Redox Umpolung

DOI: 10.1002/anie.201302460

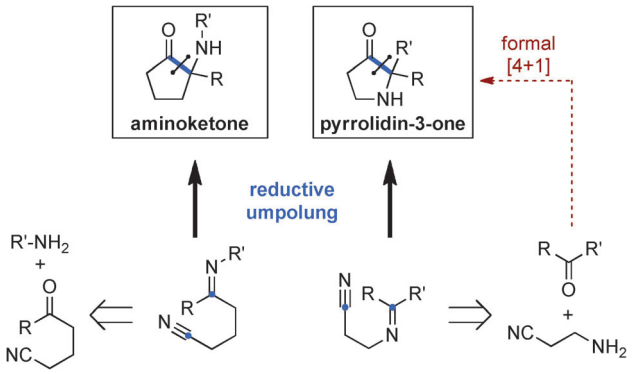
Convenient Titanium(III)-Catalyzed Synthesis of Cyclic Aminoketones and Pyrrolidinones—Development of a Formal [4+1] Cycloaddition**

*Georg Frey, Hieu-Trinh Luu, Plamen Bichovski, Markus Feurer, and Jan Streuff**

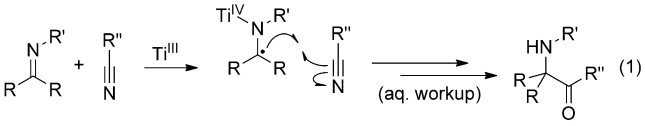
α-Aminated carbonyl compounds represent important building blocks for the synthesis of bioactive molecules.[1] Therefore, a convenient access to cyclic α-aminated ketones and the related pyrrolidin-3-one units, which are structural motifs in many natural products and pharmaceutical drug candidates, is highly desirable.[2] There are several established procedures for synthesizing these compounds,[3,4] but when full substitution at the aminated α-carbon is required, the methods for constructing these molecules are very limited.[5] To our knowledge no straightforward method for the preparation of such α-aminoketones or pyrrolidin-3-ones has been published so far.

In 2006, Oltra, Cuerva, Gansäuer, and co-workers reported a titanocene-catalyzed reductive umpolung of carbonyl compounds in a Michael-type addition.[6–8] In 2011 we established this principle for the cross-coupling of Michael acceptors to yield 1,4- or 1,6-difunctionalized products.[9] This led to the development of an enantioselective cross-coupling between ketones and nitriles[10] and more recently a Ti^{III}-catalyzed umpolung of hemiaminals was published.[11] We herein report the application of this titanium-catalyzed reductive umpolung strategy in the synthesis of aminoketone and pyrrolidinone building blocks through the direct construction of the C–C bond between the carbonyl carbon and the α-aminated carbon (Scheme 1). In this way, both motifs become available from the corresponding iminonitriles, which can be easily accessed from either commercially available or literature-known ketones by standard condensation protocols. Importantly, the sequence of ketimine formation followed by the reductive umpolung to the pyrrolidinone product represents a formal [4+1] cycloaddition, for which only few examples have been reported to date.[12,13]

Our initial idea was that a Ti^{III} catalyst (generated from a Ti^{IV} precursor and zinc metal) could be capable of promoting this transformation by a single-electron transfer to an imine and subsequent attack of the aminomethyl radical to the nitrile functionality [Eq. (1)]. Further reduction and aqueous workup would then yield the desired aminoketones.[14]



Scheme 1. Concept for the synthesis of aminoketones and pyrrolidinones by the reductive umpolung of iminonitriles.



