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Thiophosphoramide catalyzed asymmetric Michael addition of acetone to functionalized nitrostyrenes: a convenient approach to optically active tetrahydropyrans

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ABSTRACT

Thiophosphoramide **5d** was found to be an effective organocatalyst for the enantioselective Michael reaction of problematic acetone to various hydroxymethyl nitrostyrenes, affording the multisubstituted tetrahydropyrans with three stereogenic centers. The Michael addition products generated were obtained as a single diastereomer with enantioselectivities ranging from 46% to 74% ee.

1. Introduction

The multiple reactivities of the nitro functionality and the versatile valuable building blocks that are created means that the addition of nucleophiles to nitroolefins is recognized as one of the most important Michael additions in organic synthesis.[1] Over the past decade, the organocatalyzed asymmetric version of this process has attracted much attention and significant progress has been seen in this area.[2–5] In contrast to the significant amount of effort that has been devoted to investigating the asymmetric Michael addition to the simple β-substituted nitroolefins, the organocatalytic conjugated additions employing multisubstituted (functionalized) nitroolefins as the Michael acceptors remain rarely studied. The only example of a Michael addition to functionalized nitroolefins is the domino Michael-ketalization of cyclohexanone to hydroxymethyl nitroolefins developed by Chandrasekhar.[3k] It is well known that acetone is one of the most problematic substrates for the nitro-Michael addition, and that the organocatalyzed Michael addition reaction of nitroolefins is a continuing challenge. Therefore, the development of organocatalyzed asymmetric Michael additions of acetone substrates to functionalized nitroolefins would be of great interest. Herein, we report the bifunctional thiophosphoramide organocatalyzed asymmetric Michael addition of acetone to hydroxymethyl nitroolefins, affording a direct and atom-economic approach to enantiomerically enriched multisubstituted tetrahydropyrans.

2. Results and discussion

Firstly, a series of chiral pyrrolidine-based catalysts **1**–**5** were chosen as the catalyst candidates (Fig. 1). In order to evaluate the catalytic efficiency of chiral pyrrolidines, the addition of acetone to hydroxymethyl nitroolefin **6a** was first performed in neat acetone in the presence of 20 mol % of each of these catalysts as well as 10 mol % of benzoic acid as a cocatalyst (Table 1).

(*S*)-Diphenylprolinol **1**[6] and (*S*)-diphenylprolinol trimethylsilyl ether **2**,[7] which were previously reported to provide high degrees of enantioselectivities in many asymmetric transformations appeared to be not effective in this reaction (Table 1, entries 1 and 2). Pyrrolidine-based thioureas **3**,[8] and **4**,[9] which proved to be highly efficient catalysts for the Michael addition to nitroolefin, demonstrated higher catalytic activities, giving the corresponding tetrahydropyran **7a** with enantioselectivities of 47% and 40% ee, respectively (Table 1, entries 3 and 4). Our recently developed bifunctional thiophosphoramide catalysts **5**[10] also proved to be effective for this transformation. However, the substituent on the phosphorus atom has a marked influence on both the catalytic activity and the enantioselectivity. When *O*,*O*-diphenyl thiophosphoramidate **5a** was employed as the catalyst, the reaction was complete in 21 h, providing **7a** with an enantiomeric excess of 40%, whereas thiophosphinamide **5b** proved to be ineffective in this reaction (Table 1, entry 5 vs entry 6). Comparable results were observed for thiophosphoramide **5c**, which contains a tropos biphenyl skeleton (Table 1, entry 7). With respect to enantioselectivity, the best result was obtained with the bulky catalyst (*S*,a*R*)-**5d** bearing an (*R*)-binaphthyl skeleton (Table 1, entry 8, 53% ee). However, under otherwise identical conditions, bifunctional thiophosphoramide (*R*,a*R*)-**5d** afforded **7a** with an eroded enantioselectivity and reversed stereochemistry, indicating that the configuration of the newly formed stereogenic

