Direct Synthesis of Fused, Bicyclic *γ*-Butyrolactones via Tandem Reductive Cyclization−Carbonylation of Tethered Enals and Enones

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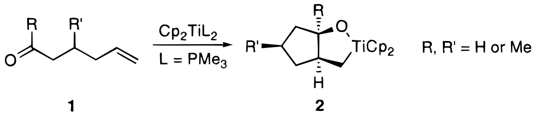
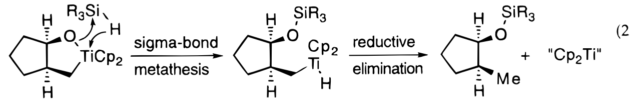
γ-Butyrolactones are ubiquitous in Nature, occurring in about 10% or more of structurally elucidated natural products.[1] An attractive route to this ring system is the [2 + 2 + 1] approach illustrated in Scheme 1A (X = O). Although a similar approach has been successfully employed for the construction of five-membered-ring carbocycles,[2] the application of this route to heterocycle synthesis is not known. Herein we report the first examples of this useful reaction.

Takaya has shown that 1-oxa-5-titanacyclopentanes, derived from insertion of aldehydes into $Cp^*_2Ti(CH_2{=}CH_2)$ ($Cp^* = \eta^5\text{-}C_5Me_5$), react with CO to give stable carbonylated metallacycles by insertion of CO into the Ti−C bond (Scheme 1B).[3] No products arising from insertion into the stronger Ti−O bond were observed. Takaya's carbonylated metallacycles were remarkably stable with respect to reductive elimination. Slow decomposition was observed at 210 °C; ethylene and CO were liberated, but no *γ*-butyrolactone products were detected.

In 1990, Whitby and Hewlett[4] reported that *δ*,*ε*-unsaturated carbonyl compounds react with $Cp_2Ti(PMe_3)_2$[5] to afford bicyclic titanium oxametallacycles (eq 1). In their initial report, the authors briefly described several metallacycle cleavage protocols but noted that "unfortunately, ...conditions for new carbon−carbon bond formation have not yet been found." We[6] and Buchwald[7] recently showed that, in the presence of 1 equiv of an appropriate silane reagent, a titanium-catalyzed reaction is possible. Reductive metallacycle cleavage, allowing for catalysis, takes place via *σ*-bond metathesis followed by reductive elimination as depicted in eq 2. This reaction sequence, however, results in the formation of a C−H bond upon metallacycle cleavage. To the best of our knowledge, carbon−carbon bond forming reactions of these titanium oxametallacycles still have not been reported. Surprisingly, carbonylation does not appear to have been studied.



(1)



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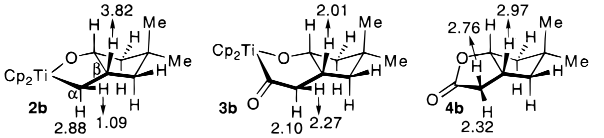


Figure 1. Diagnostic ^{1}H NMR peaks for metallacycles **2b** and **3b** and *γ*-butyrolactone **4b**.

Scheme 1

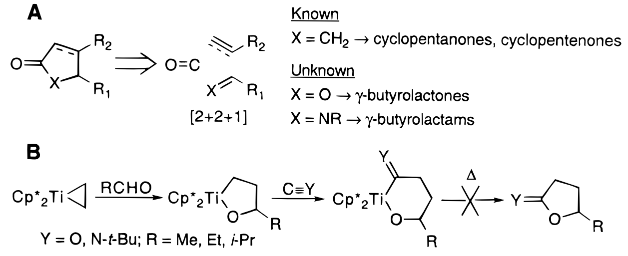
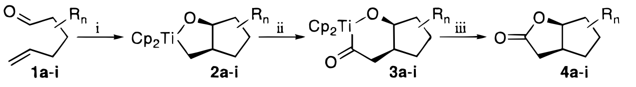
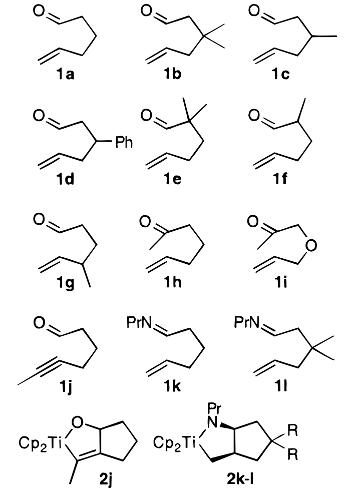


Table 1. Yield Summary for Tandem Reductive Cyclization−Carbonylation Reactions[a]



Substrate	Yield (%)[b] 2	 3	 4
1a	91[c]	83	60
1b	84[c]	44[e]	65
1c	87[c,f]	69[f]	61[f]
1d	95[c,d,f]	64[f]	57[f]
1e	90	74	57
1f	89[c,f]	63[f]	64[f]
1g	88[f]	59[f]	47[f]
1h	88	[g]	31
1i	84[c]	[g]	32
1j	89[c]	0	0
1k	81[c]	0	0
1l	94	0	0



