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Asymmetric Catalysis

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

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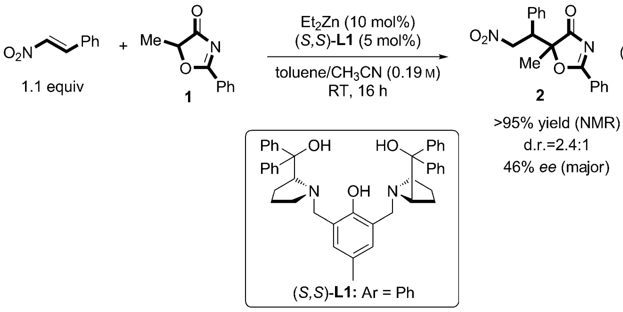
Direct, highly diastereo- and enantioselective catalytic construction of all-substituted carbon stereocenters adjacent to carbonyl groups through addition of α-disubstituted carbonyl compounds to unsaturated bonds is still a challenging feat, and successful examples are limited to the use of nucleophiles 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 5*H*-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 5*H*-oxazol-4-ones that forms all-substituted carbon stereocenters and does not require the use of pre-functionalized enolate precursors.[9,10]



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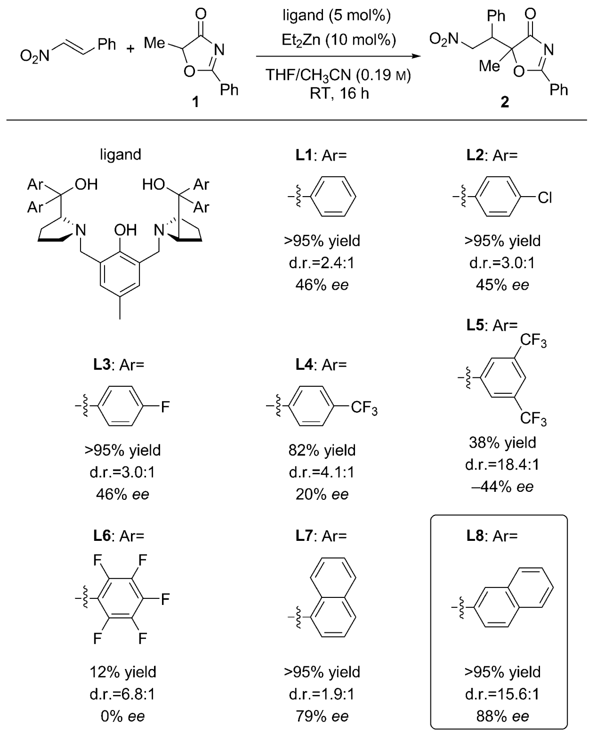
We commenced our studies by examining the addition of 5-methyl-2-phenyloxazol-4(5*H*)-one to β-nitrostyrene catalyzed by the dinuclear zinc–ProPhenol complex. Gratifyingly, the desired product could be obtained in more than 95 % yield as determined by ^{1}H NMR spectroscopy, albeit with little stereocontrol 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: Et_2Zn in hexanes (1 M, 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 ^{1}H NMR spectroscopy with mesitylene as internal standard. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. The *ee* values were determined by HPLC analysis.

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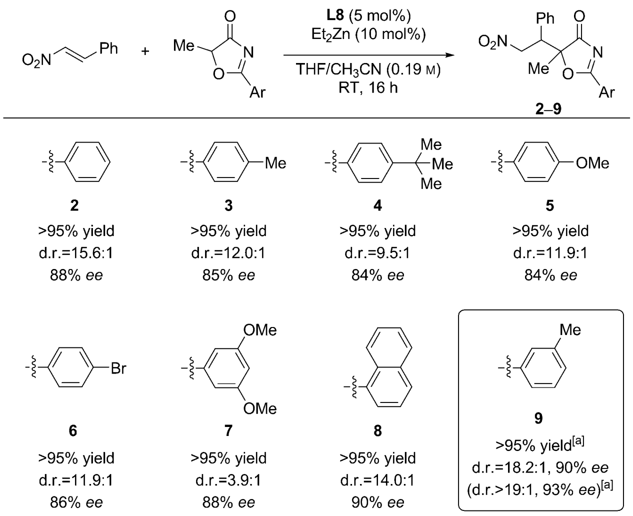
diastereoselectivity. Notably, the sense of enantioinduction was reversed. With a ligand that bears pentafluorophenyl substituents (**L6**), low reaction efficiency was observed and the major diastereomer was obtained as a racemate. A ligand with 1-naphthyl groups (**L7**) gave a significantly improved *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.

