A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines

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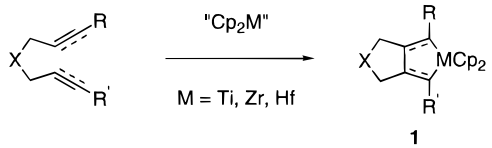
A practical titanium-catalyzed synthesis of bicyclic cyclopentenones and allylic amines is described. The process converts enyne substrates to iminocyclopentenes using 10 mol % of the air- and moisture-stable precatalyst Cp_2TiCl_2 in the presence of *n*-BuLi and triethylsilyl cyanide. The resulting iminocyclopentenes can be hydrolyzed to cyclopentenones in good yields or reduced to allylic silylamines with Red-Al or DIBALH. Treatment of the crude silylamines with acetyl chloride allows isolation of allylic amides in excellent yields.

In recent years, group IV metallocene-mediated reductive cyclizations of enynes,[1] diynes,[2] and dienes[3] have become an important methodology in organic synthesis (Scheme 1). The metallacycles formed (**1**) can be hydrolyzed, carbonylated, iminylated,[4] halogenated, and converted into a wide range of main group heterocycles[5] and highly substituted benzene derivatives.[6] These transformations have as a limitation their requirement for a stoichiometric quantity of metal.

On the basis of the observation[4] that the product of the reaction of *tert*-butyl isocyanide with titanacycle **2** is converted to iminocyclopentene **4** with loss of "titanocene" (Scheme 2), the catalytic cycle in Scheme 3 was proposed. Initial efforts with *tert*-butyl isocyanide failed due to catalyst deactivation in the presence of excess isocyanide. This problem was overcome[7] by keeping the concentration of isocyanide low in solution with trialkylsilyl cyanides ($R' = Et_3Si$, t-$Bu(Me)_2Si$),[8] which exist in equilibria with minor amounts of the isocyanides (99:1 for trimethylsilyl cyanide). Scheme 4 outlines the course of the catalytic procedure.[9]

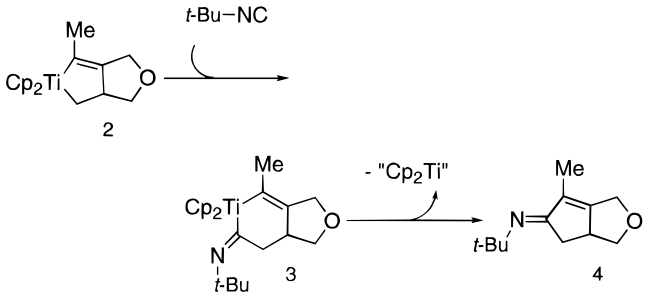
Although this process, as the first early transition metal catalyzed cyclopentenone synthesis, represents an advance in methodology, there are a number of areas where improvements can be made. A major problem is that the precatalyst $Cp_2Ti(PMe_3)_2$[10] is extremely air- and moisture-sensitive and must be handled and stored in a

Scheme 1



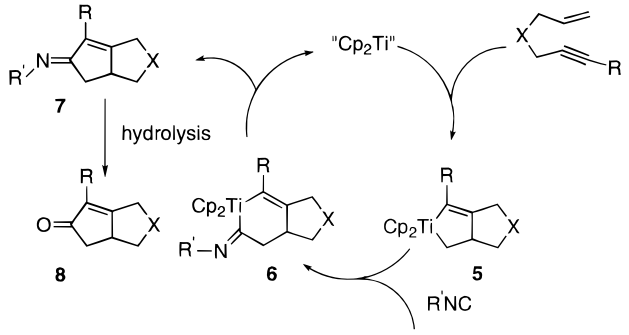
1

Scheme 2



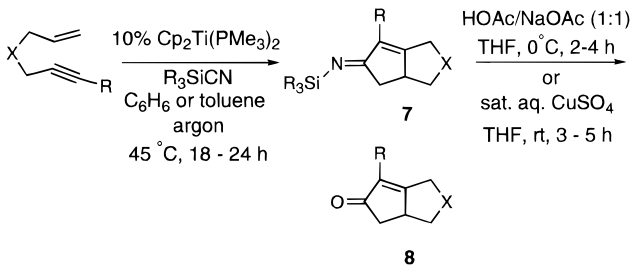
2 **3** **4**

Scheme 3



7 **8** **6** **5**

Scheme 4



7 **8**

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(2) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422.

(3) (a) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. (b) Negishi, E.-i.; Swanson, D. R.; Lamaty, F.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 5105.

(4) Buchwald, S. L.; Grossman, R. B. *J. Org. Chem.* **1992**, *57*, 5803.

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(7) (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.

