Tandem Reactions

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Diphenylprolinol Silyl Ether as a Catalyst in an Enantioselective, Catalytic, Tandem Michael/Henry Reaction for the Control of Four Stereocenters**

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The formation of carbon–carbon bonds with the control of multiple stereocenters in a single operation is not only a synthetic challenge but also a useful method for the construction of complex molecules. Tandem reactions are a very powerful example of a methodology used to achieve these aims.[1] Substituted chiral cyclohexanes are important building blocks in organic synthesis, and the control of the relative and absolute configurations is a key issue in the preparation of these versatile frameworks. The Diels–Alder cycloaddition is one widely employed method for the catalytic enantioselective synthesis of cyclohexane derivatives, most often catalyzed by either a chiral Lewis acid[2] or one of the recently developed chiral organocatalysts.[3]

Many effective organocatalysts have been developed in recent years,[4] and chiral cyclohexanes and cyclohexenes have been synthesized by organocatalysts with high enantioselectivity.[5] Diarylprolinol silyl ether, which was originally developed by Jørgensen's[5c,d,f,6] and our groups[7] independently, has recently been utilized in several enantioselective reactions.[8] We have found that diphenylprolinol silyl ether is an effective organocatalyst for the direct enantioselective Michael reaction of aldehydes and nitroalkenes to afford the Michael adduct with high *syn* selectivity and excellent enantioselectivity.[7a] After our discovery, diphenylprolinol methyl ether was found to promote the enantioselective Michael reaction of aldehydes and methyl vinyl ketone,[8a] and Enders and co-workers expanded our reaction to a triple cascade reaction for the synthesis of chiral cyclohexenecarbaldehydes with control of four stereocenters in one operation.[5e] Just recently, Jørgensen and co-workers also reported a triple cascade reaction involving diarylprolinol silyl ether.[5f] As a further application of this organocatalyst in asymmetric reactions, we have developed a highly enantioselective tandem Michael[9]/Henry[10] reaction, which affords, in a single operation, substituted chiral nitrocyclohexanecarbaldehydes with excellent diastereo- and enantioselectivities and control of four stereogenic centers.

We anticipated that pentane-1,5-dial and a nitroalkene would act as a four-carbon unit and a two-carbon unit, respectively. That is, as shown in Scheme 1, we hypothesized that enamine **2** would be generated from pentane-1,5-dial and catalyst **1** and that it would react with a nitroalkene in a Michael reaction to generate **3**, in accordance with our previous findings.[7a] Zwitterion **3** would then react with the aldehyde moiety in an intramolecular Henry reaction to provide **4**, which would be hydrolyzed to provide substituted nitrocyclohexanecarbaldehyde **5**. The order of these last two reactions might be reversed (that is, hydrolysis of iminium ion **3** followed by the Henry reaction might provide **5**).

It would be convenient if commercially available aqueous 2,5-dihydroxy-3,4-dihydrofuran solution[11] could be used as a surrogate for pentane-1,5-dial. Pentane-1,5-dial would be generated from 2,5-dihydroxy-3,4-dihydrofuran in aqueous solution under equilibrium conditions, and it is known that organocatalyst-mediated aldol[12,13] and Michael reactions[14] can proceed in aqueous conditions or in the presence of water.[15] This reaction would generate, in one operation, four stereogenic centers with the formation of two carbon–carbon bonds, and control of the relative and absolute configurations would therefore be an important issue.