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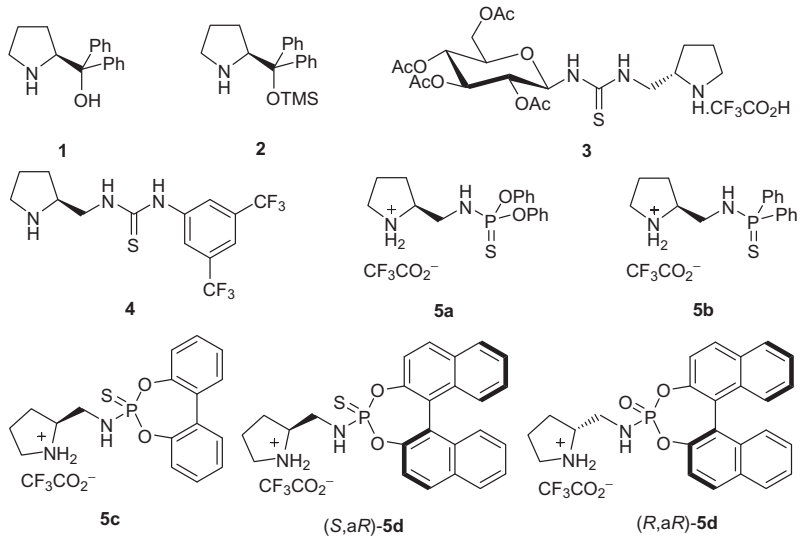
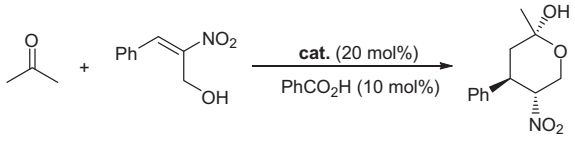


Figure 1. Different pyrrolidine-based organocatalysts.

Table 1
Catalyst evaluation[a]

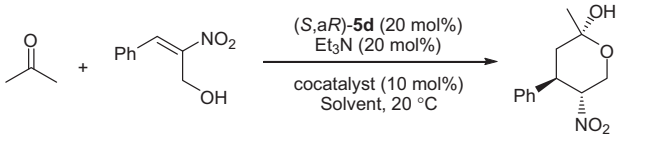


6a 7a

Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	48	Trace	ND[d]
2	**2**	48	Trace	ND[d]
3	**3**/Et_3N	48	51	47
4	**4**	48	49	40
5	**5a**/Et_3N	21	66	40
6	**5b**/Et_3N	72	Trace	ND[d]
7	**5c**/Et_3N	12	34	31
8	(*S*,a*R*)-**5d**/Et_3N	8	48	53
9	(*R*,a*R*)-**5d**/Et_3N	36	43	−11

[a] Reaction conditions: acetone (0.5 mL, 6.8 mmol), nitroolefin **7a** (0.2 mmol), 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by Chiral HPLC analysis.
[d] ND means not determined.

Table 2
Optimization of reaction conditions[a]



6a 7a

Entry	Cocatalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	—	Neat	NR[d]	—	—
2	$PhCO_2H$	Neat	8	48	53
3	CH_3CO_2H	Neat	48	43	50
4	$^tBuCO_2H$	Neat	48	34	49
5	Nicotinic acid	Neat	10	55	53
6	Nicotinic acid	$PhCH_3$	48	40	34
7	Nicotinic acid	THF	48	47	47
8	Nicotinic acid	$CHCl_3$	84	30	34
9	Nicotinic acid	EtOAc	36	51	53
10	Nicotinic acid	CH_3OH	120	Trace	ND[d]
11[e]	Nicotinic acid	Neat	14	65	53
12[f]	Nicotinic acid	Neat	30	75	54
13[g]	Nicotinic acid	Neat	72	75	57

[a] Reaction conditions: acetone (0.5 mL, 6.8 mmol) or acetone (116 mg, 10 equiv) and 0.5 mL of solvent, nitroolefin **7a** (0.2 mmol), 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC analysis.
[d] ND means not determined.
[e] The reaction was carried out at 10 °C.
[f] The reaction was performed at 0 °C.
[g] The reaction was conducted at −10 °C.

centers was determined by the chirality of pyrrolidine, rather than that of binaphthol and that (*R*,a*R*)-**5d** was a mismatched catalyst (Table 1, entry 9, −11% ee). It is worth noting that this reaction was highly diastereoselective, and only a single diastereomer was formed although three stereogenic centers were generated in this reaction.

