Titanium(III)-Catalyzed Reductive Decyanation of Geminal Dinitriles by a Non-Free-Radical Mechanism

Jens Weweler, Sara L. Younas, and Jan Streuff*

Abstract: A titanium-catalyzed mono-decyanation of geminal dinitriles is reported. The reaction proceeds under mild conditions, tolerates numerous functional groups, and can be applied to quaternary malononitriles. A corresponding desulfonylation is demonstrated as well. Mechanistic experiments support a catalyst-controlled cleavage without the formation of free radicals, which is in sharp contrast to traditional stoichiometric radical decyanations. The involvement of two TiII species in the C–C cleavage is proposed, and the beneficial role of added ZnCl₂ and 2,4,6-collidine hydrochloride is investigated.

The controlled cleavage of carbon–carbon bonds is a highly topical research area and a challenge to modern transition-metal catalysis.[1–3] One particular type is the cleavage of C–CN bonds, which can be used either as an entry point for subsequent bond-constructing events,[4] or for a reductive, selective decyanation.[5,6] In this context, the reductive decyanation of geminal dinitriles provides direct access to functionalized alkynitriles from easy-to-prepare malononitrile precursors, making it a powerful alternative to conventional nitrile α-functionalizations.[7] However, only a limited number of stoichiometric examples have been reported for this transformation to date. These comprise traditional free-radical defunctionalizations with tin hydride, tris(trimethylsilyl)silane, and NHC–borane reagents as hydrogen radical donors,[8] or strongly reducing conditions with stoichiometric amounts of SmI₂/HMPA and other so-called “super-electron donors” (Scheme 1).[9,10] With the goal to close this methodological gap, we herein report a broadly applicable catalytic reductive decyanation that proceeds in the presence of a titanium(III) single-electron-transfer catalyst.[11,12] The reaction is not to be confused with free-radical nitrile translocation reactions.[13]

The catalytic decyanation was first investigated using 2-benzylmalononitrile (1a) as substrate, having both nitriles in a homobenzylcyclic position (Scheme 2). An initial optimization study showed that nitrile 2a could be obtained in a good yield of 80% after 48 h from a reaction with titanocene dichloride (10 mol%), zinc as reducing agent, and 2,4,6-collidine hydrochloride (Coll·HCl) and chlorotrimethylsilane (TMSCl) as additives in THF at 35°C. Without either additive, the yield of 2a was inferior. The reaction was highly chemoselective (spot-to-spot) and worked also for 2-phenylmalononitrile (1b), albeit with a significantly lower yield (30%) of benzyl cyanide (2b). Interestingly, it was found that adding 2b to the decyanation of 1a also greatly diminished the reaction outcome to 23% yield. Based on previous reports on titanium(III)–nitrile complexes and our experience in titanium(III) catalysis involving nitriles,[14,15] product inhibition of the catalyst was concluded. Further experimentation revealed that this inhibition could be prevented and the catalyst activity even be improved by adding zinc chloride to the decyanations, giving 82% yield for 2a and 74% yield for 2b after only 24 h. This scenario was supported by preliminary DFT calculations, which confirmed the product inhibition and the liberation of the inhibited catalyst upon addition of ZnCl₂.[16] Only traces of the...
decyanation product were observed without the titanium catalyst.

Several malononitriles were then decyanated accordingly on 0.5 mmol scale with a simple filtration as a sufficient workup procedure (Scheme 3). The reaction showed an unusually broad substrate scope for a C–CN cleavage method. For example, decyanation at a homobenzyllic position proceeded smoothly in the presence of bromo (2c), ester (2d), acetoxy (2e), nitrile (2f), thioether (2g), ether and free alcohol functions (2h). The arylated malononitriles 1i and 1j, containing trifluoromethyl and methoxy groups, also underwent the decyanation to the corresponding benzyl nitriles 2i and 2j in 44% and 70% yield, respectively. Likewise, an ortho-tolylmalononitrile was monodecyanated in 71% yield (2k). Symmetric and unsymmetric quaternary malononitriles could be employed as well, which led to nitriles 2l–2n (54–88%). Here, the increased steric hindrance led to a lower reaction, which was compensated by a prolonged reaction time of 48 h. Other structurally diverse substrates containing cyclohexyl and indole groups smoothly underwent the decyanation to the corresponding nitriles 2o and 2p. Malononitriles containing a styryl moiety or a β-vinyl group were decyanated to give 2q and 2r in 72% and 42% (48 h) yield, respectively. The catalytic reductive decyanation reaction of 1a was also demonstrated on a 9 mmol (1.4 g) scale, resulting in a slightly lower yield (70%).

We also tested whether the reaction could be extended towards the removal of a different functional group, and it was found that α-cyanosulfone 3 indeed underwent clean desulfonylation to 2a in 56% yield (Scheme 4). As thiophenol was observed as a byproduct, the amounts of zinc and hydrochloride were increased to compensate for the additional sulfone reduction and thiolate protonation. Unreacted 3 accounted for the mass balance, and no background reaction took place. The further elaboration of this catalytic desulfonylation will be reported separately.

A series of experiments were then carried out to elucidate the decyanation mechanism. Geminal dinitriles with a tethered pent-4-en-1-yl group were previously reported to readily undergo 5-exo-trig cyclization after a homolytic C–CN cleavage under free-radical conditions.[8b,c] The titanium(III) catalysis, however, led to exclusive decyanation of compound 4 to nitrile 5 without the generation of the cyclization product 6 (Scheme 5a). Further proof of a non-free-radical mecha-

Scheme 3. Scope of the catalytic C–CN cleavage reaction.

