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Rational Design of Organocatalyst: Highly Stereoselective Michael Addition of Cyclic Ketones to Nitroolefins

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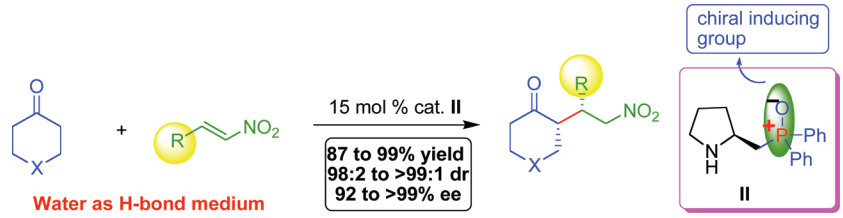
ABSTRACT



A remarkable organocatalyst that facilitates the asymmetric Michael addition of cyclic ketones to nitroolefins in excellent stereoselectivities (98:2 to >99:1 dr, 92% to >99% ee) has been developed and afforded various types of optically active nitroalkane derivatives of synthetic and biological importance. The extremely simple and practical operational procedure at room temperature increases the attractiveness of this reaction.

The important advances made in enantioselective catalytic C−C and C−H bond-forming reactions generally depend on the careful and time-consuming optimization of the structure of the chiral catalyst so as to achieve good to excellent selectivity and catalytic activity. Very subtle changes to the catalyst structure can often lead to large and unpredictable differences to the performance of the catalyst, especially in terms of the enantioselectivity.[1]

The Michael addition reaction, being one of the most general and versatile methods for formation of C−C bonds in organic synthesis, has received much attention in the development of enantioselective catalytic protocols. Most of the efforts aimed at achieving asymmetric versions of this process by using chiral organocatalysts not only showed moderate enantioselectivity but also required low temperature, an additive and a large excess of organic solvents.[2,3] Since the beginning of the new millennium, a great number of pyrrolidine-type asymmetric organocatalysts have been reported.[4−6] The cyclic five-membered secondary amine structure of these compounds is now regarded as one of the "privileged" backbones for asymmetric catalysis. The general strategies used in designing a set of new catalyts are represented below.

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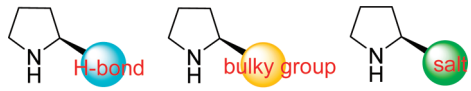


Previous strategies

Thus far, the design and development of more efficient chiral organocatalysts and practical approaches in Michael additions to achieve higher enantio- and diastereoselectivities remains a major challenge in synthetic organic chemistry. Therefore, we have developed and designed a set of new catalysts. Our design of catalyst **II** comprises of this "privileged" chiral pyrrolidine unit covalently adhered to a phosphine oxide moiety,[7] so that the former can serve as catalytic site and the latter as chiral-induction group that contains a very polar P═O bond. In order to test the feasibility of the above-mentioned catalyst, nitroolefins were chosen as Michael acceptors due to the polar nitro group and cyclohexanone as a donor for forming enamine. The strong polar P═O group may interact favorably with the nitro group via dipole interactions mediated by water to allow greater control in enantio- and diastereoselectivities (Figure 1).

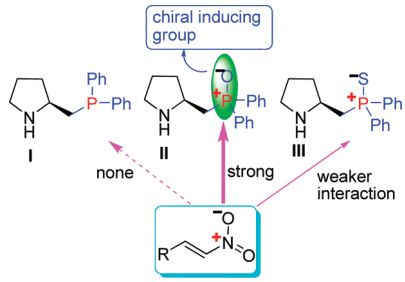


Figure 1. Structures and action of designed catalysts.

On the basis of this hypothesis, DFT calculations were carried out. Two transition-state geometries are reported to demonstrate the fact that hydrogen bonds formed with water molecules are important factors in controlling the stereochemistry (Figure 2). **TS1** is a transition state from *syn*-

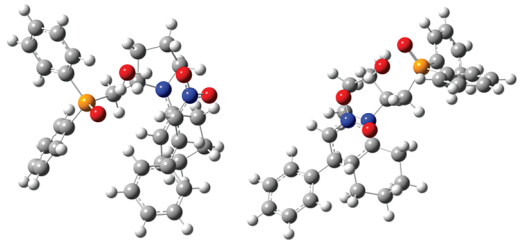
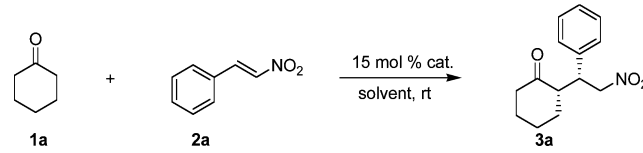


Figure 2. DFT-calculated transition state **TS1** (left) and **TS2** (right).

enamine, while **TS2** is *anti*-enamine. In **TS1**, the forming C−C bond length between enamine and nitrostyrene is 1.9901 Å, and the C═C bond of the nitrostyrene is elongated to 1.4205 Å; the hydrogen bond distance mediated by water is reasonable. In the gas phase, the energy of **TS1** is 4.36 kcal/mol lower than that of **TS2** due to the fact that the bulky phosphine group has less steric interaction with the six-membered ring in the *syn*-enamine.

