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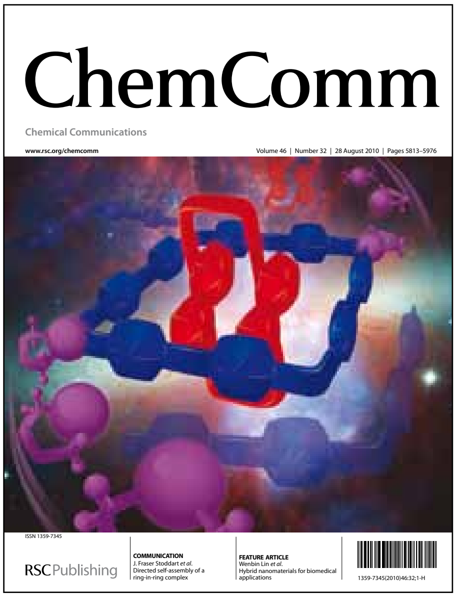

ChemComm
Chemical Communications
www.rsc.org/chemcomm
Volume 46 | Number 32 | 28 August 2010 | Pages 5813–5976
ISSN 1359-7345
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ARTICLE TYPE

The cross-selective titanium(III)-catalysed acyloin reaction

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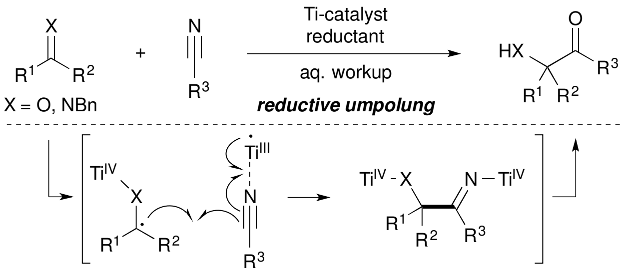
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

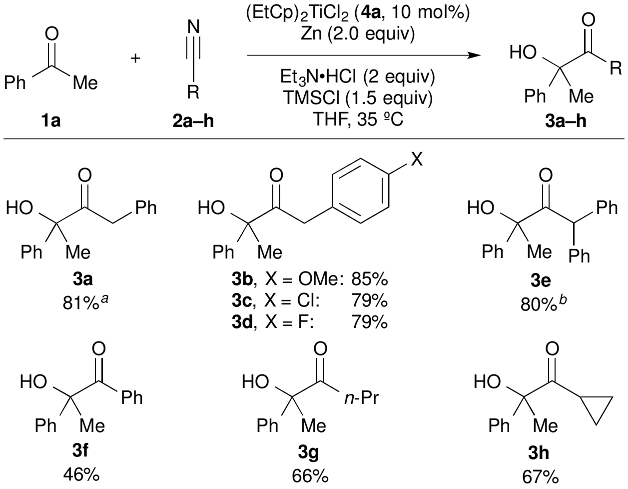
A titanium(III)-catalysed intermolecular reductive coupling of ketones or imines with nitriles is described, which gives direct access to α-hydroxylated and α-aminated ketones. This coupling reaction is cross-selective and a catalytic version of the classical acyloin condensation. A reaction mechanism that is supported by first DFT calculations is discussed.

The acyloin condensation reaction allows the formation of α-hydroxyketones (acyloins) by C-C coupling of two esters in the presence of sodium metal in liquid ammonia.[1] It is a so-called reductive "umpolung" reaction,[2] a process that enables the connection of similarly polarised coupling partners by single-electron transfer. In the past, the use of other stoichiometric reducing agents and electrochemical setups enabled the development of related intramolecular acyloin reactions,[3,4] but an intermolecular reductive cross-coupling was achieved only in a few cases.[5] Despite the usefulness of this reaction to access valuable building blocks, no corresponding catalysis has been developed with the exception of intramolecular cyclisations by our group.[6]

We herein report a catalytic intermolecular acyloin-type cross-coupling in the presence of a low-valent titanium catalyst (Scheme 1),[7] which connects various ketones or imines with nitriles for the direct construction of unsymmetrical α-hydroxy- and α-aminoketones. The reaction is highly cross-selective and the competing pinacol-type homo dimerisation of the ketone or imine is suppressed.[2b] In addition, this titanium catalysis installs tetrasubstituted α-carbons, which was particularly challenging in the synthesis of α-oxygenated or α-aminated carbonyls using alternative protocols such as organocatalysed benzoin-type couplings, for instance.[8] We propose that the mechanism proceeds via a single electron transfer to the carbonyl or imine, followed by a C-C bond forming radical coupling to the nitrile.



