Chiral Phosphoric Acid Catalyzed Diastereo- and Enantioselective 1,4-Conjugate Addition of *β*-Ketoesters to Nitroolefins

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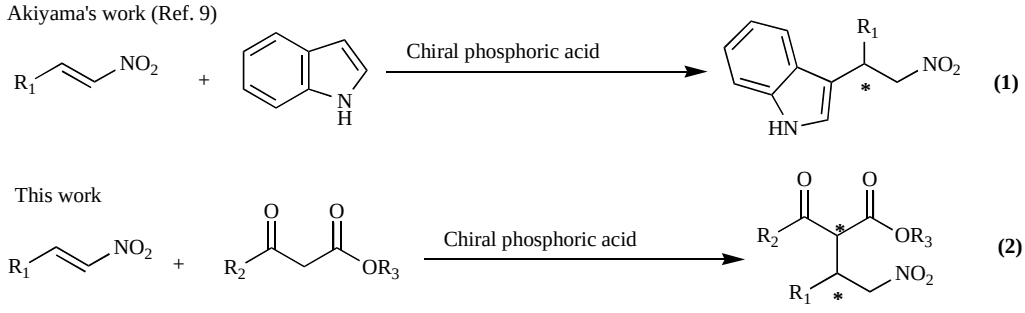
Abstract: Chiral phosphoric acid as organocatalyst for the diastereo- and enantioselectivity 1,4-conjugate addition of a variety of β-ketoesters to nitroolefins was firstly developed, providing the corresponding adducts in high yield (up to 97%) with moderate diastereoselectivities (up to 2.6:1 dr) and enantioselectivities (up to 58% ee).

Keywords: Chiral phosphoric acid, organocatalysis, asymmetric catalysis, 1,4-conjugate addition, β-ketoesters, nitroolefins.

INTRODUCTION

The asymmetric 1,4-conjugate addition of *β*-ketoesters to nitroolefins has proved to be one of the most powerful carbon-carbon-forming strategies for the preparation of valuable nitrogen-contained compounds in organic synthesis [1]. The nitro functionality in the adducts can easily be further transformed to amine [2a-e], nitrile oxide [2f], ketone or carboxylic acid [2g] and hydrogen [2h]. Due to the important synthetic potential, considerable efforts have been devoted in recent years to develope chiral metal catalysts [3] and chiral organocatalysts [4] for this class of 1,4-conjugate addition reaction [5]. However, to the best of our knowledge, despite all the significant progress made in this area, there is no report about employing a *chiral protonic acid* as catalyst for the asymmetric 1,4-conjugate addition of *β*-ketoesters to nitroolefins.

The chiral phosphoric acids, derived from chiral BINOL (BINOL = 2,2'-dihydroxy-1,1'-binaphthyl), have been developed as a class of versatile chiral protonic acids catalysts and extensively applied to a variety of catalytic asymmetric reactions [6, 7]. In general, the chiral phosphoric acid acts as a bifunctional catalyst, that is the acidic proton as acid and the P=O moiety of the catalyst as a base [6]. Moreover, among the various asymmetric reactions catalyzed by chiral phosphoric acids, most of them include imine or iminium ion as electrophiles, whereas few of them include some other electrophiles [8]. More recently, Akiyama and co-workers reported the Friedel-Crafts alkylation of indoles with nitroolefins catalyzed by chiral phosphoric acid, and firstly disclosed the nitroolefins activation catalyzed by chiral phosphoric acids (Scheme **1**, (**1**)) [9]. Prompted by this study, we recently found that chiral phosphoric acids were efficient catalysts for the asymmetric 1,4-conjugate addition of *β*-ketoesters to nitroolefins (Scheme **1**, (**2**)). It should be note that this reaction is only another example about the nitroolefins activation catalyzed by chiral phosphoric acids [10], except Akiyama's report [9]. Herein, we hope to report our preliminary results.



Scheme 1.

RESULTS AND DISCUSSION

By using ethyl 3-oxo-3-phenylpropanoate (**3a)** and *trans*-phenyl nitroolefin (**2a)** as the model compounds, a series of chiral phosphoric acid catalysts derived from (*R*)-BINOL

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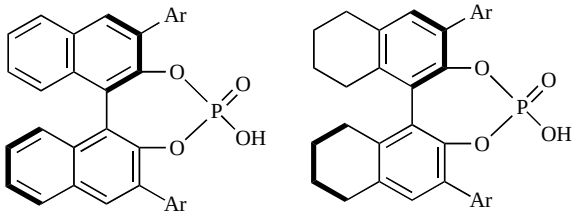


1a-e **1f-h**

1a, Ar = Ph
1b, Ar =β-naphthyl
1c, Ar = 9-phenanthrenyl
1d, Ar = 2,4,6-$(^{i}Pr)_3C_6H_2$
1e, Ar = 3,5-$(F_3C)_2C_6H_3$

1f, Ar = 2,6-$(CH_3)_2C_6H_3$
1g, Ar = 4-CF_3-C_6H_4
1h, Ar = β-naphthyl

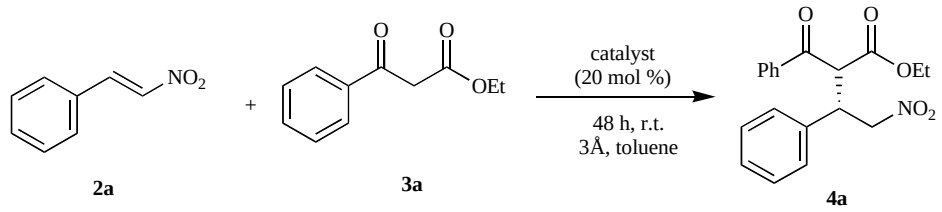
Fig. (1). Catalysts Screened for the Michael Reactions.

and (*R*)-H_8-BINOL (**1a-h**, Fig. **1**) was screened at room temperature in toluene, and the results were summarized in Table **1**. It was found that this Michael addition reaction proceeded smoothly in 20 mol % catalyst loading with molecular sieves (MS) 3 Å as additive and provided the corresponding adducts in good yields with poor diastereoselectivities and enantioselectivities (Table **1**, entries 8 *vs* 1-7) [11]. In general, among the catalysts examined, catalyst **1h** was slightly superior to other catalysts (**1a-g**) in the enantioselectivity and yield (Table **1**, entries 8 *vs* 1-7).

