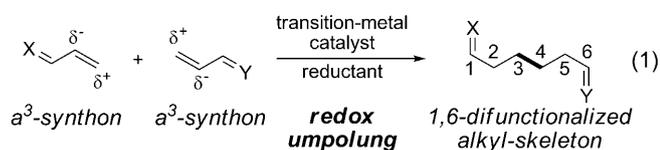


A Titanium(III)-Catalyzed Redox Umpolung Reaction for the Reductive Cross-Coupling of Enones with Acrylonitriles

Jan Streuff*^[a]

The installation of carbonyl or nitrile functionalities at the 1,2-, 1,4-, or even 1,6- positions of an alkyl chain by C–C bond formation is a challenging task for modern synthetic methods because it requires the formal coupling of two similarly polarized synthons. The concept of “umpolung”, which found wide application in synthesis and methodology development is the classical way to address this issue.^[1] In the past decades, electrochemical oxidative or reductive coupling protocols have been applied in organic synthesis to perform such connections, and important industrial applications like the Baizer–Monsanto adiponitrile process have been established.^[2,3] However, a related transition-metal-catalyzed reductive cross-coupling reaction of activated alkenes was not reported to date. In contrast, the transition-metal catalyzed or mediated reductive conjugate alkylations or alkyl-alkyl cross-coupling reactions known in the literature usually require laborious synthesis of halogenated or metalated coupling precursors, instead of employing a readily available alkene.^[4,5] To this end, a double reductive 1,4-alkylation concept was worked out that forges a 1,6-difunctionalized carbon skeleton starting from two different three-carbon acceptor synthons (a^3) in one redox economic reaction [Eq. (1)].^[6,7] It was envisioned that low valent titanium catalysts, which have found versatile application in pinacol couplings, epoxide opening and cyclization reactions, or conjugate reductions, could perform this redox umpolung reaction.^[8,9]

Screening experiments were started by reacting 2-cyclohexen-1-one (**1a**) with an excess of acrylonitrile (**2a**) in the presence of titanocene dichloride as catalyst and zinc

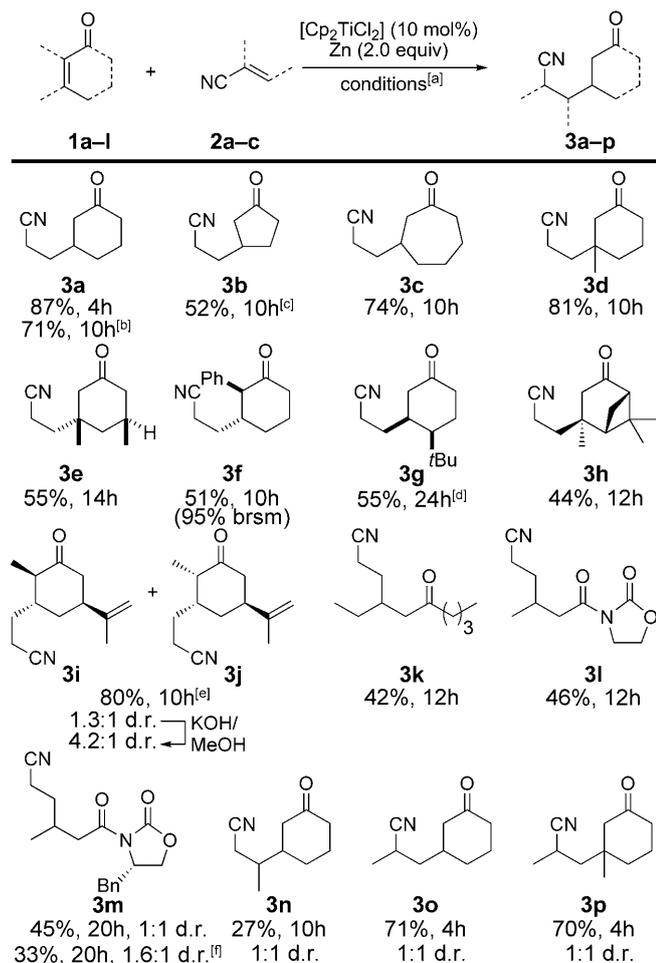


[a] Dr. J. Streuff

Institut für Organische Chemie und Biochemie
 Albert-Ludwigs-Universität Freiburg
 Albertstrasse 21, 79104 Freiburg i. Br. (Germany)
 Fax: (+49) 761-203-8715
 E-mail: jan.streuff@ocbc.uni-freiburg.de

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201100501>.

