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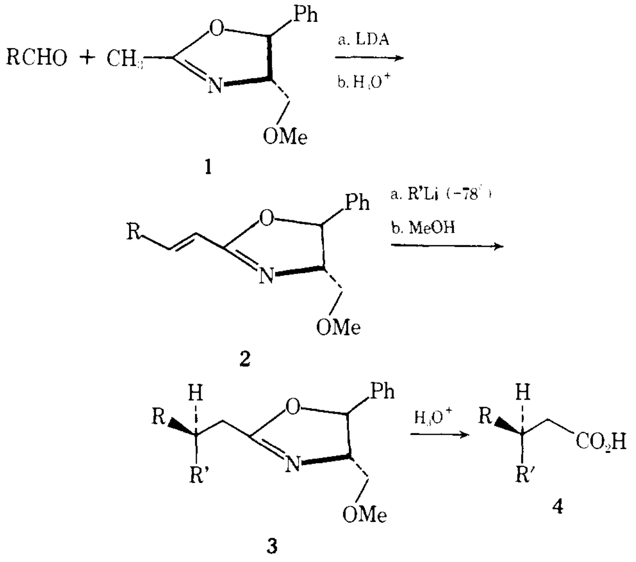
Oxazolines. XIX. An Asymmetric Synthesis of 3-Substituted Alkanoic Acids via Conjugated Addition of Organolithium Reagents to Chiral Oxazolines

Sir:

Lithiated chiral oxazolines have been recently shown to react with various electrophiles generating a new asymmetric center with considerable bias. This process has led to optically active α-alkyl alkanoic acids,[1] α-methoxy acids,[2] β-hydroxy acids,[3] α-substituted butyrolactones,[4] and 2-substituted-1,4-diols.[4] However, the utilization of these chiral oxazolines as electrophilic species has not been previously explored. We now report that (4*S*,5*S*)-2-(*trans*-1-alkenyl)-4-methoxymethyl-5-phenyloxazolines, **2**, undergo 1,4-addition reactions with various organolithium reagents producing, after hydrolysis, 3-substituted alkanoic acids **4** in high enantiomeric purity. Although asymmetric additions to electrophilic olefins (α,β-unsaturated carbonyls,[5-7] vinyl sulfoxides[8]) have been previously described, these results represent the first example possessing substantial generality, allowing recovery of the chiral reagent, and permitting the synthesis of either enantiomer from a common chiral precursor. The requisite alkenyl oxazolines **2** were prepared by condensation of the lithio salt (LDA, THF, −78°) of the commercially available 2-methyloxazoline[9] with the appropriate aldehyde followed by dehydration (TFA, benzene, reflux) of the β-hydroxyethyloxazolines[10] (Table I).



Slow dropwise addition (1-2 hr) of a THF solution (0.25-0.5 *M*) of **2** to 1.5 equiv of the organolithium reagent (diluted with THF) at −78°, under a nitrogen atmosphere, gave the adduct (presumably **6**) which, after an additional hour of stirring, was quenched with 5.0 equiv of absolute methanol (−78°). Aqueous work-up and extraction gave crude **3** which was directly hydrolyzed (3-6 *M* H_2SO_4, 3-6 hr reflux) to the 3-substituted alkanoic acid (Table I). The enantiomeric purity of the acids obtained in this manner is exceptionally high in all but one instance (Table I, entry 4) and there is some doubt as to the reliability of the reported rotation in entry 4 (ref i, Table I). Presently, the chemical yields (overall from **2**) are only moderate when allylic protons are present on the alkenyl oxazolines (entries 1-5) due to competing proton abstraction[11] by the organolithium reagents and subsequent addition of **6** to unreacted **2.** Considerable amounts (25-35 wt %) of high molecular weight polymeric material were encountered in these cases. This side process is not a serious problem for the β-styryloxazolines (entries 6 and 7) as the chiral carboxylic acids are formed in 64-66% overall yields. Nevertheless, in all cases the chemical efficiency is overshadowed by the high optical yields, and all compounds are readily prepared in multigram quantities.

