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Titanocene(III)-Promoted Reformatsky Additions

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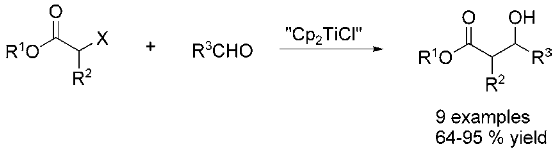
ABSTRACT



A novel method for the promotion of Reformatsky-like reactions is presented. The technique employs titanocene(III) chloride as a mild and homogeneous single-electron reductant. The reactions are rapid, operationally simple, and compatible with a wide range of functionalities. These additions are also anti diastereoselective.

The Reformatsky reaction is a well-established method for the formation of β-hydroxy esters.[1] It offers the advantages of regioselective enolate formation under nearly neutral conditions. However, the classic method employing zinc dust as a reductant can be plagued by extended reaction times and/or byproduct formation. To address these concerns, many other approaches have been developed employing either alternative elemental reductants or low-valent organometallic species.[2] Unfortunately, several employ reagents that have limitations of cost, availability, toxicity, and/or selectivity. In this communication, we describe a novel system employing titanocene(III) chloride to promote Reformatsky-like reactions that overcomes many of the aforementioned complications.

Titanocene(III) chloride (Cp_2TiCl, “Nugent’s reagent”) is a mild and useful reductant. The most popular application of this reagent is the single-electron opening of epoxides and subsequent trapping of the resulting α-hydroxy radical.[3] In addition, Cp_2TiCl has seen use in the reduction of aromatic aldehydes,[4] glycosyl halides,[5] vicinal dihalides,[6] sulfoxides,[7] and nitroarenes.[7] During our ongoing investigations using this unique reagent,[8] we noted the use of Cp_2TiCl to successfully reduce α-halo carbonyl species.[8,9] The substrate undergoes a two-electron reduction to form an enolate, which in the reported work was simply protonated upon workup to afford the unsubstituted carbonyl. We reasoned that the intermediate enolate could be trapped with electrophilic reagents such as aldehydes, leading to Reformatsky-like aldol products.

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(1) For reviews, see: (a) Shriner, R. L. *Org. React.* **1942**, *1*, 1−37. (b) Rathke, M. W. *Org. React.* **1975**, *22*, 423−460. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 111−212. (d) Fürstner, A. *Synthesis* **1989**, 571−590. (e) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 277−299.

(2) For recent examples with various reducing systems, please see the following. (a) Ge(0): Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691−697. (b) Sn: Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301−303. (c) SmI_2: Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702−1706. (d) Co(0): Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159−1163. (e) In(0): Hirashita, T.; Kinoshita, K.; Yamamura, H.; Kawai, M.; Araki, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 825−828. (f) Cr(II): Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772−3774. $TiCl_4$−Bu_4NI: (g) Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066−5068. (h) Mn*: Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807−8815. (i) $TiCl_2$: Kagayama, A.; Igarashi, K.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2579−2585.

(3) (a) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103-2112. (b) Gansäuer, A., Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788. (c) Gansäuer, A.; Rinker, B. *Tetrahedron* **2002**, *58*, 7017−7026. (d) Li, J. J. *Tetrahedron* **2001**, *57*, 1−24. (e) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997.

(4) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070−2071.

(5) Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1999**, *64*, 3987−3995.

(6) Qian, Y.; Li, G.; Zheng, X.; Huang, Y.-Z. *Synlett.* **1991**, 489−490.

(7) Zhang, Y.; Yu, Y.; Bao, W. *Synth. Commun.* **1995**, *25*, 1825−1830.

(8) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439−1442

(9) Qian, Y.; Li, G.; Huang, Y.-Z. *J. Organomet. Chem.* **1990**, *381*, 29−34.

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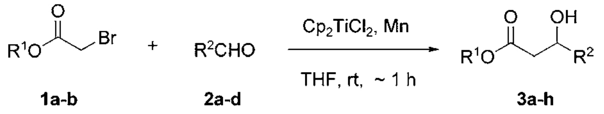
After we initiated our research, a report describing the use of zinc and catalytic amounts of titanocene to effect nonstereoselective Reformatsky additions came to our attention.[10] However, the described chemistry also proceeds in the absence of titanocene and it is unclear which species (i.e., zinc(0) or titanium(III)) is the actual reductant.[11] As such, we initiated a comprehensive study on the scope and limitations of Reformatsky-like additions employing low-valent titanocene.