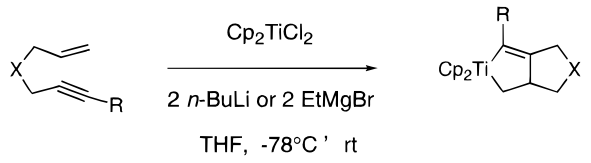
(8) Rasmussen, J. K.; Heilmann, S. M.; Krepski, L. R. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1991; pp 65−187.

(9) For other examples of catalytic reactions involving group IV metallacycles, see: (a) Kabaloui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6785. (b) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (c) Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735. (d) Knight, K. S.; Waymouth, R. M. *Organometallics* **1994**, *13*, 4542.

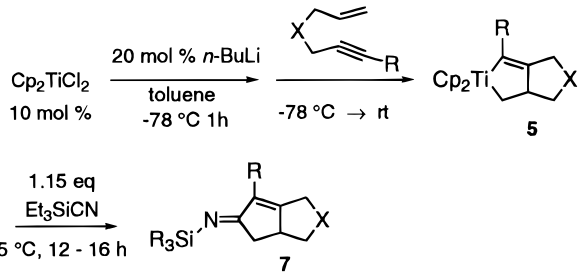
(10) Rausch, M. D.; Alt, H. G.; Kool, L. B.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 394.

0022-3263/96/1961-2713$12.00/0

Scheme 5



Scheme 6



glovebox under argon. In addition, it would be advantageous to develop a catalyst system that did not require PMe_3 due to concerns about its stench and toxicity. A method to generate the catalytically active species *in situ* from Cp_2TiCl_2, which is air- and moisture-stable and inexpensive, would greatly increase the practicality of this methodology. The yields of cyclopentenones **8** (43−80%),[7] while comparable to related syntheses,[11] are disappointing considering that iminocyclopentene formation is quantitative (^{1}H NMR). This led to the search for alternative transformations that could give products in higher yields and exploit the silylimine functionality.

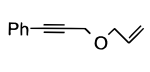
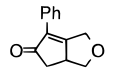
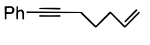
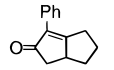
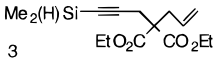
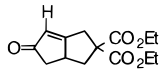
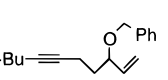
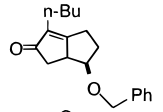
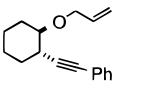
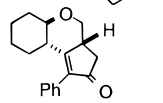
Titanacyclopentenes **5** are intermediates in the catalytic cycle depicted in Scheme 2. We have previously shown[4] that these metallacycles can be prepared from enynes by treatment with a mixture of Cp_2TiCl_2 and 2 equiv of EtMgBr or *n*-BuLi (Scheme 5). We decided, therefore, to see if the combination Cp_2TiCl_2/2 *n*-BuLi could serve as a catalyst in lieu of $Cp_2Ti(PMe_3)_2$.

Our initial attempts, employing THF as solvent, were unsuccessful. Although metallacycle formation was nearly quantitative (^{1}H NMR), the catalyst was rapidly decomposed under the reaction conditions. Attempts to run the reaction in the noncoordinating solvent toluene were hampered by the extremely low solubility of Cp_2TiCl_2. We found, however, that by using *n*-BuLi with finely ground Cp_2TiCl_2 in toluene (Scheme 6), the titanacycle **5** (X = O, R = Ph) was produced in 92% yield (^{1}H NMR) and was catalytically active at 10 mol %, the same level as with $Cp_2Ti(PMe_3)_2$.

To compare the two catalysts, a number of cyclopentenones were synthesized using the new system (Table 1). The yields indicate the processes employing Cp_2TiCl_2 and $Cp_2Ti(PMe_3)_2$ are equally effective. In addition, we found that a bicyclic enyne (Table 1, entry 5), using the new catalyst system, produces the tricyclic cyclopentenone in good yields.[12]

After developing the new *in situ* method of catalyst generation, we decided to explore other reactions of the silylimine intermediates. The chemistry of silylimines has developed rapidly in the past decade due in large part

Table 1. Comparison of Cyclopentenone Formation from Precatalysts $Cp_2Ti(PMe_3)_2$ and Cp_2TiCl_2

entry	starting material	product	$Cp_2Ti(PMe_3)_2$ yield (%)[a]	Cp_2TiCl_2 yield (%)
1			80	82
2			66	64
3			42	45
4			45 (12:1)	42 (12:1)
5			----	67[b]

[a] See Ref 7. [b] Only one diastereomer formed.

to the fact that the silyl group is easily removed from the products formed. Thus, silylimines serve as synthetic equivalents to unsubstituted imines. Hart initiated work in this area[13] by studying reductions of silylimines with $LiAlH_4$, addition reactions with alkyllithium and Grignard reagents, and condensations with ester enolates to form β-lactams.[14] The reactions of silylimines have since been expanded to include the synthesis of aziridines,[15] 1,2-amino alcohols,[16] and α-amino phosphonic acids.[17] Due to the importance of allylic amines[18] both as synthetic intermediates[19] and as biologically active compounds themselves,[20] we chose to explore hydride reductions of the silylimines produced by our methodology.[21]

After a range of reducing agents were surveyed, Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) and DIBALH were found to give high yields of the corresponding silylamines **8** (Scheme 7). In the one reported example of silylimine reduction we are aware of, the amine which was isolated had been desilylated.[13] Since silyl groups can be utilized to protect amines, the development of reaction protocols which retain them is significant.[22] Although the crude silylamines could be utilized for further transformations, their isolation proved

(11) (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1037−1064. (b) Jeony, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (c) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286. (d) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (e) Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656.

