probably be made in quantity by recombinant DNA methods.

Registry No. ATP, 56-65-5; UTP, 63-39-8; GTP, 86-01-1; CTP, 65-47-4; nuclease P_1, 54576-84-0; PNPase, 9014-12-4; PEP, 138-08-9; PK, 9001-59-6; UDP-Glc, 133-89-1; glucose, 50-99-7; G-6-P, 56-73-5.

Supplementary Material Available: Procedures for preparation of glucose-6-phosphate by using the XTP's prepared here and for immobilization of PNPase (1 page). Ordering information is given on any current masthead page.

(20) Kimhi, Y.; Littauer, U. Z. *Methods Enzymol.* **1968**, *12B*, 513–9. Starting from 540 g of the frozen cells, 880 units of PNPase were detected. After several steps of purification, 150 units of the enzyme were isolated with specific activity 6 unit/mg (1 unit will generate 1 μmol of ATP/min from poly(A) in a coupled reaction).

Asymmetric Alkylation of α-Amino Carbanions. An Enantioselective Synthesis of (*S*)-1-Alkyl-1,2,3,4-tetrahydroisoquinolines

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Asymmetric C–C bond-forming reactions have reached a high level of efficiency over the past 8 years, thus adding asymmetric synthesis to the arsenal of tools available to the organic chemist for obtaining chiral compounds.[1] Absent from these recent successes is the introduction of a C–C bond adjacent to nitrogen with simultaneous enantioselectivity, a transformation that would provide access to many alkaloids in enantiomeric form. On the basis of our earlier reports[2] describing α-amino carbanions derived from the formamidines (A–C, among others), we sought to introduce in place of the *N*-*tert*-butyl group an appropriate chiral auxiliary that would effect the diastereofacial selectivity during the alkylation of the lithio carbanion. We can now report the results of a highly successful asymmetric alkylation leading to 1-substituted tetrahydroisoquinolines in >90% enantiomeric excess with predictable absolute configuration (Table I). The enantiomeric alkylation was initially investigated by using (*R*)-(−)-α-phenethylamine (PEA) as the chiral auxiliary. Thus, tetrahydroisoquinoline **1** (Scheme I) was transformed into its *N*-formyl derivative **2**[3] and treated with Meerwein's reagent and (−)-PEA, which gave the formamidine **3a** [98%, $[\alpha]_D$ −64.94° (*c* 3.4, THF)]. Metalation of **3** with lithium diisopropylamide (1.2 equiv, THF, −78 °C) followed by addition of various alkyl halides gave the alkylated product **4a**, which was directly subjected to hydrazinolysis affording **5**. As seen from Table I, although the chemical yields (**3a** → **5**) were generally quite high, the enantioselectivity of the process was only moderate (10–52% ee). Furthermore, the absolute configurations for **5** were not consistent, the first four entries in the table giving *S* as the predominant enantiomer while the last appearing as the *R* enantiomer.[4]

We next turned to the chiral auxiliary derived from (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol previously em-

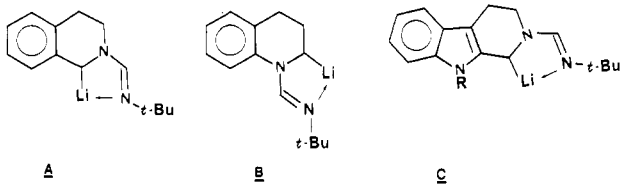
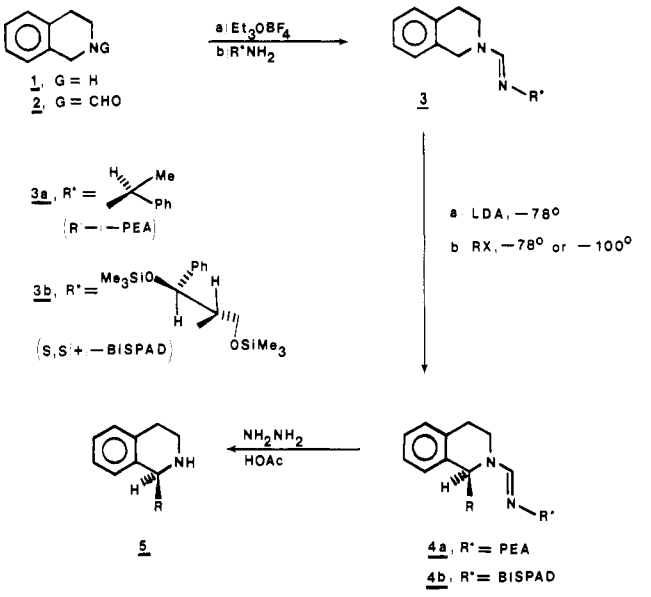