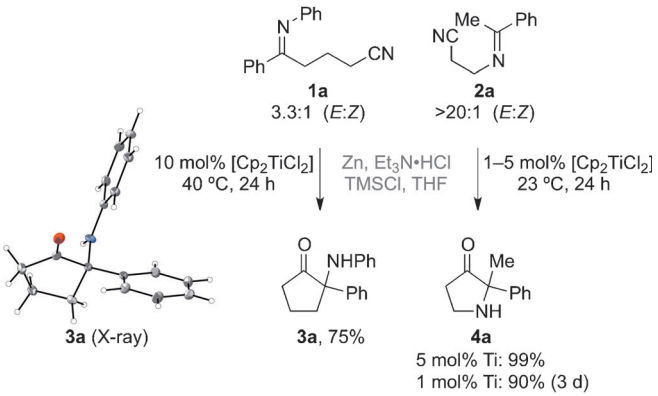
This idea was supported by several literature reports on reductive pinacol-type dimerizations of imines with a number of catalysts including $[Cp_2TiCl_2]$[7,15] and thus we started investigations towards this reductive umpolung reaction. After the first promising results, we optimized the reaction conditions for each cyclization type using substrates **1a** and **2a**.[16] Starting from iminonitrile **1a**, we found that 10 mol% $[Cp_2TiCl_2]$ and slightly elevated temperature (40 °C) were optimal to achieve high yields of aminoketone **3a** (Scheme 2). With **2a** the reaction already took place at room temperature and under these mild conditions we achieved quantitative conversion to pyrrolidinone **4a** with 5 mol% of the catalyst. With a catalyst loading of only 1 mol%, this pyrrolidinone was still isolated in 90% yield after 3 days. While this reductive cyclization already occurred in the presence of only $[Cp_2TiCl_2]$ and zinc, we noticed that the yields were typically 15–20% higher when $Et_3N{\cdot}HCl$ was added and that TMSCl had a strong beneficial effect on the reaction rate and yield.[17] Imines **1** were usually employed as isomeric mixtures and both isomers were converted smoothly to the desired product.

With the goal of developing a reliable methodology for the synthesis of α-aminoketones with a tetrasubstituted α-carbon, we tested the scope of the reaction for a variety of

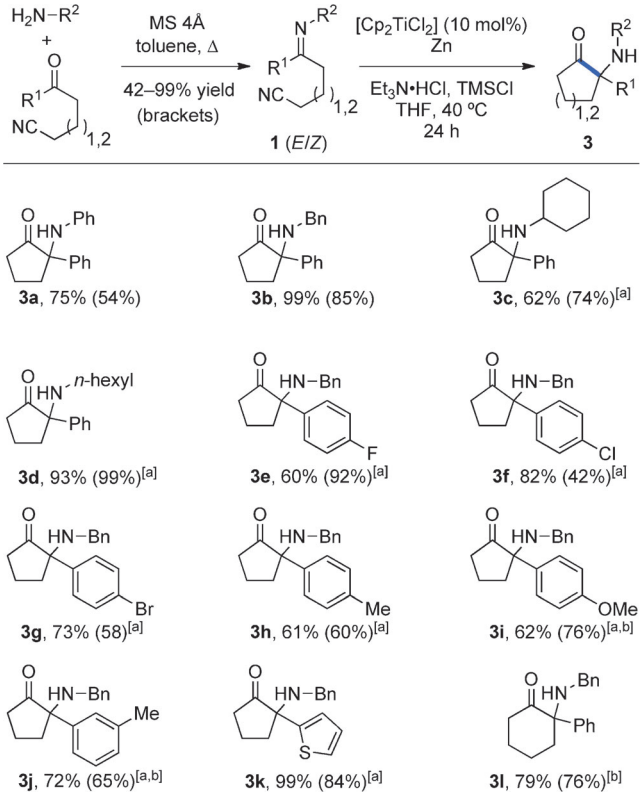
[*] G. Frey, H.-T. Luu, P. Bichovski, M. Feurer, Dr. J. Streuff
Institut für Organische Chemie und Biochemie
Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg (Germany)
E-mail: jan.streuff@ocbc.uni-freiburg.de
Homepage: http://portal.uni-freiburg.de/streuff

[**] We thank Dr. Nils Trapp for the X-ray analysis and the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302460.