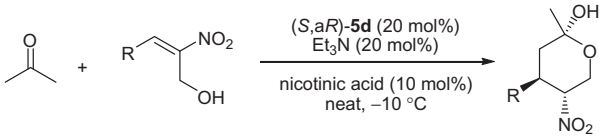
Then, in order to further improve the enantioselectivity other factors, such as cocatalyst, solvent, and reaction temperature, influencing the reaction were thoroughly investigated in the presence of 20 mol % (*S*,a*R*)-**5d**. The results are summarized in Table 2.

As shown in Table 2, the acidic cocatalyst played an important role in the reaction. No reaction occurred without the presence of acidic cocatalysts (Table 2, entry 1 vs entries 2–5). Although almost the same enantioselectivity was obtained for all the cocatalysts tested, the acid strength of the cocatalyst also seemed to have some effect on the catalytic activity. For example, more acidic benzoic acid and nicotinic acid afforded product **7a** within a shorter reaction time (Table 2, entries 2 and 5). Moreover, the use of nicotinic acid as a cocatalyst led to a slightly higher yield than that of benzoic acid. Solvent evaluation revealed that the reaction was best carried out in neat acetone. Generally, the performing of the reaction in different solvents resulted in some loss of stereocontrol (Table 2, entry 5 vs entries 6–9). The reaction was quite sluggish in a protic solvent, such as methanol (Table 2, entry 10). The enantiomeric excess of **7a** was slightly increased by decreasing the reaction temperature from 20 to −10 °C (Table 2, entries 11–13). An enantioselectivity of 57% ee was obtained at the expense of reaction time (Table 2, entry 13).

With the optimized reaction conditions in hand, we next studied the generality of the reaction with a variety of hydroxymethyl nitroolefins. The results are listed in Table 3.

As shown in Table 3, the reaction has a broad applicability with respect to the hydroxymethyl nitroolefins. Moderate to good enantioselectivities (ranging from 46% to 74% ee) were observed

Table 3
Substrate scope of (*S*,a*R*)-**5d** catalyzed asymmetric Michael addition of acetone to functionalized nitroolefins[a]



6a–j **7a–j**

Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph **a**	72	75	56
2	4-ClC_6H_4 **b**	60	55	67
3	2-BrC_6H_4 **c**	96	66	46
4	4-BrC_6H_4 **d**	68	40	71
5	3-FC_6H_4 **e**	36	44	63
6	2-$NO_2C_6H_4$ **f**	72	82	74
7	2-$MeOC_6H_4$ **g**	84	50	52
8	4-$MeOC_6H_4$ **h**	84	63	57
9	2-Furyl **i**	68	41	52
10	2-Thienyl **j**	84	68	50

[a] Reaction conditions: acetone (0.5 mL, 6.8 mmol), nitroolefin **7a** (0.2 mmol), 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC analysis.

with various hydroxymethyl substituted styrene-type nitroolefins bearing either electron-donating or electron-withdrawing substituents on the benzene ring (Table 3, entries 2–8). Moreover, the reaction also tolerated sterically hindered *ortho*-substituted nitroolefins **6c**, **6f**, and **6g**, providing the corresponding *o*-bromo, *o*-nitro, and *o*-methoxyl-substituted product with 46%, 74%, and 52% ee, respectively. In addition, not only aromatic groups but also electron-rich heteroaromatic groups, such as furyl and thienyl were suitable substituents (Table 2, entries 9 and 10).

In order to determine the relative and absolute configuration of the three newly generated stereogenic centers, single crystals suitable for X-ray crystallographic analysis were obtained from compound **7h** bearing a methoxy group.[11] As shown in Figure 2, the six-membered tetrahydropyran ring is in the chair form, the relative larger methoxyphenyl, methyl, and nitro groups occupy equatorial positions. The absolute configuration of **7h** was assigned to be (2*R*,4*R*,5*R*). The stereochemistry of the other products was assigned by analogy.

