nitrates is in accordance with the tendency reported in the oxidation of a few organic compounds.[5] The activity of the nitrates that had been powdered and dried but not supported was found to be very low (Table II). This result indicates the necessity of silica gel for the satisfactory oxidation.

The activity of some solid supports was examined in the reaction of $Zn(NO_3)_2$ and found to decrease in the order: silica gels (Merck and Fuji-Davidson, 230–300 mesh) > alumina (ICN, N-super I) > bentonite clay. Molecular sieves 3A (powder), zeolite A-4 (synthetic, 200 mesh), Celite 535, and active carbon (powder) were ineffective. This result suggests that the main function of silica gel is not to widen the surface area of metallic nitrates. Silica gel is speculated to promote the oxidation by forming a special reaction field where reagents and substrates are accumulated by adsorption and activated by hydroxyl groups of the support.

We would like to propose a radical mechanism for the oxidative cleavage of ethers by $Cu(NO_3)_2$– and $Zn(NO_3)_2$–SiO_2 on the following grounds. (1) By changing the atmosphere from nitrogen to oxygen the oxidation was suppressed (Table II). The inhibiting effect of oxygen may be explained by the presumption that the oxidation involves radicals, because radical reactions are generally influenced by the presence of oxygen. (2) The brown gas that appeared during the oxidation seems to be NO_2, which is a radical. (3) The yield of benzaldehyde and cyclohexanone was reduced to about half by the addition of 15 mol % (to $Cu(NO_3)_2$) of 2,,6-tri-*tert*-butylphenol, which is a sterically hindered radical scavenger, in the 15-min reaction of $Cu(NO_3)_2$–SiO_2 in CCl_4. The weakness of the inhibiting effect of the phenol may be explained by the speculation that the phenol and NO_2 are adsorbed and fairly fixed on the surface of silica gel. (4) Nitrites were sometimes isolated. (5) The logarithm of initial rates in the oxidation of *p*-methyl-, *p*-fluoro-, *p*-chloro-, and *p*-nitrobenzyl methyl ethers by $Cu(NO_3)_2$–SiO_2 in CCl_4 linearly depended on the Hammett substituent constants to give –0.31 as the value of ρ. The result that the electronic character of the substituents influence the reaction rates but little suggests, though not clearly, that radicals rather than ions are formed as intermediates. (6) The ratio of the initial rate of the oxidation of benzyl methyl ether to that of the ether in which α-hydrogens of the benzyl group had been replaced by deuterium (k_H/k_D) was 2.7 in the reaction of $Cu(NO_3)_2$–SiO_2 and 3.1 in the one of $Zn(NO_3)_2$. This result suggests that the cleavage of the bond between the hydrogens and α-carbon of the benzyl group is the rate-determining step. (7) Some kinds of esters, halides, and amines were also oxidized by the supported reagents.[6] The observations described above are compatible with a radical pathway. Therefore, we would like to propose the following scheme for this oxidation. The formation of NO_2 from metallic nitrates has been reported.[5] Further, it is noteworthy that N_2O_4, which is usually equilibrated with NO_2, has been reported to oxidize some kinds of organic compounds.[7] Chlorinated products were not detected in the reactions in CCl_4. This fact may be explained at least partly by the weak tendency of the solvent to be adsorbed on silica gel surface where the oxidation seems to take place.

$$(NO_3)_{n-1}M\text{–}O\text{–}NO_2 \rightarrow (NO_3)_{n-1}M\text{–}O^{\bullet} + {}^{\bullet}NO_2$$

$$R^1R^2CH\text{–}O\text{–}CHR^3R^4 + {}^{\bullet}NO_2 \rightarrow R^1R^2\dot{C}\text{–}O\text{–}CHR^3R^4 + HNO_2$$

$$R^1R^2\dot{C}\text{–}O\text{–}CHR^3R^4 + {}^{\bullet}NO_2 \rightarrow R^1R^2C(\text{–}ONO)\text{–}O\text{–}CHR^3R^4$$

$$R^1R^2C(ONO)\text{–}O\text{–}CHR^3R^4 \rightarrow R^1R^2C{=}O + R^3R^4CH\text{–}ONO$$

$$R^3R^4CH\text{–}ONO \rightarrow R^3R^4C{=}O + HNO$$

(5) Addison, C. C. *Coord. Chem. Rev.* **1966**, *1*, 58.

