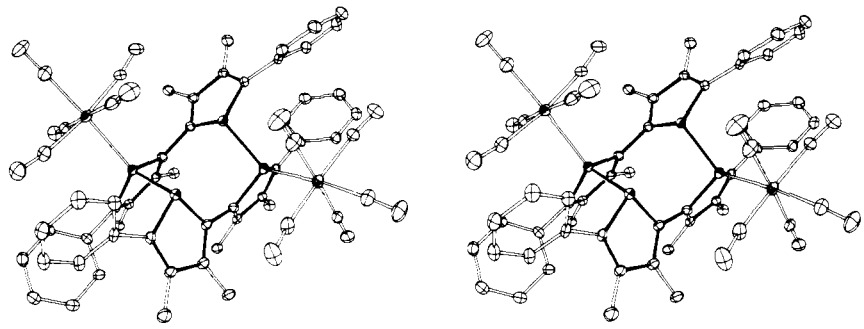

Figure 2. Stereoview of complex **5**.

$$3 + [CpFe(CO)_2]_2 \xrightarrow[150\ °C,\ 5\ h]{xylene} \text{8 (48\%)} \quad (4)$$

the synthesis of 1,1′-diphosphaferrocene,[11] gives the analogue of a bis(fulvalene)diiron, **9**[12] (eq 5).

$$6 \xrightarrow[(2)\ FeCl_2]{(1)\ MgBr_2} \text{9 (43\%)} \quad (5)$$

In this case, only one diastereoisomer is isolated. In view of the deep and recent interest in the chemistry of bis(fulvalene)-dimetal complexes,[13] the coordination chemistry of **3** obviously deserves further investigation.

In order to establish beyond any doubt the tetrameric structure of **3**, we performed an X-ray crystal structure analysis of its molybdenum complex **5**.

Single crystals of **5** were obtained by slow evaporation of a CH_2Cl_2 solution at room temperature. They belong to the monoclinic system, space group $C2/c$ with $a = 13.121$ (4) Å, $b = 16.390$ (5) Å, $c = 28.821$ (8) Å, $\beta = 93.45$ (4)°, $[C_{29}H_{22}MoO_5P_2]_2$ mol wt 1216, $Z = 4$, $\rho_c = 1.39$ g cm^{-3}.

Diffraction data were collected with the $\theta/2\theta$ flying step–scan technique using a Philips PW1100/16 automatic diffractometer and graphite monochromated Cu Kα radiation. Absorption corrections were applied with the method of Busing and Levy.[14] The structure was solved by Patterson techniques and refined by full least-squares analysis to convergence. A total of 2478 reflexions having $F^2 > 3\sigma(F^2)$ with weights as $\sigma^2(I) = \sigma^2_{counts} + (pI)^2$ were used. Final results are $R = 0.060$, $R_w = 0.075$, standard deviation of a unit-weight observation = 1.97 for $p = 0.08$. For all computations the Enraf-Nonius Structure Determination Package[15] on a PDP 11/60 computer was used.

The structure (Figures 1 and 2) consists of $(PC_6H_6–C_6H_5)_2Mo(CO)_5$ dimers related by a 2-fold crystallographic axis. Selected bond lengths and angles are given in the caption of Figure 1.

As expected, the phosphole rings are not planar: P1 is out of the mean plane C1 to C_4 by 0.140 (2) Å and P2 is out of the C7 to C10 mean plane by 0.207 (2) Å, leading to dihedral angles around C1···C4 and C7···C10 axis of 6.3 and 9.5°, respectively. The dihedral angle between the two phosphole rings is 5.18°.

Further work on these phosphole tetramers will be reported in due course.

Registry No. 1, 30540-36-4; **3**, 80737-80-0; **4**, 80737-81-1; **5**, 80753-73-7; **7**, isomer I, 80737-82-2; **7**, isomer II, 80737-83-3; **8**, isomer I, 80738-14-3; **8**, isomer II, 80779-86-8; **9**, 80738-15-4; 1-benzyl-2-phenyl-3,4-dimethylphosphole *P*-sulfide, 80737-84-4; dicyclopentadienyltetracarbonyldiiron, 12154-95-9; molybdenum hexacarbonyl, 13939-06-5.

