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Organocatalytic Asymmetric Michael Addition of 5*H*-Oxazol-4-ones to Nitroolefins

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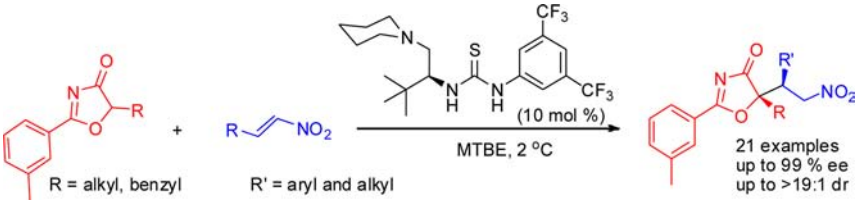
ABSTRACT



The first organocatalytic asymmetric Michael addition of 5*H*-oxazol-4-ones to nitroolefins has been developed. In the presence of easily prepared L-*tert*-leucine-derived tertiary amine/thiourea catalyst, the Michael addition of 5*H*-oxazol-4-ones to nitroolefins proceeded in an excellent diastereo- and enantioselective manner (up to 99% ee and >19:1 dr). The Michael adducts obtained are valuable precursors for the synthesis of chiral α-alkyl-α-hydroxy carboxylic acid derivatives, which represent a series of versatile building blocks in many biologically active compounds.

Enantiomeric pure α-alkyl-α-hydroxy carboxylic acid derivatives, containing an α-substituted tertiary hydroxy group of the carboxylic acid, are key chiral structural motifs, presenting in a number of natural and non-natural products as well as medicinally important agents, such as columbianadin derivatives, inonotusin A, glycosides, 4-hydroxy-4-methylglutamic acids, provitamin, and 3,4-dihydroxy-pyrrolidin-2-ones (Figure 1).[1] All these compounds display crucial biological and medicinal properties including analgesic, anti-inflammatory, and calcium-channel blocking as well as folk medicine applications for the treatment of hyperactivity, cough, tuberculosis, and mumps.[1] The development of synthetic methodologies for the preparation of chiral α-alkyl-α-hydroxy carboxylic acid derivatives has thus attracted the attention of organic chemists in the past few years.[2−5]

The direct addition of α-alkyl-α-hydroxy-substituted esters to unsaturated bonds would be the most atom-economic

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(1) For selected examples, see: (a) Yamada, S.; Nakayama, K.; Takayama, H. *Tetrahedron Lett*. **1981**, *22*, 2591. (b) Helaine, V.; Bolte, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3855. (c) Coutrot, P.; Claudel, S.; Didierjean, C.; Grison, C. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 417. (d) Zan, L.-F.; Qin, J.-C.; Zhang, Y.-M.; Yao, Y.-H.; Bao, H.-Y.; Li, X. *Chem. Pharm. Bull*. **2011**, *59*, 770. (e) Wu, X.; Wang, Y.; Huang, X.-J.; Fan, C.-L.; Wang, G.-C.; Zhang, X.-Q.; Zhang, Q.-W.; Ye, W.-C. *J. Asian Nat. Prod. Res*. **2011**, *13*, 728. (f) Zhang, Y.-B.; Li, W.; Yang, X.-W. *Phytochemistry* **2012**, *81*, 109.

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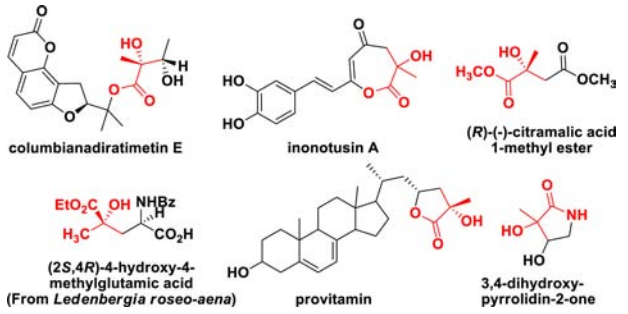


