An Intramolecular Titanium-Catalyzed Asymmetric Pauson−Khand Type Reaction[1]

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Abstract: The development of the first catalytic asymmetric Pauson−Khand type cyclization of enynes is described. The active catalyst, (*S*,*S*)-(EBTHI)Ti(CO)$_2$ (**1**), is generated in situ from (*S*,*S*)-(EBTHI)TiMe$_2$ (**2**). A variety of 1,6-enynes can be converted to the corresponding cyclopentenones in high yield (70−94%) with excellent ee's (87−96%). Limitations of the catalyst with respect to substrate structure are discussed. The absolute configurations of several of the enone products have been ascertained, and these assignments represent a reversal with respect to an assignment in the initial report. A rationale for the sense and levels of enantioselectivity for this catalyst is proposed.

Introduction

The application of transition metals to the field of organic synthesis has led to a plethora of new transformations which allow for the rapid and elegant assembly of complex carbocyclic systems.[2] A powerful and much studied example that falls in this category is the Pauson−Khand reaction,[3] which involves a cobalt-mediated formal [2 + 2 + 1] cycloaddition of an alkyne, an alkene, and CO to produce a cyclopentenone (Scheme 1a). Although much work has been devoted to investigating intermolecular variants of this transformation, it is the intramolecular Pauson−Khand cyclization of enynes (Scheme 1b) which has received the most attention in terms of synthetic application.[4] There is a high degree of efficiency embodied in this transformation, with the formation of three new C−C bonds, two rings, and a new chiral center; this reaction has been utilized as the key step in a variety of efforts in total synthesis.[5] The practicality of this process has also been improved recently with the advent of Pauson−Khand type reactions[6] requiring only catalytic amounts of Co[7] and other metals such as Ti,[8,9] Ru,[10,11] and Rh.[12,13]

Based on the frequent application of the intramolecular Pauson−Khand reaction in the total synthesis of natural products in racemic form, the availability of an asymmetric variant would be a useful tool for the organic chemist. Much effort has been devoted toward this end in the past decade, and the approaches toward a stoichiometric intramolecular version fall into two basic categories: the diastereoselective cyclization of optically active enynes and that of enynes equipped with chiral auxiliaries; this field has been the subject of a recent review.[14]

The first attempts at effecting asymmetric Pauson−Khand type cyclizations evolved from the diastereoselective cyclization of chiral enynes. Magnus conducted studies in the 1980s designed to assess the diastereoselectivity of the Pauson−Khand cyclization of a variety of chiral enynes.[15] This work culminated in the stereoselective total syntheses of coriolin, hirsutic acid, and quadrone.[5] He later applied this approach to an enantioselective synthesis of a carbocyclin analogue via an enyne derived from D-(+)-ribolactone (Scheme 2).[16] A similar route

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(1) This paper has been adapted, in part, from the following thesis: Hicks, F. A. Ph.D. Dissertation, Massachusetts Institute of Technology, 1999.

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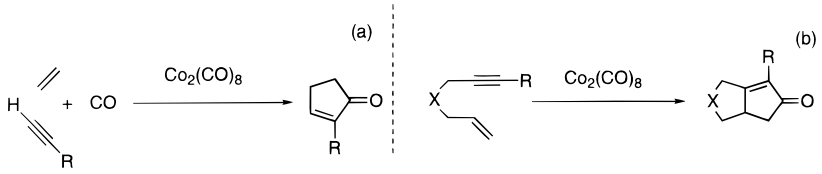
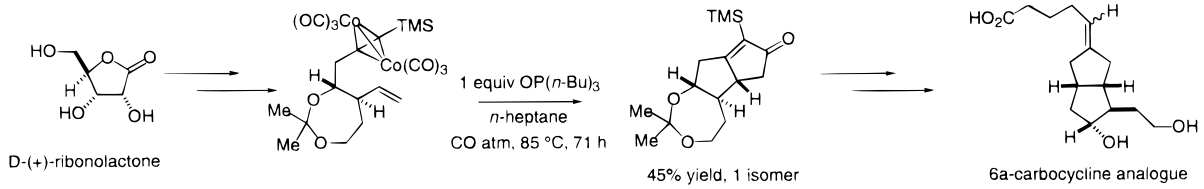
10.1021/ja990683m CCC: $18.00
Published on Web 07/20/1999

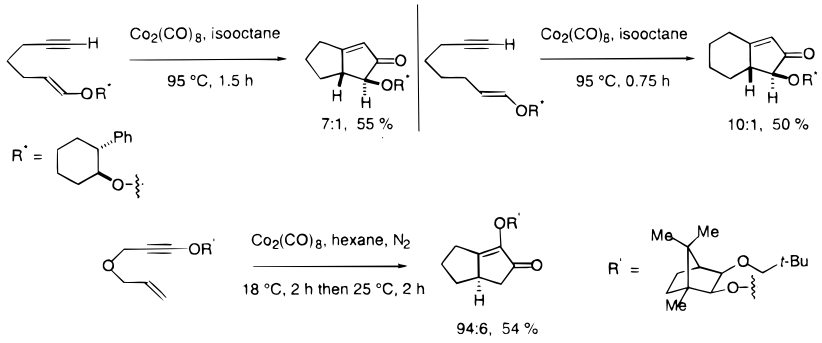
Scheme 1



Scheme 2



Scheme 3



to carbocyclin analogues was also reported by Mulzer.[17] Approaches toward (−)-dendrobine[18] and xestobergsterol[19] and total syntheses of (−)-α-kainic acid[20] and (+)-epoxydictymene[21] have since been reported utilizing this concept. However, this general tack to an asymmetric Pauson−Khand reaction is limited by the necessity to prepare an optically active enyne.

