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Direct Asymmetric Michael Additions of Ketones to Nitroolefins and Chalcones Catalyzed by a Chiral C_2-Symmetric Pyrrolidine-based Tetraamine

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C_2-Symmetric pyrrolidine-based tetraamine, available from commercially starting materials, showed good catalytic activity for asymmetric Michael additions of ketones to nitroalkenes especially to chalcones. The reactions proceeded to give the corresponding products in good yields and in a highly selective manner.

Keywords asymmetric catalysis, Michael addition, tetraamine, chalcones, enantioselectivity

Introduction

The Michael addition reaction is widely recognized as powerful tools for the generation of carbon-carbon bonds in organic synthesis.[1] During the past few years, there have witnessed a tremendous growth in the number of organocatalyzed highly stereoselective Michael addition reactions. Among the variants of asymmetric conjugation additions, Michael reactions of ketones to nitroolefins have received much attention. Stimulated by the seminal works of Barbas[2] and List,[3] a wide variety of highly effective organocatalysts have been developed for this reaction. Among all of the catalysts, proline[4] and its derivatives,[5] imidazolidinones developed by MacMillan[6] and chiral thioureas-based catalysts[7] dominated the field.

On the other hand, enantioselective catalytic Michael addition of ketones to chalcones has remained significantly less developed probably due to the low reactivity and high steric hindrance of substrates. As far as we know, only few papers have been published on the asymmetric Michael addition of ketones to chalcones. Wang *et al.* accomplished the addition of ketones to chalcones for the first time with high enantioselectivity using a chiral pyrrolidinylmethylsulfonamide catalyst.[8] Li *et al.* reported the asymmetric Michael addition of cyclopentanone to chalcones directly catalyzed by simple chiral 1,2-diaminocyclohexane-hexanedioic acid with good yields and excellent enantioselectivity.[9] We reported an amino acid ionic liquid[10] and a pyrrolidine-pyridine base catalyst[11] serving for this type Michael addition reaction. Although these catalysts were effective on this type Michael addition, they are not without their drawbacks, such as long reaction time, high catalyst loding and low chemical yields, and these will limit their further application.

Herein, in an effort to search for new and high effective catalysts serving for these reactions, in the present work, we presented a C_2-symmetric pyrrolidine-based tetraamine and the evaluation of the catalyst in asymmetric Michael addition of ketones to nitroolefins and chalcones. The reactions provided Michael adducts in good to excellent yields, diastereoselectivities and enatioselectivities.

Results and Discussion

Using the Michael addition of cyclohexanone (**3a**) and nitrostyrene (**4a**) as a model reaction, our investigation began with screening the organocatalysts **1** and **2** for their catalytic abilities. The initial reactions were performed by using 10 mol% of the catalysts at room temperature under neat condition. As can be seen from the results summarized in Table 1, catalyst **1** is not an effective catalyst for this process (Entry 1), while catalyst **2** exhibited good catalytic activity affording the corresponding products in excellent chemical yields with good diastereoselectivity and enatioselectivity (99% yield, 96∶4 *dr*, 66% *ee*, Entry 2), and this catalyst was selected for further studies. Therefore, the screening of different solvents with catalyst **2** was carried out (Entries 3—9). The results therein show that good yields were achieved in 24 h in solvents such as $CHCl_3$, THF, CH_2Cl_2 and CH_3CN, whereas ionic liquid [Bmim][PF_6], toluene and *i*-PrOH only gave moderate yields. The reaction performed in CH_3CN gave high

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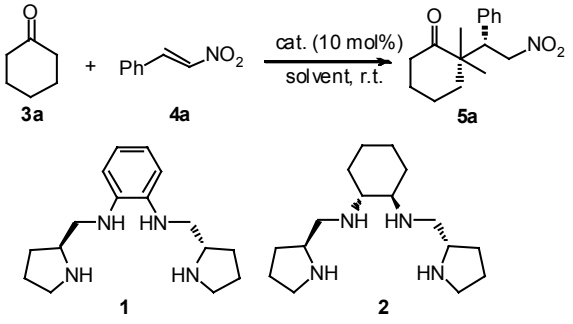
diastereoselectivity and enantioselectivity (95∶5 *dr*, 74% *ee*, Entry 9), whereas the enantioseectivity decreased in $CHCl_3$, THF, [Bmim][PF_6], toluene and *i*-PrOH (Entries 3—6 and 8), and CH_2Cl_2 gave the same *ee* value with neat condition (Entry 7).