Model experiments were conducted with nitrostyrene and cyclohexanone.[8] Initially, the conjugated addition reaction was examined in a few solvents at room temperature with catalyst **II**. Only moderate yields of the desired adduct were observed in polar solvents (Table 1, entries 4−6), whereas

Table 1. Effects of Solvents and Catalysts on the Addition of Cyclohexanone to *trans*-Nitrostyrene[a]



1a 2a 3a

entry	catalyst	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**II**	CH_2Cl_2	24	67	99:1	99
2	**II**	benzene	24	86	>99:1	>99
3	**II**	hexane	24	98	>99:1	>99
4	**II**	DMSO	24	41	97:3	90
5	**II**	MeOH	24	62	97:3	94
6	**II**	THF	24	61	98:2	98
7	**II**	neat	16	99	>99:1	>99
8	**I**	neat	16	99	97:3	91
9	**III**	neat	16	77	95:5	17
10[e]	**II**	neat	6	98	97:3	96

[a] Unless otherwise noted, all reactions were conducted using nitroolefin (0.3 mmol, 1.0 equiv) and cyclohexanone (1.5 mmol, 5.0 equiv) in the presence of 15 mol % of catalyst at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture or HPLC. [d] Determined by chiral HPLC analysis (chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 mL/min). [e] 30 mol % of catalyst **II**.

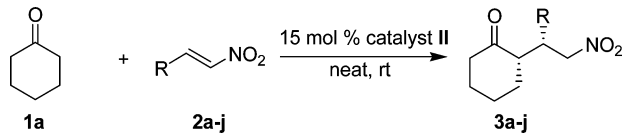
moderate to excellent yields with excellent enantioselectivities of the product were obtained in nonpolar solvents such as benzene and hexane (entries 2 and 3). Although the up to 30 mol % of catalyst loading could dramatically increase the reaction rate (entry 10), the diastereoselectivity and enantioselectivity dropped. When the reaction was tested under solvent-free conditions, we achieved almost quantitative yield with over 99% enantiomeric excess (ee) and over 99:1 diastereomeric ratio (dr).

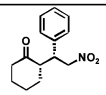
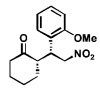
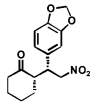
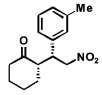
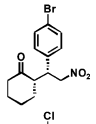
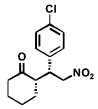
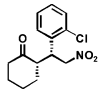
This initial finding strengthened our suggestion that the polar bond P═O of the new catalyst is an important role for the addition reaction. To further investigate the effects of dipole interaction, we tested chiral catalysts **I** (without polar bond) and **III** (bearing a P═S bond). Although moderate yield and dr were obtained when nonpolar bond catalyst **I** was used (Table 1, entry 9), there was almost no ee detected in the product. When catalyst **III** containing a weaker polar bond (P═S) was utilized, the yield was excellent but the dr and ee were slightly decreased (Table 1, entry 8). These results further demonstrated that the P═O bond in catalyst

II is indispensable in achieving excellent diastereoselectivity and enantioselectivity.

Under the optimized conditions, a variety of nitroolefins with different structures were investigated, and the results are summarized in Table 2. Various styrene-type nitroolefins

Table 2. Michael Addition of Cyclohexanone with Nitroolefins Catalyzed by **II** under Neat Conditions at Room Temperature[a]