With the best chiral catalyst **1h** being identified, we next carried out the Michael reaction of **2a** with **3a** for screening the optimal reaction conditions. As shown in Table **2**, the screening of solvent with MS 3 Å as additive revealed that the reaction proceeded smoothly in several solvent, and toluene was the most favorable solvent (Table **2**, entries 1-5). The product could be obtained in 94% yield using CH_3OH as a solvent, but the product was racemic (Table **2**, entry 4). With toluene as a solvent, further examining to molecular sieves, resulted in MS 5 Å provided better results than MS 3 Å and 4 Å (Table **2**, entries 7 *vs* 1 and 6) [11]. Interestingly, decreasing the catalyst loading from 20 mol % to 5 mol % with MS 5 Å as additive, the enantioselectivities of both isomers were improved to 41% and 45%, and the chemical yield was slightly decreased to 87% from 92% (Table **2**, entries 7 and 8). And then, carrying out the reaction with 5 mol % catalyst and MS 3 Å as additive, the reaction provided 54% and 56% ee for the two isomers in 91% chemical yield (Table **2**, entry 9). Encouraged by these results, examining the reaction by further decreasing the catalyst loading to 2.5 mol %, the reaction also completed in 72 h and provided the desired product in 83% isolated yield, however, the enantioselectivities of two diastereoisomers were both slightly decreased (Table **2**, entry 10). Unfortunately, try to decrease the temperature to 0 ^{o}C led to the reaction very sluggish, moreover, the corresponding adduct was obtained with only trace amount even though prolonging the reaction time to 7 days (Table **2**, entry 11).

With the optimal reaction conditions in hand, we determined the scope and limitations of this 1,4-conjugate addition reactions. As shown in Table **3**, for the nitroolefins having electron-donating phenyl group **2b**, electron-withdrawing phenyl group **2c-g** and heteroaromatic substituent **2h**, the chiral addition products **4b-h** were well formed in good to excellent chemical yields with moderate stereoselectivities (Table **3**, entries 2-8). Additionally, we also found that the *β*-ketoesters **3b-d** bearing electron-withdrawing substituents in the phenyl group reacted smoothly with **2a**, giving the desired products **4i-k** in range from 90% to 96% yield with moderate stereoselectivities

Table 1. Catalyst Screening[a]

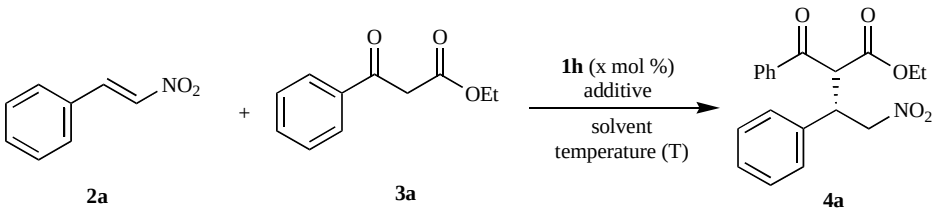


2a **3a** **4a**

Entry	Catalytst	dr[b]	ee(%)[c]	Yield(%)[d]
1	**1a**	1.4:1	7/2	71
2	**1b**	1.6:1	14/15	81
3	**1c**	1.5:1	8/6	87
4	**1d**	1.5:1	16/13	82
5	**1e**	1.5:1	5/4	86
6	**1f**	1.4:1	2/1	67
7	**1g**	1.5:1	5/5	84
8	**1h**	1.5:1	24/23	91

[a]All reactions were carried out with **2a** (0.3 mmol) and **3a** (0.1 mmol) in 0.5 mL toluene with molecular sieves (MS) 3 Å 10 mg.
[b]The ratio of diastereoselectivities were determined by HPLC analysis.
[c]Enantioselectivity in *β*-position to nitro group for major (minor) diastereomer, the ee values were determined by HPLC analysis [3m].
[d]Yields of isolated product.

Table 2. Optimizing the Reaction Conditions for the 1,4-Conjugate Addition of 3a to 2a Catalyzed by Chiral Phosphoric Acid 1h[a]

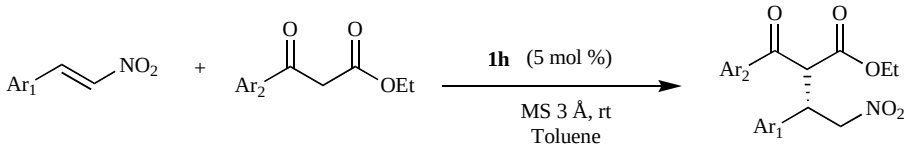


2a **3a** **4a**

Entry	Solvent	1h(x mol %)	T(°C)	Additive	dr[b]	ee(%)[c]	Yield(%)[d]
1	toluene	20	rt	3 Å	1.5:1	24/23	91
2	Et_2O	20	rt	3 Å	1.3:1	14/16	78
3	DCE	20	rt	3 Å	1.3:1	13/11	81
4	CH_3OH	20	rt	3 Å	1.4:1	2/1	94
5	xylene	20	rt	3 Å	1.4:1	20/19	72
6	toluene	20	rt	4 Å	1.2:1	6/3	20
7	toluene	20	rt	5 Å	1.6:1	33/33	92
8	toluene	5	rt	5 Å	1.5:1	41/45	87
9	toluene	5	rt	3 Å	1.5:1	54/56	91
10	toluene	2.5	rt	3 Å	1.6:1	52/51	83
11	toluene	5	0	3 Å	--	--	trace

[a]All reactions were carried out with **2a** (0 .3 mmol) and **3a** (0.1 mmol) in 0.5 mL solvent with MS 10 mg for 72 h. DCE = 1,2-dichloroethane.
[b]The ratio of diastereoselectivities were determined by HPLC analysis.
[c]Enantioselectivity in *β*-position to nitro group for major (minor) diastereomer, the ee values were determined by HPLC analysis [3m].
[d]Yields of isolated product.