Another approach which has been developed by Pericàs, Moyano, Greene, and co-workers involves the use of enynes with pendant chiral auxiliaries. Enynes with *trans*-2-phenylcyclohexanol attached to the terminus of the alkene undergo Pauson−Khand cyclization to provide products with high diastereomer ratios (7:1 for a 1,6-enyne and 10:1 for a 1,7-enyne).[22] A 1,6-enyne possessing an alkyne substituted with a camphor-derived chiral auxiliary could also be cyclized diastereoselectively (∼9:1, Scheme 3).[23] This methodology has been applied to the formal total synthesis of (+)-hirsutene[22] and the total synthesis of (+)-*β*-cuparenone[24] and (+)-15-norpentalene.[25] These chiral auxiliaries can be cleaved from the product with SmI_2 and recovered for reuse. This methodology suffers from the need to contrive an enyne synthesis around the auxiliary, much in the same manner as for the optically active enynes (vide supra).

Both of these synthetic methods require a stoichiometric amount of an optically active agent. A more efficient method would involve a catalytic, asymmetric Pauson−Khand reaction where the asymmetry is derived from an optically active catalyst. In the past 20 years, the field of asymmetric catalysis has experienced a developmental explosion.[26] In the area of asymmetric transition metal-catalyzed cycloadditions, progress has been made on the cyclization of unfunctionalized substrates. Lautens has reported good levels of enantioselectivity for both a cocatalyzed [2 + 2 + 2] homo Diels−Alder reaction[27] (55−91% ee, five examples) and an analogous cocatalyzed [4 + 2 + 2] process[28] (71−79% ee, six examples) employing norbornadiene and the chiral ligands *S*,*S*-chiraphos and *R*-prophos, respectively. A detailed investigation of a series of (+)-DIOP-related ligands was undertaken by Livinghouse for the Rh-catalyzed intramolecular Diels−Alder reaction with good results (62−87% ee, four examples).[29] When a derivative of the *trans*-chelating (*S*,*S*)-(*R*,*R*)-TRAP ligand was utilized for the Pd-catalyzed Alder-ene reaction of a series of substituted sulfonamido enynes, excellent (95% ee, one example) to good (53−76% ee, eight examples) levels of selectivity were obtained.[30,31]

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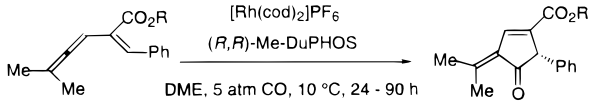
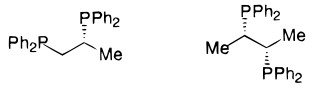
Scheme 4

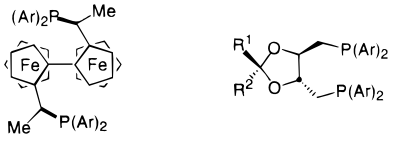


R	yield(%)	ee(%)
i-Bu	96	91.5
Et	93	92
Bn	94	95

Finally, Wender has reported a single example of the Rh-catalyzed [5 + 2] cycloaddition of a cyclopropyl diene with *S,S*-chiraphos to provide a 5,7-fused carbocycle with 63% ee.[32]



R-prophos *S,S*-chiraphos

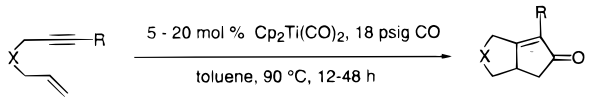


(*S,S*)-(*R,R*)-TRAP derivatives (+)-DIOP derivatives

However, besides the work presented herein,[33] only one catalytic asymmetric cyclocarbonylation reaction has been described. Ito recently reported utilizing (*R,R*)-Me-DuPHOS as a chiral ligand for the Rh-catalyzed cyclocarbonylation of vinylallenes. Several examples with moderate to good enantioselectivity (64.5−78.0% ee) were reported, while one class of substrates was cyclocarbonylated with excellent enantioselectivity (Scheme 4).[34] The large number of catalytic cyclocarbonylation reactions and the paucity of asymmetric variants emphasizes the difficulty of this transformation. There are several factors which may contribute to the problems of developing catalytic asymmetric cyclocarbonylations employing later transition metal complexes. The ligands typically employed for effecting asymmetry, such as polydentate phosphines, amines, imines, oxazolines, and hybrids thereof, may not be stable with regard to CO substitution under the forcing reaction conditions often employed in cyclocarbonylation reactions. Additionally, even if there is a highly unfavorable equilibrium with the ligand dissociated complex, it is often more reactive than the ligand-substituted one.[35] Such a situation would lead to product formation with low levels of enantioselectivty. Additionally, there are a limited number of available coordination sites for late transition metal complexes of these polydentate ligands, often necessitating the use of cationic complexes.[36]

The recently reported titanocene-catalyzed enyne cyclocarbonylation (vide supra, Scheme 5) represents an opportunity to

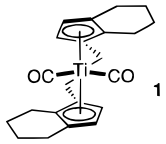
Scheme 5



circumvent these problems. Because the cyclopentadienyl ligands are covalently bound to the titanium center, it should be possible to design a chirally modified catalyst which will be stable under the conditions required for cyclocarbonylation chemistry. We elected to start our investigations with the ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl) (EBTHI) ligand, which was first introduced into group 4 chemistry by Brintzinger.[37] Its titanium complexes have found a number of applications in catalytic asymmetric hydrogenations of imines,[38] olefins,[39] and enamines[40] and hydrosilylations of ketones[41] and imines.[42] Additionally, zirconium complexes have been utilized to effect a number of enantioselective carbon−carbon bond-forming processes,[43] including several elegant applications by Hoveyda to natural product synthesis.[44]