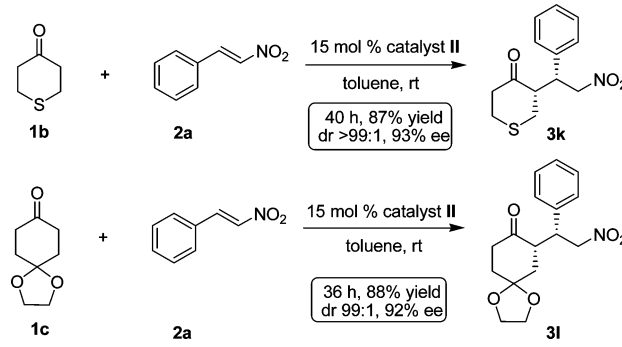


entry	reactant (R)	product	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	C_6H_5		16	99	>99:1	>99
2	2-CH_3O-C_6H_4		24	96	>99:1	97
3	3,4-methylene dioxy-C_6H_3		18	92	>99:1	>99
4	3-CH_3-C_6H_4		24	98	>99:1	98
5	2-CH_3-C_6H_4		26	95	>99:1	98
6	2-Furanyl		14	97	>99:1	>99
7	3-Furanyl		13	98	99:1	98
8	4-Br-C_6H_4		13	97	>99:1	99
9	4-Cl-C_6H_4		17	96	98:2	98
10	2-Cl-C_6H_4		24	93	99:1	99

[a] Unless otherwise noted, all reactions were conducted using nitroolefin (0.3 mmol, 1.0 equiv) and cyclohexanone (1.5 mmol, 5.0 equiv) in the presence of 15 mol % of catalyst **II** under neat conditions at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude mixture or HPLC. [d] Determined by chiral HPLC analysis (see the Supporting Information).

reacted smoothly with cyclohexanone and excellent yields, diastereoselectivities, and enantioselectivities (entries 1−10) were obtained. Generally, aryl compounds containing electron-withdrawing and electron-donating substituents influenced the result slightly, especially in dr (up to >99:1) and ee (up to >99%). The excellent enantioselectivities achieved for the heteroaryl substrates (Table 2, entries 5−7) have also indicated that they are good Michael acceptors to cyclohexanone. Furthermore, other cyclic ketones (**1b** and **1c**) also react smoothly with nitroolefin and maintained excellent stereoselectivities (Scheme 1).

Scheme 1. Different Ketones Reacted with *trans*-Nitrostyene



Based on the experimental results described above, the stereochemical outcome may be accounted for by a synclinal transition state assembly. We propose that the pyrrolidine ring will first react with a carbonyl compound to form an enamine. Subsequently, the P═O group, via a strong H-bond mediated by water, will orientate the nitro group so that the enamine will attack the nitro olefin from the *Re*-face to give the highly enantio- and diastereoselective product. This explanation is consistent with the experimental results. The absolute configuration of **3h** was determined by X-ray crystallography (Figure 3).

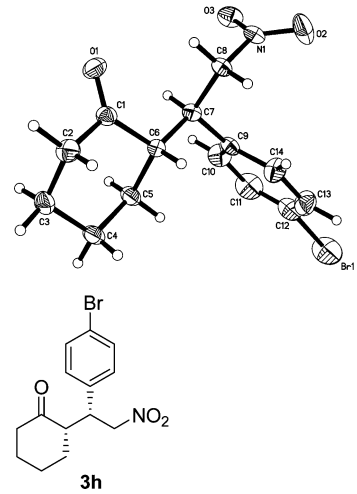
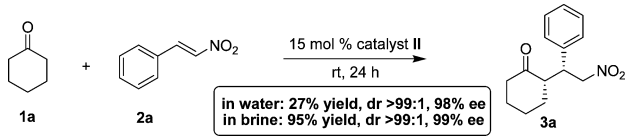


Figure 3. X-ray crystal structure of **3h**.

Performing such reactions on water[9] could potentially give rise to ideal reactions from a green chemistry perspective. In our first attempt on water, although the stereoselectivity

does not change too much, low conversion and yield were observed using catalyst **II**. When brine was used as a solvent, excellent yield and high diastereo- and enantioselectivities were provided. In these electrolyte-rich aqueous solutions, the anion intermediate is readily complexed by metal cations, which may contribute to the result (Scheme 2).

Scheme 2. Michael Reaction in Aqueous Medium



In summary, we have developed a remarkably efficient organocatalyst that facilitates the asymmetric Michael addition of cyclic ketones to nitroolefins in excellent yields (87% to 99%) and stereoselectivies (98:2 to >99:1 dr and 92% to >99% ee), hence producing various types of optically active nitroalkane derivatives of synthetic and biological importance.[10] The new catalyst containing a pyrrolidine unit and a phosphine oxide moiety is proven to be very important in controlling the stereochemistry of the adducts.The extremely practical operational procedure that involves the mixing of reactants with catalyst at room temperature increases the attractiveness of this reaction. We hope that more efficient and practical catalysts can be designed based on the nature of the reaction and that this strategy may lead to a range of enantiomeric reactions that involves rationally designed catalysts.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallographic data (CIF file of **3h**). This material is available free of charge via the Internet at http://pubs.acs.org.

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