ORGANIC LETTERS

2010
Vol. 12, No. 1
44−47

Titanocene-Catalyzed Conjugate Reduction of α,*β*-Unsaturated Carbonyl Derivatives

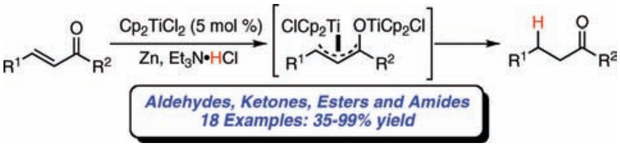
Andrew D. Kosal and Brandon L. Ashfeld*

Department of Chemistry and Biochemistry, University of Notre Dame,
Notre Dame, Indiana 46556

bashfeld@nd.edu

Received October 21, 2009

ABSTRACT



A titanocene-catalyzed conjugate reduction of α,*β*-unsaturated carbonyl derivatives has been developed. A series of carbonyl compounds including aldehydes, ketones, esters, and amides proved viable in the reduction process providing an efficient, chemoselective method for the catalytic reduction of unsaturated carbonyl derivatives.

The chemoselective 1,4-reduction of α,*β*-unsaturated carbonyl derivatives is an important tactic in organic synthesis.[1] In recent years, a number of significant advances have been made toward the development of efficient and economical protocols for achieving this transformation with substantial emphasis placed on the use of transition metal catalysts. As a result, a number of metals have been shown to facilitate the conjugate reduction of α,*β*-unsaturated carbonyls, including palladium,[2] rhodium,[3] magnesium,[4] and others,[5] of which copper hydride complexes are quite possibly the most widely utilized and have arguably demonstrated the greatest synthetic utility.[6] A number of alkali and lanthanide metal-based reagents have shown useful levels of reactivity, but the procedures often suffer from chemoselectivity issues.[7]

In many ways, concerns associated with synthetic inefficiency, the high cost of chemical research, and the need for hazardous reaction conditions can be alleviated through the use of transition metals in a catalytic fashion. To the best of our knowledge, there has yet to be discovered a

---

(1) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Haskel, A.; Keinan, E. Palladium-catalyzed 1,4-reduction (conjugate reduction). In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley: New York , 2002; Vol. 2, p 2767. (c) Shibata, I. *Organomet. News* **2004**, 53. (d) Nishiyama, H. *Kagaku (Kyoto, Jpn.)* **2005**, *60*, 72.

(2) (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (b) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1985**, *26*, 1353. (c) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314. (d) Otsuka, H.; Shirakawa, E.; Hayashi, T. *Chem. Commun.* **2007**, 1819. For examples of enantioselective conjugate reductions catalyzed by palladium, see :(e) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851. (f) Monguchi, D.; Beemelmanns, C.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Organomet. Chem.* **2008**, *693*, 867.

(3) (a) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678. (b) Wang, Z.; Zou, G.; Tang, J. *Chem. Commun.* **2004**, 1192. For examples of enantioselective conjugate reductions catalyzed by rhodium, see: (c) Kanazawa, Y.; Nishiyama, H. *Synlett* **2006**, 3343.

(4) (a) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409. (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287. (c) Hutchins, R. O.; Suchismita; Zipkin, R. E.; Taffer, I. M.; Sivakumar, R.; Monaghan, A.; Elisseou, E. M. *Tetrahedron Lett.* **1989**, *30*, 55.

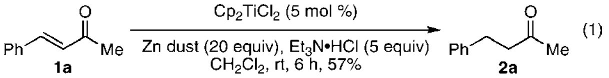
(5) (a) Keinan, E.; Perez, D. *J. Org. Chem.* **1987**, *52*, 2576. (b) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751. (c) Magnus, P.; Waring, M. J.; Scott, D. A. *Tetrahedron Lett.* **2000**, *41*, 9731.

(6) (a) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013. (b) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (c) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (d) Chiu, P. *Synthesis* **2004**, 2210. (e) Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755. For examples of enantioselective conjugate reductions catalyzed by copper, see: (f) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (g) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (h) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (i) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793. (j) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (k) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789. (l) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575. (m) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273. (n) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6177. (o) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963. (p) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329.

10.1021/ol9024315

catalytic, single electron transfer-type process that can enable the conjugate reduction of carbonyl derivatives.[8] The development of such a method would enable the controlled Barbier-type reduction of α,β-unsaturated carbonyl derivatives that can then be implemented in the context of consecutive bond forming reaction sequences including reductive alkylations and reductive aldol reactions.