Table 1 The effect of different chiral catalysts and solvents on asymmetric Michael additions of cyclohexanone and nitrostyrene[a]

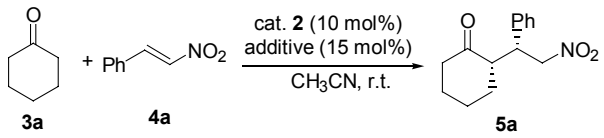


Entry	Cat.	Solvent	*t*/h	Yield[b]/%	*dr*[c][*syn*/*anti*]	*ee*[d]/%
1[e]	**1**	neat	72	<10	n.d.	n.d.
2[e]	**2**	neat	24	99	96∶4	66
3	**2**	$CHCl_3$	24	93	91∶9	58
4	**2**	THF	24	92	92∶8	59
5	**2**	[Bmim][PF_6]	24	74	94∶6	43
6	**2**	toluene	24	64	95∶5	56
7	**2**	CH_2Cl_2	24	93	94∶6	66
8	**2**	*i*-PrOH	24	76	95∶5	64
9	**2**	CH_3CN	24	97	95∶5	74

[a] All reactions were carried out in solvent (0.5 mL) by using **3a** (10 equiv., 2.0 mmol) and **4a** (0.2 mmol) in the presence of the catalysts (0.02 mmol, 10 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] **3a** (20 equiv., 4.0 mmol) was used.

Having identified CH_3CN to be the best solvent for the Michael reaction of cyclohexanone (**3a**) and nitrostyrene (**4a**), the effect of different acid additives were investigated, the results are summarized in Table 2. It has been observed that the presence of additive has a significant influence on the reaction. Initially, when we studied TFA as additive, no reaction was observed (Entry 1). This may be due to the poisoning of catalyst through salt formation. Then we utilized mild acids such as PhCOOH, AcOH, 2-napthanol, phenol and 3,5-dimethylphenol to promote the reaction (Entries 2—8). Among the employed acids, phenol and 3,5-dimethylphenol gave better results than PhCOOH, AcOH and 2-napthanol. Then we screened the amount of the additives using phenol as additive, we found that 15 mol% of additives gave the best result (Entries 5—7). Finally, we chose 3,5-dimethylphenol for the best additive in combination with catalyst **2** (98% yield, 97∶3 *dr*, 91% *ee*, Entry 8).

Table 2 The effect of different acid additives on asymmetric Michael additions of cyclohexanone and nitrostyrene[a]



Entry	Additive	*t*/h	Yield[b]/%	*dr*[c][*syn*/*anti*]	*ee*[d]/%
1	TFA	48	—	—	—
2	PhCOOH	20	97	96∶4	75
3	AcOH	20	95	94∶6	61
4	2-napthanol	20	73	99∶1	68
5	phenol	8	98	94∶6	85
6[e]	phenol	12	96	97∶3	82
7[f]	phenol	15	91	95∶5	78
8	3,5-dimethylphenol	8	98	97∶3	91

[a] All reactions were carried out in CH_3CN (0.5 mL) by using **3a** (10 equiv., 2.0 mmol) and **4a** (0.2 mmol) in the presence of catalysts **2** (0.02 mmol, 10 mol%) and acid additive (0.03 mmol, 15 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] Phenol (10 mol%) was used. [f] Phenol (20 mol%) was used.

Having established the optimal reaction conditions, the scope and the limitation of this Michael reactions with different nitroolefins were examined. As shown in Table 3 (Entries 1—8), excellent yields were achieved in only 8—12 h for all the reactions, regardless of the electronic nature of the aromatic substituents. In most cases, we obtained the *syn* products in high diastereoselectivities (up to 99∶1) and enantioselectivities (up to 91% *ee*). To further study the scope of the reaction, other ketones were also examined as the donor (Entries 9, 10), reactions proceeded smoothly to give the Michael adducts in good yields with good diastereoselectivities and moderate enantioselectivities.

After the above success, we sought to extend the catalytic activity of the C_2-symmetric pyrrolidine-based tetraamine in other Michael addition of cyclohexanone and chalcones. Then, the solvents and acid additives screenings were carried out using catalyst **2**. The initial reactions were performed by using 20 mol% of the catalysts at room temperature in different solvents. The results were shown in Table 4, CH_3CN also offered the best results than other solvents including neat condition, THF and *i*-PrOH (Entry 2). The acid additives were proved to have a significant influence on the reaction, phenol and its derivatives (Entries 5—7, 11, 12) gave better results than PhCOOH and its derivatives no matter with electron-donating or electron-withdrawing substituents (Entries 8—10). Finally, we found 4-nitrophenol was the best additive and 30 mol% of it gave the best result in only 24 h (67% yield, 97∶3 *dr*, 92% *ee*, Entry 7), and it was selected for further studies.