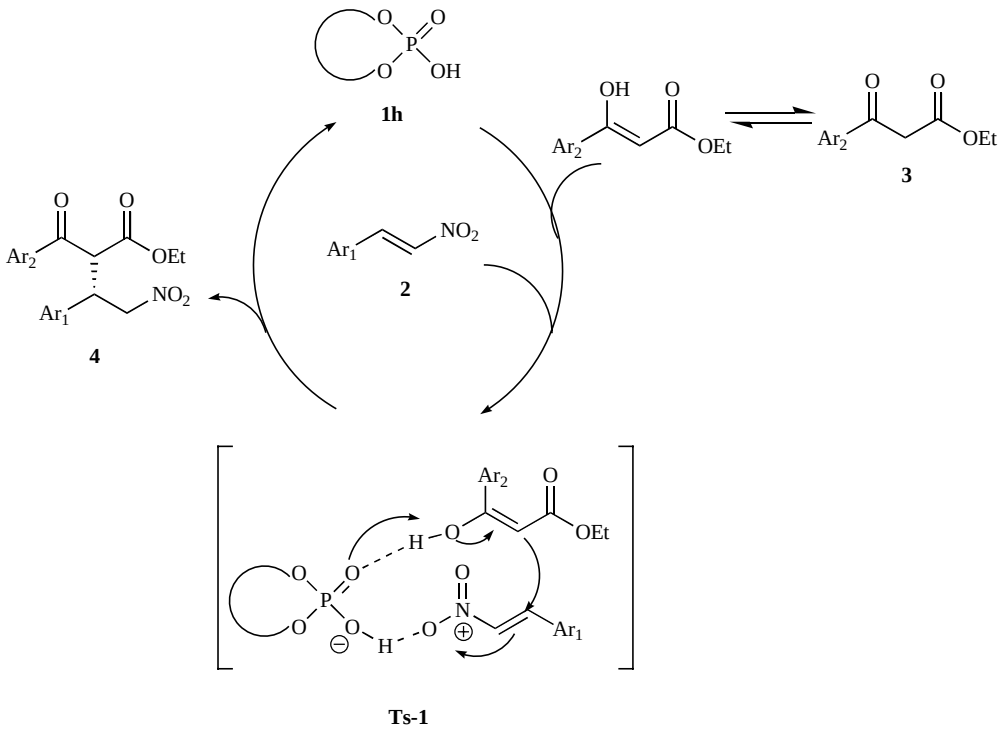
Table 3. Chiral Phosphoric Acid 1h Catalyzed 1,4-Conjugate Addition Reactions of *β*-Ketoesters to Nitroolefins[a]



2a-h **3a-d** **4a-k**

Entry	Ar_1	Ar_2	Products 4	dr[b]	ee(%)[c]	Yield(%)[d]
1	Ph (**2a**)	Ph (**3a**)	**4a**	1.4:1	54/56	91
2	*p*-Me-Ph (**2b**)	Ph (**3a**)	**4b**	2.0:1	34/34	91
3	*p*-Cl-Ph (**2c**)	Ph (**3a**)	**4c**	1.3:1	58/56	95
4	*p*-Br-Ph (**2d**)	Ph (**3a**)	**4d**	1.2:1	56/56	91
5	*m*-Br-Ph (**2e**)	Ph (**3a**)	**4e**	1.5:1	53/55	97
6	*m*-F_3C-Ph (**2f**)	Ph (**3a**)	**4f**	1.4:1	51/53	97
7	*m*-NO_2-Ph (**2g**)	Ph (**3a**)	**4g**	1.9:1	49/37	89
8	2-Furyl (**2h**)	Ph (**3a**)	**4h**	1.3:1	31/28	84
9	Ph (**2a**)	*p*-F-Ph (**3b**)	**4i**	2.6:1	55/45	96
10	Ph (**2a**)	*p*-Cl-Ph (**3c**)	**4j**	2.0:1	45/27	93
11	Ph (**2a**)	*p*-Br-Ph (**3d**)	**4k**	1.6:1	55/40	90

[a]Reactions were carried out with **2** (0.6 mmol), **3** (0.2 mmol), MS 3 Å 10 mg and 5 mol % catalyst **1h** in 1.0 mL toluene for 72 h at room temperature.
[b]The ratio of diastereoselectivities were determined by HPLC analysis.
[c]Enantioselectivity in *β*-position to nitro group for major (minor) diastereomer, the ee values were determined by HPLC analysis [3m].
[d]Yields of isolated product.



Scheme 2. Proposed catalytic cycle for the asymmetric 1,4-conjugated addition reaction of *β*-ketoesters to nitroolefins catalyzed by chiral phosphoric acid.

(Table **3**, entries 9-11). Generally, to this developed methodology, moderate diastereo- and enantioselectivities in very good chemical yields were observed for the addition of different *β*-ketoesters to nitroolefins with 5 mol % chiral phosphoric acid organocatalyst **1h** (Table **3**).

This chiral phosphoric acid catalyzed asymmetric 1,4-conjugated addition reaction of *β*-ketoesters to nitroolefins for the synthesis of compound **4** can be explained by a proposed mechanism cycle as outlined in Scheme **2**. We assume that the chiral phosphoric acid serves as bifunctional catalysts in this reaction: i) the phosphoric acid activates the nitroolefin **2** with the –OH group of acid **1h**, and ii) the phosphoryl oxygen atom of P=O acting as base forms a hydrogen bond with the hydrogen atom of the enolate of *β*-ketoesters **3**. As a result, the transition state **TS-1** is formed. This rigid conformation likely contributes to the stereoselectivity of this process. Subsequently, attack of the *β*-position of nitroolefins by the *β*-ketoesters affords the desired Michael addition product and releases the chiral catalyst **1h** (Scheme **2**).

EXPERIMENTAL SECTION

General

Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF-254) were used and compounds were visualized by irradiation with UV light. All reactions were conducted in a closed system with an atmosphere of air and were monitored by TLC. ^{1}H and ^{13}C NMR spectra were performed on a Brucker-300 MHz spectrometer for products dissolved by $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. Melting points were recorded on a Buchi Melting Point B-545 and this instrument was without correction.

