Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: G. Chen, G. Liang, Y. Wang, P. Deng and H. Zhou, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB00773J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB00773J

Journal Name

ARTICLE

A Homodinuclear Cobalt Complex for Catalytic Asymmetric Michael Reaction of β-Ketoesters to Nitroolefins

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Guanghui Chen,[a‡] Guojuan Liang,[a‡] Yiwu Wang,[b] Ping Deng[a] and Hui Zhou[a]

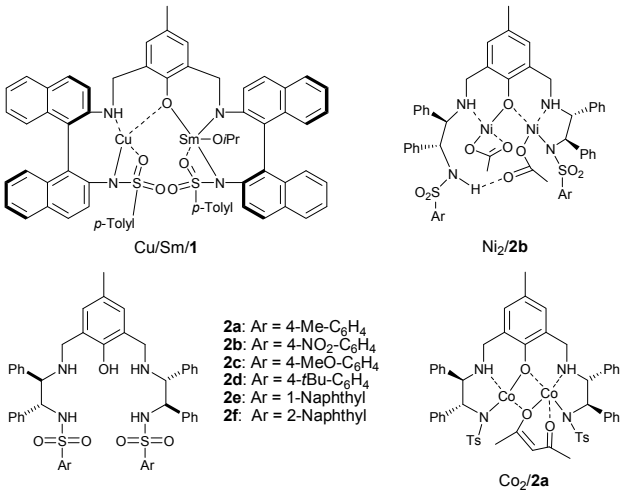
A homodinuclear Co_2/aminophenol sulfonamide complex has been developed for the asymmetric Michael reaction of β-ketoesters with nitroolefins. The procedure is capable of tolerating a wide range of substrate and excellent results (up to 99% yield, >99:1 dr and 98% ee) can also be obtained. Moreover, the reaction could be carried out on a 50 mmol scale without any decrease in the enantioselectivity and reactivity. On the basis of the results of mechanistic studies, we proposed that the Co_2/**2a** complex would be the active species and a possible catalytic cycle was described.

Introduction

Chiral bimetallic catalysts have become a powerful tool in asymmetric reactions.[1] Over the past decades, intensive efforts have been devoted to the development of new families of bimetallic asymmetric catalysts.[2-6] BINOL,[2] linked BINOL,[3] GluCAPO/FujiCAPO,[4] Schiff base,[5] bis-ProPhenol,[6] AzePhenol[7] etc. have been successfully developed as multidentate ligands to construct bimetallic complexes. As part of our ongoing studies of cooperative bimetallic complexes in asymmetric catalysis, we recently reported a new type of aminophenol sulfonamide ligands and their complexes of Cu/Sm[8a] and Ni/Ni,[8b] as well as the utility in enantioselective Henry and Mannich reactions. The Michael addition is one of the powerful tools for synthesis of functionalized organic molecules.[9] The asymmetric Michael addition of cyclic β-ketoesters to nitroolefins provides a convenient and direct route towards nitrogen-containing ketoesters with a quaternary carbon stereocenter.[10] Although great progress has been achieved, the achievement of high enantioselectivities with low catalyst loading remains an ongoing goal. Compared with organocatalysts, metal complexes are capable of combining with enolized β-ketoesters to form a chelate-ordered transition state. Herein, we report a homodinuclear Co complex (Scheme 1) for the 1,4-addition of β-ketoesters to nitroolefins.

Results and discussion

In the preliminary study, aminophenol sulfonamide ligand **2a** (Scheme 1) was complexed with various metal salts to catalyze the asymmetric Michael reaction of β-ketoesters **3a** with nitroolefins **4a**. A significant effect of the central metal ion on the diastereoselectivity and enantioselectivity was observed, as shown in Table 1. Products of low *ee* and dr were observed with



Scheme 1. Aminophenol sulfonamide ligands and dinuclear complexes.

$Ni(acac)_2$, $Zn(acac)_2$, $Fe(acac)_2$, $Fe(acac)_3$, $Mn(acac)_2$, $Mn(acac)_3$, or $Zr(acac)_2$ as the Lewis acid (Table 1, entries 2-8). Fortunately, the corresponding $Co(acac)_2$ complex could catalyze the reaction to give **5aa** in >30:1 dr and 90% *ee* (Table 1, entry 1). Different cobalt salts were also screened and $Co(acac)_2$ gave the best results (Table 1, entries 9-12).

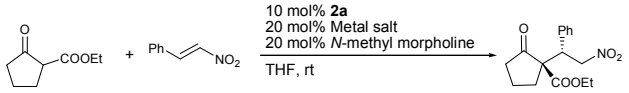
Further optimization of the reaction conditions was aimed at exploring the effectiveness of $Co(acac)_2$ with other aminophenol sulfonamide ligands (Table 2). With regard to the chiral backbone moiety, (*R,R*)-1,2-diphenylethylenediamine derived ligands were found to give superior selectivity to (*R,R*)-

[a] School of Pharmaceutical Science, Chongqing Medical University, Chongqing 400016, P. R. China. E-mail: hzhou@cqmu.edu.cn.
[b] Pharmaceutical Teaching Laboratory Centre, Chongqing Medical University, Chongqing 400016, P. R. China
‡These authors contributed equally.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8OB00773J

1,1'-binaphthyl-2,2'-diamine derived ones (Table 2, entries 1 vs. 2). Then the benzenesulfonyl moiety of the ligands was screened. The bulkier group or electron-withdrawing substituent provide worse results (Table 2, entries 3, and 5-7). The electron-donating substituent on the benzenesulfonyl moiety maintained the selectivities with decreasing yield (Table 2, entry 4). Accordingly, **2a** with *para*-methyl substituted benzenesulfonyl group was chosen as the best ligand for the next investigation.

Table 1. Screening of central metal ions in the asymmetric Michael reaction of β-ketoesters **3** with nitroolefins **4a**.[a]

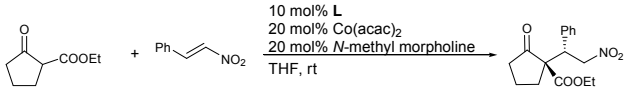


3a **4a** **5aa**

Entry	Metal salt	Yield (%)[b]	dr[c]	*ee*[c]
1[d]	$Co(acac)_2$	77	>30:1	90
2	$Ni(acac)_2$	90	3:1	2
3	$Zn(acac)_2$	81	6:1	6
4	$Fe(acac)_2$	55	5:1	8
5	$Fe(acac)_3$	45	5:1	8
6	$Mn(acac)_2$	69	5:1	0
7	$Mn(acac)_3$	76	5:1	0
8	$Zr(acac)_2$	99	4:1	0
9	$Co(OAc)_2$	35	3:1	8
10	$CoCl_2$	86	4:1	20
11	$Co(ClO_4)_2$	87	2:1	26
12	$Co(O\text{-}iPr)_2$	89	6:1	2

[a] Unless otherwise noted, all reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester (2 equiv.) in THF (0.5 mL) at rt for 36 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction time was 19 h.

Table 2. Ligand screening in the asymmetric Michael reaction of β-ketoesters **3** with nitroolefins **4a**.[a]



3a **4a** **5aa**

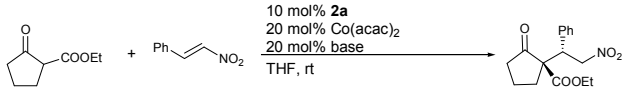
Entry	Ligand	Time (h)	Yield (%)[b]	dr[c]	*ee*[c]
1	**1**	4	19	3:1	9
2	**2a**	19	77	>30:1	90
3	**2b**	10	22	9:1	36
4	**2c**	10	61	>30:1	91
5	**2d**	10	51	23:1	84
6	**2e**	10	46	18:1	72
7	**2f**	10	53	29:1	86

[a] All reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester (2 equiv.) in THF (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

Next, different bases were examined. As shown in Table 3, the selectivities of the reaction decreased when more alkaline amines or inorganic bases were used instead of *N*-methyl morpholine probably becacuse of a stronger background reaction.