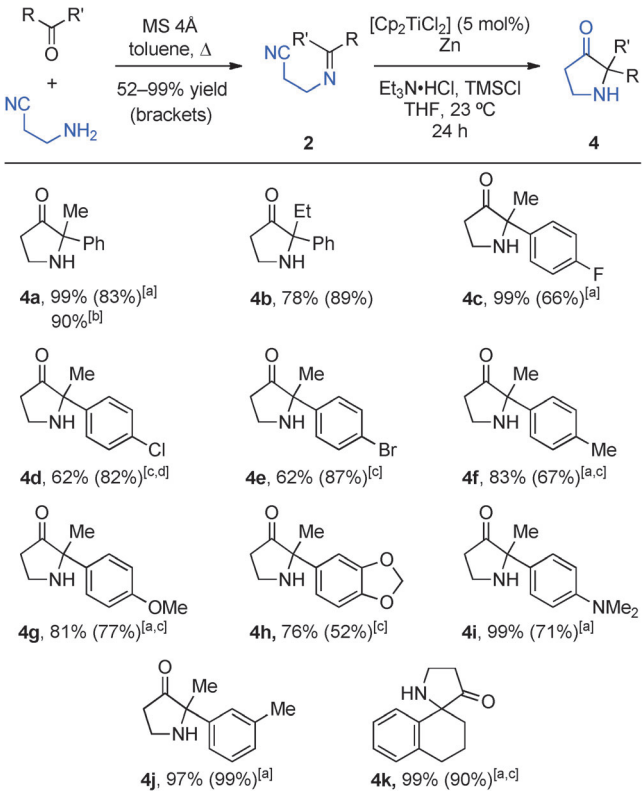
Scheme 2. First results after optimization and structural confirmation of aminoketone **3a** by X-ray analysis (thermal ellipsoids at the 50% probability level).[18]



Scheme 3. Titanium-catalyzed reductive synthesis of aminoketones. Yield of isolated product; yield of the imine formation is shown in brackets. [a] No chromatography was necessary. [b] 48 h reaction time.

imines (Scheme 3). These compounds were synthesized by condensation of the corresponding ketone with the respective amine, which usually proceeded with full conversion.[16] The reductive umpolung to form α-aminoketones **3** was then found to tolerate several substituents at the imine nitrogen. N-arylated, -benzylated, or -alkylated imines were cyclized in good to excellent yields and *N*-benzylketimine **1b** reacted quantitatively (99%). Hence, we continued exploring further variations using this group. The α-carbon could be substituted with arenes containing alkyl, alkoxy, or halogen groups (**3e–j**) as well as a heterocycle such as a 2-thiophenyl unit (**3k**). Importantly, the formation of 2-aminocyclohexanone **3l** proceeded smoothly in 79% yield and only for the cyclizations to **3i**, **3j**, and **3l** did we have to extend the reaction time to 48 h. In addition, in 9 of 12 cases our optimized protocol provided the pure products without the need for chromatography.

Afterwards, we turned our attention to the synthesis of pyrrolidinones **4** (Scheme 4). As already mentioned, these

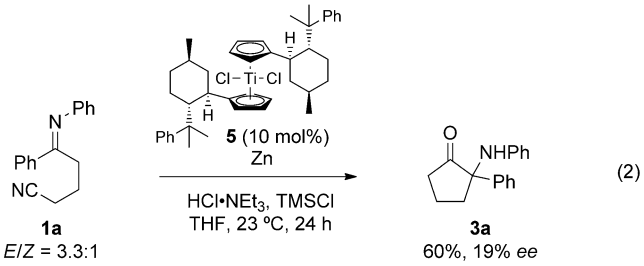


Scheme 4. Titanium-catalyzed reductive synthesis of pyrrolidinones. Formal [4+1] cycloaddition sequence. Yield of isolated product; yield of the imine formation is shown in brackets. [a] No chromatography was necessary. [b] 1 mol% catalyst, 3 d reaction time, no $Et_3N{\cdot}HCl$ added. [c] 10 mol% catalyst. [d] 48 h reaction time.