Supplementary Material Available: Listings of atomic positional and thermal parameters (Table 1), observed and calculated structure factors (×10, Table 2), bond distances and angles (Table 3), and selected mean planes (Table 4) (16 pages). Ordering information is given on any current masthead page.

(11) De Lauzon, G.; Deschamps, B.; Fischer, J.; Mathey, F.; Mitschler, A. *J. Am. Chem. Soc.* **1980**, *102*, 994.

(12) Sodium (0.078 g, 3.4×10^{-3} mol) was stirred with naphthalene (0.46 g, 3.5×10^{-3} mol) in THF (30 mL) under argon until complete dissolution. To the blue solution were added successively at room temperature and under constant stirring (a) **3** (0.6 g, 8×10^{-4} mol), (b) then after 1 h, $MgBr_2$ (0.62 g, 3.4×10^{-3} mol), (c) then, after 2 h more, $FeCl_2$ (0.26 g, 2×10^{-3} mol). One hour after the addition of $FeCl_2$, the solution was evaporated, and the residue was quickly chromatographed on a short column of silica gel with toluene. The eluted products are rechromatographed on silica gel (hexane–toluene, 80:20); yield of **9** 0.3 g (43%); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 12 H, Me), 2.90 (s, 12 H, Me), 7.2–7.6 (m, 20 H, Ph); ^{31}P NMR ($CDCl_3$) δ −40.6; mass spectrum (70 eV, 200 °C) *m/e* 856 (M, 100%); correct C, H, Fe, P elemental analyses.

(13) See, for example: Davison, A.; Smart, J. C. *J. Organomet. Chem.* **1973**, *49*, C43. Le Vanda, C.; Bechgaard, K.; Cowan, O. D.; Mueller-Westerhoff, U. T.; Eilbracht, P.; Candela, A. G.; Collins, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 3181. Smart, J. C.; Curtis, C. J. *Ibid.* **1977**, *99*, 3518. Smart, J. C.; Pinsky, B. L. *J. Am. Chem. Soc.* **1980**, *102*, 1009. Sharp, P. R.; Raymond, K. N.; Smart, J. C.; McKinney, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 753.

(14) Busing, W. R. "Crystallographic Computing"; Ahmed, F. R., Ed.; Munksgaard: Copenhagen, Denmark, 1970; p 319.

(15) Frenz, B. A. "Computing in Crystallography"; Schenk, H., Olthof-Hazenkamp, R., Van Koenigsveld, H., Bassi, G. C., Eds.; Delft University Press: Delft, Holland, 1978; p 64.

A New Design for Chiral Induction: A Highly Regioselective Differentiation between Two Identical Groups in an Acyclic Compound Having a Prochiral Center

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Recently, the utilization of optically active, simple acyclic compounds has been increasing[1] because they can be useful as

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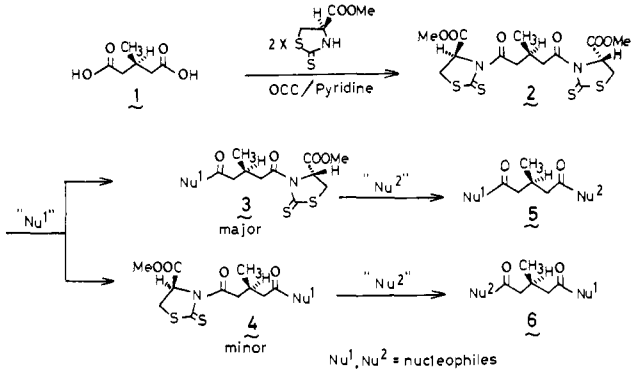
Scheme I



important starting resources for the construction of optically active acyclic key intermediates in the total synthesis of biologically active natural products, such as macrolide,[2] macrolactam,[3] polyether,[4] and β-lactam antibiotics[5] and prostaglandins.[6]