(6) The study of these reactions is now progressing.

(7) Addison, C. C. *Chem. Rev.* **1980**, *80*, 21.

Acyclic Stereoselection in the Alkylation of Chiral Dipole-Stabilized Organolithiums: A Self-Immolative Chirality Transfer Process for the Synthesis of Primary Amines[1]

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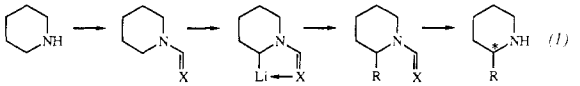
Summary: A comparison of 1,3- and 1,5-asymmetric induction shows the former to have far greater selectivity in the methylation of chiral dipole-stabilized organolithiums. The asymmetric alkylation of *N*-benzyloxazolidinones is employed as the key step in a new synthesis of primary amines by asymmetric alkylation α to nitrogen.

Sir: The elaboration of nitrogen heterocycles by alkylation α to nitrogen (eq 1) is firmly established as a useful method in organic synthesis.[2] In that the process generates a stereocenter (*), a useful and important amplification of the sequence is its application to the preparation of enantiomerically pure compounds. This has been accomplished in two strategically different ways: the use of a chiral auxiliary attached to nitrogen,[3] and by use of a chiral



(1)

(1) K.R. thanks the University of Miami for a Maytag Fellowship, 1987–90. We are grateful to the National Institutes of Health for financial support: Grant GM-37985 supported this work and Grant RR-03351 provided funds for the purchase of the 400-MHz NMR.

(2) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Ibid.* **1984**, *84*, 471–523. (c) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 1, Chapter 2.1 and Vol. 3, Chapter 1.2.

(3) For recent applications using this strategy, see: (a) Gawley, R. E.; Smith, G. A. *Tetrahedron Lett.* **1988**, *29*, 310–311. (b) Meyers A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787.

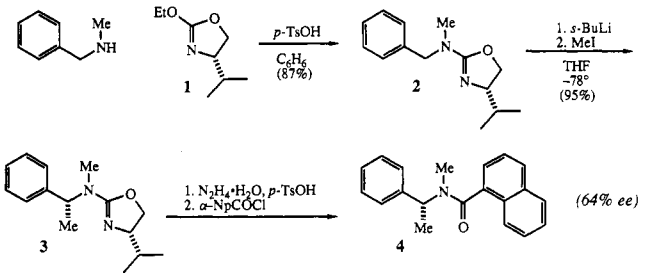
0022-3263/89/1954-3002$01.50/0

Table I. Alkylation Yields and Selectivities for Alkylation of Oxazolidinones 5

substrate	RX	product	crude % de[a]	yield,[b] %	% de[b]
5a	MeI	**6a**	96	75	>99[a,c,e]
5a	EtI	**6b**	96	74	>99[a,c,e]
5a	*n*-BuBr	**6c**	75	63	75[a]
5a	BnCl	**6d**	*d*	63	87[a,c]
5b	MeI	**6e**	96	92	>99[a,c,e]
5c	$BrCH_2CO_2$-*t*-Bu	**6f**	*d*	72	93[c]

[a] Diastereomeric excess (de) determined by 400-MHz NMR spectroscopy. [b] Analytically pure products, after recrystallization, chromatography, or Kugelrohr distillation. [c] Diastereomeric excess (de) determined by HPLC. [d] Not determined. [e] No trace of the minor diastereomer was visible by NMR spectroscopy.

