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Diastereoselective Conjugate Additions of Ethoxyvinyllithium to Aromatic and α,β-Unsaturated Oxazolines†

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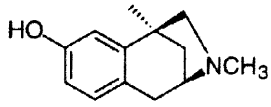
Summary: *Ethoxyvinyllithium (EVL) adds cleanly to unsaturated oxazolines, which upon hydrolytic work-up afford the corresponding ketones in high yields and excellent diastereoselectivity.*

Naphthyl oxazolines are good Michael acceptors[1] and have been used in the synthesis of natural products such as apanorphine (**1**)[2] and pododphyllotoxin (**2**).[3] This is an attractive strategy based on high yields and diastereoselectivities.



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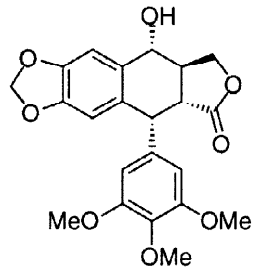

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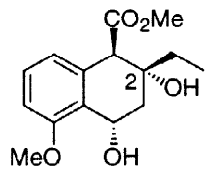

3

In a previous oxazoline based synthesis of the aklavinone AB-ring system (**3**) the incorporation of a methyl ketone at C-2 was accomplished *via* the addition of vinyllithium, followed by Wacker oxidation.[4] The product was then isolated in 72 % yield as a 14:1 ratio of diastereomers and the overall yield for the two synthetic steps was 58%. After α-hydroxylation, the methyl ketone was converted to the C-2 ethyl group. A more favorable approach would have introduced the methyl ketone, or its equivalent, in a direct manner. We now describe the first conjugate addition of an acyl anion equivalent to aromatic and unsaturated oxazolines.

† This paper is dedicated to the memory of Sir Derek H. R. Barton.

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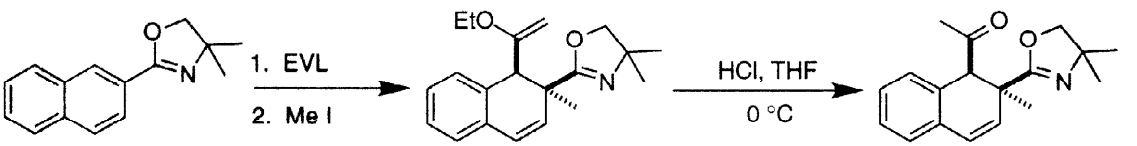
Ethoxyvinyllithium in the presence of HMPA (EVL•HMPA) has been shown to be effective for the *ortho*-lithiation of substituted aryloxazolines at low temperatures (-78 °C).[5] EVL•HMPA is also effective for the allylic deprotonation of dihydronaphthyloxazolines.[5] However, in the absence of HMPA and at higher temperatures (-10 °C), EVL has been found to undergo exclusive conjugate addition to naphthalenes. The reaction proceeded with complete diastereoselectivity (> 100:1) and excellent overall yield to the methyl ketone after hydrolysis (Scheme 1).

Scheme 1

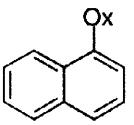
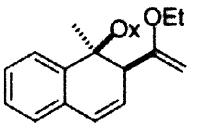
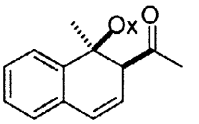
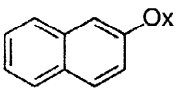
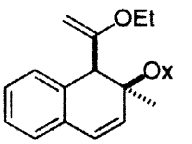
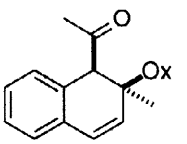
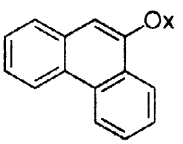
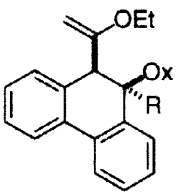
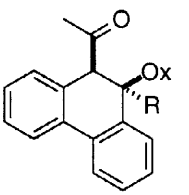
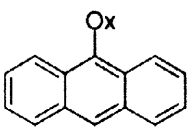
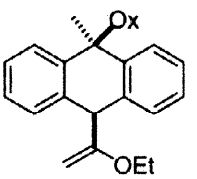
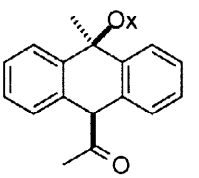
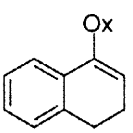
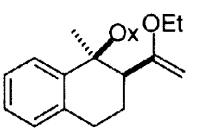
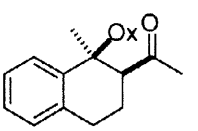


