Highly Enantioselective Catalytic Pauson−Khand Type Formation of Bicyclic Cyclopentenones

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The transition-metal promoted cyclocondensation of an alkyne, alkene, and carbon monoxide (the Pauson−Khand reaction when cobalt complexes are employed) has emerged as a highly convergent method for the synthesis of cyclopentenones from readily available starting materials.[1] Many advances relating to this methodology have been reported recently, including the development of cyclizations employing a catalytic amount of the transition-metal complex.[2] One major goal which has remained elusive is the development of a catalytic asymmetric variant of these cyclizations.[3] We report here the first successful realization of this goal.

Our recent demonstration that $Cp_2Ti(CO)_2$ is an effective catalyst for the cyclocarbonylation of enynes[2d] focused our attention on the use of its enantiomerically pure analog (*S,S*)-(EBTHI)Ti(CO)$_2$, **1** (Figure 1), in asymmetric Pauson−Khand type cyclizations. We have found that **1**, generated *in situ* from (*S,S*)(EBTHI)TiMe$_2$,[4] functions as a highly enantioselective catalyst for the conversion of enynes to cyclopentenones.

The typical experimental conditions which we utilized for this transformation are outlined in Scheme 1.[5] Attempts to effect cyclization at temperatures lower than 90 °C resulted in diminished conversion to product. The correct choice of CO pressure was also important. At CO pressures both higher and lower than 14 psig, conversion to cyclopentenone was less efficient.

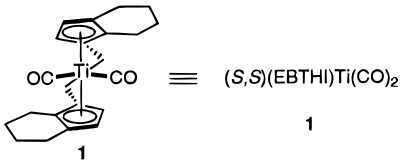
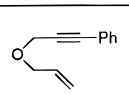
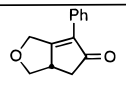
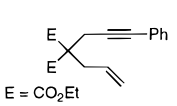
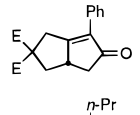
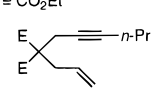
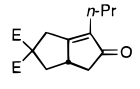
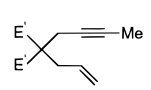
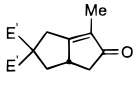
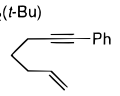
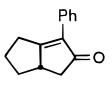
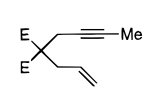
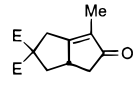
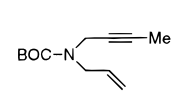
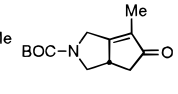
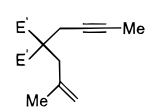
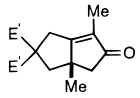


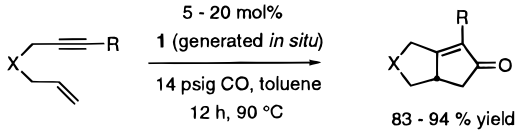
Figure 1.

Table 1. Catalytic Asymmetric Pauson−Khand Type Cyclization

Entry	Substrate	Product	Mol% (*S,S*) Cat	ee (%)[a]	Yield (%)[a]
1			20	96	85
2			7.5	94	92
3			5	89	94
4			5	89	88
5			20	87	70[b]
6			5	87	90
7			10	74	84
8			20	72	90

[a] The yields and ee's are the average of two or more experiments and represent isolated products of >95% purity by ^{1}H NMR and GC analysis. [b] Unreacted starting material (25%) detected by GC analysis.

Scheme 1



As shown in Table 1, a variety of 1,6-enynes were converted to bicyclic cyclopentenones with high enantioselectivity.[6,7] The functional group compatibility manifested by this catalyst was similar to that seen in the $Cp_2Ti(CO)_2$ cyclization.[2d] This includes toleration of ethers (entry 1), amines (entry 7), and esters (entries 2, 3, and 6). Of importance is that **1** is able to successfully cyclize substrates containing 1,1-disubstituted olefins (entry 8). The inefficient processing of substituted olefins is a weakness in many Pauson-Khand systems.[1,2] Substrates

† National Science Foundation Predoctoral Fellow, 1994−1997.

(1) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Kidlington, 1995; Vol. 12, p 703.

(2) For Ti, see: (a) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912. (b) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593. (c) Hicks, F. A.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 2713. (d) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450. For Co, see: (e) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (f) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793. (g) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (h) Lee, N. Y.; Chung, Y. K. *Tetrahedron Lett.* **1996**, *37*, 3145.

(3) For examples of stoichiometric asymmetric Pauson−Khand reactions, see: (a) Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449. (b) Castro, J.; Sorensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388. (c) Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A.; Bernardes, V.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 2153. (d) Hay, A. M.; Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Organometallics* **1995**, *14*, 4986. (e) Park, H.-L.; Lee, B. Y., Kang, Y. K.; Chung, Y. K. *Organometallics* **1995**, *14*, 3104. (f) Kerr, W. J.; Kirk, G. G.; Middlemiss, D. *Synlett* **1995**, 1085.

(4) The *in situ* preparation of (*S,S*)(EBTHI)Ti(CO)$_2$ was adapted from the related synthesis of $(CH_2)_2(C_5H_4)_2Ti(CO)_2$. See: Smith, J. A.; Brintzinger, H. H. *J. Organomet. Chem.* **1981**, *218*, 159. While **1** was not isolated, it was identified by the ^{1}H NMR spectrum. 300 MHz (C_6D_6) 4.74 (d, J = 2.4 Hz, 2 H), 4.30 (d, J = 2.4 Hz, 2 H), 2.24 (m, 8 H), 1.78 (m, 4 H), 1.51 (m, 8 H). Additionally, ^{1}H NMR indicates the presence of acetone, a coproduct also found in the Brintzinger synthesis.

