Catalytic Asymmetric Cyclocarbonylation of Nitrogen-Containing Enynes

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The asymmetric Pauson−Khand type cyclization of nitrogen-containing enynes using carbon monoxide and a catalytic amount of (EBTHI)$TiMe_2$ was examined. The influence of the nitrogen substituent and the concentration of the catalyst on the enantioselectivity of this cyclization was explored, and it has been found that enynes with an octyl-, benzyl-, or allylamino group, positioned β to the alkyne and the olefin, are cyclized with a high degree of enantioselectivity. Substrates with either bulky and/or electron-withdrawing nitrogen substituents are converted to products in low to moderate enantioselectivity.

Introduction

The transition metal-mediated cyclization of an enyne with carbon monoxide, a Pauson−Khand type reaction, is an efficient method for the construction of bicyclic cyclopentenones.[1] We have previously reported a catalytic version of this reaction utilizing commercially available $Cp_2Ti(CO)_2$ (**1**).[2,3] It was subsequently shown that an enantiomerically pure analogue of the titanocene complex, (*S*,*S*)-(EBTHI)$Ti(CO)_2$ (**2**) (EBTHI = ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl), generated in situ from (*S*,*S*)(EBTHI)$TiMe_2$ (**3**), can serve as a catalyst for this reaction.[4] Using this method, a variety of 1,6-enynes could be cyclized with high levels of enantioselectivity (Scheme 1).[5]

The intramolecular Pauson−Khand reaction is a useful method for the preparation of azaheterocycles via the cyclization of enynes in which there is a nitrogen atom tethering the alkyne and the olefin (Scheme 1, X = NR). Becker and co-workers have explored the use of the Pauson−Khand reaction for the synthesis of *N*-protected azabicyclo[3.3.0]octan-7-ones, which serve as intermediates in the synthesis of racemic tricyclic diamines and aza(nor)adamantanes possessing interesting pharmacological activity.[6] The Pauson−Khand reaction has also been used as the key step in several syntheses of (−)-kainic acid[7] and in the construction of the sesquiterpene alkaloid (−)-dendrobine.[8] In these examples, the enantiomerically enriched products obtained arise from the diastereoselective cyclization of optically active enynes. However, the diastereoselectivity can be poor and inseparable mixtures of isomers are often formed. We were therefore interested in extending the use of the titanium-catalyzed asymmetric Pauson−Khand type reaction to the synthesis of azabicyclopentenones. In this way, optically active products could be formed from the cyclization of readily available, achiral enynes, utilizing a catalytic amount of enantiomerically pure transition metal complex.

Initial attempts to cyclize nitrogen-containing enynes with **1** produced bicyclic cyclopentenones with poor to moderate levels of enantiomeric excess (ee). It became evident that the choice of the nitrogen substituent was critical to the success of the reaction. For example, replacement of a *tert*-butoxy carbonyl substituent, on the nitrogen, with a phenyl group resulted in a significant decrease in ee (from 74% to 30%). These results prompted us to undertake the systematic examination of the reaction for this class of enynes in order to find which substrates could be cyclized with a high degree of enantioselectivity.

Results and Discussion

To examine how the enantioselectivity of the cyclization changes when the nature of the *N*-substituent is altered, a series of amine-containing enynes was prepared and subjected to the reaction conditions as shown in Scheme 1.[9] The assignment of absolute configuration was based on the configuration of enone **5d** (Table 1) which was determined unambiguously from the X-ray crystal structure of the corresponding (*S*)-(+)-camphorsulfonic acid complex.[10] The product of the cyclization

(1) For a review of the Pauson−Khand reaction, see: (a) Geis, O.; Schmalz, H. G.; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 911. (b) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Ed.; Elsevier: New York, 1995; Vol. 12, p 703.

(2) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450.

(3) For catalytic Pauson−Khand reactions see work cited in ref 2. Some subsequent advances in catalytic Pauson−Khand methodology include (a) Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse T. *Tetrahedron Lett.* **1998**, *39*, 7637. (b) Belanger, D. B.; Livinghouse T. *Tetrahedron Lett.* **1998**, *39*, 7641. (c) Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782. (d) Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384. (e) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249. (f) Kim, J. W.; Chung, Y. K. *Synthesis* **1998**, 142. (g) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762. (h) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187.

