Radical Cyclizations

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Enantioselective Titanium(III)-Catalyzed Reductive Cyclization of Ketonitriles**

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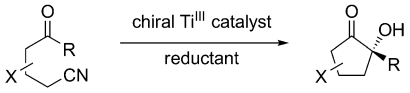
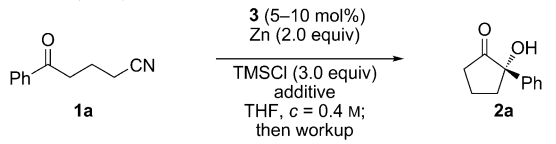
Samarium(II)-mediated reductive cyclizations are standard tools in organic chemistry and have found broad application in the synthesis of natural products and drugs.[1] Of these reactions, the reductive cyclization of ω-ketonitriles[2] is of particular interest because the resulting α-hydroxyketone (acyloin) fragment is present in over 1500 known natural products. Examples include barbacenic acid, cortistatin D, dragmacidin F, sieboldine A, and sphaerococcenol A, which all contain a ketone with a tetrasubstituted, oxygenated α-carbon.[3] In addition to SmI_2, a number of other stoichiometric reagents were successfully employed for the cyclization of ketonitriles and related reactions.[2c,d,f,4] However, asymmetric variants of such radical cyclizations are scarce and usually require stoichiometric chiral additives.[1c,5] A transition-metal catalyst in combination with an inexpensive terminal reductant instead would represent a significant advance and also enable the asymmetric cyclization.[6] Based on our recent work on the Ti^{III}-catalyzed synthesis of ketonitriles,[7] and previous reports by others that have already demonstrated the versatility of titanium catalysis in related radical reactions,[8] we reasoned that a chiral titanium-based catalyst could facilitate the desired transformation. Hence, a mild and highly enantioselective titanium(III)-catalyzed reductive ketonitrile cyclization was developed [Eq. (1)].

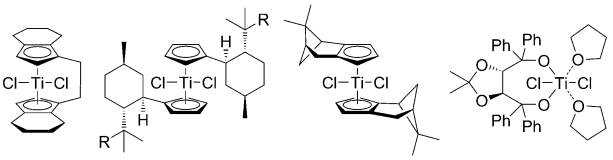


(1)

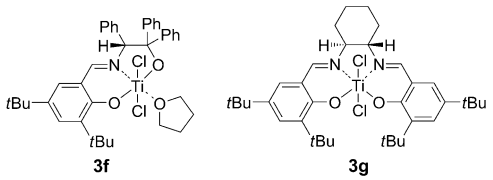
Our investigations started with 1,5-ketonitrile **1a** and we found that product **2a** formed only in the presence of the titanocene catalysts **3a–d** (Table 1, entries 1–4).[9] In detail, only Brintzinger's commercially available ansa-titanocene **3a** provided the product with high enantioselectivity (80% *ee*) and reasonable yield (67%) after workup with tetra-*n*-butylammonium fluoride (TBAF).[9a] Other catalysts such as the TADDOL- or Salen-based complexes **3e–g**, which previously showed high selectivities in pinacol coupling reactions, did not mediate this cyclization (Table 1, entries 5–7).[10] After a second screening of a variety of additives, triethylamine hydrochloride was identified to be superior and it was found that the yield and enantioselectivity of the reaction strongly depend on this hydrochloride additive (Table 1, entries 8 and 9).[11] Importantly, no reaction was observed under these conditions in the absence of catalyst and addition of radical scavengers such as BHT shut down the reaction completely.[12] Under the final optimized reaction conditions the product was obtained in 88% yield and 91% *ee* after a reaction time of 24 h at room temperature (Table 1, entry 10). The yield and enantiomeric ratio remained con-

Table 1: Catalyst optimization and additive effects.[a]





3a 3b (R=H) 3c (R=Ph) 3d 3e



3f 3g

Entry	Cat. (mol%)	Additive (equiv)	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**3a** (5)	Coll·HCl (1.3)	40	18	67	80
2	**3b** (5)	Coll·HCl (1.3)	40	18	77	25
3	**3c** (5)	Coll·HCl (1.3)	40	18	26	−20
4	**3d** (5)	Coll·HCl (1.3)	40	18	58	−55
5	**3e** (5)	Coll·HCl (1.3)	40	18	0	–
6	**3f** (5)	Coll·HCl (1.3)	40	18	0	–
7	**3g** (5)	Coll·HCl (1.3)	40	18	0	–
8	**3a** (5)	none	40	18	45	54
9	**3a** (5)	Et_3N·HCl (1.3)	40	18	72	83
10	**3a (10)**	**Et_3N·HCl (2.0)**	**23**	**24**	**88**	**91**[d]

