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CLEAVAGE OF N-ACYL OXAZOLIDONES

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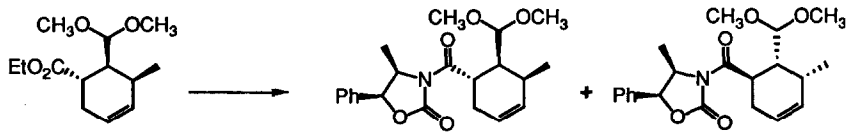
Abstract: A method has been developed to cleave sterically crowded N-acyl oxazolidones using benzyl mercaptan.

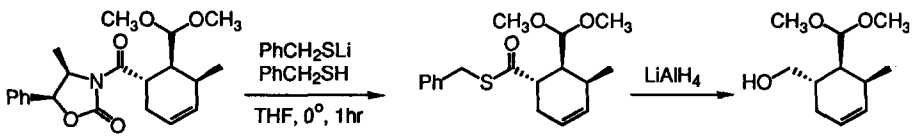
The use of chiral oxazolidones to induce asymmetry in a variety of reactions has been an important development in asymmetric synthesis[1-11]. We have used these auxialiaries successfully for the resolution of diastereomers produced in Diels-Alder reactions. However, subsequent removal of the chiral auxiliary has occasionally been difficult. In sterically congested situations, we have observed either a lack of reactivity or an inappropriate selectivity . For example, resolution of the cyclohexene derivative **1**[13,14] via the acyl oxazolidone gave **2** and **3**.



1 (Racemic) **2** **3**

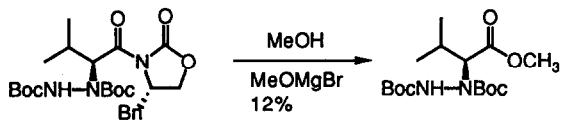
Attempted removal of the oxazolidone auxialiary from either **2** or **3** using lithium aluminum hydride, lithium borohydride, or a lithium benzyloxide system gave none of the desired product. The reductive methods led to attack at the oxazolidone carbonyl, whereas the lithium benzyloxide system led to complete recovery of starting material (2 hr at 0° C).

We find that the use of a benzyl mercaptide system derived from 2 equivalents of benzyl mercaptan and 1.5 equivalents of n-BuLi in THF at 0° C gives 90-94% yields of the desired thioesters which may then be reduced to alcohols with lithium aluminum hydride. The two-step sequence may be conveniently carried out in one pot without isolation of the thioester. Recovery of the chiral auxiliary is nearly quantitative.



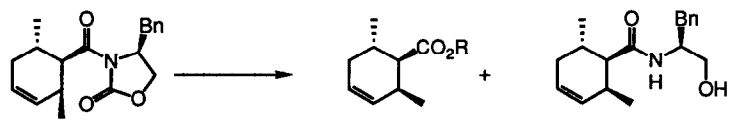
Methods for the conversion of thioesters directly to aldehydes have been reported which may enhance the value of this approach to oxazolidone cleavage.[12]

Reports of difficulties encountered in the cleavage of acyl oxazolidones have appeared before[4,5]. For example, methanolysis of the hydrazide **4** afforded **5** in only 12% yield, the remainder being derived from attack at the oxazolidone carbonyl center[5]. In this case, and in most other cases which we have seen reported, transesterification with the lithium benzyloxide system was successful.



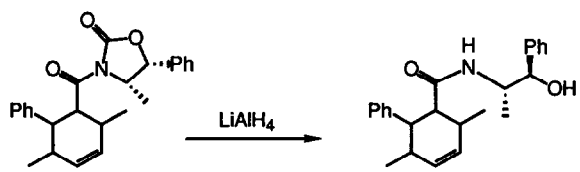
4 **5**

Subsequent to the completion of our own work, Evans reported the successful hydrolysis of sterically hindered carboximides with lithium hydroperoxide.[3b,8] His "worst case" involved the hydrolysis of the Diels Alder adduct **6** which gave none of the desired product with the lithium benzyloxide method, but gave a 76% yield of exocyclic cleavage with lithium hydroperoxide .

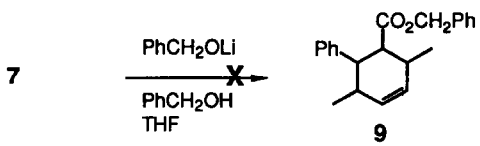


6	LiOOH	78%	16%
	LiOBn	0%	100%
	LiOH	0%	100%

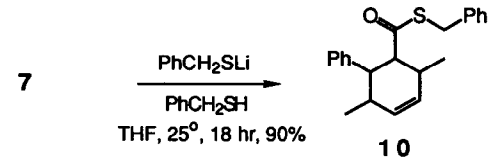
In a structurally related and even more sterically hindered case, we have found that treatment of the cinnamate-derived cyclohexene **7** (a mixture of isomers)[15,16] with lithium aluminum hydride gave an 81% yield of the hydroxy amide **8**. Treatment with the lithium benzyloxide system gave a mixture of products which were not completely characterized. However, the desired ester (**9**) was not among them. The use of the benzyl mercaptide system gave better than 90% of the desired thioester **10**, with only about 6% of product derived from attack at the endocyclic carbonyl.



