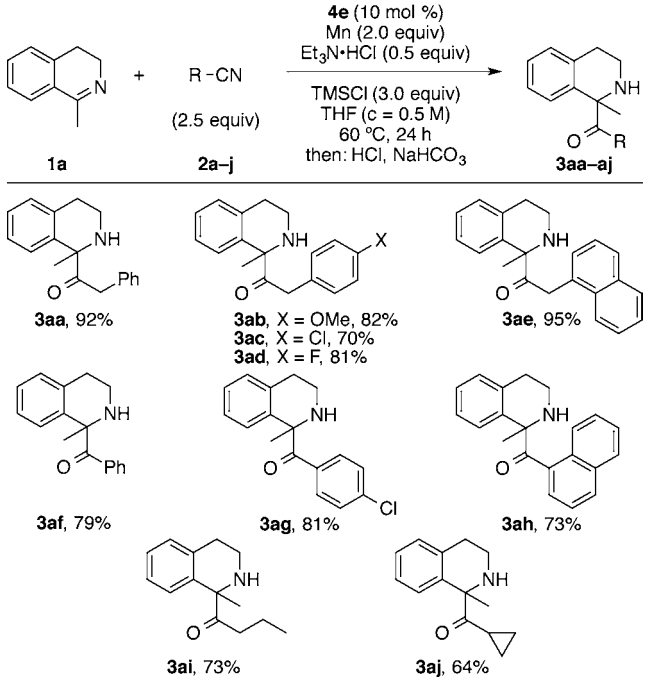
entry	catalyst	reductant	T (°C)	equiv **2a**	equiv Et_3N·HCl	yield (%)[b]
1	**4a**	Zn	35	5.0	0.5	72
2	**4b**	Zn	35	5.0	0.5	57
3	(±)-**4c**	Zn	35	5.0	0.5	76
4	**4d**	Zn	35	5.0	0.5	48
5	**4e**	Zn	35	5.0	0.5	78 (71)[c]
6	**4e**	Mg	35	5.0	0.5	0[d]
7	**4e**	Mn	35	5.0	0.5	86 (80)[c]
8	**4e**	Mn	35	5.0	1.0	81 (73)[c]
9	**4e**	Mn	35	5.0	–	68 (68)[c]
10	**4e**	**Mn**	**60**	**2.5**	**0.5**	**92 (92)**[c,e]
11	**4e**	Mn	60	2.5	0.5	78[f]
12	–	Mn	60	2.5	0.5	0[g]

[a]Conditions: **1a** (0.5 mmol), **2a** (2.5–5.0 equiv), **4a–e** (5–10 mol %), reductant (2.0 equiv), Et_3N·HCl (0–1.0 equiv), TMSCl (3.0 equiv), THF (0.5 mL, c = 1.0 M), 24 h; aq workup. [b]NMR yield with 1,3-benzodioxole as the internal standard. [c]Yield of isolated compound in brackets. [d]Only reduction and homocoupling of **1a** were observed. [e]c = 0.5 M in THF. [f]With 5 mol % $Cp_2Ti(OPh)_2$. [g]Only the reduction of **1a** to the secondary amine was observed.

quinoline **3aa** was already observed with zinc dust as the reducing agent and 0.5 equiv of triethylamine hydrochloride as the additive in THF at 35 °C (entry 1). Other catalyst precursors with modified cyclopentadienyl ligands or varying counterions were tested as well (**4b–e**, entries 2–5). Here, the *ansa*-titanocene (±)-**4c** and $Cp_2Ti(OPh)_2$ (**4e**) led to an improved conversion. The latter was then chosen as the ideal catalyst due to its availability and the excellent yield. A brief evaluation of other reducing agents revealed that no product was formed in the presence of magnesium, but reduction and homocoupling of **1a** took place (entry 6). Manganese, on the other hand, led to an increased yield of 80% (entry 7). A change in the hydrochloride amount (entries 8 and 9) or variation of the TMSCl-amount, concentration, or reaction time did not lead to any further improvement.[13] Finally, the optimized conditions were achieved by an increase of the reaction temperature to 60 °C and a reduction of the concentration (92% yield, entry 10), which also enabled a reduction of the amount of **2a** to 2.5 equiv. With 5 mol % catalyst, still 78% conversion was observed under these conditions (entry 11). No product formation took place in the absence of the catalyst (entry 12), and only reduction of **1a** to the secondary amine was observed.[14]