In search of an efficient, transition metal complex to catalyze the conjugate reduction of α,β-unsaturated carbonyl derivatives that would proceed through metal-ketyl intermediate, we looked to titanocene derivatives due to their propensity to undergo redox processes between the +3 and +4 oxidation states. Based mainly on the elegant work by Gansäuer and co-workers, we surmised that catalytic turnover could be achieved by the addition of a proton source and a mild reducing metal, such as zinc.[9] Thus, we were decidedly pleased when treatment of enone **1a** with Cp_2TiCl_2 (5 mol %), zinc dust (20 equiv), and $Et_3N{\bullet}HCl$ (5 equiv) provided the 1,4-reduction product **2a** in 57% yield (eq 1). It is important to note that Cp_2TiCl_2 is necessary for the reduction as performing the reaction in its absence failed to provide the desired saturated ketone. Additionally, we found that Cp_2TiCl_2 provided the best catalytic source of titanium, as a combination of $TiCl_3$ and zinc dust gave substantially lower yields of the reduced products and lacked reproducibility.[10]



(1)

Attempts to lower the catalyst loading resulted in increased reaction times and lower yields, presumably a result of the finite lifetime of in situ generated Cp_2TiCl. Examination of other solvents found that THF also provided the reduced product. However, the reduction proved unreliable when applied to a number of different substrates, often resulting in decomposition of the starting material or the emergence of pinacol coupling byproducts. Various other proton sources were examined, but it was determined that $Et_3N{\bullet}HCl$ provided the best overall results. Employing manganese as the reducing metal effectively led to longer reaction times and was less efficient in comparison to zinc dust.

With this initial result in hand, we focused on reducing the amount of zinc dust and $Et_3N{\bullet}HCl$ required to achieve an efficient reduction of enone **1a** (Table 1, entry 1). A decrease in the amount of zinc dust from 20 equiv to 1.1 equiv resulted in a marked drop in the yield of ketone **2a** to 33% (entry 2). Most notably, however, was the dramatic inefficiency of the reduction, and propensity for side reactions to occur, that is indicated by a mere 37% yield based on recovered starting material. The use of 2.5 equiv of zinc dust, in conjunction with 5 equiv of $Et_3N{\bullet}HCl$, resulted in a 60% yield of ketone **2a** that was comparable to the original conditions (entry 3). Attempts to reduce the amount of $Et_3N{\bullet}HCl$ from 5.0 to 2.1 equiv led to a decrease in the yield of the process (entry 4). It should be noted that in those experiments which resulted in low yields of ketone **2a**, the major side product resulted from a pinacol coupling process.[11] With these results in hand, we moved forward with the optimized conditions of 5 mol % Cp_2TiCl_2, 2.5 equiv of zinc dust, and 5 equiv of $Et_3N{\bullet}HCl$ in CH_2Cl_2.

Table 1. Optimization Studies in the Reduction of Enone **1a**[a]

entry	equiv of Zn(0)	equiv of $Et_3N{\bullet}HCl$	yield (%)[b]
1	20	5	57
2	1.1	5	33 (37)[c]
3	**2.5**	**5**	**60**
4	2.5	2.1	27 (42)[c]

[a] Conditions: enone (1 mmol), Cp_2TiCl_2 (5 mol %), Zn dust, and $Et_3N{\bullet}HCl$ in CH_2Cl_2 (0.05 M) at rt for 6 h. [b] Isolated yields. [c] Yields based on recovered starting material in parentheses.

We next turned our attention toward evaluating the overall scope of the titanium-catalyzed conjugate reduction.[12] A series of α,β-unsaturated aldehydes, ketones, esters, and amides were examined. The yields of the 1,4-reduction products ranged from good to excellent, and the results of

---

(7) (a) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121. (b) Davies, S. G.; Rodriguez-Solla, H.; Tamayo, J. A.; Garner, A. C.; Smith, A. D. *Chem. Commun.* **2004**, 2502.

(8) (a) Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* **2002**, *43*, 2013. (b) Asandei, A. D.; Chen, Y. *Macromolecules* **2006**, *39*, 7549.

