ASYMMETRIC SYNTHESIS OF HIGHLY STRAINED HETEROCYCLIC COMPOUNDS AND OF β- AND γ-AMINO ACIDS USING A VERY INNOVATIVE METHODOLOGY

*Renzo Luisi

Vito Capriati

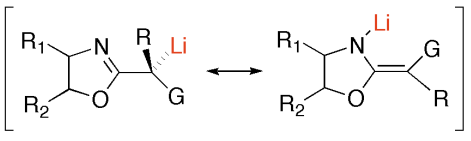
Saverio Florio

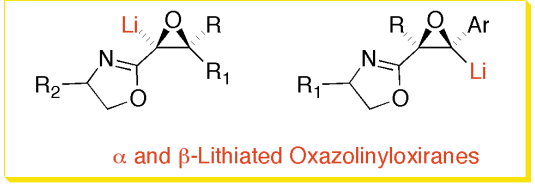
Dipartimento Farmaco-Chimico,
Università di Bari,
Via E.Orabona 4, I-70126 - Bari,
C.N.R., Istituto di Chimica dei Composti OrganoMetallici "ICCOM",
Sezione di Bari, Italy
*Tel.: +39-080-5442749;
*fax: +39-080-5442539;
*e-mail: luisi@farmchim.uniba.it.

Research in asymmetric synthesis is receiving a great impulse in industrial and academic laboratories because of a growing need for new enantiomerically pure bioactive products. The use of carbanions in carbon-carbon bond formation is a well-known methodology for the obtainment of racemic products; their use in chiral synthesis is now emerging.[1] Because of this need for chiral compounds, the development of enantioselective methods involving anions or nucleophilic intermediates has become a challenge for chemists. In this contest, the chemistry of lithiated heterosubstituted oxazolines can be considered of interest because of the possible synthetic potentials offered. In this paper we demostrate that lithiated oxazolines are useful intermediates for the preparation of *building blocks* such as amino acids and new heterocyclic derivatives with a high degree of stereo- and enantio- selectivity.

Two different types of lithiated oxazolines have been studied in some details: a) α-lithiated oxazolines and b) α- and β- lithiated oxazolinyloxiranes (**Figure 1**).

Figure 1

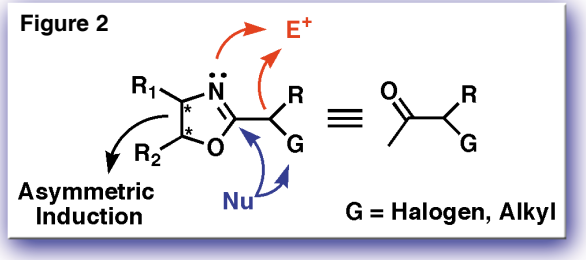




The chemistry of the oxazoline ring, which is a known masked form of carbonyl compounds,[2] has been exploited in many different areas of organic chemistry, from synthesis to catalysis, and the reactivity and applications are still an attracting area.[3] In **Figure 2** some aspects of the reactivity of these systems are highlighted. They can react as nucleophiles by the nitrogen lone pair or by the α-carbon once deprotonated, with nucleophilic species at the α-carbon if a leaving group is present, or at the C=N iminic moiety. Moreover, by using optically active oxazolines, promptly available from chiral amino alcohols, it is also possible to perform asymmetric synthesis.[3]

α-Lithiated alkyl and chloroalkyl oxazolines have attracted our attention because of their synthetic potential. They have been used as Darzens' reagents,[4] cyclopropanating reagents[5] and intermediates for vicarious nucleophilic substitution.[6]