(12) See ref 11c for a related iminocyclopentene.

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(14) Hart D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447.

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(16) Cainelli, G.; Mezzina, E.; Panunzio, M. *Tetrahedron Lett.* **1990**, *31*, 3481.

(17) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045.

(18) For a review on the synthesis of allylic amines, see: Chaabouni, R.; Cheikh, R. D.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. For a related synthesis of allylic amines with stoichiometric zirconium, see: Whitby, R. J.; Probert, G. D.; Coote, S. J. *Tetrahedron Lett* **1995**, *36*, 4113.

(19) For recent examples see: (a) Burgess, K.; Ohlmeyer. M. J. *J. Org. Chem.* **1991**, *56*, 1027. (b) Jung, M.; Rhee, H. *J. Org. Chem.* **1994**, *59*, 4719. (c) Brunker, H.-G.; Adam, W. *J. Am. Chem. Soc.* **1995**, *117*, 3976.

(20) (a) Stutz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320. (b) Delaris, G.; Dunogues, J.; Gadras, A. *Tetrahedron* **1988**, *44*, 4293 and references therein.

(21) For a review on hydride reductions of C=N, see: Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 25−78.

(22) Overman, L. E.; Okazaki, M. E.; Mishra, P. *Tetrahedron Lett.* **1986**, *27*, 4391.

Scheme 7

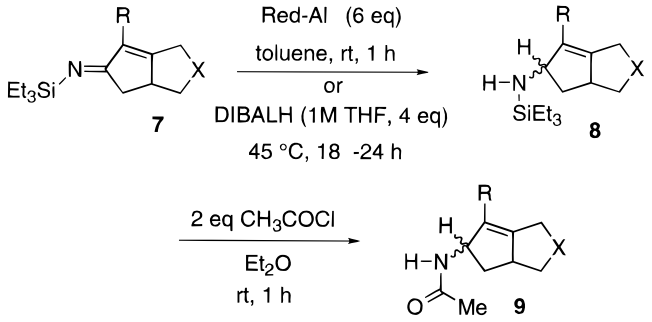
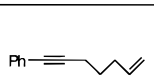
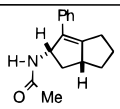
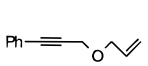
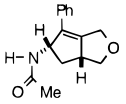
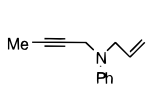
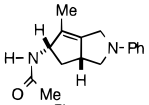
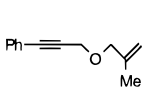
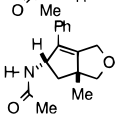
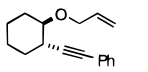
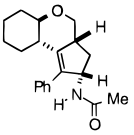
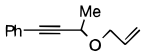
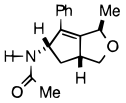
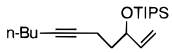
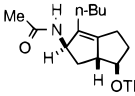
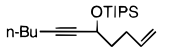
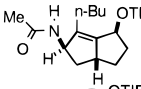
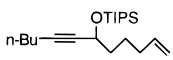
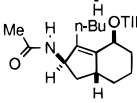


Table 2. Conversion of Enynes to Bicyclic Allylic Amides

entry	starting material	red. agent	product[a]	yield(%)	cyclopentenone yield (%)[d]
1		Red-Al		89	80
2		Red-Al		82	66
3		Red-Al		61	44
4		Red-Al		72[b]	58
5		Red-Al		72[c,e]	67
6		Red-Al		82	71 (5:1)
7		Red-Al		63[c] (1:1:3.5)	----
8		DIBAL		80[c] (4:1)	54 (1.6:1)
9		DIBAL		65[c] (16:16:2:1)	52

[a] Major diastereomer pictured. [b] Required 20 mol% catalyst for complete conversion. [c] Required 15 mol% catalyst for complete conversion. [d] See Ref 7. [e] Only diastereomer isolated.

difficult. Attempts to desilylate and isolate the free amines led to deamination and to complex mixtures of cyclopentadiene and allylic alcohol derivatives. For this reason, the silylamines were converted to amides **9** for their isolation.[23]

For most substrates (Table 2, entries 1−6), Red-Al reduction was completely diastereoselective. Reduction with DIBALH (substrate from Table 2, entry 1), however, produced a mixture of two diastereomers (3:2), with the same predominant product as from Red-Al reduction.[24] The substrate with an allylic TIPS (triisopropylsilyl) ether (Table 2, entry 7) was reduced by Red-Al, but reaction occurred only slowly at elevated temperatures to give a mixture of three diastereomers.[25] With substrates containing propargylic TIPS ethers (Table 2, entries 8 and 9), reaction with Red-Al gave only low yields of products. However, DIBALH cleanly reduces the silylimines from entries 8 and 9 to give products in high yields with varying levels of diastereocontrol.

