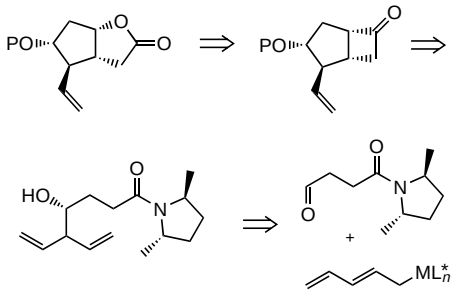
A Convergent Strategy for the Asymmetric Synthesis of Enantiomerically Pure Bicyclic Compounds by Using a Silicon-Directed Cycloaddition Reaction: The Synthesis of Enantiomerically Pure Bicyclo[3.2.0]-hept-2-en-6-one**

Jean-Michel Adam, Léon Ghosez,* and Kendall N. Houk

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday

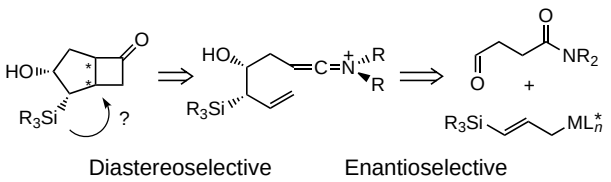
Bicyclic cyclobutanones are extremely versatile building blocks that have been used for the total synthesis of several important biologically active products.[1] Our group recently developed a convergent strategy for the synthesis of enantiopure bicyclo[3.2.0]heptanones that were further converted into various prostanoids intermediates (Scheme 1).[2] This



Scheme 1. Former approach using two chiral auxiliaries.

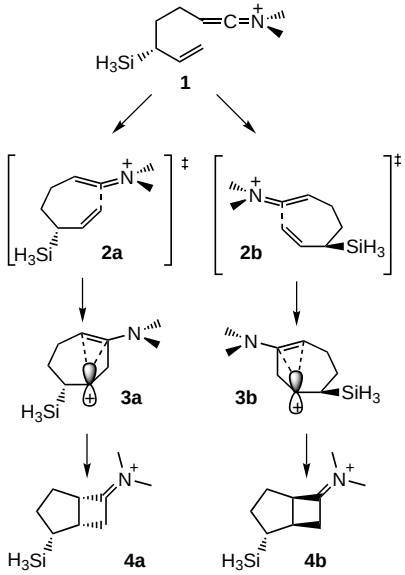
convergent strategy required two sources of chirality: the ligands L* of the metal direct the stereochemistry of the allylmetalation step, while the dimethylpyrrolidine controls the facial selectivity of the cycloaddition step. Asymmetric induction by the protected hydroxy group (1.3-induction) was indeed very poor as shown by a control experiment without a chiral pyrrolidine.[2b]

We recently considered the possibility of controlling the facial selectivity by a properly selected allylic substituent.[3] A silyl group was chosen as the stereodirecting functionality. It should be efficiently installed with the required relative and absolute configuration by the stereoselective addition of a chiral allylmetal reagent to an aldehyde (Scheme 2).



Scheme 2. Present strategy: use of a silicon-directed [2+2] cycloaddition.

We anticipated that the silyl substituent would not only activate the double bond towards electrophilic attack but would also control the facial selectivity.[4] However, since the rate and selectivity determining step of the cycloaddition involved the formation of a seven membered ring intermediate[5] (such as **3a** and **3b**, Scheme 3) we assessed our hypothesis by computational studies.



Scheme 3. Cycloaddition mechanism and face selection by the allylic silyl group.

Investigations of this reaction with ab initio and density functional theory methods[6] have led to a mechanistic scenario involving initial electrophilic attack of the keteniminium group on the alkene to form a bridged enamine cation (a distorted cyclopropylcarbinyl cation) which cyclizes with a very low activation barrier to form the cyclobutaneiminium ion (Scheme 3). In the case of the silyl-substituted substrate **1** RHF/6-31G* calculations[7] located four low-energy transition structures for the initial step of the reaction. Single point Becke3LYP/6-31G* calculations are consistent with the restricted Hartree–Fock (RHF) results. The lowest energy transition structures that lead to **4a** and **4b** (Scheme 3) are shown in Figure 1.