Figure 2



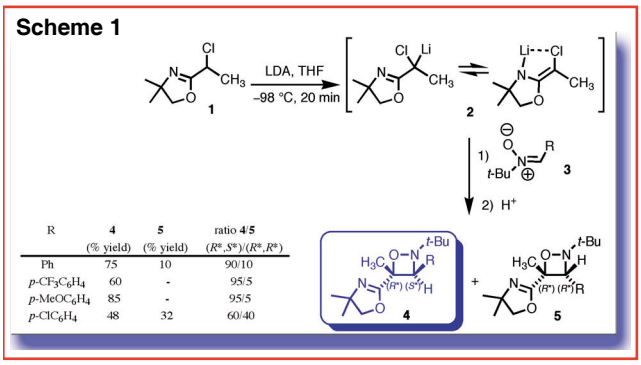
By combining the chemistry of lithiated oxazolines with that of peculiar electrophiles such as nitrones it is possible to prepare strained heterocyclic compounds,[7] stereodefined oxazolinylalkenes[8], oxazolinyl[1,2]oxazetidines[9] and β-amino acids.[10]

REACTION OF α-LITHIATED CHLOROALKYLOXAZOLINES WITH NITRONES: SYNTHESIS OF OXAZOLINYL[1,2]OXAZETIDINES.

Lithiation of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **1** with LDA at -98 °C in THF generated lithio derivative **2**, which proved to be quite stable under the reaction conditions. Spectroscopic investigations (NMR and React-IR®) showed that the lithiated intermediates is an azaenolate likely with E geometry.[11] The addition of *N*-

tert-butyl-nitrones **3** followed by quenching with sat. aq. NH_4Cl after 3h resulted in the formation of the *R*,S** oxazolinyl[1,2]oxazetidines **4** in good yield (75 %) together with a small amount of the *R*,R** isomer **5**.[9a] Reaction with aromatic nitrones gave quite good yields of oxazolinyl[1,2]oxazetidines **4** highly stereoselectively. In the case of the reaction with the *p*-chlorophenylnitrone appreciable amount of the diastereomeric oxazolinyl[1,2]oxazetidine **5** was isolated (**Scheme 1**).

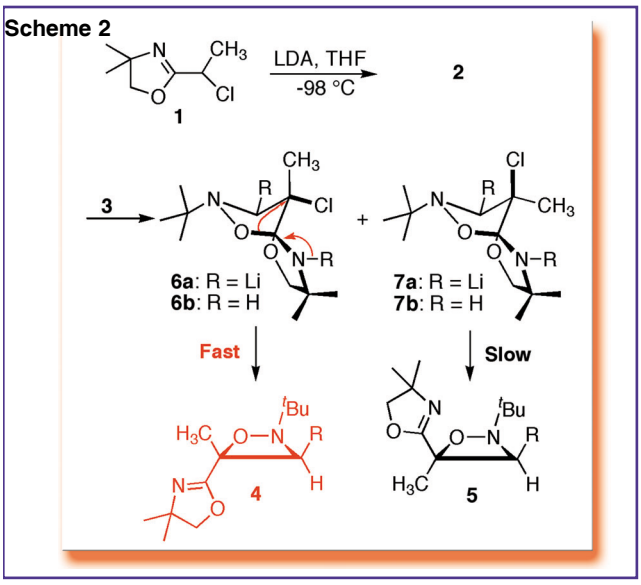
Scheme 1



R	4 (% yield)	5 (% yield)	ratio 4/5 (R^*,S^*)/(R^*,R^*)
Ph	75	10	90/10
p-$CF_3C_6H_4$	60	-	95/5
p-$MeOC_6H_4$	85	-	95/5
p-ClC_6H_4	48	32	60/40

It has been demonstrated that oxazolinyl[1,2]oxazetidines can derive from a sort of ring contraction involving spirocyclic compounds as intermediates. An investigation on the reaction mechanism[9a] using *N-tert*-butyl-α-phenylnitrone, revealed that quenching the reaction mixture at shorter reaction times (1 min) furnished the spirocyclic precursors **6b** and **7b** which have been isolated and fully characterized by NMR and X-ray analyses (**Scheme 2**).