Acetylation of the reduction products with TIPS protecting groups required the addition of 4 equiv of NEt_3 to prevent decomposition. A substrate with an allylic benzyl ether (Table 1, entry 4) was cleanly reduced with Red-Al, but it decomposed upon attempted acetylation, even in the presence of NEt_3. Presumably, reaction of the benzyl group leads to decomposition, since the substrate with an allylic TIPS ether (Table 2, entry 8) was acetylated without problem. For all substrates, reduction and acetylation of the silylimines produces allylic amides in higher yields than hydrolysis to the corresponding cyclopentenones.

In conclusion, we have developed a practical, PMe_3-free catalytic system for synthesizing bicyclic iminocyclopentenes from the air- and moisture-stable precatalyst Cp_2TiCl_2. The yields of cyclopentenones from hydrolysis are the same as previously reported for the air- and moisture-sensitive precatalyst $Cp_2Ti(PMe_3)_2$. In addition, we have developed a reduction to give allylic amides in yields which are consistently higher than hydrolysis to the cyclopentenones. Future work will include the development both of intermolecular and asymmetric versions of these and related cyclizations.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were accumulated at 300 MHz. Toluene and tetrahydrofuran were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl followed by distillation. Methylene chloride was dried by continuous refluxing over CaH_2 followed by distillation. Diethyl ether was used with no preparative drying. All enynes used for cyclization reactions, unless stated otherwise, were prepared as in Berk et al.[7] *trans*-1-(allyloxy)-2-(phenylethynyl)cyclohexane (Table 1, entry 5, and Table 2, entry 6) was prepared by ring opening of cyclohexene oxide with (phenylethynyl)lithium and $BF_3{\cdot}OEt_2$[26] followed by protection of the alcohol with allyl bromide.[27] Et_3SiCN was prepared by the procedure of Becu.[28] All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. For all products, the stereochemistry at the ring carbon α to the acetamido group was assigned on the basis of the characteristic ^1H NMR shifts. For the *endo* acetamido groups, the amide NH peak occurs at around 7 ppm in $CDCl_3$. For the *exo* acetamido groups, the amide NH peak occurs at around 5.1 ppm in $CDCl_3$. NOE data

(23) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1973**, 2475.

(24) The origins of the diastereoselectivites are unclear at the present time as the reduction of imines has received little mechanistic investigation.

(25) The cyclization reaction itself results in two diastereomers at the TIPS ether carbon (Table 2, entries 7−9). For diastereoselectivities of entries 8 and 9, see ref 7b (also contains discussion on origins of selectivities). NMR experiments have shown the selectivity for entry 7 to be 2.2:1 in favor of the *exo* TIPS ether.

(26) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(27) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.

(28) Becu, C.; Anteunis, M. J. O. *Bull. Soc. Chem. Belg.* **1987**, *96*, 115.

for one set of diastereomers from DIBALH reduction of an iminocyclopentene (Table 2, entry 5) were utilized to establish the relative stereochemistry. All other stereocenters on products were assigned by X-ray or NOE studies. Yields refer to isolated yields of compounds estimated to be >95% pure (unless otherwise noted) as determined by ^{1}H NMR and either capillary GC (known compounds) or combustion analysis (new compounds). Elemental analyses were performed by E + R Microanalytical Laboratory, Corona, NY.

General Procedure for the Conversion of Enynes to Iminocyclopentenes. A flame-dried Schlenk flask was attached to a Schlenk line and allowed to cool. Cp_2TiCl_2 (0.1 mmol, 26 mg) ground with a mortar and pestal and toluene (2−3 mL) were added to the flask, which was cooled to −78 °C. *n*-BuLi (80 μL of 2.5 M in hexanes) was added dropwise, with care to ensure that none of it touched the sides of the flask. After 1 h at −78 °C, the enyne (1.0 mmol) was added. The reaction mixture was stirred for another 1 h at −78 °C and was allowed to warm to rt over 1 h. After 3−5 h at rt, Et_3SiCN (1.15 mmol) was added. The flask was then heated overnight in an oil bath at 45−55 °C.

