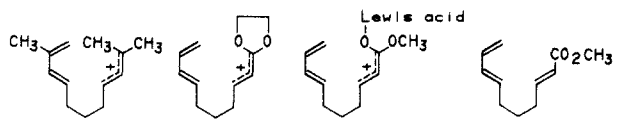
Treatment of **7**, **8**, and **9** with triflic acid in methylene chloride gave **10**, **11**, and **12**, respectively, as the only monomeric fully cyclized products.[13] Reaction conditions and yields are summarized in Table I. As indicated, the reactions are uniformly rapid and stereospecific. These examples give an indication of the potential of the ionic Diels–Alder reaction in the synthesis of diverse polycyclic molecules.

The yield of **10** was low due to problems encountered in its purification. However, when crude **10** was treated with *N*-chlorosuccinimide–silver nitrate in acetonitrile–water,[14] **13** was obtained in 34% overall yield from **7**. This series of reactions provides a quick and stereospecific entry into the cadenane ring system. Selective reduction of the isopropenyl moiety of **13** was accomplished in 79% yield using hydrogen and Wilkinson's catalyst to produce a known precursor[15] of γ_1-cadenene. Compound **11** has the correct stereochemistry to be a precursor of systems related to oplopanone.[16] Thus, a variety of naturally occurring ring systems are readily accessible via our sequence of reactions.

An analogy may be drawn between our results and those of Roush with Lewis acid and hydrofluoric acid catalyzed and uncatalyzed intramolecular Diels–Alder reactions.[17] The proposed reactive intermediates are illustrated by **14**–**17**. Ions **14**–**16** cyclize to form only trans-fused



14 **15** **16** **17**

products; **17** produces a mixture of trans- and cis-fused products. Our ionic Diels–Alder reaction would appear to involve the extreme of a continuum of transition states for the Diels–Alder reaction.[18] This continuum can be viewed as an ordering of reactions that utilize as dienophiles allyl cations (i.e., **14**), dioxolenium ions (i.e., **15**), Lewis acid complexed carbonyl derivatives (i.e., **16**), olefins bearing uncharged electron-withdrawing groups (i.e., **17**), and unactivated olefins.[19]

We are continuing to investigate the synthetic and mechanistic implications of these ionic cycloaddition reactions.

Acknowledgment. We are indebted to the National Science Foundation and to the General Medical Institute of the National Institutes of Health for grants which supported this investigation.

Registry No. **2**, 91993-46-3; **3**, 102871-00-1; **4**, 1115-08-8; **5**, 21777-31-1; **6**, 102871-01-2; **7**, 102871-02-3; **8**, 102871-03-4; **9**, 102871-04-5; **10**, 102871-05-6; **11**, 102871-06-7; **12**, 102871-07-8; **13**, 102871-08-9; (*E*)-1-bromo-4-methoxy-2-pentene, 102870-99-5; 3-methyl-2-butenal, 107-86-8; 3-phenyl-2-cyclohexenone, 10345-87-6.

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(13) The stereochemistry of **13** (and thus of **10**) was assigned from H_{4a}–H_{8a} and H_8–H_{8a} couplings of 11 Hz, as determined by a combination of multiple Eu(fod)$_3$-induced shift experiments and multiple spin-decoupling experiments. The stereochemistry of **11** was determined by deprotection to the ketone (47%), which had H_{3a}–H_{7a} and H_7–H_{7a} coupling constants of 12.4 and 10.6 Hz, respectively. Since the stereochemistry of the single isomer of **12** could not be assigned on the basis of ^{1}H NMR coupling constants, its stereochemistry was tentatively assigned by analogy to that of **2**, **10**, and **11**.

(14) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(15) Vig, O. P.; Bari, S. S.; Dua, D. M.; Rana, S. S. *Indian J. Chem., Sect. B* **1979**, *17B*, 552.

(16) Takeda, K.; Minato, H.; Ishikawa, M. *Tetrahedron, Suppl.* **1965**, *No. 7*, 219. Caine, D.; Tuller, F. N. *J. Am. Chem. Soc.* **1971**, *93*, 6311.

(17) Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674. Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267. Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264.

(18) In using the term Diels–Alder reaction, we refer only to the formal outcome of these reactions and do not indicate whether these reactions are stepwise or concerted.

(19) For a recent discussion, see: Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269. Wu, T.-C.; Houk, K. N. *Ibid.* **1985**, *26*, 2293. Brown, F. K.; Houk, K. N. *Ibid.* **1985**, *26*, 2297. See also references contained therein.