General Procedure for Chiral Phosphoric Acid 1h Catalyzed Asymmetric 1,4-Conjugated Addition Reactions of β-Ketoesters to Nitroolefins [12]

A mixture of activated powder MS 3Å (10mg), nitroolefins **2** (0.6 mmol), catalyst **1h** (6.1 mg, 0.01 mmol) and *β*-ketoesters **3** (0.02 mmol) in 1 mL toluene was added to an ordinary vial with a magnetic stirring bar at room temperature. The stirring was maintained at room temperature for 72 h and the crude reaction mixture was directly charged onto silica gel and purified by flash chromatography (petroleum ether/ethyl acetate, 10:1 to 5:1) to afford products **4**. The diastereo- and enantioselectivities were determined by HPLC using a Chiracel AD-H column.

CONCLUSION

In summary, we have developed a chiral phosphoric acids catalyzed asymmetric 1,4-conjugated addition reaction of *β*-ketoesters to nitroolefins for the synthesis of nitroalkanes compounds with molecular sieves 3 Å as additive. The corresponding valuable adducts have been isolated in high yields with moderate stereoselectivities [12]. This approach is the first example of Michael type reaction of *β*-ketoester to nitroolefins catalyzed by a chiral protonic acid organocatalyst. The further investigation into the application of chiral phosphoric acids in catalytic asymmetric reaction is currently underway in our laboratory.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

[1] For reviews, see: (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. Nitroaliphatic compounds-ideal intermediates in organic synthesis. *Chimia.,* **1979**, *33*, 1. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis.* Baldwin, J. E.; Magnus, P. D.; Eds. Pergamon Press: Oxford, **1992**. (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, **2001**.

[2] (a) Beck, A. K.; Seebach, D. Aldol- und michael-additionen fluorierter nitroalkane an aldehyde, ketone und α, β-ungesattigte carbonylverbindungen. *Chem. Ber.,* **1991**, *124*, 2897. (b) Maeri, R. E.; Heinzer, J.; Seebach, D. Preparation and reactions of silyl nitronates derived from 2,2,2-trifluoronitroethane: diastereoselective synthesis of trifluoromethyl-substituted aminoethanols and propanols. *Liebigs Ann.*, **1995**, 1193. (c) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. Solid-phase synthesis of peptidyl trifluoromethyl ketones. *J. Org. Chem.,* **1999**, *64*, 1356. (d) Barrett, A. G. M.; Spilling, C. D. Transfer hydrogenation: a stereospecific method for the conversion of nitro alkanes into amines. *Tetrahedron Lett.,* **1988**, *29*, 5733. (e) Lloyd, D. H.; Nichols, D. E. Nickel boride/hydrazine hydrate reduction of aromatic and aliphatic nitro compounds: synthesis of 4-(benzyloxy)indole and .alpha.-alkyltryptamines. *J. Org. Chem.,* **1986**, *51*, 4294. (f) Mukaiyama, T.; Hoshino, T. the reactions of primary nitroparaffins with isocyanates. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (g) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (h) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. Denitrohydrogenation of aliphatic nitro compounds and a new use of aliphatic nitro compounds as radical precursors. *Tetrahedron,* **1985**, *41*, 4013.

[3] For selected examples, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. catalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes. *J. Am. Chem. Soc.*, **1999**, *121*, 10215. (b) Hayashi, T.; Senda, T.; Ogasawara, M. Rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to nitroalkenes. *J. Am. Chem. Soc.*, **2000**, *122*, 10716. (c) Hayashi, T. Reviews on Rh-catalyzed conjugate additions of arylboronic acids to α,β-unsaturated carbonyl compounds. *Synlett.,* **2001**, 879. (d) Duursma, A.; Minnaard, A. J.; Feringa, B. L. One-pot multi-substrate enantioselective conjugate addition of diethylzinc to nitroalkenes. *Tetrahedron,* **2002**, *58*, 5773. (e) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. Dramatic improvement of the enantiomeric excess in the asymmetric conjugate addition reaction using new experimental conditions. *J. Am. Chem. Soc.*, **2002**, *124*, 5262. (f) Luchaco-Cullis, C. A.; Hoveyda, A. H. Cu-catalyzed enantioselective conjugate addition of alkylzincs to cyclic nitroalkenes: catalytic asymmetric synthesis of cyclic α-substituted ketones. *J. Am. Chem. Soc.*, **2002**, *124*, 8192. (g) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. Development of a catalytic enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes for the synthesis of endothelin-A antagonist ABT-546. Scope, mechanism, and further application to the synthesis of the antidepressant rolipram. *J. Am. Chem. Soc.*, **2002**, *124*, 13097. (h) Duursma, A.; Minnaard, A. J.; Feringa, B. L. Highly enantioselective conjugate addition of dialkylzinc reagents to acyclic nitroalkenes: a catalytic route to *β*-amino acids, aldehydes, and alcohols. *J. Am. Chem. Soc.,* **2003**, *125*, 3700. (i) Rimkus, A.; Sewald, N. First synthesis of a β^2-homoamino acid by enantioselective catalysis. *Org. Lett*., **2003**, *5*, 79. (j) Choi, H.; Hua, Z.; Ojima, I. highly enantioselective copper-catalyzed conjugate addition of diethylzinc to nitroalkenes. *Org. Lett.,* **2004**, *6*, 2689. (k) Mampreian, D. M.; Hoveyda, A. H. Efficient Cu-catalyzed asymmetric conjugate additions of alkylzinc reagents to aromatic and aliphatic acyclic nitroalkenes. *Org. Lett.,* **2004**, *6*, 2829. (l) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. Catalytic enantioselective michael addition of 1,3-dicarbonyl compounds to nitroalkenes catalyzed by well-defined chiral Ru amido complexes. *J. Am. Chem. Soc.*, **2004**, *126*, 11148. (m) Evans, D. A.; Seidel, D. Ni(II)-is[(*R,R*)-*N,N'*-dibenzylcyclohexane-1,2-diamine]Br_2 catalyzed enantioselective michael additions of 1,3-dicarbonyl compounds to conjugated nitroalkenes. *J. Am. Chem. Soc.,* **2005**, *127*, 9958. (n) Evans, D. A.; Mito, S.; Seidel, D. Scope and mechanism of enantioselective michael additions of 1,3-dicarbonyl compounds to nitroalkenes catalyzed by nickel(II)−diamine complexes. *J. Am. Chem. Soc.*, **2007**, *129*, 11583.

