Highly Stereoselective Synthesis of α-Alkyl-α-Hydroxycarboxylic Acid Derivatives Catalyzed by a Dinuclear Zinc Complex**

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Direct, highly diastereo- and enantioselective catalytic construction of all-substituted carbon stereocenters adjacent to carbonyl groups through addition of α-disubstituted carbonyl compounds to unsaturated bonds is still a challenging feat, and successful examples are limited to the use of nucleophiles that are singly activated by a mesomeric electron-withdrawing group.[1–3] The dinuclear zinc–ProPhenol complex has shown remarkable efficiency and stereoselectivities in carbon–carbon bond-forming processes that involve enolates, such as aldol reactions,[4] Mannich-type reactions,[5] and nitro-Michael reactions.[6] Despite the synthetic utility of 5H-oxazol-4-ones as α-alkyl-α-hydroxy ester surrogates, there have been relatively few reports[7] of their employment as nucleophiles since we first disclosed their use in a catalytic asymmetric allylic alkylation.[8] Herein we describe a highly diastereo- and enantioselective nitro-Michael reaction of 5H-oxazol-4-ones that forms all-substituted carbon stereocenters and does not require the use of pre-functionalized enolate precursors.[9,10]

We commenced our studies by examining the addition of 5-methyl-2-phenyloxazol-4(5H)-one to β-nitrostyrene catalyzed by the dinuclear zinc–ProPhenol complex. Gratifyingly, the desired product could be obtained in more than 95% yield as determined by 1H NMR spectroscopy, albeit with little stereocontrol after brief optimization studies (d.r. = 2.4:1, 46% ee for the major diastereomer, [Eq. 1]).

An advantage of the ProPhenol ligand is its modularity, because its diarylcarbinol substructure allows a systemic variation (Scheme 1). Slightly electron-deficient ligands L2 and L3 improved the d.r. to 3:1 without affecting the yield and enantioselectivity. Ligand L3, which bears a strongly electron-withdrawing trifluoromethyl group, decreased the reactivity of the catalyst, presumably because of its decreased Brønsted basicity. However, in this case the diastereoselectivity was increased to 4.1:1, albeit with a significant loss of enantioselectivity. With even more electron-deficient ligand L5, the product was obtained in poor yield but with excellent

Scheme 1. Impact of the ligand structure on reactivity and stereoselectivity. All reactions were run on a 0.125 mmol scale. Catalyst preparation: Et2Zn in hexanes (1 mL, 12.5 μL, 10 mol%) was added to a solution of the ligand (5 mol %) in THF, and the resulting yellow solution was stirred for 30 min at RT. Catalysis: The catalyst solution was added to a solution of β-nitrostyrene (20.5 mg, 0.1375 mmol, 1.1 equiv) and 1 (21.9 mg, 0.125 mmol, 1.0 equiv) in propionitrile, and the reaction was stirred for 16 h at RT. Yields were determined by 1H NMR spectroscopy with mesitylene as internal standard. The diastereomeric ratios were determined by 1H NMR analysis of the crude mixture. The ee values were determined by HPLC analysis.

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diastereoselectivity. Notably, the sense of enantioinduction was reversed. With a ligand that bears pentafluorophenyl substituents (L6), low reaction efficiency was observed and the major diastereomer was obtained as a racemate. A ligand with 1-naphthyl groups (L7) gave a significantly improved ee value (79%), although the d.r. was low (1.9:1). To our delight, the reaction proceeded to complete conversion with an excellent d.r. (15.6:1) and ee value (88%) by using ligand L8, which possesses the corresponding 2-naphthyl rings.

We next optimized the aryl group of oxazolone (Scheme 2). A methyl group as well as a tert-butyl group at the para position of the phenyl ring decreases the diastereomeric and enantioselectivity. The para-methoxy and para-bromo derivatives behaved similarly to the para-methyl nucleophile (3 vs. 5 and 6). Product 7 with a 3,5-dimethoxyphenyl group was obtained with a much lower diastereoselectivity, but the ee value was comparable to that of the parent phenyl system (88% ee). Product 8 was obtained with d.r. = 14:0:1 and an excellent ee value (90%) by switching to the 2-naphthyl substituent. The oxazolone with the para-methylphenyl group gave product 9 with d.r. = 18:2:1, 90% ee (d.r. > 19:1, 93% ee).

With optimized conditions in hand, the scope of the nitro olefins was examined (Scheme 3). Performing the reaction with the para-tolyl substrate gave 10 in 97% yield, d.r. > 19:1, and 92% ee. When the reaction was conducted in propionitrile under higher dilution conditions (0.08 M), even higher stereoselectivities were obtained (d.r. > 19:1 and 93% ee).