cyclizations proceeded under milder conditions, often with lower catalyst loading and quantitative yield. Together with the imine-formation step, this formal [4+1] sequence turned out to be a convenient and straightforward approach to the pyrrolidin-3-one fragment. Again, a number of substituents could be installed at the tetrasubstituted α-carbon, including various alkyl and aryl groups, with good to high yields. The fluorophenylated product **4c** was obtained in 99% yield in the presence of 5 mol% catalyst. The 4-chlorophenyl- and 4-bromophenyl-substituted products **4d,e** as well as the more electron-rich arylated products **4f–h** were obtained in good yields (62–83%) in the presence of 10 mol% titanium catalyst. Reaction with the 4-dimethylamino- and 3-methylphenyl-substituted substrates proceeded with full conversion and 97–99% yield in the presence of 5 mol% [Cp_2TiCl_2].

Even the challenging cyclization to the spirocyclic product **4k** took place, resulting in quantitative yield with 10 mol% catalyst. In summary, for both reaction types good to excellent yields were observed and simple acid–base extraction sufficed for convenient isolation of many products. It should be noted that an aryl substituent on the imine carbon was required to achieve good results.

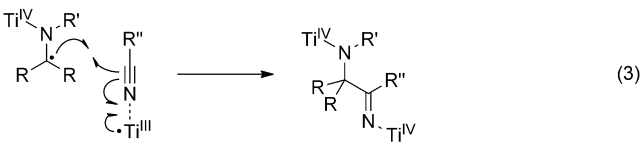
Then, we attempted the enantioselective reductive imine–nitrile coupling. After several experiments we obtained a maximum enantiomeric excess of 19% with Vollhardt's 8-phenylmenthol-derived titanocene catalyst **5** and substrate **1a**, which was used as a 3.3:1 mixture of *E*/*Z* isomers [Eq. (2)].[16,19] An experiment using stoichiometric amounts of



1a *E*/*Z* = 3.3:1 — **3a** 60%, 19% *ee* (2)

complex **5** gave similar results.[16] Other common chiral titanocene catalysts were inferior. Product **3b** arising from the corresponding benzylimine (1:1 *E*/*Z* ratio) was racemic when the same catalytic conditions were applied. Thus, one could argue that the imine configuration plays a crucial role in the asymmetric induction. But the stereoinformation is lost during the electron transfer that forms the aminomethyl radical, which we assume to take place before the enantiodiscriminating step [Eq. (1)]. We also attempted the asymmetric cyclization of **2a**, which was available exclusively as the *E* isomer. In this case, only racemic material could be obtained from these experiments. Therefore, it is likely that high enantioselectivities cannot be achieved with the conventional titanocenes and that new catalysts will have to be designed.

During our initial experiments, we did not observe any cyclization products in the absence of the titanium catalyst, even when catalytic amounts of $ZnCl_2$ were added.[16] Together with our observations of color change upon substrate addition to the preformed catalyst, the above results confirm that substrate coordination to the catalyst takes place and is necessary for the product formation to occur. This is interesting, since the Ti–N bond is significantly weaker than a Ti–O bond ($\Delta\Delta H_f^{298} = 47$ kcal mol^{-1}),[20] which plays a key role in other Ti^{III}-catalyzed reactions.[8] In addition to the initial concept shown in Equation (1), it is possible that the nitrile group is activated by a second titanium(III) species, resulting in the coordination of two titanium(IV) complexes to the product [Eq. (3)]. This was discussed for the Ti^{III}-catalyzed radical additions to nitriles after epoxide opening,[21] which is proposed to be similar to the activation of carbonyls by a Ti^{III} catalyst in Barbier-type allylations and related reactions.[22]



(3)

The fact that the cyclization of **1a** results in a lower yield with bulkier catalyst **5** could point further in that direction, because coordination of a second titanocene to the substrate would be significantly hampered in this case. We assume that the title reaction is titanium(III)-catalyzed because the initial species formed in the reduction with zinc is the well-known lime-green [Cp_2TiCl] dimer. Nevertheless, it should be noted that a titanium(II) isopropoxide alkene complex was found to promote the coupling of *N*-propylbenzaldimine with propionitrile in stoichiometric experiments.[14]

In conclusion, a convenient reductive imine–nitrile coupling was developed that provides direct access to α-aminated ketones and pyrrolidin-3-ones with tetrasubstituted α-carbons. In the latter case, the sequence of imine formation and reductive umpolung cyclization represents a formal [4+1] cycloaddition. We are now developing new catalysts for the asymmetric reaction and expanding this methodology to further substrate classes.