[a] Conditions: **1a** (0.2 mmol), catalyst **3** (5–10 mol%), zinc dust (2.0 equiv), TMSCl (3.0 equiv), additive, THF (*c* = 0.4 M), 18 h; workup: TBAF, aq. $NaHCO_3$, followed by flash chromatography. [b] Yield of isolated product. [c] Determined by GC on a chiral stationary phase. [d] Workup by acid–base extraction. Coll = collidine.

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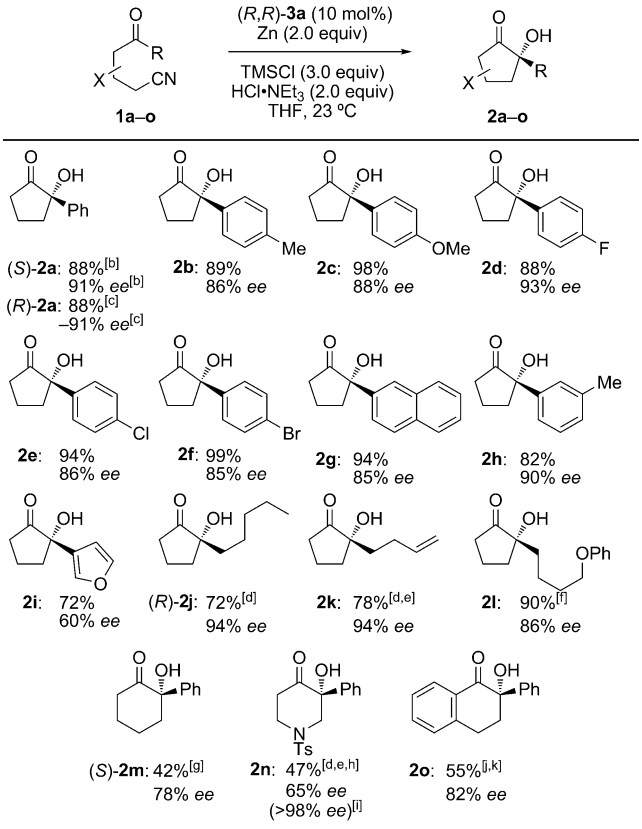
sistent for reactions carried out on scales between 0.2–3.0 mmol.

We then submitted a number of ω-ketonitriles to the optimized conditions and observed that the *R*,*R* catalyst produced the *S*-configured product and vice versa (Table 2).[13] A range of functional groups were tolerated on

Table 2: Scope of the titanium-catalyzed reductive cyclization.[a]

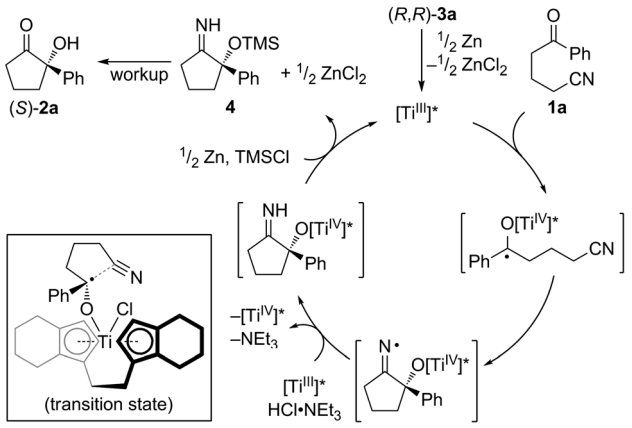


[a] Yields of isolated products. Conditions: **1** (0.2–1.0 mmol, 1 equiv), **3a** (0.1 equiv), Zn (2.0 equiv), TMSCl (3.0 equiv), HCl·NEt_3 (2.0 equiv), THF (c = 0.4 M), 23 °C, 24 h; then 1 N HCl, neutralization, extraction with CH_2Cl_2. [b] Average of three experiments. [c] (*S*,*S*)-**3a** was used instead. [d] 48 h reaction time. [e] Product purified by chromatography. [f] 96 h reaction time. [g] 72 h reaction time. [h] Workup with TBAF instead. [i] After crystallization from 2-propanol. [j] The corresponding imine required hydrolysis with HCl in THF/H_2O (55% overall yield). [k] Zn was added in two portions of 1.0 equiv, one portion initially and one after 7.5 h.

the aromatic moiety. Substrates bearing either electron-rich or electron-poor *para* substituents (**2b–f**) provided the respective products in high yield (88–99%) and high enantiomeric excess (86–93% *ee*) after 24 h reaction time.

Cyclic tertiary alcohols **2g** and **2h** with a 2-naphthyl and a *m*-tolyl group, respectively, were obtained with similar results. A heteroaromatic group, such as 3-furyl was tolerated and product **2i** was isolated in good yield and moderate enantioselectivity.[14] Importantly, the aryl substituent was not required for the reaction to proceed. Instead, different alkyl substituents were successfully installed and the desired products **2j–l** formed in good yields and high enantioselectivity at room temperature.[13] It is known that the intramolecular reaction of a ketyl radical with a nitrile to form a six-membered ring is significantly slower than that forming a five-membered ring.[2b] Still, cyclohexanone **2m** and piperidinone **2n** were synthesized in moderate yields with only slightly diminished enantioselectivities.[14] In the case of **2n** a single crystallization afforded nearly enantiomerically pure material. Finally, the challenging formation of α-hydroxytetralone **2o**, which itself can be easily reduced by the catalyst, was successful. The product was obtained in 55% yield and 82% *ee* when zinc dust was added in two portions. Here, hydrolysis of the crude imine with HCl in THF/H_2O afforded the desired product. During our initial experiments we found that the product can be isolated conveniently by simple acid–base extraction and chromatographic purification can be avoided. Of all the products in Table 2, only **2k** and **2n** required chromatographic purification.

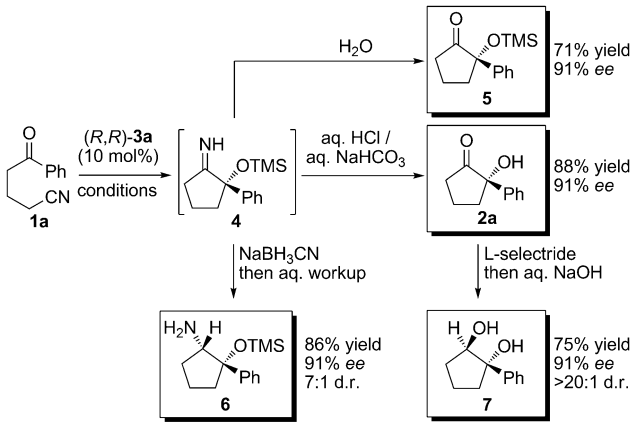
In a plausible mechanistic scenario, the low-valent titanium catalyst formed in situ first coordinates the substrate **1a** at the carbonyl group and then performs a one-electron reduction (Scheme 1). The resulting donor-stabilized radical



Scheme 1. Proposed catalytic cycle.

attacks the nitrile in an enantiodiscriminating 5-*exo* cyclization.[15] The newly formed N-centered radical is quickly reduced and the resulting titanium(IV) alcoholate quenched by TMSCl to liberate the α-oxygenated imine **4**, which is then converted into the desired product during workup. The low-valent catalyst is regenerated by Zn as the terminal reductant. A possible transition state (see box) explains the stereoselectivity of this reaction. The formation of the opposite enantiomer instead would require the phenyl group to point backwards, leading to stronger interactions with the ligand.

In addition to the aforementioned results, the still TMS-protected α-hydroxyketone **5** was isolated from the reaction mixture in 71% yield and 91% *ee* (Scheme 2). Furthermore, this titanium(III) catalysis makes it possible to synthesize vicinal amino alcohols and diols with high *syn* and *anti* selectivity, respectively. For example, when the reaction mixture was directly added to sodium cyanoborohydride in methanol, the corresponding TMS-protected *syn*-amino alcohol **6** was obtained in high diastereomeric ratio (7:1 d.r.). This



Scheme 2. Stereoselective synthesis of 1,2-difunctionalized derivatives.

also proves that the postulated imine **4** is indeed the primary product of the catalysis. Along these lines, α-hydroxyketone **2a** was transformed with perfect diastereoselectivity into *trans*-diol **7** by sequential reduction with L-selectride.[16] Again, no chromatographic separation was required in the synthesis of **7** starting from **1a**.

In summary, we have developed a titanium(III)-catalyzed asymmetric reductive coupling of ketones with nitriles. The cyclic α-hydroxyketone products were formed in good yield and high enantioselectivity and a number of aromatic and aliphatic substitution patterns, heterocyclic groups, and annulated rings were tolerated. The reaction was applied to the stereoselective synthesis of tertiary *syn*-amino alcohols and *trans*-diols. In most cases the isolation of analytically pure product was possible by a simple and practical extraction procedure. Our ongoing investigations now focus on the elucidation of the reaction mechanism and the development of related cyclizations.

Experimental Section

Representative procedure: A 10 mL Schlenk tube closed with a rubber septum and containing a magnetic stir bar was evacuated, heated with a heat gun for one minute, and backfilled with argon. Triethylamine hydrochloride (55 mg, 0.4 mmol, 2.0 equiv) was added, followed by zinc dust (26.2 mg, 0.4 mmol, 2.0 equiv) and catalyst **3a** (7.7 mg, 0.02 mmol, 10 mol%). Stirring was started and the tube was evacuated again for one minute and backfilled with argon. Degassed THF (0.5 mL, tolerated water content: 10–300 ppm) was added and the mixture stirred until the color of the mixture changed (ca. 1–2 min) from red to green (depending on the water content). Substrate **1a** (34.6 mg, 0.2 mmol) was quickly added followed by chlorotrimethylsilane (76 μL, 0.6 mmol, 3.0 equiv). The septum was replaced by a greased glass stopper and a metal clip and the mixture was stirred for 24 h at room temperature (23 °C). Dichloromethane (1 mL) was added to the reaction and the mixture was transferred to a separatory funnel containing 15 mL of ice-cold aq. 1N HCl and 40 mL of ice-cold diethyl ether. The reaction vessel was rinsed with an additional 2 mL of cold diethyl ether. The mixture was briefly shaken and the aqueous layer quickly separated and collected. This aqueous extraction was repeated six times. The collected aqueous layers were stirred until the deprotection was complete by TLC (about 5–10 min) then carefully neutralized to pH 8 (sat. aq. $NaHCO_3$) and extracted with dichloromethane (3 × 10 mL). The dichloromethane layer was dried (Na_2SO_4), filtered, and concentrated to yield the analytically pure product **2a** in 88% yield and 91% *ee*.

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[11] We believe that coordination of the hydrochloride to the catalyst takes place resulting in the observed effect. See also: A. Gansäuer, M. Behlendorf, D. von Laufenberg, A. Fleckhaus, C. Kube, D. V. Sadasivam, R. A. Flowers II, *Angew. Chem.* **2012**, *124*, 4819 – 4823; *Angew. Chem. Int. Ed.* **2012**, *51*, 4739 – 4742. For detailed information on the screening of additives, see the Supporting Information.

[12] The cyclization can take place in the abscence of a Ti catalyst, but harsher conditions (20 equiv Zn, 6 equiv TMSCl, lutidine, reflux in THF) are required (see Ref. [2f]).

[13] The absolute configuration was determined for (*S*)-**2a** and (*S*)-**2m** by asymmetric dihydroxylation and subsequent oxidation of 1-phenylcyclopentene and 1-phenylcyclohexene, respectively. In addition, the specific optical rotations matched literature reports (see Ref. [6d]). The absolute configuration of **2j** was assigned by CD spectroscopy (see the Supporting Information).

[14] In general, the size of the α-substituent and the newly formed ring appear to influence the coordination of the substrate to the catalyst and thus the enantioselectivity. In the case of **2n**, hydrogen bonding might have an additional effect.

[15] Additional activation of the nitrile by the catalyst is also possible. For details, see: A. Fernández-Mateos, P. H. Teijón, L. M. Burón, R. R. Clemente, R. R. González, *J. Org. Chem.* **2007**, *72*, 9973 – 9982.

[16] The relative configuration of **6** was confirmed by a NOESY experiment. Product **7** and the corresponding *syn*-diol were independently synthesized to assign the relative configuration (see the Supporting Information).