[4] For selected examples, see: (a) List, B.; Pojarliev, P.; Martin, H. J. efficient proline-catalyzed michael additions of unmodified ketones to nitro olefins. *Org. Lett.*,**2001**, *3*, 2423. (b) Enders, D.; Seki, A. Proline-catalyzed enantioselective michael additions of ketones to nitrostyrene. *Synlett.,* **2002**, 26. (c) Andrey, O.; Alexakis, A.; Bernardinelli, G. Asymmetric michael addition of α-hydroxyketones to nitroolefins catalyzed by chiral diamine. *Org. Lett.,* **2003**, *5*, 2559. (d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.*, **2003**, *125*, 12672. (e) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. Direct asymmetric organocatalytic michael reactions of α,α-disubstituted aldehydes with *β*-nitrostyrenes for the synthesis of quaternary carbon-containing products. *Org. Lett*., **2004**, *6*, 2527. (f) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. A new class of chiral pyrrolidine−pyridine conjugate base catalysts for use in asymmetric michael addition reactions. *J. Am. Chem. Soc.*, **2004**, *126*, 9558. (g) Li, H.; Wang, Y.; Tang, L.; Deng, L. Highly enantioselective conjugate addition of malonate and *β*-ketoester to nitroalkenes: asymmetric C−C bond formation with new bifunctional organic catalysts based on cinchona alkaloids. *J. Am. Chem. Soc.,* **2004**, *126*, 9906. (h) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. Stereocontrolled creation of adjacent quaternary and tertiary stereocenters by a catalytic conjugate addition. *Angew. Chem. Int. Ed. Engl.*, **2005**, *44*, 105. (i) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. Enantio- and diastereoselective michael reaction of 1,3-dicarbonyl compounds to nitroolefins catalyzed by a bifunctional thiourea. *J. Am. Chem. Soc*., **2005**, *127*, 119.

[5] For selected reviews, see: (a) Sibi, M. P.; Manyem, S. Enantioselective conjugate additions. *Tetrahedron,* **2000**, *56*, 8033-8061. (b) Krause, N.; Hoffmann-Röder, A. Recent advances in catalytic enantioselective michael additions. *Synthesis,* **2001**, 171. (c) Berner, O. M.; Tedeschi, L.; Enders, D. Asymmetric michael additions to nitroalkenes. *Eur. J. Org. Chem.,* **2002**, 1877. (d) Tsogoeva, S. B. Recent advances in asymmetric organocatalytic 1,4-conjugate additions. *Eur. J. Org. Chem*., **2007**, 1701.

[6] For reviews on chiral phosphoric acid catalysis, see: (a) Connon, S. J. Chiral phosphoric acids: powerful organocatalysts for asymmetric addition reactions to imines. *Angew. Chem. Int. Ed. Engl*., **2006**, *45*, 3909. (b) Akiyama, T. Stronger brønsted acids. *Chem. Rev*., **2007**, *107*, 5744.

[7] For selected examples on chiral phosphoric acid catalysis, see: (a) Uraguchi, D.; Terada, M. Chiral brønsted acid-catalyzed direct mannich reactions *via* electrophilic activation. *J. Am. Chem. Soc*., **2004**, *126*, 5356. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective mannich-type reaction catalyzed by a chiral brønsted acid. *Angew. Chem. Int. Ed. Engl.,* **2004**, *43*, 1566. (c) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. Chiral brønsted acid catalyzed enantioselective hydrophosphonylation of imines: asymmetric synthesis of α-amino phosphonates. *Org. Lett.*, **2005**, *7*, 2583. (d) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. Enantioselective mannich-type reaction catalyzed by a chiral brønsted acid derived from TADDOL. *Adv. Synth. Catal.,* **2005**, *347*, 1523. (e) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y. Antilla, J. C. Brønsted acid-catalyzed imine amidation. *J. Am. Chem. Soc*., **2005**, *127*, 15696. (f) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D.W. C. Enantioselective organocatalytic reductive amination. *J. Am. Chem. Soc*., **2006**, *128*, 84. (g) Seayad, J.; Seayad, A. M.; List, B. Catalytic asymmetric pictet-spengler reaction. *J. Am. Chem. Soc.,* **2006**, *128*, 1086. (h) Rueping, M.; Sugiono, E.; Azap, C. A highly enantioselective brønsted acid catalyst for the strecker reaction. *Angew. Chem. Int. Ed. Engl*., **2006**, *45*, 2617. (i) Akiyama, T.; Morita, H.; Fuchibe, K. chiral brønsted acid-catalyzed inverse electron-demand Aza Diels-Alder reaction. *J. Am. Chem. Soc*., **2006**, *128*, 13070. (j) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. Highly enantioselective organocatalytic biginelli reaction. *J. Am. Chem. Soc*., **2006**, *128*, 14802. (k) Itoh, J.;