[a] Reaction conditions: (i) $Cp_2Ti(PMe_3)_2$, pentane, 25 °C, 2 h; (ii) CO (1 atm), pentane, 25 °C, 12 h; (iii) air (1 atm), pentane, 25 °C, 4 h. [b] Reaction yields, indicated by column heading, are for the overall transformation carried out without isolation of organometallic intermediates. All reported yields are for isolated products purified by crystallization or column chromatography. [c] Reference 2. [d] Improved yield. [e] Low yield is due to the high solubility of the product in pentane hampering product crystallization. Reaction yield is much higher. [f] Formed as a mixture of diastereomers (diastereomer ratios: 1.5:1 for **2c**−**4c**; 2.3:1 for **2d**−**4d**; 4.5:1 for **2f**−**4f**; 1.8:1 for **2g**−**4g**). [g] A reasonably pure product could not be isolated from the reaction mixture by crystallization.

Titanium metallacycles **2a**−**l** were prepared by reacting substrates **1a**−**l** (Table 1) with $Cp_2Ti(PMe_3)_2$ (eq 1). Upon treatment of complexes **2a**−**i** with CO (1 atm, 25 °C), carbonylated metallacycles **3a**−**i** were formed via insertion of CO into the Ti−C bond (Table 1). As expected, the carbonylated metallacycles did not spontaneously undergo reductive elimination at room temperature and could be isolated as purple,

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(1) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94−110.

(2) See, for example: (a) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y. S.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793−8794. (b) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5505−5506. (c) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593−8601. (d) Bernardes, V.; Verdaguer, X.; Kardos, N.; Riera, A.; Moyano, A.; Pericas, M. A.; Greene, A. E. *Tetrahedron Lett.* **1994**, *35*, 575−578. (e) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Vanpelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199−7207. (f) Schore, N. E. *Org. React. (N.Y.)* **1991**, *40*, 1−90. (g) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917−920.

(3) Mashima, K.; Haraguchi, H.; Oyoshi, A.; Sakai, N.; Takaya, H. *Organometallics* **1991**, *10*, 2731−2736.

(4) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684−1686.

(5) (a) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24* , 394. (b) Binger, P.; Müller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krüger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035.

(6) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787−6788.

(7) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785−6786.

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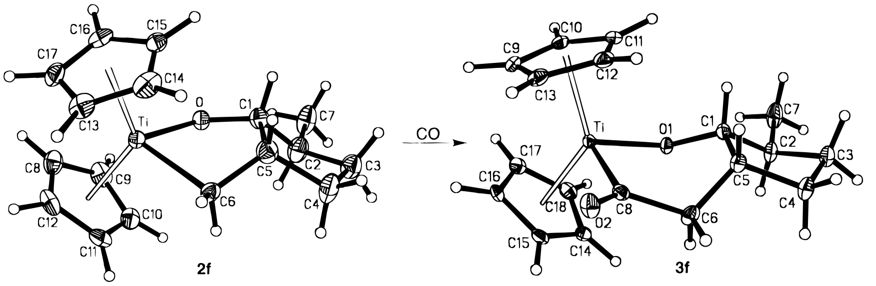

Figure 2. ORTEP drawings of metallacycle **2f** and its carbonylation product, **3f**.

microcrystalline solids. The presence of a titanium acyl moiety was supported by IR ($\nu_{C=O}$ = 1618−1625 cm^{-1}) and ^{13}C NMR ($\delta_{C=O}$ = 289−290 ppm).[8] Exclusive insertion of CO into the Ti−C is suggested by ^{1}H NMR. The widely separated, diastereotopic protons (AMX pattern) for the TiCH$_2$ moiety[9] of the starting metallacycle are replaced by the slightly separated signals (ABX pattern) for Ti(C═O)CH$_2$ (Figure 1).

X-ray quality crystals of the major diastereomer of metallacycle **2f** (from pentane/heptane solution) and carbonylation product **3f** (from toluene solution) could be obtained by slow solvent evaporation (1−3 weeks, 25 °C). Molecular structures, established by single-crystal X-ray analysis, are shown in Figure 2. In **3f**, the Ti−C$_8$ bond distance of 2.218(3) Å and the Ti−O$_1$ bond distance of 1.850(2) Å are normal for single, covalent bonds. The Ti···O$_2$ interatomic distance of 3.117 Å and the Ti−C$_8$−O$_1$ bond angle of 128.3(2)° indicate an η^1 bonding mode for the Ti−acyl moiety.