This effect was even more pronounced by a nitro group (14, 76% yield, d.r. = 3:1.1, 64% ee). The variety of meta substituents were well tolerated, giving the corresponding products (15-18) in excellent yields and with high degrees of stereoselectivity. Notably, the reaction proceeded on a 0.125 mmol scale without any deleterious effect to give compound 16, and its enantiopurity could be upgraded to 99% ee through recrystallization. In contrast, substrates with ortho substituents are more challenging. Significantly decreased enantioselectivities were observed when the corresponding ortho-tolyl and 1-naphthyl substrates were employed (44% ee).
for 19 and 56% ee for 20, respectively), although the reactivity was good. The reaction with ortho-fluorophenyl nitro olefin showed much better enantioselectivity (70% ee for 21). This result clearly indicates that the steric bulk at the ortho position is deleterious for enantioinduction. Heteroaromatic substrates were well tolerated. The 2- and 3-furyl substrates as well as substrates that bear a thiophene moiety gave the corresponding products (22–25) in excellent yields with good stereoselectivities. The N-Boc-protected 3-indole nitro olefin afforded product 26 with 84% ee despite the fact that the substrate is ortho substituted; in this case, the detrimental effect of ortho substitution on enantioselectivity is diminished by the smaller ring size. Ferrocene-containing product 27 was obtained with d.r. > 19:1 and 98% ee. The absolute configuration of 27 was unambiguously established as (R,R) by single crystal X-ray analysis (Figure 1).

The α,β,γ,δ-unsaturated nitro olefin gave product 28 in 97% yield with d.r. = 12.6:1 and 92% ee. An aromatic group at the terminal carbon atom of the diene is not required, as excellent enantioselectivities. A synthetically versatile alkyne substrate was converted to product 35. Even the substrate with a zincaphilic sulfide was tolerated and gave desired product 36 with excellent stereoselectivities.

The combination of 5-allyloxazolone and α,β,γ,δ-unsaturated nitro olefin gave diene 37, which was cleanly meta-sized to spirocyclic cyclopentene 38 [Eq. (2)]. The oxazolone ring was opened to α-hydroxy carboxamide 39 with base.[13]

In summary, we have developed a highly stereoselective addition reaction of 5-allyloxazole-(4(SH))-ones to various nitro olefins. This process provides a range of highly functionalized α-alkyl-α-hydroxycarboxylic acid derivatives in high yields. It is notable that the stereoselective event was uniquely enabled by L8, which has not yet been used as a ligand in catalytic asymmetric transformations. This dramatic differential effect imparts great potential to the ProPhenol family of ligands and emphasizes the critical role that the modularity of this ligand may play in optimizing the design of the chiral space for asymmetric induction. Further studies employing such α-disubstituted nucleophiles are currently under way and will be reported in due course.

![Figure 1](image)

**Figure 1.** Single crystal X-ray diffraction analysis of 27. Thermal ellipsoids at 50% probability.

**Scheme 4.** Scope of 5-allyloxazole-(4(SH))-ones. All reactions were run on a 0.125 mmol scale under the conditions described in Scheme 1 with L8 (0.08 mmol) in propionitrile. Yields of isolated products are given. The diastereomeric ratios were determined by 1H NMR analysis of the crude mixture. The ee values were determined by HPLC analysis. [α]-nitrostyrene:oxazolone 1:1 [0.1375 mmol].

**Experimental Section**

Catalyst Preparation: (S,S)-L8 (5.2 mg, 6.25 μmol, 5 mol%) was weighed in a flame-dried microwave vial and the vial was sealed with a rubber septum, carefully evacuated, and back-filled with nitrogen (× 2), evacuated once again and back-filled with argon. Freshly distilled THF (0.07 mL) was injected into this vial and Et2Zn (1.2 mmol, 10 mol%) was added by a microsyringe at RT. The resulting yellow solution was stirred for 30 min at RT.

**Catalysis:** Oxazol-(4(SH))-one (0.125 mmol, 1.0 equiv) and nitro olefin (0.138 mmol, 1.1 equiv) were weighed in a flame-dried culture tube and the tube was sealed with a rubber septum, carefully evacuated, and back-filled with nitrogen (× 2), evacuated once again and back-filled with argon. Propionitrile (0.15 mL) was injected into...
the vial and the catalyst solution was subsequently added with vigorous stirring at RT. After 16 h, the reaction was diluted with ether (2 mL), quenched with 5% KH₂PO₄, and diluted with H₂O (1 mL). The mixture was stirred for 5 min at RT and the phases were separated. The aqueous phase was extracted with ether (3 x 1.5 mL) and the combined organic phases were concentrated. The crude material was analyzed by ¹H NMR spectroscopy in order to determine diastereoselectivity. The recovered crude material was purified by flash column chromatography on silica gel typically using a mixture of petroleum ether/EtOAc = 5:1 as eluent.

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A dinuclear zinc–ProPhenol catalyst enables highly enantioselective nitro-Michael reactions with oxazol-4(5H)-ones as nucleophilic substrates (see scheme, Nap = 2-naphthyl). This work highlights the utility of the ProPhenol family of ligands. The modular nature of these ligands proved crucial in the optimization of reaction conditions to achieve excellent stereoselectivities.