Akiyama, T.; Fuchibe, K. Chiral brønsted acid catalyzed enantioselective Aza-Diels-Alder reaction of brassard's diene with imines. *Angew. Chem. Int. Ed*., **2006**, *45*, 4796. (l) Rueping, M.; Azap, C. Cooperative coexistence: effective interplay of two brønsted acids in the asymmetric synthesis of isoquinuclidines. *Angew. Chem. Int. Ed*., **2006**, *45*, 7832. (m) Li, G.; Liang, Y.; Antilla, J. C. A Vaulted biaryl phosphoric acid-catalyzed reduction of α-imino esters: the highly enantioselective preparation of α-amino esters. *J. Am. Chem. Soc*., **2007**, *129*, 5830. (n) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral brønsted acid catalyzed enantioselective mannich-type reaction. *J. Am. Chem. Soc*., **2007**, *129*, 6756. (o) Zhou, J.; List, B. Organocatalytic asymmetric reaction cascade to substituted cyclohexylamines. *J. Am. Chem. Soc*., **2007**, *129*, 7498. (p) Terada, M.; Machioka, K.; Sorimachi, K. Chiral brønsted acid-catalyzed tandem aza-ene type reaction/cyclization cascade for a one-pot entry to enantioenriched piperidines. *J. Am. Chem. Soc*., **2007**, *129*, 10336. (q) Rueping, M.; Antonchick, A. P.; Brinkmann, C. Dual catalysis: a combined enantioselective brønsted acid and metal-catalyzed reaction - metal catalysis with chiral counterions. *Angew. Chem. Int. Ed*., **2007**, *46*, 6903. (r) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. Vinylogous mannich-type reaction catalyzed by an iodine-substituted chiral phosphoric acid. *Adv. Synth. Catal*., **2008**, *350*, 399.

[8] For selected examples, see: (a) Nakashima, D.; Yamamoto, H. Design of chiral *N*-triflyl phosphoramide as a strong chiral brønsted acid and its application to asymmetric Diels−Alder reaction. *J. Am. Chem. Soc*., **2006**, *128*, 9626. (b) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. Chiral brønsted acids in the catalytic asymmetric nazarov cyclization-the first enantioselective organocatalytic electrocyclic reaction. *Angew. Chem. Int. Ed*., **2007**, *46*, 2097. (c) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. Brønsted acid-catalyzed desymmetrization of *meso*-aziridines. *J. Am. Chem. Soc*., **2007**, *129*, 12084. (d) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. Asymmetric brønsted acid catalysis: enantioselective nucleophilic substitutions and 1,4-additions. *Angew. Chem. Int. Ed*., **2008**, *47*, 593. (e) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. Chiral phosphoric acid catalyzed asymmetric friedel-crafts alkylation of indoles with simple *α,β*-unsaturated aromatic ketones. *Eur. J. Org. Chem*., **2008**, 1406. (f) Jiao, P.; Nakashima, D.; Yamamoto, H. Enantioselective 1,3-dipolar cycloaddition of nitrones with ethyl vinyl ether: the difference between brønsted and lewis acid catalysis. *Angew. Chem. Int. Ed*., **2008**, *47*, 2411.

[9] Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral phosphoric acid catalyzed enantioselective friedel-crafts alkylation of indoles with nitroalkenes: cooperative effect of 3 å molecular sieves. *Angew. Chem. Int. Ed*., **2008**, *47*, 4016.

[10] In most of the Michael addition reaction of nitroolefins, the general feature of this reaction is Michael donor activated by a base or Lewis acid or Michael acceptor activated by a Lewis acid, but Michael acceptor activated by a protonic acid have never seen before. For reviews on Michael reactions, see: ref. (5).

[11] The powdered molecular sieves used in this work must be activated by placing the powder under vacuum and heating with the flame of spirit lamp.

[12] Spectral data for Michael addition products (Table **3**, **4a-k**) [3m]:

Ethyl 2-benzoyl-4-nitro-3-phenylbutanoate (4a): White solid, yield 91%, ratio of diastereomers 1.4:1, Mp 78.9-80.6 °C, $[\alpha]_D^{25}$ -1.13 (*c* 0.44, $CHCl_3$). IR (KBr): 3064, 2982, 2924, 1725, 1686, 1598, 1554, 1449, 1284, 1263, 1090, 1020, 981, 877, 700, 563 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62-7.60 (m, 1H), 7.41-7.30 (m, 2H), 7.30-7.22 (m, 5H), 4.96-4.91 (m, 1H), 4.80-4.76 (m, 2H), 4.50-4.44 (m, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.95 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.52-7.47 (m, 1H), 7.41-7.30 (m, 2H), 7.22-7.19 (m, 5H), 4.96-4.91 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 192.6, 167.7, 166.9, 136.8, 136.3, 136.0, 135.8, 134.2, 133.8, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 77.9, 62.2, 61.9, 57.0, 56.4, 43.1, 43.0, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 8.01 min, t_r (minor) = 14.51 min; 54% ee; Second (minor) diastereomer: t_r (major) = 12.26 min, t_r (minor) = 21.56 min, 56% ee.

Ethyl 2-benzoyl-4-nitro-3-p-tolylbutanoate (4b): White solid, yield 91%, ratio of diastereomers 2.0:1, Mp 126.9-128.3 °C, $[\alpha]_D^{25}$ -0.76 (*c* 0.39, $CHCl_3$). IR (KBr): 3056, 2981, 2922, 1734, 1681, 1596, 1580, 1548, 1516, 1450, 1381, 1262, 1158, 1117, 1014, 970, 824, 681, 560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.85-7.42 (m, 4H), 7.16-7.13 (m, 1H), 7.13-7.10 (m, 2H), 4.93-4.90 (m, 1H), 4.77-4.73 (m, 2H), 4.43-4.40 (m, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.85-7.42 (m, 1H), 7.16-7.13 (m, 2H), 7.13-7.10 (m, 2H), 7.07-7.00 (m, 2H), 4.93-4.90 (m, 3H), 4.43-4.40 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.9, 192.7, 167.7, 167.0, 138.0, 137.8, 136.0, 135.9, 134.4, 133.7, 133.6, 133.1, 129.6, 129.5, 128.9, 128.8, 128.7, 128.6, 128.1, 127.8, 78.1, 62.1, 61.9, 57.1, 56.5, 42.8, 42.7, 21.0, 20.9, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 8.21 min, t_r (minor) = 13.93 min; 34% ee; Second (minor) diastereomer: t_r (major) = 11.51 min, t_r (minor) = 17.17 min, 34% ee.

