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Authors: Jens Weweler, Sara L. Younas, and Jan Streuff

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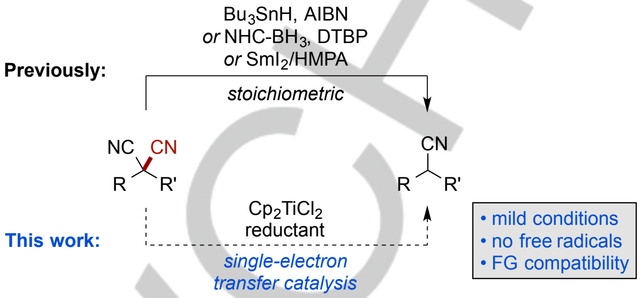
Titanium(III) Catalyzed Reductive Decyanation of Geminal Dinitriles by a Non-Free Radical Mechanism

Jens Weweler,[a] Sara L. Younas[a] and Jan Streuff*[a]

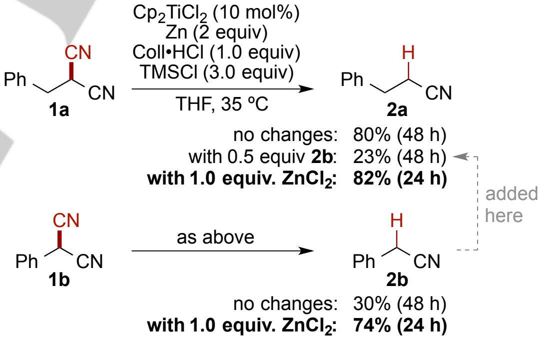
Abstract: A titanium catalyzed mono-decyanation of geminal dinitriles is reported. The reaction proceeds under mild conditions, tolerates numerous functional groups, and can be applied to quaternary malononitriles. A corresponding desulfonylation is demonstrated as well. Mechanistic experiments support a catalyst-controlled cleavage without the formation of free radicals, which is in sharp contrast to traditional stoichiometric radical decyanations. The involvement of two Ti^{III} species in the C-C cleavage is proposed and the beneficial role of added $ZnCl_2$ and Coll•HCl 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 alkylnitriles 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-trimethylsilylsilane, and NHC-borane reagents as hydrogen radical donors,[8] or strong reducing conditions with stoichiometric amounts of SmI_2/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 in 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 homobenzylic 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 ºC. 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%) in 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 improved if zinc chloride was added 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 by the addition of $ZnCl_2$.[16] Only traces of the decyanation product were observed without the titanium catalyst.



Scheme 1. Free radical decyanations and the envisioned titanium(III) catalysis.



Scheme 2. Initial optimization studies.

Several malononitriles were then decyanated accordingly on a 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, the decyanation at a homobenzylic position proceeded smoothly in presence of bromo (**2c**), ester (**2d**), acetoxy (**2e**), nitrile (**2f**), thioether (**2g**), ether and free alcohol functions (**2h**). 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 mono-decyanated in 71% yield (**2k**). Symmetric and unsymmetric quaternary malononitriles could be employed as well, which led to the nitriles **2l**–**2n** (54–88%). Here, the increased steric hindrance led to a slower reaction, which was compensated by a prolonged reaction time of 48 h. Other structurally diverse substrates containing cyclohexyl and indole groups smoothly underwent the

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[a] J. Weweler, S. L. Younas, Dr. J. Streuff
Institut für Organische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstr. 21, 79104 Freiburg im Breisgau, Germany
E-mail: jan.streuff@ocbc.uni-freiburg.de

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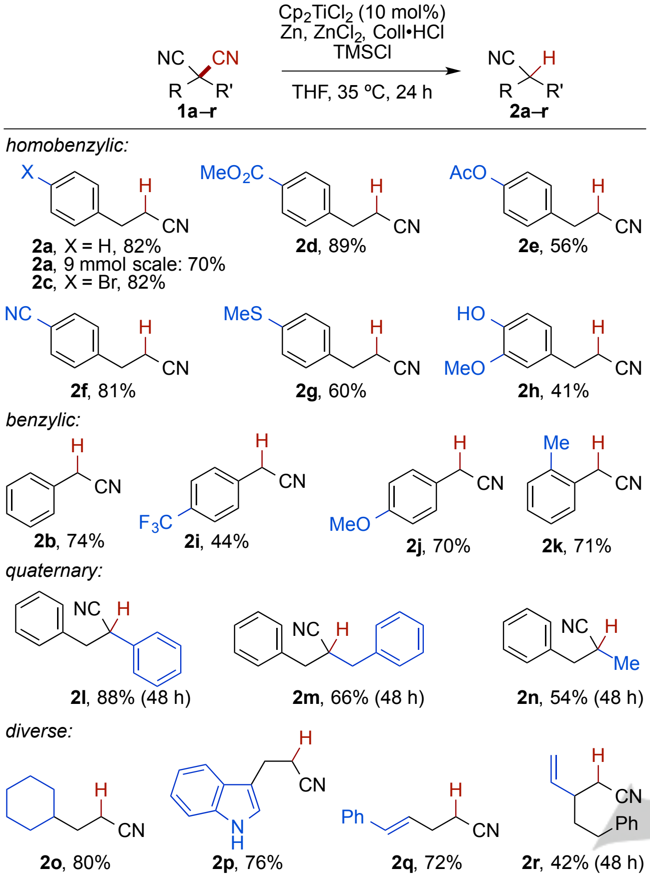
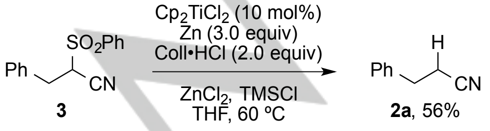


Scheme 3. Scope of the catalytic C-CN cleavage reaction.