(4) For a review of the asymmetric Pauson−Khand reaction, see Ingate S. T.; Marco-Contelles, J. *Org. Prep. Proced. Int.*, **1998**, *30*, 121.

(5) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688.

(6) (a) Becker, D. P.; Flynn, D. L. *Tetrahedron* **1993**, *49*, 5047. (b) Becker, D. P.; Flynn, D. L. *Tetrahedron Lett.* **1993**, *34*, 2087. (c) Flynn, D. L.; Becker, D. P.; Spangler, D. P.; Nosai, R.; Gullikson, G. W.; Moummi, C.; Yang, D.-C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1613.

(7) (a) Yoo, S.-e.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968. (b) Yoo, S.-E.; Lee, S.-H.; Jeong, N.; Cho, I. *Tetrahedron Lett.* **1993**, *34*, 3435. (c) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169.

(8) Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1992**, 443.

(9) When the substrates for which R = Me and X = $CH_3C(O)N$, HN, or LiN were subjected to the reaction conditions, an intractable mixture of products resulted.

(10) X-ray structure parameters have been deposited in the Cambridge database.

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Scheme 1

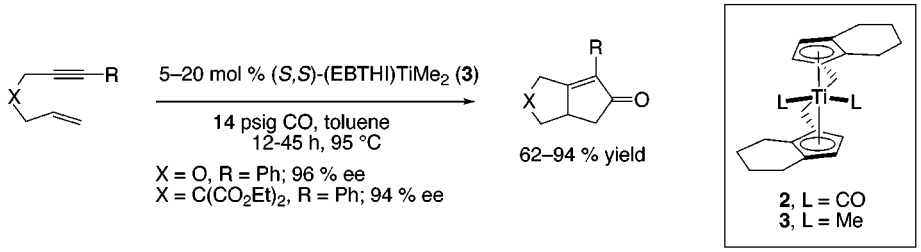
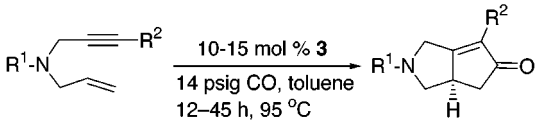


Table 1. Cyclization of Various Nitrogen-Containing Enynes



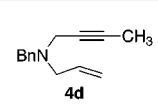
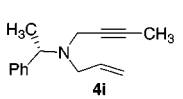
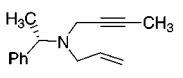
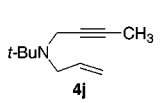
entry	R^1	R^2	mol % (*S,S*)-**2**	ee (%)[a]	yield (%)[d]
a	*n*-octyl	Me	10	>95[b]	76
b	allyl	Me	10	94[c]	91
c	allyl	Ph	15	92	81
d	Bn	Me	15	92[c]	82
e	*t*-Boc	Me	10	74	84
f	Ts	Me	13	31[b]	93
g	Ph	Me	10	30−48[c]	81
h	*t*-BuC(O)	Me	15	4−22	81

[a] Unless indicated otherwise, ee's were determined by chiral GC. [b] ee determined by ^{1}H NMR (reduction of the ketone followed by derivatization as the Mosher ester). [c] ee determined by chiral HPLC. [d] Yields are the average of two experiments and represent isolated products of >95% purity by ^{1}H NMR, GC analysis, and in the case of new compounds, elemental analysis.

catalyzed by (*S,S*)-(**2**) was found to be the *R* isomer.[11] Although good yields of enones were obtained in each case, the ee's of these products varied considerably (Table 1).[12] It was found that enynes joined by an *N*-octyl, *N*-allyl, or *N*-benzyl group were cyclized with a high degree of enantioselectivity. In contrast, when the alkene and alkyne moieties were linked by an aniline, amide, or sulfonamide, the products were formed with low ee's. In the instance where the nitrogen was part of a carbamate group, moderate levels of enantioselectivity were realized. It appears that substrates in which the nitrogen center is relatively electron-rich are transformed to enones with much higher levels of enantioselectivity than in the cases where the nitrogen atom is electron deficient.