Reductive elimination of γ-butyrolactones **4a**−**i** from metallacycles **3a**−**i** could be induced thermally or oxidatively or upon treatment with a suitable Lewis acid. We found that simply exposing the carbonylated metallacycles to air cleanly and reproducibly gave γ-butyrolactone products in fair to good yields. The entire reaction sequence of reductive cyclization, carbonylation, and reductive elimination could also be carried out directly without isolation of organometallic intermediates (Table 1).[10]

Metallacycle **2j**, obtained by reductive cyclization of internal alkyne **1j**, did not react with CO (1 atm) at ambient temperature. Imine-derived metallacycles **2k** and **2l** (from **1j** and **1l**) also failed to react with CO. In both cases starting metallacycle could be recovered from the reaction mixture quantitatively. The failure of **2j** to react with CO may be attributable to the increase strength of the Ti−C$_{\text{vinyl}}$ (vs Ti−C$_{\text{alkyl}}$) bond in the metallacycle. The lack of reactivity of imine-derived metallacycles may be related to the increased steric bulk resulting from the replacement of a divalent oxygen with a trivalent nitrogen in the metal coordination sphere.

Heating toluene solutions of metallacycles **2a**−**i** with CO (1 atm) to 80 °C significantly accelerated the rate of carbonyl insertion and reductive elimination. Carbonylation reactions performed at elevated temperatures lead to direct formation of γ-butyrolactone products in a single step.[11] Heating of toluene solutions of metallacycles **2j**−**l**, however, did not lead to carbonyl insertion. Although starting material was consumed, neither carbonylated metallacycles nor five-membered-ring heterocycles (from reductive elimination) could be detected in these reaction mixtures.[12]

In summary, we have reported a titanium-mediated synthesis of γ-butyrolactones which proceeds via the reaction sequence of reductive coupling−carbonylation−reductive elimination. Notable features of this new procedure are the mild reaction conditions (ambient temperature and pressure) and the readily available titanium reagent (prepared in one step from commercially available Cp$_2$TiCl$_2$). The current procedure has been successfully applied to the intramolecular coupling of aldehydes or ketones to terminal olefins. We are currently attempting to derive similar protocols for the conversion of the less reactive metallacycles derived from imines or alkynes to corresponding five-membered-ring heterocycles.[13]

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and listings of fractional atomic coordinates and anisotropic thermal parameters for metallacycles **2f** and **3f** (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(8) Although the carbonyl carbon resonance was not observable in stable C$_6$D$_6$ solutions, it was observable in CDCl$_3$. In CDCl$_3$, the complexes decomposed slightly during the course of data acquisition.

(9) (a) Widely separated, diastereotopic TiC*H*$_2$ protons seems to be a general characteristic of chiral titanocene metallacycles. For the monocyclic 1-oxa-5-titanacyclopentanes studied by Bercaw[9b] and Takaya,[3] there are an upfield signal at δ 0.3−0.4 and a downfield signal at δ 2.2−2.3. For bicyclic 1-oxa-5-titanacyclopentanes **1a**−**l**, there are an upfield signal at δ 0.82−1.11 and a downfield signal at δ 2.85−2.99. (b) Cohen, S. A.; Bercaw, J. E. *Organometallics* **1985**, *4*, 1006−1014.

(10) To a solution of 330 mg (1 mmol) of Cp$_2$Ti(PMe$_3$)$_2$ in 15 mL of pentane was added directly 98 mg (1 mmol) of 5-hexenal **1a**. After being stirred for 2 h at room temperature, the reaction mixture was filtered through a pad of Celite and rinsed with pentane to give a reddish solution of metallacycle **2a**. To this solution was introduced atmospheric pressure of carbon monoxide via a balloon at room temperature for an additional 12 h. The solution color changed from red to deep red-purple, indicating formation of **3a**. After 20 mL of ethyl ether was added, the reaction mixture was exposed to air and stirred for 4 h, during which time it turned bright yellow and a precipitate formed. The resulting yellow mixture was filtered through a pad of silica gel, rinsed with 3:1 ether/pentane (2 × 40 mL). The filtrate was concentrated under reduced pressure to give a yellow liquid residue, which was chromatographed on silica gel using 5:1 hexanes/EtOAc as eluent to give the lactone product as a colorless liquid. Yield: 76.0 mg (60.3%).

(11) The only identifiable titanium-derived byproduct observed in the final reaction mixture was Cp$_2$Ti(CO)$_2$ (^{1}H NMR (C$_6$D$_6$) δ 4.56; IR (heptane) ν_{CO} = 1895, 1974 cm^{-1}).

(12) The only identifiable products observed in these reaction mixtures were Cp$_2$Ti(CO)$_2$ and, in low yield, the acyclic aldehyde (from **2j**) or imine (from **2k**,**l**) used to form the metallacycle substrate.

(13) Preliminary studies indicate that replacing CO with more Lewis basic isonitriles results in a faster insertion followed by an unexpected rearrangement: W. E. Crowe, A. T. Vu, manuscript in preparation.