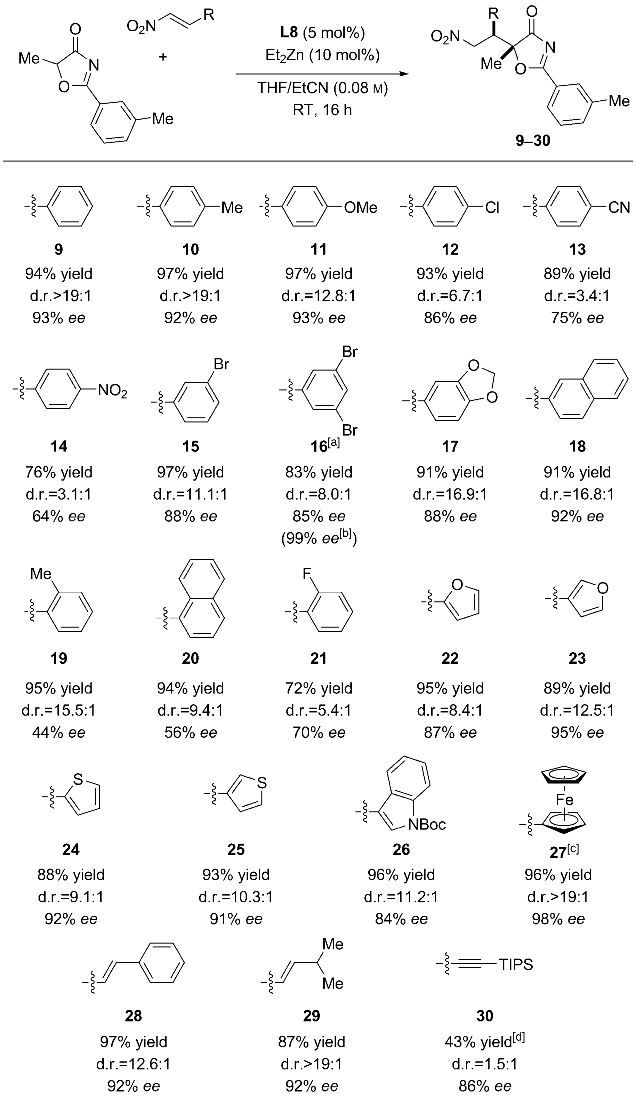
We next optimized the aryl group of oxazolone (Scheme 2). A methyl group as well as a *tert*-butyl group at the *para* position of the phenyl ring decreases the diastereo- and enantioselectivity. The *para*-methoxy and *para*-bromo derivatives behaved similarly to the *para*-methyl nucleophile



Scheme 2. Optimization of the nucleophile structure. All reactions were run on a 0.125 mmol scale under the conditions described in Scheme 1 with **L8** and different nucleophiles. 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. [a] Reaction conducted in propionitrile (0.08 M).

(**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 *meta*-methylphenyl group gave product **9** with d.r. = 18.2:1 and 90% *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*).

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*, while the *para*-methoxy substrate gave **11** in 97% yield, d.r. = 12.8:1, and 93% *ee*. The inductively electron-withdrawing chloro substituent at the *para* position slightly decreased the d.r. (6.7:1) and *ee* value (86%), whereas an analogous cyano group, a mesomeric electron-withdrawing



Scheme 3. Addition of 5-methyloxazole-4(5*H*)-one to various nitro olefins. All reactions were run on a 0.125 mmol scale under the conditions described in Scheme 1 with **L8** (0.08 M) 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. [a] 0.5 mmol scale; reaction on a 0.125 mmol scale: 90% yield, d.r. = 8.4:1, 84% *ee*. [b] From the mother liqueur of a single recrystallization. [c] Absolute configuration established as (*R*,*R*) by single crystal X-ray analysis. [d] Yield of the major isomer.

group, gave reduced selectivities (**13**, d.r. = 3.4:1, 75% *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 0.5 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 product **29** was obtained with high stereoselectivity. A substrate containing a triple bond also participated in the addition reaction, and gave **30** in 43% yield, d.r. = 1.5:1, and 86% *ee*.