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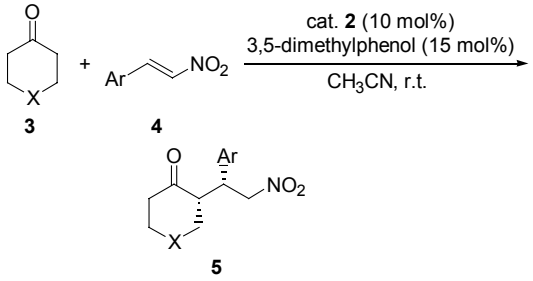
Table 3 Michael reaction of ketones to nitroolefins[a]



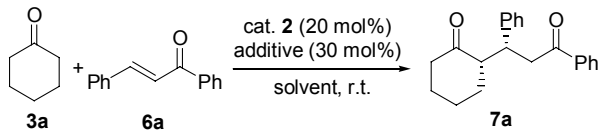
Entry	X	Ar	Product	*t*/h	Yield[b]/%	*dr*[c] [*syn*/*anti*]	*ee*[d]/%
1	CH_2	Ph	**5a**	8	98	97∶3	91
2	CH_2	4-FC_6H_4	**5b**	8	93	94∶6	84
3	CH_2	4-ClC_6H_4	**5c**	8	86	82∶18	85
4	CH_2	3-ClC_6H_4	**5d**	10	86	89∶11	81
5	CH_2	4-MeC_6H_4	**5e**	12	93	90∶10	85
6	CH_2	4-$OMeC_6H_4$	**5f**	8	96	90∶10	77
7	CH_2	2,4-$Cl_2C_6H_3$	**5g**	12	89	95∶5	75
8	CH_2	1-naphthyl	**5h**	8	99	95∶5	85
9	C[O-$(CH_2)_2$O]	Ph	**5i**	8	84	85∶15	63
10	O	Ph	**5j**	10	94	95∶5	66

[a] All reactions were carried out in CH_3CN (0.5 mL) by using **3** (10 equiv., 2.0 mmol) and **4** (0.2 mmol) in the precence of catalyst **2** (0.02 mmol, 10 mol%) and 3,5-dimethylphenol (0.03 mmol, 15 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.

With the optimal conditions in hand, we then explored the generality of this reaction with a variety of chalcones, the results are summarized in Table 5. The present catalytic system is tolerant to a broad range of chalcones with aromatic systems (Ar^1) possessing electron-withdrawing or electron-donating substituents (84%—93% *ee*, Entries 2—9). Excellent levels of enantioselectivities (90%—92% *ee*) and diastereoselectivities (≥95∶5) were obtained for reactions of chalcones containing different aromatic substituents (Ar^2) (Entries 10—12). To further study the scope of catalyst **2** in Michael additions, other cyclic ketones were also examined as the donor (Entries 10—12), reactions with *N*-methyl-4-piperidone and tetrahydro-4*H*-pyran-4-one gave the Michael adducts in good yields (71%—84%) with excellent enantioselectivities (88% *ee*). Reaction of cyclopentanone occurred in high yield (91%), but the diastereoselectivity was low (81∶19), and the major isomer had a comparably lower *ee* (60%) (Entry 12).

The stereochemistries of the major products were determined by comparision of their HPLC spectra with other previous studies.[5c,7b,7i,8-11,13,14] To account for the stereochemical outcome of the Michael reaction, plausible transition states to rationalize the high levels of enantio- and diastereoselectivity of Michael addition reactions of ketones with nitroolefins and chalcones

Table 4 The effect of different solvents and acid additives on asymmetric Michael additions of cyclohexanone and chalcone[a]



Entry	Solvent	Additive	*t*/h	Yield[b]/%	*dr*[c] [*syn*/*anti*]	*ee*[d]/%
1[e]	neat	—	36	50	97∶3	74
2	CH_3CN	—	36	63	96∶4	79
3	THF	—	72	31	96∶4	74
4	*i*-PrOH	—	36	41	98∶2	70
5	CH_3CN	phenol	24	54	96∶4	81
6	CH_3CN	3,5-dimethyl-phenol	24	58	96∶4	81
7	CH_3CN	4-nitrophenol	24	67	97∶3	92
8	CH_3CN	PhCOOH	48	49	95∶5	80
9	CH_3CN	4-methoxy-benzoic acid	48	40	94∶6	79
10	CH_3CN	4-bromoben-zoic acid	48	41	95∶5	76
11[f]	CH_3CN	4-nitrophenol	48	60	95∶5	91
12[g]	CH_3CN	4-nitrophenol	48	63	97∶3	92

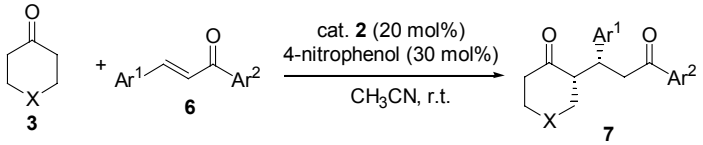
[a] All reactions were carried out in solvents (0.5 mL) using **3a** (10 equiv., 2.0 mmol) and **6a** (0.2 mmol) in the presence of catalysts **2** (0.04 mmol, 20 mol %) and acid additive (0.06 mmol, 30 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis. [e] **3a** (20 equiv., 4.0 mmol) was used. [f] 4-Nitrophenol (20 mol%) was used. [g] 4-Nitrophenol (40 mol%) was used.

are shown in Figure 1 (States A and B). One of the secondary amine of the pyrrolidine ring activates the ketones through the formation of an enamine intermediate, the NH protons can provide transition state stabilization through hydrogen bonding interaction with nitroolefins nitryl group (State A) or chalcone carbonyl group (State B), then, the enamine intermediate adds to the *Si*-face of nitroolefins and chalcones, the Michael adducts are obtained in a highly selective manner after hydrolysis.

