γ-Butyrolactone Synthesis via Catalytic Asymmetric Cyclocarbonylation

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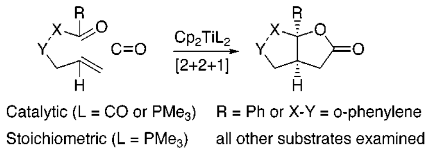
The butyrolactone ring is an integral building block of many natural products.[2] An atom economic route toward the formation of this important skeleton is a formal [2+2+1] cycloaddition of an alkene, a carbonyl, and carbon monoxide. The first example of this Hetero-Pauson−Khand reaction was reported from our laboratory where δ,ϵ-unsaturated ketones and aldehydes were converted to fused, bicyclic γ-butyrolactone products via the cyclocarbonylation reaction shown in Scheme 1.[3] Although Buchwald[4] has recently reported a catalytic version of this transformation using $Cp_2Ti(PMe_3)_2$ or $Cp_2Ti(CO)_2$, this method is limited to aryl ketone substrates (Scheme 1). Development of a general catalytic protocol and an asymmetric version of this transformation would be a significant improvement. Herein we report a general catalytic cyclocarbonylation of enals and enones using a chiral titanocene catalyst that also affords the first example of the asymmetric version of this reaction.[5]

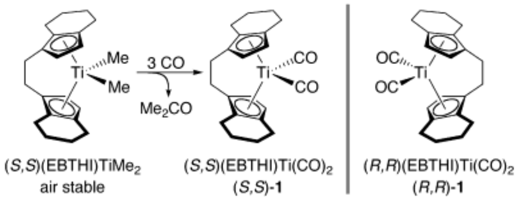
$Cp_2Ti(CO)_2$ (formed under catalytic conditions) does not react with most δ,ϵ-unsaturated ketone and aldehyde substrates, rendering cyclocarbonylation reactions stoichiometric. Ansa-metallocene complexes often exhibit markedly different reactivity than their unbridged counterparts. In particular, Brintzinger has shown that ansa-titanocene dicarbonyl complexes are substantially less stable than $Cp_2Ti(CO)_2$.[6] We therefore reasoned that the ansa-metallocene (EBTHI)$Ti(CO)_2$ (**1**, Scheme 2) might be more reactive than $Cp_2Ti(CO)_2$ toward cyclocarbonylation substrates and tested the utility of **1** as a catalyst. An attractive feature of catalyst **1** is that it can be generated in situ from the air stable precursor (EBTHI)$TiMe_2$ (Scheme 2). In analogy to the Petasis olefination reagent,[7] Cp_2TiMe_2, (EBTHI)$TiMe_2$ can be easily handled as a solid on the benchtop—without making special provisions to exclude oxygen or moisture.

In a typical experiment a mixture of substrate (see Table 1) and catalyst **1**[8] in toluene was heated at 100 °C, under CO pressure,[9] in the presence of excess PMe_3.[10,17] The catalyst system worked well both for enal and enone substrates forming fused

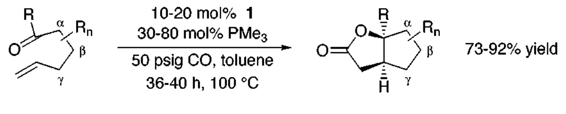
Scheme 1. The Hetero-Pauson−Khand Reaction



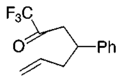
Scheme 2



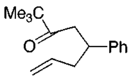
γ-butyrolactones in very good to excellent yield without any side reaction (eq 1, Table 1).



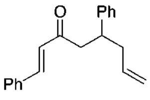
Cyclocarbonylation of trifluoromethyl ketone **2**[11] or *tert*-butyl ketone **3** was not successful; no significant lactone formation was observed even after 4 days under standard reaction conditions. The attempted cyclocarbonylation of δ,ϵ-unsaturated aryl ketone **4** also did not afford the desired lactone product. Instead this substrate underwent a vinylogous pinacol coupling reaction (stoichiometric in titanium) to produce a highly substituted cyclopentanol derivative **5**.[12]



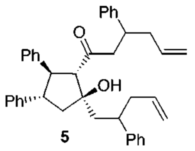
2



3



4



5

Diastereofacial selectivity was investigated using racemic **1** to cyclocarbonylate substrates possessing a preexisting stereocenter. A mixture of diastereomeric lactones was obtained for substrates possessing a β-carbon stereocenter (entries 1−4), and essentially perfect diastereofacial selectivity was observed for substrates possessing a stereocenter at the α- or γ-carbon (entries 5 and 6). Observed diastereoselectivities are markedly higher than those obtained in corresponding room temperature, stoichiometric reactions reported previously.[3] This may be attributable to the elevated reaction temperature used in the catalytic reactions.[13]

Preliminary studies using enantiomerically pure (*r,r*) or (*s,s*) catalyst (Scheme 2) revealed a substrate dependent enantioselec-

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[1] Present address: Albany Molecular Research, Inc.: Albany, NY 12203.