Results and Discussion

Development of Reaction Conditions. Our initial investigations centered around the development of a synthesis of the requisite catalyst (*S,S*)-(EBTHI)Ti(CO)$_2$ (**1**). The conversion of



(*S,S*)(EBTHI)Ti(CO)$_2$

titanocene dialkyl derivatives to the corresponding dicarbonyl complexes under a CO atmosphere is a well-documented process.[45] Presumably, initial CO coordination and migratory insertion generates a transient alkyl acyl derivative, which undergoes reductive elimination to generate the η^2-ketone complex.[46] Subsequent ligand exchange with CO produces the dicarbonyl. In particular, dimethyl ethylene-1,2-biscyclopentadienyltitanium, which contains a ligand framework closely related to EBTHI, was converted to the dicarbonyl in high yield

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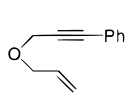
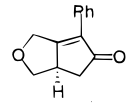
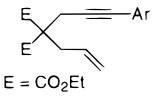
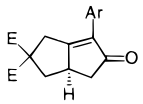
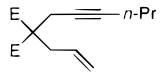
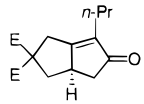
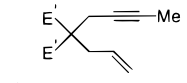
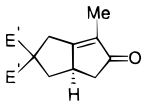
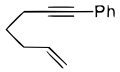
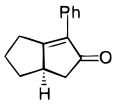
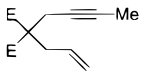
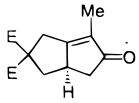
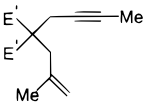
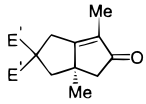
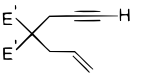
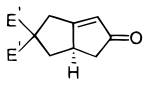
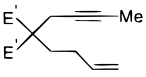
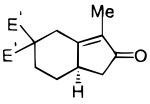
Table 1. Catalytic Asymmetric Cyclocarbonylation of Enynes

Entry	Substrate	Product	Mol% (*S,S*) Cat	ee (%)	Yield (%)
1			20	96	85
			2 Ar = Ph, 7.5	94	92
			3 Ar = *p*-MeOC$_6$H$_4$, 7.5	92	89
2 - 6			4 Ar = *p*-ClC$_6$H$_4$, 10	90	82
	E = CO_2Et		5 Ar = *p*EC$_6$H$_4$, 10	87	84
			6 Ar = *p*CF$_3$C$_6$H$_4$, 10	93	88
7			5	89	94
8			5	89	88
	E'=CO_2(*t*-Bu)				
9			20	87	70
10			5	87	90
11			20	72	90
12			20	50	87
13			20	47	77

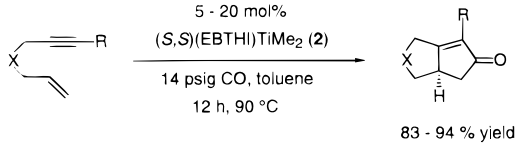
using this methodology.[47] Initial NMR tube experiments revealed that heating (*S,S*)-(EBTHI)TiMe$_2$ (**2**)[48] under 12 psig CO at 90 °C did, indeed, produce the corresponding dicarbonyl complex **1** and acetone. Addition of 1 equiv of an enyne (Table 1, entry 1) to the NMR tube followed by heating at 90 °C led to the formation of the desired cyclopentenone in >95% ee. For the purposes of catalytic cyclizations, dicarbonyl **1** was formed in situ from **2** under the reaction conditions.

A direct route to **1** involving reductive carbonylation of (*S,S*)-(EBTHI)TiCl$_2$ was later developed (eq 1).[49] It was thought that

$$(S,S)\text{-(EBTHI)TiCl}_2 \xrightarrow[\text{THF, 50 °C, 1.5 h}]{\text{Mg, cat. HgCl}_2\text{, 18 psig CO}} \underset{\mathbf{1}}{(S,S)\text{-(EBTHI)Ti(CO)}_2} \quad 55\%\ \text{yield} \qquad (1)$$

the isolated dicarbonyl complex might serve as a more effective precatalyst than **2**. However, a survey of several enynes under several sets of reaction conditions revealed that there was no significant advantage to the use of isolated **1** as the precatalyst. Due to the greater stability and ease of synthesis of **2**, it was utilized as the precatalyst for the synthetic work described herein.

Scheme 6



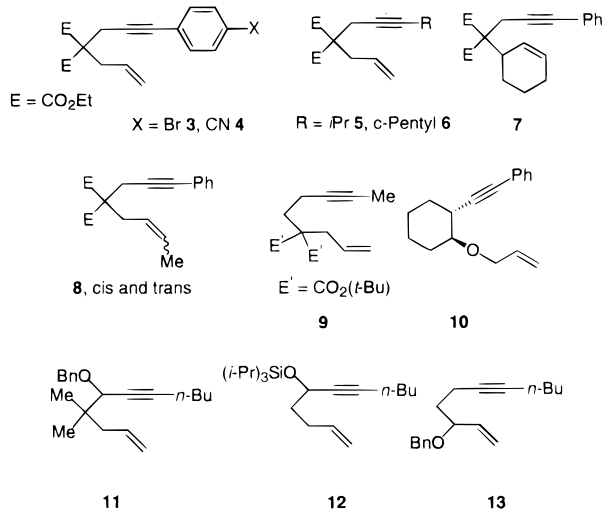
Synthetic Scope. Under the appropriate reaction conditions (Scheme 6), a variety of simple 1,6-enynes (Table 1, entries 1−10) can be converted to the corresponding cyclopentenones with excellent levels of enantioselectivity. The functional group tolerance displayed by this catalyst system appears to be similar to that seen for the titanocene-catalyzed Pauson−Khand type reaction. Aliphatic and aromatic ethers (entries 1 and 3), aliphatic and aromatic ethyl esters (entry 5), an aromatic chloride and trifluoromethyl group (entries 4 and 6), and a terminally unsubstituted alkyne (entry 12) are all compatible with this methodology. A few discrepancies have been found with regard to the aromatic functional groups, however, in that enynes

(47) Smith, J. A.; Brintzinger, H. H. *J. Organomet. Chem.* **1981**, *218*, 159.