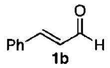
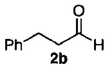
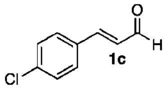
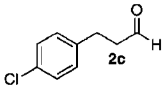
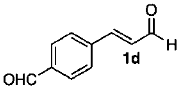
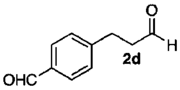
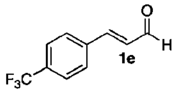
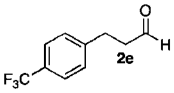
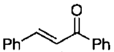
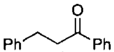
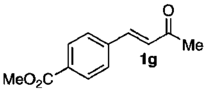
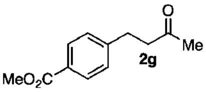
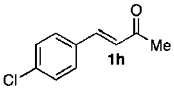
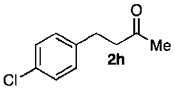
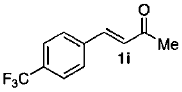
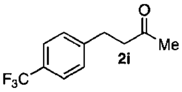
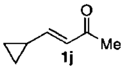
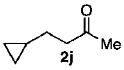
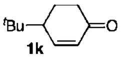
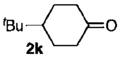
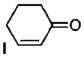
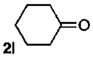
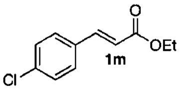
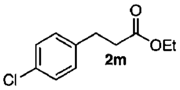
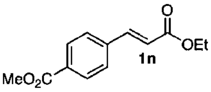
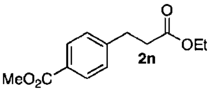
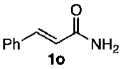
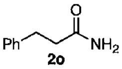
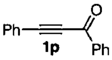
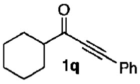
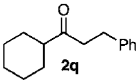
(9) (a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3206. (b) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.—Eur. J.* **2003**, *9*, 531. (c) Rosales, A.; Oller-López Juan, L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628. (d) Gansäuer, A.; Franke, D.; Lauterbach, T.; Nieger, M. *J. Am. Chem. Soc.* **2005**, *127*, 11622. (e) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Muck-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (f) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Muck-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359. (g) Gansäuer, A.; Fan, C.-A.; Keller, F.; Karbaum, P. *Chem.—Eur. J.* **2007**, *13*, 8084. (h) Gansäuer, A.; Fan, C.-A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484. (i) Friedrich, J.; Walczak, K.; Dolg, M.; Piestert, F.; Lauterbach, T.; Worgull, D.; Gansäuer, A. *J. Am. Chem. Soc.* **2008**, *130*, 1788. (j) Estévez, R. E.; Justicia, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J. M.; Oltra, J. E. *Chem.—Eur. J.* **2009**, *15*, 2774.

(10) (a) Karrer, P.; Yen, Y.; Reichstein, I. *Helv. Chim. Acta* **1930**, *13*, 1308. (b) Pons, J.-M.; Santelli, M. *Tetrahedron Lett.* **1986**, *27*, 4153. (c) Jung, M. E.; Hogan, K. T. *Tetrahedron Lett.* **1988**, *29*, 6199. (d) Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* **2002**, *43*, 2013. (e) Asandei, A. D.; Chen, Y. *Macromolecules* **2006**, *39*, 7549.

(11) (a) Knoop, C. A.; Studer, A. *Adv. Synth. Catal.* **2005**, *347*, 1542. (b) Chatterjee, A.; Joshi, N. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2007**, *46B*, 1475. (c) Hirao, T. *Top. Curr. Chem.* **2007**, *279*, 53. (d) Paradas, M.; Campana, A. G.; Estevez, R. E.; Alvarez de Cienfuegos, L.; Jimenez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *74*, 3616.

(12) **Representative procedure: 4-phenylbutan-2-one**. A solution of Cp_2TiCl_2 (2.6 mg, 0.01 mmol, 5 mol%), zinc dust (33.5 mg, 0.51 mmol, 2.5 equiv), and triethylamine hydrochloride (140 mg, 1.0 mmol, 5 equiv) was stirred in CH_2Cl_2 (1.5 mL) for 10 min or until the solution had turned from red to green. A solution of *trans*-4-phenyl-3-butene-2-one (30 mg, 0.20 mmol) in CH_2Cl_2 (2.5 mL) was then added via syringe. The reaction was stirred until starting material was consumed as monitored by TLC (*p*-anisaldehyde). The mixture was quenched with saturated aqueous NH_4Cl (10 mL). The solution was passed through celite and extracted with Et_2O (3 × 10 mL), and the combined organic fractions were washed with saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to give 16.7 mg (55%, 57% by 400 MHz ^1H NMR referenced to naphthalene) of **2a** as a clear colorless oil. ^1H NMR and ^{13}C NMR data are consistent with literature values: Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.