Received: March 24, 2013
Published online: June 5, 2013

Keywords: catalysis · radical reactions · reduction · titanium · umpolung

[1] For reviews, see: a) A. Russo, C. D. Fusco, A. Lattanzi, *RSC Adv.* **2012**, *2*, 385–397; b) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637–1656; c) T. Vilaivan, W. Bhanthumnavin, *Molecules* **2010**, *15*, 917–958; d) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584–4671; e) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364–4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292–4300; f) E. Erdik, *Tetrahedron* **2004**, *60*, 8747–8782; g) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377–1385.

[2] Selected examples: a) M. A. H. Ismail, M. N. Aboul-Enein, K. A. M. Abouzid, D. A. A. E. Ella, N. S. M. Ismail, *Bioorg. Med. Chem.* **2009**, *17*, 3739–3746; b) T. Yasuzawa, T. Iida, K. Muroi, M. Ichimura, K. Takahashi, H. Sano, *Chem. Pharm. Bull.* **1988**, *36*, 3728–3731; c) S. M. Nasirov, L. G. Kuz′mina, Y. T. Struchkov, I. A. Israilov, M. S. Yunusov, S. Y. Yunusov, *Chem. Nat. Compd.* **1980**, *16*, 55–60; d) R. H. F. Manske, R. Rodrigo, D. B. MacLean, D. E. F. Gracey, J. K. Saunders, *Can. J. Chem.* **1969**, *47*, 3585–3588; e) Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, T. Harayama, *Chem. Pharm. Bull.* **1968**, *16*, 82–91.

[3] For leading references, see: a) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097; b) D. A. DiRocco, T. Rovis, *Angew. Chem.* **2012**, *124*, 6006–6008; *Angew. Chem. Int. Ed.* **2012**, *51*, 5904–5906; c) R. Matsubara, S. Kobayashi, *Angew. Chem.* **2006**, *118*, 8161–8163; *Angew. Chem. Int. Ed.* **2006**, *45*, 7993–7995; d) A. Villar, C. H. Hövelmann, M. Nieger, K. Muñiz, *Chem. Commun.* **2005**, 3304–3306; e) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361; f) S. K.-Y. Leung, J.-S. Huang, J.-L. Lang, C.-M. Che, Z.-Y. Zhou, *Angew. Chem.* **2003**, *115*, 354–357; *Angew. Chem. Int. Ed.* **2003**, *42*, 340–343; g) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; h) J.-L. Liang, X.-Q. Yu, C.-M. Che, *Chem. Commun.* **2002**, 124–125; i) D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753; j) S. Lociuro, L. Pellacani, P. A. Tardella,

Tetrahedron Lett. **1983**, *24*, 593 – 596; k) P. W. Neber, A. v. Friedolsheim, *Liebigs Ann. Chem.* **1926**, *449*, 109 – 134; l) P. Rabe, K. Kindler, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 466 – 467.

[4] Selected references: a) R. Akue-Gedu, P. Gautret, J.-P. Lelieur, B. Rigo, *Synthesis* **2007**, 3319 – 3322; b) S. Berlin, C. Ericsson, L. Engman, *J. Org. Chem.* **2003**, *68*, 8386 – 8396; c) A. Westerlund, J.-L. Gras, R. Carlson, *Tetrahedron* **2001**, *57*, 5879 – 5883; d) A. Hirshfeld, W. Taub, E. Glotter, *Tetrahedron* **1972**, *28*, 1275 – 1287.