[2] Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94−110.

[3] Crowe, W. E.; Vu, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 1557−1558.

[4] (a) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818−5819. (b) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424−4431.

[5] Some preliminary experiments were run at Emory University, Atlanta, GA 30322.

[6] Smith, J. A.; Brintzinger, H. H. *J. Organomet. Chem.* **1981**, *218*, 159−167.

[7] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

[8] (EBTHI)$Ti(CO)_2$ was generated in situ from (EBTHI)$TiMe_2$ following the procedure reported in: Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688−11689. For a similar synthesis of $(CH_2)_2(C_5H_4)_2Ti(CO)_2$, see: Smith, J. A.; Brintzinger, H, H. *J. Organomet. Chem.* **1981**, *218*, 159.

[9] CO pressure of the reaction vessel was set to 50 psi at the inception of the reaction and generally increased to 60−65 psi during reaction at 100 °C.

[10] 100% conversion occurred in the presence of excess PMe_3, whereas without excess PMe_3 only 50−60% conversion was observed. For a similar effect of PMe_3 on related reaction see ref 3b. Addition of excess PMe_3 was also found to decrease the amount of catalyst (from 20 mol % to 10 mol %) necessary for complete conversion.

[11] Trifluoromethyl ketone on treatment with a stoichiometric amount of catalyst under similar conditions resulted in a complex mixture of products (TLC). In this case the highly electrophilic carbonyl carbon of the substrate probably participated in the reaction with the cyclopentadienyl ring of titanocene. For a precedence of such a reaction see: Gleiter, R.; Wittwer, W. *Chem. Ber*. **1994**, *127*, 1797.

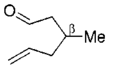
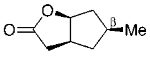
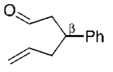
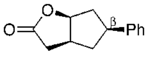
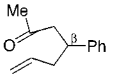
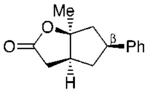
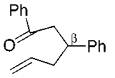
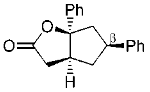
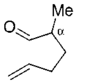
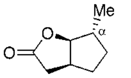
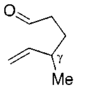
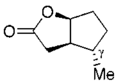
[12] Unsaturated aryl ketones were reported to react with $Cp_2Ti(CO)_2$ to generate highly substituted cyclopentanol in good yield. See: Schobert, R.; Maaref, F.; Durr, S. *Synlett* **1995**, 83.

[13] Buchwald (ref 4) reported high diastereoselectivity for cyclocarbonylation reactions run at 70 °C and attributed the selectivity enhancement to reversible metallacycle formation allowing equilibration of thermodynamically favored isomers.

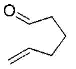
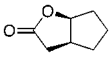
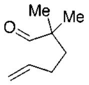
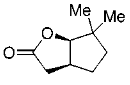
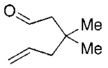
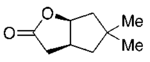
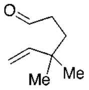
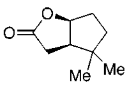
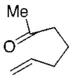
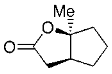
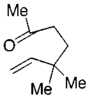
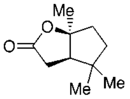
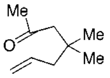
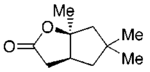
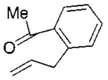
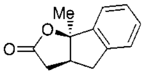
10.1021/ja005568m CCC: \$20.00

Table 1. Catalytic Cyclocarbonylation Reactions

Diastereoselective Reactions[b]

entry	Substrate	Product	Yield (%)	ratio[c]
1			92	4.6:1
2			89	10:1
3[d]			73	8.5:1
4[e]			76	19:1
5			79	>95:5[f]
6			90	>95:5[f]

Enantioselective Reactions

entry	Substrate	Product[g]	Yield (%)	catalyst	ee (%)
7			84	(*S*,*S*)-**1**	0
8			91	(*S*,*S*)-**1**	0
9			87	(*S*,*S*)-**1** (*R*,*R*)-**1**	58 60[h]
10			86	(*S*,*S*)-**1**	89
11[d]			80	(*S*,*S*)-**1** (*R*,*R*)-**1**	90 89[h]
12[d]			88	(*S*,*S*)-**1**	90
13[d]			93	(*S*,*S*)-**1**	58
14[d]			96	(*S*,*S*)-**1**	38

