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# Noyori's Ts-DPEN Ligand: Simple yet Effective Catalyst for the Highly Enantioselective Michael Addition of Acetone to Nitroalkenes

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**Keywords:** Organocatalysis / Michael addition / Asymmetric synthesis / Amines

Highly enantioselective Michael addition of acetone to a variety of nitroalkenes promoted by simple chiral primary amine bifunctional catalysts (e.g., Noyori's Ts-DPEN ligand) together with terephthalic acid in excellent yields (84–99 %) and enantioselectivities (93–98 % *ee*) is reported.

## Introduction

The asymmetric Michael addition has emerged as one of the most powerful and efficient methods for C–C bond formation in organic synthesis.[1] Over the past years, various efficient chiral organocatalysts have been developed for the enantioselective Michael addition of aldehydes,[2] ketones,[3] and 1,3-dicarbonyl compounds[4] to nitroalkenes. In 2006, Córdova and co-workers[5] reported the first chiral primary amine-catalyzed Michael additions of ketones to nitroalkenes. Since then, several effective organic small molecules such as primary amine–thiourea,[6] cinchona alkaloid derivatives,[7] and bispidine-based primary–secondary amine[8] have been developed for this addition. Although excellent results have been achieved by these systems, few excellent protocols for the asymmetric Michael addition of acetone to nitroalkenes are reported.[9] The successful design of a simple and highly effective chiral catalyst for the Michael reaction of acetone to nitro olefins with excellent enantioselectivities is still a challenging task.

Over the past decade, a remarkable number of enantioselective reactions promoted by hydrogen-bond activation have been identified, providing solutions to challenging transformations of important molecules for asymmetric synthesis.[10] In 1995, Noyori and co-workers first introduced *N*-[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide (Ts-DPEN) as a chiral ligand for the highly efficient asymmetric transfer hydrogenation of ketones and imines.[11] Xu[12] first reported the asymmetric Michael addition of 1,3-dicarbonyl compounds to nitro olefins directly catalyzed by this simple bifunctional organocatalyst in moderate yields and enantioselectivities. Most recently, Zhao[13] reported the Michael reactions of 3-methyl-2-pyrazolin-5-one with α,β-unsaturated ketones by using Ts-DPEN as a catalyst in poor enantioselectivities. To date, this simple and commercially available Ts-DPEN ligand has not caught enough attention in the area of small-molecule catalysis.

As a part of our continuing interests in asymmetric small-molecule catalysis,[14] we recognized that Noyori's Ts-DPEN ligand, commercially available at a low cost, bearing an amino sulfonamide moiety and a primary amino group on the chiral scaffold may activate the reaction substrate through hydrogen bonding provided by the amino sulfonamide moiety in a manner similar to that observed for primary amine–thiourea bifunctional catalysts that have been shown to offer synergistic cooperation or dual activation functionalities in the Michael addition of ketones to nitro olefins. Herein, we wish to report the simple bifunctional chiral primary amine sulfonamide catalyzed enantioselective Michael addition of acetone to a very wide range of nitroalkenes in excellent yields (up to 99%) and enantioselectivities (up to 98% *ee*).

## Results and Discussion

Initially, a variety of optically active primary amines shown in Figure 1 were screened as catalysts, and the reaction of acetone with *trans*-β-nitrostyrene was used as a model reaction at room temperature in $CH_2Cl_2$; the results are summarized in Table 1. Primary amine–thiourea derivatives **1a** and **1b** were found to be highly efficient (up to 91% yield) for this asymmetric addition, whereas only moderate enantioselectivities (69 and 75% *ee*; Table 1, Entries 1 and 2) were obtained. To our delight, the reaction proceeded smoothly when simple primary amine sulfonamide deriva-