Ethyl 2-benzoyl-3-(4-chlorophenyl)-4-nitrobutanoate (4c): Colorless liquid, yield 95%, ratio of diastereomers 1.3:1, $[\alpha]_D^{25}$ -1.30 (*c* 0.38, $CHCl_3$). IR (neat): 3070, 2983, 2923, 1736, 1686, 1598, 1580, 1556, 1512, 1448, 1379, 1228, 1163, 1104, 1016, 979, 881, 837, 732, 560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.04 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62-7.28 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.91-4.87 (m, 1H), 4.77-4.72 (m, 2H), 4.50-4.44 (m, 1H), 3.88 (q, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62-7.42 (m, 3H), 7.20-7.16 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.91-4.87 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 167.5, 166.8, 135.9, 135.7, 134.3, 134.0, 132.5, 132.0, 130.1, 130.0, 129.8, 129.7, 129.0, 128.9, 128.8, 128.7, 128.5, 78.0, 62.3, 62.0, 57.0, 56.3, 42.4, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 9.03 min, t_r (minor) = 16.32 min; 58% ee; Second (minor) diastereomer: t_r (major) = 14.64 min, t_r (minor) = 22.77 min, 56% ee.

Ethyl 2-benzoyl-3-(4-bromophenyl)-4-nitrobutanoate (4d): Colorless liquid, yield 91%, ratio of diastereomers 1.2:1, $[\alpha]_D^{25}$ -2.98 (*c* 0.47, $CHCl_3$). IR (neat): 3064, 2981, 1734, 1685, 1596, 1555, 1489, 1448, 1377, 1260, 1185, 1075, 912, 880, 826, 688, 555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.04 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.60-7.40 (m, 3H), 7.29-7.26 (m, 2H), 7.04-7.01 (m, 2H), 4.92-4.87 (m, 1H), 4.77-4.73 (m, 2H), 4.50-4.44 (m, 1H), 3.89 (q, *J* = 7.2 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.85 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.60-7.40 (m, 3H), 7.20-7.17 (m, 2H), 6.93-6.90 (m, 2H), 4.92-4.87 (m, 3H), 4.50-4.44 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.4, 192.3, 167.4, 166.7, 135.9, 135.8, 135.7, 135.4, 134.3, 134.0, 132.1, 132.0, 130.0, 129.7, 129.0, 128.9, 128.8, 128.6, 122.4, 122.2, 77.7, 62.4, 62.1, 56.7, 56.1, 42.5, 42.3, 13.8, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 10.12 min, t_r (minor) = 21.11 min; 56% ee; Second (minor) diastereomer: t_r (major) = 14.66 min, t_r (minor) = 26.61 min, 56% ee.

Ethyl 2-benzoyl-3-(3-bromophenyl)-4-nitrobutanoate (4e): Colorless liquid, yield 97%, ratio of diastereomers 1.5:1, $[\alpha]_D^{25}$ -1.77 (*c* 0.45, $CHCl_3$). IR (neat): 3063, 2981, 2923, 1735, 1685, 1596, 1555, 1476, 1448, 1377, 1282, 1186, 1076, 1022, 979, 880, 787, 696, 588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): major isomer δ 8.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.62-7.53 (m, 2H), 7.52-7.41 (m, 2H), 7.37-7.25 (m, 1H), 7.25-7.20 (m, 2H), 4.95-4.88 (m, 1H), 4.90-4.88 (m, 2H), 4.50-4.44 (m, 1H), 3.90 (q, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.52-7.41 (m, 3H), 7.37-7.25 (m, 2H), 7.20-7.10 (m, 2H), 4.95-4.88 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.4, 192.3, 167.4, 166.7, 139.1, 138.6, 135.6, 134.4, 134.0, 131.5, 131.4, 131.3, 131.1, 130.4, 129.0, 128.9, 128.8, 128.6, 122.9, 122.8, 77.6, 62.4, 62.1, 56.7, 56.2, 42.6, 42.5, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 8.36 min, t_r (minor) = 12.82 min; 53% ee;

Second (minor) diastereomer: t_r (major) = 10.41 min, t_r (minor) = 14.32 min, 55% ee.

Ethyl 2-benzoyl-4-nitro-3-(2-(trifluoromethyl)phenyl)butanoate (4f): Colorless liquid, yield 97%, ratio of diastereomers 1.4:1, $[\alpha]_D^{25}$ -2.22 (*c* 0.26, $CHCl_3$). IR (neat): 3067, 2984, 2925, 1735, 1686, 1697, 1580, 1557, 1449, 1378, 1330, 1285, 1167, 1127, 1023, 980, 910, 805, 547 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.63-7.42 (m, 7H), 4.98-4.91 (m, 1H), 4.90-4.78 (m, 2H), 4.50-4.44 (m, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.83 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.63-7.42 (m, 7H), 4.98-4.91 (m, 3H), 4.50-4.44 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 192.2, 167.4, 166.7, 137.9, 137.5, 136.0, 135.5, 134.3, 134.0, 131.9, 131.7, 131.6, 129.4, 128.9, 128.8, 128.7, 128.4, 125.2, 125.1, 125.0, 124.7, 121.9, 77.5, 62.3, 62.0, 56.7, 56.0, 42.8, 42.7, 42.5, 13.7, 13.3. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 6.14 min, t_r (minor) = 9.30 min; 51% ee; Second (minor) diastereomer: t_r (major) = 7.95 min, t_r (minor) = 10.79 min, 53% ee.

Ethyl 2-benzoyl-4-nitro-3-(2-nitrophenyl)butanoate (4g): Colorless liquid, yield 89%, ratio of diastereomers 1.9:1, $[\alpha]_D^{25}$ -1.30 (*c* 0.23, $CHCl_3$). IR (neat): 3071, 2982, 2929, 1734, 1685, 1597, 1556, 1532, 1448, 1351, 1261, 1097, 1021, 978, 889, 809, 688, 582 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.22-8.20 (m, 2H), 8.06 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.87-7.84 (m, 2H), 7.56-7.43(m, 4H), 5.00-4.93 (m, 1H), 4.84-4.80 (m, 2H), 4.60 (m, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 8.22-8.20 (m, 3H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.56-7.43 (m, 4H), 5.00-4.93 (m, 3H), 4.60 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.1, 168.0, 167.7, 167.4, 166.8, 164.6, 164.3, 136.6, 136.1, 132.4, 132.3, 132.2, 132.1, 131.7, 131.6, 131.3, 131.2, 128.8, 128.7, 128.3, 128.2, 128.0, 127.9, 116.1, 116.0, 115.8, 115.7, 77.9, 77.8, 62.2, 61.9, 56.9, 56.1, 43.1, 43.0, 13.8, 13.5. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 13.08 min, t_r (minor) = 20.98 min; 49% ee; Second (minor) diastereomer: t_r (major) = 17.22 min, t_r (minor) = 26.48 min, 37% ee.