[a] Reaction conditions were as follows (see eq 1): 50 psig CO, 100 °C, 36−40 h, toluene. Unless otherwise indicated, all reactions were run with 10 mol % **1** (generated in situ) and 30 mol % PMe_3. [b] Racemic **1** was used. [c] Ratio refers to the mixture of epimers at C2, C3, or C4. All products were exclusively cis-fused within the limits of detection. [d] 50 mol % PMe_3 was used. [e] 20 mol % **1** and 80 mol % PMe_3 were used. [f] Only one diastereomer detected by ^{1}H NMR. [g] Product configuration depicted is for the reaction run with (*S*,*S*)-**1**. [h] Reactions run with the (*R*,*R*)-**1** catalyst gave a product configuration enantiomeric to that depicted in the table for the (*S*,*S*)-**1** catalyst.

tivity as summarized in Table 1 (entries 7−14).[14] Of the eight substrates examined, four aldehydes and four methyl ketones, three reacted with high enantioselectivity (89−90% ee), three reacted with moderate enantioselectivity (38−60% ee), and two reacted with no enantioselectivity (0% ee).

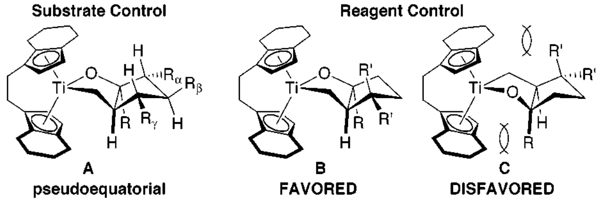


Figure 1. Potential stereocontrol elements.

Metallacycle intermediates corresponding to major reaction products are shown in Figure 1 where the conformations of the fused cyclopentane and oxatitanacycle rings are based on our previously reported crystal structure.[3] For diastereoselective reactions of chiral substrates (substrate control, structure **A**), the major diastereomer formed corresponds to the metallacycle intermediate where the α-, *β*-, or *γ*-carbon substituent adopts a pseudoequatorial alignment (R_α, R_β, or $R_\gamma \neq$ H). For enantioselective reactions of achiral substrates, the major enantiomer formed corresponds to metallacycle **B** (in the six reactions which proceed selectively). The most selective reactions (entries 10−12) correspond to substrates which place methyl groups in one or both of the positions (R and/or R′ = Me) which would seem to maximize the steric difference between the diastereomeric metallacycles **B** (favored) and **C** (disfavored). Results obtained with other substrates (entries 9, 13, 14) show, however, that enantioselectivity is also influenced by factors not evident from inspection of structures **B** and **C**.

In conclusion, we have developed a general catalytic protocol for the intramolecular Hetero-Pauson−Khand cyclization. Notable features of this new catalytic reaction are the operational simplicity of the procedure (air stable catalyst precursor and mild reaction conditions) and the remarkable effect of the ansa bridge in promoting catalytic activity. Although the use of ansa-bridging to specifically tune the steric environment of metallocene complexes has been widely utilized, other reactivity changes promoted by ansa bridging have received far less attention.[15] The ansa effect responsible for the enhanced reactivity of **1** is a previously unexploited design feature for metallocene catalyzed reactions; we are currently attempting to determine its precise nature.[16]

Acknowledgment. Support of this work by funds provided by the National Institutes of Health (R01 GM53172) and Louisiana State University is gratefully acknowledged. We thank Drs. Dale Treleaven and Frank Zhou for assistance with 2D NMR experiments.

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

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(14) Product absolute stereochemistry was assigned using the Pirkle chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol to induce chemical shift inequivalence in the α proton signals of enantiomeric lactone products: Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.

(15) (a) Churchill, D.; Shin, J. H.; Hascall, T.; Hahn, J. M.; Bridgewater, B. M.; Parkin, G. *Organometallics* **1999**, *18*, 2403. (b) Lee, H.; Desrosiers, P. J.; Guzei, I.; Rheingold, A. L.; Parkin, G. *J. Am. Chem. Soc.* **1998**, *120*, 3255. (c) Lee, H.; Bonanno, J. B.; Hascall, T.; Cordaro, J.; Hahn, J. M.; Parkin, G. *J. Chem. Soc., Dalton Trans.* **1999**, 1365. (d) Shin, J. H.; Parkin, G. *Chem. Commun.* **1999**, 887.

(16) We believe that the ansa bridge of the (EBTHI)Ti(CO)$_2$ complex provides a driving force for the reductive cyclization in the form of ansa strain which is released upon formation of the metallacycle intermediate.

(17) Experimental procedure: A dry Fisher-Porter bottle was charged with substrate, (EBTHI)TiMe$_2$, PMe_3 and toluene, then attached to a Schlenk line, evacuated, and backfilled with 50 psig of CO. The reaction was heated at 100 °C for 36−40 h, then cooled to room temperature and CO pressure cautiously released inside a fume hood. The reaction mixture was filtered (silica gel), washed (Et_2O), concentrated under reduced pressure, and purified by flash column chromatography.