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%).

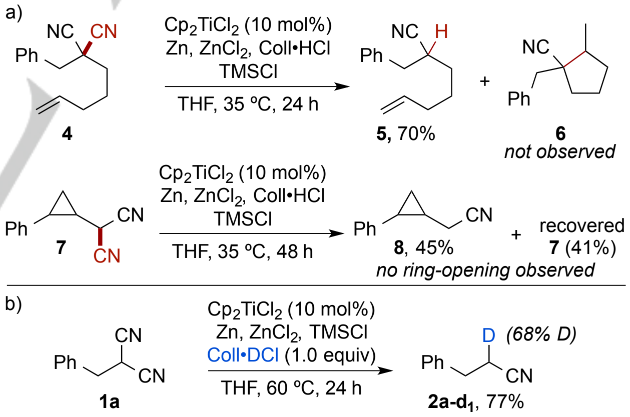
We also tested whether he reaction could be extended towards the removal of a different functional group and it was found that α-cyanosulfone **3** did indeed undergo a clean desulfonylation to **2a** in 56% yield (Scheme 4). Since thiophenol was observed as a byproduct, the amounts of zinc and hydrochloride 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.



Scheme 4. Titanium(III) catalyzed desulfonylation.

A series of experiments was 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 a 5-exo-trig cyclization after a homolytic C-CN cleavage under free radical conditions.[8b,c] The titanium(III) catalysis, however, led to an 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 mechanism was unambiguously obtained by the decyanation of radical clock substrate **7** that only led to the desired nitrile **8** without any formation of ring-opening products. The decyanation of **1a** was then carried out with 94%-deuterated Coll•DCl to confirm that the newly introduced hydrogen atom was transferred via a proton transfer from the collidinium salt. A 68% deuterium incorporation was achieved, while a reaction with Coll•HCl run in THF-d$_8$ as solvent resulted in no deuterium transfer. Next, the order in catalyst was determined from two experiments run with 5.0 and 12.5 mol% Cp$_2$TiCl$_2$ on a 4 mmol scale that were followed by NMR analysis of taken samples (Figure 1). A visual kinetic analysis then revealed a second order in catalyst by time normalization.[17] A plot yield vs. $t\,[\mathrm{cat}]^{2.0}$ led to an excellent overlay of the two curves, which confirmed a second order in the catalyst.

We also investigated the direct effect of added ZnCl$_2$ on the titanium(III) catalyst by cyclic voltammetry (Figure 2). The voltammograms of Zn-reduced Cp$_2$TiCl$_2$ were recorded in the presence of Coll•HCl, ZnCl$_2$, or Coll•HCl and ZnCl$_2$ (each in a ten-fold excess to simulate the conditions of the catalysis). With added Coll•HCl, the ion pair [CollH]$^+$ [Cp$_2$TiCl$_2$]$^-$ ($E = -1.25$ V)



Scheme 5. a) Negative radical clock experiments. b) Deuteration experiment confirming the introduction of the new hydrogen via proton transfer.

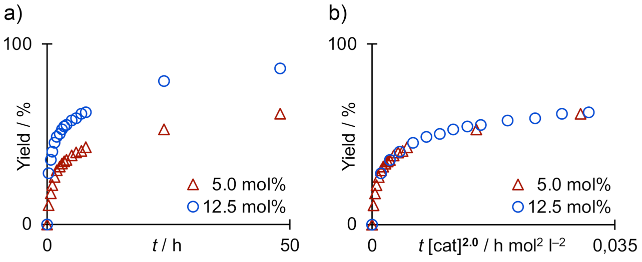


Figure 1. a) Reaction kinetics of experiments with 5 and 12.5 mol% catalyst. b) Variable time normalization analysis revealing a catalyst order of 2.0.