Conclusions

In conclusion, we have developed C_2-symmetric pyrrolidine-based tetraamine as a highly effective organocatalyst. The tetraamine catalyst, easily prepared from commercially available *L*-proline, is capable of catalyzing highly enantioselective and diastereoselective Michael additions of ketones to nitroolefins especially ketones to chalcones. It is one of few universal catalysts that can be employed in both of these two kinds of Michael additions to give high yields and good to excellent diastereoselectivities and enantioselectivities. Based on

Table 5 Asymmetric Michael reaction of ketones and chalcones[a]



Entry	X	Ar^1	Ar^2	Product	*t*/h	Yield[b]/%	*dr*[c] [*syn*/*anti*]	*ee*[d]/%
1	CH_2	Ph	Ph	**7a**	24	67	97∶3	92
2	CH_2	4-F-C_6H_4	Ph	**7b**	48	70	>99∶1	93
3	CH_2	2-Cl-C_6H_4	Ph	**7c**	48	77	76∶24	87
4	CH_2	3-Cl-C_6H_4	Ph	**7d**	48	73	94∶6	90
5	CH_2	4-Cl-C_6H_4	Ph	**7e**	48	78	91∶9	84
6	CH_2	4-Br-C_6H_4	Ph	**7f**	24	71	96∶4	84
7	CH_2	4-Me-C_6H_4	Ph	**7g**	24	70	98∶2	92
8	CH_2	Ph	4-ClC_6H_4	**7h**	24	88	99∶1	90
9	CH_2	2-Cl-C_6H_4	4-OMe-C_6H_4	**7i**	72	61	99∶1	92
10	N(CH_3)	Ph	Ph	**7j**	48	84	83∶17	88
11	O	Ph	Ph	**7k**	48	71	97∶3	88
12	none	Ph	Ph	**7l**	24	91	81∶19	60

[a] All reactions were carried out in CH_3CN (0.5 mL) by using **3** (10 equiv., 2.0 mmol) and **6** (0.2 mmol) in the presence of catalysts **2** (0.04 mmol, 20 mol%) and 4-nitrophenol (0.06 mmol, 30 mol%) at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.

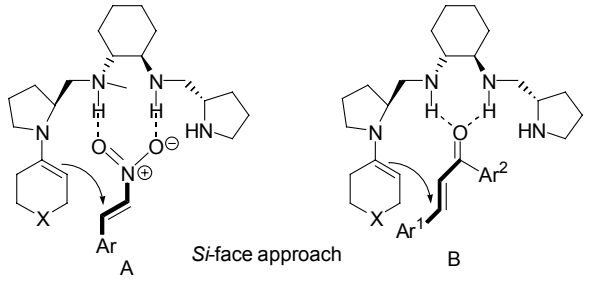


Figure 1 Proposed transition states for **2**-catalyzed Michael reaction.

the experimental results, plausible transition states and the mode of activity of the organocatalyst with the substrate were deduced. Further investigation into the use of this organocatalyst in asymmetric catalysis is still in progress.

Experimental

General information

All the solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz. ^{1}H and ^{13}C NMR chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants (*J*) are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, double; t, triplet; m, multiplet. HR-MS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. HPLC analysis was performed on Shimadzu CTO-10AS by using a Chiralpak AD-H, OD-H or AS-H column purchased from Daicel Chemical Industries. The chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China), and were used without purification prior to use. All reactions unless otherwise noted were carried out directly under air.

Synthesis of organocatalysts

Catalysts **1** and **2** are prepared according to previously reported method[12] from commercially available Boc-*L*-proline, (1*R*,2*R*)-1,2-diaminocyclohexane and *o*-phenylenediamine. The catalyst **1** was obtained in 67% yield as a dark oil, **2** in 62% yield as a colorless oil.

Typical procedure for asymmetric Michael reaction of ketones with nitroolefins

3,5-Dimethylphenol (0.03 mmol, 15 mol%) was added to a mixture of catalyst **2** (0.02 mmol, 10 mol%) and ketones **3** (10 equiv., 2.0 mmol) in CH_3CN (0.5 mL) at room temperature under air. The reaction mixture was stirred for 10 min, and then nitroolefins **4** (0.2 mmol) were added. The homogeneous reaction mixture was stirred at room temperature for 8—12 h. The reaction mixture was directly loaded onto a silica gel column eluting with various mixtures of petroleum ether : EtOAc to afford the Michael adducts **5a**—**5j**.