The favored transition structure (**2a**, which leads to **4a**) has a nearly perfect staggered tether between the alkene and the keteniminium group, and with the C–Si bond aligned with the alkene π orbitals. This alignment provides stabilization of the transition state by a β effect. By contrast, the lowest energy transition state for attack on the opposite face of the alkene has the silyl group disposed in the plane of the alkene where it

[*] Prof. Dr. L. Ghosez, J.-M. Adam
Laboratoire de Chimie Organique de Synthèse
Université catholique de Louvain
place L. Pasteur 1, B-1348 Louvain-la-Neuve (Belgium)
Fax: (+32) 10-474-168
E-mail: ghosez@chor.ucl.ac.be
Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry
University of California
405 Hilgard Avenue, Los Angeles, CA 90095-1569 (USA)

[**] This work was supported by FRIA (fellowship to J.-M.A), FNRS (fellowship to J.-M.A), the Ministère de l'Education et de la Recherche Scientifique de la Communauté française de Belgique (Actions concertées 91/96-145 and 96/01–197), and the University of California, Los Angeles (grant to J.-M.A).

  1433-7851/99/3818-2728 $ 17.50+.50/0

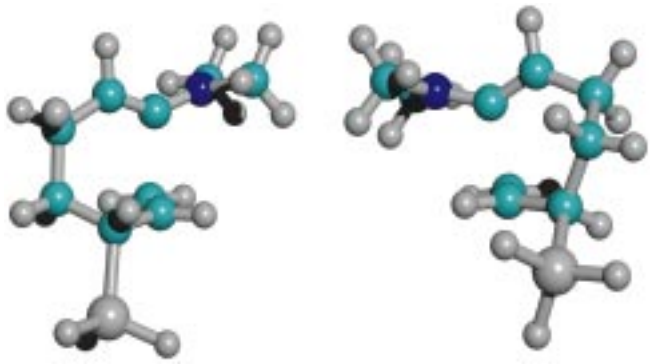
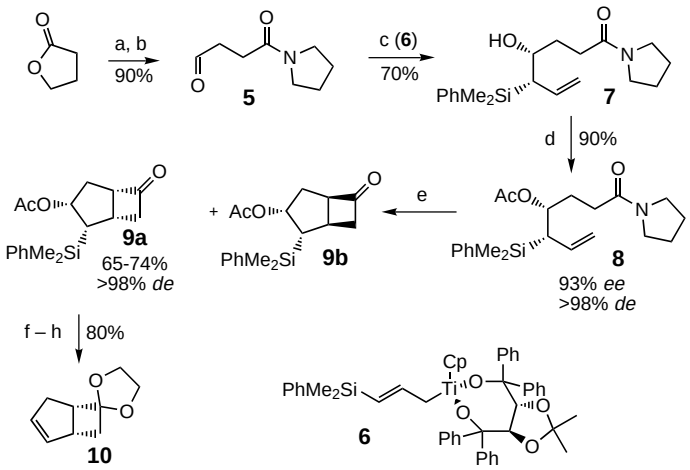


Figure 1. Relevant transition states for the cycloaddition of **1**: left: **2a**, 0 kcal mol^{-1} (RHF/6-31G*//RHF/6-31G*), 0 kcal mol^{-1} (Becke3LYP/6-31G*//RHF/6-31G*); right: **2b**, 2.98 kcal mol^{-1} (RHF/6-31G*//RHF/6-31G*), 3.21 kcal mol^{-1} (Becke3LYP/6-31G*//RHF/6-31G*).

provides negligible stabilization. Having these predictions in hand, we compared them with the experimental results.