Scheme 1 Concept of a titanium-catalysed intermolecular acyloin reaction.



Scheme 2 Ti-catalysed cross-coupling of acetophenone with various nitriles. Conditions: **1a** (0.5 mmol), **2** (5 equiv), **4a** (10 mol%), zinc (2 equiv), TMSCl (1.5 equiv), Et_3N•HCl (2.0 equiv), abs. THF (c = 1.0 M), 35 ºC, 48 h; TBAF (1 M in THF) then H_2O. Isolated yields. [a] 24 h reaction time. [b] The reaction was quenched with TBAF (1 M in THF) followed by aq. 1 N HCl.

We explored the coupling of acetophenone (**1a**) with an excess of benzyl cyanide (**2a**, 5 equiv) as standard substrates, chlorotrimethylsilane (1.5 equiv) and triethylamine hydrochloride (2 equiv) as additives and zinc (2 equiv) as terminal reductant (Scheme 2). In first optimisation studies bis(ethylcyclopentadienyl)titanium(IV) chloride (**4a**) was identified as the most efficient catalyst.[9] Workup after 24 h led to the isolation of the desired product **3a** in 81% yield and its structure was unambiguously verified by X-ray analysis. Importantly, with a reduced excess of nitrile **2a** (1.5 equiv) still a high yield of 70% was maintained. The group of Hirao attempted this intermolecular coupling in an earlier study with titanocene dichloride (**4b**) as catalyst and imidazole as additive but no formation of **3a** was observed.[10] In our hands, these conditions were unsuccessful too and the addition of imidazole appeared to suppress the reaction.

We further investigated different nitriles in the reductive coupling with acetophenone (**1a**) as substrate (Table 2). Compared to benzyl cyanide the 4-methoxy substituted benzyl cyanide was superior (85% yield, **3b**). Chlorine or fluorine substitution resulted both in 79% yield for products **3c** and **3d**. The reaction worked equally well with the bulkier

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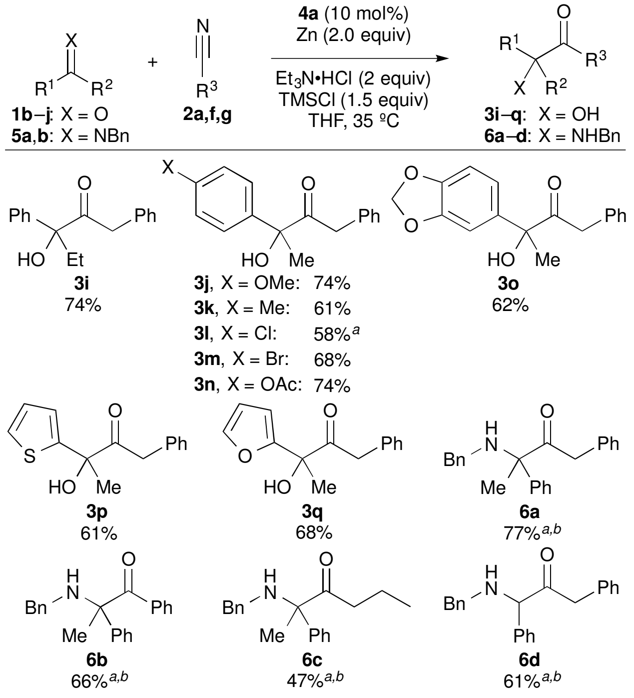
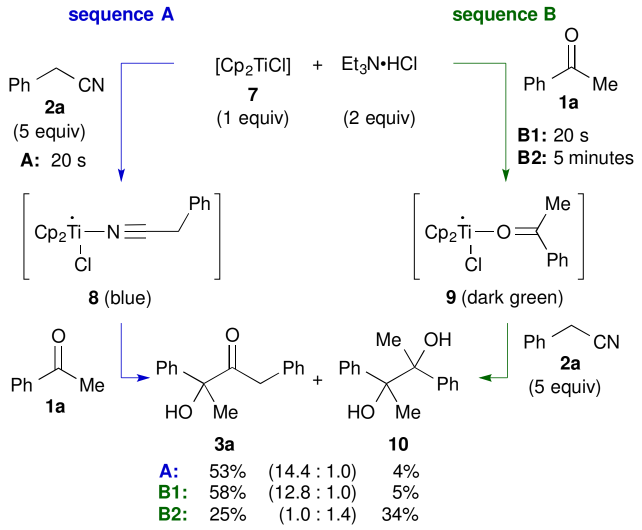