Figure 1. Selected natural and non-natural products.

protocol;[2a] however, low reactivity of the nucleophiles raised doubts on applicability. The first breakthrough was reported by Trost and co-workers in 2004, in which they introduced 5*H*-oxazol-4-ones as α-alkyl-α-hydroxy ester surrogates in a chiral diphosphinemolybdenum catalyzed highly enantioselective allylic alkylations.[3] Since then, the research groups of Misaki, Ye, and Wang have successively developed asymmetric aldol, Michael, and Mannich reactions by using 5*H*-oxazol-4-ones as nucleophiles.[4] Very recently, our group also introduced a highly enantio- and diastereoselective organocatalytic Mannich reaction of 5*H*-oxazol-4-ones to aryl/alkyl imines, successfully affording important α-methyl-α-hydroxy *β*-amino acid derivatives, such as the α-methylated C-13 side chains of Taxol and Taxotere.[4e]

In 2012, Trost and co-workers presented the first asymmetric Michael reaction of 5*H*-oxazol-4-ones to nitroolefins catalyzed by a dinuclear zinc complex, affording a range of highly functionalized α-alkyl-α-hydroxy carboxylic acid derivatives with excellent results.[5] Nevertheless, to the best of our knowledge, no report has yet been published on the organocatalytic asymmetric variant of this productive Michael reaction, which is still highly desirable and represents a formidable task. As part of our ongoing research efforts toward the organocatalytic asymmetric construction of tertiary alcohols,[6,4e] we thus became interested in the development of an efficient organocatalytic asymmetric Michael additions of 5*H*-oxazol-4-ones to nitroolefins.

Initially, to probe the feasibility of the proposed strategy under the organic catalyst, 5*H*-oxazol-4-one **1a** was treated with nitroolefin **2a** in the presence of Et_3N in THF at 26 °C. We found that the reaction worked smoothly, accessing the desired adduct **3aa** with 85% yield in 5:1 dr after 24 h

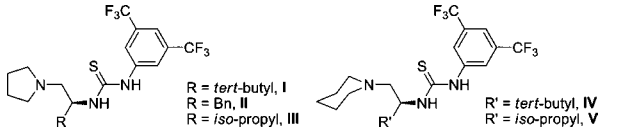
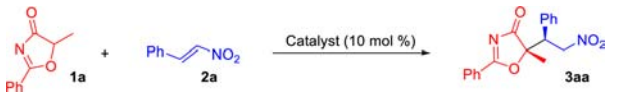


Figure 2. Catalyst structures.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)	dr[d]
1	Et_3N	THF	26	24	85	NA	5:1
2	**I**	THF	26	18	90	24	10:1
3	**II**	THF	26	18	97	4	6:1
4	**III**	THF	26	18	84	46	10:1
5	**IV**	THF	26	18	84	64	10:1
6	**V**	THF	26	18	96	55	10:1
7	**IV**	toluene	26	18	90	78	11:1
8	**IV**	CH_2Cl_2	26	18	93	69	11:1
9	**IV**	CH_3CN	26	18	47	50	9:1
10	**IV**	EA	26	18	91	76	12:1
11	**IV**	CPME[e]	26	18	96	75	9:1
12	**IV**	MTBE[f]	26	18	96	81	10:1
13	**IV**	MTBE	10	24	92	83	10:1
14	**IV**	MTBE	2	40	95	88	16:1
15	**IV**	MTBE	−10	40	75	85	16:1

[a] The reaction was carried out with 0.05 mmol of **1a**, 0.055 mmol of **2a**, and 0.005 mmol of catalyst in 0.5 mL of solvent. [b] Isolated yield. [c] Determined by HPLC methods. [d] Determined by ^{1}H NMR analysis. [e] CPME = cyclopentyl methyl ether. [f] MTBE = *tert*-butyl methyl ether.