The precursor for the cycloaddition was readily obtained by the addition of aldehyde **5**[8] to a solution of the (*E*)-γ-silyl-substituted allyltitanium reagent **6**,[9] which was generated in situ at $-78\,^{\circ}C$ (Scheme 4). Work-up and flash chromatography gave a single homoallylic alcohol (70% yield) with



Scheme 4. Asymmetric synthesis of **10**: a) Et_3N, pyrrolidine, reflux, 15 h; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; c) *n*BuLi (1.13 equiv), $Me_2PhSiCH_2CHCH_2$ (1.13 equiv), THF, 25 min, RT, (*R*,*R*)-Cl-TiCpTADDOL (1.25 equiv; TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol), 1 h, $-78\,^{\circ}C$, **5**, 4 h, $-78\,^{\circ}C$, NH_4F_{sat}, 15 h, RT, flash chromatography (100% AcOEt); d) AcCl (4 equiv), pyridine (5 equiv), 4 h, RT, CH_2Cl_2; e) di-*tert*-butylmethylpyridine (1.5 equiv), Tf_2O (1.1 equiv, addition over 3 h), CH_2Cl_2, 3 h, RT, 1M HCl, 40 h, flash chromatography (Et_2O/hexane 50/50); f) 1,2-ethanediol, *p*-toluenesulfonic acid, toluene, Dean–Stark distillation; g) KOH/MeOH, reflux; h) NaH/THF, reflux, flash chromatography.

93% *ee*. Acetylation of the alcohol gave the amide **7**, which was treated with triflic anhydride (Tf_2O) in the presence of a hindered base to generate the keteniminium triflate. Intramolecular [2+2] cycloaddition[10] followed by hydrolysis gave a 32:1 mixture of bicyclo[3.2.0]heptanones **9a** and **9b**. This high facial selectivity is in complete agreement with the theoretical prediction. Flash chromatography gave pure **9a** (yield 65–74%, 93% *ee*, >98% *de*). The absolute configuration of **9a** was established by an X-ray diffraction analysis on an enantiopure sample (>99% *ee*) obtained by recrystallization from hexane.[11]

Compound **9a** was readily converted (three steps, no purification of intermediates) into the enantiopure protected bicyclo[3.2.0]hept-2-en-6-one **10** (80% yield).[12] This compound and the corresponding cyclobutanone were until now only accessible by routes involving a resolution step.[1g, 13] They are key intermediates in the reported syntheses of brefeldin A,[1b] vasiprost,[14] numerous prostanoids,[1c,f,g, 15] and magellaninone.[16] They have also been used in the design of new ligands for rhodium-catalyzed asymmetric hydrogenation.[17]

The results reported here illustrate a highly convergent synthetic strategy that should be applicable to a wide variety of cyclobutanones fused to a carbo-[10] or heterocycle[18] by selecting the appropriate aldehyde–amide precursor. Also, the replacement of the keteniminium moiety by another functional group capable of undergoing (cyclo)addition to the allylsilane group should extend the scope of this synthetic strategy considerably.