(48) Xin, S.; Harrod, J. F. *J. Organomet. Chem.* **1995**, *499*, 181.

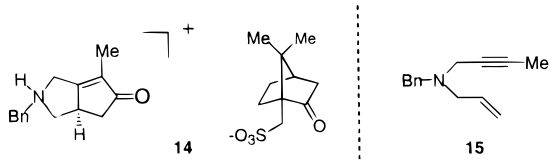
(49) The procedure for this reaction was adapted from the corresponding reductive carbonylation of Cp$_2$TiCl$_2$: Sikora, D. J.; Moriarty, K. J.; Rausch, M. D. In *Inorganic Syntheses*; Angelici, R. J., Ed.; John Wiley and Sons: New York, 1990; Vol. 28, p 248.

containing aryl bromides or nitriles (**3** and **4**) provided only poor levels of conversion to the corresponding enones under catalytic conditions.



The most significant differences observed between in situ generated **1** and titanocene dicarbonyl, in terms of synthetic scope, arise from the increased steric hindrance of the EBTHI ligand in comparison to that of Cp_2. While enynes containing substituted alkynes, e.g., phenyl, methyl, or *n*-alkyl (entries 2, 7, and 10), can be cyclized with both catalysts, substrates containing the larger *i*-Pr and *c*-pentyl groups (**5** and **6**) produced no cyclopentenone with **1**. Additionally, enynes possessing 1,2-disubstituted olefins (**7** and **8**) were not substrates for **1**, and an enyne containing a 1,1-disubstituted olefin (entry 11) required much higher quantities of catalyst (20 mol % for **1** vs 5 mol % for $Cp_2Ti(CO)_2$) to attain complete conversion. While a 1,7-enyne (entry 13) can be cyclized with the asymmetric catalyst at elevated catalyst levels (20 mol % for **1** vs 10 mol % for $Cp_2Ti(CO)_2$), other 1,7-enynes (**9** and **10**) which can be cyclized by titanocene dicarbonyl produced no enone upon exposure to **1** under the reaction conditons. Attempts to cyclize 1,6-enynes substituted in either the propargylic or allylic position (**11**−**13**) also met with failure. Even the simple 1,6-enynes, which can be cyclized with (*S*,*S*)-(EBTHI)$Ti(CO)_2$, reveal the influence of this phenomenon. While the enynes in entries 1 and 9 can be converted to product with 5 mol % $Cp_2Ti(CO)_2$, the cyclization of these substrates, which lack geminal diester substitution and the corresponding benefit provided by the Thorpe−Ingold effect, proved more difficult for **1**, requiring 20 mol % precatalyst. All these discrepancies can be explained on the basis of the increased steric hindrance at the titanium center of **1** relative to that in $Cp_2Ti(CO)_2$.

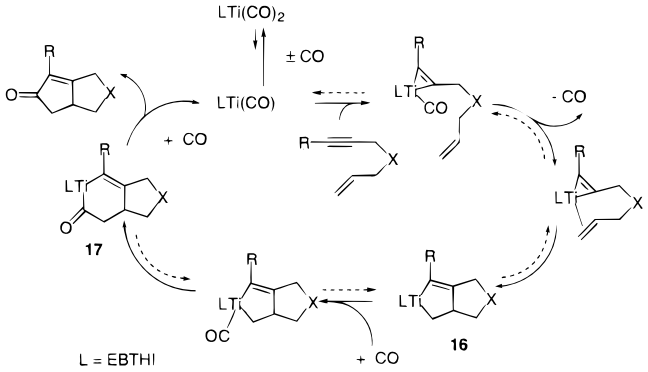
Absolute Configuration, Mechanism, and Mode of Stereoinduction. We have previously reported a tentative assignment of the absolute configuration of the enone from Table 1, entry 9, based on an X-ray crystal structure.[33] However, the level of uncertainty in the configuration of the chiral center prevented us from making a definitive assignment. Subsequently we have found that the enone products are actually of the opposite absolute configuration. This has been determined from the X-ray crystal structure of the (*S*)-camphorsulfonate salt of enone **14**, which was synthesized via the catalytic asymmetric Pauson−Khand type cyclization of enyne **15**.[50] This assignment



has been confirmed by another approach based upon ^1H NMR analyses. Stereoselective Luche reduction of the initially obtained cyclopentenone leads to the formation of the allylic alcohol as a single or highly predominant compound. Conversion of the allylic alcohol into both diastereomeric α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters and comparison of the resulting ^1H NMR spectra in $CDCl_3$ using the modified Mosher protocol[51] clearly revealed the absolute configuration of the new chiral centers to be as shown in Table 1 (see Experimental Procedures for details). The technique has been applied to four enones (entries 3−6 in Table 1), all of which corroborate the absolute configuration assignment determined by X-ray crystalography. This method was previously used by Ito to assign the absolute configuration of the related dieneones obtained in the asymmetric cyclocarbonylation mentioned earlier.[34,52]

The mechanism for this transformation is believed to be analogous to the one proposed for the titanocene-catalyzed enyne cyclocarbonylation (Scheme 7),[9] leaving the question of which

Scheme 7



step in this mechanism is stereochemistry determining. If the formation of metallacyclopentene **16** is kinetically controlled, then the selectivity of olefin insertion into the titanacyclopropene is the key step. However, the formation of group 4 metallacyclopentenes is documented to be a reversible process.[53] The selectivity of metallacycle formation could, therefore, represent the relative thermodynamic stabilities of the diastereomers of **16**. Finally, a kinetic partitioning at the point of CO insertion or an equilibration between diastereomeric acyl complexes **17** cannot be ruled out a priori as possible enantiodetermining steps.