Conversion of Iminocyclopentenes to Allylic Silylamines. General Procedure A. The reaction was cooled to rt, and Red-Al (6 mmol equiv of "H", 840 μL) was added. After 1 h at rt, the reaction was quenched into 50 mL each of 5% NaOH and ether, and the aqueous layer was extracted with 2 × 50 mL of ether. The combined organic extracts were washed with brine and dried over $MgSO_4$, and the crude product mixture was concentrated to 15 mL.

General Procedure B. The reaction was cooled to rt, and DIBALH (4 mL of 1 M in THF) was added. After the reaction was heated to 50 °C overnight, it was quenched into 50 mL each of 5% NaOH and ether. The aqueous layer was extracted with 2 × 50 mL of ether, and the combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product mixture was concentrated to 15 mL.

General Procedure for the Conversion of Silylamines to Amides. Acetyl chloride (2 mmol, 143 μL) was added to the crude silylamine. After 1 h at rt, the reaction was quenched with 50 mL each of 5% NaOH and ether. The aqueous layer was extracted with 2 × 50 mL of ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to produce the crude product.

3-((Triisopropylsilyl)oxy)-1-undecen-6-yne (Table 2, Entry 8). Undec-1-en-6-yn-3-ol[7] (30 mmol) was protected by the procedure of Corey.[29] The product was purified by flash chromatography (hexane) to yield 2.8 g (30%) of a pale yellow liquid. ^{1}H NMR (300MHz, $CDCl_3$): δ 5.76 (m, 1 H), 5.14 (m, 1 H), 5.03 (m, 1 H), 4.32 (quart, J = 3.0 Hz, 1 H), 2.15 (m, 4 H), 1.74 (m, 1 H), 1.64 (m, 1 H), 1.40 (m, 4 H), 1.04 (m, 21 H), 0.88 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 114.4, 80.4, 79.7, 73.0, 37.4, 31.2, 21.9, 18.4, 18.1, 14.3, 13.6, 12.4. IR (neat, cm^{-1}): 2943, 2866, 1464, 1382, 1093, 1067, 991, 922, 837, 681. Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.64; H, 12.03.

Tricyclic Cyclopentenone (Table 1, Entry 5). The silylimine from *trans*-1-(allyloxy)-2-(phenylethynyl)cyclohexane (240 mg, 1.0 mmol) was obtained using a modification of the general procedure with 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The toluene was removed from the Schlenk flask *in vacuo*, and the crude silylimine was cannula transferred with 30 mL of THF to a 250 mL Schlenk flask under argon. Three mL of saturated aqueous $CuSO_4$ was added dropwise followed by vigorous stirring of the mixture for 4 h at rt. The reaction mixture was extracted with 50 mL each of 0.5 N HCl and ether, and the aqueous layer was reextracted with 2 × 50 mL ether. The combined organic layers were washed with 0.5 N NaOH and brine and dried over $MgSO_4$ to afford the crude product. Purification by flash chromatography (ether:hexane = 4:1) afforded 180 mg (67%) of an off-white solid. Mp: 118−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (m, 3 H), 7.01 (m, 2 H), 4.27 (dd, J = 6.2, 10.2 Hz, 1 H), 3.18 (t, J = 11.0 Hz, 1 H), 3.0 (m, 2 H), 2.50 (dd, J = 7.0, 18.6 Hz, 1 H), 2.31 (m, 1 H), 1.90 (m, 2 H), 1.62 (m, 1 H), 1.40 (m, 3 H), 1.06 (m, 2 H), 0.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 174.2, 138.7, 133.1, 129.9, 127.7, 127.6, 81.9, 73.6, 48.7, 41.0, 36.2, 33.2, 28.1, 25.6, 24.2. IR (KBr, cm^{-1}): 2920, 2858, 1692, 1643, 1443, 1108, 1092, 1003, 707. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.66; H, 7.72. The relative stereochemistry for the product was determined by X-ray crystallographic analysis.

3-Acetamido-2-phenylbicyclo[3.3.0]oct-1-ene (Table 2, Entry 1). 1-Phenyl-6-hepten-1-yne (170 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The crude amide was purified by filtering and washing several times with cold pentane to yield 195 mg (83%) of a white solid. Mp: 141−143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (t, J = 7.5 Hz, 3 H), 7.24 (d, J = 7.5 Hz, 2 H), 7.02 (s, 1 H), 3.46 (m, 1 H), 3.15 (dd, J = 9.6, 16.8 Hz, 1 H), 3.00 (m, 1 H), 2.72 (m, 1 H), 1.94 (s, 3 H), 1.78 (m, 1 H), 1.50 (m, 4 H), 1.33 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 136.4, 132.8, 128.9, 127.9, 126.8, 125.0, 50.6, 41.2, 38.2, 35.4, 31.5, 25.4, 24.1. IR (KBr, cm^{-1}): 3282, 2945, 2858, 1664, 1517, 1492, 1356, 1267, 764, 693. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.75; H, 8.15. If reduction was accomplished with procedure B, two diastereomers (3:2) were obtained. The two crude amides were separated and purified by flash chromatography (ethyl acetate:hexane = 1:1). The minor diastereomer was isolated as 70 mg (30%) of a white solid. Mp: 147−149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 3 H), 7.15 (m, 2 H), 5.80 (m, 1 H), 5.37 (m, 1 H), 3.20 (m, 3 H), 2.37 (m, 1 H), 2.13 (m, 1 H), 1.95 (m, 2 H), 1.86 (s, 3 H), 1.15 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 153.6, 135.8, 128.4, 128.3, 126.6, 126.1, 60.9, 50.8, 40.0, 32.3, 28.7, 25.5, 23.4. IR (KBr, cm^{-1}): 3307, 2956, 2859, 1644, 1538, 1497, 1443, 1372, 1303, 1152, 768, 693. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.50; H, 8.12.