Scheme 2

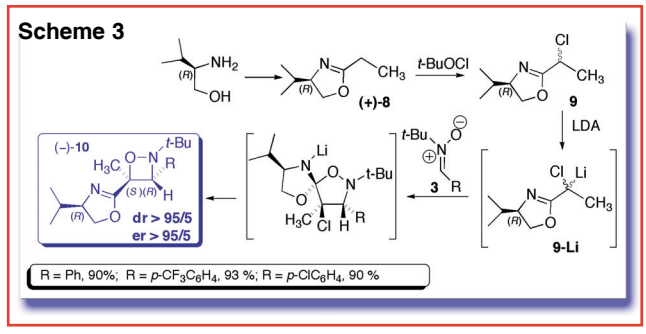


The observed high stereoselectivity has been rationalized on the basis of stereoelectronic effects and looking at the orbitals involved in the reaction. As the Cl leaving group departs, electrons in the σ bond to the migrating group (oxygen) have to flow into the C-Cl σ* orbital. The best overlap between these two orbitals (σ and σ*) occurs when they are set *anti*-periplanar to each other. Such a *anti*-periplanar requirement is not allowed for **7a** which converts more slowly into the oxazetidine **5**. In an experiment planned to support the above considerations, a sample of **6b** was treated with 1 equiv. of LDA in THF (-98 °C, THF): oxazetidine **4** formed quantitatively thus proving the stereospecificity of the reaction.

Considering the high diastereoselectivity of the addition reaction of nitrones to lithiated 2-(1-chloroethyl)-2-oxazoline **2**, it was almost obvious to test the chiral version of such a reaction by using readily accessible chiral 2-(1-chloroethyl)-2-oxazolines.[9b]

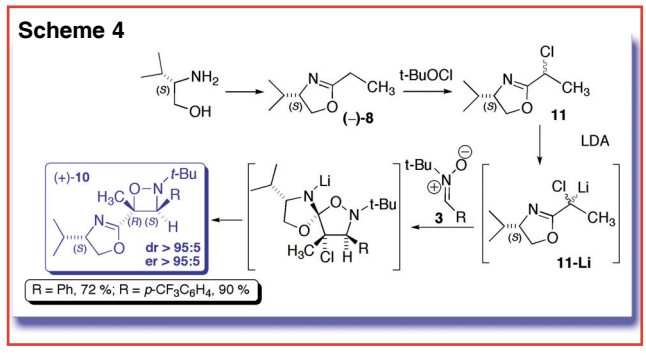
The (4*R*)-2-ethyl-4-isopropyl-2-oxazoline (+)-**8** (Scheme 3) was prepared from D-valinol and triethylorthopropionate.[12] Chlorination of (+)-**8** with *tert*-butylhypochlorite, according to a known procedure,[13] gave an almost 1:1 diastereomeric mixture of the correspondig 2-chloroethyl-2-oxazoline **9**. All attempts to separate such a diastereomeric mixture failed, so we decided to use it as such. Lithiation of (4*R*,1'S)/(4*R*,1'*R*)-**9** with LDA, followed by the addition of nitrones **3**, afforded the oxazolinyl[1,2]oxazetidines (-)-**10** in a high yield (>90 %) and excellent stereoselectivity (dr > 95/5, er > 95/5) (**Scheme 3**).

Scheme 3



Equally stereoselective were the reactions of oxazoline (4*S*,1'*S*)/(4*S*,1'*R*)-**11**, similarly prepared as a 1:1 mixture of diastereomers from L-valinol, with nitrones. The addition of nitrones **3** to lithiated oxazoline **11-Li**, generated by lithiation of **11**, produced the oxazolinyl[1,2]oxazetidines (+)-**10** in an excellent yield (>72 %) and stereoselectivity (dr > 95/5, er > 95/5). (**Scheme 4**).