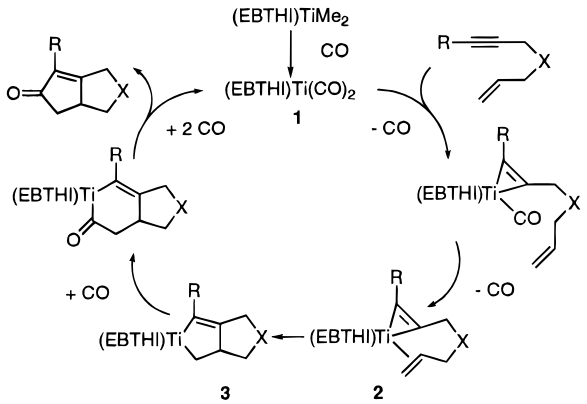
(5) **General Procedure:** In an argon filled glovebox, a dry sealable Schlenk flask is charged with (*S,S*)-(EBTHI)TiMe$_2$ (0.025 mmol, 8 mg), toluene (2 mL), and the substrate (0.50 mmol). The Schlenk is removed from the glovebox, attached to a Schlenk line, evacuated, and backfilled with 14 psig CO. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. The reaction mixture is heated to 90 °C for 12−16 h. After cooling the reaction mixture to room temperature, the CO is cautiously released in the hood. The crude reaction mixture is filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography. **Note:** All substrates were passed through a plug of alumina (except for entry 1) in the glovebox to remove adventitious moisture. The substrate for entry 1 was distilled under vacuum and stored in the glovebox.

(6) The absolute configuration for these products was assigned based upon an X-ray crystal structure of the cyclopentenone from entry 5. Details will be published in the full paper.

(7) We note that a 1,6-enyne containing a terminal alkyne and a 1,7-enyne could be cyclized with this catalyst system (20 mol%) but with lower levels of enantioselectivity (51 and 47% ee, respectively).

S0002-7863(96)03045-4 CCC: $12.00

Scheme 2



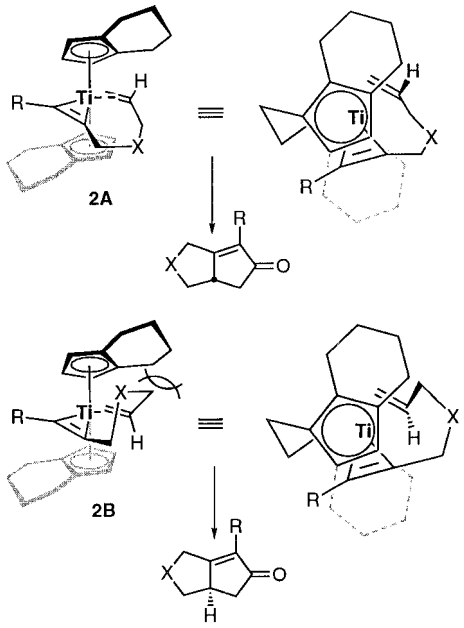
which were geminally substituted (entries 2, 3, 4, and 6) required significantly less catalyst for cyclization (5−7.5 vs 20 mol%) than the substrates lacking backbone substitution (entries 1 and 5); presumably this is due to the Thorpe−Ingold effect.[8] This is in contrast to the results obtained with the corresponding $Cp_2Ti(CO)_2$ system, where all these substrates were cyclized with 5 mol% catalyst.[2d,9]

While the exact course of this transformation is unclear,[10] Scheme 2 shows one possible pathway. After initial formation of **1**, the two CO ligands are replaced, in a stepwise fashion, by the enyne, to give intermediate **2**. Reductive cyclization of **2** yields metallacycle **3**. Subsequent CO insertion and reductive elimination produce the cyclopentenone. Presumably the enantioselectivity determining step in this mechanism is metallacycle formation (**2** → **3**). Two reasonable intermediates leading to the diastereomeric metallacycles are shown in Scheme 3. Intermediate **2B** possesses an unfavorable steric interaction between the enyne backbone and the EBTHI ligand. Intermediate **2A**, which leads to the major enantiomer, suffers from no such interaction.

Utilizing this model, we can rationalize the reduced enantioselectivity obtained for the substrate shown in entry 8. For the 1,1-disubstituted olefin, replacing the olefinic hydrogen with a methyl group should decrease the energy difference between the two diastereomeric intermediates in Scheme 3, leading to the observed decrease in enantioselectivity.

For the substrate shown in entry 7, the effect of the amide substituent (the X group in Scheme 3) is critical. When the carbamate is replaced by a phenyl group, the cyclization also proceeds to completion using 10 mol% catalyst, but, surprisingly, the product obtained is racemic. We currently have no explanation for the effects of different nitrogen substituents on the enantioselectivity of the reaction.

Scheme 3



In summary, we have developed the first catalytic asymmetric Pauson−Khand type cyclization. A variety of 1,6-enynes is converted to the corresponding bicyclic cyclopentenones with good to excellent enantioselectivity. We are currently investigating the substrate scope, mechanism, and the development of an intermolecular version of this process.

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Supporting Information Available: Representative experimental procedures as well as spectroscopic characterization of all products (5 pages). See any current masthead page for ordering and Internet access instructions.

JA9630452

(8) The Thorpe−Ingold effect has often been demonstrated to promote the Pauson−Khand cyclization. For examples, see ref 1.

(9) Hicks, F. A.; Buchwald, S. L. Unpublished results.

(10) There is evidence that cyclocarbonylations involving $Cp_2Ti(CO)_2$ do not proceed by this exact mechanism.[2d] However, any related mechanism must involve metallacycle formation as the enantioselectivity determining step. All related modes of metallacycle formation still involve the same steric issues presented here.