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Diphenylprolinol Silyl Ether as a Catalyst in an Asymmetric, Catalytic, and Direct Michael Reaction of Nitroethanol with α,β-Unsaturated Aldehydes

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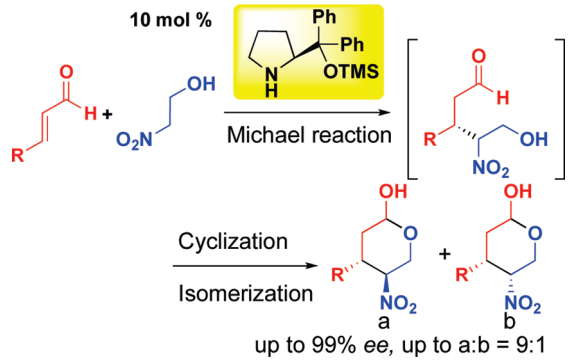
ABSTRACT



Diphenylprolinol silyl ether was found to be an effective organocatalyst in the enantioselective and direct Michael reaction of nitroethanol and α,β-unsaturated aldehydes, affording the 1-hydroxy-*trans*-3,4-disubstituted tetrahydropyrans after isomerization. The generated Michael addition products are useful synthetic intermediates, which can be converted into chiral tetrahydropyran with a quaternary stereocenter, 3-substituted *cis*- and *trans*-prolines, and α-amino acid derivatives.

Enantiomerically pure α-amino acids are extremely important organic substances because they are found in many biologically active compounds. Accordingly, several methods have been developed for the synthesis of the enantiomerically pure α-monosubstituted α-amino acids.[1] The Michael reaction of glycine equivalents and an electron-deficient alkene is one such method.[2]

Nitroethanol possesses nitro and hydroxy functionalities, which are easily transformed into amine and carboxylic acid moieties by reduction and oxidation, respectively. Thus, nitroethanol is regarded as a synthetic equivalent of the α-amino acid, glycine.[3]

In the past few years, organocatalysis has been intensively studied.[4] Many types of organocatalysts with unique proper-

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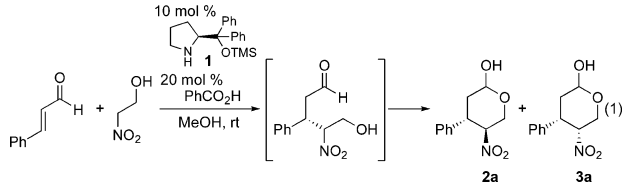
ties have been reported. Our group[5] and Jørgensen and coworkers[6] independently developed diarylprolinol silyl ether as an effective organocatalyst that has subsequently been widely used by many research groups.[7] Just recently, we[5e] and Jørgensen's group[6c] reported the asymmetric Michael reaction of 4-substituted-2-oxazolinone and α,β-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether, which affords α,α-disubstituted α-amino acid equivalents with excellent enantioselectivity. As we previously reported, the asymmetric Michael reaction of nitroalkane and α,β-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether[5d,8] and nitroethanol was expected to react with α,β-unsaturated aldehydes, generating α-monosubstituted α-amino acid equivalents, the successful realization of which will be described in this communication.

Our scenario is as follows: nitroethanol should react with α,β-unsaturated aldehyde to generate the Michael adduct, γ-nitroaldehyde, which would cyclize to afford substituted tetrahydropyrans **2** and **3**. Although diastereoselectivity of **2** and **3** is expected to be low in view of the previous results for nitroethane in which low diastereoselectivity is obtained,[5d] isomerization would convert *cis*-isomer **3** into the more thermodynamically stable *trans*-isomer **2** (eq 1, Scheme 1). Tetrahydropyran **2** would be a useful synthetic

Scheme 1

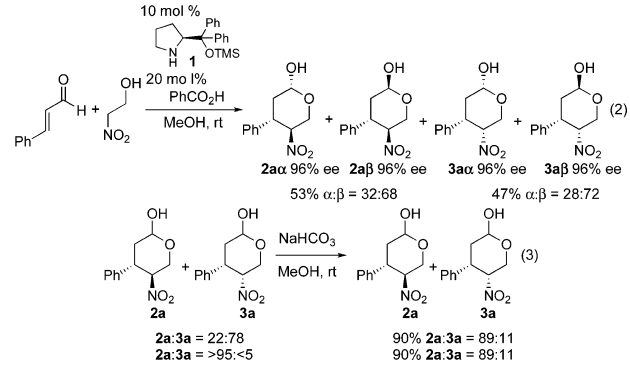


intermediate with several functional groups for the synthesis of nitrogen-containing molecules.