The sensitivity of the reaction to the nature of the nitrogen substituent led us to examine whether the diastereoselective cyclization of substrate **4i** using **1**[2] was possible. We had hoped that the α-methylbenzyl moiety would serve as an effective chiral auxiliary. Disappointingly, the reaction of enantiomerically pure **4i** with **1** or racemic **3** as catalysts gave enone with no diastereoselectivity. The reaction of **4i** employing either (*S,S*)- or the (*R,R*)-**2** resulted in products with similar diastereomeric ratios; no significant double diastereoselection was observed.[13] We were surprised to find that the α-methyl-benzyl-substituted enone was formed with low diastereoselectivity given that the benzyl-substituted amine (**4d**) could be converted to the corresponding enone with a high degree of enantioselectivity. To determine whether the decrease in ee was due to an increase in steric bulk of the N-substituent, the reaction of *N-tert*-butylamine (**4j**) was carried out and found to provide enone of low and variable ee. Furthermore, the ee of the product isolated from several experiments varied from 12 to 48% (vide infra).

Table 2. Steric Effects of Nitrogen Substitution on ee

Entry	Substrate	Product	ee or de (%)	Config. of **3**	Mol % **3**	Yield (%)[a]
1	 **4d**		92[b]	(*S,S*)	15	82
2	 **4i**		68	(*S,S*)	10	86
3			57	(*R,R*)	10	87
4	 **4j**		12-48[c]	(*S,S*)	10	62[d]

[a] Yields are the average of two experiments and represent isolated products of >95% purity by ^{1}H NMR, GC, and elemental analysis. [b] ee determined by chiral HPLC. [c] ee determined by chiral GC. [d] Unreacted starting material (23%) was detected by GC analysis.

For certain examples, we observed a dependence of the enantioselectivity of the reaction on the concentration of the catalyst. The cyclization of these enynes displayed very low enantioselectivities which was found to increase with increasing concentration. For example, reaction of **4g** where [(*S,S*)-**3**] = 5, 9, and 13 mM gave **5g** with 30, 36, and 48% ee, respectively. The ee of **5h** increased from 4 to 22% when the concentration of **3** was increased from 6 to 18 mM for the cyclization of **4h**. Attempts to further increase the ee of the product by performing the cyclizations at higher concentrations resulted in incomplete conversion of the substrates to products and no significant increase in ee. The cyclization of the *N-tert*-butylamine (**4j**) was also carried out at various concentrations; the enantioselectivities of the reaction varied widely and no correlation with catalyst concentration was observed. In contrast, for the cyclization of the *N*-benzyl-substituted amine (**4d**), a substrate which provides enone with a high ee, similar changes in catalyst concentration had no effect on the ee of the enone (**5d**) which was formed.

(11) We assume that all enones cyclized with the (*S,S*)-catalyst have the same absolute configuration.

(12) The cyclization of (*N*-allyl-*N*-benzyl)-2-(1-hexynyl)aniline was carried out under the standard reaction conditions using 15% of the catalyst. The corresponding azabicyclo[4.3.0]nonenone was isolated in 70% yield, but with an ee of only 55%.

(13) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

Conclusion

We have investigated the influence of *N*-substituents, with different electronic and steric characteristics, on the enantioselectivity of the cyclocarbonylation of nitrogen-containing enynes. In addition, we have examined the effect of catalyst concentration on these reactions. High levels of enantioselectivity can be achieved for the cyclization of nitrogen-containing enynes bearing an electron rich, sterically small nitrogen-substituent.[14] Two of the nitrogen substituents of choice for the reaction, benzyl and allyl, are known to be useful protecting groups for amines.[15] Through this study, (EBTHI)Ti(Me)$_2$ (**3**) has proven an effective precatalyst for the asymmetric synthesis of nitrogen-containing bicyclic cyclopentenones.