Table 2. Titanium-Catalyzed Conjugate Reduction[a]

entry	substrate	product	yield (%)[b]
1	 **1b**	 **2b**	78
2	 **1c**	 **2c**	49
3	 **1d**	 **2d**	75
4	 **1e**	 **2e**	41
5	 **1f**	 **2f**	96
6	 **1g**	 **2g**	99
7	 **1h**	 **2h**	91 (98)[c]
8	 **1i**	 **2i**	91
9	 **1j**	 **2j**	57[d]
10	 **1k**	 **2k**	95[d]
11	 **1l**	 **2l**	90[d]
12	 **1m**	 **2m**	68
13	 **1n**	 **2n**	56 (>99)[c]
14	 **1o**	 **2o**	35 (76)[c]
15	 **1p**	**2f**	55[e]
16	 **1q**	 **2q**	40[e]

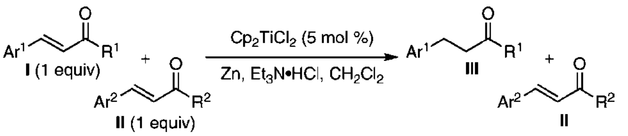
[a] Conditions: alkene (1 mmol), Cp_2TiCl_2 (5 mol %), Zn dust (2.5 mmol), and Et_3N•HCl (5 mmol) in CH_2Cl_2 (0.05 M). [b] Yields calculated by 400 MHz ^{1}H NMR to an internal standard (naphthalene). [c] Yields in parentheses based on recovered starting material. [d] THF and collidine•HCl were used in place of CH_2Cl_2 and Et_3N•HCl. [e] Cp_2TiCl_2 (10 mol %), Zn dust (5 equiv), and Et_3N•HCl (10 equiv).

our findings are summarized in Table 2. The conjugate reduction of aryl-substituted α,*β*-unsaturated aldehydes provided the corresponding reduced aldehydes in good yields (entries 1−4). Conjugated enones with *β*-aryl (entries 5−8) and *β*-alkyl (entries 9−11) substitution provided the corresponding saturated ketones in excellent yields. Additionally, acylic (entries 5−9) and cyclic (entries 10 and 11) enones performed equally well in the reduction sequence. Of particular note, enone **1j** containing a cyclopropane ring at the *β*-carbon underwent reduction in 57% yield without strain-driven ring expansion of the cyclopropane ring (entry 9). Interestingly, when the conjugate reduction of *β*-alkyl-substituted enones was performed in CH_2Cl_2, only decomposition of the starting enone was observed. However, by switching the solvent from CH_2Cl_2 to THF, and the proton source to collidine•HCl, an excellent yield of the desired saturated ketones could be obtained (entries 9−11). Aromatic enoates provided the corresponding saturated esters in good yields (entries 12 and 13), along with unsubstituted enamides (entry 14). Ynones also proved viable substrates providing the corresponding fully saturated carbonyl compounds in good yields (entries 15 and 16). In general, these results demonstrate the ease with which an inexpensive titanocene catalyst can facilitate the conjugate reduction of α,*β*-unsaturated carbonyl derivatives.

On the basis of our observations, the following generalizations can be made. First, the efficiency of the reduction was highly dependent upon the concentration of titanocene catalyst. If the reactions were performed with greater than 10 mol % titanocene, or at reaction concentrations greater than 1 M, substantial amounts of pinacol coupling products were observed. Additionally, α,*β*-unsaturated substrates with *β*-aryl rings substituted with electron-withdrawing groups provided the reduced products in excellent yields, whereas those containing electron-donating substituents failed to undergo reduction resulting in a quantitative recovery of starting material.

To determine the chemoselectivity of the catalytic conjugate reduction protocol, a series of competition studies were performed (Table 3). Treatment of a 1:1 mixture of enone **1a** and enoate **1r** to catalytic Cp_2TiCl_2 in the presence of zinc dust and Et_3N•HCl provided a 53% yield of the 1,4-reduced enone **2a** and 95% yield of the unreacted enoate **1r** (entry 1). Likewise, subjection of enal **1b** and enoate **1r** to

Table 3. Chemoselectivity in the Conjugate Reduction[a]

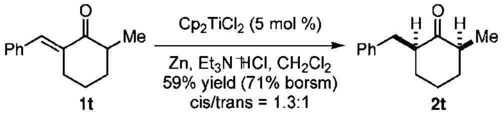


entry	I	II	yield of III (%)	yield of II (%)
1	**1a**	Ar^2 = Ph, R^2 = OEt (**1r**)	53 (**2a**)	95 (**1r**)
2	**1b**	**1r**	76 (**2b**)	95 (**1r**)
3	**1b**	**1a**	73 (**2b**)	91[b] (**1a**)
4	**1i**	Ar^2 = *p*-MeO-C_6H_4, R^2 = Me (**1s**)	78 (**2i**)	87 (**1s**)

