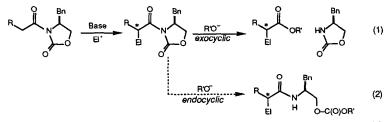# CONTRASTERIC CARBOXIMIDE HYDROLYSIS WITH LITHIUM HYDROPEROXIDE

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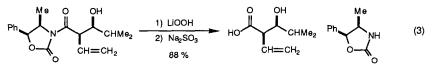Harvard University
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Abstract: The use of lithium hydroperoxide for the highly regioselective hydrolysis of a range of carboximides is described. Numerous cases are provided where the regioselectivities exhibited by this reagent are dramatically different than the complementary reactions with hydroxide.

Substituted oxazolidone heterocycles have proven to be versatile chiral auxiliaries for the construction of enantiomerically pure substances (eq 1). Enolates derived from their N-acyl conjugates have been documented to react with a variety of carbon and heteroatomic electrophiles with high diastereoselection, which has led to the development of practical methods for asymmetric enolate alkylation,[1] acylation,[2] amination,[3] azidation,[4] bromination,[5] hydroxylation,[6] and aldol addition.[7] Similarly, α,β-unsaturated N-acyloxazolidones have proven to be useful dienophiles in Lewis-acid catalyzed Diels-Alder reactions.[8] The utility of these chiral carboximides for the construction of complex molecules largely depends on the availability of mild, selective methods for the nondestructive removal of these chiral hetrocycles without attendant racemization of the newly created stereocenter(s). In this Letter we wish to report the exceptional selectivity and reactivity displayed by lithium hydroperoxide for oxazolidone "deacylation", rendering it the reagent of choice for chiral auxiliary removal from imides in which exocyclic carbonyl reactivity is supressed due to steric hindrance (*vide infra*). The site of nucleophilic cleavage of N-acyloxazolidones is subject to both steric and electronic factors. In the absence of significant steric crowding in the vicinity of the exocyclic carbonyl function, electronic factors direct hydrolysis or transesterification in the desired fashion affording the newly constructed carboxylic acid derivative along with recovered chiral auxiliary (eq 1). However, as the steric requirements of the R group are elevated, increasing competition from the unwanted reaction involving reagent attack at the endocyclic auxiliary carbonyl is observed (eq 2).
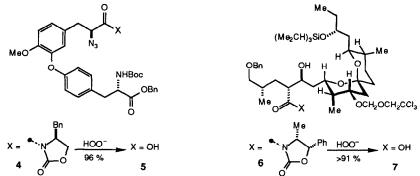

We have previously described methods for the racemization-free removal of the chiral auxiliary via transesterification (LiOBn,[1] Ti(OBn)$_4$,[5] BrMgOMe[6]), transamination (Me$_2$AlN(OR)R),[9] hydrolysis (LiOH),[5] and reduction (LiBH$_4$).[7b] Of these reagents, lithium benzyloxide has proven to be the most generally useful oxygen nucleophile which displays the greatest exocyclic carbonyl regioselectivity for the most sterically congested substrates.[10]

During a recent study in which we sought nonreductive methods for the deacylation of the very sensitive crotonate imide aldol adducts (eq 3), it was noted that the LiOOH mediated hydrolysis not only resulted in the supression of olefin conjugation, which is a major problem with more basic reagents, e.g. LiOH, but also afforded excellent regioselectivity for the desired mode of hydrolysis.[7b]
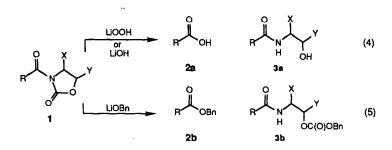

$$\text{(3)}$$

The data in the Table illustrate the important extensions of this reaction and document the finding that *LiOOH displays greater exocyclic cleavage regioselectivity than all reagents previously examined, and that this phenomenon is general for all classes of oxazolidone-derived carboximides as yet encountered.* The substrates studied are representative of the most sterically hindered examples of each class of carboximides that we have prepared. The superiority of the LiOOH protocol (eq 4), to both LiOH hydrolysis and the experimentally less convenient LiOBn transesterification is readily apparent. In all cases, the recovered yield of the oxazolidone chiral auxiliary, isolated by a simple extraction procedure (*vide infra*), corresponded closely to the isolated yield of the carboxylic acid 2. An impressive example of the exceptional insensitivity of LiOOH to substrate steric effects is provided by the Diels-Alder adduct (entry C). This imide, which can be viewed as a "worst-case" substrate, afforded exclusively oxazolidone ring cleavage products with all nucleophilic reagents tried except LiOOH, which afforded the desired carboxylic acid in 76% yield along with a 72% recovery of the chiral auxiliary.