Experimental Section

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. Anhydrous toluene was purchased from Aldrich and used as supplied. CO was scientific grade (minimum purity 99.997%) from MG Industries. Flash chromatography was performed on E. M. Science Kieselgel 60 (230−400 mesh). Substrates were stored in the glovebox to prevent decomposition over long periods of time. Substrates that were transferred into the glovebox during periods of the year when the humidity in the lab was high were filtered through a plug of alumina (in the glovebox) to remove adventitious moisture. Yields refer to isolated yields of compounds of greater than 95% purity as estimated by ^{1}H NMR, capillary GC, and in the case of previously unknown compounds, elemental analysis. **Yields 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**. Unless otherwise noted, the enantiomeric excesses (% ee) of the products were directly measured by chiral GC using a Chiraldex B-PH or G-TA 20 m × 0.25 mm (ASTEC) capillary column or by chiral HPLC on a Chiralcel OD or OJ 25 cm × 0.46 cm column (Daicel Chemical Ind., Ltd.).

Dimethyl (*S,S*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium (3). To a Schlenk tube under argon was added (*S,S*)-(EBTHI)TiCl$_2$[16] (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 Et$_2$O (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. The ^{1}H NMR spectrum matched the published spectrum.[17] $[\alpha]^{23}_D$ +28.0° (*c* 1.0, toluene).

Procedure for the Asymmetric Conversion of Enynes to Cyclopentenones. In an argon-filled glovebox, a dry resealable Schlenk tube is charged with (*S,S*)-(EBTHI)TiMe$_2$, toluene (3 mL), and the substrate. The Schlenk tube is sealed, removed from the glovebox, attached to a Schlenk line, evacuated, backfilled with ca. 4 psig CO, and then evacuated and backfilled with 14 psig CO. The Schlenk tube is sealed and heated at 95 °C for 12−45 h.[18] After cooling the reaction mixture to room temperature, the CO pressure is carefully released in the hood. Unless otherwise noted, the crude reaction mixture is filtered through a plug of silica gel with the aid of ether, concentrated, and purified by flash chromatography.

6-Methyl-3-*n*-octyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5a). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (12 mg, 0.035 mmol) was used to convert diallyl(2-butynyl)amine (**4a**) (45 mg, 0.20 mmol) to the desired product in 23 h. Purification by flash chromatography (0.5−1% NH$_3$ saturated MeOH, ether) afforded 37 mg (74% yield) of a yellow oil. The ee was determined to be >95% due to the presence of only one isomer in the ^{1}H NMR after reduction with NaBH$_4$/CeCl$_3$[19] and conversion to the Mosher's ester with (*S*)-MTPA.[20] $[\alpha]^{23}_D$ +154° (*c* 3.2, C$_6$D$_6$). ^{1}H NMR (500 MHz, C$_6$D$_6$): δ 3.56 (d, J = 16.8 Hz, 1 H): 2.88 (t, J = 7.6 Hz, 1 H); 2.67 (m, 1 H); 2.54 (d, J = 16.8 Hz, 1 H); 2.40 (m, 1 H); 2.25 (m, 2H); 1.73 (dd, J = 17.4, 3.7 Hz, 1 H); 1.61 (t, J = 1.1 Hz, 3 H); 1.43−1.10 (m, 13 H); 0.92 (t, J = 7.0 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, C$_6$D$_6$): δ 177.0, 131.7, 110.5, 58.7, 56.2, 52.5, 43.3, 39.5, 32.3, 30.0, 29.8, 29.0, 27.7, 23.1, 14.4, 8.8.. IR (neat): 1711, 1677. Anal. Calcd for C$_{16}$H$_{27}$NO: C, 77.07; H, 10.91. Found: C, 77.12; H, 10.97.

3-Allyl-6-methyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5b). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (16 mg, 0.047 mmol) was used to convert diallyl(2-butynyl)amine (**4b**) (42 mg, 0.28 mmol) to the desired product in 23 h. The reaction mixture was concentrated without passing through silica. Purification by flash chromatography (3% NH$_3$ saturated MeOH, ether) afforded 48 mg (96% yield) of a yellow oil. The ee was determined to be 94% by chiral HPLC (OJ column). $[\alpha]^{22}_D$ +141° (*c* 4.0, toluene). ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.80 (m, 1 H) 5.11 (dm, J = 17.5 Hz, 1 H); 5.01 (dd, J = 7.0, 1.5 Hz, 1 H); 3.52 (d, J = 17.0 Hz, 1 H); 2.99 (m, 1 H); 2.84 (m, 2 H); 2.63 (m, 1 H); 2.57 (d, J = 17.0 Hz, 1 H); 2.24 (dm, J = 17.8 Hz, 1 H); 1.70 (dt, J = 17.5, 3.5 Hz, 1 H); 1.57 (d, J = 1.0 Hz, 3 H); 1.37 (m, 1 H). ^{13}C{^{1}H} NMR (125 MHz, C$_6$D$_6$): δ 207.2, 176.8, 136.2, 131.8, 116.6, 58.7, 58.2, 52.0, 43.3, 39.4, 8.8. IR (neat): 1711, 1679. Anal. Calcd for C$_{11}$H$_{15}$NO: C, 74.54; H, 8.53. Found: C, 74.59; H, 8.36.