(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)-cyclohexanone (5a)[5c,7b,13] Yield 98%; *syn*/*anti*＝97∶3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52—1.19 (m, 1H), 1.79—1.52 (m, 4H), 2.10—2.04 (m, 1H), 2.49—2.33 (m, 2H), 2.68

(ddd, J=8.1, 8.4, 11.7 Hz, 1H), 3.76 (dt, J=4.5, 9.9 Hz, 1H), 4.63 (dd, J=9.9, 12.3 Hz, 1H), 4.95 (dd, J=4.5, 12.6 Hz, 1H), 7.16 (d, J=6.9 Hz, 2H), 7.34—7.23 (m, 3H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 9.91 min (minor) and 12.04 min (major), 91% *ee*.

(*S*)-2-[(*R*)-1-(4-Fluorophenyl)-2-nitroethyl]-cyclohexanone (5b)[7i] Yield 93%; *syn*/*anti*=94∶6; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29—1.17 (m, 1H), 1.84—1.52 (m, 4H), 2.14—2.06 (m, 1H), 2.44—2.34 (m, 1H), 2.51—2.45 (m, 1H), 2.70—2.63 (m, 1H), 3.78 (td, J=10.1, 4.5 Hz, 1H), 4.61 (dd, J=12.5, 10.1 Hz, 1H), 4.95 (dd, J=12.5, 4.5 Hz, 1H), 7.02 (t, J=8.6 Hz, 2H), 7.18—7.15 (m, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 25∶75, flow rate 0.7 mL/min, λ=254 nm, retention time: 8.93 min (minor) and 10.81 min (major), 84% *ee*.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-cyclohexanone (5c)[7i,13] Yield 86%; *syn*/*anti*=82∶18; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17—1.28 (m, 1H), 1.51—1.82 (m, 4H), 2.06—2.13 (m, 1H), 2.33—2.50 (m, 2H), 2.61—2.68 (m, 1H), 3.76 (dt, J=10, 4.4 Hz, 1H), 4.59 (dd, J=10.4, 12.8 Hz, 1H), 4.94 (dd, J=4.4, 12.4 Hz, 1H), 7.03—7.18 (m, 2H), 7.28—7.31 (m, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 10.78 min (minor) and 16.07 min (major), 85% *ee*.

(*S*)-2-((*R*)-1-(3-Chlorophenyl)-2-nitroethyl)-cyclohexanone (5d)[13,14] Yield 86%; *syn*/*anti*=89∶11; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23—1.29 (m, 1H), 1.53—1.83 (m, 4H), 2.07—2.14 (m, 1H), 2.34—2.51 (m, 2H), 2.62—2.69 (m, 1H), 3.76 (dt, J=10, 4.4 Hz, 1H), 4.61 (dd, J=10, 12.8 Hz, 1H), 4.95 (dd, J=4.4, 12.8 Hz, 1H), 7.05—7.10 (m, 1H), 7.17 (s, 1H), 7.25—7.27 (m, 2H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=210 nm, retention time: 15.97 min (minor) and 28.15 min (major), 81% *ee*.

(*S*)-2-((*R*)-2-Nitro-1-*p*-tolylethyl)-cyclohexanone (5e)[7i,13] Yield 93%; *syn*/*anti*=90∶10; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17—1.28 (m, 1H), 1.51—1.80 (m, 4H), 2.03—2.11 (m, 1H), 2.31 (s, 3H), 2.34—2.41 (m, 1H), 2.44—2.50 (m, 1H), 2.63—2.69 (m, 1H), 3.72 (dt, J=10, 4.4 Hz, 1H), 4.60 (dd, J=10, 12.4 Hz, 1H), 4.92 (dd, J=4.8, 12.4 Hz, 1H), 7.04 (d, J=8.0 Hz, 2H), 7.12 (d, J=7.6 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 7.84 min (minor) and 9.83 min (major), 85% *ee*.

(*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)-cyclohexanone (5f)[5c,7i] Yield 96%; *syn*/*anti*=90∶10; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30—1.16 (m, 1H), 1.83—1.51 (m, 4H), 2.13—2.03 (m, 1H), 2.52—2.32 (m, 2H), 2.69—2.60 (m, 1H), 3.71 (dt, J=4.5, 9.9 Hz, 1H), 3.78 (s, 3H), 4.58 (dd, J=9.9, 12.0 Hz, 1H), 4.91 (dd, J=4.5, 12.3 Hz, 1H), 6.85 (d, J=8.7 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 12.72 min (minor) and 15.67 min (major), 77% *ee*.

(*S*)-2-((*R*)-1-(2,4-Dichlorophenyl)-2-nitroethyl)-cyclohexanone (5g)[7i] Yield 89%; *syn*/*anti*=95∶5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29—1.38 (m, 1H), 1.57—1.83 (m, 4H), 2.08—2.13 (m, 1H), 2.32—2.48 (m, 2H), 2.82—2.89 (m, 1H), 4.23—4.29 (m, 1H), 4.82—4.93 (m, 2H), 7.18—7.25 (m, 2H), 7.40 (t, J=1.6 Hz, 1H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 10∶90, flow rate 0.7 mL/min, λ=210 nm, retention time: 15.29 min (minor) and 26.38 min (major), 75% *ee*.