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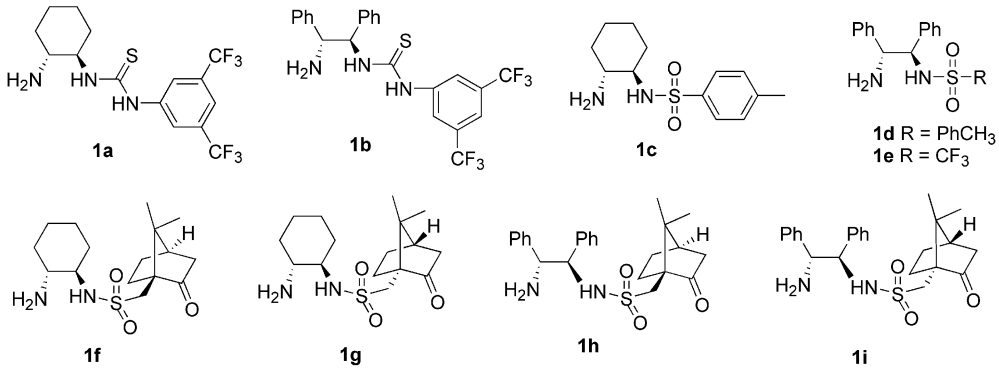
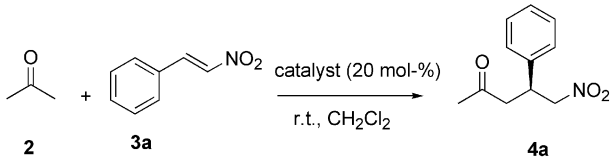



Figure 1. Chiral primary amine catalysts evaluated.

tives **1c**–**i** were used; better enantioselectivities were also obtained (73–92%*ee*; Table 1, Entries 3–9). Particularly, catalyst **1d** afforded the product in good yield and excellent enantioselectivity (92%*ee*; Table 1, Entry 4), and this catalyst was selected for further studies. These results demonstrate that the amino sulfonamide moiety may play a key role in promoting the enantioselectivity of the reaction.

Table 1. The screening of chiral primary amine catalysts **1a**–**i**.[a]

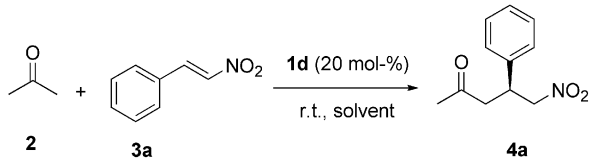



| Entry | Catalyst | Time [h] | % Yield[b] | % *ee*[c] |
|---|---|---|---|---|
| 1 | **1a** | 72 | 91 | 69 |
| 2 | **1b** | 72 | 91 | 75 |
| 3 | **1c** | 192 | 78 | 73 |
| 4 | **1d** | 192 | 62 | 92 |
| 5 | **1e** | 192 | 57 | 86 |
| 6 | **1f** | 192 | 81 | 74 |
| 7 | **1g** | 192 | 72 | 82 |
| 8 | **1h** | 192 | 61 | 83 |
| 9 | **1i** | 192 | 29 | 91 |

[a] Unless otherwise specified, all reactions were carried out with acetone (**2**, 2.0 mmol), *trans*-β-nitrostyrene (**3a**, 0.20 mmol), and the catalyst (0.04 mmol, 20 mol-%) in $CH_2Cl_2$ (1 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] The *ee* values were determined by HPLC with the use of a Chiral Whelk-01 column.

A series of solvents were then investigated, and the results are listed in Table 2. These results revealed that the solvent has a significant effect on the rate and the enantioselectivity of the reaction. Polar solvents such as $CH_3OH$, DMF, and DMSO resulted in poor yields (8–29%) and moderate to good enantioselectivities (17–84%*ee*; Table 2, Entries 10–15), probably because these solvents weaken or retard the formation of hydrogen bonds between *trans*-β-nitrostyrene and the amino sulfonamide moiety of **1d**. By contrast, nonpolar or low polar solvents such as toluene, *p*-xylene, benzene, $CH_2Cl_2$, and cyclohexane gave better yields (62–87%) and enantioselectivities (90–97%*ee*; Table 2, Entries 1–4). When saturated brine was used as the solvent, an excellent yield (99%) was obtained, but only good enantioselectivity (82%*ee*) was achieved (Table 2, Entry 9). When the reaction was carried out in toluene, the best enantioselectivity (97%*ee*) and a good yield (80%) were obtained (Table 2, Entry 2), and this solvent was selected for further optimization. These results strongly demonstrate that hydrogen-bond formation has an important effect on both the reactivity and the enantioselectivity of the reaction.