3-Allyl-6-phenyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5c). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (9 mg, 0.026 mmol) was used to convert diallyl(3-phenylpropargyl)-amine (34 mg, 0.16 mmol) to the desired product in 26 h. Purification by flash chromatography (0−20% ethyl acetate, ether) afforded 31 mg (81% yield) of a yellow oil. The ee was determined to be 92% by chiral GC (G-TA column). $[\alpha]^{23}_D$ −17° (*c* 3.1, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, J = 7.8 Hz, 2 H); 7.39 (m, 2 H); 7.31 (m, 1 H); 5.93 (ddt, J = 17.3, 10.0, 6.4 Hz, 1 H); 5.24 (dd, J = 17.1, 1.5 Hz, 1 H); 5.15 (dd, J = 9.8, 1.0 Hz, 1 H); 4.32 (d, J = 18.6 Hz, 1 H); 3.42 (t, J = 7.8 Hz, 1 H); 3.36−3.17 (m, 4 H); 2.79 (dd, J = 17.6, 6.4 Hz, 1 H); 2.31 (dd, J = 17.6, 3.9 Hz, 1 H); 1.99 (dd, J = 10.7, 8.3 Hz, 1 H). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ 207.0, 179.3, 134.9, 134.2, 131.1, 128.4, 128.1, 127.9, 117.6, 58.7, 57.9, 54.1, 43.4, 41.1. IR (neat): 1706, 1648. Anal. Calcd for C$_{16}$H$_{17}$NO: C, 80.3; H, 7.16. Found: C, 79.84; H, 6.90.

3-Benzyl-6-methyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5d). The general procedure employing (*S,S*)-(EBTHI)TiMe$_2$ (11 mg, 0.031 mmol) was used to convert allyl(benzyl)(2-butynyl)amine (50 mg, 0.25 mmol) to the desired product in 45 h. Purification by flash chromatography (ether) afforded 43 mg (76% yield) of a yellow oil. The ee was determined to be 93% by chiral HPLC (OD column). $[\alpha]^{23}_D$ +164° (*c* 4.2, toluene). ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 7.28−7.08 (m, 5 H); 3.50 (d, J = 13.2 Hz, 1 H); 3.43 (d, J = 16.9 Hz, 1 H); 3.29 (d, J = 13.2 Hz, 1 H);2.79 (t, J = 7.4 Hz, 1 H); 2.62 (m, 1 H); 2.51 (d, J = 16.8 Hz, 1 H);

(14) It should be noted that each of the electron-deficient enyne substituents is also sterically large, and the low degree of enantioselectivity may be attributed solely to steric effects. The cyclization of an enyne with a small, electron-withdrawing *N*-substituent, such as a formamide, would resolve this issue. However, previous experiments (footnote 9, X = CH$_3$C(O)N) indicate this type of substrate to be incompatible with the catalyst system. We thank a referee for helpful comments on this issue.

(15) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994.

(16) Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650.

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

(18) It is important to take appropriate safety precautions when using carbon monoxide, particularly at elevated pressure. All operations should be carried out in an efficient fume hood behind a blast shield.

(19) Clive, D.; Cole, D.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396.

(20) Ward, D.; Rhee, C. *Tetrahedron Lett.* **1991**, *32*, 7165.

2.20 (dd, J = 17.4, 6.4 Hz, 1 H); 1.51 (s, 3 H); 1.66 (dd, J = 17.4, 3.6 Hz, 1 H). $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6): δ 211.5, 176.8, 139.4, 131.8, 128.8, 128.6, 127.4, 60.1, 58.5, 52.3, 43.3, 39.4, 8.7. IR (neat): 1710, 1673, 1678. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54. Found: C, 79.05; H, 7.47.