Ethyl 2-benzoyl-3-(furan-2-yl)-4-nitrobutanoate (4h): Colorless liquid, yield 84%, ratio of diastereomers 1.3:1, $[\alpha]_D^{25}$ -1.32 (*c* 0.37, $CHCl_3$). IR (neat): 3063, 2984, 2937, 1736, 1686, 1597, 1556, 1449, 1377, 1262, 1096, 1079, 1016, 981, 885, 742, 532 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.60-7.56 (m, 2H), 7.50-7.44 (m, 1H), 7.32 (s, 1H), 6.26-6.23 (m, 2H), 5.02-4.92 (m, 1H), 4.84-4.81 (m, 2H), 4.50-4.44 (m, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 1.04 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.92 (d, *J* = 7.2 Hz, 2H), 7.50-7.44 (m, 3H), 7.20 (s, 1H), 6.15-6.12 (m, 2H), 5.02-4.92 (m, 3H), 4.50-4.44 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 192.6, 167.3, 167.0, 149.7, 149.6, 142.6, 142.4, 135.6, 135.5, 134.1, 133.9, 128.8, 128.7, 128.6, 128.5, 110.4, 108.6, 108.5, 75.8, 62.1, 62.0, 54.8, 53.9, 37.0, 36.9, 13.7, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 9.20 min, t_r (minor) = 13.30 min; 31% ee; Second (minor) diastereomer: t_r (major) = 10.30 min, t_r (minor) = 15.40 min, 28% ee.

Ethyl 2-(4-fluorobenzoyl)-4-nitro-3-phenylbutanoate (4i): White solid, yield 96%, ratio of diastereomers 2.6:1, Mp 74.8-92.8 °C, $[\alpha]_D^{25}$ -0.71 (*c* 0.28, $CHCl_3$). IR (KBr): 3087, 2984, 2927, 1722, 1685, 1599, 1555, 1506, 1456, 1379, 1299, 1262, 1150, 1020, 983, 849, 764, 561 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.09 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.29-7.25 (m, 3H), 7.22-7.08 (m, 4H), 4.94-4.88 (m, 1H), 4.78-4.76 (m, 2H), 4.50-4.44 (m, 1H), 3.88 (q, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.88 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.29-7.25 (m, 4H), 7.22-7.08 (m, 3H), 4.94-4.88 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7, 167.6, 166.9, 136.6, 136.1, 135.9, 135.7, 133.8, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 77.9, 62.2, 61.9, 56.9, 56.2, 43.1, 43.0, 13.8, 13.5. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 8.53 min, t_r (minor) = 14.37 min; 55% ee; Second (minor) diastereomer: t_r (major) = 11.82 min, t_r (minor) = 16.85 min, 45% ee.

Ethyl 2-(4-chlorobenzoyl)-4-nitro-3-phenylbutanoate (4j): White solid, yield 93%, ratio of diastereomers 2.0:1, Mp 115.8-118.6 °C, $[\alpha]_D^{25}$ -10.1 (*c* 0.43, $CHCl_3$). IR (KBr): 3066, 2961, 1736, 1687, 1590, 1561, 1425, 1401, 1377, 1281, 1231, 1212, 1090, 1031, 988, 878, 832, 765, 586 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32-7.26 (m, 4H), 7.22-7.18 (m, 1H), 4.95-4.87 (m, 1H), 4.79-4.76 (m, 2H), 4.50-4.44 (m, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.32-7.26 (m, 3H), 7.22-7.18 (m, 2H), 4.95-4.87 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.6, 191.5, 167.4, 166.8, 140.9, 140.4, 136.5, 136.1, 134.4, 134.1, 130.3, 129.9, 129.2, 129.1, 129.0, 128.9, 128.4, 128.2, 127.9, 78.0, 62.3, 62.1, 57.0, 56.2, 43.1, 43.0, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 9.24 min, t_r (minor) = 15.54 min; 45% ee; Second (minor) diastereomer: t_r (major) = 12.72 min, t_r (minor) = 19.21 min, 27% ee.

Ethyl 2-(4-bromobenzoyl)-4-nitro-3-phenylbutanoate (4k): White solid, yield 90%, ratio of diastereomers 1.6:1, Mp 121.9-123.8 °C, $[\alpha]_D^{25}$ -10.1 (*c* 0.49, $CHCl_3$). IR (KBr): 3031, 2986, 2926, 1725, 1685, 1584, 1556, 1496, 1455, 1384, 1294, 1260, 1166, 1070, 1024, 983, 882, 830, 700, 567 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): major isomer, δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.32-7.26 (m, 3H), 7.22-7.18 (m, 2H), 4.94-4.87 (m, 1H), 4.77-4.76 (m, 2H), 4.50-4.44 (m, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); minor isomer, δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.32-7.26 (m, 3H), 7.22-7.18 (m, 2H), 4.94-4.87 (m, 3H), 4.50-4.44 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.9, 191.8, 167.4, 166.7, 136.5, 136.1, 134.8, 134.5, 132.2, 132.1, 130.3, 130.0, 129.7, 129.2, 129.0, 128.9, 128.2, 127.9, 125.9, 78.0, 62.4, 62.1, 57.0, 56.2, 43.1, 43.0, 13.9, 13.6. The ee was determined by HPLC with a Chiralcel AD-H column (85:15 hexanes: isopropanol, 1 mL/min, 254 nm); First (major) diastereomer: t_r (major) = 10.09 min, t_r (minor) = 17.56 min; 55% ee; Second (minor) diastereomer: t_r (major) = 13.73 min, t_r (minor) = 21.89 min, 40% ee.