Experimental Section

7: $[\alpha]_D^{20} = -45$ ($c = 1$ in CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3386$ (O–H), 1628 (C=O), 1451 cm^{-1} (C=C); ^{1}H NMR (300 MHz, [D$_6$]DMSO, 20 °C): $\delta = 7.2-7.6$ (m, 5H, Ph), 5.87 (ddd, ^3J(H,H) = 17.1, 10.4, 10.4 Hz, 1H, *H*C=CH$_2$), 4.89 (dd, ^3J(H,H) = 10.3, ^2J(H,H) = 2 Hz, 1H, *H*–CH=CH (*cis*)), 4.74 (dd, ^3J(H,H) = 17.25, ^2J(H,H) = 2 Hz, 1H, *H*–CH=CH (*trans*)), 4.66 (d, ^3J(H,H) = 5.8 Hz, 1H, HO), 3.6 (m, 1H, *H*COH), 3.31 (t, ^3J(H,H) = 6.32 Hz, 2H, CH$_2$N), 3.20 (t, ^3J(H,H) = 6.59 Hz, 2H, CH$_2$N), 2.15 (t, ^3J(H,H) = 7.42 Hz, 2H, CH$_2$C=O), 1.65–1.9 (m, 5H, CH$_2$CH$_2$NCO, CHSi), 1.4–1.65 (m, 2H, C*H*$_2$CH$_2$C=O) (assignments were confirmed by COSY); ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 170.6$, 138.4, 135.95, 133.97, 128.63, 127.42, 113.86, 69.67, 45.97, 45.19, 41.39, 32.51, 30.90, 25.62, 23.95, −3.36, −3.56; MS (CI, CH$_4$/N$_2$O, +Q1MS): *m*/*z* (%): 360 (4) [*M*+29], 332 (6) [*M*+1], 314 (64), 254 (12), 180 (100), 135 (18); HPLC (Chiralpack AS, hexane/*i*PrOH 95/5, 1 mL min^{-1}, 30 °C, 224 nm): $t_R = 33$ min (other enantiomer at 23 min, other diastereoisomer at 20 and 26 mins); elemental analysis calcd for $C_{19}H_{29}NO_2Si$: C 68.84, H 8.82, N 4.22; found: C 68.58, H 9.09, N 4.24.

9a: $[\alpha]_D^{20} = +24$ ($c = 1.25$ in CH_2Cl_2); IR (KBr): $\tilde{\nu} = 3040$ (C–H), 1782 (C=O), 1739 cm^{-1} (C=O); ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C, TMS): $\delta =$ 7.3–7.5 (m, 5H, Ph), 5.44 (dd, ^3J(H,H) = 4, 4 Hz, 1H, HCOAc), 3.66 (m, 1H, CHC=O), 3–3.2 (m, 3H, CHCH$_2$C=O), 2.29 (d, ^2J(H,H) = 14.8 Hz, 1H, CHCOAc (*endo*)), 1.87 (s, 3H, CH$_3$C=O), 1.76–1.94 (dd below signal at 1.87, 1H, CHCOAc (*exo*)), 1.53 (dd, ^3J(H,H) = 7, 3.9 Hz, 1H, CHSi), 0.40 (s, 3H, MeSi), 0.39 (s, 3H, MeSi) (assignments were confirmed by COSY); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 212.7$, 169.9, 138.1, 133.6, 129.3, 128, 80.6, 64.5, 51.4, 39.5, 37.6, 32.5, 21.3, −2.1; MS (EI, 70 eV): *m*/*z* (%): 302 (4) [M^+], 260 (20), 182 (22), 135 (100); HPLC (Chiralpack AD, hexane (0.1% diethylamine)/EtOH 97.5/2.5, 1 mL min^{-1}, 20 °C, 254 nm): $t_R = 10.6$ min (other enantiomer at 8.6 min); GC (MN-OPTIMA5 column, He 70 kPa, 200 °C → 290 °C at 3 °C min^{-1}): $t_R = 13.95$ min (minor isomer at 13.63 min); elemental analysis calcd for $C_{17}H_{22}O_3Si$: C 67.51, H 7.33; found: C 67.47, H 7.35.

Received: April 9, 1999 [Z13267IE]
German version: *Angew. Chem.* **1999**, *111*, 2897–2899

Keywords: asymmetric synthesis · cycloadditions · cyclobutanones · metalations · silicon