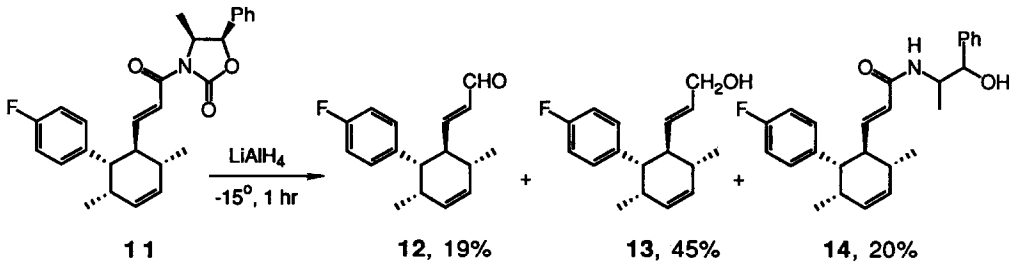
7 **8**

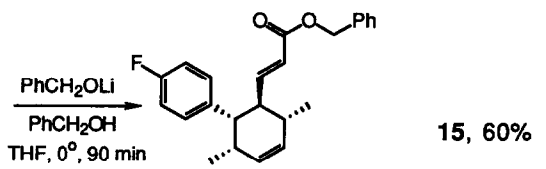


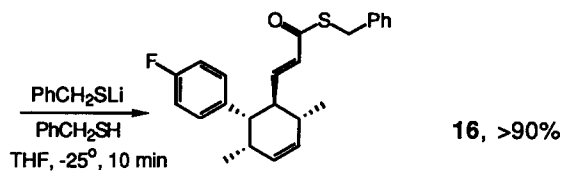
7 **9**



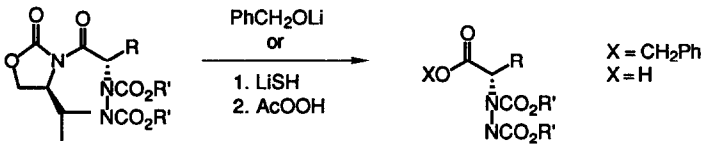
Cleavage of the unsaturated system **11**[16,17] with lithium aluminum hydride gave about 21% of the hydroxy amide **14** with mediocre (but unoptimized) yields of desired products. The benzyl alkoxide system worked reasonably well, but with lower yields than were obtained with the benzyl mercaptan system. No products arising from 1,4-addition were observed in these reactions.







Thus, in sterically demanding situations, cleavage of acyl oxazolidones may proceed with difficulty with the standard methods, providing low, or in some cases, no yields of the desired products. In our hands, this problem was solved cleanly through the use of a lithium benzyl mercaptide system in a fashion analogous to that described for the use of the lithium benzyl oxide system. The lithium benzyl mercaptide system displays a much greater exocyclic cleavage regioselectivity than other methods we have tried. Furthermore, although detailed kinetic studies were not undertaken, rates of reaction of this system were much greater than for the lithium benzyloxide system even in cases where the latter system worked well. We have seen only one other example of the use of sulfur nucleophiles to effect this type of cleavage.[9] In this case, (conversion of **17** to **18**) the problem encountered was racemization of the product formed after transesterification with lithium benzyl oxide rather than attack at the oxazolidone carbonyl.



17 18

This result, together with our own, suggest that, in sterically hindered cases, and in cases where racemization is of concern, the use of the highly nucleophilic, less basic mercaptide anion system may offer advantages over the lithium benzyloxide system. We are unable to offer a convincing mechanistic rationale for the greater exo-selectivity of the mercaptide system. However, the discussion by Evans and co-workers of the lithium hydroperoxide results may have relevance for our own results.[8]

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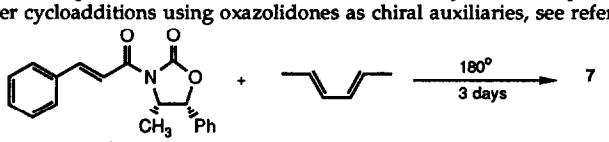
15) Prepared via thermal, uncatalyzed Diels-Alder cycloaddition of 2,4-hexadiene with the chiral cinnamoyl derivative **19**. The reaction proceeded without useful stereoselectivity. For examples of highly stereoselective, catalyzed Diels-Alder cycloadditions using oxazolidones as chiral auxiliaries, see reference 3.



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16) U.S. Patent 4,876,280, Oct. 24, 1989.
17) Structure determined by X-ray crystallography by Mr. A. Widmer, Sandoz, Ltd., Basle, Switzerland.

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