(*S*)-2-((*R*)-1-(Naphthalen-1-yl)-2-nitroethyl)-cyclohexanone (5h)[5c,7i,13] Yield 99%; *syn*/*anti*=95∶5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30—1.19 (m, 1H), 1.69—1.47 (m, 4H), 2.10—2.04 (m, 1H), 2.52—2.39 (m, 2H), 2.85 (br s, 1H), 4.76 (br s, 1H), 4.86—4.96 (m, 1H), 5.07 (dd, J=4.2, 12.6 Hz, 1H), 7.58—7.36 (m, 4H), 7.80 (d, J=8.1 Hz, 1H), 7.85 (d, J=8.1 Hz, 1H), 8.15 (s, 1H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 20∶80, flow rate 1.0 mL/min, λ=210 nm, retention time: 12.38 min (minor) and 17.18 min (major), 85% *ee*.

(*S*)-7-[(*R*)-2-Nitro-1-phenylethyl]-1,4-dioxaspiro-[4.5]decan-8-one(5i)[7i] Yield 84%; *syn*/*anti*=85∶15; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57 (t, J=13.4 Hz, 1H), 1.70 (ddd, J=13.0, 5.5, 3.5 Hz, 1H), 1.97 (td, J=13.0, 5.1 Hz, 1H), 2.06 (ddt, J=13.0, 6.6, 3.5 Hz, 1H), 2.48 (dd, J=13.8, 5.1, 3.5 Hz, 1H), 2.76—2.68 (m, 1H), 3.08 (ddd, J=13.0, 10.1, 5.5 Hz, 1H), 4.01—3.82 (m, 5H), 4.63 (dd, J=12.5, 9.8 Hz, 1H), 4.96 (dd, J=12.5, 4.7 Hz, 1H), 7.19—7.17 (m, 2H), 7.36—7.26 (m, 3H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 20∶80, flow rate 1.0 mL/min, λ=210 nm, retention time: 13.88 min (minor) and 21.40 min (major), 63% *ee*.

(*R*)-Tetrahydro-3-((*R*)-2-nitro-1-phenylethyl)-pyran-4-one (5j)[14] Yield 94%; *syn*/*anti*=95∶5; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52—2.72 (m, 2H), 2.84—2.92 (m, 1H), 3.27 (dd, J=9.0, 11.7 Hz, 1H), 3.66—3.87 (m, 3H), 4.10—4.18 (m, 1H), 4.64 (dd, J=9.9, 12.6 Hz, 1H), 4.93 (dd, J=4.5, 12.9 Hz, 1H), 7.17—7.41 (m, 5H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 20∶80, flow rate 1.0 mL/min, λ=254 nm, retention time: 10.33 min (minor) and 18.45 min (major), 66% *ee*.

Typical procedure for asymmetric Michael reaction of ketones with chalcones

Catalyst **2** (0.04 mmol, 20 mol%) and 4-nitrophenol (0.06 mmol, 30 mol%) were added to a mixture of ketones **3** (10 equiv., 2.0 mmol) and chalcones **6** (0.2 mmol) in CH_3CN (0.5 mL) at room temperature. The mixture was stirred vigorously and monitored by TLC. When the reaction was finished, the mixture was purified by flash silica gel chromatography eluting with various mixtures of petroleum ether : EtOAc to afford

the desired products **7a**—**7m**.

(*S*)-2-((*R*)-3-Oxo-1,3-diphenylpropyl)-cyclohexanone (7a)[8] Yield 67%; *syn*/*anti*=97∶3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23—1.30 (m, 1H), 1.59—1.81 (m, 4H), 1.95—2.03 (m, 1H), 2.36—2.49 (m, 1H), 2.52—2.58 (m, 1H), 2.75 (dt, J=10.2, 4.8 Hz, 1H), 3.25 (dd, J=9.9, 16.5 Hz, 1H), 3.51 (dd, J=4.2, 16.5 Hz, 1H), 3.75 (dt, J=9.6, 3.9 Hz, 1H), 7.12—7.16 (m, 3H), 7.22—7.32 (m, 2H), 7.40—7.49 (m, 2H), 7.50—7.57 (m, 1H), 7.89 (d, J=7.2 Hz, 2H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 40∶60, flow rate 0.5 mL/min, λ=254 nm, retention time: 13.64 min (minor) and 20.91 min (major), 92% *ee*.

(*S*)-2-((*R*)-1-(4-Fluorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7b)[8] Yield 70%; *syn*/*anti*>99∶1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21—1.28 (m, 1H), 1.53—1.81 (m, 4H), 1.97—2.05 (m, 1H), 2.37—2.47 (m, 1H), 2.50—2.56 (m, 1H), 2.72 (dt, J=10.0, 4.8 Hz, 1H), 3.20 (dd, J=10.0, 16.0 Hz, 1H), 3.51 (dd, J=4.0, 16.0 Hz, 1H), 3.74 (dt, J=10.0, 4.0 Hz, 1H), 6.96 (t, J=8.8 Hz, 2H), 7.14—7.18 (m, 2H), 7.44 (t, J=7.6 Hz, 2H), 7.54 (t, J=7.2 Hz, 1H) 7.93 (d, J=7.5 Hz, 2H); HPLC analysis: Chiralpak OD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 7.85 min (minor) and 8.42 min (major), 93% *ee*.