6-Methyl-3-(*tert*-butyl)carbamate-3-azabicyclo[3.3.0]-oct-5-en-7-one (5e). The general procedure employing (*S,S*)-(EBTHI)$TiMe_2$ (16 mg, 0.050 mmol) was used to convert *tert*-butyl (*N*-allyl-*N*-2-butynyl)carbamate[21] (105 mg, 0.50 mmol) to the desired product in 12 h. Purification by flash chromatography (30% ether, hexanes) afforded 102 mg (86% yield) of an off white solid, mp 88−90 °C. The ee was determined to be 74% by chiral GC (B-PH column). $[\alpha]^{23}_D$ +127° (*c* 0.7, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[5]

6-Methyl-3-*p*-toluenesulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5f). The general procedure employing (*S,S*)-(EBTHI)$TiMe_2$ (6 mg, 0.018 mmol) was used to convert [*N*-allyl-*N*-(2-butynyl)]-*p*-toluenesulfonamide (**4f**) (34 mg, 0.13 mmol) to the desired product in 19 h. Purification by flash chromatography (75% ether, hexanes) afforded 35 mg (94% yield) of a white solid, mp 108−109 °C. The ee was determined to be 31% by ^1H NMR integration of diastereomers formed after reduction with $NaBH_4/CeCl_3$[19] and conversion to the Mosher's ester with (*S*)-MTPA.[20] $[\alpha]^{24}_D$ −44° (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 8.1 Hz, 2 H); 7.35 (d, J = 8.0 Hz, 2 H); 4.24 (d, J = 15.9 Hz, 1 H); 4.00 (m, 2 H); 3.01 (bs, 1 H); 2.65−2.54 (m, 3 H); 2.45 (s, 3 H); 2.03 (dd, J = 14.8, 3.4 Hz, 1 H); 1.69 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 207.9, 171.3, 144.2, 134.2, 133.8, 130.1, 127.5, 52.8, 46.9, 41.8, 39.3, 21.7, 8.9. IR (neat): 1709, 1680, 1596. Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.84; H, 5.88. Found: C, 61.82; H, 6.26.

6-Methyl-3-phenethyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5g). The general procedure employing (*S,S*)-(EBTHI)-$TiMe_2$ (12 mg, 0.036 mmol) was used to convert *N*-(3-phenyl-2-butynyl)-*N*-allylaniline (**4g**) (60 mg, 0.32 mmol) to the desired product in 19 h. Purification by flash chromatography (25% EtOAc, hexanes) afforded 60 mg (88% yield) of a light orange solid, mp 100−103 °C. The ee was determined to be 43% by chiral HPLC (OD column). $[\alpha]^{23}_D$ −102 (*c* 2.4, $CHCl_3$). The ^1H NMR spectrum matched the published spectrum.[2]

3-Pivaloyl-6-methyl-3-azabicyclo[3.3.0]oct-5-en-7-one (5h). The general procedure employing (*S,S*)-(EBTHI)$TiMe_2$ (18 mg, 0.053 mmol) was used to convert [*N*-allyl-*N*-(2-butynyl)]pivalamide (**4h**) (67 mg, 0.35 mmol) to the desired product in 26 h. Purification by flash chromatography (25−75% ethyl acetate, hexanes) afforded 58 mg (81% yield) of a white solid, mp 108−110 °C. The ee was determined to be 22% by chiral GC (B−PH column). $[\alpha]^{23}_D$ −4° (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 4.50−4.25 (m, 3 H); 3.25−3.15 (bs, 1 H); 3.05−2.95 (m, 1 H); 2.70 (dd, J = 18.0, 6.2 Hz, 1 H); 2.17 (dd, J = 18.0, 3.2 Hz, 1 H); 1.79 (s, 3 H); 1.30 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.9, 176.6, 171.3, 133.4, 52.7, 47.0, 39.2, 38.8, 27.4, 8.6. IR (KBr): 1716, 1684, 1626. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.68; H, 8.51.