(50) Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* In press.

(51) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

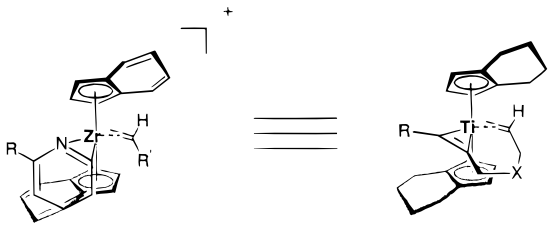
(52) For the application of this method of absolute configuration determination to transition metal mediated carbocyclizations, see: (a) Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295. (b) Reference 27. (c) Reference 28.

(53) (a) Agnel, G.; Owczarczyk, Z.; Negishi, E.-i. *Tetrahedron Lett.* **1992**, *33*, 1543. (b) Reference 59.

(54) The compound was prepared according to the literature procedure, with the modification that a catalytic amount of $HgCl_2$ was added: Lefeber, C.; Baumann, W.; Tillack, A.; Kempe, R.; Görls, H.; Rosenthal, U. *Organometallics* **1996**, *15*, 3486.

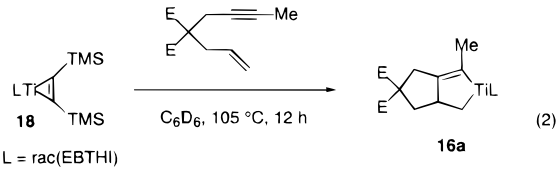
(55) The metallacyclopentene derived from the enyne in entry 10 was prepared and identified in an NMR tube reaction. The use of excess enyne was necessary to ensure clean and efficient metallacycle formation. Therefore, it is difficult to assign all the peaks for the metallacycle, but its presence and diastereomeric purity are clearly indicated by a single set of four indenyl doublets: δ 6.78 (J = 2.75 Hz, 1 H); 6.55 (J = 2.75 Hz, 1 H); 4.79 (J = 1.83 Hz, 1 H); 4.61 (J = 1.83 Hz, 1 H).

Scheme 8[a]



[a] Ethylene bridges omitted for clarity.

In an attempt to determine whether the formation of metallacyclopentenes **16** proceeded diastereoselectively, a route to their synthesis was developed. Heating the bis trimethylsilyl acetylene complex of rac(EBTHI)Ti (**18**)[54] in the presence of an enyne (Table 1, entry 10) led to the formation of the desired metallacyclopentene **16a** as indicated by ^{1}H NMR (eq 2).[55] Additionally, this complex was formed as essentially one

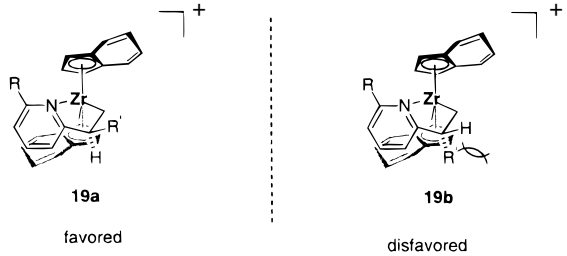


L = rac(EBTHI) (2)

diastereomer.[56] This suggests that the enantioselectivity of the cyclocarbonylation reaction utilizing optically pure EBTHI complexes probably arises from either a highly selective olefin insertion into the titanacyclopropene intermediate or the differences in thermodynamic stability of the diastereomers of **16**. However, this result does not rule out the possibility that enantioselectivity is derived from the relative rates of CO insertion into the diastereomeric metallacycles **16** or an equilibrium between the resulting acyl species **17**, as was mentioned earlier. In a related zirconium-catalyzed diene cyclization which proceeds with high levels of enantioselectivity, the formation of the intermediate zirconacyclopentane occurs with essentially no selectivity, indicating the stereochemistry-determining step happens later in the catalytic cycle.[57]

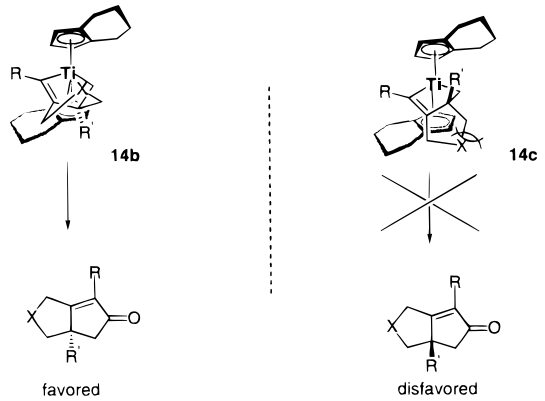
Examination of the literature on (EBTHI)MX_2-promoted carbon−carbon bond-forming reactions reveals that Jordan's work on the synthesis of diastereomerically enriched azazirconacycles from cationic (EBI)zirconium pyridyl complexes bears a number of similarities to the cyclocarbonylation reaction.[58] The reaction involves the insertion of a monosubstituted olefin into an η^2-bound pyridyl, a process which mimics the intramolecular olefin insertion into the η^2-alkyne (Scheme 8). The relative thermodynamic stability of the resulting diastereomeric azazirconacycles, obtained from experimental studies and consistent with molecular modeling calculations, has a large dependence on the presence of an ortho substituent on the pyridine ring (R in Schemes 8 and 9), which interacts strongly with the cyclohexadienyl moiety of the EBI ligand. This interaction leads to a severe tilting of the pyridyl moiety to alleviate the strain, forcing the alkene substituent (R′ in Schemes 8 and 9) into close contact with the cyclopentadienyl portion of the EBI ligand in **19b**. The combination of these destabilizing

Scheme 9[a]



[a] Ethylene bridges omitted for clarity.