Several acyclic compounds having optical activity have been obtained by degradation of natural products, such as sugars,[2d,e,3,4d,6a,7] terpenes,[4b] amino acids,[2a,5a,b] and other compounds,[4b,6b,c] or by enzymatic,[8] microbiological,[9] and chemical asymmetric syntheses.[4a,10]

Highly selective transformations of enantiotopic groups attached to a prochiral center in a symmetrical molecule have been performed exclusively by some special enzymes, e.g., α-chymotrypsin,[8c] pig liver esterase,[8a,d] and horse liver alcohol dehydrogenase.[8b] Some papers have reported on nonenzymatic methods to distinguish the prochiral ligands of an equivalent derivative, but these methods are unsatisfactory from the viewpoint of the optical yield.[11]

Here we wish to report a highly regioselective differentiation between two identical groups in an acyclic compound [3-methylglutaric acid (**1**)] having a prochiral center; the process

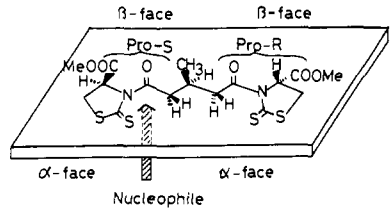
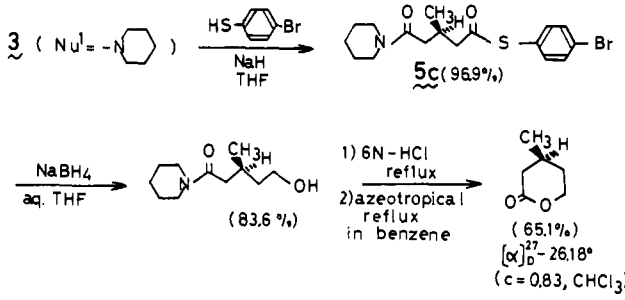


Figure 1.

Scheme II

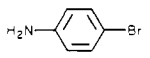
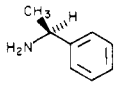
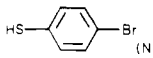
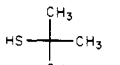
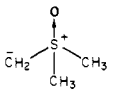
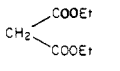


is outlined in Scheme I. The design of this procedure was based upon information obtained from our series of studies on the monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione (ATT)[12] and its application.[13] It is quite difficult under usual chemical conditions to distinguish the pro-*S* ligand ($HOOCCH_2-$) from the pro-*R* ligand ($-CH_2COOH$) of 3-methylglutaric acid (**1**). However, in the molecule of the optically active diamide **2**, the sterical situation between the pro-*S* and the pro-*R* ligands may be different. The fairly strong dipole–dipole repulsion[14] between the thiocarbonyl and the amide carbonyl groups and the repulsion between the pro-*S* and the pro-*R* groups may regulate the stereochemistry of compound **2** to stabilize a favorable W-shape (or a slightly modified) conformation at low temperature (Figure 1). In the assumed W-shape structure, the α face of the pro-*S* ligand should be least hindered in comparison with the other three faces (i.e., β face of the pro-*S* ligand and α and β faces of the pro-*R* ligand). Therefore, a suitable nucleophile may preferably attack the amide carbonyl carbon atom of the pro-*S* side from the least hindered α face in the transition state. Then the key diamide **2** was subjected to X-ray analysis;[15] its crystallographic structure was found to have a slightly twisted W-shape conformation, supporting in principle our working hypothesis.

Thus, aminolysis of diamide **2** [yellow needles from EtOAc–Et_2O, mp 113–114 °C, $[\alpha]_D^{25}$ −163.90° (*c* 1.00, EtOAc)], prepared as usual[12] by the treatment of 3-methylglutaric acid (**1**) with 4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione [4(*R*)-MCTT][16] in the presence of DCC in pyridine, was tried in CH_2Cl_2 with several amines at room temperature or at −30 °C in order to find the best nucleophile, "Nu[1]".[17] The result showed that cyclic secondary amines displayed excellent regioselectivity (78–87%) especially at −30 °C, as expected. The ratio of two diastereomers, **3** and **4**, was checked by high-pressure liquid