Table I. Asymmetric Alkylation of Chiral 1,2,3,4-Tetrahydroisoquinolines, 3

RX[a]	1-alkyltetrahydroisoquinolines 5: chem yield, %[c]	$[\alpha]_D^{24}$ (EtOH),[d] deg	ee,[e] %	confn[e]
3a (R = (*R*)-(−)-PEA)				
MeI	85	+0.90	10	*R*
i-BuBr	84	+13.67	27	*R*
n-BuBr	93		19	*R*
$PhCH_2Br$	97	+13.00	35	*R*
$PhCH_2CH_2Br$	89		52	*S*
3b (R = (*S,S*)-(+)-BISPAD)				
MeI	80	−7.25	80	*S*
MeI[b]	79	−8.96	>99	*S*
i-BuI[b]	85	−47.21	91	*S*
n-BuBr[b]	80	−50.30	91	*S*
$PhCH_2Br$[b]	70	−35.71	93	*S*
$PhCH_2CH_2Br$[b]	65	−38.69	>99	*S*

[a] Alkyl halides added at −78 °C unless otherwise noted. [b] Alkyl halides added at −100 °C (liquid N_2–MeOH). [c] Based on formamidines **3a** or **3b**. [d] Rotations are for hydrochloride salts, since the free bases tend to air-oxidize slowly on standing. [e] Determined by preparing the 1-naphthoyl amides of **5** (1.5 equiv of 1-naphthoyl chloride, dichloromethane) and by purification by radial chromatography. This was injected onto the covalent phenylglycine-modified Spherisorb S5NH column (Regis Chemical Co.) incorporated in a Waters 440 HPLC instrument. For details of this technique see: Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatog.* 1980, *192*, 143. The elution solvent was 10% isopropanol–hexane, and the integration of the peaks (254 nm) was based on ratios of previously injected racemates of naphthoyl amides of **5**. The absolute configurations are assigned by order of elution and comparison with (*S*)(−)-7.

Scheme I



(1) Asymmetric C–C bond-forming reactions have been summarized in part: Eliel, E.; Otsuka, S. In "Asymmetric Reactions and Processes in Chemistry"; American Chemical Society: Washington, D.C., 1982; ACS Symp. Ser., No. 185. For additional recent achievements in asymmetric C–C bond forming reactions see: (a) Evans, D. A.; Bartoli, J. *Tetrahedron Lett.* **1982**, *23*, 807. (b) Schollkopf, U.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 977. (c) Enders, D.; Eichenauer, H. *Chem. Ber.* **1980**, *112*, 2933. (d) Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Ghosez, L.; DeClercq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 2921. (e) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *Ibid.* **1981**, *103*, 3081, 3088.

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(3) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Org. Synth.* **1961**, *41*, 13.

(4) A large number of racemic α-naphthoyl amides of secondary amines have been separated by using the chiral stationary phase column developed by Pirkle (footnote e, Table I), and absolute configurations have been verified by order of elution. This is the subject of a separate report to be published.