Scheme 10[a]



[a] Ethylene bridges omitted for clarity.

interactions dictates the selective formation of **19a** (Scheme 9). While this rationale was derived from the thermodynamic stability of the azazirconacycles, a kinetic analysis of olefin insertion predicts the same diastereomeric product.[58]

A similar argument can explain both the sense of enantioselection for the enyne cyclocarbonylation and the fact that certain substrates were cyclized with moderate levels of selectivity. The tilting of the η^2-alkyne would lead to the preferential formation of metallacyclopentene **14b**, where the unfavorable steric interaction between the enyne tether and the cyclopentadienyl portion of the EBTHI ligand is avoided (Scheme 10). As with Jordan's work, an analysis based upon kinetically controlled olefin insertion into the metallacyclopropene predicts the same isomer. The interaction between the terminal alkyne substituent appears to play the same role as the ortho substituent on the pyridine ring; without this crucial steric interaction, as in the case of a terminally unsubstituted enyne (Table 1, entry 12), low levels of enantioselectivity are observed. When the olefinic moiety of the enyne is 1,1-disubstituted (Table 1, entry 11), destabilizing interactions are now present in both diastereomeric intermediates, leading to decreased ee's in the cyclopentenone products. It should be noted that this substrate still gives enone with a noticeably higher ee than the enyne with a terminally unsubstituted alkyne, emphasizing the relative importance of the two key interactions (the positioning of R is more important than R′) to the overall asymmetric induction. The cyclization of a 1,7-enyne also proceeded with low levels of enantioselectivity (Table 1, entry 13), presumably due to the increased levels of conformational flexibility in the metallacycle, which allows for the alleviation of the strain generated by the key interactions in both diastereomeric metallacycles.

Conclusion

The development of the first catalytic asymmetric Pauson−Khand type enyne cyclocarbonylation has been described. The

(56) The diastereoselective cyclization of an enyne by the *rac*-(EBTHI) moiety serves as an accurate model for the enantioselective cyclization of an enyne by the (*S*,*S*)-(EBTHI) moiety.

(57) Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615.

(58) (a) Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 4491. (b) Dagorne, S.; Rodewald, S.; Jordan, R. F. *Organometallics* **1997**, *16*, 5541.

catalytic species (*S,S*)-(EBTHI)Ti(CO)$_2$ (**1**) was generated in situ from (*S,S*)-(EBTHI)TiMe$_2$ (**2**). A variety of 1,6-enynes were converted to the corresponding cyclopentenones with excellent levels of enantioselectivity (87−96% ee). The methodology has limitations in terms of substrate scope due to the sterically hindered nature of the EBTHI ligand; 1,6-enynes substituted in the allylic and propargylic positions, some 1,7-enynes, and enynes containing 1,2-disubstituted olefins could not be cyclized with **1**. The absolute configuration of the enone products has been established by comparison to the X-ray structure of a related enone and by the modified Mosher analysis of the allylic MPTA esters derived from several of the enones. These assignments represent a reversal of an assignment from our initial report. A rationale for the observed absolute configuration and levels of asymmetric induction has been proposed which involves diastereoselective formation of a titanacyclopentene intermediate.

Experimental Procedures

General Considerations. All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres glovebox under an atmosphere of argon or using standard Schlenk techniques under argon. Toluene was distilled under argon from molten sodium. CO was scientific grade (minimum purity 99.997%) from MG Industries. ***Note:*** *It is important to take appropriate safety precautions when dealing with CO under elevated pressures; all reactions should be conducted in an efficient fume hood behind a blast shield.* Enynes were prepared as previously reported.[9,59,60] All other reagents were available from commercial sources and were used without further purification, unless otherwise noted. Except for entry 1 of Table 1, all substrates were filtered through a plug of alumina in a glovebox to remove adventitious moisture. The substrate for entry 1 was distilled under vacuum and stored in the glovebox.

Flash chromatography was performed on E. M. Science Kieselgel 60 (230−400 mesh). Yields refer to isolated yields of compounds of greater than 95% purity, as estimated by capillary GC and ^{1}H NMR analyses and, in the case of unknown compounds, elemental analysis. *In general, yields and ee's indicated in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly.* Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian XL-500, or a Varian Unity 300 instrument. Gas chromatography (GC) analyses were performed on a Hewlet-Packard 5890 gas chromatograph with a 3392A integrator and FID detector using a 25-m capillary column with cross-linked SE-30 as a stationary phase. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter. High-performance liquid chromatography (HPLC) was conducted using a Hewlett-Packard model 1050 pumping system with a Hewlett-Packard model 1040A ultraviolet detector. Chiral GC analyses were conducted using a 5890 Hewlett-Packard Series II gas chromatograph with an FID detector. Elemental analyses were performed by E + R Analytical Laboratory, Inc.