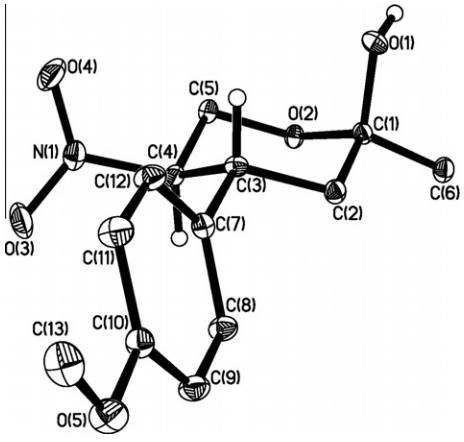


Figure 2. X-ray structure tetrahydropyran **7h**. Most of the hydrogen atoms have been omitted for clarity.

Even though the exact mechanism is still unclear for this reaction, based on our previous report,[10a] it is believed that thiophosphoramide **5d** functions as a bifunctional organocatalyst. The pyrrolidine ring first reacts with acetone to form an enamine with the aid of nicotinic acid. Subsequently, the acidic hydrogen activates and orientates the nitro group through hydrogen-bonding interactions so that the enamine acts as a nucleophile and enantioselectively attacks the nitroolefin, which triggers the second tandem ketalization to afford tetrahydropyrans **7a–j** in an intramolecular fashion.

3. Conclusions

We have developed a highly diastereoselective as well as enantioselective Michael addition of acetone to functionalized nitrostyrenes to provide a direct and atom-economic asymmetric synthetic route toward optically active tetrahydropyrans. This protocol is of considerable interest since this six-membered heterocyclic component is widely found in biologically active molecules and natural products.

4. Experimental

4.1. General procedure for thiophosphoramide (*S*,a*R*)-5d catalyzed asymmetric tandem Michael-ketalizations

A mixture of thiophosphoramide (*S*,a*R*)-**5d** (22.4 mg, 0.04 mmol) and triethylamine (4.0 mg, 0.04 mmol) in acetone (0.5 mL, 6.8 mmol) was stirred at room temperature for 30 min. Then, nicotinic acid (2.5 mg, 0.02 mmol) was added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added functionalized nitroolefin **6** (0.2 mmol) at the required temperature. After the reaction was complete (monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc 3:1) to afford the desired tetrahydropyran **7**.

4.1.1. (2*R*,4*R*,5*R*)-2-Methyl-5-nitro-4-phenyltetrahydro-2*H*-pyran-2-ol 7a

White solid, 75% yield, mp 94–96 °C. $[\alpha]_D^{20} = +23.2$ (*c* 1.0, $CHCl_3$), 56% ee. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.50 (s, 3H, CH_3), 1.82 (t, 1H, *J* = 13.6 Hz), 2.12 (dd, *J* = 3.6 and 13.6 Hz, 1H), 2.18 (br s, 1H, OH), 3.83 (dt, *J* = 4.0 and 12.8 Hz, 1H), 4.08 (dd, *J* = 4.4 and 10.4 Hz, 1H), 4.37 (t, *J* = 10.4 Hz, 1H), 4.84 (dt, *J* = 4.4 and 11.2 Hz, 1H), 7.20–7.32 (m, 5H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 29.3, 41.0, 62.0, 86.5, 95.5, 127.2, 127.8, 129.0, 138.8. HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_4$ $[M+Na]^+$: 260.0893, found 260.0892. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 10.39 (major) and 27.99 min (minor).

4.1.2. (2*R*,4*R*,5*R*)-4-(4-Chlorophenyl)-2-methyl-5-nitro-tetrahydro-2*H*-pyran-2-ol 7b

White solid, 55% yield, mp 84–86 °C. $[\alpha]_D^{20} = +18.8$ (*c* 1.0, $CHCl_3$), 67% ee. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.50 (s, 3H, CH_3), 1.79 (t, *J* = 13.6 Hz, 1H), 2.05 (s, 1H, OH), 2.11 (dd, *J* = 4.0 and 13.6 Hz, 1H), 3.84 (dt, *J* = 4.0 and 12.4 Hz, 1H), 4.07–4.13 (m, 1H), 4.37 (t, *J* = 10.4 Hz, 1H), 4.79 (dt, *J* = 4.8 and 11.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H arom), 7.30 (d, *J* = 8.4 Hz, 2H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.2, 40.5, 41.0, 61.9, 86.4, 95.4, 128.6, 129.2, 133.7, 137.4. HRMS (ESI) *m/z* calcd for $C_{12}H_{14}ClNO_4$, $[M-H]^-$: 270.0539, found 270.0533. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 13.14 (major) and 21.63 min (minor).