(Table 1, entry 1). Next, we endeavored to investigate the asymmetric reaction conditions. As a kind of bifunctional catalyst, L-amino acid-derived tertiary amine/thioureas are very easily prepared, and their efficacy has been proven in many asymmetric reactions.[7] Most recently, we reported direct vinylogous conjugate additions using L-*tert*-leucine-derived tertiary amine/thiourea **I** as the catalyst (Figure 2) which could be easily prepared and displayed a strong stereocontrolling ability.[7f] In this context, we investigated the reaction between 5*H*-oxazol-4-one **1a** and nitroolefin **2a** in the presence of 10 mol % of **I** at first (Table 1, entry 1). The process led to the desired Michael adduct **3aa** with

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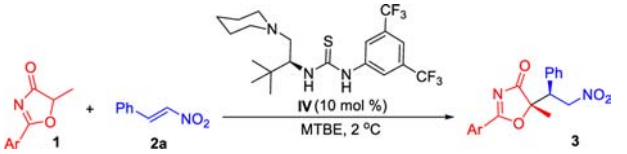
24% ee and 10:1 dr. Subsequently, we screened catalysts **II** and **III** derived from L-phenylalanine and L-valine (entries 2 and 3) and found that catalyst **III** gave higher enantioselectivity (46% ee, entry 3). These results indicate that the side chain of the catalyst should be important to influence the stereoselectivity. In an attempt to improve the catalyst, we replaced pyrrolidinyl (the Brønsted base functional group) in **I** and **III** with piperidinyl to afford catalysts **IV** and **V** (Figure 2). Results from reactions with the piperidine catalysts revealed that the ee of adduct **3aa** improved to 64% when catalyst **IV** was used (Table 1, entry 5). Accordingly, catalyst **IV** was used for further investigations in different solvents and temperatures (entries 6–14). We found that the reactions performed in less polar solvents proceeded well and with high enantioselectivities. MTBE proved best with respect to catalytic reactivity and enantioselectivity (98% yield, 81% ee, entry 11). Lower reaction temperatures slightly improved the enantio- and diastereoselectivity and the optimal temperature is at 2 °C (88% ee, entry 13).

Table 2. Asymmetric Michael Addition of 5*H*-Oxazol-4-ones **1** to Nitroolefin **2a**[a]



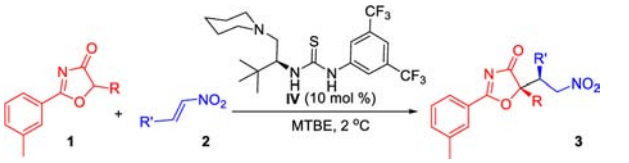
entry	**1**, (Ar)	**3**	time (h)	yield[b] (%)	ee[c] (%)	dr[d]
1	**1b** (4-MePh)	**3ba**	40	87	88	11:1
2	**1c** (3-FPh)	**3ca**	60	90	90	>19:1
3	**1d** (3-ClPh)	**3da**	40	93	90	>19:1
4	**1e** (3-MePh)	**3ea**	40	98	94	>19:1
5	**1f** (3-MeOPh)	**3fa**	21	92	84	10:1
6	**1g** (2-MePh)	**3ga**	40	83	83	7:1

[a] The reaction was carried out with 0.05 mmol of **1**, 0.055 mmol of **2a** and 0.005 mmol **IV** in 0.5 mL of solvent. [b] Isolated yield. [c] Determined by HPLC methods. [d] Determined by ^{1}H NMR analysis.

Next, we began to investigate the influence of the aryl group of 5*H*-oxazol-4-ones (**1b**–**g**) in affecting stereoselectivity. The results are summarized in Table 2. 5*H*-Oxazol-4-one **1b** with a methyl group at the *para* position of the phenyl ring gave similar enantioselectivity, but the diastereoselectivity decreased (entry 1). When substituent groups (F, Cl, methyl, methoxy) were introduced at the *meta* position of the phenyl ring (**1c**–**f**, entries 2–5), both enantio- and diastereoselectivity improved with the exception of 5*H*-oxazol-4-one **1f** (entry 5). Adduct **3ea** with a *m*-methylphenyl group was obtained with the best results (94% yield, 94% ee, > 19:1 dr, entry 4). The diastereo- and enantioselectivity decreased when 5*H*-oxazol-4-one **1g** with an *o*-methylphenyl group was used (entry 6).