That this asymmetric synthesis can give rise to *either enantiomer* of a 3-substituted alkanoic acid from the same *chiral oxazoline* is evidenced by entries 5 and 6 on the table. Both *S*-(+) and *R*-(−) 3-phenylpentanoic acid were

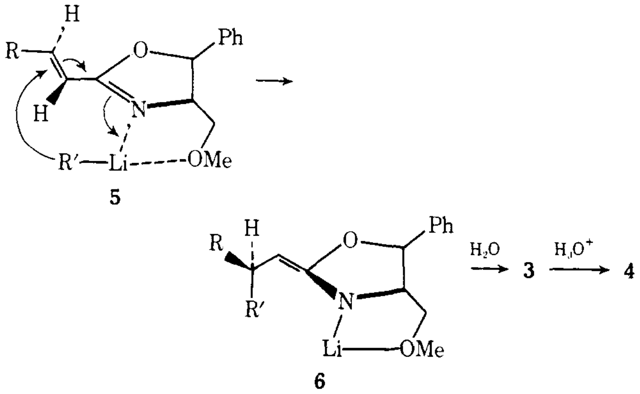
Table I. Optically Active 3-Substituted Alkanoic Acids from 2-(1-Alkenyl)oxazolines

	Oxazolines, 2				Acids, 4				
Entry	R	Yield, %	$[\alpha]^{25}{}_{589}$	R'Li[c]	Overall yield, %	Obsd $[\alpha]^{25}{}_{589}$[d]	Lit. $[\alpha]^{25}{}_{589}$	Optical purity, %	Config
1	Me	53[a]	+38.0° (*c* 10.0)[b]	Et	30	−7.44° (neat)	−8.15° (neat)[f]	92	*R*
2	Me			*n*-Bu	38	+3.84° (neat)	−4.2° (neat)[g]	91	*R*
3	Me			Ph	34	+55.8° (*c* 9.82)[e]	−57.2° (*c* 9.80)[e,h]	98	*S*
4	Et	42	+31.1° (*c* 10.0)[b]	*n*-Bu	49	+2.84° (neat)	+4.69° (neat)[i]	61	*R*
5	Et			Ph	31	+45.8° (*c* 7.05)[e]	−49.66° (*c* 7)[j]	92	*S*
6	Ph	65	122° (*c* 10.0)[b]	Et	66	−48.0° (*c* 9.49)[e]		97	*R*
7	Ph			*n*-Bu	64	−27.8° (neat)	−23.1° (neat)[k]	>95	*R*[l]

[a] Contained ~7% of the cis isomer; yields are based upon the 2-methyl-2-oxazoline. [b] Chloroform solutions. [c] Ethyllithium was used as a 1.22 *M* solution in benzene–ether (70:30); *n*-butyllithium was used as a 2.48 *M* solution in hexane; phenyllithium was used as a 1.53 *M* solution in benzene–ether (70:30). [d] Rotations were measured on a Jasco DIP-180 automatic polarimeter at 25° in a 1-cm³ (10 cm) cell. [e] Benzene was used as the solvent. [f] C. G. Overberger and I. Cho, *J. Org. Chem.*, 33, 3321 (1968). [g] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 95, 153 (1932). [h] H. Rupe, *Justus Liebigs Ann. Chem.*, 369, 311 (1909); configuration assigned by V. Prelog and H. Scherrer, *Helv. Chim. Acta.*, 42, 2227 (1959). [i] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 115, 401 (1936); this is a calculated rotation value and unpublished results from our laboratory tend to indicate that the value is too high. [j] L. Lardicci, R. Menicagli, and P. Salvadori, *Gazz. Chim. Ital.*, 98, 738 (1968). [k] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 97, 563 (1932). [l] Configuration assigned as *R*(−) by CD curve comparison with *R*-(−)-3-phenylpentanoic acid.

obtained in greater than 90% enantiomeric purity by simply reversing the order of introduction of the two substituents, R and R′. An asymmetric synthesis of *R*-(−)-3-phenylbutyric acid **4** (R = Ph, R′ = Me) was reported by Tsuchihashi[8] to occur in 40% overall yield and in 95% enantiomeric purity by conjugate addition of malonate ion to a chiral β-styryl sulfoxide. However, the conjugate addition proceeded with 60% bias and the high optical yield was realized only after separation of the diastereomers. This result should be compared with the present study (entry 3) which gives *S*-(+)-3-phenylbutyric acid in 34% overall yield and at least 98% enantiomeric purity after simple hydrolysis of the intermediate **3**.[13] It should be noted that 3-phenylheptanoic acid (entry 7) obtained via this process possessed a specific rotation substantially greater than that previously reported from resolution techniques (ref *1*, Table I). It is assumed that this higher value would represent 95–98% optical purity based upon the results from entries 5 and 6.