Oxazoline-Mediated Asymmetric Alkylation of Amines

Summary: Chiral oxazolines serve as readily available auxiliaries for the functionalization of secondary amines and for mediating their alkylation via their conjugate bases, which are dipole-stabilized anions. Both attachment and removal of the chiral auxiliary occur in routinely high yield. *Homochiral* 1-substituted tetrahydroisoquinolines are available as either enantiomer by selection of the appropriate enantiomer of valine, both of which are commercially available.

Sir: The fascinating field of dipole-stabilized anion chemistry was reviewed in 1978.[1] Six years later, another review[2] was devoted exclusively to updating the subject of metalations adjacent to a functionalized nitrogen. Nevertheless, the subject received little or no mention in two recent monographs on carbanions.[3] In spite of the broad interest, successful *asymmetric* amine alkylations via dipole stabilized anions are few. Meyers has demonstrated that formamidines derived from chiral amino alcohols such as (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol[4] or L-valinol[5] give excellent optical yields, which are significantly better than several other chiral amines[6] in the alkylation of tetrahydroisoquinoline formamidines. Recently, Meyers reported on the application of L-valinol derived formamidines to the synthesis of indole alkaloids.[7] Unfortunately, these chiral formamidines are unable to mediate the deprotonation of heterocycles for which the proton adjacent to nitrogen is not also allylic or benzylic.[8]

In entering this field, we hoped to design a system which would accomplish asymmetric alkylation of amines in high chemical and optical yields and which would be applicable to the elaboration of both saturated and allylically activated heterocycles. Our approach to the problem began

(1) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275-316.

(2) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471-523.

(3) (a) Stowell, J. C. *Carbanions in Organic Synthesis*; Wiley-Interscience; New York, 1979. (b) Bates, R. B.; Ogle, C. A. *Carbanion Chemistry*; Springer-Verlag: Berlin, 1983.

(4) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117-118.

(5) (a) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458-459; *Angew. Chem.* **1984**, *96*, 448-449. (b) Dickman, D. A.; Meyers, A. I. *Tetrahedron Lett.* **1986**, *27*, 1465-1468.

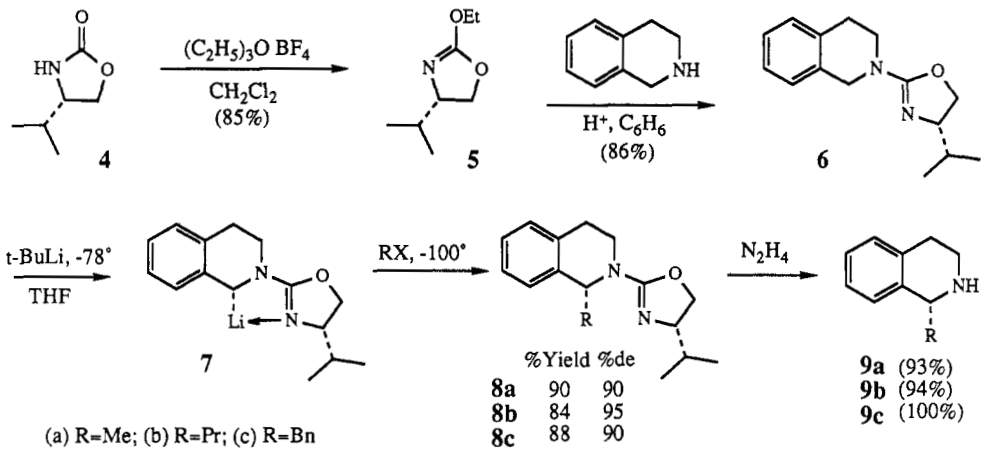
(6) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361-1370.

(7) Loewe, M. F.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3291-3294.

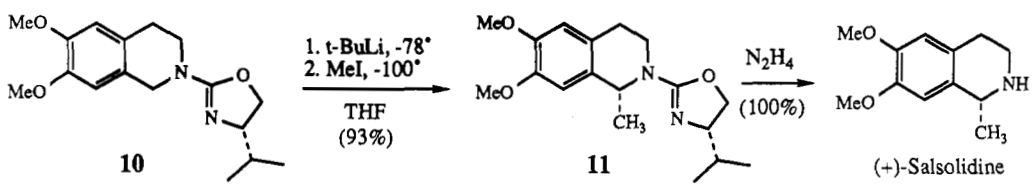
(8) (a) Loewe, M. F.; Boes, M.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 3295-3298. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974-7978.