Determination of Enantiomeric Purity. The enantiomeric excesses (% ee) were primarily determined by chiral GC. For entries 1, 9, 12, and 13 of Table 1, a Chiraldex B-PH 20-m × 0.25-mm (ASTEC) capillary column was used. For entries 7, 8, 10, and 11, a Chiraldex G-TA 20-m × 0.25-mm (ASTEC) capillary column was used. For entry 2, the ee was determined by chiral HPLC on a Chiralcel OD 25-cm × 0.46-cm column (Daicel Chemical Ind., Ltd.). For entries 3−6, the ee was determined from the ^{19}F NMR analyses of the MTPA esters derived from the allylic alcohol obtained from selective Luche reduction of the corresponding enone.

***rac*-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dicarbonyl (1).** To a Schlenk flask in an Ar-filled glovebox were added *rac*-(EBTHI)TiCl$_2$ (272 mg, 0.71 mmol), Mg powder (57 mg, 2.38 mmol), HgCl$_2$ (127 mg, 0.47 mmol), and THF (5 mL). The Schlenk flask was removed from the glovebox and evacuated and backfilled with 18 psig CO on a vacuum line in a hood. The sealed Schlenk flask was placed in a 45 °C oil bath for 1 h until the solution changed color to a dark brown-yellow. The Schlenk flask was allowed to cool to room temperature, and the THF was removed in vacuo. The Schlenk flask was transferred into the glovebox, and the insoluble impurities were removed via filtration of a pentane solution of the crude product through a pad of Celite. The pentane was removed in vacuo to afford 120 mg (46%) of a light brown powder. Mp: 150−153 °C. ^{1}H NMR (300 MHz, C_6D_6): δ 4.76 (d, J = 2.9 Hz, 2 H); 4.31 (d, J = 2.9 Hz, 2 H); 2.32−2.22 (m, 10 H); 1.84−1.77 (m, 4 H); 1.63 (m, 2 H); 1.44 (m, 2 H). ^{13}C NMR (75 MHz, C_6D_6): δ 268.6, 128.7, 128.4, 128.1, 120.9, 113.9, 108.4, 92.4, 90.1, 30.0, 25.0, 24.9, 24.1, 23.4. IR (pentane solution, cm^{-1}): 1962, 1881. Anal. Calcd for $C_{22}H_{24}O_2Ti$: C, 71.71; H, 6.08. Found: C, 71.68; H, 6.57.

***(S,S)*-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dicarbonyl (1).** The same procedure mentioned above for the racemic dichloride was employed with (*S,S*)-(EBTHI)TiCl$_2$ (100 mg, 0.26 mmol), Mg powder (21 mg, 0.875 mmol), HgCl$_2$ (47 mg, 0.173 mmol), and THF (3 mL) for 1.5 h to afford 52 mg (55%) of a light brown powder. Mp: 134−136 °C. $[\alpha]^{23}_D$ = −145 (c = 0.60, toluene). The ^{1}H NMR spectrum matched that of the racemic complex. Anal. Calcd for $C_{22}H_{24}O_2Ti$: C, 71.71; H, 6.08. Found: C, 71.39; H, 5.66.

Dimethyl (*S,S*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)-titanium (2). To a Schlenk flask under argon were added (*S,S*)-(EBTHI)TiCl$_2$ (700 mg, 1.83 mmol) and Et$_2$O (50 mL), and the flask was placed in a water bath. A solution of MeLi in pentane (1.4 M, 7 mL, 5.0 mmol) was added slowly, and the reaction was allowed to stir at room temperature for 4 h. The solvent was removed in vacuo, and the crude product was taken into the glovebox. The product was dissolved in hexane (50 mL), and insoluble impurities were removed by filtration through a plug of Celite, followed by rinsing with hexane. The solvent was removed in vacuo to yield 520 mg (83% yield) of the desired product as yellow-orange crystals. Mp: 78−80 °C. $[\alpha]^{23}_D$ = +28.0 (c = 1.0 toluene). The ^{1}H NMR spectrum matched the published spectrum.[48]

General Procedure for the Asymmetric Conversion of Enynes to Cyclopentenones. In an argon-filled glovebox, a dry sealable Schlenk flask was charged with (*S,S*)-(EBTHI)TiMe$_2$ (8 mg, 0.025 mmol), toluene (3 mL), and the substrate (0.50 mmol). The Schlenk flask was removed from the glovebox, evacuated, and backfilled with 14 psig CO. ***Caution:*** *Appropriate precautions should be taken when performing reactions under elevated CO pressure.* The reaction mixture was heated to 90 °C for 12−16 h. After the reaction mixture was cooled to room temperature, the CO was cautiously released in the hood. In the air, the crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography.

2-Phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (Entry 1). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (16 mg, 0.05 mmol) was used to convert 3-(allyloxy)-1-phenyl-1-propyne[59] (43 μL, 0.25 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 4:6) afforded 44 mg (88% yield) of a clear oil. The ee was determined to be 96%. $[\alpha]^{26}_D$ = −7.69 (c = 0.52, CHCl$_3$). The ^{1}H NMR spectrum matched the published spectrum.[59]

Diethyl 2-Phenyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 2). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (12 mg, 0.0375 mmol) was used to convert diethyl 1-phenyl-6-hepten-1-yne-4,4-dicarboxylate[60] (157 mg, 0.50 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 2:1) afforded 157 mg (92% yield) of a clear oil. The ee was determined to be 94%. $[\alpha]^{26}_D$ = +20.4 (c = 2.1, CHCl$_3$). The ^{1}H NMR spectrum matched the published spectrum.[60]

Diethyl 2-(*p*-Methoxyphenyl)-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 3). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (6 mg, 0.0175 mmol) was used to convert diethyl 1-(*p*-methoxyphenyl)-6-hepten-1-yne-4,4-dicarboxylate[9] (81 mg, 0.234 mmol) to the desired product in 16 h. Purification by flash chromatography (hexane:ether = 3:2) afforded 77 mg (88% yield) of a white solid. Mp: 61−63 °C. The ee was determined to be 93% on the basis of the ^{19}F NMR spectrum of the corresponding (*R*)-MTPA ester of the

(59) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593.