Subsequently, we examined the effect of solvents in the presence of 10 mol% **2a**-$Co(acac)_2$ complex. As shown in Table 4. Excellent selectivities were obtained in most of the solvents examined (Table 4, entries 2-6). When the halogenated hydrocarbons were used as solvents, the reaction rate was much improved (Table 4, entries 2-4). Therefore, CH_2ClCH_2Cl was chosen as the best solvent for this reaction considering the reactivity and selectivity (Table 4, entry 3).

Table 3. Screening of bases in the asymmetric Michael reaction of β-ketoesters **3** with nitroolefins **4a**.[a]

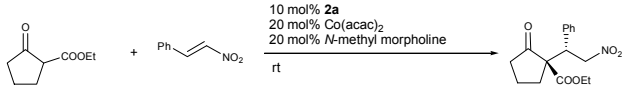


3a **4a** **5aa**

Entry	Base	Time (h)	Yield (%)[b]	dr[c]	*ee*[c]
1	NMM[d]	19	77	>30:1	90
2	Et_3N	12	86	13:1	80
3	iPr_2NEt	22	56	18:1	87
4	DMAP[e]	19	57	5:1	42
5	KOAc	12	89	6:1	22
6	K_2CO_3	12	88	5:1	21

[a] All reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester (2 equiv.) in THF (0.5 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC. [d] NMM = *N*-methyl morpholine. [e] DMAP = 4-dimethylaminopyridine.

Table 4. Effect of solvent in the asymmetric Michael reaction of β-ketoesters 3 with nitroolefins 4a. [a]



3a **4a** **5aa**

Entry	Base	Time (h)	Yield (%)[b]	dr[c]	*ee*[c]
1	THF	19	77	>30:1	90
2	CH_2Cl_2	2	97	>30:1	96
3	$ClCH_2CH_2Cl$	2	99	>50:1	98
4	CH_3Cl	4	97	21:1	95
5	CH_3CN	12	98	>30:1	90
6	Toluene	12	99	>30:1	94

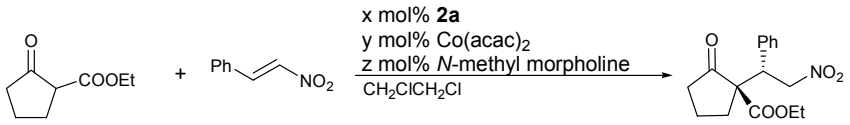
[a] All reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester (2 equiv.) in a certain solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

To reduce the catalyst loading, the catalytic system was further optimized, with the results summarized in Table 5. When the catalyst loading was reduced from 10 mol% to 2 mol%, a lower reaction rate was obtained with smaller *ee* (Table 5, entries 1-3). When the ratio of **2a** to $Co(acac)_2$ was changed from 1:2 to 1:1, a greatly reduced *ee* was obtained with smaller dr and reaction rate (Table 5, entries 3 vs. 4). To our delight, when the molar ratio of **2a**/$Co(acac)_2$ was increased from 1:2 to 1:3 or 1:4, the product was obtained with higher enantioselectivity (Table 5, entries 3 vs. 5-7). The reaction rate could recovery and the selectivities were maintained when the amount of base increased to 40 mol% (Table 5, entries 8 vs 1 and 6). The screening of temperature showed 0 °C was the best (Table 5, entries 8-11). The molar

View Article Online
DOI: 10.1039/C8OB00773J

ratio of nitroolefin to ketoester could reduce to 1:1.1 with an acceptable reaction time (Table 5, entries 13 vs. 10 and 12). On the basis of these results, the catalyst loading successfully reduced to 1 mol% with maintained yield, dr, and *ee* (Table 5, entry 14). At the ratio of 1:4 (**2a**/Co(acac)$_2$), the catalyst loading could reduce to 0.5 mol% with double reaction time and slightly lower *ee* (Table 5, entries 16 vs. 14 and 15). Hence, we found that treat of β-ketoester **3a** and nitroolefin **4a** in the presence of **2a** (1 mol%) and Co(acac)$_2$ (3 mol%) together with *N*-methyl morpholine (40 mol%) gave the desired product **5aa** in 99% yield with >50:1 dr and 98% *ee*.

Table 5. Further optimization of the reaction.[a]



3a **4a** **5aa**

Entry	x	y	Ratio of **2a**/Co	z	Molar ratio of nitroolefin to ketoester	T (°C)	Time (h)	Yield (%)[b]	dr[c]	*ee*[c]
1	10	20	1/2	20	1:2	rt	2	99	>50:1	98
2	5	10	1/2	20	1:2	rt	12	98	>50:1	97
3	2	4	1/2	20	1:2	rt	23	77	>30:1	91
4	2	2	1/1	20	1:2	rt	23	42	9:1	16
5	2	5	1/2.5	20	1:2	rt	23	73	>30:1	93
6	2	6	1/3	20	1:2	rt	23	76	>30:1	96
7	2	8	1/4	20	1:2	rt	23	74	>30:1	96
8	2	6	1/3	40	1:2	rt	3	91	>50:1	98
9	2	6	1/3	40	1:2	35	3	71	>30:1	96
10	2	6	1/3	40	1:2	0	3	99	>50:1	98
11	2	6	1/3	40	1:2	-10	3	96	>50:1	97
12	2	6	1/3	40	1:1	0	23	96	>50:1	98
13	2	6	1/3	40	1:1.1	0	12	99	>50:1	98
14[d]	1	3	1/3	40	1:1.1	0	12	99	>50:1	97
15[e]	0.5	1.5	1/3	40	1:1.1	0	72	81	>30:1	84
16[e]	0.5	2	1/4	40	1:1.1	0	24	97	>50:1	94

[a] Unless otherwise noted, all reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester in CH_2ClCH_2Cl (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was carried out on 0.4 mmol scale (nitroolefin) and β-ketoester in CH_2ClCH_2Cl (1.0 mL). [e] The reaction was carried out on 0.8 mmol scale (nitroolefin) and β-ketoester in CH_2ClCH_2Cl (2.0 mL).

Under the optimal reaction conditions (Table 5, entry 14), a variety of nitroolefin substrates including aryl substrates with electron-donating substituents or electron-withdrawing substituents, heteroaromatic, aliphatic, condensed-ring and α, β-unsaturated nitroolefins were investigated and the desired products were obtained in excellent yields (only one exception, Table 6, entry 2) with excellent diastereomeric ratios and excellent *ee* (Table 6, entries 1-19). For the less reactive aliphatic nitroolefins, more catalyst loading was required (Table 6, entries 20 and 21). Some substrates were selected to try the catalyst loading of 0.5 mol% and the corresponding products were obtained in good to excellent yields with excellent dr and *ee*, while the reaction time was prolonged (Table 6, entries 22-25). Moreover, the reaction could be carried out on a 50 mmol scale without any decrease in the enantioselectivity and reactivity (Table 6, entry 26).

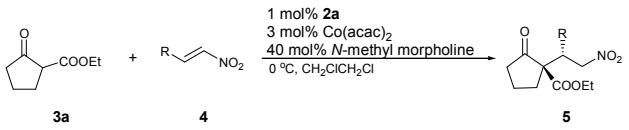
Other β-ketoesters were also reacted in this catalytic system and the scope and limitations of β-ketoesters are summarized in Table 7. The reaction conditions were optimized for each β-ketoesters. When five-membered oxygen heterocycle (**3b**), six-membered ring (**3c**), and acyclic 3-substutited β-ketoesters (**3d**) were used in this asymmetric transformation, increased catalyst loading was required for good reactivities and selectivities (Table 7, entries 1-3). Ethyl acetoacetate (**3e**) gave the corresponding product in high enantioselectivities (99% and 99% *ee*) with high reactivity on 1 mol% catalyst loading, but the diastereoselectivity was decreased sharply (1:1 dr, Table 7, entry 4).