Scheme I

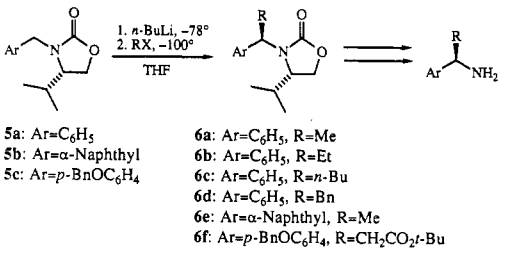


heterocycle whereby an existing stereocenter directs the stereochemical course of the alkylation, but is later destroyed.[4] When the chiral auxiliary is recoverable, the former category constitutes an "asymmetric synthesis," whereas the latter has been termed a "self-immolative" chirality transfer process.[5] We now report the first examples of the stereoselective alkylation of chiral, acyclic dipole-stabilized organolithiums[6] and a self-immolative chirality transfer protocol for the synthesis of primary amines.

Initially, we evaluated ethoxyoxazoline 1[7] as a chiral auxiliary. As shown in Scheme I, condensation of 1 with *N*-methylbenzylamine (benzene, *p*-TsOH, reflux) afforded aminooxazoline **2** in 87% yield. Metalation (BuLi, THF, −78 °C) and alkylation with methyl iodide afforded **3** in 95% yield. After removal of the chiral auxiliary (N_2H_4·H_2O, *p*-TsOH, 95% EtOH, reflux, 74%), the enantiomer ratio was determined by Pirkle analysis of the corresponding naphthamide, **4**.[8] Consistent with the sense of asymmetric induction in the isoquinoline series,[9] the major enantiomer is *R*, but the enantiomeric excess is only 64% (4:1 selectivity).

In the hopes of finding a system that would provide higher diastereoselection, we felt that a reasonable approach would be to examine a system in which the existing stereocenter is closer to the newly created one. Thus, we examined the *N*-benzyloxazolidinone **5a** (Scheme II). In comparing **2** to **5**, note that alkylation of **5** is a case of 1,3-stereoselection while former is 1,5-stereoselection. It was hoped that the closer proximity of the stereocenter would enhance the diastereoselection. Pending the successful alkylation of **5** to **6**, we planned to dissect the nitrogen from the heterocycle (vide infra).

Scheme II



Scheme III

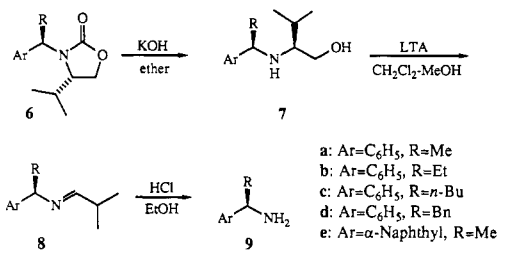


Table II. Individual Yields for 6 → 9 (See Scheme III) and Enantiomeric Excess Determination of Amines 9 by Pirkle Analysis[8] of the Corresponding Naphthamides

	6 → 7	7 → 8	8 → 9	abs config	% ee
a	76	93	91	*R*	92
b	83	95	84	*R*	92
c	67	91	87	*R*	70
d	65	93	81	*R*	85
e	63	94	91	*R*	100

The metalation of **5a** occurs smoothly under standard conditions (*n*-BuLi, THF, −78 °C) and alkylation with methyl iodide (−100 °C) gives **6a** in quantitative yield. The selectivity, as determined by 400-MHz NMR, is 50:1 (96% diastereomeric excess, de). A single recrystallization improves the de to >99% (none of the minor diastereomer visible by NMR). The absolute configuration of the new stereocenter is *R* (vide infra). Table I summarizes this experiment and other similar ones, all of which indicate that 1,3-induction in chiral dipole stabilized organolithium alkylations is a highly stereoselective process.

In order to employ this reaction in a synthesis of amines, the nitrogen must be excised from the heterocycle. To dissect the oxazolidinone, we envisioned a hydrolytic cleavage of the C_2–N amide bond and an oxidative cleavage of the C_4–C_5 carbon–carbon bond as key steps. Reducing this protocol to practive required considerable experi-

(4) For a recent study using this approach, see: Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944–1954.

(5) Although this term was originally used in the context of a single reaction, Eliel has extended its usage to a sequence of reactions when a stereocenter is deliberately destroyed after creation of another: Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1983; Vol. 2, chapter 5, pp 125–155, see footnote 1, p 137.