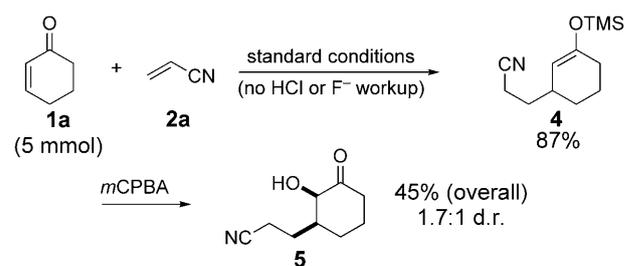
powder as stoichiometric reductant in THF. First attempts achieved only low turnover numbers and **3a** was received in a maximum yield of 35%.^[10] However, it was quickly discovered that addition of trimethylsilyl chloride successfully circumvents product inhibition by formation of the corresponding TMS-enol ether **4**, which is easily hydrolyzed to the desired cyclohexanone product during workup.^[11] After careful experimentation, reaction conditions were identified that give complete conversion and 87% yield in the presence of 10 mol% of the titanium catalyst in THF as optimal reaction medium within only 4 hours (Scheme 1). The catalyst amount was successfully reduced to 5 mol% and a yield of 71% was received after a reaction time of 10 hours. However, an excess of inexpensive acrylonitrile is necessary to assure suppression of reduction and homo-coupling products. Using other hydrochlorides such as collidine hydrochloride was less successful as well as the substitution of zinc with manganese as terminal reductant. To demonstrate the scope of this double-reductive alkylation reaction, a series of substrates was submitted to the optimized conditions on a 1 mmol scale. Enones with different ring sizes such as cyclopentenone and cycloheptenone also worked well (**3b,c**) and quaternary carbon centers were formed smoothly when 3-methyl-2-cyclohexen-1-one and the 3,5-dimethyl derivative were employed (**3d,e**).^[12] With 2-phenylcyclohexenone the corresponding *trans*-product **3f** was formed in a clean reaction in 51% yield while the *syn*-product **3g** was received from 4-*tert*-butyl cyclohexenone ($^3J_{\text{HH}} = 3 \text{ Hz}$). The polysubstituted and sterically congested terpenoids (*S*)-verbenone and (*S*)-carvone formed the desired products in 44% and 80% yield, respectively (**3h–j**). In both cases, the diastereoselectivity for the C–C bond forming step was high (>10:1 and 9:1, respectively) and the remote olefin functionality of carvone remained unaffected. The stereochemical outcome in case of **3i** and **3j** is in very good agreement with previously reported radical mediated 1,4-alkyl additions to carvone and related molecules.^[13] In addition, **3j** was partially epimerized into **3i** by treatment with KOH in methanol for 30 minutes and thus the overall diastereomeric ratio was increased to 4.2:1.^[14] An acyclic enone and unsaturated oxazolidinoneamides also formed the desired products in moderate yields (**3k–m**). By replacing TMSCl with AlEt₂Cl, the diastereomeric ratio of product **3m** was slightly improved to 1.6:1.^[6a] In the following, the flexibility of the reaction towards the nitrile acceptor was also probed and it was found that crotonitrile was sig-



Scheme 1. Scope and limitations of the reductive coupling. [a] Reaction conditions: **1** (1.0 mmol), **2** (5.0 mmol), $[\text{Cp}_2\text{TiCl}_2]$ (10 mol%), zinc powder (2.0 mmol), HCINeT_3 (1.3 mmol), TMSCl (1.5 mmol), THF ($c = 0.4 \text{ M}$), $T = 35^\circ\text{C}$. Then aq. HCl or TBAF. [b] Carried out with $[\text{Cp}_2\text{TiCl}_2]$ (5 mol%). [c] Reaction was run in the dark. [d] Reaction run at 25°C . [e] Combined yield. [f] TMSCl was substituted by AlEt_2Cl (2.0 equiv), which was precomplexed to the substrate at 0°C . brsm=based on recovered starting material, Cp=cyclopentadiene, d.r.=diastereomeric ratio, TBAF=tetra-*n*-butylammonium fluoride, TMS=trimethylsilyl.