The suitability of this method of oxazolidone deacylation for complex natural product synthesis is illustrated by the additional examples provided below. The conversion of 4 to 5 in 96% yield demonstrates the exceptional chemoselectivity of LiOOH for carboximide hydrolysis in the presence of unactivated esters.[11] The high yield of 7 obtained from the LiOOH mediated hydrolysis of aldol adduct 6 is in direct contrast to the mediocre result obtained on attempted transamination (Me_3Al, MeONHMe-HCl) of this substrate.[12]

A general experimental procedure for peroxide mediated hydrolysis is as follows. A 0.05 M solution of the substrate in 3:1-THF/H_2O[13] is treated at 0 °C with 4-8 equiv of 30% H_2O_2 followed by 2.0 equiv of LiOH. The resulting mixture is stirred at 0-25 °C until the substrate has been consumed (<15 min–15 h), and the excess peroxide (peracid) is quenched at 0 °C with a 10% excess of 1.5 N aq Na_2SO_3. After buffering to pH 9-10 with aqueous $NaHCO_3$ (optional) and evaporation of the THF, the oxazolidone chiral auxiliary is recovered by CH_2Cl_2 extraction. The carboxylic acid is isolated by EtOAc extraction of the acidified (pH 1-2) aqueous phase.
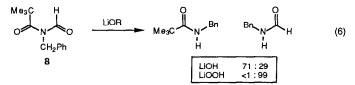
$$\text{1} \xrightarrow[\text{or}]{\text{LiOOH}}\text{LiOH} \quad \text{2a} \quad \text{3a} \qquad (4)$$

$$\text{1} \xrightarrow{\text{LiOBn}} \quad \text{2b} \quad \text{3b} \qquad (5)$$

Table. Hydrolysis and Transesterification of N-Acyloxazolidones **1** (eq 4,5).[a]

Entry	Substrate (1)	Reagent	Yield 2, %[b]	Yield 3, %[b]
A		LiOOH	91	6
		LiOBn	51	--
		LiOH	16	76
B		LiOOH	98	1
		LiOBn[c]	52	33
		LiOH	42	52
C		LiOOH	76	16
		LiOBn	0	100[d]
		LiOH	0	100
D		LiOOH	96	4
		LiOH	6	89
E		LiOOH[e]	93	3
		LiOH	14	86
F		LiOOH	98	<1
		LiOH	43	30
G		LiOOH	76[f]	8
		LiOH	2[f]	98

[a] LiOOH hydrolyses were performed as indicated in the text. LiOH hydrolyses were conducted under directly analogous conditions in the absence of HOOH. LiOBn transesterifications were conducted in THF at -50 °C as previously described (ref. 1). [b] Isolated yield of enantiomerically (diastereomerically) pure (>99:1) product. [c] Reaction run at -70 °C. [d] Combined yield of **3a** + **3b**. [e] LiOOH hydrolysis of the unsilylated substrate gave extensive intramolecular acyl transfer. [f] Isolated yield of oxazolidone.

The complementary regioselectivity exhibited by LiOOH and LiOH in carboximide hydrolysis is not limited to cyclic cases (eq 6). *Thus, while basic hydrolysis of the acyclic imide 8 led to the anticipated preferential cleavage of the formyl moiety by a 71:29 ratio, LiOOH afforded >99:1 selectivity for cleavage of the pivaloyl group.* These rather surprising results suggest that the pivaloyl carbonyl in **8**, while being sterically hindered, might be electronically activated due to A-1,3 strain interactions which destabilize those planar imide conformations neccessary for effective resonance interaction with the formamido group.

LiOH	71 : 29
LiOOH	<1 : 99

(6)

The origin of the extraordinary insensitivity of LiOOH to steric hindrance in carboximide hydrolysis is intriguing; however, the development of a mechanistic model supported by control experiments is beyond the scope of this study. Nonetheless, some qualitative observations are in order. For example, by virtue of the lower basicity of HOO^- (pK_A (HOOH) = 11.6 vs pK_A (HOH) = 15.8), attack by this nucleophile on the imide carbonyl would be expected to be more reversible than that of HO^-.[14] Thus, as a working model, *we feel that while the regioselectivity of HO^- mediated hydrolysis may be governed by the relative rates of formation of the two tetrahedral intermediates, the regioselectivity of HOO^- cleavage might be determined by their relative breakdown rates, which should be comparatively insensitive to steric effects.* In addition, HOO^- should be an effectively smaller nucleophile than HO^- in aqueous solution as a consequence of its substantially smaller solvation energy.[15]

References and Notes

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10) Aldol adducts generally give significantly higher yields with the Weinreb transamination method (ref. 9.).
11) While normal esters (i.e. EtOAc) are unreactive toward HOO^-, active esters (e.g. PhOAc) react with a 400-fold rate enhancement relative to that of HO^- : Wiberg, K. B. *J. Am. Chem. Soc.* **1955**, *77*, 2519-2522. Also see ref. 14.
12) Levin, J. I.; Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, *12*, 989-993. We thank Dr. Todd Jones for these results.
13) To minimize possible side reactions resulting from hydroxy radical formation due to trace transition metals, we have routinely employed BHT-stabilized THF and redistilled water.
14) For a discussion of this point as it pertains to ester hydrolysis see: Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622-2637.
15) Recent results, theoretical as well as experimental, suggest that differential solvation may be totally responsible for the enhanced nucleophilicity of HOO^- over that of HO^-, the so called alpha-effect. See: Evanseck, J. D.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1987**, *109*, 2349-2353 and references contained therein. For a critical review on the origin of the alpha effect see: Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *26*, 313-319.