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7c)[8] Yield 77%; *syn*/*anti*=76∶24; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20—1.39 (m, 1H), 1.57—1.83 (m, 4H), 2.00—2.09 (m, 1H), 2.36—2.43 (m, 1H), 2.56—2.58 (m, 1H), 2.89 (dt, J=10.0, 4.8 Hz, 1H), 3.38 (dd, J=10.0, 15.6 Hz, 1H), 3.57 (dd, J=4.0, 16.0 Hz, 1H), 4.22 (dt, J=10.0, 4.0 Hz, 1H), 7.09 (t, J=7.2 Hz, 1H), 7.17 (t, J=7.2 Hz, 1H), 7.26—7.31 (m, 2H), 7.41 (t, J=7.2 Hz, 2H), 7.51 (t, J=7.2 Hz, 1H), 7.93 (d, J=7.2 Hz, 2H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 40∶60, flow rate 0.5 mL/min, λ=254 nm, retention time: 12.24 min (minor) and 20.18 min (major), 87% *ee*.

(*S*)-2-((*R*)-1-(3-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7d)[11] Yield 73%; *syn*/*anti*=94∶6; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21—1.29 (m, 1H), 1.53—1.81 (m, 4H), 1.99—2.04 (m, 1H), 2.34—2.42 (m, 1H), 2.46—2.52 (m, 1H), 2.70 (dt, J=10.0, 4.8 Hz, 1H), 3.22 (dd, J=9.6, 16.4 Hz, 1H), 3.49 (dd, J=3.6, 16.4 Hz, 1H), 3.71 (dt, J=9.6, 3.6 Hz, 1H), 7.08—7.20 (m, 4H), 7.42 (t, J=7.6 Hz, 2H), 7.52 (t, J=7.2 Hz, 1H), 7.90 (d, J=7.6 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 10.62 min (minor) and 20.17 min (major), 90% *ee*.

(*S*)-2-((*R*)-1-(4-Chlorophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7e)[11] Yield 78%; *syn*/*anti*=91∶9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20—1.29 (m, 1H), 1.62—1.81 (m, 4H), 1.95—2.05 (m, 1H), 2.31—2.53 (m, 2H), 2.65—2.72 (m, 1H), 3.19 (dd, J=9.9, 16.5 Hz, 1H), 3.50 (dd, J=4.2, 16.5 Hz, 1H), 3.71 (dt, J=9.6, 3.9 Hz, 1H), 7.10—7.13 (m, 2H), 7.20—7.23 (m, 2H), 7.40—7.44 (m, 2H), 7.51—7.54 (m, 1H), 7.90 (d, J=6.8 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 14.25 min (minor) and 18.30 min (major), 84% *ee*.

(*S*)-2-((*R*)-1-(4-Bromophenyl)-3-oxo-3-phenylpropyl)-cyclohexanone (7f)[10] Yield 71%; *syn*/*anti*=96∶4; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.26—1.29 (m, 1H), 1.62—1.81 (m, 4H), 1.97—2.03 (m, 1H), 2.35—2.55 (m, 2H), 2.71 (dt, J=10.0, 4.8 Hz, 1H), 3.20 (dd, J=16.37, 9.79 Hz, 1H), 3.51 (dd, J=16.4, 3.9 Hz, 1H), 3.70 (dt, J=9.8, 3.9 Hz, 1H), 7.09 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 7.45 (d, J=7.8 Hz, 2H), 7.56 (t, J=7.3 Hz, 1H), 7.92 (d, J=7.2 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 0.9 mL/min, λ=254 nm, retention time: 16.80 min (minor) and 20.86 min (major), 84% *ee*.

(*S*)-2-((*R*)-3-Oxo-3-phenyl-1-*p*-tolylpropyl)-cyclohexanone (7g)[11] Yield 70%; *syn*/*anti*=98∶2; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21—1.40 (m, 1H), 1.56—1.87 (m, 4H), 1.96—2.06 (m, 1H), 2.30 (s, 3H), 2.30—2.43 (m, 1H), 2.49—2.57 (m, 1H), 2.69 (dt, J=10.0, 4.8 Hz, 1H), 3.19 (dd, J=9.2, 15.6 Hz, 1H), 3.47 (dd, J=2.8, 16.0 Hz, 1H), 3.67 (dt, J=10.0, 4.0 Hz, 1H), 7.07 (d, J=7.2 Hz, 4H), 7.43 (t, J=6.8 Hz, 2H), 7.52 (t, J=6.0 Hz, 1H), 7.93 (d, J=7.2 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 10∶90, flow rate 1.0 mL/min, λ=254 nm, retention time: 11.33 min (minor) and 16.45 min (major), 92% *ee*.