3-Acetamido-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 2). 3-(Allyloxy)-1-phenyl-1-propyne (170 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The crude amide was purified by filtration and washing several times with cold pentane to yield 215 mg (89%) of a white solid. Mp: 120−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (t, J = 7.2 Hz, 3 H), 7.22 (d, J = 7.2 Hz, 2 H), 7.10 (s, 1 H), 3.87 (t, J = 8.1 Hz, 1 H), 3.64 (m, 3 H), 3.52 (m, 1 H), 3.18 (m, 2 H), 2.94 (m, 1 H), 1.94 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 135.6, 133.6, 129.1, 127.7, 127.1, 122.6, 75.7, 72.1, 51.8, 39.2, 39.0, 24.0. IR (KBr, cm^{-1}): 3292, 2963, 2833, 1665, 1515, 1490, 1366, 1268, 1088, 1044, 766, 693. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04. Found: C, 73.99; H, 7.05.

3-Acetamido-2-methyl-7-phenyl-7-azabicyclo[3.3.0]oct-1-ene (Table 2, Entry 3). *N*-(2-Butynyl)-*N*-allylaniline (247 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 7:3) to afford 156 mg (61%) of a light orange solid. Mp: 174−176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (t, J = 8.1 Hz, 2 H), 6.67 (t, J = 7.5 Hz, 1 H), 6.59 (d, J = 7.8 Hz, 2 H), 6.55 (s, 1 H), 3.46 (t, J = 9.0 Hz, 1 H), 3.28 (m, 3 H), 3.15 (m, 1 H), 3.00 (m, 2 H), 2.70 (d, J = 16.0 Hz, 1 H), 2.03 (s, 3 H), 1.60 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 148.4, 130.9, 129.1, 122.4, 116.5, 112.9, 55.7, 51.2, 50.8, 39.2, 37.9, 23.8, 11.8. IR (KBr, cm^{-1}): 3321, 2940, 1661, 1600, 1505, 1476, 1369, 1338, 1274, 1187, 746, 690. Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.76. Found: C, 74.79; H, 7.75.

3-Acetamido-5-methyl-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 4). 3-((2-Methyl-2-propenyl)oxy)-1-phenyl-1-propyne (372 mg, 2.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.20 mmol of Cp_2TiCl_2, 0.40 mmol of *n*-BuLi, and 6 mL of toluene. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 3:2) to give 370 mg (75%) of a white solid. Mp: 127−129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (t, J =

(29) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett* **1981**, *22*, 3455.

7.3 Hz, 3 H), 7.21 (d, J = 7.0 Hz, 2 H), 7.11 (s, 1 H) 3.82 (dd, J = 7.2, 8.7 Hz, 1 H), 3.72 (d, J = 8.4 Hz, 1 H), 3.51 (d, J = 8.7 Hz, 2 H), 3.33 (d, J = 17.7 Hz, 1 H), 3.14 (m, 1 H), 2.93 (d, J = 17.7 Hz, 1 H), 1.96 (s, 3 H), 1.30 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 135.1, 132.1, 128.5, 127.2, 126.6, 121.9, 80.5, 72.0, 58.2, 46.6, 45.6, 24.8, 23.5. IR (KBr, cm^{-1}): 3233, 2959, 2846, 1662, 1638, 1520, 1496, 1352, 1274, 1062, 922, 768, 695. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.65; H, 7.44. To determine the relative stereochemistry at the ring carbon α to the acetamido group, the iminocyclopentene was also reduced by procedure B to yield a mixture of two diastereomers (3:2). The major diastereomer was the same one obtained exclusively with procedure A. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of each diastereomer. Irradiation of the C-5 methyl group at δ 1.4 (C_6D_6) of the major diastereomer gave no enhancement of the amide NH at δ 6.85, while the same experiment produced a 2% enhancement in the minor diastereomer. The stereochemistry for the two diastereomers was therefore assigned as shown:

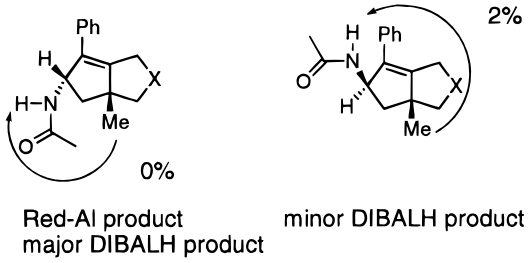
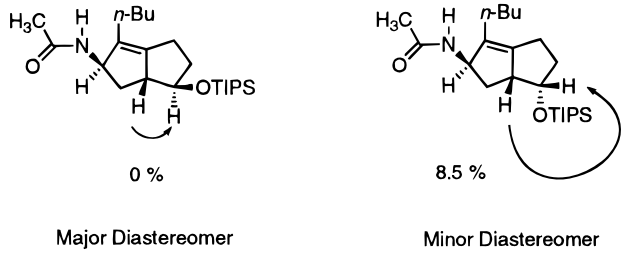


Table 2, Entry 5. *trans*-1-(Allyloxy)-2-(phenylethynyl)-cyclohexane (240 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*- BuLi, and 5 mL of toluene. The reduction was effected by procedure A with the modification that the reaction was heated for 2 h at 50 °C. The product was purified by flash chromatography (ether: hexane = 9:1) to give 224 mg (72%) of a pale orange solid. The product exists as approximately a 3:2 mixture of amide rotamers by NMR. Although the product is unstable at room temperature for extended periods, it can be stored in the freezer with little decomposition. Mp: 50−53 °C. It proved difficult to assign ^{1}H peaks to the individual rotamers, so a list of peaks without assignments or integrations is given. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.26 (m), 7.12 (d), 6.64 (s), 6.18 (s), 5.92 (s), 4.00 (dd), 3.81 (m), 3.50 (t), 3.28 (m), 3.13 (m), 2.89 (m), 2.77 (m), 2.68 (m), 1.94 (m), 1.85 (s), 1.81 (s), 1.71−0.87 (m), 0.35 (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 167.6, 141.7, 138.7, 137.7, 136.4, 129.2, 128.9, 128.5, 127.5, 127.2, 122.9, 112.8, 77.5, 77.1, 70.8, 68.0, 50.6, 48.3, 47.5, 44.0, 43.0, 42.5, 36.2, 34.6, 33.0, 32.6, 30.6, 26.6, 26.2, 24.9, 24.6, 24.2, 24.0. Ir (neat, cm^{-1}): 3288, 2932, 2857, 1682, 1514, 1450, 1367, 1260, 1100, 1012, 867, 751, 700. The relative stereochemistry of the tricyclic ring system was assigned based upon analogy to the related tricyclic ketone (Table 1, entry 5).

3-Acetamido-8-methyl-2-phenyl-7-oxabicyclo[3.3.0]oct-1-ene (Table 2, Entry 6). 3-(Allyloxy)-1-phenyl-1-butyne (186 mg, 1 mmol) was converted to the iminocyclopentene by the general procedure. The reduction was accomplished with procedure A. The product was purified by flash chromatography (ethyl acetate:hexane = 4:1) to give 210 mg (82%) of a 95:5 mixture of diastereomers as a white solid. Recrystallization from ether yields 185 mg (73%) of a single diastereomer as a white solid. Mp: 118−120 °C. ^{1}H NMR (300 MHz, $CDCL_3$): δ 7.40 (t, J = 7.2 Hz, 3 H), 7.25 (m, 2 H), 7.05 (s, 1 H), 4.18 (t, J = 7.8 Hz, 1 H), 3.60 (quin, J = 5.5 Hz, 1 H), 3.43 (t, J = 8.4 Hz, 1 H), 3.26 (m, 1 H), 3.06 (m, 3 H), 1.96 (s, 3 H), 1.11 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9, 135.4, 132.8, 129.2, 127.8, 127.3, 122.4, 80.3, 74.2, 58.6, 39.9, 38.9, 24.2, 21.0. IR (KBr, cm^{-1}): 3296, 2966, 2849, 1665, 1516, 1493, 1355, 1254, 1056, 758, 696. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.51; H, 7.51.