To gain a preliminary insight into the mechanism, the relationship between the *ee* values of ligand **2a** and product **5aa** at different ratios of **2a** to Co(acac)$_2$ (1:2, 1:3 and 1:4) was investigated (Figure 1).[11] A perfect linear effect was observed at these examined ratios with the addition of *N*-methyl morpholine, which suggested that the monomeric catalyst might be the active species. Without the addition of *N*-methyl morpholine, to our surprise, resulted in a negative non-linear effect. This change in non-linear effect indicated either a change in mechanism or a structural change of the chiral catalyst. The ESI-MS studies were also carried out.[12] All the spectrums of the 1:1, 1:2, 1:3, and 1:4 **2a**/Co(acac)$_2$ mixture whether or not to add the *N*-methyl morpholine displayed ions at *m/z* 1078 and 1096, which corresponded to Co$_2$/**2a**. Moreover, all the spectrums of the mixture of nitroolefin **4a** and **2a**/Co(acac)$_2$ in the ratios of 1:2, 1:3, and 1:4 whether or not to add the *N*-methyl morpholine displayed ions at *m/z* 1227, 1228 or 1245, which corresponded to [Co$_2$/**2a** + **4a**]. On

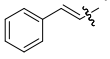
View Article Online
DOI: 10.1039/C8OB00773J

the basis of these analysis, we speculated that the Co_2/**2a** complex (Figure 1)[13] would be the active species.

Table 6. Asymmetric Michael addition of ethyl 2-oxocyclopentanecarboxylate to different nitroolefins.[a]



3a **4** **5**

Entry	R	Time (h)	Yield (%)[b]	dr[c]	*ee*[c]
1	Ph (**5aa**)	12	99	>50:1	97
2	2-MeC_6H_4 (**5ab**)	42	70	>99:1	97
3	3-MeC_6H_4 (**5ac**)	42	99	>30:1	97
4	4-MeC_6H_4 (**5ad**)	15	99	>50:1	97
5	4-$MeOC_6H_4$ (**5ae**)	48	99	>99:1	96
6	4-FC_6H_4 (**5af**)	12	99	>99:1	97
7	2-BrC_6H_4 (**5ag**)	12	97	>30:1	96
8	4-BrC_6H_4 (**5ah**)	12	99	>30:1	96
9	2-ClC_6H_4 (**5ai**)	12	99	>30:1	97
10	3-ClC_6H_4 (**5aj**)	12	98	>30:1	97
11	4-ClC_6H_4 (**5ak**)	12	97	>30:1	97
12	2-$NO_2C_6H_4$ (**5al**)	12	99	>50:1	97
13	3-$NO_2C_6H_4$ (**5am**)	12	99	>30:1	94
14	4-$NO_2C_6H_4$ (**5an**)	48	99	>50:1	95
15	 (**5ao**)	48	98	>50:1	95
16	2-furyl (**5ap**)	12	99	>50:1	94
17	2-thienyl (**5aq**)	48	99	>30:1	95
18	1-naphthyl (**5ar**)	62	96	>99:1	97
19	2-naphthyl (**5as**)	48	98	>50:1	98
20[d]	n-butyl (**5at**)	12	99	>99:1	97
21[e]	n-octyl (**5au**)	20	93	>99:1	98
22[f]	Ph (**5aa**)	24	97	>50:1	94
23[f]	4-$MeOC_6H_4$ (**5ae**)	120	80	29:1	98
24[f]	2-ClC_6H_4 (**5ai**)	84	92	>50:1	92
25[f]	2-naphthyl (**5as**)	120	98	>50:1	91
26[g]	Ph (**5aa**)	12	98	>50:1	97

[a] Unless otherwise noted, all reactions were carried out on 0.4 mmol scale (nitroolefin) and β-ketoester (1.1 equiv.) in CH_2ClCH_2Cl (1.0 mL) with **2a** (1 mol%) and $Co(acac)_2$ (3 mol%). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy and chiral HPLC. [d] 2 mol% of **2a** and 6 mol% of $Co(acac)_2$ were used. [e] 5 mol% of **2a** and 15 mol% of $Co(acac)_2$ were used. [f] The reaction was carried out on 0.8 mmol scale (nitroolefin) and β-ketoester (1.1 equiv.) in CH_2ClCH_2Cl (2.0 mL) with **2a** (0.5 mol%) and $Co(acac)_2$ (2 mol%). [g] The reaction was carried out on 50 mmol scale (nitroolefin) and β-ketoester (1.1 equiv.) in CH_2ClCH_2Cl (125 mL) with **2a** (1 mol%) and $Co(acac)_2$ (3 mol%).

The postulated catalytic cycle is summarized in Figure 2.[14] We assume that the β-keto ester would coordinate to the acetylacetone-complexed Co with the assistance of *N*-methyl morpholine to generate a new Co-enolate. The nitroolefin would be activated by another Co. The Co_2/**2a** regenerates with the help of *N*-methyl morpholine after the 1,4-addition via bimetallic transition state and deprotonation. We think more than one Co_2/**2a** would be involved in the transition state without the addition of *N*-methyl morpholine, which is why a negative non-linear effect was observed without the addition of *N*-methyl morpholine. TS1 and TS2 are proposed to rationalize the asymmetric induction. As illustrated in Figure 2, the enolate oxygen is coordinated to Co in the more Lewis acidic equatorial position for maximal activation, whereas the keto functionality is positioned by a suitable Co by avoiding the steric repulsion of Ts (TS1-I *vs.*, TS1-II, Figure 2).

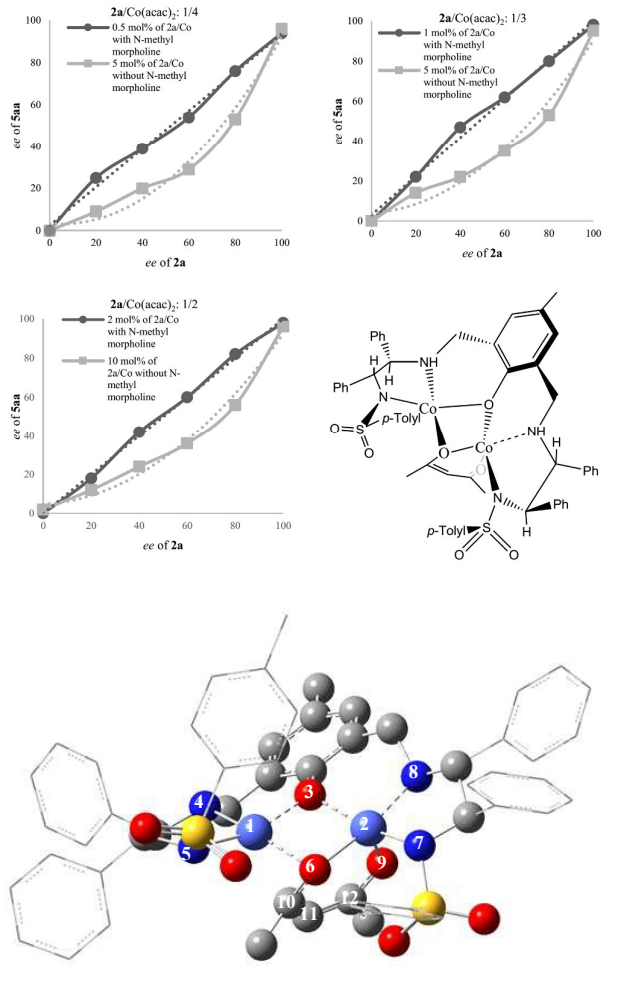
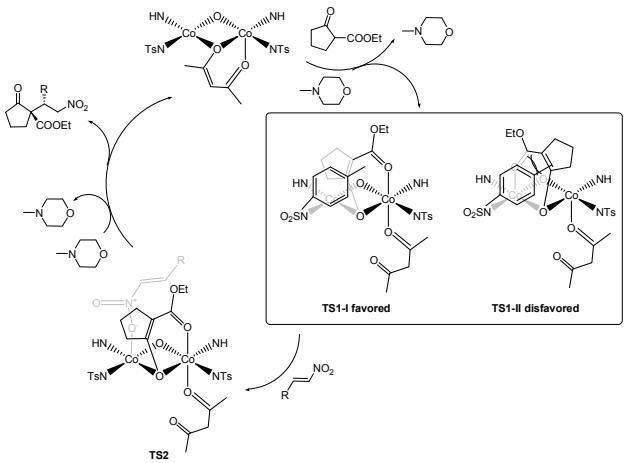


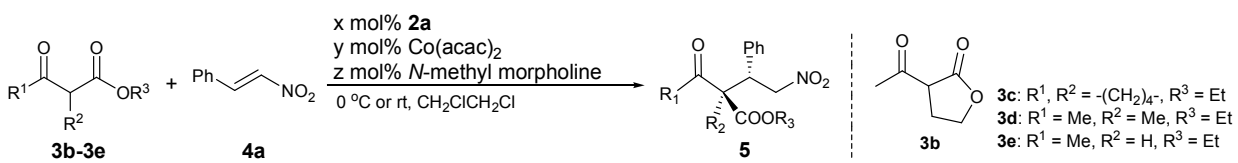
Figure 1. Non-linear effect and the structure of the dinuclear Co-aminophenol sulfonamide complex optimized by DFT.