With the optimized reaction conditions in hand, we evaluated the performance of the organocatalytic asymmetric Michael reactions between 5*H*-oxazol-4-ones **1** and

Table 3. Asymmetric Michael Addition of 5*H*-Oxazol-4-ones **1** to Nitroolefins **2**[a]



entry	**1**, (R)	**2**, (R')	*t* (h)	**3**	yield (%)[b]	ee (%)[c]
1	**1e**, (Me)	**2a**, (Ph)	40	**3ea**	93	94
2	**1e**, (Me)	**2b**, (4-CNPh)	30	**3eb**	91	91
3	**1e**, (Me)	**2c**, (4-ClPh)	35	**3ec**	89	94
4	**1e**, (Me)	**2d**, (4-BrPh)	35	**3ed**	85	94
5	**1e**, (Me)	**2e**, (3-CNPh)	30	**3ee**	79	95
6	**1e**, (Me)	**2f**, (3-ClPh)	35	**3ef**	87	93
7	**1e**, (Me)	**2g**, (3-BrPh)	35	**3eg**	91	91
8	**1e**, (Me)	**2h**, (4-MePh)	40	**3eh**	87	94
9	**1e**, (Me)	**2i**, (4-*i*PrPh)	42	**3ei**	99	92
10	**1e**, (Me)	**2j**, (2-MePh)	50	**3ej**	99	90
11	**1e**, (Me)	**2k**, (2-MeOPh)	48	**3ek**	99	94
12	**1e**, (Me)	**2l**, (4-MeOPh)	48	**3el**	96	96
13	**1e**, (Me)	**2m**, (2-naphthyl)	48	**3em**	95	93
14	**1e**, (Me)	**2n**, (3-thiophenyl)	48	**3en**	84	92[d]
15	**1e**, (Me)	**2o**, (2-furan)	60	**3eo**	84	90[e]
16	**1e**, (Me)	**2p**, ()	45	**3ep**	89	94
17	**1e**, (Me)	**2q**, (cylcohexyl)	90	**3eq**	42	78
18	**1h**, (Et)	**2a**, (Ph)	50	**3ha**	94	91
19	**1i**, (*i*Pr)	**2a**, (Ph)	96	**3ia**	70	98
20	**1j**, (*n*Bu)	**2a**, (Ph)	60	**3ja**	99	99
21	**1k**, (Bn)	**2a**, (Ph)	96	**3ka**	85	95

[a] The reaction was carried out with 0.10 mmol of **1**, 0.11 mmol of **2**, and 0.01 mmol of **IV** in 1.0 mL of solvent. [b] Isolated yield of major diastereomer of **3** (dr > 19:1, determined by ^{1}H NMR analysis). [c] Determined by HPLC methods. [d] dr = 16:1. [e] dr = 10:1

nitroolefins **2** (Figure 3) by using 10 mol % of L-*tert*-leucine-derived tertiary amine/thiourea catalyst **IV** (Table 3). We first examined the viability of various aryl nitroolefins (**2a**–**o**) with different electronic and steric properties using 5*H*-oxazol-4-one **1e** as the nucleophile (entries 1–15). Adducts **3ea**–**eo** could be obtained with 79–99% yield, 90–96% ee and 10:1 to > 19:1 dr. Our studies showed that the introduction of various substituents onto phenyl groups of aryl nitroolefins did not affect the enantio- and diastereoselectivities. We are delighted to find that the α,*β*,*γ*,*δ*-unsaturated nitroolefin **2p** produced adduct **3ep** in 89% yield with 94% ee and > 19:1 dr (entry 16).