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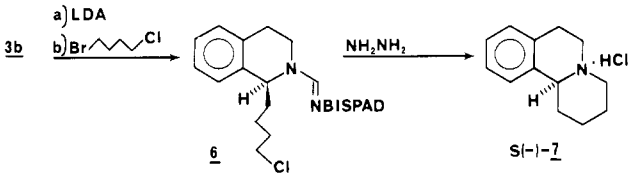
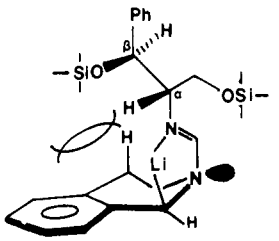
ployed in our laboratory for other asymmetric processes.[5] Silylation of the aminodiol with hexamethyldisilazane gave the bis-silylated phenylaminodiol (BISPAD).[6] The latter was treated with *N*-formyltetrahydroisoquinoline **2** to form the chiral formamidine **3b**.[6] Metalation of **3b** (LDA, −78 °C, THF) and addition

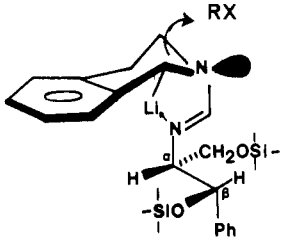


of various alkyl halides (−100 °C) furnished **4b**, which was heated in hydrazine–acetic acid, providing the 1-substituted tetrahydroisoquinolines **5** in good yields with enantiomeric excesses in excess of 90% for every case (Table I).[6] Furthermore, all five examples afforded the *S* configuration at C-1 of the isoquinoline. The effect of the temperature during the alkylation of **3b** can be seen in the table when methyl iodide was added at −78 °C giving the 1-methyl isoquinoline in 80% ee. Although not shown, the other alkyl halides also gave a 10–20% decrease in enantiomeric purity when added to the chiral lithio salt at −78 °C. This highly efficient enantioselective alkylation was further extended to provide the benzoquinolizine **7** in 90.3% ee by use of 1-bromo-4-chlorobutane as the electrophile. Thus, metalation of **3b** (−78 °C) followed by the addition of the dihalobutane (−100 °C) gave the chlorobutyl adduct **6**, which without purification was directly cyclized during hydrazinolysis[6] to (*S*)-hexahydrobenzoquinolizine in 70.3% yield (from **3b**); **7**·HCl: mp 260–262 °C, $[\alpha]_D^{24}$ −126.2° (*c* 0.42, EtOH).[7] In all cases the chiral BISPAD was recovered after hydrazine treatment and may be recycled for further use.

The high sense of chiral induction observed for the BISPAD auxiliary may presently be attributed to the conformational preference of the diastereomeric lithium salts D and E. In the



D



E

former, the enantiomeric BISPAD appears to lie over the plane of the isoquinoline ring whereas in E it is placed out and away from the isoquinoline due to the *S* configuration at the α-carbon. This conformational preference is much less apparent in the α-phenylethylamine (PEA) auxiliary, hence the lower alkylation selectivity. Furthermore, models indicate that the N-Cα bond is free to rotate, thus effectively blocking the bottom side of the E, which results in alkylation from the top side, giving the observed *S* configuration to the products. The configuration at the β-carbon may play a minor role since valinol trimethylsilyl ether or leucinol trimethylsilyl ether also give rather high enantioselective alkylation.[8] The main requirement appears to be a relatively bulky substituent at the β-carbon. Although the reaction has not yet been attempted, the enantiomeric BISPAD should favor D leading to the (*R*)-1-substituted tetrahydroisoquinolines, **5**. As alluded to earlier, the enantioselectivity is quite sensitive to the alkylation temperature, and if performed at −50 °C or higher, the products are formed in much lower enantiomeric excesses (0–30%). This is undoubtedly due to the difference in alkylation rates for D and E and their relative populations. Further studies on this interesting process are underway with a variety of prochiral amines.

Acknowledgment. We are grateful to the National Science Foundation for financial support. The award (to L.M.F.) of a postdoctoral fellowship by the National Institutes of Health is also acknowledged. We are indebted to Professor W. H. Pirkle for his assistance in the HPLC determinations of enantiomeric purity.