4.1.3. (2*R*,4*R*,5*R*)-4-(2-Bromophenyl)-2-methyl-5-nitro-tetrahydro-2*H*-pyran-2-ol 7c

Yellow oil, 66% yield, $[\alpha]_D^{20} = -8.2$ (*c* 1.0, $CHCl_3$), 46% ee. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.49 (s, 3H), 2.08–2.24 (m, 2H), 2.30 (br s, 1H),

4.15 (dd, J = 8.8 and 10.8 Hz, 1H), 4.43 (t, J = 10.8 Hz, 1H), 4.52 (dd, J = 2.8 and 13.2 Hz, 1H), 5.00–5.13 (m, 1H), 7.09–7.13 (m, 1H arom), 7.27–7.32 (m, 2H arom), 7.57 (d, J = 8.0 Hz, 1H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.1, 33.4, 37.2, 62.0, 81.5, 95.5, 124.8, 128.1, 129.0, 133.0, 133.8, 136.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}BrNO_4$, $[M+Na]^+$: 337.9998, found 338.0003. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 11.36 (major) and 12.65 min (minor).

4.1.4. (2*R*,4*R*,5*R*)-4-(4-Bromophenyl)-2-methyl-5-nitrotetrahydro-2*H*-pyran-2-ol 7d

White solid, 40% yield, mp 95–97 °C. $[\alpha]_D^{20} = +16.8$ (c 1.0, $CHCl_3$), 71% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 3H, CH_3), 1.79 (t, J = 13.6 Hz, 1H), 2.11 (dd, J = 4.0 and 13.6 Hz, 1H), 2.17 (br s, 1H), 3.83 (dt, J = 4.0 and 12.8 Hz, 1H), 4.09 (dd, J = 4.8 and 10.8 Hz, 1H), 4.37 (t, J = 10.8 Hz, 1H), 4.79 (dt, J = 4.8 and 11.2 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H arom), 7.45 (d, J = 8.4 Hz, 2H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.3, 40.5, 40.9, 61.9, 86.3, 95.4, 121.7, 129.0, 132.1, 137.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}BrNO_4$, $[M+Na]^+$: 337.9998, found 338.0005. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 14.00 (major) and 21.67 min (minor).

4.1.5. (2*R*,4*R*,5*R*)-4-(3-Fluorophenyl)-2-methyl-5-nitrotetrahydro-2*H*-pyran-2-ol 7e

Yellow oil, 64% yield, mp 73–77 °C. $[\alpha]_D^{20} = +14.4$ (c 1.0, $CHCl_3$), 63% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 3H, CH_3), 1.80 (t, J = 13.6 Hz, 1H), 2.14 (dd, J = 4.0 and 13.6 Hz, 1H), 2.18 (br s, 1H, OH), 3.87 (dt, J = 4.0 and 12.4 Hz, 1H), 4.10 (dd, J = 4.4 and 12.8 Hz, 1H), 4.37 (t, J = 10.8 Hz, 1H), 4.82 (dt, J = 4.8 and 10.8 Hz, 1H), 6.93–7.02 (m, 3H arom), 7.28–7.32 (m, 1H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.3, 40.7, 40.9, 61.9, 86.2, 95.4, 114.2 (d, J = 21.8 Hz), 114.8 (d, J = 21.0 Hz), 123.0 (d, J = 2.8 Hz), 130.5 (d, J = 8.2 Hz), 141.4 (d, J = 7.1 Hz), 163.0 (d, J = 247.1 Hz). HRMS (ESI) m/z calcd for $C_{12}H_{14}FNO_4$, $[M+Na]^+$: 278.0799, found 278.0797. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 9.78 (major) and 19.95 min (minor).