View Article Online
DOI: 10.1039/C8OB00773J

Figure 2. Postulated catalytic cycle.

Table 7. Scope and limitations of β-ketoesters.[a]



Entry	3	5	x	y	z	T (°C)	Time (h)	Yield (%) [b]	dr[c]	ee[c]
1[d]	**3b**	**5ba**	3	9	40	0	12	99	7:1	94
2[e]	**3c**	**5ca**	10	20	20	rt	62	87	>30:1	98
3[e]	**3d**	**5da**	5	15	40	0	62	97	>99:1	98
4[f]	**3e**	**5ea**	1	3	40	0	12	99	1:1	99/99

[a] Unless otherwise noted, all reactions were carried out on 0.2 mmol scale (nitroolefin) and β-ketoester (1.1 equiv. or 2 equiv.) in CH_2ClCH_2Cl (0.5 mL). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy and chiral HPLC. [d] 1.1 equiv. β-Ketoester was used. [e] 2 equiv. β-Ketoester was used. [f] The reaction was carried out with 0.4 mmol scale (nitroolefin) and β-ketoester (1.1 equiv.) in CH_2ClCH_2Cl (1.0 mL).

Conclusions

We have developed a new homodinuclear Co aminophenol sulfonamide complex for the asymmetric Michael addition of β-ketoesters to nitroolefins. This simple experimental protocol affords various optically active nitrogen-containing ketoesters with a quaternary carbon stereocenter in high yields (up to 99%) with excellent diastereomeric ratios (up to >99:1) and excellent enantioselectivities (up to 98%) with 0.5-10 mol% catalyst. Moreover, the reaction could be carried out on 50 mmol scale without any decrease in the enantioselectivity and reactivity. Further efforts are underway for the application of the desired catalyst to other reactions.

Experimental Section

General: Commercial reagents were used as purchased. NMR spectra were recorded in the deuterated solvents as stated, using residual non-deuterated solvent as internal standard. High resolution mass spectra were recorded with a Bruker Solari XFT-ICR-MS system. The enantiomeric excess (*ee*) was determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with UV detector at 210 nm. Optical rotations were measured on a commercial polarimeter and are reported as follows: $[\alpha]_D^T$ (c = g/100 mL, solvent). The aminophenol sulfonamide ligands were prepared according to the literature.[8] The absolute configuration of **5aa**, **5ai-5ak**, **5ap**, **5ar**, **5ba**, **5ca**, **5da**, and **5ea** was determined by comparison of the HPLC retention time and optical rotations with the literature data.[10k,10l,10n,10q,10r,10s] The absolute stereochemistry of **5ab-5ah**, **5al-5an**, **5ao**, **5aq**, **5as**, **5at**, and **5au** was assigned by analogy.

General procedure for the asymmetric Michael Reaction of β-ketoesters with nitroolefins: Ligand **2a** (0.004 mmol, 1 mol%) and $Co(acac)_2$ (0.012 mmol, 3 mol%) were stirred in CH_2ClCH_2Cl (0.5 ml) at 35 °C for 30 min. The reaction mixture was cooled to 0 °C and then nitroolefins **4** (0.4 mmol), ethyl 2-oxocyclopentanecarboxylate **3a** (0.44 mmol, 1.1 equiv.), *N*-methyl morpholine (0.16 mmol, 40 mol%) and CH_2ClCH_2Cl (0.5 ml) were successively added. The stirring was continued until the reaction proceeded completely. The residue was purified by column chromatography (PE/EA =1:30 to 1:8) on silica gel to afford **5**.

(*R*)-ethyl 1-((*S*)-2-nitro-1-phenylethyl)-2-oxocyclopentane carboxylate (5aa): Pale yellow oil; 121.1 mg, 99% yield with >50:1 dr and 97% *ee*: $[\alpha]^{26}_D$ = -24.8 (*c* 0.94, $CHCl_3$) (ref.[10k]: $[\alpha]^{20}_D$ = +5.5 (*c* 1.0, $CHCl_3$, 91:9 dr, 97% *ee*)); ^1H NMR (600 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.16 (dd, *J* = 13.6, 3.8 Hz, 1H), 5.00 (dd, *J* = 13.6, 11.0 Hz, 1H), 4.24-4.14 (m, 2H), 4.06 (dd, *J* = 11.0, 3.7 Hz, 1H), 2.38-2.30 (m, 2H), 2.04-1.86 (m, 3H), 1.83-1.77 (m, 1H), 1.26 (t, *J* = 7.3 Hz, 3H). HPLC (Chiralcel ODH column), hexane/2-propanol 80:20, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 12.8 min (major enantiomer), 8.7 min (minor enantiomer); t_R(minor diastereomer) = 10.4 min (major enantiomer), 7.6 min (minor enantiomer).

(*R*)-ethyl 1-((S)-2-nitro-1-*o*-tolylethyl)-2-oxocyclopentane carboxylate (5ab): Pale yellow oil; 89.9 mg, 70% yield, >99:1 dr, 97% *ee*; ; $[\alpha]^{26}_D$ = +16.2 (*c* 0.66, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 1H), 7.17-7.12 (m, 3H), 5.25 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.94 (dd, *J* = 13.3, 10.9 Hz, 1H), 4.37 (dd, *J* = 10.8, 3.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 2.40-2.34 (m, 2H), 2.18-2.10 (m, 1H), 1.99-1.90 (m, 3H), 1.25 (s, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 98:2, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 19.6 min (major enantiomer), 14.9 min (minor enantiomer); t_R (minor diastereomer) = 13.2 min (major enantiomer), 11.2 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-*m*-tolylethyl)-2-oxocyclopentane carboxylate (5ac): Pale yellow oil; 126.8 mg, 99% yield, >30:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –22.6 (*c* 1.20, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.6 Hz, 1H), 7.08-7.02 (m, 3H), 5.16 (dd, *J* = 13.6, 3.7 Hz, 1H), 5.00 (dd, *J* = 13.6, 11.0 Hz, 1H), 4.24-4.16 (m, 2H), 4.01 (dd, *J* = 10.9, 3.7 Hz, 1H), 2.39-2.31 (m, 2H), 2.31 (s, 3H), 2.07-1.87 (m, 3H), 1.85-1.77 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a