(*S*)-2-((*R*)-1-(4-Phenyl)-3-oxo-3-(4'-Chlorophenyl)-propyl)-cyclohexanone (7h)[8] Yield 88%; *syn*/*anti*=99∶1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22—1.27 (m, 1H), 1.62—1.80 (m, 4H), 1.97—2.05 (m, 1H), 2.35—2.55 (m, 2H), 2.73 (dt, J=10.2, 10.0, 4.9 Hz, 1H), 3.15 (dd, J=15.9, 9.6 Hz, 1H), 3.50 (dd, J=15.9, 4.0 Hz, 1H), 3.70 (dt, J=9.9, 4.0 Hz, 1H), 7.11—7.20 (m, 3H), 7.26 (d, J=7.5 Hz, 2H), 7.39 (d, J=8.6 Hz, 2H), 7.86 (d, J=8.6 Hz, 2H); HPLC analysis: Chiralpak AS-H column, *i*-PrOH/hexane 40∶60, flow rate 0.5 mL/min, λ=254 nm, retention time: 12.82 min (minor) and 17.88 min (major), 90% *ee*.

(*S*)-2-((*R*)-1-(2-Chlorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl)-cyclohexanone (7i)[11] Yield 61%; *syn*/*anti*=99∶1; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29—1.39 (m, 1H), 1.57—1.85 (m, 4H), 2.01—2.06 (m, 1H), 2.36—2.44 (m, 1H), 2.48—2.54 (m, 1H), 2.89 (dt, J=10.0, 4.8 Hz, 1H), 3.32 (dd, J=10.0, 16.0 Hz, 1H), 3.84 (s, 3H), 3.54 (dd, J=4.0, 16.4 Hz, 1H), 4.24 (dt, J=9.6, 3.6 Hz, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.09 (t, J=6.8 Hz, 1H), 7.18 (t, J=7.2 Hz, 1H), 7.27—7.32 (m, 2H), 7.95 (d, J=8.8 Hz, 2H); HPLC analysis: Chiralpak OD-H column, *i*-PrOH/hexane 30∶70, flow rate 1.0 mL/min, λ=254 nm, retention time: 6.16 min (minor) and 8.07 min (major), 92% *ee*.

(*R*)-3-((*R*)-3-Oxo-1,3-diphenylpropyl)-1-methylpiperidin-4-one (7j)[11] Yield 84%; *syn*/*anti*=83∶17 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04—2.14 (m, 1H), 2.20 (s, 3H), 2.34 (s, 1H), 2.37—2.47 (m,

1H), 2.58 (d, J=14.2 Hz, 2H), 2.71—2.88 (m, 2H), 3.28 (dd, J=16.5, 9.3 Hz, 2H), 3.48 (d, J=14.3 Hz, 1H), 3.90 (s, 1H), 7.23 (dd, J=14.4, 7.3 Hz, 3H), 7.40 (d, J=7.4 Hz, 2H), 7.88 (d, J=7.3 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 20∶80, flow rate 0.6 mL/min, λ=254 nm, retention time: 17.15 min (minor) and 21.32 min (major), 88% *ee*.

(*R*)-3-((*R*)-3-Oxo-1,3-diphenylpropyl)-tetrahydropyran-4-one (7k)[11] Yield 71%; *syn*/*anti*=97∶3 (by ^{1}H NMR); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45—2.59 (m, 1H), 2.69—2.85 (m, 2H), 3.28—3.50 (m, 3H), 3.54—3.66 (m, 1H), 3.82—4.03 (m, 3H), 7.10—7.35 (m, 4H), 7.38—7.49 (m, 2H), 7.48—7.54 (m, 1H), 7.87 (d, J=6.4 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 15∶85, flow rate 0.7 mL/min, λ=254 nm, retention time: 24.58 min (minor) and 27.30 min (major), 88% *ee*.

(*R*)-2-((*S*)-3-Oxo-1,3-diphenylpropyl)-cyclopentanone (7l)[9] Yield 91%; *syn*/*anti*=81∶19; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51—1.60 (m, 1H), 1.65—1.75 (m, 1H), 1.87—1.90 (m, 2H), 2.06 (dd, J=9.0, 18.6 Hz, 1H), 2.21—2.27 (m, 1H), 2.46 (dd, J=8.7, 17.1 Hz, 1H), 3.36 (dd, J=7.5, 16.8 Hz, 1H), 3.70 (dd, J=7.5, 14.4 Hz, 1H), 3.87 (dd, J=6.3, 16.5 Hz, 1H), 7.17—7.29 (m, 5H), 7.42 (t, J=7.5 Hz, 2H), 7.53 (t, J=7.2 Hz, 1H), 7.91 (d, J=7.2 Hz, 2H); HPLC analysis: Chiralpak AD-H column, *i*-PrOH/hexane 50∶50, flow rate 1.0 mL/min, λ=254 nm, retention time: 7.56 min (major) and 10.76 min (minor), 60% *ee*.

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