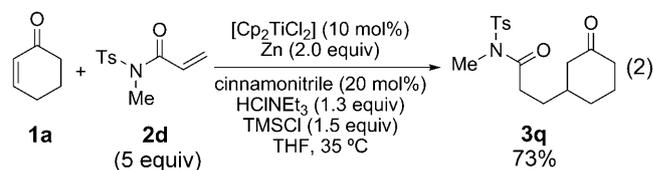
nificantly less reactive than acrylonitrile but still gave an isolable amount of the product diastereomers (27%). However, methacrylonitrile showed similar reactivity to acrylonitrile (**3o,p**) and again, a quaternary center was formed. In principle, the TMS-enol ether intermediates can be isolated from the reaction mixture. For example, enol ether **4** was obtained in 87% yield as a single regioisomer (Scheme 2). The corresponding TES- and TBS-enol ethers were synthesized in the same manner with good regioselectivities.^[14] Further transformation of these silyl enol ethers was exemplified by Rubottom oxidation of **4**.

The acrylonitriles can be substituted with acrylamides as long as they have a sufficiently low-lying LUMO. A proof of principle was carried out by employing *N*-methyl-*N*-tosylacrylamide, which was smoothly transformed into the result-



Scheme 2. Isolation of the silyl ether intermediate as single regioisomer. Treatment with *m*CPBA yields α -hydroxyketone **5**. CPBA=chloroperoxybenzoic acid.

ing ϵ -ketoamide **3q** in 73% yield [Eq. (2)]. It was observed that catalytic amounts of cinnamitrile help to promote this reaction.



When the catalyzed 1,4-alkylation was attempted on a series of substrates that would form a second, vicinal quaternary carbon, the corresponding tertiary allylic alcohol was isolated instead (Figure 1). A 3-*tert*-butyl substituent, for ex-

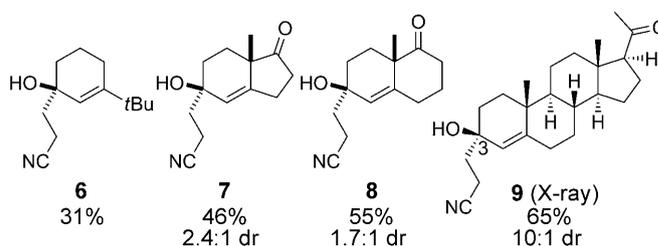
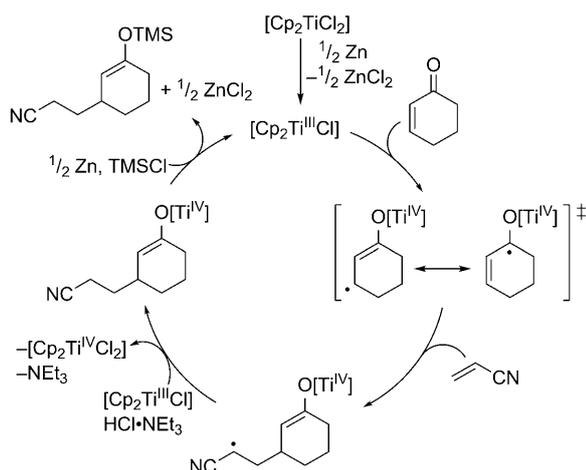


Figure 1. Increased sterical bulk shifts the reaction outcome towards 1,2-addition. For the reaction conditions, see Scheme 1.

ample, showed the same effect and led to formation of **6**, which is prone to water elimination. Interestingly, a free ketone is easily tolerated by the reaction and products **7** and **8** were produced in 46% and 55% yield with moderate diastereoselectivity from the common diketone precursors. Notably, the Wieland–Miescher diketone also led to a small amount of the 1,4-addition product (14%) containing two adjacent quaternary carbons. In case of progesterone, a 10:1 mixture of both C-3 epimers was isolated in 65% yield. The relative configuration of the major diastereomer (**9**) was unambiguously determined by X-ray crystallographic analysis.^[14,15]



Scheme 3. Proposed catalytic cycle. The turnover of the second catalyst equivalent is not drawn for clarity reasons.

A reasonable catalytic cycle could start with the generation of a titanium(III) catalyst by reduction of $[\text{Cp}_2\text{TiCl}_2]$ with zinc (Scheme 3). This species (for simplification the dimeric form is not drawn), which has been studied in detail before,^[16] transfers a single electron to the enone substrate and an allylic radical is generated. This electron-rich radical adds to acrylonitrile at the β position of the former enone, thus generating a less nucleophilic radical next to the cyano group.^[17] This intermediate is quickly reduced and protonated by a second Ti^{III} species and the resulting Ti^{IV} enolate is displaced by TMS chloride. Finally, the catalyst is regenerated in another reduction step.