Scheme 3 Ti-catalysed acyloin reaction employing various ketones and imines. Conditions: **1** or **5** (0.5 mmol), **2** (5 equiv), **4a** (10 mol%), zinc (2 equiv), TMSCl (1.5 equiv), Et_3N•HCl (2.0 equiv), abs. THF (c = 1.0 M), 35 ºC, 48 h; TBAF (1 M in THF) then H_2O. Isolated yields. [a] With 3 equiv TMSCl. [b] With 0.5 equiv Et_3N•HCl and catalyst **4b** (10 mol%).



Scheme 4 Stoichiometric reactions with precoordination of acetophenone or benzyl cyanide. Product ratios were determined by crude NMR.

diphenylacetonitrile and delivered the corresponding product **3e** in 80% yield. With benzonitrile the reaction was slower leading to 46% of α-hydroxyketone **3f**. Aliphatic nitriles could be employed as well (**3g**, 66%) and even cyclopropyl carbonitrile was successfully transformed into the desired product **3h** in 67% yield. Here, only traces of the corresponding ring-opening product **3g** (<5%) were observed.[11] We then examined the cross-coupling of various ketones with benzyl cyanide (Scheme 3). With propiophenone instead of acetophenone 74% of the desired product **3i** was isolated. In a similar manner, acetophenones further substituted at the aromatic moiety gave good results ranging from electron rich (**3j**,**k**,**o**) to electron poor derivatives (**3l**–**n**). In case of **3l**, the addition of 3 equiv of TMSCl provided the highest yield. Heterocyclic ketones bearing a thiophenyl or furyl unit were smoothly converted to the corresponding products **3p** and **3q** (61% and 68% yield). Furthermore, we probed the direct synthesis of α-aminoketones by substitution of the ketone precursor with an imine. To our delight, the coupling proceeded in a similar fashion and aminoketones **6a**–**c** with a fully substituted α-carbon were isolated in 47–77% yield. Here, it was observed that a reduction of the amount of Et_3N•HCl to 0.5 equiv was beneficial for the reaction outcome and that titanocene dichloride (**4b**) as catalyst provided the best results.[9] The reaction also worked well with an aldimine (**6d**), which demonstrates that the reaction is not limited to ketimine precursors. In all cases no product formation was observed in absence of the catalyst.

To gain first information about the underlying reaction mechanism, experiments with stoichiometric amounts of $[Cp_2TiCl]$ (**7**) were carried out (Scheme 4). The influence of the order of addition on the product distribution was probed by mixing in situ generated **7** with benzyl cyanide (5 equiv, sequence A) or acetophenone (sequence B),[12] followed by addition of the second reaction partner. The coordination of benzyl cyanide resulted in formation of a blue complex, which matched the reported colour for titanium(III)-nitrile complexes such as **8**.[13] Subsequent addition of acetophenone (1 equiv) gave product **3a** together with a small amount of diol diastereomers **10** in a ratio of 14.4:1. The pre-coordination of acetophenone gave a dark-green solution indicating the formation of **9**, but the product ratio after subsequent addition of the nitrile was nearly the same (12.8:1) (sequence B1). Pre-stirring acetophenone with **7** for 5 minutes (sequence B2), changed this ratio in favor of **10**, indicating a competing pinacol coupling reaction of acetophenone.[14] An excess of the nitrile, suppressed this side-reaction. These results indicate an equilibrium reaction between **8** and **9**, in which ketone and nitrile compete for the coordination to the titanium.