We chose nitrostyrene as our model nitroalkene. We first used water as the solvent, but the reaction scarcely proceeded because the solid nitrostyrene did not dissolve. Next, the use of organic solvents such as CH_2Cl_2, toluene, *N*,*N*-dimethylformamide (DMF), hexane, and tetrahydrofuran (THF) was investigated, under which conditions compounds **5a–d** could be isolated (Table 1). Both the yield and the diastereomer ratio were dependent on the solvent. After some experimentation, it was found that **5a** was obtained in good yield with high diastereoselectivity and excellent enantioselectivity when THF was used as the solvent. That is, after stirring of the reaction mixture comprising nitrostyrene with 2,5-dihydroxy-3,4-dihydrofuran solution (50% in water) in THF in the presence of catalyst **1** (10 mol%) for 17 h, **5a** was obtained in 66% yield and nearly optically pure (99% *ee*), along with the other diastereomers (**5b–d**), also with excellent enantioselectivities (Table 1, entry 6). As the generation of **5b** was not indicated in the ^{1}H NMR spectrum of the crude reaction mixture, **5b** was thought to be formed by isomerization during column chromatography (see below). It should be noted that a large-scale experiment was possible and the loading of catalyst **1** can be reduced to 2 mol%; in this

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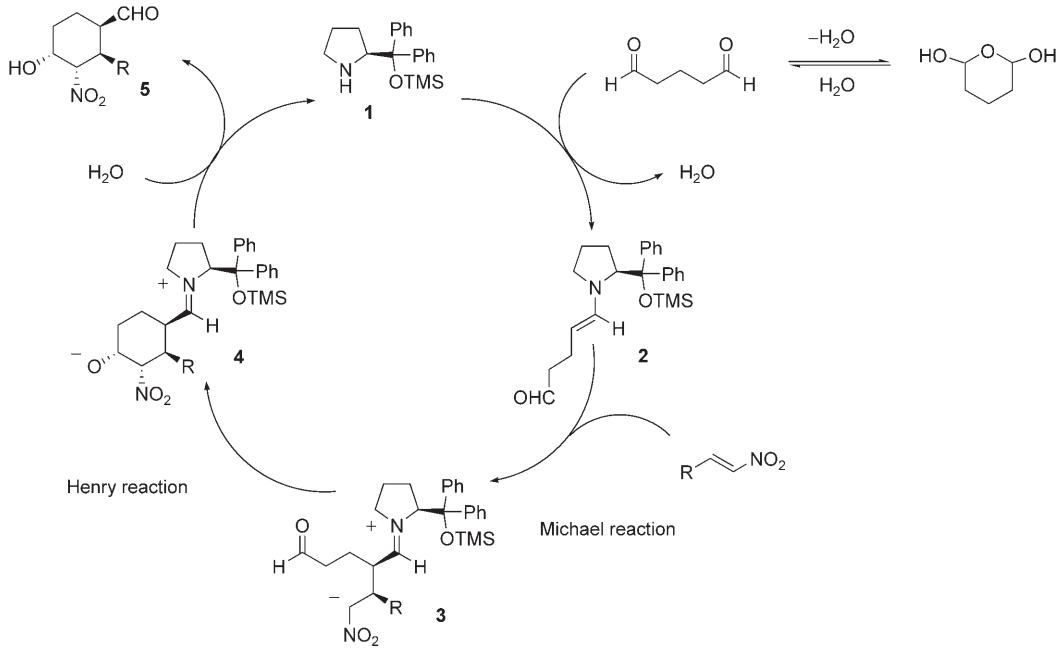
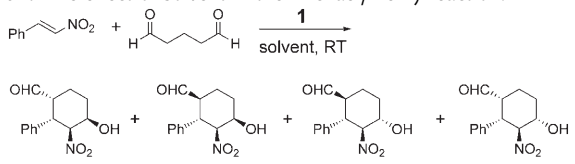


Scheme 1. The reaction mechanism. TMS: trimethylsilyl.

Table 1: The effect of solvent in the Michael/Henry reaction.[a]



5a **5b** **5c** **5d**

Entry	Solvent	*t* [h]	Yield [%][b]	**5a**/**5b**/**5c**/**5d**[c]	*ee* value of **5a** [%][d]
1	CH_2Cl_2	6	64	63:24:4:9	99
2	toluene	8	58	64:24:6:6	99
3	DMF	10	90	70:17:6:7	99
4	hexane	15	64	58:33:6:3	96
5	THF	13	81	80:9:5:6	99
6[e]	THF	17	88	75:8:8:9	99 (94,[f] 99,[g] 87[h])
7[i]	THF	22	92	73:8:7:12	99

