# Diastereoselective Synthesis of $\gamma$-Butyrolactones from Enones Mediated or Catalyzed by a Titanocene Complex

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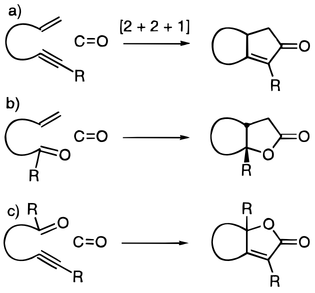
The Pauson−Khand reaction is a powerful transformation that is widely used by organic chemists for the synthesis of cyclopentenones.[1] It involves the formal [2 + 2 + 1] addition of an alkyne, an alkene, and a CO (see Scheme 1a) mediated or catalyzed by cobalt complexes and is an excellent example of atom economy in organic synthesis.[2] Herein we report a heteroatom variant of the intramolecular Pauson−Khand reaction mediated by $Cp_2Ti(PMe_3)_2$ in which either the alkyne or, as demonstrated in one case, the alkene can be replaced with a carbonyl for the diastereoselective synthesis of $\gamma$-butyrolactones or a fused butenolide, respectively (Scheme 1b,c). We have also found that in some cases, this transformation can be accomplished using a catalytic amount of titanium complex. We note that while this work was in progress, a similar method for the synthesis of $\gamma$-butyrolactones using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$ was reported.[3]

We[4,5] and others[6] have recently reported a catalytic reductive cyclization of enones and enals to cyclopentanols using $Cp_2Ti(PMe_3)_2$ (Scheme 2, pathway "a"). In this reaction, the Ti−O bond of the intermediate oxatitanacycle **1** is cleaved via $\sigma$-bond metathesis with a silane.[7] The resulting titanocene alkyl hydride **4** undergoes ligand-induced reductive elimination[8] to form silylated cyclopentanols **5** and to regenerate the catalyst. This work represents the first catalytic reductive cyclization of unsaturated heteroatom-containing fragments. We have been interested in further developing this reaction sequence to yield more highly functionalized products by taking advantage of the potential reactivity of the Ti−C bond in metallacycle **1**. Although insertion into the Ti−C bond in titanium alkoxides is not as facile as in all-carbon titanium species due to the interaction of the oxygen lone pairs with the titanium,[9] prior work from our laboratory[10] and others[3,11] has demonstrated that the insertion of CO into this type of bond is feasible. Indeed we have found that, upon treatment of metallacycle **1** with CO, carbonylated metallacycle **2** is formed (Scheme 2, pathway "b"). We have confirmed the structure of this intermediate by X-ray crystallography. Reductive elimination is induced thermally (70 °C), resulting in the formation of lactone **3** and $Cp_2Ti(CO)_2$. It should be noted that reductive elimination also occurs when metallacycle **2** is exposed to air, but the reaction is not as clean, resulting in significantly lower yields.[3]

**Scheme 1**



**Scheme 2**

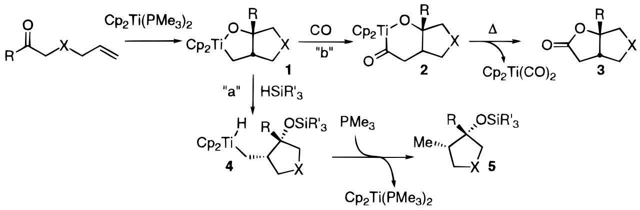


Table 1 shows the results of the hetero Pauson−Khand reaction. The substrates shown are transformed in good to excellent yields and with complete diastereoselectivity to the corresponding $\gamma$-butyrolactones. As shown in Scheme 3, two stoichiometric protocols have been developed. The transformation can be affected using either $Cp_2Ti(PMe_3)_2$[12] or, as shown in a few cases, a method in which the titanocene reagent is generated *in situ* from the air- and moisture-stable $Cp_2TiCl_2$, $PMe_3$ and *n*-BuLi (Table 1, entries 2, 3, and 10).[5,13,14]

The hetero Pauson−Khand cyclization of the ynone (Table 1, entry 8) is of particular interest, since the insertion of CO into the hindered Ti−C(sp$^2$) bond has not been demonstrated in previous studies. For this substrate, slightly higher pressures (20 psig) and temperatures (85 °C) are used. Under these conditions, reductive elimination does not occur thermally; instead, reductive elimination is induced by exposure to air during chromatography.