4.1.6. (2*R*,4*R*,5*R*)-2-Methyl-5-nitro-4-(2-nitrophenyl)-tetrahydro-2*H*-pyran-2-ol 7f

Yellow oil. 82% yield, $[\alpha]_D^{20} = -156.8$ (c 1.0, $CHCl_3$), 74% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 3H, CH_3), 1.77 (t, J = 13.6 Hz, 1H), 2.34 (br s, 1H, OH), 2.40 (dd, 4.0 and 13.6 Hz, 1H), 4.15 (dd, J = 4.8 and 10.4 Hz, 1H), 4.34 (t, J = 10.4 Hz, 1H), 4.53 (dt, J = 4.0 and 12.4 Hz, 1H), 5.01 (dt, J = 4.4 and 10.8 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H arom), 7.46 (d, J = 7.6 Hz, 1H arom), 7.60 (t, J = 7.6 Hz, 1H arom), 7.82 (d, J = 8.0 Hz, 1H arom),. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.0, 35.7, 41.1, 62.0, 94.5, 95.4, 125.0, 127.4, 128.4, 133.1, 133.5, 150.3. HRMS (ESI) m/z calcd for $C_{12}H_{14}N_2O_6$, $[M+Na]^+$: 305.0744, found 305.0746. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 25.59 (minor) and 31.56 min (major).

4.1.7. (2*R*,4*R*,5*R*)-4-(2-Methoxyphenyl)-2-methyl-5-nitrotetrahydro-2*H*-pyran-2-ol 7g

Yellow oil, 33% yield, $[\alpha]_D^{20} = +6.0$ (c 1.0, $CHCl_3$), 52% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49 (s, 3H), 2.06 (d, J = 8.8 Hz, 2H), 2.20 (br s, 1H, OH), 3.86 (s, 3H, OCH_3), 4.07–4.13 (m, 2H), 4.38 (t, J = 10.4 Hz, 1H), 5.26 (dt, J = 4.4 and 11.2 Hz, 1H), 6.86–6.92 (m, 2H arom), 7.16 (d, J = 7.6 Hz, 1H arom), 7.23 (t, J = 7.6 Hz, 1H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 30.3, 32.8, 44.7, 55.5, 62.6, 81.8, 91.5, 111.2, 121.2, 127.6, 128.5, 129.3, 156.9. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO_5$, $[M+Na]^+$: 290.0999, found 290.0992. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 10.41 (major) and 11.79 min (minor).

4.1.8. (2*R*,4*R*,5*R*)-4-(4-Methoxyphenyl)-2-methyl-5-nitrotetrahydro-2*H*-pyran-2-ol 7h

White solid, 53% yield, mp105–108 °C. $[\alpha]_D^{20} = +21.0$ (c 1.0, $CHCl_3$), 57% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 3H, CH_3), 1.81 (t, J = 13.6 Hz, 1H), 2.11 (dd, J = 4.0 and 13.6 Hz, 1H), 2.18 (br s, 1H), 3.78 (s, 3H, OCH_3), 3.80–3.83 (m, 1H), 4.07 (dd, J = 4.4 and 10.4 Hz, 1H), 4.38 (t, J = 10.4 Hz, 1H), 4.79 (dt, J = 4.0 and 10.8 Hz, 1H), 6.81 (d, J = 8.0 Hz, 2H arom), 7.14 (d, J = 8.4 Hz, 2H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.4, 40.3, 41.1, 55.2, 62.1, 86.9, 95.6, 114.3, 128.2, 130.8, 159.1. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO_5$, $[M+Na]^+$: 290.0999, found 290.1000. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 16.09 (major) and 21.81 min (minor).

4.1.9. (2*R*,4*S*,5*R*)-4-(Furan-2-yl)-2-methyl-5-nitrotetrahydro-2*H*-pyran-2-ol 7i

White solid, 41% yield, mp75–78 °C. $[\alpha]_D^{20} = +8.2$ (c 1.0, $CHCl_3$), 52% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 3H, CH_3), 1.92 (t, J = 13.2 Hz, 1H), 2.13 (br s, 1H, OH), 2.18–2.22 (m, 1H), 3.0–4.08 (m, 2H), 4.34 (t, J = 10.8 Hz, 1H), 4.81 (dt, J = 4.8 and 11.2 Hz, 1H), 6.12 (d, J = 3.2 Hz, 1H arom), 6.28 (s, 1H arom), 7.33 (s, 1H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.3, 34.7, 38.0, 61.6, 84.7, 95.2, 106.8, 110.3, 142.3, 152.1. HRMS (ESI) m/z calcd for $C_{10}H_{13}NO_5$, $[M+Na]^+$: 250.0686, found 250.0690. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 11.05 (major) and 43.14 min (minor).