(6) In the past, we (e.g., ref 7 and 9) and others (inter alia, ref 2a,b) have referred to these species as dipole-stabilized anions. However, the chemistry of these lithiated species does not correlate with that predicted for the free anions. Nevertheless, stereoelectronic factors do influence the chemistry of such species, so we suggest the term "dipole-stabilized organometallic" as a more accurate descriptor. For a recent ab initio study of a dipole-stabilized anion and organolithium which discusses this point, see: Bartolotti, L. J.; Gawley, R. E. *J. Org. Chem.* **1989**, *54*, 2980–2982.

(7) For an explanation of the how auxiliary 1 was designed, see: Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175–181. For a comparison study of several related auxiliaries, see ref 9.

(8) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138–140.

(9) For an extensive study of the stereoselective alkylation of tetrahydroisoquinolyloxazolines, see: Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211–2217.

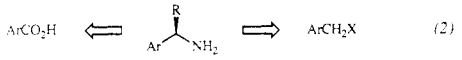
mentation, but the general route that evolved is shown in Scheme III. The oxazolidinone nucleus of **6** is exceptionally robust, but yielded to hydrolysis when subjected to Gassman's recipe[10] for unsolvated KOH in ether (6 equiv of KO-*t*-Bu, 2 equiv of H_2O, ether, 4–24 h). The single exception was **6f**, which afforded only cinnamic acid derivatives under a variety of acidic and basic hydrolysis conditions.[11] Oxidative cleavage of the amino alcohols **7a–e** to the imines **8a–e** occurred in excellent yield ($Pb(OAc)_4$, 2:1 CH_2Cl_2–MeOH, 0 °C, 2 min), at which point hydrolysis to the liberated primary amines **9a–e** was routine (HCl, EtOH, 6–24 h). Table II details the yields for the conversion of **6a–e** to **9a–e**.

The absolute configuration and enantiomeric excess (ee) of the amines **9a–e** were determined by Pirkle analysis of the corresponding naphthamides.[8] The results are summarized in Table II. In all cases, the absolute configuration was *R*, although the percent of the products was diminished from the percent of the oxazolidinones **6a–d**. Thus, there appears to be some racemization in the conversion **6** to **9** for some of the substrates studied. The lead tetraacetate oxidation step is most likely the culprit, since cyclization of **7b** and **7e** with phosgene afforded **6b** and **6e** of undiminished diastereomeric excess.

The starting *N*-benzyloxazolidinones **5** may be prepared in either of two ways. Most obviously, the parent oxazolidinone may be alkylated with the appropriate benzyl halide (KH, THF, BnX, cat. Bu_4NI). Alternatively, **5** is available by cyclization of the corresponding *N*-benzylvalinol derivatives, which are in turn prepared by $LiAlH_4$ reduction of benzoyl valines.[12]

Conclusion

We have reported the first examples of acyclic stereoselection in the alkylation of chiral dipole stabilized organolithiums. A comparison of 1,5- vs 1,3-induction revealed significantly greater selectivity for the latter. The successful conversion of oxazolidinones **5** to chiral primary amines **9** constitutes a new method for the synthesis of primary amines by asymmetric alkylation. The resultant overall transformations, illustrated in eq 2, convert benzyl halides or carboxylic acids into chiral primary amines by a self-immolative chirality transfer from valine.



(2)

Supplementary Material Available: Experimental details for the synthesis and characterization of all compounds (7 pages). Ordering information is given on any current masthead page.

(10) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275–6.

(11) We had intended **6f** to be a precursor of β-tyrosine. For a recent synthesis of a β-tyrosine derivative, and leading references to the occurence of this rare amino acid in peptide antibiotics, see: Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630–1631.

(12) For example, the reduction of *N*-benzoylvaline to *N*-benzylvalinol is achieved in 76% yield: Smith, G. A.; Hart, G.; Chemburkar, S.; Goicoechea-Pappas, M.; Rein, K.; Anklekar, T. V.; Smith, A. L.; Gawley, R. E. *Organic Syntheses*; Wiley: New York, 1989; Collect. Vol. VII, in press.