In the following, the reductive acylation of **1a** was carried out with various nitriles (Scheme 3) and good to excellent yields were achieved (64–95%). In this manner, 1,1-disubstituted tetrahydroisoquinolines with different arylacetyl or naphthylacetyl groups were received in a straightforward fashion (**3aa–aj**). Good results were also obtained for the synthesis of C1-benzoylated or C1-naphthoylated products (**3af–ah**), and importantly, alkyl nitriles such as butyro- or cyclopropanecarbonitrile could be employed as well (**3ai**, **aj**). An opening of the cyclopropyl ring was not observed.

Scheme 3. Reductive Acylation of 1a with Various Nitriles



By variation of the dihydroisoquinoline C1-substituent we could demonstrate that alkyl and aryl groups of diverse bulkiness were tolerated at this position as well (Scheme 4). Furthermore, good yields were achieved with ethyl, isopropyl, and cyclohexyl groups (**3ba–da**) and the coupling proceeded without problems in the presence of phenyl or 2-thiophenyl substituents (**3ea,fa**). Product **3fa** was even isolated in

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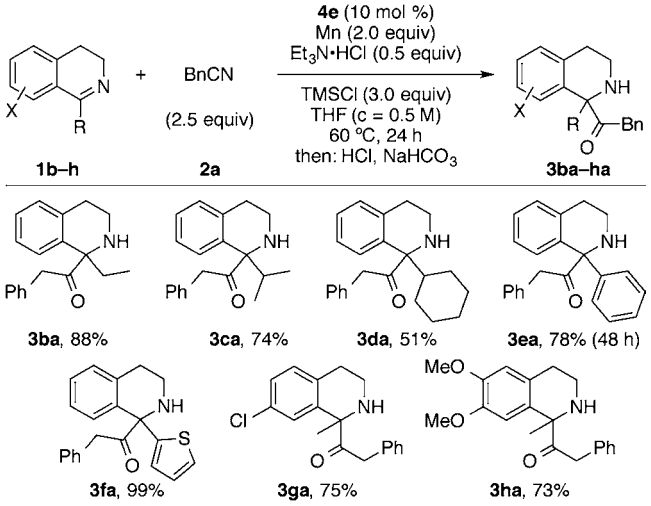
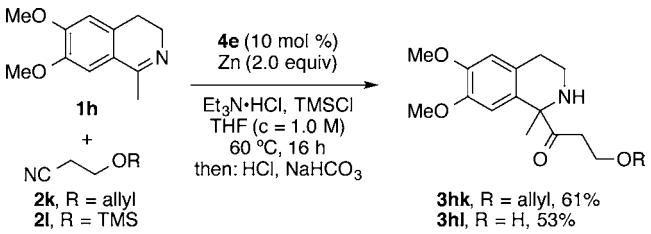
Scheme 4. Reductive Acylation of 3,4-Dihydroisoquinolines with Benzyl Cyanide



quantitative yield. Dihydroisoquinolines that were chlorinated or methoxylated at the aromatic backbone could be employed as well, and products **3ga** and **3ha** were obtained in 75% and 73% yield, respectively. Tetrahydroisoquinolines with oxygenation at position 6/7 play an important role as structural motifs of natural products,[1] and therefore **1h** was reacted with allyloxypropionitrile **2k** (Scheme 5). This way, an additional

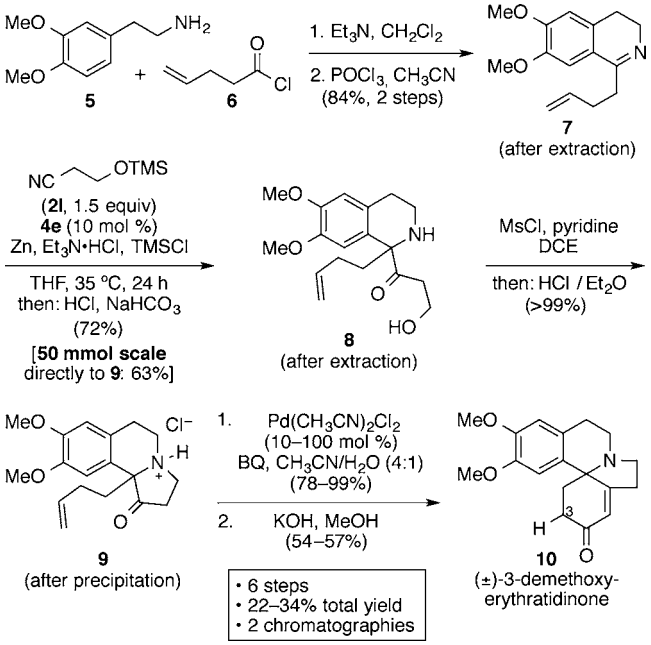
Scheme 5. Reactions with 3-Oxypropionitriles Afford Products for Further Functionalizations