4.1.10. (2*R*,4*S*,5*R*)-2-Methyl-5-nitro-4-(thiophen-2-yl)-tetrahydro-2*H*-pyran-2-ol 7j

White solid, 68% yield, mp 88–89 °C. $[\alpha]_D^{20} = +23.2$ (c 1.0, $CHCl_3$), 50% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 3H, CH_3), 1.87 (t, J = 13.6 Hz, 1H), 2.19 (br s, 1H, OH), 2.29 (dd, J = 4.0 and 13.6 Hz, 1H), 4.07 (dd, J = 4.8 and 10.8 Hz, 1H), 4.19 (dt, J = 4.4 Hz and 12.8 Hz, 1H), 4.36 (t, J = 10.8 Hz, 1H), 4.73 (dt, J = 4.8 and 10.8 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H arom), 6.93 (t, J = 3.6, 4.8 Hz, 1H arom), 7.20 (d, J = 5.2 Hz, 1H arom). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 29.3, 36.4, 41.7, 62.0, 87.9, 95.5, 124.5, 125.3, 127.0, 142.1. HRMS (ESI) m/z calcd for $C_{10}H_{13}NO_4S$, $[M+Na]^+$: 266.0457, found 266.0459. HPLC analysis (Chiralpak AD-H column, Hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 225 nm): R_t = 6.75 (major) and 21.18 min (minor).

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References

1. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001; (b) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612–615.
2. For reviews, see: (a) Berner, A. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894; (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716.
3. For the most recent examples of organocatalytic asymmetric Michael additions of ketones or aldehydes to nitro olefins, see: (a) Yang, Z.; Liu, J.; Liu, X.; Wang, Z.; Feng, X.; Su, Z.; Hu, C. *Adv. Synth. Catal.* **2008**, *350*, 2001–2006; (b) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem. Eur. J.* **2008**, *14*, 7504–7507; (c) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719–4721; (d) Xu, D.-Q.; Yue, H.-D.; Luo, S.-P.; Xia, A.-B.; Zhang, S.; Xu, Z.-Y. *Org. Biomol. Chem.* **2008**, *6*, 2054–2057; (e) Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.;

Wang, Y.-F.; Zhang, S.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2008**, 1049–1053; (f) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722–4724; (g) Mandal, T.; Zhao, C. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714–7717; (h) Tuchman-Shukron, L.; Portnoy, M. *Adv. Synth. Catal.* **2009**, *351*, 541–546; (i) Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772–3775; (j) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153–156; (k) Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadeesh, B. *Chem. Commun.* **2009**, 4985–4987; (l) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927–1930; (m) Xu, D.-Z.; Shi, S.; Wang, Y. *Eur. J. Org. Chem.* **2009**, 4848–4853; (n) Liu, J.; Yang, Z.; Liu, X.; Wang, Z.; Liu, Y.; Bai, S.; Lin, L.; Feng, X. *Org. Biomol. Chem.* **2009**, *7*, 4120–4127; (o) Han, B.; Xiao, Y. C.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2009**, *11*, 4660–4663; (p) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354–3356; (q) Ni, B.; Zhang, Q.; Dhungana, K.; Headley, A. D. *Org. Lett.* **2009**, *11*, 1037–1040; (r) Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2009**, *7*, 4279–4284; (s) Lo, C.-M.; Chow, H.-F. *J. Org. Chem.* **2009**, *74*, 5181–5191; (t) Uehara, H.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2009**, *48*, 9848–9852; (u) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50–51; (v) Dong, X.-Q.; Teng, H.-L.; Tong, M.-C.; Huang, H.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, 6840–6842; (w) Li, B.-L.; Wang, Y.-F.; Luo, S.-P.; Zhong, A.-G.; Li, Z.-B.; Du, X.-H.; Xu, D.-Q. *Eur. J. Org. Chem.* **2010**, 656–662; (x) Ma, H.; Liu, K.; Zhang, F.-G.; Zhu, C.-L.; Nie, J.; Ma, J.-A. *J. Org. Chem.* **2010**, *75*, 1402–1409; (y) Peng, L.; Xu, X.-Y.; Wang, L.-L.; Huang, J.; Bai, J.-F.; Huang, Q.-C.; Wang, L.-X. *Eur. J. Org. Chem.* **2010**, 1849–1853.