To realize this scenario, the reaction of cinnamaldehyde and nitroethanol was selected as a model, and the Michael reaction was examined using diphenylprolinol trimethylsilyl ether **1** as a catalyst in the presence of benzoic acid in MeOH.[5d]

Four diastereomers of tetrahydropyran derivatives **2aα**, **2aβ**, **3aα**, and **3aβ** were obtained quantitatively. *Trans*-**2a** and *cis*-**3a** isomers were partially separated by column chromatography and the enantiomeric excess of **2aα** and **2aβ**, and those of **3aα** and **3aβ** were found to be the same and excellent values (eq 2, Scheme 2). By the use of the partially

Scheme 2



separated isomers **2a** and **3a**, the isomerization of **2a** and **3a** was investigated under several basic conditions. When a mixture of **2a** and **3a** (**2a**:**3a** = 22:78) was treated with inorganic bases such as K_2CO_3, $CaCO_3$, $KHCO_3$, $NaHCO_3$, and Cs_2CO_3 in MeOH, $NaHCO_3$ was found to be effective in affording the mixture, in which the *trans*-isomer is formed predominantly (**2a**:**3a** = 89:11) with good conversion yield. When pure *trans*-isomer **2a** was treated under the same conditions, a mixture of *trans*- and *cis*-isomers was obtained with the same ratio (**2a**:**3a** = 89:11, eq 3). These results indicate that there is equilibrium between *trans*- and *cis*-isomers and that its ratio is 89:11 in MeOH. Michael and isomerization reacions can be performed in a single-pot operation. That is, after the treatment of cinnamaldehyde and nitroethanol with **1** and $PhCO_2H$ at room temperature for 20 h, addition of $NaHCO_3$ to the reaction mixture and further stirring for 48 h afforded tetrahydropyran derivatives **2a** and **3a** in good yield with high diastereoselectivity and excellent enantioselectivity (Table 1, entry 1).

After the reaction conditions were optimized, the generality of the reaction was investigated, and the results are summarized in Table 1. The reaction has broad applicability. Not only phenyl but also the 2-naphthyl-substituted acrolein

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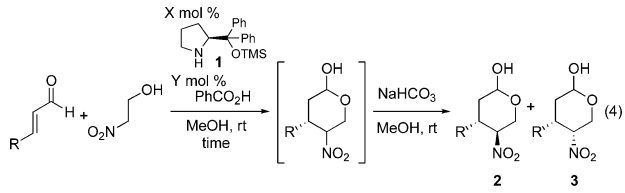
Table 1. One-Pot Michael and Isomerization Reaction of α,β-Unsaturated Aldehyde and Nitroethanol[a]



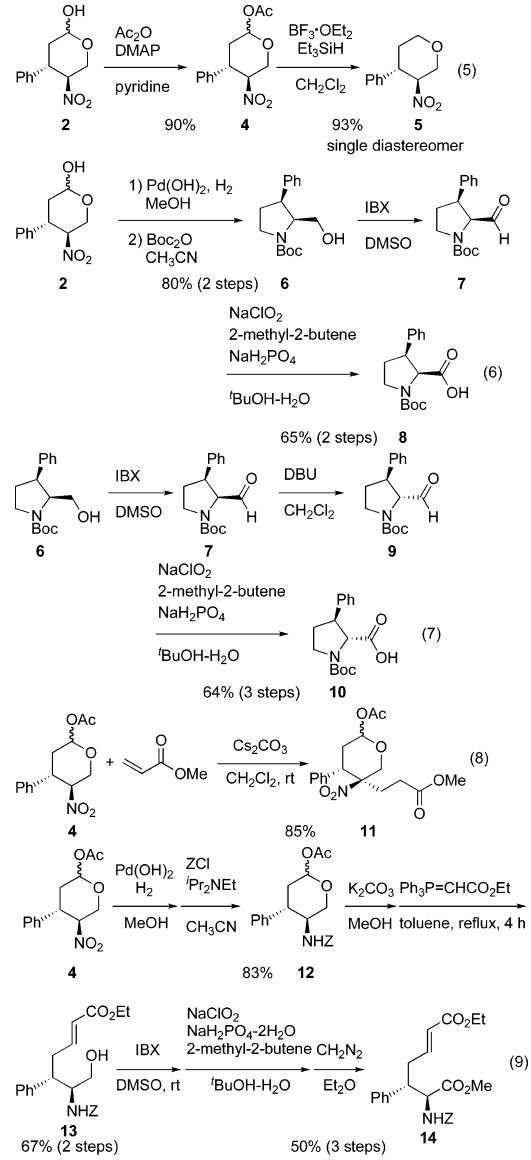
entry	R	X (mol %)	Y (mol %)	time (h)[b]	2:3[c]	yield (%)[d]	ee (%)[e]
1	Ph	10	20	20	89:11	86	95
2	Ph	2	4	46	84:16	87	96
3	2-naphthyl	10	20	28	87:13	92	94
4	p-$NO_2C_6H_4$-	10	20	15	86:14	80	99
5	p-BrC_6H_4-	10	20	15	86:14	85	93
6	p-$MeOC_6H_4$-	10	20	26	84:16	95	93
7	o-$MeOC_6H_4$-	10	20	21	85:15	94	94
8	furyl	10	20	26	80:20	80	91
9	thienyl	10	20	21	90:10	82	94
10	$PhCH_2CH_2$	10	0	27	76:24	76	92
11	cyclohexyl	20	0	79	76:24	55	96
12	isobutyl	20	0	71	78:22	72	92

