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Diphenylprolinol Silyl Ether as a Catalyst in an Enantioselective, Catalytic Michael Reaction for the Formation of α,α-Disubstituted α-Amino Acid Derivatives

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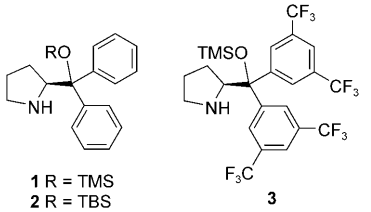
Enantiomerically pure α,α-disubstituted α-amino acids are extremely important organic substances as they are found in many biologically active compounds.[1] Much attention has been paid to enantiomerically pure non-natural α-amino acids such as the α,α-disubstituted ones. A Michael reaction of an α-substituted α-amino acid equivalent and an electron-deficient alkene is one of the methods that can be used for the preparation of such α,α-disubstituted α-amino acids. Although there are several synthetic methods for the formation of α-monosubstituted amino acids by the Michael reaction of α-unsubstituted α-amino acid equivalents,[2] there is no efficient method for the formation of chiral α,α-disubstituted α-amino acid derivatives with high enantioselectivity from an asymmetric Michael reaction.

However, rapid advances have been made with the reaction using a small organic molecule as catalyst, a so-called organocatalyst.[3] Our group[4] and Jørgensen and co-workers[5] independently developed diarylprolinol silyl ether as an effective organocatalyst that has subsequently been widely used by many research groups.[6] Our group developed the ene reaction,[4b] the Diels–Alder reaction,[4c,g] the Michael reaction of nitroalkane,[4e] and the formal aza-[3+3] cycloaddition reaction.[4f] These reactions proceed via an iminium ion intermediate, generated from an α,β-unsaturated aldehyde and diarylprolinol silyl ether. We thought that 4-substituted 2-aryl-2-oxazoline-5-one would act as a synthetic equivalent of an α-substituted α-amino acid. Whereas MacMillan and co-workers used a silyl enol ether of oxazolinone as a Michael donor in one of the examples of the cascade reaction,[7] we thought that oxazolinone could be used directly, without transformation to its silyl enol ether, to afford the synthetically versatile chiral α,α-disubstituted α-amino acid derivatives. Herein we report on the direct and enantioselective Michael reaction of an α,β-unsaturated aldehyde and 4-substituetd-2-aryl-2-oxazoline-5-one using diphenylprolinol silyl ether as catalyst. In this reaction quaternary and tertiary chiral centers would be continuously generated, and the control of not only enantioselectivity but also diastereoselectivity would be a key issue. During the investigation of this reaction, Jørgensen and co-workers reported the same Michael reaction.[8] However, their best reaction conditions and the catalyst used are slightly different to ours.

The reaction of cinnamaldehyde and 4-methyl-2-phenyl-2-oxazoline-5-one was selected as a model, and the Michael reaction was examined using diphenylprolinol trimethylsilyl ether **1** (Figure 1) as the catalyst. The product was treated with a Wittig reagent, and the corresponding α,β-unsaturated ester was isolated and characterized (Table 1). The enantiomeric excess was determined by chiral HPLC analysis of the ester. First, the solvent was screened using 20 mol% of the catalyst **1** at room temperature (Table 1). Polar solvents



1 R = TMS
2 R = TBS
3

Figure 1. Organocatalysts examined in this study.

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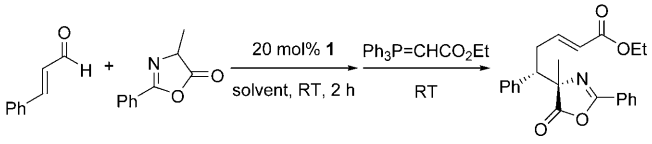
Table 1. The effect of solvent in the reaction of cinnamaldehyde and phenyl oxazolinone catalyzed by **1**.[a]



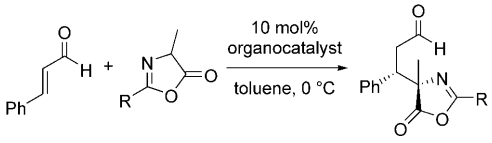
Entry	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	toluene	68	1.2:1	79
2	CH_2Cl_2	79	1.1:1	56
3	AcOEt	69	1.2:1	58
4	hexane	59	1.2:1	71
5	Et_2O	60	1.5:1	65
6	MeCN	66	1:1	22
7	DMF	44	1.1:1	40
8	benzene	52	1.5:1	68
9	xylene	50	1.2:1	63
10	mesitylene	51	1.4:1	72

[a] Unless otherwise shown, reactions were performed employing cinnamaldehyde (0.15 mmol), oxazolinone (0.23 mmol), catalyst **1** (0.03 mmol), and solvent (0.3 mL) at room temperature for 2 h. [b] Yield of isolated product. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Optical purity of the major isomer, which was determined by chiral HPLC analysis.

such as MeCN and DMF gave low enantioselectivity, whereas good results were obtained using aromatic solvents. The best enantioselectivity (79% *ee*) was obtained when toluene was used.