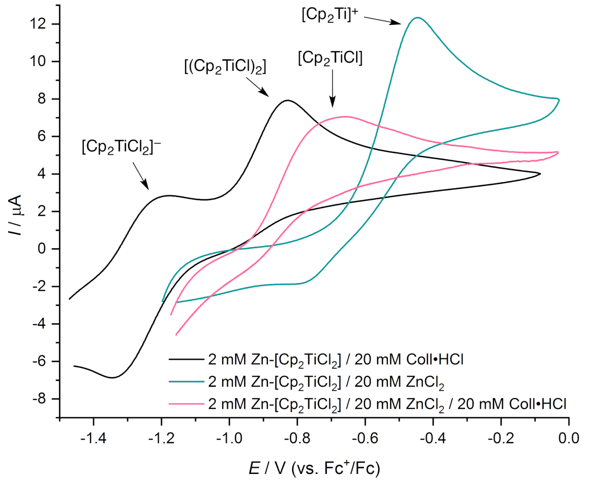
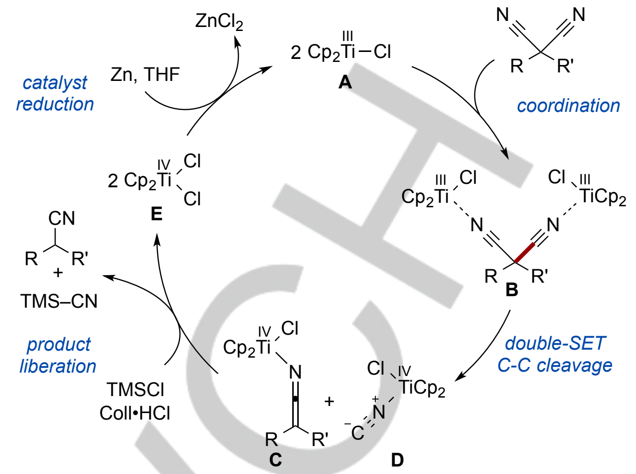


Figure 2. Cyclic voltammograms of Zn-Cp_2TiCl_2 with added Coll•HCl, added $ZnCl_2$, and added $ZnCl_2$ and Coll•HCl, all at a sweep rate of 0.1 V s^{-1}.



Scheme 6. Proposed simplified catalytic cycle.

and the dimer $[(Cp_2TiCl)_2]$ ($E = -0.81$ V) were observed.[18–20] Usually, Zn-reduced solutions of Cp_2TiCl_2 also show the monomer $[Cp_2TiCl]$ ($E = -0.75$ V),[20] which appeared to be absent under these conditions. With $ZnCl_2$ added, however, the cation $[Cp_2Ti]^+$ ($E = -0.43$ V)[20] became the only observable species.[21] This was in agreement with the earlier proposal that $[Cp_2TiCl]$ and $ZnCl_2$ form a closely bound ion pair in solution.[22,23] Based on previous studies on cationic titanium(III) species, we concluded that this ion pair was $[Cp_2Ti]^+ [ZnCl_3]^-$.[12g,15] If Coll•HCl *and* $ZnCl_2$ were simultaneously added, the oxidation peak of $[Cp_2Ti]^+$ vanished again and $[Cp_2TiCl]$ appeared as only visible species.[20,21] Hence, the combination of Coll•HCl and $ZnCl_2$ led to a shift of the equilibria connecting all species towards the active catalyst monomer. We attributed this to the formation of $[CollH]^+ [ZnCl_3(THF)]^-$ from Coll•HCl and $ZnCl_2(THF)_2$, which was calculated to release $\Delta G = -8.5$ kcal mol^{-1}.[16] Whether the addition of $ZnCl_2$ also has a beneficial effect on the catalyst reduction step, as recently found for a titanium(III) catalysis with Cp^*TiCl_3,[12e] was not investigated at this time.

A first mechanistic proposal was derived (Scheme 6), in which the geminal dinitrile coordinated two equivalents of in situ generated $[Cp_2TiCl]$ (**A**), giving complex **B**. Then, the single-electron-transfer (SET) from both titanium(III) centers triggered the C-C cleavage, giving one equivalent of ketenimine-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 was in agreement with the observed second order in catalyst and the non-free radical behavior. A protonation of **C** by Coll•HCl then released the nitrile product and Cp_2TiCl_2 (**E**). The reaction of **D** with TMSCl simultaneously liberated the second equivalent of **E** and formally one equivalent of TMSCN. The formation of cyanide [presumably TMSCN or $Zn(CN)_2$] was confirmed by an ion chromatographic analysis of the aqueous layer obtained from the workup. Finally, zinc regenerated 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 via single-electron-transfer catalysis. The reaction proceeds under mild conditions, can be applied to a broad substrate scope, and it shows an excellent chemoselectivity. It has been demonstrated that the cleavage does not proceed via 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 ongoing and will be reported in due course.

Acknowledgements

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Keywords: C-C activation • catalysis • cyanides • electron transfer • titanium

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[23] $[Cp_2Ti]^+$ is usually not present in solutions of zinc-reduced Cp_2TiCl_2 but generated during the CV measurement, see ref. 20. In our case, however, the presence of ten catalyst equivalents of $ZnCl_2$ led to the exclusive formation of $[Cp_2Ti]^+$.

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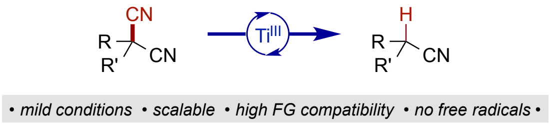

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