  1433-7851/99/3818-2729 $ 17.50+.50/0

[1] a) L. A. Paquette, T. M. Heidelbaugh, *Synthesis* **1998**, 495 – 508; b) E. J. Corey, P. Carpino, *Tetrahedron Lett.* **1990**, *31*, 7555 – 7558; c) P. W. Collins, S. Djuric, *Chem. Rev.* **1993**, *93*, 1533 – 1564; d) D. J. Kertesz, A. F. Kluge, *J. Org. Chem.* **1988**, *53*, 4962 – 4968; e) A. F. Kluge, D. J. Kertesz, C. O. Yang, H. Y. Wu, *J. Org. Chem.* **1987**, *52*, 2860 – 2868; f) E. W. Collington, H. F. Finch, C. J. Wallis, *Tetrahedron Lett.* **1983**, *24*, 3121 – 3124; g) E. W. Collington, C. J. Wallis, I. Waterhouse, *Tetrahedron Lett.* **1983**, *24*, 3125 – 3128; h) G. Audran, K. Mori, *Eur. J. Org. Chem.* **1998**, 57 – 62; i) I. A. Cotterill, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2585 – 2586; j) A. E. Greene, M. J. Luche, J. P. Deprés, *J. Am. Chem. Soc.* **1983**, *105*, 2435 – 2439.

[2] a) D. Depré, PhD thesis, Université catholique de Louvain (Belgium), **1998**; b) L. Y. Chen, L. Ghosez, *Tetrahedron: Asymmetry* **1991**, *2*, 1181 – 1184.

[3] T. J. Cholerton, E. W. Collington, H. Finch, D. Williams, *Tetrahedron Lett.* **1988**, *29*, 3369 – 3372. Diastereocontrol of an intramolecular [2+2] cycloaddition of a keteniminium salt by an allylic alkoxy group has been reported albeit in low yield. In our case, however, this approach failed, and gave a 1:1 mixture of diastereisomers in low yields.

[4] For nice examples of diastereoselective reactions on chiral allylsilanes, see a) C. E. Masse, L. A. Dakin, B. S. Knight, J. S. Panek, *J. Org. Chem.* **1997**, *62*, 9335 – 9338; b) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293 – 1316; c) K. Mikami, T. Maeda, N. Kishi, T. Nakai, *Tetrahedron Lett.* **1984**, *25*, 5151 – 5154.

[5] H. Saimoto, C. Houge, A. M. Hesbain-Frisque, A. Mockel, L. Ghosez, *Tetrahedron Lett.* **1983**, *24*, 2251 – 2254.

[6] J. M. Adam, K. N. Houk, unpublished results.

[7] Gaussian 94 (Revision A.1), M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Peterson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker; J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian Inc., Pittsburgh, PA, **1995**.

[8] L. Ghosez, I. Markó, A. M. Hesbain-Frisque, *Tetrahedron Lett.* **1986**, *27*, 5211.

[9] A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321 – 2336.

[10] I. Markó, B. Ronsmans, A. M. Hesbain-Frisque, S. Dumas, L. Ghosez, B. Ernst, H. Greuter, *J. Am. Chem. Soc.* **1985**, *107*, 2192.

[11] J. M. Adam, L. Ghosez, B. Tinant, *Z. Kristallogr. NCS* **1999**, in press (CCDC no. 1267/187).

[12] a) R. F. Newton, D. P. Reynolds, N. M. Crossland, D. R. Kelly, S. M. Roberts, *J. Chem. Soc. Chem. Commun.* **1979**, 683 – 684; b) for ^{13}C NMR references, see R. Benn, H. Butenschön, R. Mynott, W. Wisniewski, *Magn. Reson. Chem.* **1987**, *25*, 653 – 655.

[13] a) For leading references on enzymatic resolutions, see G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *Tetrahedron: Asymmetry* **1996**, *7*, 277 – 282; b) K. Tanaka, O. Kakinoki, F. Toda, *Tetrahedron: Asymmetry* **1992**, *3*, 517 – 520; c) H. Greuter, J. Dingwall, P. Martin, D. Bellus, *Helv. Chim. Acta* **1981**, *64*, 2812 – 2820.

[14] a) K. Mills (Glaxo Group Ltd), EP-B 297853, **1989**; b) Glaxo Group Ltd, BE-B 897763, **1984**; P. Hallett, E. W. Collington, N. F. Hayes, C. J. Wallis, A. Wadsworth, GB-B 2097397A, **1982**; and references therein.