A mechanism which correctly predicts the proper configuration of the 3-substituted alkanoic acids and may tentatively be used as an operational scheme involves underside entry[14] of the organolithium reagent to the anti-trans conformer of the alkenyl oxazoline **5**. The lithio adduct **6**, which is now a metalated "enamine" should also be capable of behaving as an nucleophile and is identical with the intermediates previously reported[1] to react with electrophiles producing α-alkyl alkanoic acids. A study to evaluate additions of various nucleophiles to **2** as well as the creation of a second chiral center by electrophilic additions to **6** is underway.



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(10) Recently, **2** (R = aryl) has been prepared in good yield by azeotropic removal of water from a toluene solution of aromatic aldehydes and **1** using $ZnCl_2$ as a catalyst.

(11) We have observed that *cis*-**2** (R = Me), prepared in 40% yield from the 2-(trimethylsilylmethyl)oxazoline, LDA, and acetaldehyde[12] gave almost exclusively proton abstraction when treated with organolithium reagents. *cis*-**2**, upon standing (1 week) or heating above 90° isomerized to *trans*-**2**.

(12) Cis olefins have been directly prepared using substituted trimethylsilyl carbanions and carbonyl compounds: P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975), and references cited therein.

(13) To date, we have been unable to effect an efficient addition of methyllithium to **2**, and thus synthesis of the optical antipodes in entries 1–3 has not been achieved.

(14) All evidence points to a strong complexation of lithium ion to the nitrogen and methoxyl group and hence to bottomside approach (A. I. Meyers et al., manuscript submitted as full account of earlier reports on asymmetric synthesis using chiral oxazolines). Furthermore, we have been able to solubilize LiCl with **1** in tetrahydrofuran over and above a blank solution indicating the strong affinity of lithium ion to the chelating environment of **1** or **4** (M. Druelinger, research in progress).

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Synthesis of Stable Homopolyatomic Anions of Antimony, Bismuth, Tin, and Lead. The Crystal Structure of a Salt Containing the Heptaantimonide(3−) Anion

Sir:

We wish to report the achievement of a solution to a long-standing problem, a general route to the isolation of stable derivatives of the polyatomic anions of the heavy post-transition metals that have long been known primarily as solutions of the corresponding alkali metal intermetallic phases in liquid ammonia. The method utilizes the strong complexing ability of 2,2,2-crypt[1,2] for the cation to prevent the usual decomposition reactions wherein electrons from the polyanions are partially transferred back to the alkali metal to form the parent alloy.

Zintl and coworkers[3-5] have provided the broadest and most thorough characterization of ammonia solutions of the polyatomic anions of tin, lead, arsenic, antimony, bismuth, sulfur, selenium, and tellurium through potentiometric titrations and alloy extractions. For the systems considered here they reported evidence for the nine species $Sn_9{}^{4-}$, $Pb_{7,9}{}^{4-}$, $Sb_{3,5,7}{}^{3-}$, and $Bi_{3,5,7(?)}{}^{3-}$. Evaporation of the ammonia yielded highly colored but amorphous solids which analyzed as the last-listed ion for each element together with $Na(NH_3)_n{}^+$ cations. All such products lost ammonia before crystallization and reverted to known binary alloys. The latter in general do not exhibit compositions or structures which correspond to the observed solution species. Since that time results have substantially been peripheral,[6,7] and no synthesis and structural characterization of any phase containing an isolated polymetal "Zintl" anion has been reported although Kummer and Diehl[8] have briefly noted the preparation of a red, slightly stable phase $Na_4Sn_9{\cdot}6\text{–}8en$ (en = ethylenediamine).

The impetus for the present work was provided by the above observations coupled with the recent demonstration that the addition of crypt gives a considerable enhancement of the solubility of the alkali metals in diverse solvents[9] and allows the isolation and structural determination of the salt $[Na(crypt)^+]Na^-$.[10] The extremely strong complexation of sodium and potassium ions by crypt, with formation constants of 10^4 to 10^{10} in various solvents, suggested that the otherwise favorable delocalization of electrons from the polyanion back into the alkali metal ion to form a metallic structure could be prevented by this coordination. In all cases reported here a solution of crypt in en has been found to readily react with the appropriate alloy phase to yield a highly colored solution from which a crystalline derivative can be isolated.

Alloy samples have been prepared by fusing the appropriate amounts of the elements in sealed tantalum tubing as before.[7] Because of the cost of crypt (\$115 g^{-1}, EM Laboratories) most preparations have been on the milligram scale and characterizations, by crystallography. For example, the reaction of powdered NaSb or $NaSb_3$ with crypt in