[5] a) F.-g. Sun, S. Ye, *Org. Biomol. Chem.* **2011**, *9*, 3632 – 3635; b) K.-J. Wu, G.-Q. Li, Y. Li, L.-X. Dai, S.-L. You, *Chem. Commun.* **2011**, *47*, 493 – 495; c) J. Robertson, A. J. Tyrrell, P. T. Chovatia, S. Skerratt, *Tetrahedron Lett.* **2009**, *50*, 7141 – 7143; d) X.-W. Sun, W. Wang, M.-H. Xu, G.-Q. Lin, *Tetrahedron Lett.* **2008**, *49*, 5807 – 5809; e) A. Alex, B. Larmanjat, J. Marrot, F. Couty, O. David, *Chem. Commun.* **2007**, 2500 – 2502; f) J. L. Moore, M. S. Kerr, T. Rovis, *Tetrahedron* **2006**, *62*, 11477 – 11482; g) D. A. Evans, D. S. Johnson, *Org. Lett.* **1999**, *1*, 595 – 598; h) R. S. Atkinson, E. Barker, P. J. Edwards, G. A. Thomson, *Tetrahedron Lett.* **1994**, *35*, 7863 – 7866; i) J. K. Crandall, T. Reix, *Tetrahedron Lett.* **1994**, *35*, 2513 – 2516; j) D. Desmaële, N. Champion, *Tetrahedron Lett.* **1992**, *33*, 4447 – 4450; k) J. Patjens, R. Ghaffari-Tabrizi, P. Margaretha, *Helv. Chim. Acta* **1986**, *69*, 905 – 907; l) D. G. Farnum, G. R. Carlson, *Synthesis* **1972**, 191 – 192; m) C. Sandris, G. Ourisson, *Bull. Soc. Chim. Fr.* **1958**, 345 – 349.

[6] R. E. Estévez, J. L. Oller-López, R. Robles, C. R. Melgarejo, A. Gansäuer, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2006**, *8*, 5433 – 5436.

[7] For a review on metal-catalyzed reductive umpolung reactions, see: J. Streuff, *Synthesis* **2013**, *45*, 281 – 307.

[8] For selected reviews on Ti^{III}-mediated and -catalyzed reactions, see: a) B. Rossi, S. Prosperini, N. Pastori, A. Clerici, C. Punta, *Molecules* **2012**, *17*, 14700 – 14732; b) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 121 – 189; c) A. Gansäuer, J. Justicia, C.-A. Fan, D. Worgull, F. Piestert, *Top. Curr. Chem.* **2007**, *279*, 25 – 52; d) J. M. Cuerva, J. Justicia, J. L. Oller-López, J. E. Oltra, *Top. Curr. Chem.* **2006**, *264*, 63 – 91; e) A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem.* **2003**, *115*, 5714 – 5731; *Angew. Chem. Int. Ed.* **2003**, *42*, 5556 – 5573; f) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771 – 2788; g) A. Fürstner, B. Bogdanović, *Angew. Chem.* **1996**, *108*, 2582 – 2609; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442 – 2469. For key references, see: h) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849 – 12859; i) T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986 – 997.

[9] J. Streuff, *Chem. Eur. J.* **2011**, *17*, 5507 – 5510.

[10] J. Streuff, M. Feurer, P. Bichovski, G. Frey, U. Gellrich, *Angew. Chem.* **2012**, *124*, 8789 – 8792; *Angew. Chem. Int. Ed.* **2012**, *51*, 8661 – 8664.

[11] X. Zheng, X.-J. Dai, H.-Q. Yuan, C.-X. Ye, J. Ma, P.-Q. Huang, *Angew. Chem.* **2013**, *125*, 3578 – 3582; *Angew. Chem. Int. Ed.* **2013**, *52*, 3494 – 3498.