functionalization was introduced to the resulting product **3hk**, which could enable further manipulations at a later stage. By coupling **1h** with TMS-oxypropionitrile **2l** the free alcohol became directly accessible allowing instant subsequent transformations. Here, good yields of 61% and 53% were received with zinc and a higher concentration.

To demonstrate a first application of this titanium-catalyzed C1-acylation, we developed a racemic synthesis of the erythrina alkaloid 3-demethoxyerythratidinone (**10**) with the title reaction as the key step (Scheme 6). Since this molecule had been synthesized in the past several times,[3b,15] it was our goal to achieve a short, convenient, and scalable synthesis with high total yield. Starting from phenyl ethyl amine **5** and pentenoyl chloride **6**, dihydroisoquinoline **7** was received after extraction in 84% overall yield in a sequence of quantitative amide formation and a Bischler–Napieralski cyclization.[16] Product **7** was directly submitted to a titanium-catalyzed reductive cross-coupling with nitrile **2l**, which gave a 72% yield of **8**. Here, 1.5 equiv of the nitrile and a mild temperature of 35 °C were already sufficient. After acid–base extraction, the product was directly mesylated, which resulted in the cyclization to the corresponding pyrrolidinone that could be conveniently precipitated by treatment with HCl in ether. This sequence

Scheme 6. Total Synthesis of (±)-3-Demethoxyerythratidinone



from **7** to **9** could be carried out even on a 50 mmol scale (63% yield).

The resulting hydrochloride **9** was of great advantage for the following Wacker oxidation of the homoallylic group: Previously, this oxidation was reported to fail in the presence of the free amine.[15c] Precursors having N-neighboring electron-withdrawing groups were the only successful substrates.[3,15,17] Hydrochloride **9**, on the other hand, was smoothly oxidized to the corresponding ketone in the presence of $Pd(CH_3CN)_2Cl_2$ in quantitative yield.[18,19] On a 5 mmol scale, this oxidation was performed with 10 mol % $Pd(CH_3CN)_2Cl_2$ giving an excellent 78% yield. The final literature-known aldol condensation (lit: 41–50%)[15d,h] gave in our hands a 57% yield and was successfully scaled to 5 mmol (54%).[20] This resulted in an outstanding 34% total yield of target compound **10** (22% on the 5–50 mmol scale), and it should be pointed out that only the last two steps required a chromatographical purification. Consequently, this was one of the most efficient syntheses of an erythrina alkaloid starting from commercially available materials.

In summary, a reductive C1-acylation of 3,4-dihydroisoquinolines was developed that proceeds via a titanium(III)-catalyzed cross-coupling with a nitrile. The method is regio- and chemoselective, enables a facile access to 1,1-disubstituted tetrahydroisoquinolines, and is broadly applicable. It could become highly valuable for the synthesis of synthetic drugs and natural product building blocks. This was exemplified in the form of a highly efficient racemic total synthesis of the erythrina alkaloid 3-demethoxyerythratidinone (**10**). This work therefore closed a methodological gap and provided an alternative, unconventional access to tetrahydroisoquinoline-based target compounds. Further works on the application of this method will follow in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Materials and methods, extended screening table, detailed experimental procedures, and ^{1}H, ^{13}C spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00987.

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Notes

The authors declare no competing financial interest.

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(13) See Supporting Information.

(14) An asymmetric variant was attempted during our initial screening experiments, and several chiral titanocene catalysts were tested. The highest enantioselectivity was achieved with (*R*,*R*)-(ebthi) $TiCl_2$ as the catalyst (17% ee).

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(19) Typical solvents such as DMF or 1,4-dioxane were not suitable.

(20) Good yields required the use of degassed methanol.

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