Scheme 4. Titanium(III)-catalyzed desulfonylation.

Scheme 5. a) Negative radical clock experiments. b) Deuteration experiment confirming the introduction of the new hydrogen by proton transfer.
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Coll·HCl led to a shift in the equilibria connecting all species towards the catalyst monomer. We attributed this to the formation of [CollH]·[ZnCl₂(THF)] from Coll·HCl and ZnCl₂(THF), which was calculated to release ΔG = −8.5 kcal mol⁻¹.[16] Whether the addition of ZnCl₂ also has a beneficial effect on the catalyst reduction step, as recently found for a titanium(III) catalysis with Cp*TiCl₃,[25] was not investigated at this time.

A first mechanistic proposal was derived (Scheme 6), in which the geminal dinitrile coordinates two equivalents of in situ generated [Cp₃TiCl] (A), giving complex B. Then, analysis then revealed the order in catalyst by time normalization.[17] A plot of the yield versus t × [cat]² was led to an excellent overlay of the two curves, which confirmed the second order in the catalyst.

We also investigated the direct effect of the added ZnCl₂ on the titanium(III) catalyst by cyclic voltammetry (Figure 2). The voltammograms of Zn-reduced Cp₃TiCl₃ were recorded in the presence of Coll·HCl, ZnCl₂, or Coll·HCl and ZnCl₂ (each in tenfold excess to simulate the conditions of the catalysis). With added Coll·HCl, the ion pair [CollH]·[Cp₃TiCl₃]⁺ (E = −1.25 V) and the dimer [[Cp₃TiCl]₂] (E = −0.81 V) were observed.[16–20] Usually, Zn-reduced solutions of Cp₃TiCl₃ also show the monomer [Cp₃TiCl] (E = −0.75 V),[20] which appeared to be absent under these conditions. With added ZnCl₂, however, the cation [Cp₃Ti⁺] (E = −0.43 V)[20] became the only observable species.[21] This was in agreement with the earlier proposal that [Cp₃TiCl] and ZnCl₂ form a closely bound ion pair in solution.[16–21] Based on previous studies on cationic titanium(III) species, we concluded that this ion pair was [Cp₃Ti⁺][ZnCl₂].[21] When Coll·HCl and ZnCl₂ were added simultaneously, the oxidation peak of [Cp₃Ti⁺] vanished again and [Cp₃TiCl] appeared as the only visible species.[20–21] Hence, the combination of single electron transfer (SET) from both titanium(III) centers triggers the C–C cleavage, giving one equivalent of keteniminium–titanium(IV) complex C and N-coordinated titanium(IV) cyanide complex D or, alternatively, its C-coordinated isomer. The participation of two titanium(III) species in the C–CN scission is in agreement with the observed second order in catalyst and the non-free-radical behavior. Prototization of C by Coll·HCl then releases the nitrile product and Cp₃TiCl₂ (E). The reaction of D with TMSCl simultaneously liberates the second equivalent of E and formally one equivalent of TMSCN. The formation of cyanide [presumably TMSCN or Zn(CN)₂] was confirmed by ion chromatographic analysis of the aqueous layer obtained from the workup. Finally, zinc regenerates the titanium(III) catalyst.

In conclusion, a titanium(III)-catalyzed decyanation of geminal dinitriles has been developed that represents the first example of such a decyanation reaction proceeding by single-electron-transfer catalysis. The reaction occurs under mild conditions, features a broad substrate scope, and shows excellent chemoselectivity. It has been demonstrated that the cleavage does not proceed through a free-radical mechanism but via a unique catalyst-controlled C–CN scission involving two titanium species, which renders it complementary to previous decyanation protocols. Further applications towards other C–C and C–heteroatom bond cleavage reactions are currently being studied and will be reported in due course.
is usually not present in solutions of zinc-reduced but generated during the CV measurement; see [8].

For recent examples, see: a) Y. Chengbo, T. Dahmen, A. Ganssäuer, J. Norton, Science 2019, 364, 764 – 767; b) T. Liedtke, T. Hille, S. Klar, A. Ganssäuer, ChemSusChem 2019, 12, 3166 – 3171; c) L. H. Leijendecker, J. Weweler, T. M. Leuther, D. Kratzert, J. Streuff, Chem. Eur. J. 2019, 25, 3382 – 3390; d) Z. Zhang, R. B. Richrath, A. Ganssäuer, ACS Catal. 2019, 9, 3208 – 3212; e) X. Wu, W. Hao, K.-Y. Ye, B. Jiang, G. Pombar, Z. Song, S. Lin, J. Am. Chem. Soc. 2018, 140, 14836 – 14843; f) T. Liedtke, P. Spanring, L. Riccardi, A. Ganssäuer, Angew. Chem. Int. Ed. 2018, 57, 5006 – 5010; Angew. Chem. 2018, 139, 5100 – 5104; g) R. B. Richrath, T. Olyschiuger, S. Hildebrandt, D. G. Enny, G. D. Fianu, R. A. Flowers II, A. Ganssäuer, Chem. Eur. J. 2018, 24, 6371 – 6379; h) V. K. Chenniappan, S. Silwai, R. J. Rahaim, ACS Catal. 2018, 8, 4539 – 4544; i) L. H. Leijendecker, J. Weweler, T. M. Leuther, J. Streuff, Angew. Chem. Int. Ed. 2017, 56, 6103 – 6106; Angew. Chem. 2017, 129, 6199 – 6202.

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For details on the DFT calculations and the interpretation of the CV results, see the Supporting Information.

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