View Article Online
DOI: 10.1039/C8OB00773J

Chiralcel ODH column, hexane/2-propanol 98:2, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 18.0 min (major enantiomer), 13.1 min (minor enantiomer); t_R (minor diastereomer) = 14.4 min (major enantiomer), 10.9 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-*p*-tolylethyl)-2-oxocyclopentane carboxylate (5ad): Pale yellow oil; 127.1 mg, 99% yield, >50:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –34.3 (*c* 0.89, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = +24.0 (c 0.25, $CHCl_3$) in 92:8 dr and 97% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 20.6, 8.1 Hz, 4H), 5.14 (dd, *J* = 13.5, 3.8 Hz, 1H), 4.98 (dd, *J* = 13.4, 11.1 Hz, 1H), 4.25-4.15 (m, 2H), 4.05 (dd, *J* = 11.0, 3.8 Hz, 1H), 2.39-2.30 (m, 2H), 2.29 (s, 3H), 2.04-1.95 (m, 2H), 1.94-1.87 (m, 1H), 1.84-1.77 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 98:2, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 19.5 min (major enantiomer), 15.2 min (minor enantiomer); t_R (minor diastereomer) = 14.5 min (major enantiomer), 12.3 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5ae): Yellow oil; 133.7 mg, 99% yield, >99:1 dr, 96% *ee*; $[\alpha]^{26}_D$ = –30.0 (*c* 0.97, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = +32.6 (c 0.5, $CHCl_3$) in 87:13 dr and 85% ee]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.11 (dd, *J* = 13.4, 3.8 Hz, 1H), 4.95 (dd, *J* = 13.3, 11.2 Hz, 1H), 4.24-4.15 (m, 2H), 4.04 (dd, *J* = 11.1, 3.8 Hz, 1H), 3.76 (s, 3H), 2.39-2.29 (m, 2H), 2.01-1.94 (m, 2H), 1.94 – 1.87 (m, 1H), 1.84-1.76 m, 1H), 1.26 (t, *J* = 7.2 Hz,3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 19.6 min (major enantiomer), 15.8 min (minor enantiomer); t_R (minor diastereomer) = 11.6 min (major enantiomer), 14.6 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5af): Pale yellow oil; 128.5 mg, 99% yield, >99:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –23.9 (*c* 0.77, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = + 33.3 (c 0.30, $CHCl_3$) in 99:1 dr and 92% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26-7.22 (m, 2H), 6.99-6.94 (m, 2H), 5.13 (dd, *J* = 13.6, 3.7 Hz, 1H), 4.95 (dd, *J* = 13.6, 11.2 Hz, 1H), 4.20-4.14 (m, 2H), 4.03 (dd, *J* = 11.1, 3.7 Hz, 1H), 2.39-2.30 (m, 2H), 2.06-1.97 (m, 1H), 1.94-1.87 (m, 2H), 1.85-1.77 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 18.1 min (major enantiomer), 10.7 min (minor enantiomer); t_R (minor diastereomer) = 13.7 min (major enantiomer), 9.2 min (minor enantiomer).

(*R*)-ethyl 1-((*R*)-1-(2-bromophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5ag): Pale yellow oil; 149.7 mg, 97% yield, >30:1 dr, 96% *ee*; $[\alpha]^{26}_D$ = +13.7 (*c* 0.97, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H), 7.31-7.27 (m, 1H), 7.15-7.10 (m, 1H), 5.46 (dd, *J* = 13.8, 3.5 Hz, 1H), 5.05 (dd, *J* = 13.6, 10.7 Hz, 1H), 4.50 (dd, *J* = 10.6, 3.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.48 (t, *J* = 7.6 Hz, 2H), 2.24-2.17 (m, 1H), 2.12-2.05 (m, 1H), 1.98-1.88 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK IA column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 6.8 min (major enantiomer), 6.4 min (minor enantiomer); t_R (minor diastereomer) = 7.8 min (major enantiomer), 8.3 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5ah): Pale yellow oil; 153.1 mg, 99% yield, >30:1 dr, 96% *ee*; $[\alpha]^{26}_D$ = –29.6 (*c* 0.94, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.17-7.14 (m, 2H), 5.15 (dd, *J* = 13.7, 3.7 Hz, 1H), 4.96 (dd, *J* = 13.7, 11.2 Hz, 1H), 4.21-4.14 (m, 2H), 4.01 (dd, *J* = 11.1, 3.7 Hz, 1H), 2.41-2.31 (m, 2H), 2.09-2.01 (m, 1H), 1.95-1.87 (m, 2H), 1.86-1.80 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 70:30, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 12.2 min (major enantiomer), 8.2 min (minor enantiomer); t_R (minor diastereomer) = 9.4 min (major enantiomer), 6.9 min (minor enantiomer).

(R)-ethyl 1-((R)-1-(2-chlorophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5ai): Pale yellow oil; 135.4 mg, 99% yield, >30:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = +11.5 (*c* 0.85, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = –23.0 (c 0.5, $CHCl_3$) in 92:8 dr and 94% ee]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.23–7.13 (m, 2H), 5.44 (dd, *J* = 13.9, 3.4 Hz, 1H), 5.04 (dd, *J* = 13.4, 11.3 Hz, 1H), 4.49 (dd, *J* = 10.6, 3.1 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.47–2.34 (m, 2H), 2.20 (m, 1H), 2.07–1.97 (m, 1H), 1.93–1.83 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 10.3 min (major enantiomer), 9.7 min (minor enantiomer); t_R(minor diastereomer) = 12.7 min (major enantiomer), 9.1 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5aj): Pale yellow oil; 133.7 mg, 98% yield, >30:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –17.6 (*c* 0.94, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = +22.0 (c 0.5, $CHCl_3$) in 91:9 dr and 92% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.20 (m, 3H), 7.17-7.14 (m, 1H), 5.18 (dd, *J* = 13.9, 3.6 Hz, 1H), 4.98 (dd, *J* = 13.9, 11.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.96 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.42-2.30 (m, 2H), 2.14-2.06 (m, 1H), 1.95-1.82 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 14.8 min (major enantiomer), 10.7 min (minor enantiomer); t_R (minor diastereomer) = 9.3 min (major enantiomer), 12.3 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-2-oxocyclo pentanecarboxylate (5ak): Pale yellow oil; 132.3 mg, 97% yield, >30:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –22.9 (*c* 0.94, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_D$ = +37.0 (c 1.0, $CHCl_3$) in 91:9 dr and 93% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H), 7.22-7.19 (m, 2H), 5.14 (dd, *J* = 13.7, 3.7 Hz, 1H), 4.95 (dd, *J* = 13.6, 11.2 Hz, 1H), 4.21-4.14 (m, 2H), 4.01 (dd, *J* = 11.1, 3.6 Hz, 1H), 2.39-2.30 (m, 2H), 2.07-1.99 (m, 1H), 1.95-1.86 (m, 2H), 1.85-1.78 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 15.6 min (major enantiomer), 10.7 min (minor enantiomer); t_R (minor