In conclusion, a titanium-catalyzed double-reductive alkylation of enones was developed that employs readily available alkene precursors and leads to 1,6-difunctionalized ketonitriles by a redox umpolung process. The regioselectivity can be shifted to yield tertiary 1,4-cyanoalcohols by increased sterical demand. This reaction does not only allow for the catalytic formation of $\text{sp}^3\text{-sp}^3$ carbon-carbon bonds, but also gives rise to regioselectively formed silyl enol ethers, which can be intercepted and employed in follow-up chemistry. We are currently exploring this chemistry further toward an enantioselective protocol and other coupling partners. A detailed mechanistic investigation will follow.

Experimental Section

Representative procedure (3a): A flame-dried 50 mL-Schlenk tube was charged under argon atmosphere with a magnetic stir bar and triethylamine hydrochloride (179 mg, 1.3 mmol, 1.3 equiv). Stirring was started and the vessel was evacuated and backfilled with argon after a few minutes. Zinc powder (131 mg, 2.0 mmol, 2.0 equiv) was added, followed by titanocene dichloride (25 mg, 0.1 mmol, 10 mol %) and absolute THF (2.5 mL). The reaction vessel was placed in an oil bath with a temperature of 35 °C. Once the color change of the slurry from purple-brownish to lime-green was complete, cyclohexenone (97 μL , 1.0 mmol, 1.0 equiv) was rapidly added, followed by acrylonitrile (332 μL , 5.0 mmol, 5 equiv) and TMS-Cl (190 μL , 1.5 mmol, 1.5 equiv). Upon addition of substrate the mixture turned deep-green and changed to deep-purple when the

acrylonitrile was added. After 4 h, workup was carried out by addition of 1 N aqueous HCl (10 mL) and stirring for 30 min. Dichloromethane (20 mL) was added and the organic layer was separated followed by extraction of the aqueous phase with dichloromethane (3 \times 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, hexanes/ethyl acetate = 3:2, R_f = 0.45). The product (**3a**) was obtained as a colorless oil in 87% yield (131.1 mg). ^1H NMR (250 MHz, CDCl_3): δ = 1.31 (ddd, J = 3.1, 10.9, 14.0 Hz, 1H), 1.52–1.71 (m, 1H), 1.60 (dd, J = 5.4, 7.2 Hz, 1H), 1.66 (dd, J = 4.3, 7.0 Hz, 1H), 1.74–2.06 (m, 4H), 2.13–2.41 (m, 3H), 2.32 ppm (t, J = 7.3 Hz, 2H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 14.42, 24.48, 30.12, 31.37, 37.49, 40.90, 46.82, 119.07, 209.84 ppm; IR (NaCl): $\bar{\nu}$ = 2939, 2868, 2245, 1711, 1451, 1425, 1348, 1318, 1285, 1230, 1170, 1104, 1060, 949, 868, 755 cm^{-1} ; MS (EI, 70 eV): m/z (%): 151.1 [M^+] (76), 122.1 (18), 108.1 (100), 97.1 (41), 80.1 (8), 55.3 (40), 41.3 (14); HRMS (EI) calcd for $\text{C}_9\text{H}_{15}\text{ON}^+$: 151.09971, found: 151.09960.

Acknowledgements

I wish to thank Prof. B. Breit for his generous support and the Fonds der Chemischen Industrie for financial support in form of a Liebig Fellowship. Dr. Manfred Keller is acknowledged for X-ray crystallographic analysis.