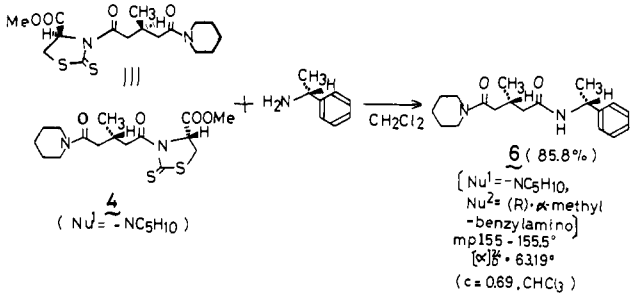
(1) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3 and references cited therein.
(2) (a) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *Ibid.* **1975**, *97*, 3513. (c) Seuring, B.; Seebach, D. *Liebigs Ann. Chem.* **1978**, 2044. (d) Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 1479. (e) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843.
(3) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshultz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.
(4) (a) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262 and references cited therein. (b) Collum, D. B.; McDonald, J. H.; III; Still, W. C. *Ibid.* **1980**, *102*, 2120 and references cited therein. (c) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *Ibid.* **1979**, *101*, 6789. (d) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *Ibid.* **1980**, *102*, 1155.
(5) (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (b) Baldwin, J. E.; Au, A.; Christie, M.; Haber, S. B.; Hesson, D. *Ibid.* **1975**, *97*, 5957.
(6) (a) Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272 and references cited therein. (b) Paul, K. G.; Johnson, F.; Favara, D. *Ibid.* **1976**, *98*, 1285. (c) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759.
(7) A review in Japanese entitled "Chiral Synthesis of Natural Products from Carbohydrate Precursors": Ohrui, H. *J. Synth. Org. Chem. Jpn.* **1981**, *39*, 275 and references cited therein.
(8) (a) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y. F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. (b) Irwin, A. J.; Jones, J. B. *Ibid.* **1977**, *99*, 556. (c) Cohen, S. G.; Khedouri, E. *Ibid.* **1961**, *83*, 4228. (d) Huang, F.-C.; Lee, L. F. H.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J.; Caspi, E.; Eck, C. R. *Ibid.* **1975**, *97*, 4144.
(9) (a) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (b) Leuenberger, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chim. Acta* **1979**, *62*, 455. (c) Schmid, M.; Barner, R. *Ibid.* **1979**, *62*, 464. (d) Zell, R. *Ibid.* **1979**, *62*, 474. (e) Chen, C.-S.; Fujimoto, Y.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 3580.
(10) (a) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797 and references cited therein. (b) Cohen, N.; Lopresti, R. J.; NeuKome, C.; Jancz, G. *J. Org. Chem.* **1980**, *45*, 582 and earlier references in this series. (c) Trost, B. M.; Klum, T. P. *J. Am. Chem. Soc.* **1981**, *103*, 1864.
(11) (a) Schwartz, P.; Carter, H. E. *Proc. Natl. Acad. Sci., U.S.A.* **1954**, *40*, 499. (b) Altschul, R.; Bernstein, P.; Cohen, S. G. *J. Am. Chem. Soc.* **1956**, *78*, 5091.
(12) (a) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841. (b) Nagao, Y.; Miyasaka, T.; Seno, K.; Yagi, M.; Fujita, E. *Chem. Lett.* **1981**, 463. (c) Fujita, E. *Pure Appl. Chem.* **1981**, *53*, 1141.
(13) (a) Nagao, Y.; Seno, K.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 4931. (b) Nagao, Y.; Takao, S.; Miyasaka, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1981**, 286.
(14) Ohno, A. In "Organic Chemistry of Sulfur"; Oae, S. Ed.; Plenum Press: New York, **1977**; p 189.
(15) Crystallographic structures of compounds **2** and **5b** and their data are available as supplementary material.
(16) 4(*R*)-MCTT ($[\alpha]_D^{21}$ −67.00° (*c* 1.10, $CHCl_3$)) is easily prepared from L-cysteine methyl ester hydrochloride and carbon disulfide in the presence of Et_3N: Nagao, Y.; Yagi, M.; Ikeda, T.; Fujita, E. *Tetrahedron Lett.*, in press.
(17) All reactions were carried out by using 0.2 mmol of active diamide **2** and 0.2 mmol of amine in CH_2Cl_2 (5 mL in the case at room temperature or 15 mL in the case at −30 °C).
(18) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3487.