(60) Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498.

corresponding allylic alcohol. $[\alpha]^{23}_D = +34.3$ ($c = 0.67$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Diethyl 2-(*p*-Chlorophenyl)-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 4). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (6 mg, 0.0175 mmol) was used to convert diethyl 1-(*p*-chlorophenyl)-6-hepten-1-yne-4,4-dicarboxylate[9] (61 mg, 0.175 mmol) to the desired product in 20 h. Purification by flash chromatography (hexane:ether = 2:1) afforded 53 mg (81% yield) of a clear liquid. The ee was determined to be 93% on the basis of the ^{19}F NMR spectra of the (*R*)-MTPA ester of the corresponding allylic alcohol. $[\alpha]^{23}_D = +44.6$ ($c = 0.56$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Diethyl 2-(*p*-Ethyl benzoate)-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 5). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (6 mg, 0.0175 mmol) was used to convert diethyl 1-(*p*-ethyl benzoate)-6-hepten-1-yne-4,4-dicarboxylate[9] (61 mg, 0.175 mmol) to the desired product in 20 h. Purification by flash chromatography (hexane:ether = 2:1) afforded 53 mg (81% yield) of a clear liquid. The ee was determined to be 91% on the basis of the^{19}F NMR spectrum of the (*S*)-MTPA ester of the corresponding alcohol. $[\alpha]^{23}_D = +44.7$ ($c = 0.85$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Diethyl 2-(*p*-Trifluoromethylphenyl)-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 6). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (6 mg, 0.0175 mmol) was used to convert diethyl 1-(*p*-trifluoromethylphenyl)-6-hepten-1-yne-4,4-dicarboxylate[9] (67 mg, 0.175 mmol) to the desired product in 14 h. Purification by flash chromatography (hexane:ether = 3:1) afforded 65 mg (90% yield) of a clear liquid. The ee was determined to be 94% on the basis of the ^{19}F NMR of the (*S*)-MTPA ester of the corresponding allylic alcohol. $[\alpha]^{23}_D = +35.0$ ($c = 0.80$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Diethyl 2-*n*-Propyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 7). The general procedure was used to convert diethyl 1-*n*-propyl-6-hepten-1-yne-4,4-dicarboxylate[60] (140 mg, 0.50 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 2:1) afforded 142 mg (92% yield) of a clear oil. The ee was determined to be 89%. $[\alpha]^{26}_D = +117.1$ ($c = 0.70$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[60]

Di-*tert*-butyl 2-Methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 8). The general procedure was used to convert di-*tert*-butyl 7-octen-2-yne-5,5-dicarboxylate[59] (154 mg, 0.50 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 4:1) afforded 151 mg (90% yield) of a white solid. Mp: 76−78 °C. The ee was determined to be 89%. $[\alpha]^{26}_D = +86.5$ ($c = 1.3$ $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[59]

2-Phenylbicyclo[3.3.0]oct-1-en-3-one (Entry 9). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (16 mg, 0.05 mmol) was used to convert 1-phenyl-6-hepten-1-yne[59] (43 mg, 0.25 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 7:3) afforded 36 mg (73% yield) of a white solid. Mp: 78−80 °C. The ee was determined to be 87%. $[\alpha]^{26}_D = -19.6$ ($c = 0.46$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[59]

Diethyl 2-Methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 10). The general procedure was used to convert diethyl 7-octen-2-yne-5,5-dicarboxylate[59] (126 mg, 0.50 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 3:2) afforded 130 mg (93% yield) of a clear liquid. The ee was determined to be 87%. $[\alpha]^{26}_D = +86.4$ ($c = 1.3$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[59]

Di-*tert*-butyl 2,5-Dimethylbicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 11). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (16 mg, 0.05 mmol) was used to convert di-*tert*-butyl 7-methyl-7-octen-2-yne-5,5-dicarboxylate[9] (81 mg, 0.25 mmol) to the desired product in 12 h. Purification by flash chromatography (hexane:ether = 4:1) afforded 80 mg (91% yield) of a clear liquid. The ee was determined to be 72%. $[\alpha]^{26}_D = +86.8$ ($c = 0.38$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Di-*tert*-butyl 3-Oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Entry 12). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (16 mg, 0.05 mmol) was used to convert di-*tert*-butyl 6-hepten-1-yne-4,4-dicarboxylate[9] (73 mg, 0.25 mmol) to the desired product in 13 h. Purification by flash chromatography (hexane:ether = 1:1) afforded 68 mg (85% yield) of a clear liquid. The ee was determined to be 50%. $[\alpha]^{26}_D = -95.0$ ($c = 0.20$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[9]

Di-*tert*-butyl 2-Methyl-3-oxobicyclo[3.4.0]non-1-en-8,8-dicarboxylate (Entry 13). The general procedure employing (*S*,*S*)-(EBTHI)$TiMe_2$ (16 mg, 0.05 mmol) was used to convert di-*tert*-butyl 8-nonen-2-yne-4,4-dicarboxylate[59] (81 mg, 0.25 mmol) to the desired product in 14 h. Purification by flash chromatography (hexane:ether = 7:3) afforded 66 mg (76% yield) of a clear liquid. The ee was determined to be 47%. $[\alpha]^{26}_D = -52.3$ ($c = 0.44$, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[59]

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Supporting Information Available: Details on the absolute configuration assignments for Table 1, entries 3−6 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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