During these investigations, we found that the substituent at the 2-position of oxazoline affected the enantioselectivity. Thus the catalyst was examined using both phenyl- and *p*-methoxyphenyl-substituted oxazolinone in toluene at 0°C or at room temperature (Table 2). While good enantioselectivity (81% *ee*) was obtained with the phenyl-substituted substrate (Table 2, entry 1), the *p*-methoxyphenyl derivative gave higher enantioselectivity (90% *ee*) when trimethylsilyl ether was used as catalyst **1** (Table 2, entry 2). Similar findings were observed when using the *tert*-butyldimethylsilyl ether catalyst **2**. Whereas 67% *ee* was observed in the reaction of the phenyl-substituted substrate (Table 2, entry 3), good enantioselectivity was realized when *p*-methoxyphenyl oxazolinone was used (Table 2, entry 4). When the reaction was conducted at 0°C, the best enantioselectivity (97% *ee*) was obtained, along with an increase in the diastereoselectivity (Table 2, entry 5). However, under the same reaction conditions the trifluoromethyl-substituted diarylprolinol silyl ether **3** was not effective; it afforded the Michael adduct in 17% yield with recovery of the starting material (Table 2, entry 6). When the reaction was performed at room temperature using catalyst **3**, the yield increased to 74% and good enantioselectivity (89% *ee*) was obtained (Table 2, entry 7). These results indicate that the diphenylprolinol *tert*-butyldimethylsilyl ether **2** is the best catalyst under the present reaction conditions in terms of the enantioselectivity, diastereoselectivity, and reactivity.

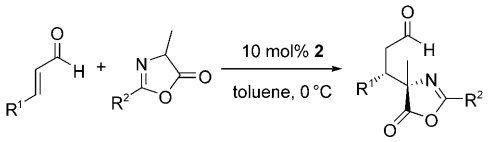
Table 2. The effect of organocatalyst in the Michael reaction.[a]



Entry	Cat.	R	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1**	Ph	0	17	64	1.3:1	81
2	**1**	An	0	16	68	2.1:1	90
3	**2**	Ph	0	19	71	1.2:1	67
4	**2**	An	23	2	79	1.2:1	89
5	**2**	An	0	18	73	2.2:1	97
6	**3**	An	0	48	17	1:1	91
7	**3**	An	23	20	74	1.3:1	89

[a] Unless otherwise shown, reactions were performed employing cinnamaldehyde (0.24 mmol), oxazolinone (0.2 mmol), catalyst (0.02 mmol), and toluene (0.4 mL) at 0°C or 23°C for the indicated time; An = *p*-$MeOC_6H_4$-. [b] Yield of isolated aldehyde. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Optical purity of the major isomer, which was determined by chiral HPLC analysis of the α,β-unsaturated ester by the reaction of aldehyde with $Ph_3P{=}CHCO_2Et$.

Table 3. Catalytic asymmetric Michael reaction of 4-methyloxazolinone.[a]



Entry	R^1	R^2	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	An	18	73	2.2:1	97
2	2-naphthyl	An	18	73	2.0:1	93
3	*p*-ClC_4H_4	An	16	83	2.2:1	92
4	An	An	17	76	1.7:1	73
5	Me	An	6	74	>20:1	97
6	Me	Ph	5	72	>20:1	97
7	cyclohexyl	An	30	63	9.2:1	98
8	cyclohexyl	Ph	30	66	7.6:1	99
9	Et	Ph	5	77	>20:1	99
10	*i*Pr	Ph	9	70	14:1	99
11	*i*Bu	Ph	7	74	>20:1	92

[a] Unless otherwise shown, reactions were performed employing aldehyde (0.24 mmol), oxazolinone (0.2 mmol), catalyst **2** (0.02 mmol), and toluene (0.4 mL) at 0°C for the indicated time; An = *p*-$MeOC_6H_4$-. [b] Yield of isolated aldehyde. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Optical purity of the major isomer; see the Supporting Information for the determination of the enantioselectivity.

