5H-Oxazol-4-ones as Building Blocks for Asymmetric Synthesis of α-Hydroxycarboxylic Acid Derivatives

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5H-Alkyl-2-phenyl-oxazol-4-ones **3**, though differing from 4H-4-alkyl-2-phenyl-oxazol-5-ones (commonly known as azlactones) only in the relative position of oxygen and nitrogen atoms, are a greatly overlooked and underutilized class of heterocycles.[1] We saw in them a potential class of nucleophiles that would provide easy access to α-hydroxy acids.[2] Our recent success in Mo-catalyzed AAA to control diastereo- and enantioselectivity at the nucleophile using azlactones[3] led us to expect similar results with "oxalactims".[4] Due to the dearth of information in the literature with regards to a general synthesis of oxalactims, we decided to implement a simple two-step process to make them, as shown in Scheme 1.[5] α-Bromo acid halides are condensed with benzamide in the presence of pyridine at 60 °C to form diamide **2**. Oxalactims can then be obtained from cyclization of **2** in DMA containing sodium fluoride with microwave irradiation at 180 °C in under 10 min in 44–82% yields.

Scheme 1. Synthesis of 5H-Alkyl-2-phenyl-oxazol-4-one (Oxalactims)
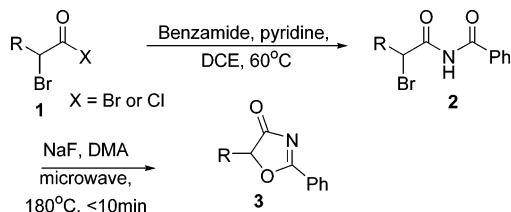
Initial studies examined the reaction shown in eq 1 with Ar = Ph and R = CH₃. Due to its past history of clean generation of enolates, we relied on hexamethyldisilamide (HMDS) as the base. Lithium turned out to be the counterion of choice, giving higher yield, regio-, diastereo-, and enantioselectivity over both sodium and potassium, as shown in Table 1.
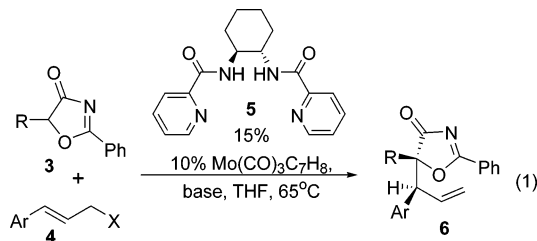
Carbonate served as a better leaving group than phosphate. Thus, reaction of the lithium enolate of methyl oxalactim with methyl cinnamyl carbonate gave 91% yield of the desired adduct with a branched-to-linear ratio of 99:1. The diastereomeric ratio of the branched product was 11.5:1, and the major diastereomer had an enantiomeric excess of greater than 99%. The branched-to-linear ratio as well diastereomeric ratio were determined using ¹H NMR, whereas chiral HPLC was used to determine the enantiomeric excess.

Table 1. Optimization of Mo–AAA Using Methyl Oxalactim

entry	X	base	yield	b/l	dr	ee
1	OCO₂CH₃	KHMDS	88%	6.7:1	1.4:1	80%
2	OCO₂CH₃	NaHMDS	80%	24:1	2.7:1	98%
3	OCO₂CH₃	LiHMDS	91%	99:1	11.5:1	>99%
4	OP(O)(C₂H₅)₂	LiHMDS	90%	7:1	8.1:1	96%

Table 2. Mo–AAA of Oxalactims

Entry	Ar[a]	R	Yield(%)[b,c]	b/l[d]	dr	ee(%)
1	(MeO, OMe aryl)	CH₃	82(91)	12:1	18:1	>99
2[e]	(o-Br aryl)	CH₃	78	27:1	24:1	99
3	(cyclohexenyl)	CH₃	54(73)	12:1	12:1	98
4	(isobutenyl)	CH₃	77	14:1	12:1	89
5	Ph	(n-butyl)	86	49:1	9:1	>99
6	Ph	(allyl)	97	8:1	10:1	>99
7	(thienyl)	(isopropyl)	89(96)	14:1	10:1	99
8	Ph	(tert-butyl)	70(90)	5.5:1	20:1	>99
9	Ph	(cyclohexyl)	74(89)	9:1	12:1	>99
10	Ph	(benzyl)	84(99)	--[f]	7.4:1	>99

[a] In all cases X = OCO₂CH₃. [b] Yield in parentheses based on recovered starting material. [c] All reactions were worked up after 16 h. [d] b/l = branched to linear regioisomeric ratio. [e] Substrate was
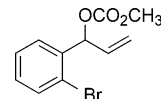
[f] b/l > 95/5.