View Article Online
DOI: 10.1039/C8OB00773J

diastereomer) = 12.1 min (major enantiomer), 9.1 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-(2-nitrophenyl)ethyl)-2-oxocyclopentanecarboxylate (5al): Yellow oil; 139.2 mg, 99% yield, >50:1 dr, 97% *ee*; $[\alpha]^{26}_{D}$ = –79.7 (*c* 0.95, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.46-7.41 (m, 1H), 5.36 (dd, *J* = 14.3, 3.5 Hz, 1H), 5.05 (dd, *J* = 14.3, 10.7 Hz, 1H), 4.65 (dd, *J* = 10.7, 3.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.55-2.42 (m, 2H), 2.22-2.16 (m, 1H), 2.05-1.99 (m, 2H), 1.95-1.87 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK IA column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 11.6 min (major enantiomer), 9.9 min (minor enantiomer); t_R (minor diastereomer) = 13.5 min (major enantiomer), 14.6 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-(3-nitrophenyl)ethyl)-2-oxocyclopentanecarboxylate (5am): Pale yellow oil; 139.0 mg, 99% yield, >30:1 dr, 94% *ee*; $[\alpha]^{26}_{D}$ = –16.5 (*c* 0.77, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 – 8.21 (m, 1H), 8.17-8.13 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 5.27 (dd, *J* = 14.1, 3.5 Hz, 1H), 5.06 (dd, *J* = 14.0, 11.2 Hz, 1H), 4.26-4.16 (m, 2H), 4.09 (dd, *J* = 11.1, 3.5 Hz, 1H), 2.48-2.41 (m, 1H), 2.34-2.29 (m, 1H), 2.19-2.11 (m, 1H), 1.99-1.85 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK ADH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 15.8 min (major enantiomer), 15.1 min (minor enantiomer); t_R (minor diastereomer) = 18.4 min (major enantiomer), 16.8 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-2-oxocyclopentanecarboxylate (5an): White solid; 139.7 mg, 99% yield, >50:1 dr, 95% *ee*; $[\alpha]^{26}_{D}$ = –27.5 (*c* 0.70, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +43.6 (c 0.5, $CHCl_3$) in 91:9 dr and 90% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 5.23 (dd, *J* = 14.0, 3.5 Hz, 1H), 5.04 (dd, *J* = 14.0, 11.2 Hz, 1H), 4.23 – 4.08 (m, 2H), 4.11 (dd, *J* = 11.1, 3.5 Hz, 1H), 2.47-2.40 (m, 1H), 2.36-2.31 (m, 1H), 2.16-2.08 (m, 1H), 1.99-1.93 (m, 1H), 1.91-1.85 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK ASH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 43.4 min (major enantiomer), 47.2 min (minor enantiomer); t_R (minor diastereomer) = 64.9 min (major enantiomer), 39.9 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-nitro-4-phenylbut-3-en-2-yl)-2-oxocyclopentanecarboxylate (5ao): Pale yellow oil; 129.1 mg, 98% yield, >50:1 dr, 95% *ee*; $[\alpha]^{26}_{D}$ = –67.2 (*c* 0.91, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +58.5 (c 1.0, $CHCl_3$) in 91:9 dr and 92% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.26 (m, 4H), 7.25-7.21 (m, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.8, 9.6 Hz, 1H), 4.99 (dd, *J* = 12.7, 3.4 Hz, 1H), 4.62 (dd, *J* = 12.7, 10.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.52-3.46 (m, 1H), 2.48-2.41 (m, 2H), 2.32-2.24 (m, 1H), 2.12-2.05 (m, 1H), 2.04-1.96 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 14.7 min (major enantiomer), 16.3 min (minor enantiomer); t_R (minor diastereomer) = 13.2 min (major enantiomer), 11.2 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(furan-2-yl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (5ap): Pale yellow oil; 117.4 mg, 99% yield, >50:1 dr, 94% *ee*; $[\alpha]^{26}_{D}$ = –45.6 (*c* 0.99, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +20.0 (c 0.5, $CHCl_3$) in 95:5 dr and 98% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.0 Hz, 1H), 6.29 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 4.96-4.86 (m, 2H), 4.43 (dd, *J* = 10.3, 4.1 Hz, 1H), 4.25-4.15 (m, 2H), 2.49-2.43 (m, 1H), 2.37-2.30 (m, 1H), 2.15-2.08 (m, 1H), 2.00-1.93 (m, 2H), 1.77-1.68 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK IC column, hexane/2-propanol 70:30, flow rate = 0.7 mL/min, 210 nm. t_R (major diastereomer) = 14.5 min (major enantiomer), 11.8 min (minor enantiomer); t_R (minor diastereomer) = 23.6 min (major enantiomer), 11.6 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-oxocyclopentanecarboxylate (5aq): Pale yellow oil; 123.8 mg, 99% yield, >30:1 dr, 95% *ee*; $[\alpha]^{26}_{D}$ = –24.8 (*c* 0.94, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +43.0 (c 0.50, $CHCl_3$) in 94:6 dr and 94% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 5.0 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 1H), 6.91 (dd, *J* = 4.9, 3.7 Hz, 1H), 5.12 (dd, *J* = 13.6, 3.5 Hz, 1H), 4.92 (dd, *J* = 13.6, 10.6 Hz, 1H), 4.40 (dd, *J* = 10.6, 3.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.46-2.35 (m, 2H), 2.14-2.06 (m, 2H), 2.03-1.96 (m, 1H), 1.92-1.84 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 17.2 min (major enantiomer), 10.8 min (minor enantiomer); t_R (minor diastereomer) = 15.1 min (major enantiomer), 9.4 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(naphthalen-1-yl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (5ar): Yellow oil; 136.7 mg, 96% yield, >99:1 dr, 97% *ee*; $[\alpha]^{26}_{D}$ = –25.6 (*c* 0.33, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +34.0 (c 0.5, $CHCl_3$) in 91:9 dr and 93% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.6 Hz, 1H), 7.80 (dd, *J* = 25.7, 8.1 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.58-7.53 (m, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 5.51 (dd, *J* = 13.7, 3.8 Hz, 1H), 5.14 (dd, *J* = 13.7, 10.4 Hz, 1H), 5.01 (dd, *J* = 10.4, 3.8 Hz, 1H), 4.24-4.15 (m, 2H), 2.41-2.34 (m, 1H), 2.27-2.16 (m, 2H), 1.91-1.82 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK IC column, hexane/2-propanol 80:20, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 16.0 min (major enantiomer), 12.2 min (minor enantiomer); t_R (minor diastereomer) = 18.4 min (major enantiomer), 11.1 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-(naphthalen-2-yl)-2-nitroethyl)-2-oxocyclopentanecarboxylate (5as): Pale yellow oil; 139.6 mg, 98% yield, >50:1 dr, 98% *ee*; $[\alpha]^{26}_{D}$ = –31.2 (*c* 1.20, $CHCl_3$) [ref.[10k]: $[\alpha]^{20}_{D}$ = +34.0 (c 0.5, $CHCl_3$) in 92:8 dr and 94% *ee*]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80-7.76 (m, 3H), 7.72 (s, 1H), 7.49-7.44 (m, 1H), 7.39 (dd, *J* = 8.6, 1.5 Hz, 1H), 5.25 (dd, *J* = 13.7, 3.8 Hz, 1H), 5.14 (dd, *J* = 13.7, 11.0 Hz, 1H), 4.25-4.19 (m, 3H), 2.40-2.30 (m, 2H), 2.05-1.97 (m, 2H), 1.95-1.87 (m, 1H), 1.85-1.77 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 70:30, flow rate = 1 mL/min, 210 nm. t_R (major

View Article Online
DOI: 10.1039/C8OB00773J

diastereomer) = 11.5 min (major enantiomer), 28.8 min (minor enantiomer); t_R (minor diastereomer) = 9.7 min (major enantiomer), 14.8 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-1-nitropentan-2-yl)-2-oxocyclopentane carboxylate (5at): Colourless oil; 107.8 mg, 99% yield, >99:1 dr, 97% *ee*; $[\alpha]^{26}_D$ = –48.3 (*c* 0.76, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (dd, *J* = 14.0, 4.8 Hz, 1H), 4.36 (dd, *J* = 14.0, 5.6 Hz, 1H), 4.20-4.12 (m, 2H), 2.86-2.80 (m, 1H), 2.61-2.55 (m, 1H), 2.47-2.39 (m, 1H), 2.33-2.25 (m, 1H), 2.05-1.98 (m, 2H), 1.97-1.90 (m, 1H), 1.46-1.36 (m, 2H), 1.29-1.22 (m, 5H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 213.28, 169.35, 76.48, 62.84, 61.91, 40.42, 38.19, 32.44, 31.05, 20.79, 19.39, 13.92. The *ee* value was determined by HPLC analysis using a CHIRALPAK IC column, hexane/2-propanol 98:2, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 26.5 min (major enantiomer), 31.3 min (minor enantiomer); t_R (minor diastereomer) = 32.8 min (major enantiomer), 28.5 min (minor enantiomer); ESI-HRMS calcd for $C_{13}H_{21}NNaO_5^+$ $[M+Na]^+$: 294.1312, found 294.1312.

(*R*)-ethyl 1-((*S*)-1-nitrononan-2-yl)-2-oxocyclopentane carboxylate (5au): Colourless oil; 122.1 mg, 93% yield, >99:1 dr, 98% *ee*; $[\alpha]^{26}_D$ = –40.7 (*c* 0.69, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.87 (dd, *J* = 14.0, 4.9 Hz, 1H), 4.36 (dd, *J* = 14.0, 5.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.84-2.78 (m, 1H), 2.60-2.54 (m, 1H), 2.46-2.39 (m, 1H), 2.33-2.25 (m, 1H), 2.04-1.97 (m, 2H), 1.97-1.90 (m, 1H), 1.36-1.22 (m, 15H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 213.28, 169.33, 76.44, 62.88, 61.90, 40.66, 38.19, 31.65, 31.04, 30.27, 29.43, 28.96, 27.61, 22.54, 19.40, 14.01, 13.92. The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 98:2, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer) = 9.1 min (major enantiomer), 7.2 min (minor enantiomer); t_R (minor diastereomer) = 8.0 min (major enantiomer), 7.6 min (minor enantiomer); ESI-HRMS calcd for $C_{17}H_{29}NNaO_5^+$ $[M+Na]^+$: 350.1938, found 350.1937.