Table I. Treatment of 3 ($Nu^1 = -NC_5H_{10}$) with Several Nucleophiles (Nu^2)

Nu^2	product[a]	mp, °C	$[\alpha]^{25}D$, deg ($CHCl_3$)	yield,[b] %
	**5a**	124–125	+0.98 (*c* 1.02)	99.0
	**5b**	155–155.5	−63.48 (*c* 0.66)	93.0
	**5c**[c]	oil	−1.39 (*c* 1.73)	96.9
	**5d**	oil	−4.02 (*c* 1.32)	85.4
	**5e**[d]	130–131.5	+2.30 (*c* 1.00)	76.0
	**5f**[e]	oil	−3.63 (*c* 2.40)	98.5

[a] Satisfactory spectral and analytical data were obtained in compounds **5**: $Nu^1 = -NC_5H_{10}$. [b] Isolated yield. [c] To a suspension of *p*-bromothiophenol (1 mmol) and NaH (1 mmol) in THF (5 mL) was added compound **3** (0.5 mmol) in THF (3 mL) and stirred at room temperature for 10 min in N_2. [d] To an in situ reagent[18] obtained by refluxing trimethylsulfoxonium chloride (2 mmol) and NaH (1.5 mmol) in THF (3 mL) for 2 h in N_2 was added compound **3** (0.5 mmol) in THF (2 mL). The mixture was stirred at room temperature for 10 min. [e] To a suspension of sodium diethylmalonate (ca. 2 mmol) prepared in THF (3 mL) as usual was added compound **3** (1 mmol) in THF (3 mL) and stirred for 1 h. The product **5f** is shown to be a mixture of the keto and enol form in a 4:6 ratio (^1H NMR analysis).

Scheme III



chromatography (HPLC). The best result was obtained with piperidine as Nu^1.

As exemplified by the case of piperidine as Nu^1, separation of the diasteromeric mixture [5.9 g, 73.6% yield from **2** (10 g)] on a silica gel column with *n*-hexane–Et_2O–EtOAc (2:2:1) afforded a pure major component **3** [$Nu^1 = -NC_5H_{10}$, 4.3 g, yellow needles from Et_2O, mp 95.5–96 °C, $[\alpha]_D^{25}$ −99.0° (*c* 1.00, EtOAc)] and a pure minor component **4** [$Nu^1 = -NC_5H_{10}$, 0.58 g, yellow oil]. For confirmation of the structure and absolute configuration of compound **3** ($Nu^1 = -NC_5H_{10}$), it was chemically converted into the known (−)-(3*S*)-3-methylvalerolactone[8b] (see Scheme II). Also, the structure and stereochemistry of **5b**, prepared by aminolysis of **3** ($Nu^1 = -NC_5H_{10}$) with (*S*)-(α-methylbenzyl)amine (see Table I), were determined by X-ray analysis.[15]

The stereochemistry of the minor product **4** ($Nu^1 = -NC_5H_{10}$) was also established by its transformation into compound **6** [$Nu^1 = -NC_5H_{10}$, Nu^2 = (*R*)-(α-methylbenzyl)amino], the enantiomer of compound **5b** (see Scheme III and Table I).

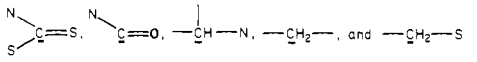
Finally, compound **3** ($Nu^1 = -NC_5H_{10}$) was subjected to "the monitored reaction" employing several nucleophiles "Nu^2" and gave optically pure acyclic products **5a–f** in high yields (Table I). These products should be useful as synthons for the total synthesis of natural products.