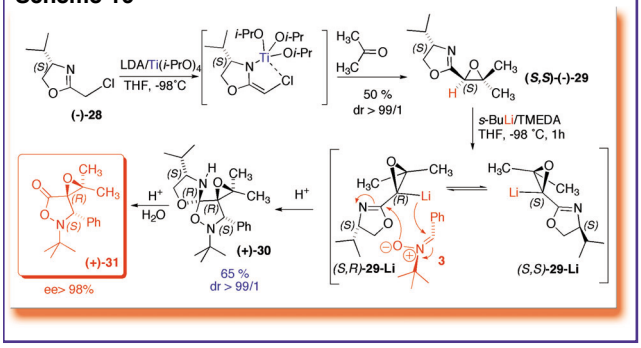
Scheme 4



It was interesting and quite intriguing to note that the reactions of a diastereomeric mixture of lithiated 2-(1-chloroethyl)-2-oxazolines (4*R*,1'*S*)/(4*R*,1'*R*)-**9-Li** and (4*S*,1'*S*)/(4*S*,1'*R*)-**11-Li** with nitrones occured highly stereoselectively and enantioselectively.

(3*R*,4*R*,7*S*,11*S*)-(+)-**30** as a single diastereoisomer in a very good yield (**Scheme 16**). The structure and absolute configuration of (+)-**30** was ascertained from 2D-NOESY correlations and finally confirmed by an X-ray analysis. The explanation for the observed diastereoselection resides in the way the li- thiated oxazolinyloxirane and the nitrone **3** interact each other. It is worth pointing out that the configuration at the C-3 of **30** was ascertained to be opposite (*R*) to that of the starting oxazolinyloxirane (*S,S*)-(-)-**29**,[26] testifying that an inversion had occurred at this carbon.

Scheme 16

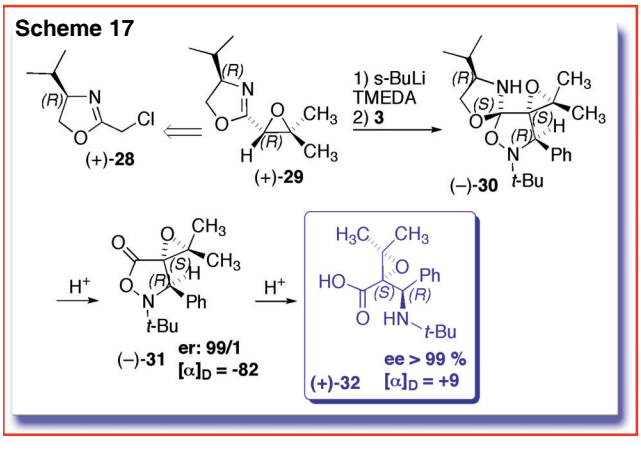


The configuration to the three newly created stereogenic centres is presumably established in the nucleophilic addition of the lithiated oxirane on the *re* face of **3**. Assuming that the lithiated oxiranes (*S,S*)-**29-Li** and (*S,R*)-**29-Li** may interconvert is, then, the diastereomeric lithiated oxirane (*S,R*)-**29-Li** (having the isopropyl group on the C-4 of the oxazoline ring far away from the oxirane C-Li bond) that preferentially reacts with the nitrone, for experiencing a lower steric hindrance producing (3*R*,4*R*,7*S*,11*S*)-**30**.

Treatment of (+)-**30** with aq oxalic acid afforded optically active 5-isoxazolidinone (+)-**31** highly enantioenriched (ee > 99 %) and in good yield (76 %).

Similarly, lithiation of oxazolinyloxirane (*R,R*)-(+)-**29** (dr 98/2, ee > 99 %, $[\alpha]_D$ = +79) (**Scheme 17**) followed by the addition of **3** furnished, via (3*S*,4*S*,7*R*,11*R*)-(-)-**30**, the enantiomeric 5-isoxazolidinone (-)-**31** in high optical purity (ee > 99 %, $[\alpha]_D$ = -82) and good yield (60 %); this one could be quantitatively reduced to the corresponding epoxy amino acid (+)-**32** (ee > 99 %, $[\alpha]_D$ = +9).

Scheme 17



In conclusion, novel dispirocyclic compounds, epoxyisoxazolidinones and α-epoxy-β-amino acids can simply and highly stereoselectively be obtained just combining the chemistry of lithiated oxazolinyloxiranes with that of nitrones, which are the nitrogen fragment sources.