(R)-3-acetyl-3-((S)-2-nitro-1-phenylethyl)-dihydrofuran-2(3H)-one (5ba): White solid; 54.9 mg, 99% yield, 7:1 dr, 94% *ee*; $[\alpha]^{19}_D$ = +17.0 (*c* 0.59, CH_2Cl_2) [Ref.[10n]: $[\alpha]^{r.t.}_D$ = –4 (*c* 0.41, CH_2Cl_2) in 67:33 dr and 73% *ee*]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.27 (m, 3H), 7.23–7.18 (m, 2H), 5.00 (dd, *J* = 13.4, 11.3 Hz, 1H), 4.67 (dd, *J* = 13.4, 3.6 Hz, 1H), 4.28 (dd, *J* = 11.2, 3.4 Hz, 1H), 4.05–3.99 (m, 1H), 3.31–3.24 (m, 1H), 2.53–2.46 (m, 6.5 Hz, 1H), 2.28 (s, 3H), 2.23–2.15 (m, 1H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/EtOH 80:20, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer, 94% *ee*) = 16.5 min (major enantiomer), 10.9 min (minor enantiomer); t_R (minor diastereomer) = 37.5 min (major enantiomer), 14.4 min (minor enantiomer).

(*R*)-ethyl 1-((*S*)-2-nitro-1-phenylethyl)-2-oxocyclohexane carboxylate (5ca): Colourless oil; 55.9 mg, 87% yield, >30:1 dr, 98% *ee*; $[\alpha]^{23}_D$ = +59.6 (*c* 0.88, $CHCl_3$) [Ref.[10r]: $[\alpha]^{25}_D$ = –91.5 (*c* 1.02, $CHCl_3$) in 98:2 dr and 99% *ee*]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.15 (m, 3H), 7.09–7.06 (m, 2H), 5.00 (dd, *J* = 13.5, 3.2 Hz, 1H), 4.72 (dd, *J* = 13.3, 11.4 Hz, 1H), 4.19–4.09 (m, 2H), 3.93 (dd, *J* = 11.3, 3.0 Hz, 1H), 2.47–2.34 (m, 2H), 2.04–1.92 (m, 2H), 1.67–1.53 (m, 3H), 1.43–1.35 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK IC column, hexane/2-propanol 90:10, flow rate = 1 mL/min, 210 nm. t_R (major diastereomer, 98% *ee*) = 17.9 min (major enantiomer), 14.8 min (minor enantiomer); t_R (minor diastereomer) = 27.0 min (major enantiomer), 13.9 min (minor enantiomer).

(2*R*,3*S*)-ethyl 2-acetyl-2-methyl-4-nitro-3-phenylbutanoate (5da): Colourless oil ; 56.7 mg, 97% yield, >99:1 dr, 98% *ee*; $[\alpha]^{23}_D$ = +52.46 (*c* 0.75, $CHCl_3$) [Ref.[10r]: $[\alpha]^{25}_D$ = –69.9 (*c* 0.93, $CHCl_3$) in 91:9 dr and 99% *ee*]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3H), 7.12–7.10 (m, 2H), 4.99–4.86 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 10.9, 3.3 Hz, 1H), 2.17 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.23 (s, 3H). The *ee* value was determined by HPLC analysis using a Chiralcel ODH column, hexane/2-propanol 90:10, flow rate = 0.9 mL/min, 210 nm. t_R (major diastereomer, 98% *ee*) = 27.2 min (major enantiomer), 10.9 min (minor enantiomer); t_R (minor diastereomer) = 17.8 min (major enantiomer), 12.0 min (minor enantiomer).

(3*R*)-ethyl 2-acetyl-4-nitro-3-phenylbutanoate (5ea): White wax; 110.2 mg, 99% yield (~1:1 mixture of diastereomers), 99% and 99% *ee*; $[\alpha]^{19}_D$ = –56.22 (*c* 0.96, $CHCl_3$) [Ref.[10s]: $[\alpha]^{24}_D$ = +50.5 (*c* 1.00, $CHCl_3$) in ~1:1 dr and 93% *ee*]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.16 (m, 5H), 4.87–4.71 (m, 2H), 4.25–4.14 (m, 2H), 4.09 (d, *J* = 10.0 Hz, 0.5H), 4.01 (d, *J* = 9.7 Hz, 0.5H), 3.94 (q, *J* = 7.1 Hz, 1H), 2.27–2.01 (s, 3H), 1.27–0.94 (t, *J* = 7.1 Hz, 3H). The *ee* value was determined by HPLC analysis using a CHIRALPAK ADH column, hexane/2-propanol 90:10, flow rate = 0.8 mL/min, 210 nm. t_R (first diastereomer, 99% *ee*) = 15.2 min (major enantiomer), 10.9 min (minor enantiomer); t_R (second diastereomer, >99% *ee*) = 16.5 min (major enantiomer), 29.9 min (minor enantiomer).

Conflicts of Interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the generous financial support by the National Nature Science Foundation of China (21672031), Fundamental and Advanced Research Projects of Chongqing City (cstc2016jcyjA0250 and cstc2017jcyjAX0352), Scientific and Technological Research Program of Chongqing Municipal Education Commission (KJ1702014).

Notes and references

1 For reviews of chiral bimetallic catalysts, see: (*a*) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed.*, 1997, **36**, 1236-1256; (*b*) M. Shibasaki, N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187-2210; (*c*) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.*, 2002, **344**, 3-15; (*d*) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.*, 2006, **35**, 269-279; (*e*) M. Shibasaki, S. Matsunaga, *J. Organomet. Chem.*, 2006, **691**, 2089-2100; (*f*) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.*, 2009, **42**, 1117-1127; (*g*) J. Park, S. Hong, *Chem. Soc. Rev.*, 2012, **41**, 6931-6943; (*h*) S. Matsunaga, M. Shibasaki, *Synthesis*, 2013, **45**, 421-437; (*i*) S. Matsunaga, M. Shibasaki, *Chem. Commun.*, 2014, **50**, 1044-

View Article Online
DOI: 10.1039/C8OB00773J

1057; (*j*) B. M. Trost, M. J. Bartlett, *Acc. Chem. Res.*, 2015, **48**, 688-701; (*k*) M. M. Lorion, K. Maindan, A, R. Kapda, L. Ackermann, *Chem. Soc. Rev.*, 2017, **46**, 7399-7420; (*l*) J. Fu, X. Huo, B. Li, W. Zhang, *Org. Biomol. Chem.*, 2017, **15**, 9747-9759; (*m*) D. R. Pye, N. P. Mankad, *Chem. Sci.*, 2017, **8**, 1705-1718.

2 For selected examples in conjugate additions using BINOL based ligands, see: (*a*) T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 104-106; (*b*) N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 16178-16179; (*c*) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 12419-12427; (*d*) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13419-13427; (*e*) K. Endo, M. Ogawa, T. Shibata, *Angew. Chem. Int. Ed.*, 2010, **49**, 2410-2413.

3 For selected examples in conjugate additions using linked BINOL based ligands, see: (*a*) N. Kumagai, S. Matsunaga, M. Shibasaki, *Org. Lett.*, 2001, **3**, 4251-4254; (*b*) K. Majima, R. Takita, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 15837-15845; (*c*) S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2582-2590.

4 For selected examples in conjugate additions using GluCAPO/FujiCAPO based ligands, see: (*a*) T. Mita, K. Sasaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 514-515; (*b*) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 6072-6073.