Table 2. The effect of reaction solvents.[a]




| Entry | Solvent | Time [h] | % Yield[b] | % *ee*[c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 192 | 62 | 92 |
| 2 | $PhCH_3$ | 120 | 80 | 97 |
| 3 | *p*-xylene | 192 | 87 | 95 |
| 4 | cyclohexane | 192 | 73 | 90 |
| 5 | $ClCH_2CH_2Cl$ | 192 | 48 | 91 |
| 3 | $CHCl_3$ | 192 | 48 | 91 |
| 7 | hexane | 192 | 37 | 85 |
| 8 | $Et_2O$ | 192 | 38 | 92 |
| 9 | saturated brine | 192 | 99 | 82 |
| 10 | $H_2O$ | 192 | 29 | 84 |
| 11 | $CH_3OH$ | 192 | 20 | 54 |
| 12 | $(CH_3)_2CHOH$ | 192 | 14 | 81 |
| 13 | DMF | 192 | trace | n.d. |
| 14 | $CH_3CN$ | 192 | 16 | 50 |
| 15 | DMSO | 192 | 15 | 17 |
| 16 | acetone | 192 | 8 | 78 |

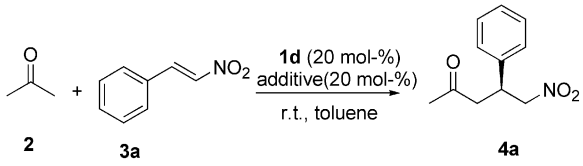
[a] Unless otherwise specified, all reactions were carried out with acetone (**2**, 2.0 mmol), *trans*-β-nitrostyrene (**3a**, 0.20 mmol), and catalyst **1d** (0.04 mmol, 20 mol-%) in the solvent (1 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] The *ee* values were determined by HPLC with the use of a Chiral Whelk-01 column.

To further improve the yield and enantioselectivity of the reaction, a wide range of acid and base additives[15] were studied, and the results are summarized in Table 3. Among the acids screened, *p*-hydroxybenzoic acid and terephthalic

acid were found to be promising additives, as they afforded the best results in terms of both yield and enantioselectivity (Table 3, Entries 8 and 9). Acetic acid, benzeneacetic acid, and *m*-hydroxybenzoic acid also provided good yields and enantioselectivities (Table 3, Entries 3, 5, 11). However, stronger acids such as trifluoromethanesulfonic acid reduced the reactivity and gave a poor yield (25%; Table 3, Entry 15). Base additives such as imidazole, DIPEA, TEA, and DMAP were also evaluated and no significant improvement was obtained (Table 3, Entries 16–19). Finally, terephthalic acid was selected as the additive for further investigation (Table 3, Entry 9).

Table 3. The effect of additives.[a]



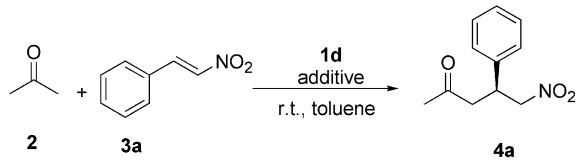

| Entry | Additive | % Yield[b] | % *ee*[c] |
|---|---|---|---|
| 1 | – | 80 | 97 |
| 2 | HCOOH | 54 | 95 |
| 3 | AcOH | 87 | 95 |
| 4 | PhCOOH | 71 | 90 |
| 5 | $PhCH_2COOH$ | 94 | 93 |
| 6 | $4\text{-}H_3CC_6H_4COOH$ | 52 | 94 |
| 7 | $4\text{-}ClC_6H_4COOH$ | 67 | 91 |
| 8 | $4\text{-}HOC_6H_4COOH$ | 99 | 94 |
| 9 | $4\text{-}HOOCC_6H_4COOH$ | 99 | 95 |
| 10 | $4\text{-}O_2NC_6H_4COOH$ | 52 | 91 |
| 11 | $3\text{-}HOC_6H_4COOH$ | 86 | 92 |
| 12 | $2\text{-}HOC_6H_4COOH$ | 39 | 92 |
| 13 | $2,6\text{-}F_2C_6H_3COOH$ | 57 | 91 |
| 14 | $4\text{-Cl-}2\text{-}O_2NC_6H_3COOH$ | 15 | 92 |
| 15 | $CF_3COOH$ | 25 | 84 |
| 16 | imidazole | 90 | 92 |
| 17 | DMAP | 70 | 95 |
| 18 | DIPEA | 40 | 94 |
| 19 | $Et_3N$ | 30 | 93 |