6-Methyl-3-(*S*)-(−)-phenethyl-3-azabicyclo[3.3.0]oct-5-en-7-one (Table 2, entry 2). The general procedure employing (*S,S*)-(EBTHI)$TiMe_2$ (9 mg, 0.026 mmol) was used to convert allyl(2-butynyl)[(*S*)-α-methylbenzyl]amine (**4i**) (49 mg, 0.23 mmol) to the desired product in 24 h. The reaction mixture was concentrated without filtration through silica. Purification by flash chromatography (85% ether, hexanes) afforded 48 mg (87% yield) of a yellow oil. The diastereomeric ratio of the product was determined to be 4.3:1 by ^1H NMR integration. $[\alpha]^{22}_D$ −20° (*c* 2.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, major isomer): δ 7.37−7.24 (m, 5 H); 4.08 (d, J = 17.5 Hz, 1 H); 3.46 (q, J = 6.5 Hz, 1 H); 3.22 (d, J = 17.5 Hz, 1 H); 3.04 (m, 1 H); 3.00 (m, 1 H); 2.53 (dd, J = 18.0, 6.0 Hz, 1 H); 2.00 (dd, J = 18.0, 3.0 Hz, 1 H); 1.73 (s, 3 H); 1.45 (d, J = 6.5 Hz, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, major isomer): δ 209.1, 178.4, 144.4, 131.8, 128.4, 127.2, 127.1, 64.9, 57.2, 51.2, 43.1, 39.6, 22.4, 8.6. IR (neat, mixture of isomers): 1710, 1673. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.81; H, 7.72.

Table 2, entry 3. The same procedure as for Table 2, entry 2, employing (*R,R*)-(EBTHI)$TiMe_2$ afforded 47 mg (84% yield) of a yellow solid. The diastereomeric ratio of the product was determined to be 1:3.5 by ^1H NMR integration. mp 55−58 °C. $[\alpha]^{22}_D$ −162° (*c* 2.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, major isomer): δ 7.42−7.24 (m, 5 H); 3.65 (d, J = 17.6 Hz, 1 H); 3.58 (t, J = 7.6 Hz, 1 H); 3.47 (q, J = 6.5 Hz, 1 H); 3.16 (m, 1 H); 2.93 (d, J = 17.6 Hz, 1 H); 2.64 (dd, J = 17.6 Hz, 6.4, 1 H); 2.13 (dd, J = 17.6, 3.4 Hz, 1 H); 1.97 (m, 1 H); 1.73 (m, 1 H); 1.62 (m, 2 H); 1.42 (d, J = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, major isomer): δ 209.5, 178.7, 144.8, 131.7, 128.5, 127.1, 127.0, 65.3, 56.5, 52.3, 43.1, 39.7, 23.0, 8.6. IR (neat, mixture of isomers): 1706, 1671. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.78; H, 7.95.

6-Methyl-3-*tert*-Butyl-3-azabicyclo[3.3.0]oct-5-en-7-one (Table 2, entry 4). The general procedure employing (*S,S*)-(EBTHI)$TiMe_2$ (18 mg, 0.053 mmol) was used to convert allyl(*tert*-butyl)(2-butynyl)amine (86 mg, 0.520 mmol) to the desired product in 10 h. Unreacted starting material (19%) was detected by GC analysis. The reaction mixture was concentrated without filtration through silica. Purification by flash chromatography (3% NH_3 saturated MeOH, ether) afforded 62 mg (62% yield) of a yellow solid, mp 70−72 °C. The ee was determined to be 28% by chiral GC (B-PH column). $[\alpha]^{22}_D$ +79° (*c* 1.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (d, J = 16.5 Hz, 1 H); 3.42 (d, J = 17.1 Hz, 1 H); 3.30 (t, J = 7.7 Hz, 1 H); 3.10 (bs, 1 H); 2.62 (dd, J = 17.9 Hz, 6.5, 1 H); 2.09 (m, 2 H); 1.72 (s, 3 H); 1.12 (s, 9 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 209.7, 178.8, 131.7, 52.9, 51.3, 45.8, 43.1, 39.8, 25.8, 8.7. IR (neat): 1703, 1666. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.55; H, 9.77. Found: C, 74.57; H, 9.91.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical characterization of enyne substrates. See any current masthead page for ordering and Internet access instructions. This material is available free of charge via the Internet at http://pubs.acs.org.

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