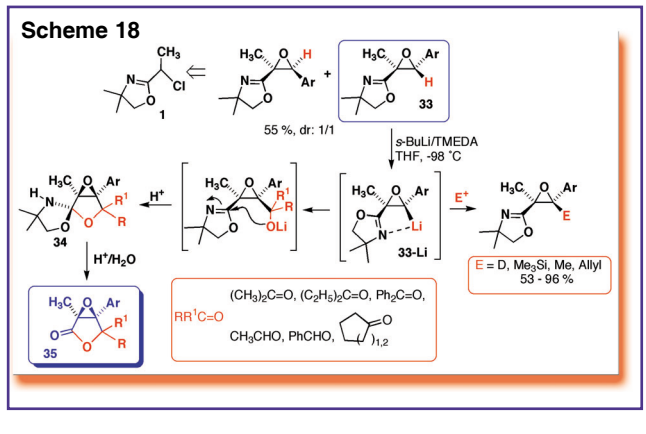
REACTION OF β–LITHIATED OXAZOLINYLOXIRANES: STEREOSELECTIVE SYNTHESIS OF α,β-EPOXY-γ-BUTYROLACTONES.

β-Lithiated oxazolinyloxiranes, generated by deprotonation of the corresponding oxazolinyloxiranes, showed a configurational stability that allowed the preparation of useful intermediates in organic synthesis such as α,β-epoxy-γ-butyrolactones.[20b] α,β-Epoxy-γ-butyrolactones, in particular, intervene in synthetic routes to precursors of natural products such as epolactaene, which has a potent neurite outgrowth activity in a human neuroblastoma cell line SH-SYS5,[27] of (+)-cerulenine, a potent fungal inactivator of fatty acid synthetase,[28] and of α-methylenebis-γ-butyrolactones.[29]

Lithiation of epoxides **33** (*s*-BuLi/TMEDA, Et_2O, -98 °C) (**Scheme 18**) produced oxiranyllithiums **33-Li**, which proved to be stable at low temperature for several hours. Trapping of **33-Li** with electrophiles (D_2O, MeI, Me_3SiCl and allyl chloride) afforded tetrasubstituted epoxides in good to excellent yields upon warming to room temperature and conventional work-up.

The stabilizing assistance to oxiranyllithiums **33-Li** is likely provided by both the oxazolinyl and the aryl groups. Lithium cation is probably coordinated by the aza-group of the oxazolinyl ring in lithiated species. β-Lithiation of substituted oxiranes has been recently described.[29] In all cases, the reaction of lithiated oxiranes proceeded stereospecifically with complete retention of configuration, thus proving the configurational stability of such lithiated species. Interestingly, the reaction of lithiated oxiranes **33-Li** with ketones afforded quite good yields of spirocyclic compounds **34**, whose structure was established on the basis of spectroscopic evidences. In all cases, in the FT-IR spectrum $\nu_{C=N}$ of the oxazoline ring (typically at 1660 cm^{-1}) was lacking and in the ^{13}C-NMR a resonance at ca. 118 ppm, characteristic of a sp^3 heterosubstituted carbon

Scheme 18

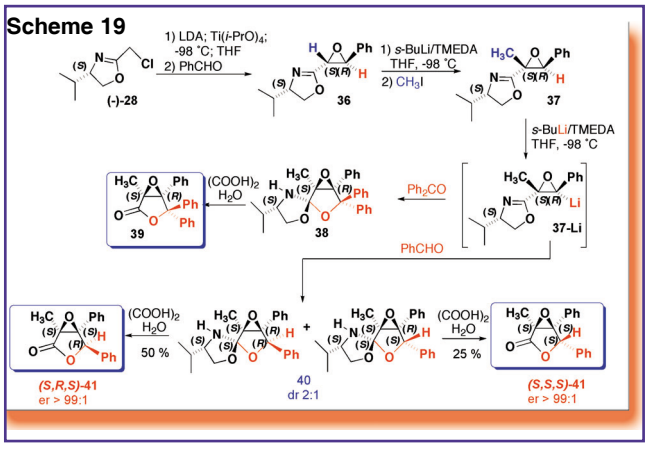


atom, was observed instead of the Csp^2 resonance of the C=N of the oxazoline ring.