In the hetero Pauson−Khand reaction reported here, the $\gamma$-butyrolactones are formed with complete diastereoselectivity. This is in contrast to the results obtained in our previous work on the catalytic reductive cyclization of enones to cyclopentanols[4,5] and to the recent report by Crowe.[3] For example, cyclopentanols derived from substrates with substituents $\beta$ to the carbonyl (Table 1, entry 3) give at best a 6:1 ratio of product cyclopentanols, and reactions of substrates with heteroatoms in the backbone (Table 1, entry 6) are essentially nonselective (see Scheme 4). This marked difference in diastereoselectivity can be explained by comparing the conditions under which these two reactions are run. The catalytic reductive cyclization

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[‡] National Science Foundation Predoctoral Fellow, 1994−1997.

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(12) Representative procedure: A dry sealable Schlenk tube is charged with 0.5 mmol of substrate, 0.55 mmol of $Cp_2Ti(PMe_3)_2$, and 2 mL of toluene in an argon-filled glovebox. The reaction flask is removed from the glovebox, evacuated and backfilled with 15 psig CO, and heated to 70 °C for 15−18 h. After cooling to room temperature, the crude reaction mixture is filtered through a plug of silica gel and rinsed through with diethyl ether, and the resulting mixture is purified by flash chromatography.

(13) Hicks, F. A.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 2713.

(14) The *in situ* titanocene generation is an important practical result as $Cp_2Ti(PMe_3)_2$ is pyrophoric, extremely air- and moisture-sensitive, and must be stored and handled in a glove box under argon. The yields from the *in situ* protocol are slightly lower than with the preformed $Cp_2Ti(PMe_3)_2$ but are still good to excellent (80−98%). See supporting information for experimental details.

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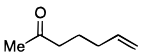
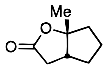
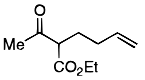
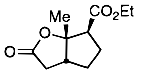
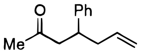
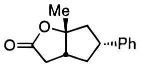
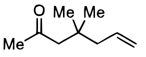
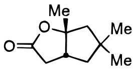
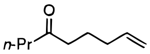
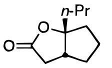
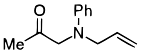
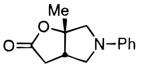
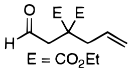
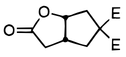
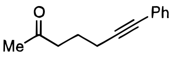
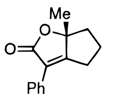
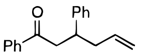
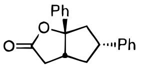
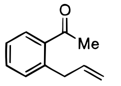
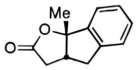
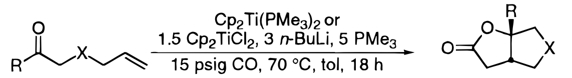
**Table 1.** Titanocene-Mediated Hetero Pauson−Khand Reaction

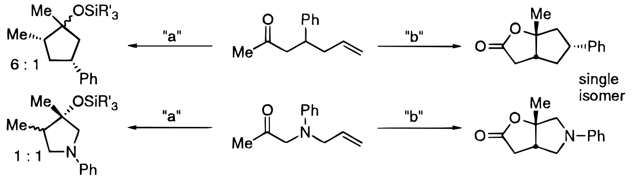
| Entry | Substrate | Product[a] | Isolated Yield (%)[b, c] |
|---|---|---|---|
| 1 |  |  | 65 |
| 2 |  |  | 90 (80) |
| 3 |  |  | 92 (81) |
| 4 |  |  | 85 |
| 5 |  |  | 95 |
| 6 |  |  | 80 |
| 7 |  |  | 61 |
| 8[d] |  |  | 28 |
| 9[e] |  |  | 54[81][f] |
| 10 |  |  | 95 (98) |

[a] Reaction conditions are with 1.1 eq $Cp_2Ti(PMe_3)_2$ at 15 psig CO and 70 °C for 18 h, unless otherwise noted. [b] Isolated yields of products > 95% purity as determined by $^{1}H$ NMR, GC, and are analytically pure. Yields are an average of 2 or more runs. [c] Yields in paretheses are those obtained from the *in situ* generation of the titanium reagent from 1.5 eq $Cp_2TiCl_2$, 3 eq *n*-BuLi, and 5 eq $PMe_3$. [d] Reaction run at 20 psig CO at 85 °C. [e] Reaction run at 1 atm CO at 90 °C. [f] Yield in brackets was obtained by reaction of the substrate with 1.1 eq $Cp_2Ti(CO)_2$ at 90 °C under argon.