[a] Unless otherwise noted, the reaction was performed by employing β-nitrostyrene (0.27 mmol), 2,5-dihydroxy-3,4-dihydrofuran (50% in solution, 147 μL, 0.81 mmol), and organocatalyst **1** (0.054 mmol) in the indicated solvent (0.54 mL) at room temperature. [b] Yield of an isolated mixture of **5a**–**d**. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral phase. [e] Catalyst **1** was employed at a concentration of 10 mol%. [f] *ee* value of **5b**. [g] *ee* value of **5c**. [h] *ee* value of **5d**. [i] Conditions: Nitrostyrene (36.7 mmol), 2,5-dihydroxy-3,4-dihydrofuran (13.3 mL), catalyst **1** (2 mol%, 238.7 mg) and THF (36.7 mL).

experiment, **5a** was obtained in 67% yield with 99% *ee* (Table 1, entry 7).

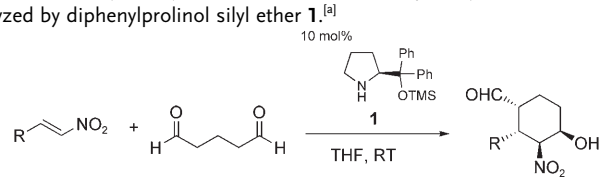
As excellent conditions had been discovered, the generality of the reaction was investigated by using several nitroalkenes. The results, recorded in the presence of 10 mol% of catalyst **1**, are summarized in Table 2. The reaction is fast with electron-deficient aryl-substituted nitroethenes, while it is slow with electron-rich, aryl-substituted ones. Excellent enantioselectivities were obtained regardless of the substituents on the aryl moiety (Table 2, entries 1–7). Not only aromatic groups but also heteroaromatic groups, such as furan and indole, could be successfully employed as the 2-substitutent of the nitroethene to afford the respective cyclohexane derivatives with excellent enantioselectivity (Table 2, entries 8 and 9). Furthermore, 4-phenyl-1-nitro-1,3-butadiene or a nitroalkene substituted with an alkyl group such as a cyclohexyl moiety can also act as effective two-carbon units in this reaction (Table 2, entries 10 and 11).

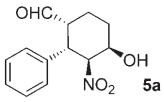
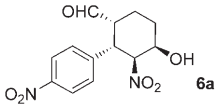
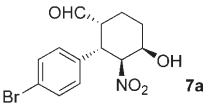
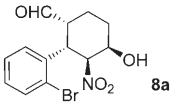
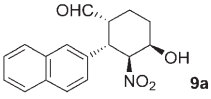
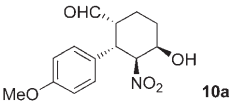
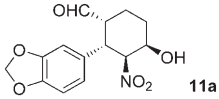
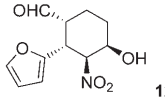
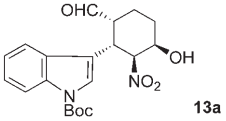
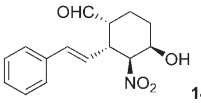
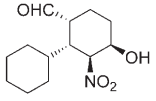
The major product obtained, **5a** (**5a**/**5b** 13:1, **5a**: 99% *ee*), was isomerized by thin-layer chromatography (TLC),[16] to afford **5b** in 93% yield with 96% *ee*; the formyl group in **5b** has been isomerized from the axial to equatorial position under the weak acidic conditions of the silica gel. When **5a** was treated with a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in MeOH, **5a** was isomerized to **5c** in 80% yield with 95% *ee*. In **5c**, not only the formyl group but also the hydroxy group has been isomerized into the equatorial position while the same excellent enantioselectivity is maintained. Deprotonation and protonation, as well as retro-Henry and Henry reactions, proceed under these basic conditions. DBU also isomerizes **5b** into **5c** in 83% yield with 96% *ee*. Thus, synthesis can be directed to give selectively any one of three (**5a**–**c**) out of the eight ($2^3 = 8$) possible different substituted nitrocyclohexanecarbaldehydes through the tandem Michael/Henry reaction followed by the proper isomerization conditions (Scheme 2).