0022-3263/86/1951-3076$01.50/0

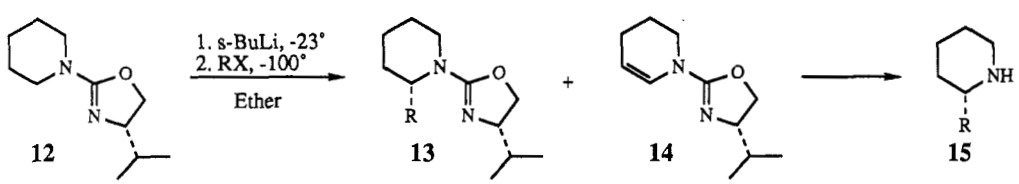
Scheme I

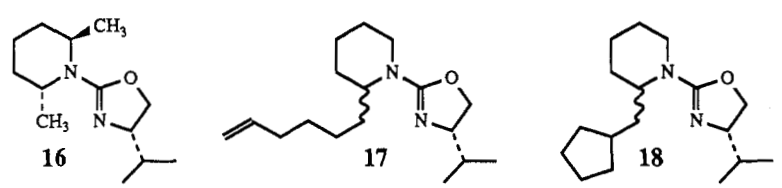


Scheme II

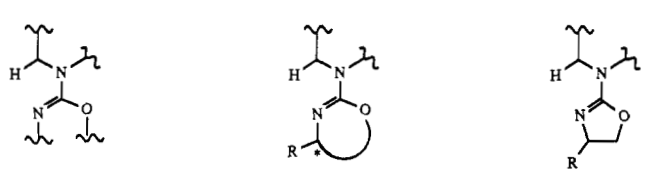


Scheme III





with an evaluation of the viability of pseudoureas (i.e., **1**) as mediators for dipole stabilized anion formation. In



order to impart rigidity to the system, we elected to enclose the system in a ring (i.e., **2**). For asymmetric induction, the stereogenic center should be near the likely site of alkyllithium coordination: the imine nitrogen. The ready availability of chiral amino alcohols from amino acids[9] seemed well suited to our purpose, and the system that evolved is the generalized aminooxazoline **3**.

The first chiral auxiliary selected, (*S*)-ethoxyoxazoline **5**, was constructed simply by alkylation[10] of the well-known[11] oxazolone **4** with Meerwein's reagent[12] (1 equiv. CH_2Cl_2, 25 °C, overnight, 85%) (Scheme I); condensation with the secondary amine (e.g., 1 equiv of tetrahydroisoquinoline, catalytic *p*-TsOH, C_6H_6, reflux 2 h, dry over CaH_2, and distill) was routine and afforded aminooxazoline **6** in 86% yield.

The metalation of aminooxazoline **6** occurred smoothly using any isomer of butyllithium in THF, and alkylation of its anion, **7**, afforded 1-substituted tetrahydroisoquinolines **8a–c** (Scheme I) in excellent yield and with high degrees of asymmetric induction (as determined by capillary GC). The most reliable conditions were metallation at −78 °C and quench at −100 °C. We observed a lack of asymmetric induction dependence on either the structure of the base or the temperature of the deprotonation and increased asymmetric induction as the temperature of the quench was lowered. For example, when **6** was deprotonated at −78 °C and quenched at −78, −100, and −120 °C, **8a** was obtained in 60%, 90%, and 92% diastereomeric

(9) Smith, G. A.; Gawley, R. E. *Org. Synth.* **1984**, *63*, 136–139. For a better procedure, see ref 8b.
(10) Coppola, G. M. *J. Heterocycl. Chem.* **1981**, *18*, 767–770.
(11) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
(12) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, pp 1080–1082. The reagent can be stored indefinitely at −20 °C as a crystalline solid in an inert atmosphere. Commercially available solutions are not recommended.

excess, respectively (90% chemical yield in all cases).

The absolute configuration of the major diastereomer was determined to be *R* by Pirkle column HPLC analysis of **9a–c**, after removal of the oxazoline.[13] Thus, the electrophile appears on the same side of the product as the oxazoline isopropyl, when the oxazoline is drawn with the nitrogen toward the carbanion. An important feature of the process as it applies to the synthesis of *homochiral* (optically pure) products is the fact that in all cases, *the major isomer could be separated from its epimer* by radial chromatography.[14]

Removal of the oxazoline with hydrazine ($N_2H_4 \cdot H_2O$, *p*-TsOH, EtOH, reflux 3 h) afforded the tetrahydroisoquinolines **9a–c** in excellent yield.