After a brief exploration designed to determine optimal conditions, we successfully coupled a variety of α-halo esters with aldehydes[12] to produce β-hydroxy esters in good to excellent yields (Table 1). In the optimized procedure, the reagents are added sequentially to tetrahydrofuran at room temperature. After a short time (typically < 1 h) the starting materials are completely consumed and the product can be obtained after a simple workup and chromatographic isolation. We highlight the operational simplicity of this method; the reaction uses commercially available reagents that are neither moisture- nor air-sensitive. The reaction byproducts are nontoxic manganese and titanium salts that are readily separated from the desired product. Also, the mildness of the titanocene(III) reagent (due to the low redox potential compared with other reducing systems) suggests use with complex substrates found in total synthesis.

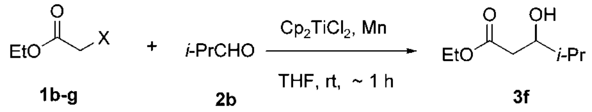
Table 1. Reformatsky-like Addition of Unbranched α-Halo Esters to Aliphatic Aldehydes



entry	R^1	R^2	product	yield (%)
1	Bn	n-C_7H_{15}	**3a**	88
2	Bn	i-Pr	**3b**	90
3	Bn	n-Pr	**3c**	95
4	Bn	$PhCH_2CH_2$	**3d**	94
5	Et	n-C_7H_{15}	**3e**	78
6	Et	i−Pr	**3f**	89
7	Et	n-Pr	**3g**	78
8	Et	$PhCH_2CH_2$	**3h**	92

The reaction course was found to vary greatly depending on the substituent positioned α to the ester carbonyl (Table 2).[13] α-Halo esters all proved to be reactive, though the reaction of the α-chloro ester is somewhat sluggish compared to bromide- and iodide-substituted substrates (entry 1 vs entries 2 and 3). Surprisingly, we found ethyl glycolates, protected as either the toluenesulfonate ester or as a benzoate or acetate ester, to be unreactive.

Table 2. Reformatsky Addition of Variously α-Substituted Esters



entry	"X"	yield (%)	time (h)[a]	E_{pc} (V)[b]
1	Cl	88	6	−3.25
2	Br	78	1	−2.61
3	l	82	1	−2.32
4	OTs			−2.99
5	Bz			−3.16
6	OAc			>−3.3

[a] Determined by GC/MS. [b] Reduction potentials were recorded in freshly distilled and degassed THF using a glassy carbon working electrode and a 0.01 M Ag/$AgNO_3$ (in acetonitrile) reference electrode. This electrode has a potential of ca. 0.3 V vs SCE.

In an attempt to quantify these observations, we employed cyclic voltammetry to gauge the ease of reduction of the substrates. As illustrated in Table 2, there is not a good correlation of reactivity with reducibility. Thus, while ethyl 2-chloroacetate is an excellent substrate, the α-tosyl, benzoyl, and acetoxy derivatives are not despite displaying very similar reduction potentials. This suggests that the reduction is an inner-sphere electron-transfer event.[14]

We presume that the halide is abstracted via a single electron transfer by an equivalent of Cp_2TiCl to produce radical **5** adjacent to the ester carbonyl. Further reduction by another equivalent of Cp_2TiCl results in the formation of enolate **6**.[15] Trapping of this enolate with an aldehyde leads to the observed products (Scheme 1).

Reformatsky additions of branched α-halo esters have traditionally been troubled by poor stereochemical control. Recent efforts have resulted in the development of methods for syn-selective condensations,[2b,d] but the complementary anti-selective Reformatsky reaction remains elusive.[2f] Our initial investigation of the stereochemistry of this addition is depicted in Scheme 2. Treatment of ethyl bromopropionate

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(10) (a) Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941. (b) Ding, Y.; Zhao, Z. B.; Zhou, C. M. *Tetrahedron* **1997**, *53*, 2899−2906. Note added in proof: A reviewer brought to our attention a very recent report by Ding where it is suggested that low-valent titanocene initially reduces the α-halo species to the radical, which is in turn further reduced by zinc to afford (presumably) the zinc enolate. Please see: (c) Ding, Y.; Zhao, G.; Chen, L. *Tetrahedron Lett.* **2003**, *44*, 2611−2614.

(11) We observe no reaction in the absence of titanocene (employing manganese as the terminal reductant), and the observed stereoselectivity (vide infra) confirms that a low-valent titanium species is the actual reductant.