Conditions shown in entry 3 of Table 1 were adopted as the standard for further exploration of the reaction. Variation of Ar and R substituents, as in eq 1, with carbonate as the leaving group gave us results summarized in Table 2. In all cases except entry 4, enantiomeric excesses of 98% or higher were observed. Even the racemic substrate (entry 2), which is usually prone to give lower ee values than its linear counterpart, worked well. The nonaromatic substrates (entries 3, 4) also functioned well under these reaction
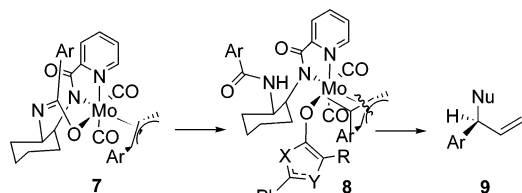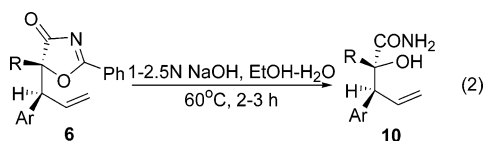
Figure 2. Stereochemistry at the nucleophile.

Table 3. Hydrolysis of Oxalactims to α-Hydroxy Amides

	Ar	R	Yield		Ar	R	Yield
1	Ph	CH₃	79%	3	[thiophene]	[isopropyl]	86%
2	[o-Br-phenyl]	CH₃	82%	4	Ph	[isopropyl]	77%

to the nucleophile as well as the electrophile. A useful feature of the AAA is the presence of a double bond in the product, which allows for further structural elaboration. For example, combining an AAA with a ring-closing metathesis provides access to chiral cyclic products (eq 3). The product of Table 2, entry 6, can undergo ring-closing metathesis, yielding cyclic hydroxy carboxamides after hydrolysis. This represents the first example of using 5-alkyl-2-phenyl-oxazol-4-ones (oxalactims) as nucleophiles, leading to facile asymmetric synthesis of tertiary α-hydroxy acids.

Supporting Information Available: Full experimental procedures, synthesis of oxalactims, and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Figure 1. Stereochemistry at the electrophile.

conditions, though showing a slight loss in diastereoselectivity. The lower ee observed in entry 4 appears to be a characteristic of this particular substrate.[6] There appears to be some steric effect on the regioselectivity with some loss as the size of the R group increases (entries 5–9). Curiously, the benzyl group (entry 10) gives virtually a single regioisomer in contrast to the isobutyl substituent (entry 7). We believe this may be due to the fact that it can rotate edgewise in a fashion so as to present very little steric bulk.

Even though the relative and absolute stereochemistry of these compounds is yet to be determined, a rationale consistent with our results in the Mo-catalyzed reaction of azlactones as well as Pd-catalyzed reactions of these oxalactims provides a reasonable basis for its assignment. The structure of the metal bound π-allyl is as shown in Figure 1, **7**.[7–9] With the approach of the nucleophile, the weakly bound amide carbonyl group of the ligand is dissociated and the nucleophile takes its place as in **8**. The nucleophile is then internally delivered, to result in the stereochemistry at the electrophile as observed in **9**. The nucleophile itself can approach the electrophile from either of its two faces as shown in Figure 2. Path A is clearly favored as the least sterically demanding in the transition state, hence resulting in the stereochemistry at the nucleophile as depicted. This hypothesis is supported in the case of azlactones (X = O, Y = N) by the X-ray structure, and the stereochemical outcome is as shown.[3]

Products from the Mo–AAA reaction could be easily opened to the corresponding α-hydroxy amides (eq 2) by treatment with 1 N NaOH in ethanol at 60 °C. Some examples are shown in Table 3.

The corresponding carboxylic acids can, in turn, be uneventfully obtained by diazotization of the primary amides by treatment at room temperature with isoamyl nitrite in anhydrous 1,4-dioxane and 2 M HCl in diethyl ether.[10]
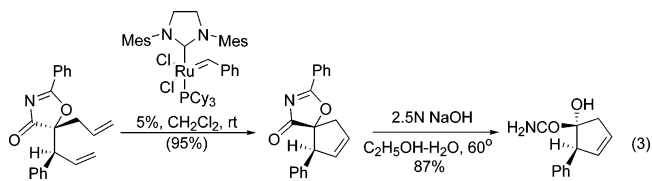
The high levels of regio-, diastereo-, and enantioselectivity demonstrated in the Mo-catalyzed AAA reactions of oxalactims as the nucleophile gives easy access to unusual α-hydroxy acids. It should be noted that excellent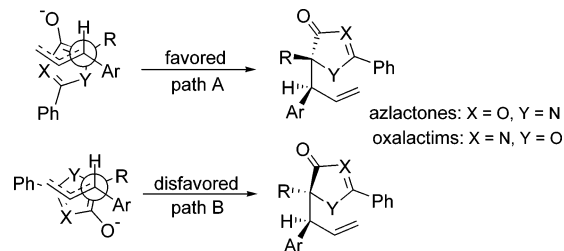 stereocontrol occurs both with respect