[a] Unless otherwise specified, all reactions were carried out with acetone (**2**, 2.0 mmol), *trans*-β-nitrostyrene (**3a**, 0.20 mmol), catalyst **1d** (0.04 mmol, 20 mol-%), and the additive (0.04 mmol, 20 mol-%) in toluene (1 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] The *ee* values were determined by HPLC with the use of a Chiral Whelk-01 column.

Other parameters, for example, the amount of acetone, catalyst loading, and reactant concentration, were also investigated, but no superior results were obtained (Table 4). Through these screenings, the optimized reaction conditions were found to be a combination of **1d** (20 mol-%), terephthalic acid (20 mol-%), acetone (10 equiv.), and toluene as the solvent at room temperature for 5 d.

Under the optimized reaction conditions, the scope and the limitations of this Michael reaction with different nitroalkenes were examined. As shown in Table 5, excellent yields (up to 99%) and enantioselectivities (up to 98%*ee*) were achieved with various nitroalkenes bearing either electron-donating or electron-withdrawing substituents in the

Table 4. The effect of the amount of acetone, catalyst loading, and reactant concentration.[a]




| Entry | Acetone [equiv.] | Catalyst [mol-%] | Conc. [M] | % Yield[b] | % *ee*[c] |
|---|---|---|---|---|---|
| 1 | 10 | 20 | 0.2 | 99 | 95 |
| 2 | 5 | 20 | 0.2 | 91 | 95 |
| 3 | 2 | 20 | 0.2 | 51 | 93 |
| 4 | 10 | 15 | 0.2 | 91 | 95 |
| 5 | 10 | 10 | 0.2 | 75 | 95 |
| 6 | 10 | 20 | 0.4 | 82 | 92 |
| 7 | 10 | 20 | 0.1 | 75 | 93 |
| 8 | 10 | 20 | 0.05 | 60 | 93 |

[a] Unless otherwise specified, all reactions were carried out with acetone (**2**, 2.0 mmol), *trans*-β-nitrostyrene (**3a**, 0.20 mmol), terephthalic acid (0.04 mmol, 20 mol-%), and catalyst **1d** (0.04 mmol, 20 mol-%) in toluene (1 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] The *ee* values were determined by HPLC with the use of a Chiral Whelk-01 column.

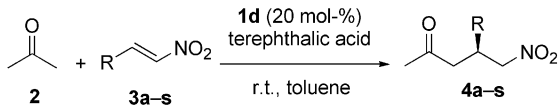
*para* (Table 5, Entries 2–7), *meta* (Table 5, Entries 8 and 9), or *ortho* position (Table 5, Entries 10–13) of the aromatic ring, regardless of the nature and the position of the substituted group on the aromatic ring. To broaden the substrate scope to include heteroaromatic nitroalkenes, reactions were carried out under the optimized conditions and excellent yields and enantioselectivities were obtained (Table 5, Entries 18 and 19).

Importantly, we sensed the application and significance of our process in the synthesis of specific chiral pharmaceuticals or related intermediates, because of the generality and representation of the reaction. Especially, most of the target products are solids, which may be easily recrystallized to afford enantiopure compounds (>99%*ee*), and commercially available catalyst **1d** is cheap and may be easily separated and reused. Thus, we are now devising and processing this reaction and hope to extend its application in the large-scale manufacture of related chiral molecules. All this may provide multiple approaches and choices for chiral pharmaceutical preparations.

On the basis of the experimental results described above, we suggest a plausible dual activation model.[16] The two substrates involved in the reaction are activated simultaneously by Ts-DPEN, as shown in Figure 2. The carbonyl group of acetone is assumed to interact with the primary amine moiety of Ts-DPEN via an imine intermediate. The acid additive is proposed to activate the imine through removal of the proton from the imine, thus increasing the nucleophilic ability of the reacting carbon center. The H-sulfonamide activates the nitro olefins through a single hydrogen bond, which enhances the electrophilicity of the olefin.