5 For selected examples in conjugate additions using Schiff base based ligands, see: (*a*) E. F. DiMauro, M. C. Kozlowski, *Org. Lett.*, 2001, **3**, 1641-1644; (*b*) C. Mazet, E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2008, **47**, 1762-1765; (*c*) Z. Chen, M. Furutachi, Y. Kato, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.*, 2009, **48**, 2218-2220; (*d*) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 9168-9169; (*e*) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666-3667; (*f*) M. Furutachi, Z. Chen, S. Matsunaga, M. Shibasaki, *Molecules*, 2010, **15**, 532-544; (*g*) H. Mitsunuma, S. Matsunaga, *Chem. Commun.*, 2011, **47**, 469-471.

6 For selected examples in conjugate additions using bis-ProPhenol based ligands, see: (*a*) B. M. Trost, S. Hisaindee, *Org. Lett.*, 2006, **8**, 6003-6005; (*b*) B. M. Trost, C. Müller, *J. Am. Chem. Soc.*, 2008, **130**, 2438-2439; (*c*) B. M. Trost, J. Hitce, *J. Am. Chem. Soc.*, 2009, **131**, 4572-4573; (*d*) D. Zhao, Y. Wang, L. Mao, R. Wang, *Chem. Eur. J.*, 2009, **15**, 10983-10987; (*e*) D. Zhao, Y. Yuan, A. S. C. Chan, R. Wang, *Chem. Eur. J.*, 2009, **15**, 2738-2741; (*f*) D. Zhao, L. Mao, Y. Wang, D. Yang, Q. Zhang, R. Wang, *Org. Lett.*, 2010, **12**, 1880-1882; (*g*) D. Zhao, L. Mao, D. Yang, R. Wang, *J. Org. Chem.*, 2010, **75**, 6756-6763; (*h*) D. Zhao, L. Mao, L. Wang, D. Yang, R. Wang, *Chem. Commun.*, 2012, **48**, 889-891; (*i*) B. M. Trost, K. Hirano, *Angew. Chem. Int. Ed.*, 2012, **51**, 6480-6483; (*j*) B. Zhang, F. Han, L. Wang, D. Li, D. Yang, X. Yang, J. Yang, X. Li, D. Zhao, R. Wang, *Chem. Eur. J.*, 2015, **21**, 17234-17238.

7 For selected examples in conjugate additions using AzePhenol based ligands, see: (*a*) Y. Hua, X. Han, X. Yang, X. Song, M. Wang, J. Chang, *J. Org. Chem.*, 2014, **79**, 11690-11699; (*b*) Y. Hua, M. Liu, P. Huang, X. Song, M. Wang, J. Chang, *Chem. Eur. J.*, 2015, **21**, 11994-11998; (*c*) S. Liu, N. Shao, F. Li, X. Yang, M. Wang, *Org. Biomol. Chem.*, 2017, **15**, 9465-9474; (*d*) Y. Gao, Y. Hua, M. Wang, *Adv. Synth. Catal.*, 2018, **360**, 80-85.

8 (*a*) Y. Li, P. Deng, Y. Zeng, Y. Xiong, H. Zhou, *Org. Lett.*, 2016, **18**, 1578-1581; (*b*) S. Zhang, P. Deng, J. Zhou, M. Liu, G. Liang, Y. Xiong, H. Zhou, *Chem. Commun.*, 2017, **53**, 12914-12917.

9 For recent reviews, see: (*a*) C. Hawner, A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295-7306; (*b*) X. Liu, L. Lin, X. Feng, *Acc. Chem. Res.*, 2011, **44**, 574-587; (*c*) H. Pellissier, *Adv. Synth. Catal.*, 2015, **357**, 2745-2780; (*d*) T. Govender, P. I. Arvidsson, G. E. M. Maguire, H. G. Kruger, *Chem. Rev.*, 2016, **116**, 9375-9437; (*e*) D. A. Alonso, A. Baeza, R. Chinchilla, C. Cómez, G. Guillena, I. M. Pastor, D. Ramón, *Molecules*, 2017, **22**, 895; (*f*) M. Hayashi, R. Matsubara, *Tetrahedron Lett.*, 2017, **58**, 1793-1805; (*g*) A. Mondal, S. Bhowmick, A. Ghosh, T. Chanda, K. C. Bhowmick, *Tetrahedron: Asymmetry,* 2017, **28**, 849-875; (*h*) C. Hui, F. Pu, J. Xu, *Chem. Eur. J.*, 2017, **23**, 4023-4036.

10 For recent examples of the addition of 1,3-diketones to nitroolefins, see: (*a*) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416-14417; (*b*) Z. Yu, X. Liu, L. Zhou, L. Lin, X. Feng, *Angew. Chem. Int. Ed.*, 2009, **48**, 5195-5198; (*c*) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.*, 2009, **74**, 5562-5567; (*d*) J. Luo, L. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.*, 2009, **11**, 427-440; (*e*) R. Manzano, J. M. Andrés, M. D. Muruzábal, R. Pedrosa, *Adv. Synth. Catal.*, 2010, **352**, 3364-3372; (*f*) C. Min, X. Han, Z. Liao, X. Wu, H. Zhou, C. Dong, *Adv. Synth. Catal.*, 2011, **353**, 2715-2720; (*g*) H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee, C. E. Song, *Chem. Commun.*, 2011, **47**, 9621-9623; (*h*) D. B. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem.*, 2012, **10**, 5825-5829; (*i*) A. Lattanzi, C. D. Fusco, A. Russo, A. Poater, L. Cavallo, *Chem. Commun.*, 2012, **48**, 1650-1652; (*j*) X. Li, X. Li, F. Peng, Z. Shao, *Adv. Synth. Catal.*, 2012, **354**, 2873-2885; (*k*) P. Chauhan, W. S. Chimni, *Asian J. Org. Chem.*, 2012, **1**, 138-141; (*l*) K. S. Rao, R. Trivedi, M. L. Kantam, *Synlett*, 2015, **26**, 221-227; (*m*) E. I. Jiménez, W. E. V. Narváez, C. A. Román-Chavarría, J. Vazquez-Chavez, T. Rocha-Rinza, M. Hernández-Rodríguez, *J. Org. Chem.*, 2016, **81**, 7419-7431; (*n*) S. Ričko, J. Svete, B. Štefane, A. Perdih, A. Golobič, A. Meden, U. Grošelj, *Adv. Synth. Catal.*, 2016, **358**, 3786-3796; (*o*) M. S. Ullah, S. Itsuno, *Molecular Catalysis*, 2017, **438**, 239-244; (*p*) J. M. Andrés, M. González, A. Maestro, D. Naharro, R. Pedrosa, *Eur. J. Org. Chem.*, 2017, **2017**, 2683-2691; (*q*) J. M. Andrés, J. Losada, A. Maestro, P. Rodriguez-Ferrer, R. Pedrosa, *J. Org. Chem.*, 2017, **82**, 8444-8454; (*r*) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.*, 2005, **44**, 105-108; (*s*) D. A. Evans, S. Mito, D. Seidel, *J. Am. Chem. Soc.*, 2007, **129**, 11583-11592.

11 (*a*) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* 1998, **37**, 2922-2959; (*b*) H. B. Kagan, *Adv. Synth. Catal.* 2001, **343**, 227-233; (*c*) T. Satyanarayana, S. Abaham, H. B. Kagan, *Angew. Chem. Int. Ed.* 2009, **48**, 456-494.

12 For more detailed results of ESI-MS analysis, see the ESI.

13 The detailed geometry of Co_2/**2a** optimized by DFT (density functional theory) is shown in ESI.

14 For the related mechanism of 1,4-addition of β-ketoesters to nitroalkenes catalyzed by dinuclear Ni-schiff base and dunuclear Co-schiff base, see ref. 5f and 5g.

View Article Online
DOI: 10.1039/C8OB00773J

A Homodinuclear Cobalt Complex for Catalytic Asymmetric Michael Reaction of β-Ketoesters to Nitroolefins

Guanghui Chen, Guojuan Liang, Yiwu Wang, Ping Deng, and Hui Zhou*