The formation of spirocyclic compounds **34** could likely be explained with the nucleophilic addition of the intermediate alkoxides on the C=N of the oxazoline ring. Such a cyclization took place diastereoselectively furnishing just one diastereomer. This seems to indicate that the intermediate alkoxides, originated by the stereospecific reaction of **33-Li** with ketones, attack just one of the two diastereotopic faces of the oxazoline moiety.

The present oxazolinyloxiranyl anion-based methodology to epoxylactones has been successfully extended to the preparation of optically pure α,β-epoxybutyrolactones.[20b] Optically pure (*S,S,R*)-oxazolinyloxirane **36** was prepared from (*S*)-4-isopropyl-2-chloromethyloxazoline **(-)-28**, as reported.[25]

Scheme 19



2-Chloromethyl-2-oxazoline **(-)-28** was first lithiated, transmetalated with Ti(*i*-PrO)$_4$ and then reacted with benzaldehyde to furnish (*S,S,R*)-epoxide **36** the stereochemistry of which was assigned on the basis of the NMR data and unequivocally confirmed by an X-Ray analysis. Treatment of **36** with *s*-BuLi/TMEDA and trapping with CH_3I gave the trisubstituted epoxide **37** in a stereoselective way with complete retention of configuration at the α-carbon(**Scheme 19**).

Lithiation of **37** and reaction of **37-Li** with benzophenone produced spirocyclic compound **38** (only one diastereomer) in a good yield. Its hydrolysis with oxalic acid afforded quantitatively epoxylactone **39** with very good er value (**Scheme 19**). In the reaction of lithiated **37-Li** with benzaldehyde a mixture of two diastereoisomers (2:1 ratio) of spirocyclic compounds **40** was detected by ^{1}H NMR. These were separated and hydrolysed to give quantitatively diastereomeric epoxylactones (*S,R,S*)- and (*S,S,S*)-**41** with excellent er values.

CONCLUSION

The present work highlights the importance of lithiated oxazolines in synthetic organic chemistry for the preparation of new heterocyclic compounds. This new methodology is a reliable tool in the chemists' hands when a stereoselective synthesis of such compounds is needed. A future extension of the work will focus on the possibility to use this chemistry for the preparation of natural products or biological active molecules.

REFERENCIAS

1. For application of carbanions in asymmetric synthesis see: a) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A.; *Acc. Chem. Res.;* **2000**; *33*(10); 715-727. b) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282-2316. c) Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 716 - 738.

2. Meyers, A. I.; Reuman, M. *Tetrahedron* **1994**, *50*, 2297.

3. For applications of oxazolines in asymmetric synthesis and catalysis see: a) Jew, S.; Lee, Y.; Lee, J.; Kang, M. J,; Jeong, B.; Lee, J.H.; Yoo, M.; Kim, M.; Choi, S.; Ku, J.; Park H. *Angew. Chem. Int. Ed.* **2004**, *43*, 2382 -2385. b) Gossage, R. A.; Jenkins, H. A.; Yadav, P. N. *Tetrahedron Lett.* **2004**, *45*, 7689 - 7691. c) Capriati, V.; Florio, S.; Luisi, R. *Current Org. Chem.* **2004**, *8*, 1529 - 1545.

4. a) Florio, S.; Troisi, L.; Capriati, V. *J. Org. Chem.* **1995**, *60*, 2279. b) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781. c) Florio, S.; Troisi, L.; Capriati, V. *Tetrahedron Lett.* **1998**, *39*, 7951. d) Florio, S.; Troisi, L.; Capriati, V. *Tetrahedron Lett.* **2003**, *59*, 1381.