[15] a) A. M. M. Mjalli, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1989**, 2105; b) R. F. Newton, S. M. Roberts, *Tetrahedron* **1980**, *36*, 2163 – 2196; c) T. W. Hart, M. T. Comté, *Tetrahedron Lett.* **1985**, *26*, 2713 – 2716; d) B. F. Reifling, *Tetrahedron Lett.* **1985**, *26*, 2063 – 2064; e) C. O. Meese, *Liebigs Ann. Chem.* **1992**, 1217 – 1223.

[16] G. C. Hirst, T. O. Johnson, Jr., L. E. Overman, *J. Am. Chem. Soc.* **1993**, *115*, 2992 – 2993.

[17] B. Adger, U. Berens, M. J. Griffiths, M. J. Kelly, R. McCague, J. A. Miller, C. F. Palmer, S. M. Roberts, R. Selke, U. Vitinius, G. Ward, *Chem Commun.* **1997**, 1713 – 1714.

[18] B. Gobeaux, L. Ghosez, *Heterocycles* **1989**, *28*, 29.

SMTP-1: The First Functionalized Metalloporphyrin Molecular Sieves with Large Channels**

Kuan-Jiuh Lin*

In memory of Ta-shue Chou

Zeolites have emerged as an exciting area of supramolecular chemistry. In particular, crystalline zeolites or zeotypes with uniform pore sizes of 10 – 20 Å have diverse applications as catalysts, molecular sieves, and biosensors.[1–3] Recently, attention has turned toward organic and coordination zeolites to perform specific functions that are not available with inorganic zeolites. However, only a few examples of network structures with large cavities or channels have been demonstrated.[4] Moreover, the problems of fragility, acidity, and thermal stability of the host lattice have not been overcome.[5] Hence, the design and preparation of robust, air-stable, porous coordination zeolites provides a considerable challenge in materials chemistry.

We are exploring ways to construct new classes of coordination zeolites by hydrothermal synthesis,[6] a powerful technique often applied to the synthesis of zeolites. Encouraged by our recent success in exploiting the symmetry and functionality of the dianionic squarate ligand $C_4O_4^{2-}$ as a robust and rigid tether for the construction under hydrothermal conditions of coordination solids having open frameworks, we turned to the dianion tpyp (H_2tpyp = 5,10,15,20-tetrakis(4-pyridyl)porphyrin) as the molecular building block, as it has four equally spaced pyridyl groups linked to a porphyrin ring that gives it a rigid conformation. We surmised that the reaction of tpyp with a divalent first-row transition metal should yield a metalloporphyrinate material with nanometer-scale voids.[4c, 7] Porphyrin-based architectures have diverse potential applications as biomimetic models and as functional materials for the transport of energy, charge, molecules, and ions.[8]

We synthesized one cobalt(II) and two manganese(II) porphyrinates, which we collectively named SMTP-1 (*s*upramolecular *m*aterials in *T*aiwan *p*orphyrin, number 1), by employing hydro(solvent)thermal conditions. Crystals of all products were grown in a static autoclave at 200 °C under autogenous pressure for 48 h. Most reactions yielded bunched aggregates of individual crystals, but single crystals large enough for X-ray diffraction studies were also obtained.[9] Crystalline SMTP-1 is stable in air and is insoluble in water.

[*] Prof. K.-J. Lin[+]
Institute of Chemistry, Academia Sinica
Nankang, 11529, Taipei (Taiwan)
Fax: (+886) 2-27831237
E-mail: kjlin@chem.sinica.edu.tw

[+] Current address:
Department of Chemistry, National Chung-Hsing University
Taichung (Taiwan)

[**] I am greatly indebted to Gene-Hsiang Lee and Prof. Yu Wang at the National Taiwan University for X-ray data collection and refinement, and to Dr. Chin-Ti Chen and Prof. Sunney I. Chan for constructive discussions. This work was supported by the Academia Sinica and the National Science Council of the Republic of China.

  1433-7851/99/3818-2730 $ 17.50+.50/0