Moreover, we conducted the reaction of **1e** with the aliphatic nitroolefin **2q** and reasonable results were obtained (entry 17). Other 5*H*-oxazol-4-ones **1h**–**k** with different substituents at the C^5-position, such as ethyl, isopropyl, *n*-butyl and benzyl, also gave the corresponding adducts **3ha**–**ka** in good to excellent yields with excellent enantio- and diastereoselectivites (entries 18–21). The results indicate that more hindered substituent at the C^5-position of 5*H*-oxazol-4-one should help increase the reaction enantioselectivity but make the reactivity lower. The absolute configurations of Michael adducts could be assigned from the analyses of ^{1}H NMR and HPLC of the diastereomers of **3ea** with the known data reported by Trost and co-workers.[8]

Based on the observed stereochemistry of the Michael adduct, a plausible transition-state model was proposed (Figure 3). The hydrogen at the C^5-position of 5*H*-oxazol-4-one was deprotonated by piperidine group of the catalyst **IV**, and the activated 5*H*-oxazol-4-one enolate should then attack the thiourea-activated nitroolefin from the *Re* face. This proposed transition state makes the results in Table 2, on the substituent effect of the aryl ring of 5*H*-oxazol-4-one, easily understood.

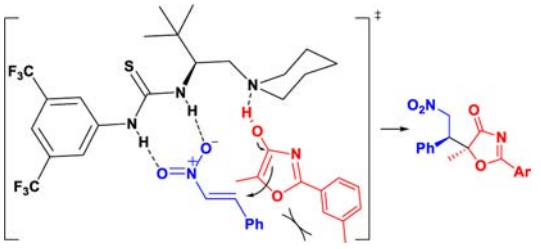
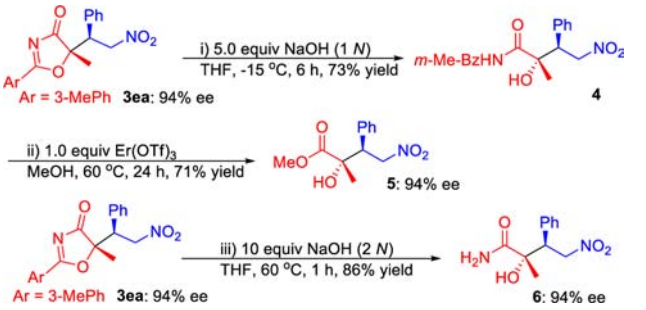


Figure 3. Selected natural and non-natural products.

Subsequently, the transformations of the Michael adducts into α-alkyl-α-hydroxy carboxylic acid derivatives were conducted as shown in Scheme 1. When the hydrolysis of **3ea** was conducted in the presence of 5.0 equiv of NaOH (1 N in H_2O) in THF at −15 °C, an α-methyl-α-hydroxy imide **4** was obtained in 73% yield. In the presence of $Er(OTf)_3$, imide **4** could be conveniently converted to the corresponding ester **5** with 94% ee, which represents a versatile chiral building block due to bearing readily modified ester and nitro groups. Interestingly, the amide **6** could be achieved when treated **3ea** with 10 equiv of NaOH (2 N in H_2O) at 60 °C for 6 h without compromising the ee value.

Scheme 1. Transformation of the Michael Adducts



In conclusion, we have developed the first organocatalytic asymmetric Michael addition of 5*H*-oxazol-4-ones to nitroolefins with excellent diastereo- and enantioselectivities (up to 99% ee and > 19:1 dr) by using easily prepared L-*tert*-leucine-derived tertiary amine/thiourea catalyst. From the Michael adducts, several α-alkyl-α-hydroxycarboxylic acid derivatives as significant intermediates to access various corresponding natural and non-natural products, as well as medicinally important agents, could be obtained from simple modifications. Investigations into the extension of 5*H*-oxazol-4-ones in other organocatalytic asymmetric reactions to achieve other α-alkyl-α-hydroxy carboxylic acid derivatives are ongoing.

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Supporting Information Available. General information, typical experimental procedures, characterization, and HPLC and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(8) See the Supporting Information for details.

The authors declare no competing financial interest.