[a] The reaction conditions: α,β-unsaturated aldehyde (0.60 mmol), nitroethanol (0.90 mmol), catalyst **1** (0.060 mmol), $PhCO_2H$ (0.12 mmol), and $NaHCO_3$ (3.0 mmol) in MeOH (1.2 mL) were employed. See the Supporting Information in detail. [b] The reaction time for the first Michael reaction. [c] Diastereomeric ratio was determined by ^1H NMR or ^{13}C NMR. [d] Yield of isolated products **2** and **3**. [e] Enantiomeric excess of **2**, which was determined by chiral HPLC analysis after conversion to the corresponding acetyl ester.

derivative gave an excellent result (entry 3). When the substituent is electron deficient, such as *p*-nitro or *p*-bromophenyl, the reaction also proceeds efficiently, generating the substituted tetrahydropyrans with good diastereoselectivities and excellent enantioselectivities (entries 4 and 5). Acrolein derivatives possessing electron-rich aromatic substituents such as *p*- and *o*-methoxyphenyl are also good substrates, generating excellent results (entries 6 and 7). Not only aromatic groups but also heteroaromatic groups such as furyl and thienyl are suitable substituents (entries 8 and 9). Alkyl-substituted acroleins were employed successfully, in which better results were obtained without the addition of $PhCO_2H$. That is, the reaction of acroleins possessing 2-phenylethyl, cyclohexyl, and isobutyl moieties proceeds in the presence of catalyst **1**, affording the tetrahydropyran derivatives with excellent enantioselectivity (entries 10−12). Although we used 10 mol % of the catalyst, the catalyst loading can be reduced to 2 mol %. Namely, in the presence of 2 mol % of **1** and 4 mol % of benzoic acid, the reaction of cinnamaldehyde proceeded efficiently, affording the desired product in 87% yield without compromising the enantioselectivity (96% ee, entry 2).

The substituted tetrahydropyran **2** is a useful synthetic intermediate because it possesses several functional groups, the transformations of which were investigated next. Tetrahydropyran **2** was converted into acetoxytetrahydropyran **4**, which was reduced with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to afford the *trans*-3,4-disubstituted tetrahydropyran **5** in 93% yield (eq 5, Scheme 3). When hydroxypyran **2** was treated with H_2 in the presence of $Pd(OH)_2$, reduction of the nitro group and a successive intramolecular reductive amination occurred to provide the pyrrolidine derivative, which was isolated as the *N*-Boc-protected 2,3-*cis*-disubstituted pyrrolidine **6** in 80% yield over two steps. Oxidation with *o*-iodoxybenzoic acid (IBX)[9] gave *cis*-aldehyde **7**, which was further oxidized under Kraus conditions[10] to provide *cis*-3-phenylproline derivative **8** (eq 6). On the other hand, *trans*-aldehyde **9** was obtained by the isomerization of *cis*-isomer **7** with DBU, followed by oxidation to afford *trans*-3-phenylproline derivative **10** (eq 7). By these methods,

Scheme 3



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cis- and *trans*-3-substituted prolines can be synthesized stereoselectively from the same starting material. The absolute configuration of the methyl ester of **8** was determined by a comparison of its optical rotation with that of the literature.[11]

When acetoxytetrahydropyran **4** was treated with methyl acrylate in the presence of Cs_2CO_3, the Michael reaction proceeded smoothly to generate the product **11** as a single isomer. It should be noted that the reaction proceeds with excellent diastereoselectivity with the generation of a quaternary stereocenter (eq 8).

When acetoxytetrahydropyran **4** was reduced with H_2 in the presence of $Pd(OH)_2$, the amine was generated, which was treated with ZCl and *i*-Pr_2EtN to afford **12** in 83% yield over two steps. Hydrolysis of the ester, followed by the Wittig reaction, afforded amino alcohol **13**. By oxidation of the alcohol to the carboxylic acid and conversion of the carboxylic acid to the ester, α-amino ester derivative **14** was synthesized stereoselectively (eq 9).

In summary, we report that 1-hydroxy-*trans*-3,4-disubstituted tetrahydropyrans can be synthesized by the asymmetric and direct Michael reaction of nitroethanol and α,*β*-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether as an organocatalyst, followed by isomerization. Good diastereoselectivity and excellent enantioselectivity have been obtained for a broad range of α,*β*-unsaturated aldehydes. We have also demonstrated that the products are useful synthetic intermediates with functional groups, which were successfully converted into chiral tetrahydropyran with a quaternary stereocenter, 3-substituted *cis*- and *trans*-prolines, and α-amino acid derivatives.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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