While the relative configuration was determined from ^{1}H NMR coupling constants, the absolute configuration of **7c**, with a *p*-bromophenyl group, was determined by the advanced Mosher's α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) method.[17]

In summary, we have developed a highly diastereo- and enantioselective tandem Michael/Henry reaction that is catalyzed by readily available diphenylprolinol silyl ether

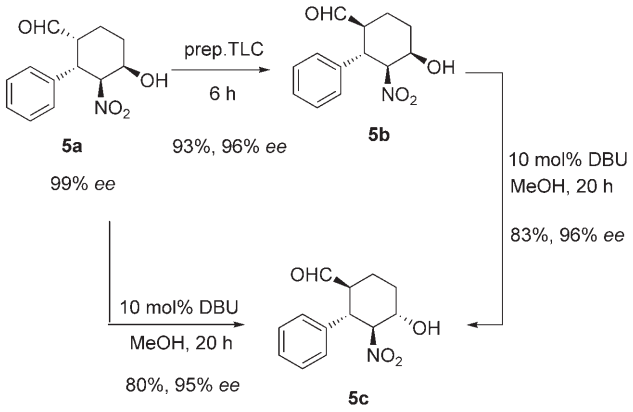
Table 2: Catalytic asymmetric tandem Michael/Henry reactions catalyzed by diphenylprolinol silyl ether **1**.[a]



Entry	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	 **5a**	17	66	99
2	 **6a**	3.5	71	97
3	 **7a**	4	64	99
4	 **8a**	5	56	99
5	 **9a**	6	66	99
6	 **10a**	20	60	98
7	 **11a**	21	63	99
8	 **12a**	20	68	99
9	 **13a**	15	58	98
10	 **14a**	10	55	98
11[d]	 **15a**	24	45	99

[a] Unless otherwise noted, the reaction was performed by employing nitroalkene (0.27 mmol), 2,5-dihydroxy-3,4-dihydrofuran (50% in solution, 147 μL, 0.81 mmol), and organocatalyst **1** (0.027 mmol) in THF (0.54 mL) at room temperature. [b] Yield of isolated product. [c] The optical yield was determined by HPLC analysis on a chiral phase column. [d] 20 mol% of the catalyst and 0.27 mL of THF were employed. Boc: *tert*-butoxycarbonyl.

(**1**) and is suitable for the synthesis of substituted nitrocyclohexane derivatives with control of four stereogenic centers. Successive isomerization under two different sets of conditions can diastereoselectively convert the tandem product into a different stereoisomer in each case, without compromising the enantioselectivity. The cyclohexane derivative obtained is a useful chiral synthetic intermediate that possesses several functional groups.



Scheme 2. Isomerization from **5a** to **5b** and **5c**.

Experimental Section

Typical procedure for the synthesis of **5** (Table 2, Entry 1): **1** (8.8 mg, 0.027 mmol) was added to a mixture of 1-phenyl-2-nitroethylene (40.3 mg, 0.27 mmol) and 2,5-dihydroxy-3,4-dihydrofuran solution (50% in water, 147 μL, 0.81 mmol) in THF (0.54 mL) at room temperature. After the reaction mixture had been stirred for 17 h at this temperature, the reaction was quenched by addition of 1N hydrochloric acid and the organic materials were extracted twice with ethyl acetate. The combined organic extracts were washed five times with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by neutral silica gel column chromatography (hexane/AcOEt 2:1) gave 4-hydroxy-3-nitro-2-phenylcyclohexanecarbaldehyde (50.6 mg, 0.20 mmol) in 88% yield as a diastereomeric mixture (**5a**/**5b**/**5c**/**5d** 75:8:8:9). The enantiomeric excess was determined by HPLC with a Chiralpak IA column (hexane/2-propanol 25:1; flow rate: 1.0 mL min^{-1}; minor enantiomer $t_r = 46.9$ min, major enantiomer $t_r = 57.8$ min).

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