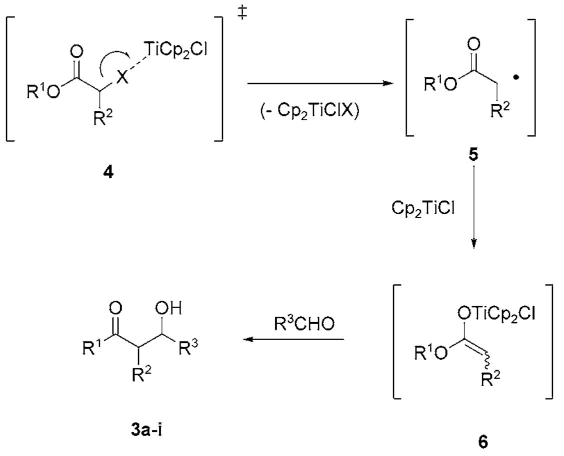
(12) Attempts at employing aromatic aldehydes were unsuccessful due to competitive reduction of the aldehyde moiety by the low-valent titanium reagent. See ref 4.

(13) For an example employing the reduction of an α-benzoate ester, see: (a) Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 2411−2417. For an example of a Reformatsky-like transformation involving α-sulfonate esters, see: (b) Burkhardt, E. R.; Doney, J. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2022−2039.

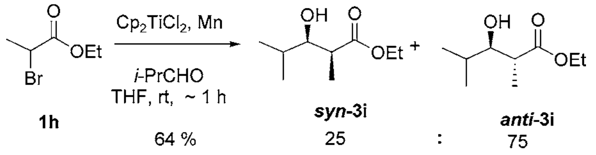
(14) Similar mechanism has been proposed for the titanocene(III)-promoted reduction of epoxides. See ref 3.

(15) For simplicity, we choose to represent the intermediate as the titanium enolate species; this seems reasonable in the face of the known oxophilicity of titanium. However, the effects of the mildly Lewis acidic manganese(II) salts (formed as the reaction proceeds) are unknown and cannot be discounted. For an interesting discussion of the role of counterion in Cp_2TiCl chemistry, please see: Enemærke, R. J.; Hjøllund, G. H.; Daasbjerg, K.; Skrydstrup, T. *C. R. Acad. Sci., Ser. IIc: Chim.* **2001**, *4*, 435−438.

Scheme 1. Titanocene-Mediated Reformatsky Addition



Scheme 2. Anti-Selective Addition of Ethyl Bromopropionate to Isobutyraldehyde



(**1h**) with Cp_2TiCl in the presence of isobutyraldehyde resulted in a 75:25 ratio of the expected aldol products (**3i**) favoring the anti isomer. This result is in accord with previous work employing titanocene enolates.[16]

We were unable to alter the product ratio by adding Lewis bases (e.g., HMPA and DMPU)[17] or by varying the reaction temperature or the order of addition of the reagents. This suggests that the observed stereochemistry is the result of product equilibration.[18] To explore this option, the reaction was monitored by GC/MS as a function of time; the chemistry was conducted at 0 °C in order to slow the reaction progress. Within experimental error, the ratio of diastereomers remained constant over the entire time period.

While these results suggest kinetic selectivity, we remained unconvinced and decided to employ molecular mechanics to determine the difference in ground-state energy between the two diastereomers. It showed that the energy difference (O−Li in place of OH) is ca. 0.8 kcal/mol, with the anti product being more stable. At 20 °C (room temperature), this predicts a product ratio that is in accord with our experimental findings. Thus, we *tentatively conclude* that the experimentally observed ratio reflects a thermodynamic rather than a kinetic partitioning.

In conclusion, we offer a novel, titanocene(III)-promoted approach to the Reformatsky reaction. This method employs easily handled, readily available starting materials, and the conditions are exceedingly mild. Further studies on the mechanistic and stereochemical implications of this reaction and the use of this method in complex syntheses are underway and will be reported in due course.

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Supporting Information Available: Cyclic voltammetry details, ^1H and ^{13}C NMR data for products **3a−i**, and a sample procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Hedenström, E.; Andersson, F.; Hjalmarsson, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1513−1518. (b) Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037−2040.

[17] Kagan, H. B.; Namy, J.-L. *Top. Organomet. Chem.* **1999**, *2*, 155−198.

[18] Traditional zinc-promoted Reformatsky reactions are thought to give thermodynamic product mixtures; usually this favors the anti isomer. See ref 1c.