## Scheme 3



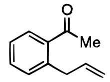
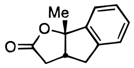
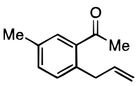
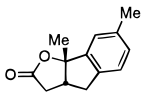
## Scheme 4



(pathway "a") is run at low temperature (−20 °C), so the selectivities are under kinetic control. These conditions prevent the metallacycle from equilibrating to the thermodynamically favored isomer. However, the hetero Pauson−Khand reaction (pathway "b") is run at 70 °C, allowing complete conversion to a single isomer of metallacycle **1**.[15]

We note that the phenyl ketone (Table 1, entry 9) is not a viable substrate for our previously reported catalytic reductive cyclization reaction, presumably due to the large phenyl group blocking the silane from reaction with the Ti−O bond of metallacycle **1**. Since insertion in the hetero Pauson−Khand reaction occurs at the Ti−C bond of the intermediate metallacycle, this substrate is smoothly converted to the corresponding γ-butyrolactone.

**Table 2.** Catalytic Conversion of Acetophenone Derivatives to γ-Butyrolactones

| Entry[a] | Substrate | Product | Mol % $Cp_2Ti(PMe_3)_2$ | Isolated Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 10 | 98 |
| 2 |  |  | 10 | 89 |

[a] The reactions are run with rigorously anhydrous enone and 0.1 eq $Cp_2Ti(PMe_3)_2$ in toluene at 18 psig CO and 105 °C for 15 - 18 h.

The reductive cyclization of enones reported earlier is catalytic due to the ability of the metal byproduct, $Cp_2Ti(PMe_3)_{(1\text{ or }2)}$, to react with the enone starting material to reform metallacycle **1**. In general, the enone starting materials in Table 1 do not react with the byproduct of the hetero Pauson−Khand reaction, $Cp_2Ti(CO)_2$, under the conditions of the reaction. However, we have found that acetophenone derivatives with the phenyl fused to the backbone of the enone (Table 2) can be converted to their corresponding γ-butyrolactones in excellent yield using 10 mol % of $Cp_2Ti(PMe_3)_2$. Table 2 shows the preliminary results from this discovery, which suggest that the acetophenone derivatives are able to induce displacement of the CO ligands from the relatively unreactive $Cp_2Ti(CO)_2$ complex to form metallacycle **1**. This complex has previously been shown to react with phenylacetylenes,[16] ketenes,[17] and $CO_2$ equivalents;[18] the ready reaction with enones was somewhat unexpected. We believe that acetophenone-containing substrates can activate the $Cp_2Ti(CO)_2$ by transient electron transfer or by forming a charge transfer complex. We are currently investigating the use of additives and electron transfer catalysts[19] to activate $Cp_2Ti(CO)_2$ to extend the substrate scope of this new catalytic process. We note that the phenyl ketone substrate (Table 1, entry 9) does not transform catalytically, but the stoichiometric reaction of this substrate with $Cp_2Ti(CO)_2$ results in a 25% higher yield than that obtained using $Cp_2Ti(PMe_3)_2$.

In conclusion, we have developed a diastereoselective and high-yielding synthesis of γ-butyrolactones from enones either mediated by $Cp_2Ti(PMe_3)_2$ or using $Cp_2Ti(PMe_3)_2$ as a precatalyst. We have also described the first example of the formation of a fused butenolide from an ynone using the same metal reagent. We are currently investigating the development of a general catalytic protocol and a catalytic, asymmetric version of this transformation.

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**Supporting Information Available:** Complete experimental procedures as well as analytical and spectroscopic data for all new compounds and spectroscopic data for known organic products (8 pages). Ordering information is given on any current masthead page.

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(15) We note that if the reaction is run at room temperature, the diasteroselectivities suffer.[3]

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