A plausible catalytic cycle is shown in Scheme 5 with the cross-coupling of acetone with acetonitrile and **4b** as catalyst as a model system. First DFT calculations of the reaction energies on the PBE0/def2-TZVPP//BP86/def2-SV(P)-level (Gaussian 09) support this mechanistic scenario.[15–19] The SMD model was applied for the calculation of solvation energies on the BP86/def2-SV(P)-optimised structures.[20] The cycle starts with the formation of the low-valent titanium species **A** from Cp_2TiCl_2 (**G**) and zinc (Figure 3). This titanium(III)-complex coordinates the nitrile, forming an adduct **B**, which is in equilibrium with the corresponding ketone-complex **C**. Both titanium(III)-complexes (**B** and **C**) are converted in the C-C bond formation via a probably transition-state free radical combination (**D**) to complex **E**.[21] The two Ti-O bonds are subsequently cleaved by the hydrochloride and TMSCl resulting in formation of **H** as primary product. Together with the negative free energy for the reduction of two equivalents **G** to **A** the overall Gibbs free energy of this cycle was found to be negative at room temperature. This catalytic cycle is in agreement with our earlier observations[6] and the conclusions of others for related

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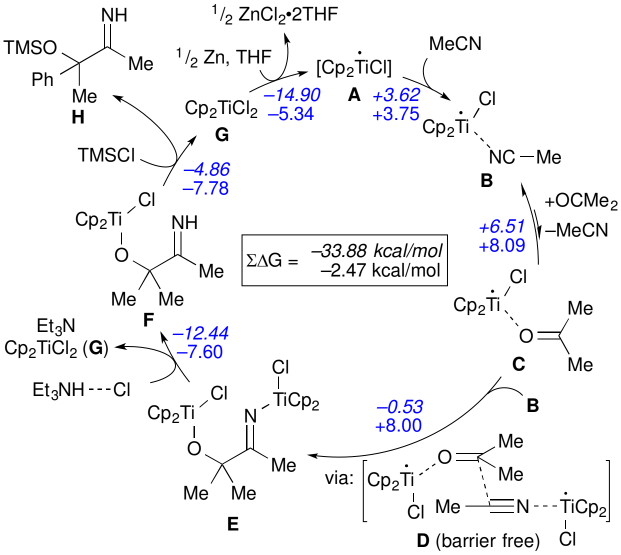

Scheme 5 Proposed mechanism and calculated energies ΔG (kcal/mol) in the gas-phase (italics) and in solution.

pinacol coupling reactions,[22] as well as for titanium catalysed radical addition reactions to carbonyls and nitriles, for which the coordination of a second Ti^{III}-species was discussed.[3c,23] The structure of Zn-reduced titanocenes **4** in solution depends in part on its bulkiness and can involve equilibria between monomeric, dimeric, and $ZnCl_2$-bridged Ti^{III}-species.[2b,7,24] In an elegant study by Daasbjerg, Grimme, Gansäuer and co-workers on the titanium(III)-catalysed opening of epoxides, a half-opened catalyst dimer was proposed in the case of **4b** to be the most reactive reducing complex.[25] In addition, the hydrochloride additive was assumed to prevent catalyst deactivation by coordination to the catalyst.[7h] Hence, the mechanism of the catalytic acyloin reaction herein could be more complex.

In conclusion, we have developed a versatile intermolecular acyloin-type cross-coupling that proceeds in the presence of a low-valent titanium catalyst and zinc as stoichiometric reductant. This methodology gives fast access to important α-hydroxyketone and α-aminoketone building blocks with a fully substituted α-carbon, which are difficult to synthesise by other ways. A plausible mechanistic scenario was presented that was supported by first DFT calculations.

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG).

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data, and NMR spectra for all new compounds and computational details. Crystallographic data in CIF or other electronic format for CCDC 948380. See DOI: 10.1039/b000000x/

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