EVL added cleanly to oxazolines **4-8** to give the intermediate enol ethers (**9-13**). However, **9** was prone to decomposition, leading to disappointing yields of both **9** and the corresponding ketone **14**. Presumably the remaining C-C double bond has migrated toward conjugation and polymerization became a problem. However, the analogous dihydro derivative **13** was smoothly formed and hydrolyzed cleanly to the corresponding ketone **18** (*vide supra*). To avoid decomposition, the crude enol ethers were generally hydrolyzed without purification, although they could be isolated by column chromatography over neutral alumina. Only one diastereomer was observed by NMR and GC analysis of the crude addition mixtures. The relative stereochemistry of **13** was assigned by NMR coupling constant analysis and is consistent with previous oxazoline results which showed exclusively *trans*-addition. The remaining examples were assigned by analogy.

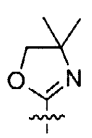
With the exception of **9**, acidic hydrolysis of the crude enol ethers provided the corresponding ketones (**15-18**) in good yield. Although epimerization of the α-carbon is possible, it was not observed. The ketones were formed in a completely stereoselective manner with retention of stereochemistry as confirmed by x-ray crystallographic analysis of ketone **18**.

To demonstrate further the potential of this new methodology, acetyl-oxazoline **16** (R = CH_3) was reduced with sodium borohydride to afford **19** as a single diastereomer.[6] Treatment of **19** with hydrochloric acid overnight afforded the lactone **20** in 77 % yield which led to three selective and

contiguous stereocenters (Scheme 2). Studies are currently underway to examine the absolute stereocontrol of EVL additions to chiral aromatic and unsaturated oxazoline substrates.

Substrate	Enol Ether	Ketone		Yield (%) Enol Ether	Yield (%) Ketone[1]
 **4**	 **9**	 **14**		50	16
 **5**	 **10**	 **15**		98	81
 **6**	 **11**	 **16**	R = CH_3 R = allyl	98	82 76
 **7**	 **12**	 **17**		97	84
 **8**	 **13**	 **18**		66	89

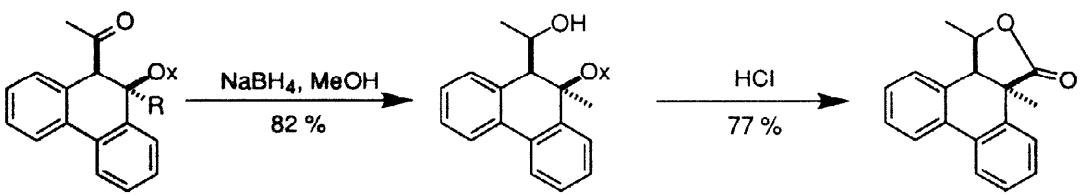
[1] Represents isolated yield from initial substrate without isolation of enol ether

Ox = 

General Procedure:

The starting oxazolines were prepared from the corresponding acids according to literature procedures.[1] Ethoxyvinyllithium was prepared from freshly distilled ethoxyvinyl ether (5 eq) by treatment with *tert*-butyllithium (5 eq) in THF. The resulting solution was then added *via* cannula to a stirred solution of the oxazoline (1 eq) in THF at -10 °C. After 24 h the electrophile (5.5 eq) was added and stirred 30 min followed by the addition of saturated aqueous ammonium chloride. After extracting (x2) with ethyl acetate and evaporating the solvents the crude vinyl ether was dissolved in a 3:1 mixture of HCl (1 M) and THF and stirred 30 min at 0 °C. Saturated sodium bicarbonate was then added and the aqueous phase extracted (x2) with ethyl acetate. The product (**13-17**) was isolated by column chromatography.

Scheme 2



16 (R = CH_3) **19** **20**

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References

1. a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. c) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 6437. d) Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 5714.
2. Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265.
3. Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.*, **1988**, *110*, 7854.
4. Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592.
5. a) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815. b) Shimano, M.; Meyers, A. I. *Tetrahedron Lett.* **1997**, *38*, 5415.
6. The relative stereochemistry of the newly formed center has not been determined.