3-Acetamido-2-butyl-6-((triisopropylsilyl)oxy)bicyclo[3.3.0]oct-1-ene (Table 2, Entry 7). 3-((Triisopropylsilyl)-oxy)-1-undecen-6-yne (324mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The reduction was accomplished by procedure A with the modification of heating the reaction overnight at 50 °C. To prevent product decomposition, the acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 3:2) to afford 236 mg (63%) of a mixture of three diastereomers (1:1:3.5) as a light yellow oil. A second chromatography allowed the first diastereomer to be isolated as a light yellow solid, but the other two diastereomers could not be separated. First diastereomer. Mp: 88−90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23 (m, 2 H), 4.14 (t, J = 3.2 Hz, 1 H), 2.66 (m, 1 H), 2.25 (m, 2 H), 2.03 (m, 4 H), 1.95 (s, 3 H), 1.42 (m, 3 H), 1.28 (m, 3 H), 1.03 (m, 21 H), 0.85 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 146.0, 131.2, 71.1, 61.1, 54.8, 38.3, 30.2, 25.9, 23.6, 22.6, 20.9, 18.2, 18.1, 13.9, 12.4. IR (KBr, cm^{-1}): 3252, 3068, 2956, 2865, 1639, 1557, 1463, 1376, 1297, 1152, 1063, 1012, 882, 803, 682. Anal. Calcd for $C_{23}H_{43}NO_2Si$: C, 70.17; H, 11.01. Found: C, 70.32; H, 10.99. To determine the relative stereochemistry of the OTIPS group for the major diastereomeric product from Table 2, entry 7, an NOE study was undertaken. Irradiation of the C-5 proton at δ 3.83 (C_6D_6) of the major diastereomer gave no enhancement of the C-6 proton at δ 2.70, while the same experiment produced an 8.5% enhancement in the first minor diastereomer. The stereochemistry for the two diastereomers was therefore assigned as shown:



3-Acetamido-2-butyl-8-((triisopropylsilyl)oxy)bicyclo[3.3.0]oct-1-ene (Table 2, Entry 8). 5-((Triisopropylsilyl)-oxy)-1-undecen-6-yne (324 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol of *n*-BuLi, and 5 mL of toluene. The reduction was accomplished with procedure B, and acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 3:2) to afford 300 mg (80%) of a 4:1 mixture of diastereomers as a light yellow oil. A pure sample of the major diastereomer was obtained by a second chromatography. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (quart, J = 9 Hz, 1 H), 4.8 (s, 1 H), 4.56 (d, J = 9 Hz, 1 H), 2.87 (m, 1 H), 2.43 (m, 1 H), 2.22 (m, 1 H), 1.97 (m, 4 H), 1.75 (m, 1 H), 1.57 (s, 3 H), 1.40 (m, 4 H), 1.14 (m, 21 H), 0.95 (t, J = 7.0 Hz, 3 H), 0.75 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.0, 148.8, 133.9, 68.2, 60.0, 44.4, 41.9, 38.8, 30.5, 29.8, 28.4, 23.4, 23.1, 18.1, 13.8, 12.5. IR (neat, cm^{-1}): 3275, 2956, 2865, 1650, 1556, 1464, 1373, 1296, 1052, 883, 681. Anal. Calcd for $C_{23}H_{43}NO_2Si$: C, 70.17; H, 11.01. Found: C, 70.29; H, 11.10. The stereochemistry of the TIPS ether was assigned on the basis of NOE studies on the corresponding cyclopentenone.[7]

3-Acetamido-2-butyl-9-((triisopropylsilyl)oxy)bicyclo[3.4.0]non-1-ene (Table 2, Entry 9). 6-((Triisopropylsilyl)-oxy)-1-dodecen-7-yne (336 mg, 1.0 mmol) was converted to the iminocyclopentene by the general procedure with the modification of 0.15 mmol of Cp_2TiCl_2, 0.30 mmol *n*-BuLi, and 5 mL of toluene. In addition, the reaction time at rt was increased to overnight. The reduction was affected by procedure B, while acetylation was carried out by the general procedure with the addition of 4 equiv of NEt_3. The product was purified by flash chromatography (ether:hexane = 7:3) to give 253 mg (65%) of a mixture of four diastereomers (16:16:2:1) as a yellow oil. The

first diastereomer was isolated by a second chromatography as a light yellow solid. First diastereomer. Mp: 74−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (d, J = 9 Hz, 1 H), 4.92 (m, 1 H), 4.62 (t, J = 2.8 Hz, 1 H), 2.8 (m, 1 H), 2.05 (m, 1 H), 1.9 (s, 3 H), 1.82 (m, 6H), 1.77 (m, 1 H), 1.39 (m, 1 H), 1.20 (m, 4 H), 0.99 (m, 21 H), 0.83 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.2, 144.6, 132.3, 64.8, 55.8, 40.4, 37.9, 36.3, 35.7, 30.0, 24.9, 23.5, 22.4, 19.9, 18.1, 13.8, 12.3. IR (neat, cm^{-1}): 3273, 2932, 2864, 1644, 1556, 1463, 1372, 1078, 1031, 883, 785, 680. Anal. Calcd for $C_{24}H_{45}NO_2Si$: C, 70.70; H, 11.13. Found: C, 70.98; H, 11.12. The stereochemistry of the TIPS ether was assigned on the basis of NOE studies on the corresponding cyclopentenone.[7]

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