Supplementary Material Available: Experimental details and complete physical data for all compounds (6 pages). Ordering information is given on any current masthead page.

(5) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 568.
(6) See supplementary material.
(7) mp 260–261 °C, $[\alpha]_D$ −140.0° (*c* 0.04, EtOH) for pure *S* enantiomer derived from degradation of virosecurinine (Craig, J. C.; Chan, R. P. K.; Roy, S. K. *Tetrahedron* **1967**, *23*, 3573).
(8) Use of valinol and leucinol trimethylsilyl ethers led to 1-substituted tetrahydroisoquinolines in 88–91% ee; however, the chemical yields are not yet satisfactory (Y. Kubota, research in progress).

Molecular Orbital Study of the Homocyclopropenylium Cation

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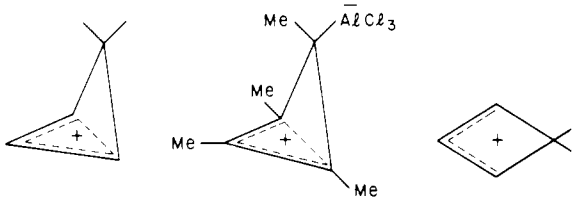
Received September 2, 1982

The homocyclopropenylium cation (**1**; see also Figure 1) is the



1 (C_s) 2 (C_s) 3 (C_{2v})

simplest homoconjugated system[1] and the first species for which homoaromatic character was invoked.[2] It is also one of the best characterized homoaromatic compounds in a field where structural and thermodynamic information is difficult to obtain. Thus the structure of a derivative (**2**) is known,[3] and the barrier to ring inversion in **1** has been measured[4]—the activation energy for this latter process is usually considered to provide a measure of the energy difference between **1** and **3**, which has been termed the homoaromatization energy.[5] While qualitative theoretical arguments are successful in explaining the homoaromatic character of **1**,[6-8] quantitative calculations have given uneven results.[9] Semiempirical MO treatments (MINDO/2,[10] MINDO/3[8,11]) of **1** have enjoyed remarkable success, but ab initio Hartree–Fock (HF) calculations (STO-2G,[11,12] STO-3G,[12,13] 4-31G[12]) have failed

(1) Reviews: (a) Winstein, S. *Chem. Soc., Spec. Publ.* **1967**, *No. 21*, 5; *Q. Rev. Chem. Soc.* **1969**, *23*, 141. (b) Warner, P. M. In "Topics in Nonbenzenoid Aromatic Character"; Nozoe, T., Breslow, R., Hafner, K., Ito, S., Murata, I., Eds.; Hirokawa: Tokyo, 1976; Vol. 2. (c) Paquette, L. A., *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 106.
(2) (a) Applequist, D. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 4012. (b) Woods, W. G.; Carboni, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 5653. (c) Kiefer, E. F.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 784.
(3) Krüger, C.; Roberts, P. J.; Tsay, Y.-H.; Koster, J. B. *J. Organomet. Chem.* **1974**, *78*, 69.
(4) (a) Olah, G. A.; Staral, J. S.; Liang, G. *J. Am. Chem. Soc.* **1974**, *96*, 6233. (b) Olah, G. A.; Staral, J. S.; Spear, R. J.; Liang, G. *Ibid.* **1975**, *97*, 5489.
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(6) (a) Haddon, R. C. *Tetrahedron Lett.* **1974**, 2797. (b) Haddon, R. C. *Aust. J. Chem.* **1977**, *30*, 1.
(7) Hehre, W. J. *J. Am. Chem. Soc.* **1974**, *96*, 5207.
(8) Jorgensen, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 6784.
(9) Radom, L.; Poppinger, D.; Haddon, R. C. *Carbonium Ions* **1976**, *5*, 2303.
(10) Schoeller, W. W.; Schenck, G. E. *Tetrahedron* **1973**, *29*, 425.
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