Keywords: cross-coupling • enones • radical reactions • titanium • umpolung

- a) R. W. Hoffmann, *Elemente der Syntheseplanung*, Elsevier, München, **2006**; b) A. B. Smith, III, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365–377; c) M. Schmittel, *Top. Curr. Chem.* **1994**, *169*, 183–230; d) D. Seebach, *Angew. Chem.* **1979**, *91*, 259–278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
- a) K. D. Moeller, *Synlett* **2009**, 1208–1218; b) *Encyclopedia of Electrochemistry, Vol. 8, Organic Electrochemistry* (Ed.: H. J. Schäfer), Wiley-VCh, Weinheim, **2004**; c) *Organic Electrochemistry* (Eds.: H. Lund, O. Hammerich), Marcel Dekker, New York, **2000**; for a related cobalt-catalyzed dimerization, see: d) C.-C. Wang, P.-S. Lin, C.-H. Cheng, *Tetrahedron Lett.* **2004**, *45*, 6203–6206.
- a) K. Weissmerl, H.-J. Arpe, *Industrielle Organische Chemie*, VCH, Weinheim, **1988**; b) M. M. Baizer, *Tetrahedron* **1984**, *40*, 935–969; c) M. M. Baizer, *Chem. Ind.* **1979**, 435–439.
- For reviews, see: a) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039–1075; b) A. Rudolph, M. Lautens, *Angew. Chem.* **2009**, *121*, 2694–2708; *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670; c) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823.
- Recent contributions: a) W. Li, N. Chen, J. Montgomery, *Angew. Chem.* **2010**, *122*, 8894–8898; *Angew. Chem. Int. Ed.* **2010**, *49*, 8712–8716; b) S. Ogoshi, T. Haba, M. Ohashi, *J. Am. Chem. Soc.* **2009**, *131*, 10350–10351; c) C.-Y. Ho, H. Ohmiya, T. F. Jamison, *Angew. Chem.* **2008**, *120*, 1919–1921; *Angew. Chem. Int. Ed.* **2008**, *47*, 1893–1895; d) H.-T. Chang, T. T. Jayanth, C.-C. Wang, C.-H. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 12032–12041; e) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; f) C.-C. Wang, P.-S. Lin, C.-H. Cheng, *J. Am. Chem. Soc.* **2002**, *124*, 9696–9697.
- For related stoichiometric umpolung reactions, see: a) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560; b) G. Pandey, M. K. Ghorai, S. Hajra, *Tetrahedron Lett.* **1998**, *39*, 8341–8344; c) M. Schmittel, A. Burghart, W. Malisch, J. Reising, R. Söllner, *J. Org. Chem.* **1998**, *63*, 396–400.
- For a review on redox economy, see: N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896–2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867.

- [8] Selected reviews: a) A. Gansäuer, C.-A. Fan, F. Keller, P. Karbaum, *Chem. Eur. J.* **2007**, *13*, 8084–8090; b) A. Gansäuer, J. Justicia, C.-A. Fan, D. Worgull, F. Piestert, *Top. Curr. Chem.* **2007**, *279*, 25–52.
- [9] a) A. Gansäuer, L. Shi, M. Otte, *J. Am. Chem. Soc.* **2010**, *132*, 11858–11859; b) A. D. Kosal, B. L. Ashfeld, *Org. Lett.* **2010**, *12*, 44–47; c) A. Gansäuer, D. Worgull, K. Knebel, I. Huth, G. Schnakenburg, *Angew. Chem.* **2009**, *121*, 9044–9047; *Angew. Chem. Int. Ed.* **2009**, *48*, 8882–8885; d) J. Justicia, I. Sancho-Sanz, E. Álvarez-Manzaneda, J. E. Oltra, J. M. Cuerva, *Adv. Synth. Catal.* **2009**, *351*, 2295–2300; e) 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; f) R. E. Estévez, M. Paradas, A. Millán, T. Jiménez, R. Robles, J. M. Cuerva, J. E. Oltra, *J. Org. Chem.* **2008**, *73*, 1616–1619; g) A. Gansäuer, C.-A. Fan, F. Keller, J. Keil, *J. Am. Chem. Soc.* **2007**, *129*, 3484–3485; h) 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; i) A. Gansäuer, *Chem. Commun.* **1997**, 457–458.
- [10] For an alternative route to products **3**, see: M. C. P. Yeh, P. Knochel, *Tetrahedron Lett.* **1988**, *29*, 2395–2396.
- [11] TMSCl has shown a beneficial role in previous Ti^{III}-catalyses (see references 8b, 9c and 9i for example).
- [12] Cyclopentenone is known to add to acrylonitriles in a [2+2] addition, therefore the reaction was carried out in the dark: D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3–22.
- [13] A. Arase, Y. Masuda, A. Suzuki, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2275–2279.
- [14] See the Supporting Information for details.
- [15] CCDC-801986 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.
- [16] R. J. Enemærke, J. Larsen, T. Skrydstrup, K. Daasbjerg, *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864.
- [17] For an overview on the selectivity in C–C bond forming radical reactions, see: a) B. Giese, *Angew. Chem.* **1985**, *97*, 555–567; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553–565; b) B. Giese, *Angew. Chem.* **1983**, *95*, 771–782; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753–764.

Received: February 14, 2011
Published online: April 12, 2011