This novel nonenzymatic asymmetric synthesis is not only useful as a practical synthetic tool but also as an aid in the elucidation of the action of enzymes such as α-chymotrypsin[8c] and pig liver esterase.[8a,d] Thus we have established a new concept that the introduction of the two same chiral ligands, e.g., two 4(*R*)-MCTT groups, into a symmetrical molecule having a prochiral center changes its original symmetrical nature (environment) into the unsymmetrical nature (environment).[19] This new concept can be widely applied to other similar reactions (e.g., differentiation between enantiotopic groups in meso compounds), and such studies are now in progress.

Registry No. 1, 626-51-7; **2**, 80963-69-5; **3**, 80963-70-8; **4**, 80963-71-9; **5a**, 80963-72-0; **5b**, 80963-73-1; **5c**, 80963-74-2; **5d**, 80963-75-3; **5e**, 80963-76-4; **5f**, keto form, 80963-77-5; **5e**, enol form, 80963-78-6; **6**, 80963-79-7; H_2N-*p*-C_6H_4Br, 106-40-1; $PhCHMeNH_2$, 3886-69-9; Br-*p*-C_6H_4SH, 106-53-6; Me_3CSH, 75-66-1; $Me_2S(O){:}CH_2$, 5367-24-8; $CH(CO_2Et)_2$, 105-53-3; 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione, 80963-80-0.

Supplementary Material Available: Crystallographic details, tables of atomic positional and thermal parameters, and perspective views for **2** and **5b** (11 pages). Ordering information is given on any current masthead page.

(19) On the ^{13}C NMR (JEOL FX270) chart of diamide **2** in $CDCl_3$ solution, duplicte signals assignable to the following carbon atoms were observed:



We express our thanks to Dr. K. Matsushita (JEOL Co., Ltd.) for the determination of the ^{13}C NMR spectra.

Remarkably High Regioselective Deprotonation and Alkylation of Unsymmetrical Imines at the More Substituted α-Carbon Atom

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Received October 13, 1981

After the pioneering work of Stork[1a] and Wittig[1b] in 1963, studies showing that metalation of imines and their subsequent alkylation occur selectively syn to the substituent of the sp^2-hybridized nitrogen atom regardless of either symmetrical or unsymmetrical substitution of the imines have proved to be extremely useful for synthetic organic chemistry.[2,3] Theoretical and ex-

(1) (a) Stork, G.; Dowd, S. *J. Am. Chem. Soc.* **1963**, *85*, 2178–2180. (b) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem.* **1963**, *75*, 978–979.

(2) (a) Wittig, G.; Frommeld, H. D. *Chem. Ber.* **1964**, *97*, 3548–3559. (b) Wittig, G.; Reiff, H. *Angew. Chem.* **1968**, *80*, 8–15. (c) Larcheveque, M.; Valette, G.; Cuvigny, T.; Normant, H. *Synthesis* **1975**, 256–259. (d) Cuvigny, T.; Larcheveque, M.; Normant, H. *Justus Liebigs Ann. Chem.* **1975**, 719–730. (e) Harvey, W. E.; Tarbell, D. S. *J. Org. Chem.* **1967**, *32*, 1679–1681. (f) Nagata, W.; Hayase, Y. *J. Chem. Soc. C* **1969**, 460–466. (g) Evans, D. *J. Am. Chem. Soc.* **1970**, *92*, 7593–7595. (h) Stork, G.; Benaim, J. *Ibid.* **1971**, *93*, 5938–5939. (i) Wittig, G.; Fischer, S.; Tanaka, M. *Justus Liebigs Ann. Chem.* **1973**, 1075–1081. (j) House, J. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102–3107. (k) Jacobsen, R. M.; Raths, R. A.; McDonald, J. H. *Ibid.* **1977**, *42*, 2545–2549. (l) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033. (m) Whitesell, J. K.; Whitesell, M. A. *J. Org. Chem.* **1977**, *42*, 377–378. (n) Kitamoto, M.; Hiroi, K.; Terashima, S. *Chem. Pharm. Bull.* **1974**, *22*, 459–464 and references therein.

(3) (a) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999–8001. (b) Fraser, R. R.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 47–48. (c) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429.

0002-7863/82/1504-2081$01.25/0