In terms of the substituents at the β-position of acrolein, not only a phenyl and a naphthyl group (Table 3, entries 1, 2) but also an aryl group possessing an electron-withdrawing group (Table 3, entry 3) were successfully used to afford the Michael product with excellent enantioselectivity. However, the electron-rich aromatic group afforded the product in good yield with moderate enantioselectivity (Table 3, entry 4). In the reaction of alkyl substituents, the reaction

proceeded in a highly diastereo- and enantioselective manner. When the β substituents of acrolein were methyl and cyclohexyl, then good to excellent enantio- and diastereoselectivities were obtained in the reactions of both 2-phenyl- and 2-methoxyphenyl-substituted oxazolinone (Table 3, entries 5–8). Thus, in the alkyl-substituted acrolein derivatives the generality was examined using 2-phenyl oxazolinone. Nearly perfect enantioselectivity and excellent diastereoselectivity were realized in the reaction of β-alkyl-substituted acroleins (Table 3, entries 9–11).

Next, the Michael donor was investigated using crotonaldehyde as a Michael acceptor (Table 4). In terms of the substituent at the 4-position of oxazolinone, not only the methyl group but also the isobutyl, benzyl, indolylmethyl, and methylthioethyl groups were successfully used to afford the Michael product in good yield and with excellent enantioselectivity. The chiral α,α-disubstituted amino acids of alanine, leucine, phenylalanine, tryptophan, and methionine derivatives can be synthesized with excellent enantioselectivities.

In conclusion, we have found that diphenylprolinol *tert*-butyldimethylsilyl ether **2** is an effective organocatalyst for a highly enantioselective Michael reaction of α,β-unsaturated aldehydes with 4-substituted oxazolinone. The obtained Michael products, which are α,α-disubstituted, quaternary α-amino acid derivatives possessing the γ-formyl functional group, are useful chiral synthetic intermediates, as has also been shown by Jørgensen and co-workers.[8]

Experimental Section

Typical experimental procedure (Table 3, entry 1): To a mixture of oxazolinone (35 mg, 0.2 mmol), catalyst **2** (6.5 mg, 0.02 mmol), and toluene (0.4 mL) was added cinnamaldehyde (30 μL, 0.24 mmol) successively at 0 °C. The reaction mixture was stirred for 18 h at that temperature. The reaction mixture was directly purified by silica gel column chromatography (ethyl acetate/hexane = 1:5 to 1:3) to afford (3*S*)-3-((*S*)-4,5-dihydro-4-methyl-5-oxo-2-(4-methoxyphenyl)oxazoyl-4-yl)-3-phenylpropanal (49.2 mg, 0.15 mmol) in 73% yield as a diastereomeric mixture (major isomer/minor isomer = 2.2:1). The diastereomeric ratio was determined by ^{1}H NMR spectrum.

The product was converted into the corresponding α,β-unsaturated ester using ethyl(triphenylphosphoranylidene)acetate, and the enantioselectivity was determined by HPLC using a Chiralpak IC column (30:1 hexane/2-propanol), 1.0 mL min^{-1}, major isomer t_R = 23.3 min, minor enantiomer t_R = 21.1 min. Enantiometric excess of the major isomer was 97% *ee*.

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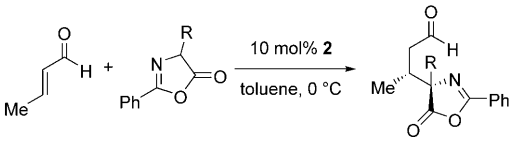
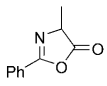
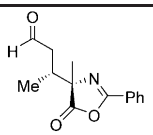
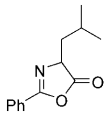
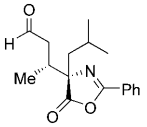
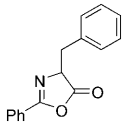
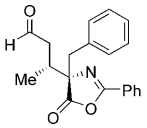
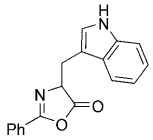
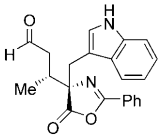
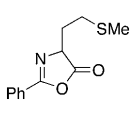
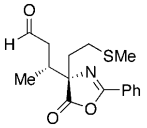
Keywords: amino acids · asymmetric catalysis · Michael reaction · organocatalysis

Table 4. Catalytic asymmetric Michael reaction of 4-substituted oxazolinone with crotonaldehyde.[a]



Entry	Oxazolinone	Product	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1			5	72	>20:1	97
2			3	74	9.3:1	91
3			2	83	11:1	96
4			2	62	5.2:1	97
5			3	89	>20:1	92

[a] Unless otherwise shown, reactions were performed employing crotonaldehyde (0.24 mmol), oxazolinone (0.2 mmol), catalyst **2** (0.02 mmol), and toluene (0.4 mL) at 0 °C for the indicated time. [b] Yield of isolated aldehyde. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Optical purity of the major isomer; see the Supporting Information for the determination of the enantioselectivity.

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