The sequence was applied to the synthesis of (*R*)-(+)-salsolidine. Thus, (*S*)-tetrahydroisoquinolinyloxazoline **10** was metalated (*t*-BuLi, THF, −78 °C) and alkylated (MeI, −100 °C) to give **11** in 93% yield as a 9:1 mixture of diastereomers (Scheme II), which were separable by radial chromatography.[14] The oxazoline moiety was removed by hydrazinolysis as above, affording (*R*)-(+)-salsolidine in quantitative yield. Pirkle column analysis[13] and sign of rotation[15] confirmed the stereochemical assignment.

(*S*)-Piperidinooxazoline **12** was prepared in 63% yield as described above. Metalation was best accomplished as a 0.5 M solution in ether[16] (*sec*-BuLi, −23 °C, 2 h); alkylation with methyl iodide or trimethylsilyl chloride at −100 °C afforded 2-substituted piperidinooxazolines **13a–b** in 30% and 70% yields, respectively, *each as a single diastereomer* (Scheme III). This constitutes the first example of an asymmetric alkylation of a nonbenzylic position adjacent to nitrogen. In the case of **13a**, an oxidation product tentatively identified as **14** was obtained,[17] along with about 20% of **12**.[18] Cleavage of the oxazoline moiety could be accomplished as before; however, attempts to isolate **15** from the aqueous hydrolysis mixture were unsuccessful. The absolute configuration of **13** is not known with certainty but is assigned as *R* by analogy with the isoquinolines. The degree of asymmetric induction (100% de) was proven by independent synthesis of a mixture of the two possible epimers (*d,l*-**15a** + **5**) and coinjection on a capillary GC column. Metalation and methylation of **13a** afforded (*trans*-2,6-dimethylpiperidino)oxazoline **16**, again as the only detectable isomer (along with unreacted starting material).

Attempts to alkylate **12** with other alkyl halides were not as successful. For example, *n*-propyl bromide afforded a mixture of **14** and **13c** as a 1:1 mixture of diastereomers (0% de). Suspecting a radical combination pathway, the anion was quenched with hexenyl bromide. Two (preparatively) inseparable alkylation products were formed, tentatively assigned structures **17** and **18** on the basis of their mass spectra, each as a 1:1 mixture of diastereomers. Formation of these products is consistent with a radical combination pathway, with consumption of the 5-hexenyl radical competing with cyclization to cyclopentylmethyl radical followed by bond formation. Thus, there appears to be a subtle balance of electronic factors governing the coupling reactions in these systems that we do not completely understand as yet. We are currently investigating these factors and will report our findings in due course.

Acknowledgment. This work was supported by the National Science Foundation. We are grateful to Professor A. I. Meyers for making us aware of his recent results prior to their publication.

Registry No. **4**, 17016-83-0; **5**, 102922-29-2; **6**, 102922-30-5; **8a**, 102922-31-6; **8b**, 102922-32-7; **8c**, 102922-33-8; **9a**, 84010-66-2; **9b**, 102922-41-8; **9c**, 57680-87-2; **10**, 102922-34-9; **11** (isomer 1), 102922-28-1; **11** (isomer 2), 102922-35-0; **12**, 102922-36-1; **13a**, 102922-42-9; **13b**, 102922-43-0; **13c** (isomer 1), 102922-44-1; **13c** (isomer 2), 102922-45-2; **14**, 102922-37-2; **16**, 102922-38-3; **17** (isomer 1), 102922-39-4; **17** (isomer 2), 102922-46-3; **18** (isomer 1), 102922-40-7; **18** (isomer 2), 102922-47-4; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; (+)-salsolidine, 54193-08-7; trimethylsilyl chloride, 75-77-4; methyl iodide, 74-88-4; 6-bromo-1-hexene, 2695-47-8; piperidine, 110-89-4; *n*-propyl bromide, 106-94-5.

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(13) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504–2506.

(14) Radial chromatography refers to centrifugally accelerated, radial preparative TLC, using a Chromatotron available from Harrison Research, Palo Alto, CA 94036. For good separation of aminooxazolines, the plates must be first deactivated with a solution of 15% triethyl amine in hexane and then rinsed with hexane. Elution is achieved with 15–20% ethyl acetate in hexane.

(15) Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214.

(16) Both the solvent and the concentration are critical to the deprotonation.

(17) A similar product has been observed in the alkylation of lithiated piperidine formamidines: Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270–3276.

(18) On the basis of the efficient formation of **13b**, we believe the deprotonation of **12** is complete under the stated conditions and presume the methyl iodide (which had been purified) is the proton source, possibly by dehydrohalogenation.