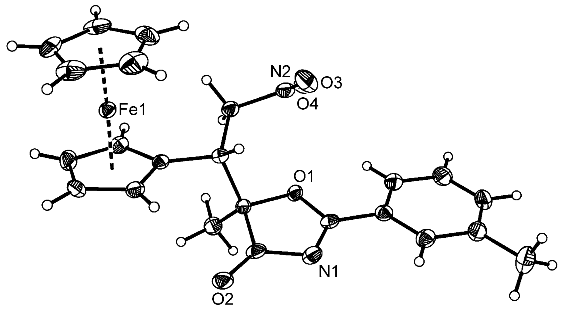
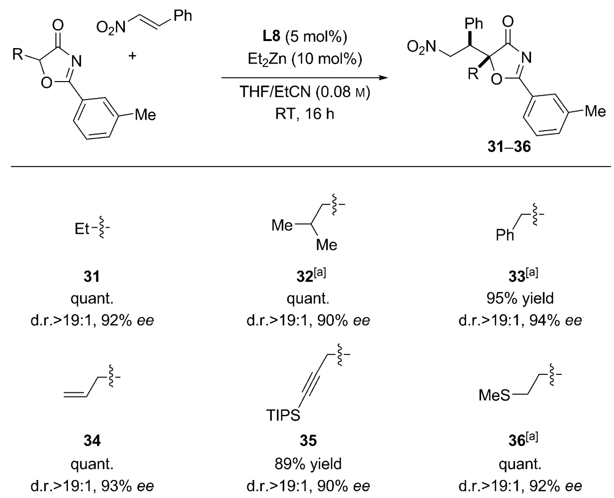


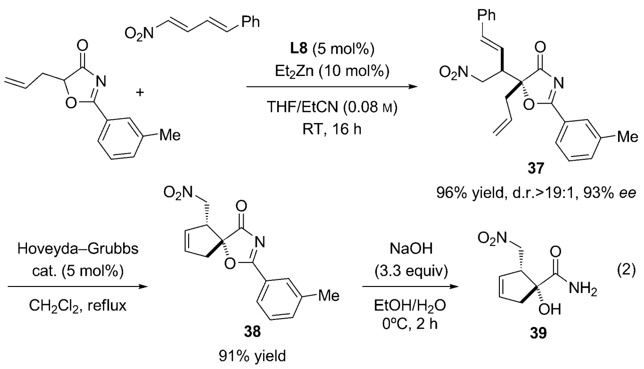
Figure 1. Single crystal X-ray diffraction analysis of **27**. Thermal ellipsoids at 50% probability.

The alkyl substituent of 5-alkyloxazole-4(5*H*)-ones was also varied (Scheme 4). The 5-ethyl oxazolone afforded the desired product **31** quantitatively, d.r. > 19:1, and 92% *ee*. The even more sterically-demanding 2-isobutyloxazolone gave product **32** quantitatively, d.r. > 19:1, and 90% *ee*. The benzyl- and allyloxazolones afforded products **33** and **34** with 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.



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

The combination of 5-allyloxazolone and α,β,γ,δ-unsaturated nitro olefin gave diene **37**, which was cleanly metathesized to spirocyclic cyclopentene **38** [Eq. (2)]. The oxazolone ring was opened to α-hydroxy carboxamide **39** with base.[11]



In summary, we have developed a highly stereoselective addition reaction of 5-alkyloxazole-4(5*H*)-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.

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 Et_2Zn (1 M in hexanes, 12.5 μL, 12.5 μmol, 10 mol%) was added by a microsyringe at RT. The resulting yellow solution was stirred for 30 min at RT.

Catalysis: Oxazol-4(5*H*)-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% KH_2PO_4, and diluted with H_2O (1 mL). The mixture was stirred for 5 min at RT and the phases were separated. The aqueous phase was extracted with ether (3×1.5 mL) and the combined organic phases were concentrated. The crude material was analyzed by ^{1}H 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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