Table 5. Michael reaction of acetone to nitrostyrenes.[a]




| Entry | R | % Yield (product)[b] | % *ee*[c] |
|---|---|---|---|
| 1 | Ph | 99 (**4a**) | 95 |
| 2 | 4-$FC_6H_4$ | 87 (**4b**) | 96 |
| 3 | 4-$ClC_6H_4$ | 94 (**4c**) | 96 (>99)[d] |
| 4 | 4-$BrC_6H_4$ | 99 (**4d**) | 96 |
| 5 | 4-$O_2NC_6H_4$ | 92 (**4e**) | 96 |
| 6 | 4-$H_3CC_6H_4$ | 91 (**4f**) | 95 |
| 7 | 4-$H_3COC_6H_4$ | 85 (**4g**) | 97 |
| 8 | 3-$O_2NC_6H_4$ | 90 (**4h**) | 97 |
| 9 | 3-$FC_6H_4$ | 92 (**4i**) | 94 |
| 10 | 2-$ClC_6H_4$ | 90 (**4j**) | 97 |
| 11 | 2-$BrC_6H_4$ | 87 (**4k**) | 97 |
| 12 | 2-$O_2NC_6H_4$ | 99 (**4l**) | 97 |
| 13 | 2-$H_3COC_6H_4$ | 94 (**4m**) | 98 |
| 14 | 3,4-$(H_3CO)_2C_6H_3$ | 91 (**4n**) | 97 |
| 15 | 3,4,5-$(H_3CO)_3C_6H_2$ | 84 (**4o**) | 96 |
| 16 | 1-naphthyl | 97 (**4p**) | 94 |
| 17 | 6-$H_3CO$-1-naphthyl | 88 (**4q**) | 93 |
| 18 | 2-furyl | 96 (**4r**) | 98 |
| 19 | 2-thienyl | 98 (**4s**) | 96 |

[a] Unless otherwise specified, all reactions were carried out with acetone (**2**, 2.0 mmol), nitroalkene **3** (0.20 mmol), terephthalic acid (0.04 mmol, 20 mol-%), and catalyst **1d** (0.04 mmol, 20 mol-%) in toluene (1 mL) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC with the use of a Chiral Whelk-01 column or a chiralpak AD-H or chiralpak OD-H column; the absolute configurations were determined by comparison with literature data.[9g,9h] [d] After single recrystallization from EtOAc/hexane (1:10).

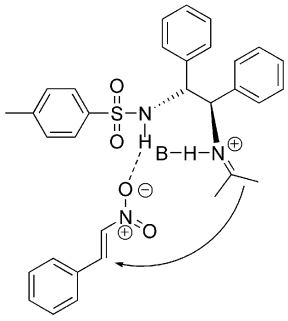


Figure 2. Possible transition-state model for the reaction.

## Conclusions

In summary, we have developed a highly enantioselective Michael reaction of acetone with nitro olefins catalyzed by a simple and commercially available primary amine bifunctional catalyst, represented by Noyori's Ts-DPEN ligand, in excellent yields (84–99%) and enantioselectivities (93–98%*ee*). These excellent results and the availability and recycling of the catalyst make the current reaction potentially applicable in the large-scale manufacture of related chiral pharmaceuticals under industrially accepted conditions and at a low cost. Further investigations of this reaction and the application of this catalyst in other asymmetric catalytic reactions are in progress.

## Experimental Section

**Typical Procedure:** Catalyst **1d** (0.04 mmol) was added to a stirred solution of acetone (**2**, 2.0 mmol) in the solvent (1 mL) under an atmosphere of air. The resulting solution was stirred for 5 min prior to the addition of nitro olefin **3** (0.20 mmol) and the additive (0.04 mmol). After stirring for the indicated reaction time at room temperature (monitored by TLC), the crude adduct was purified by column chromatography (petroleum ether/ethyl acetate, 10:1). The enantiomeric excess of the pure product was determined by chiral HPLC analysis.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, spectra, and NMR spectroscopic data for complexes **4a**–**s**.

## Acknowledgments

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