[12] Usually such [4+1] cycloadditions involve 1,3-conjugated systems and CO, carbenes, or related partners. Selected examples: a) F. Beaumier, M. Dupuis, C. Spino, C. Y. Legault, *J. Am. Chem. Soc.* **2012**, *134*, 5938 – 5953; b) J. P. Moerdyk, C. W. Bielawski, *Nat. Chem.* **2012**, *4*, 275 – 280; c) T. Ohmura, K. Masuda, I. Takase, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 16624 – 16625; d) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 7812 – 7813; e) M. Murakami, K. Itami, Y. Ito, *Angew. Chem.* **1995**, *107*, 2943 – 2946; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2691 – 2694.

[13] For other formal [4+1] cycloadditions, see: a) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres, C. Bolm, *J. Am. Chem. Soc.* **2012**, *134*, 6924 – 6927; b) T. Inami, S. Sako, T. Kurahashi, S. Matsubara, *Org. Lett.* **2011**, *13*, 3837 – 3839; c) Z. Shi, B. Tan, W. W. Y. Leong, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2010**, *12*, 5402 – 5405; d) A. Mizuno, H. Kusama, N. Iwasawa, *Angew. Chem.* **2009**, *121*, 8468 – 8470; *Angew. Chem. Int. Ed.* **2009**, *48*, 8318 – 8320; e) R. W. Coscia, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 2496 – 2498; f) P. G. Andersson, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1992**, *114*, 8696 – 8698; g) L. S. Liebeskind, R. Chidambaram, *J. Am. Chem. Soc.* **1987**, *109*, 5025 – 5026.

[14] For examples of stoichiometric reductive imine–nitrile coupling, see: a) Y. Gao, Y. Yoshida, F. Sato, *Synlett* **1997**, 1353 – 1354; b) J. E. Hill, P. E. Fanwick, I. P. Rothwell, *Organometallics* **1992**, *11*, 1775 – 1777.

[15] For example, see: a) P. Vairaprakash, M. Periasamy, *Tetrahedron Lett.* **2008**, *49*, 1233 – 1236; b) B. Hatano, A. Ogawa, T. Hirao, *J. Org. Chem.* **1998**, *63*, 9421 – 9424; c) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron Lett.* **1998**, *39*, 3333 – 3336; d) P. Liao, Y. Huang, Y. Zhang, *Synth. Commun.* **1997**, *27*, 1483 – 1486.

[16] For details see the Supporting Information.

[17] For a discussion on similar additive effects, see: A. Gansäuer, M. Behlendorf, D. v. 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.

[18] CCDC 924705 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] R. L. Halterman, K. P. C. Vollhardt, *Organometallics* **1988**, *7*, 883 – 892.

[20] Gaseous state values: ΔH_f^{298} (Ti-N) = 111 kcal mol^{-1}; ΔH_f^{298} (Ti – O) = 158 kcal mol^{-1}. See: J. A. Dean, *Lange's Handbook of Chemistry*, *15th ed.*, McGraw-Hill, New York, **1999**, p. 4.52.

[21] a) A. Fernández-Mateos, P. H. Teijón, L. M. Burón, R. R. Clemente, R. R. González, *J. Org. Chem.* **2007**, *72*, 9973 – 9982; b) A. Fernández-Mateos, L. M. Burón, R. R. Clemente, A. I. R. Silvo, R. R. González, *Synlett* **2004**, 1011 – 1014.

[22] a) J. Muñoz-Bascón, I. Sancho-Sanz, E. Álvarez-Manzaneda, A. Rosales, J. E. Oltra, *Chem. Eur. J.* **2012**, *18*, 14479 – 14486; b) J. Justicia, I. Sancho-Sanz, E. Álvarez-Manzaneda, J. E. Oltra, J. M. Cuerva, *Adv. Synth. Catal.* **2009**, *351*, 2295 – 2300; c) R. E. Estévez, J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. García-Ruiz, R. Robles, A. Gansäuer, J. M. Cuerva, J. E. Oltra, *Chem. Eur. J.* **2009**, *15*, 2774 – 2791; d) A. Rosales, J. L. Oller-López, J. Justicia, A. Gansäuer, J. E. Oltra, J. M. Cuerva, *Chem. Commun.* **2004**, 2628 – 2629.