[a] Conditions: 1 mmol of each substrate, Cp_2TiCl_2 (5 mol %), Zn dust (2.5 equiv), and Et_3N•HCl (5 equiv) in CH_2Cl_2 (0.05 M) at rt for 6 h. [b] Zn dust (1.5 equiv) and Et_3N•HCl (3 equiv).

the same conditions resulted in the selective 1,4-reduction of **1b** to provide the saturated aldehyde **2b** in 76% yield (entry 2). We were also able to demonstrate that 1,4-reduction of α,*β*-unsaturated aldehyde **1b** (73% yield) could be achieved selectively in the presence of enone **1a** (entry 3). Finally, a chemoselective reduction of electron-deficient enone **1i** in the presence of the electron-rich enone **1s** was accomplished in 78% yield and 87% recovered **1s**. Thus, the chemoselective reduction of more electrophilic α,*β*-unsaturated carbonyl derivatives can be achieved under the titanocene-catalyzed conditions described herein.

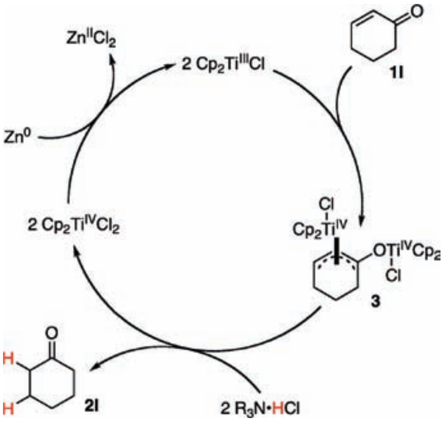
We next sought to examine the diastereoselectivity oberseved in the reduction of a chiral α,*β*-unsaturated ketone. We identified enone **1t** as ideally suited to examine the stereochemical outcome of the resulting protonation event. However, when enone **1t** was subjected to the titanium-catalyzed conjugate reduction conditions, a 1.3:1 ratio of diastereomers was formed in which the all equatorial substituted ketone **2t** was favored. Unfortuantely, all attempts to examine the stereoselectivity at the *β*-carbon of α,*β*-unsaturated carbonyl substrates by reduction of the corresponding tetrasubstituted olefin were unsuccessful.[13]



(2)

On the basis of Gansäuer's reports, and our own findings, a proposed catalytic cycle for the titanocene-catalyzed conjugate reduction is illustrated in Scheme 1.[9j] Initial reduction of the precatalyst $Cp_2Ti^{IV}Cl_2$ to the active reducing species $Cp_2Ti^{III}Cl$ is accomplished by a catalytic quantity of zinc dust. Coordination of $Cp_2Ti^{III}Cl$ to the carbonyl moiety in enone **1l** initiates a reallocation of electron density to provide an intermediate ketyl radical that sequesters a second equivalent of titanocene(III) through a rapid radical−radical annihilation to provide the bis-titanium(IV)-bound intermediate **3**. Protonation of the titanium alkoxide and allyl motifs by $Et_3N{\cdot}HCl$ provides the saturated ketone **2l** and $Cp_2Ti^{IV}Cl_2$. A second reduction of $Cp_2Ti^{IV}Cl_2$ with zinc dust provides $Cp_2Ti^{III}Cl$ and completes the catalytic cycle.

Scheme 1. Proposed Catalytic Cycle



In conclusion, we have demonstrated how $Cp_2Ti^{IV}Cl_2$ can be used as an efficient catalyst for the conjugate reduction of α,*β*-unsaturated carbonyl derivatives. A series of α,*β*-unsaturated aldehydes, ketones, esters, unsubstituted amides, and ynones underwent chemoselective conjugate reduction by utilizing a catalytic quantity of titanocene. The catalytic reduction process should be amenable to an asymmetric protocol through the installation of chiral ligands on the titanium complex. Studies directed toward the development of a catalytic asymmetric reduction of α,*β*-unsaturated carbonyl derivatives and the exploitation of titanium-bound intermediates for cascade carbon−carbon bond-forming reactions are ongoing and will be reported in due course.

Acknowledgment. The authors would like to thank the reviewers for their helpful comments and the University of Notre Dame for financial support of this research.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9024315

---

(13) Reduction of 3,5-dimethyl-2-cyclohexen-1-one resulted in decomposition and a complex mixture of products.