5. a) Capriati, V.; Florio, S.; Luisi, R.; Rocchetti, M. T. *J. Org. Chem.* **2002**, *67*, 759. b) Rocchetti, M. T.; Fino, V.; Capriati, V.; Florio, S.; Luisi, R. *J. Org. Chem.* **2003**, *68*, 1394.

6. a) Florio, S.; Lorusso, P.; Granito, C.; Ronzini, L.; Troisi, L. *Eur. J. Org. Chem.* **2003**, 4053. b) Florio, S.; Lorusso, P.; Luisi, R.; Granito, C.; Ronzini, L.; Troisi, L. *Eur. J. Org. Chem.* **2004**, 2118-2124.

7. Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9713-9719.

8. Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Tetrahedron* **2001**, *42*, 9183-9186.

9. a) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2002**, 2961-2969. b) Luisi, R.; Capriati, V.; Florio, S.; Piccolo, E. *J. Org. Chem.* **2003**, *68*, 10187.

10. Luisi, R.; Capriati, V.; Florio, S.; Vista, T. *J. Org. Chem.* **2003**, *68*, 9861-9864.

11. Abbotto, A.; Bradamante, S.; Florio, S.; Capriati, V. *J. Org. Chem.* **1997**, *62*, 8937.

12. a) Kamata, K.; Agata, I., Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113-3116. b) Meyers, A. I. J. *Heterocyclic Chem.* **1998**, *35*, 991, and ref. therein.

13. Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Tralli, C.; Troisi, L. *Synthesis* **2001**, *15*, 2299-2306.

14. Unpublished results.

15. a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996,** *79*, 913. b) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437.

REFERENCIAS

16. For reviews on the synthesis of β-amino acids, see: a) *Enantioselective Synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley-VCH:New York, 1997. b) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.***1999,** *6*, 983.

17. For some recent reviews on oxiranyl anions, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303-3325. (b) Mori, Y. *Rev. Heteroatom Chem.* **1997**, *17*, 183-211. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 12, 1625-1642. (d) Florio, S., Ed. Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry. *Tetrahedron* **2003**, *59*, 9683-9864.

18. a) Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2605-2608. b) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731-734. c) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557-4558. d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445-2448. e) Kuramochi, K.; Itaya, H.; Nagata, S.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 7367-7370.

19. a) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042-4050. b) Dunn, S. F. C.; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans. I* **1992**, 2863-2870. c) Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc. Chem. Commun.* **1988**, 645-647. d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835-4840. e) Yamauchi. Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4*, 173.

20. a) Capriati, V.; Favia, R.; Florio, S.; Luisi, R. *Arkivoc* **2003**, *(xiv)*, 77-86. b) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.,* **2002**, *4*, 1551.

21. Luisi, R.; Capriati, V.: Carlucci. C.; Degennaro, L..; R.; Florio, S. *Tetrahedron* **2003**, *59*, 9707-9712.

22. It has been reported that the reaction of the same oxiranyllithiums with aldehydes proceeded with very poor diastereoselectivity. See: Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409-417.

23. Luisi, R.; Capriati, V.: Carlucci. C.; Degennaro, L..; R.; Florio, S. *Org. Lett.* **2003**, *5*, 2723-2726.

24. a) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575-1578. b) Shindo, M.; Itoh, K.; Tsuchiya, C.; Shishido, K. *Org. Lett.* **2002**, *4*, 3119-3121.

25. Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2001**, 2035-2039.

26. The two lithiated diastereomeric species (*S,S*)-**29-Li** and (*S,R*)-**29-Li** equilibrate under the experimental conditions: see ref. 21.

27. Kuramochi, K.; Itaya, H.; Nagata, S.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 7367-7370.

28. Mani, N. S.; Townsend, C. A. *J. Org. Chem.* **1997**, *62*, 636-640.

29. Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T., Thonyoo, P. *J. Org. Chem.* **2001**, *66*, 4692-4694.

Congresos