Inside–Outside Stereoisomerism. 4.† An Unusual Rearrangement of the *trans*-Bicyclo[5.3.1]undecan-11-yl Radical

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Summary: Deoxygenation of 11-hydroxy-*trans*-bicyclo[5.3.1]undecane leads to the formation of both the trans- and the cis-bridged hydrocarbons. The mechanistic studies described herein are consistent with the formation of *cis*-bicyclo[5.3.1]undecane via a sequence of transannular hydrogen atom abstractions leading to the formation of the bicyclo[5.3.1]undecan-1-yl tertiary radical, which, on reduction with tri-*n*-butyltin hydride, leads to the formation of the cis-fused hydrocarbon.

Sir: The intramolecular dioxenone photocycloaddition reaction provides unique synthetic approaches for the preparation of carbocyclic structures with unusual structural and chemical properties.[2] We have recently reported the application of this methodology to the synthesis of trans or "inside–outside"[3] bicyclo[5.3.1]undecan-11-one, **1** (Scheme I), which is ca. 10 kcal/mol less stable than the corresponding cis isomer, **2**.[2a] In an effort to prepare the parent hydrocarbon, *trans*-bicyclo[5.3.1]undecane, **6**, the deoxygenation of **1** was examined. We report herein that treatment of the *trans*-bicyclo[5.3.1]undecan-11-yl xanthate, **4**, with a stoichiometric amount of tri-*n*-butyltin hydride[4] leads to the predominant formation of *cis*-bicyclo[5.3.1]undecane, **5**. Our preliminary studies directed toward the elucidation of the mechanism of this unusual stereochemical isomerization are outlined below.

While **1** was inert to standard thioketalization conditions and even to reduction with sodium borohydride (2 equiv, ethanol, 25 °C), treatment with lithium aluminum hydride (2 equiv, tetrahydrofuran, 25 °C, 83%) led to the formation of 11-hydroxy-*trans*-bicyclo[5.3.1]undecane, whose structure was assigned as the α-epimer, **3**, the result of hydride

†Dedicated to Professor Josef Fried on the occasion of his 75th birthday. For the previous paper in this series, see: Winkler, J.; Hey, J.; Williard, P. *Tetrahedron Lett.* **1988**, 4691.

(1) Recipient of the American Cyanamid Young Faculty Award (1989–1992) and a National Institutes of Health Research Career Development Award (1988–1993). Fellow of the Alfred P. Sloan Foundation (1987–1989).

(2) For examples of the use of the intramolecular dioxenone photocycloaddition reaction, see: (a) Winkler, J.; Hey, J.; Williard, P. *J. Am. Chem. Soc.* **1986**, *108*, 6425. (b) Winkler, J.; Hey, J.; Darling, S. *Tetrahedron Lett.* **1986**, 5959. (c) Winkler, J.; Hey, J.; Hannon, F.; Williard, P. *Heterocycles* **1987**, *25*, 55. (d) Henegar, K.; Winkler, J. *Tetrahedron Lett.* **1987**, 1051. (e) Winkler, J.; Henegar, K.; Williard, P. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (f) Winkler, J.; Hey, J.; Williard, P. *Tetrahedron Lett.* **1988**, 4691. For the intermolecular photocycloaddition of dioxenones, see: Baldwin, S.; Wilkinson, J. *J. Am. Chem. Soc.* **1980**, *102*, 3634.

(3) For a recent review, see: Alder, R. *Acc. Chem. Res.* **1983**, *16*, 321. For other syntheses of inside-outside bicycloalkanes, see: (a) References 2e and 2f. (b) Funk, R.; Olmstead, T.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (c) McMurry, J.; Hodge, C. *J. Am. Chem. Soc.* **1984**, *106*, 6450. (d) Gassman, P. G.; Hoye, R. *J. Am. Chem. Soc.* **1981**, *103*, 215, 2496, 2498. (e) Haines, A.; Harntiang, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2577. (f) Gassman, P.; Thummel, R. *J. Am. Chem. Soc.* **1972**, *94*, 7183. (g) Park, C.; Simmons, J. *J. Am. Chem. Soc.* **1972**, *94*, 7184.

(4) Barton, D.; McCombie, S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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