4. For the most recent examples of organocatalytic asymmetric Michael additions of 1, 3-dicarbonyl compounds to nitro olefins, see: (a) Ju, Y.-D.; Xu, L.-W.; Li, L.; Lai, G.-Q.; Qiu, H.-Y.; Jiang, J.-X.; Lu, Y. *Tetrahedron Lett.* **2008**, *49*, 6773–6777; (b) Gao, P.; Wang, C.; Wu, Y.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2008**, 4563–4566; (c) Zhang, Z.; Dong, X.-Q.; Chen, D.; Wang, C.-J. *Chem. Eur. J.* **2008**, *14*, 8780–8783; (d) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431–1433; (e) Peng, F.-Z.; Shao, Z.-H.; Fan, B.-M.; Song, H.; Li, G.-P.; Zhang, H.-B. *J. Org. Chem.* **2008**, *73*, 5202–5205; (f) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195–5198; (g) Li, H.; Zu, L.; Xie, H.; Wang, W. *Synthesis* **2009**, 1525–1530; (h) Li, H.; Zhang, S.; Yu, C.; Song, X.; Wang, W. *Chem. Commun.* **2009**, 2136–2138; (i) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437–440; (j) McGarraugh, P. G.; Brenner, S. E. *Tetrahedron* **2009**, *65*, 449–455; (k) Diego, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 6163–6168; (l) Jiang, X.; Zhang, Y.; Liu, X.; Zhang, G.; Lai, L.; Wu, L.; Zhang, J.; Wang, R. *J. Org. Chem.* **2009**, *74*, 5562–5567; (o) Oh, Y.; Kim, S. M.; Kim, D. Y. *Tetrahedron Lett.* **2009**, *50*, 4674–4676; (p) Pu, X.; L, P.; Peng, F.; Zhang, H.; Shao, Z. *Eur. J. Org. Chem.* **2009**, 4622; (q) Pu, X.-W.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *Tetrahedron* **2010**, *66*, 3655.
5. Examples of organocatalytic asymmetric Michael additions of other carbon-centered nucleophiles to nitro olefins, see: (a) Hanessian, S.; Govindan, S.; Warrier, J. S. *Chirality* **2005**, *17*, 540–543; (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969; (c) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897–3900; (d) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293–5296; (e) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391–1394; (f) Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2006**, *4*, 63–70; (g) Ding, M.; Zhou, F.; Qian, Z.-Q.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 2912–2914; (h) Li, X.; Zhang, B.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, *352*, 416–424.
6. (a) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579–2582; (b) Urushima, T.; Yasui, Y.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 2966–2969.
7. Some recent examples for silylated diaryl-2-pyrrolidinemethanol catalyzed asymmetric reaction, see: (a) Mielgo, A.; Velilla, I.; Gomez-Bengoa, E.; Palomo, C. *Chem. Eur. J.* **2010**, *16*, 7496–7502; (b) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656–4660; (c) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356–3359; (d) Jiang, K.; Jia, Z.-J.; Yin, X.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 2766–2769; (e) Wu, X.; Dai, X.; Nie, L.; Fang, H.; Chen, J.; Ren, Z.; Cao, W.; Zhao, G. *Chem. Commun.* **2010**, 2733–2735; (f) Scroggins, S. T.; Chi, Y.; Frechet, J. M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2393–2396.
8. Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141–3147.
9. Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901–2904.
10. (a) Lu, A.; Wu, R.; Wang, Y.; Zhou, Z.; Wu, G.; Fang, J.; Tang, C. *Eur. J. Org. Chem.* **2010**, 2057–2061; (b) Lu, A.; Liu, T.; Wu, R.; Wang, Y.; Zhou, Z.; Wu, G.; Fang, J.; Tang, C. *Eur. J. Org. Chem.* **2010**, 5777–5781; (c) Lu, A.; Wu, R.; Wang, Y.; Zhou, Z.; Wu, G.; Fang, J.; Tang, C. *Eur. J. Org. Chem.* **2010**. doi:10.1002/ejoc.201000892.
11. CCDC-804323 contains the crystallographic data for **7h**. These data may be obtained free of charge from The Cambridge Crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif.