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Rhodium-catalyzed asymmetric hydrogenation of β-cyanocinnamic esters with the assistance of a single hydrogen bond in a precise position

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With the assistance of hydrogen bonds, the first asymmetric hydrogenation of β-cyanocinnamic esters has been developed, affording chiral β-cyano esters with excellent enantioselectivities (up to 99% *ee*). This novel methodology provides an efficient and concise synthetic route to chiral GABA-derivatives, such as (*S*)-Pregabalin, (*R*)-Phenibut, (*R*)-Baclofen. Interestingly, in this system, the catalyst with single H-bond donor performed better than that with double H-bond donors, which is a novel discovery in the metalorganocatalysis area.

Hydrogen bonding, an important noncovalent interaction, plays a crucial role in biosystem and enzyme catalysis. Inspired by the enzyme catalysis, the strategy of hydrogen bonding has been elaborated and successfully applied in numerous cases of organocatalysis in the past two decades, which provide the synthetic community with many solutions for organic synthesis.[1] Among these successful catalysts, thiourea is a special motif for hydrogen bonding. As a double hydrogen donor, thiourea could activate carbonyl compounds by lowering their LUMO energy.[2] Effective bonding with neutral functional groups, potent binding affinity, and high tunability make thiourea catalysts versatile for many kinds of organic reactions.[3] Herein, with our ferrocene-thiourea chiral bisphosphine ligands (ZhaoPhos series) which are cooperation of transition metal catalysis and organocatalysis, we focused on whether both two hydrogen bonds of the thiourea group are essential in the transformation. When the asymmetric hydrogenation of β-cyanocinnamic esters, very challenging substrates in this area, were carried out, the catalyst (**L1**) with only one H-bond donor in a precise position performed better than ZhaoPhos (possesses two H-bond donors) on both reactivity and enantioselectivity. This novel discovery provides a new insight for the catalyst design in both organocatalysis and metalorganocatalysis area.

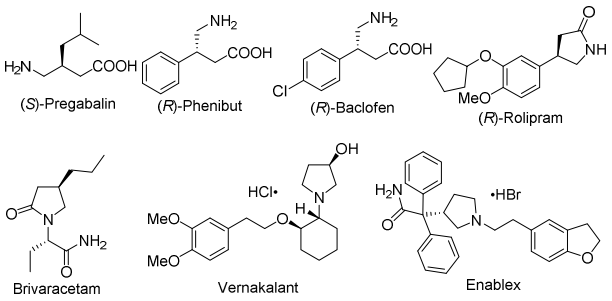

Figure 1. Chiral GABA derivatives in pharmaceuticals.

Chiral γ-aminobutyric acids (GABA) are an essential class of compounds in neuroscience,[4] and many of them are drugs or have potential biological activities in the area of neurotransmitters and brain science,[5] such as Pregabalin,[6] Phenibut,[7] Baclofen[8] (Figure 1). In addition, many chiral GABA derivatives are common motifs in many drugs, such as Rolipram,[9] Brivaracetam,[10] Vernakalant[11] and Enablex[12] (Figure 1). Thus, the synthesis of chiral GABA and their derivatives has attracted a great deal of interest, but very limited approaches have been developed. These synthetic methods include the following: enzymatic kinetic resolution,[13] biocatalytic asymmetric reduction,[14] asymmetric conjugate reduction with polymethylhydrosiloxane (PMHS)[15] and asymmetric Michael addition.[16] However, asymmetric hydrogenation of β-cyanocinnamic esters, the most straightforward access to synthesize chiral GABA derivatives, has never been reported.

Over the past decades, transition metal catalyzed asymmetric hydrogenation of functionalized olefins has emerged as a powerful and environmentally friendly approach to generate chiral compounds.[17] With the rapid development of catalytic systems, many types of olefins bearing functional groups such as carbonyl,[18] sulfonyl,[19] cyano group[20] and nitryl,[21] were hydrogenated in high ee's and activities. However, asymmetric hydrogenation of β-cyanocinnamic esters has not been reported, which can be explained by two reasons: (1) The electron-withdrawing ester group and nitrile

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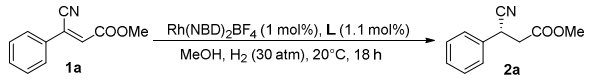
group that can sharply reduce the electron density of C=C bond are very unbeneficial for the C=C bond's coordination to the metal center, which leads to the low reactivity of these substrates; (2) The linearity of the nitrile group, which is not suitable for the assistant coordination between the C=C bond and metal catalyst, makes it very difficult to achieve high enantioselectivities.[20a,b] As a result of these factors, it is a very difficult task to achieve satisfactory results of the β- cyanocinnamic esters asymmetric hydrogenation with the classical bidentate diphosphine/Rh system as summarized in Table 1. Methyl

Table 1. Ligand screening for the Rh-catalyzed asymmetric hydrogenation of **1a**[a]



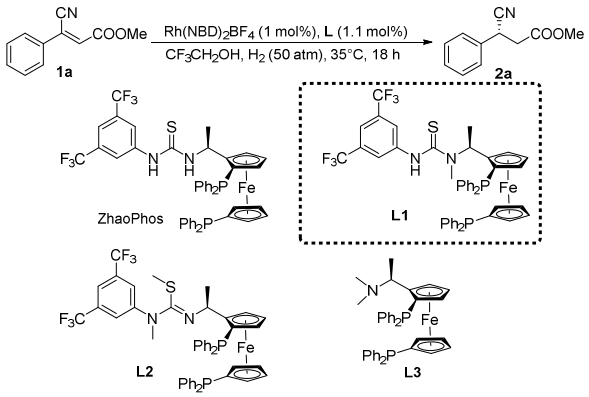
Entry	Ligand	Conv. [%][b]	ee [%][c]
1	(*Rc*,*Sp*)-DuanPhos	19	*rac*
2	(*S*)-Binapine	trace	-
3	(*S*,*S*)-Me-DuPhos	trace	-
4	(*R*,*R*)-QuinoxP*	23	*rac*
5	(*S*)-BINAP	trace	-
6	(*S*)-SegPhos	trace	-
7	(*S*)-DTBM-SegPhos	trace	-
8	(*R*,*S*)-tBu-JosiPhos	25	*rac*
9	(*R*)-TaniaPhos	35	-7
10	(*R*)-WalPhos	trace	-
11	ZhaoPhos	28	84

[a]All reactions were carried out with a $[Rh(NBD)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in 1 mL of methanol, at 20 °C, under hydrogen (30 atm) for 18 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of the product **2a**, methyl (*R*)-3-cyano-3-phenylpropanoate, with that reported in the literature; see Ref 14c.

(*Z*)-3-cyano-3-phenylacrylate as a model substrate, a series of bidentate diphosphine ligands including P-chiral diphosphine ligands (entries 1-4), ligands having axial chirality (entries 5-7) and ferrocenyl chiral bisphosphorus ligands (entries 8-10) were tested, giving low to even trace conversions and almost racemic products, which disclosed that the classical catalyst systems cannot complete this task. Recently, substrate orientation by hydrogen bonds as a strategy in asymmetric hydrogenation has been studied and some progress have been made.[22] Therefore, ~~from another perspective,~~ we tried to utilize the ester group whose carbonyl is a very good H-bond acceptor to improve the reactivity of the electron-deficient substrate by employing the ZhaoPhos bearing H-bond donors. Although the preliminary result was moderate (entry 11, 28% conversion with 84% ee), it inspired us to a further exploration.

In order to obtain optimal reaction conditions, a serious of solvents were screened (summarized in SI). When the reaction was carried out with 50 atm H_2 gas at 35 °C in CF_3CH_2OH, full conversion was attained with 95% ee.

Table 2. Evaluation of a series of bisphosphine-thiourea Ligands[a]



Entry	Ligand	Conv. [%][b]	ee [%][c]
1	ZhaoPhos	99	95
2	***L1***	***99***	***98***
3	**L2**	trace	-
4	**L3**	5	7

[a]All reactions were carried out with a $[Rh(NBD)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in 1 mL of trifluoroethanol, at 35 °C, under hydrogen (50 atm) for 18 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase.

To obtain insight into this catalytic system, another three chiral ligands **L1**-**L3** were employed and the results were summarized in table 2. To our surprise, the *N* methylation of ZhaoPhos led to a increase of the enantioselectivity (entry 2, 98% ee), which is quite different from the previous results we reported.[18f, 23] In comparison, when both N-H were replaced, almost no conversion was detected (entry 3), which indicated the importance of hydrogen bonds in this reaction. In addition, the ligand **L3** without thiourea group showed very low activity and enantioselectivity (entry 4). These results displayed that the thiourea motif efficiently activated the carbonyl group through hydrogen-bonding interaction and worked as an excellent directing role. Moreover, **L1** is superior to ZhaoPhos, which indicates that one hydrogen bond in a precise position is better than two in this asymmetric transformation.

With an optimized set of conditions in hand, we explored the substrate scope and generality of this catalytic reaction. To confirm the universality of the phenomenon that **L1** is superior to ZhaoPhos, almost each substrate has been compared (Scheme 1). We thought that enhancement of the steric hindrance of the ester would influence this transformation, however, the results indicated that these changes of the substrate have a slight impact on the reaction (**2a**-**2c**). Many functional groups, such as methyl (**2d**), methoxy (**2e**), phenyl (**2f**), trifluoromethyl (**2g**), and halides (**2h**, **2i** and **2j**), at the

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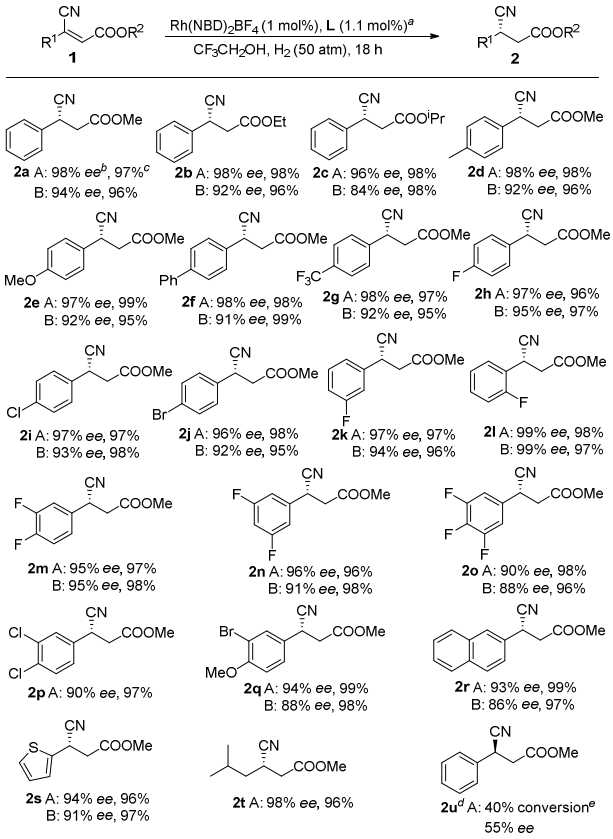
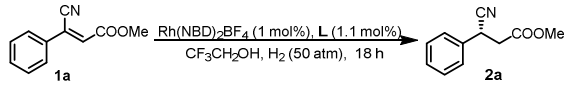
para position of the phenyl group are compatible with this transformation. Using **L1**, substrates with *meta*- or *ortho*-substitution on the phenyl group are also tolerated and 97% ee and 99% ee values were obtained (**2k** and **2l**). Constantly, polyfluorinated compounds exist in drug molecules,[24] so a series of polyfluorinated substrates were examined. Substrates with 3,4-difluoro and 3,5-difluoro on the phenyl group were tested, and good yields with excellent enantioselectivities were achieved (**2m** and **2n**). In comparison, when the 3,4,5-trifluoro compound **1o** was employed, the adduct **2o** was produced slightly



Scheme 1. Substrate scope. Condition A: **L** = **L1**, 20 °C. Condition B: **L** = ZhaoPhos, 35 °C. [a]All reactions were carried out with a $[Rh(NBD)_2]BF_4$/L/substrate ratio of 1:1.1:100, in 1 mL of trifluoroethanol, under hydrogen (50 atm) for 18 h. [b]Determined by HPLC analysis using a chiral stationary phase. [c]Isolated yield.[d](*E*)-**1a** was used. [e]Determined by ^{1}H NMR spectroscopy.

compromised ee values, which may be due to the electron-poor property of **1o** as discussed above. Other disubstituted substrates could also be accommodated, as exemplified by **2p** and **2q**. Moreover, good yields and excellent enantioselectivities were obtained with substrates containing other aromatic fragments, including naphthalenes and thiophenes (**2r** and **2s**). To our delight, when the aryl substituent was changed to an alkyl group, such as isobutyl, the product **2t** which can be readily converted to (*S*)-Pregabalin was produced with 98% ee. All the results reflect a fact that **L1** bearing a single H-bond donor is more suitable than ZhaoPhos to this reaction. Moreover, when (*E*)-**1a** was employed, much lower reactivity and enantioselectivity were obtained, but the configuration of **2u** can support our viewpoint that the enantioselectivity is inducted by the ester group of the substrates.

Table 3. The comparison of ZhaoPhos and **L1**[a]



Ligand		T(°C) 0	20	35	60
ZhaoPhos	ΔG_{HB} (kcal/mol)	-13.4	-12.2	-11.4	-10.0
	ee	97[b](20[c])	95(94)	95(99)	92(99)
L1	ΔG_{HB} (kcal/mol)	-16.4	-15.3	-14.5	-13.2
	ee	99(60)	98(99)	98(99)	93(99)

[a]All reactions were carried out with a $[Rh(NBD)_2]BF_4$/L/substrate ratio of 1:1.1:100, in 1 mL of trifluoroethanol, under hydrogen (50 atm) for 18 h. [b]Ee values were determined by HPLC analysis using a chiral stationary phase. [c]Conversions were determined by ^{1}H NMR spectroscopy.

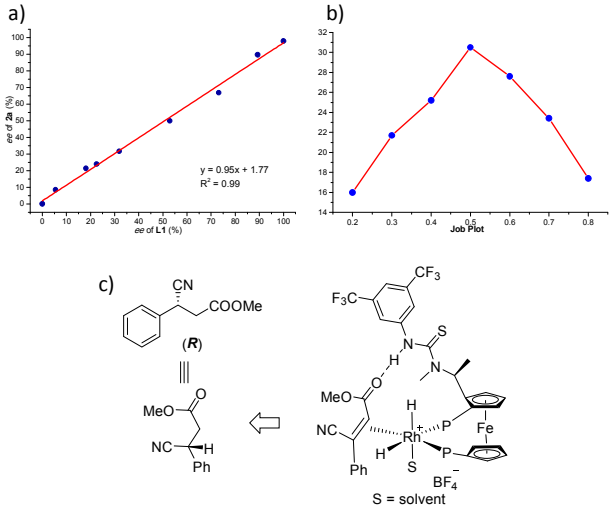


Figure 2. a) Hydrogenation of **1a** using **L1** of varying ee, the line corresponds to a least-squares linear regression of the data with slope = 0.95, intercept = 1.77, and r^2 = 0.99; b) Job plot, x = c(**L1**)/[c(**L1**)+c(**1a**)], y = $\Delta\delta*10^4$*c(**L1**)/[c(**L1**)+c(**1a**)]; c) Proposed hydrogen bonding between the reactive Rh species and **1a**.

To gain a better understanding of the performance of ZhaoPhos and **L1**, free energies (kcal/mol) for hydrogen bonds between different substrates with the ligand (ΔG_{HB}) were evaluated by B3LYP-GD3BJ /6-31G** method,[25] as summarized in table 3. To our supprise, the free energy for the hydrogen bond between **1a** and ZhaoPhos is smaller than that between **1a** and **L1**, even at different temperature, which can explain the experimental results very well. These results indicate that one H-bond can perfom better than two ones in this reaction, thus we proposed that the stronger hydrogen

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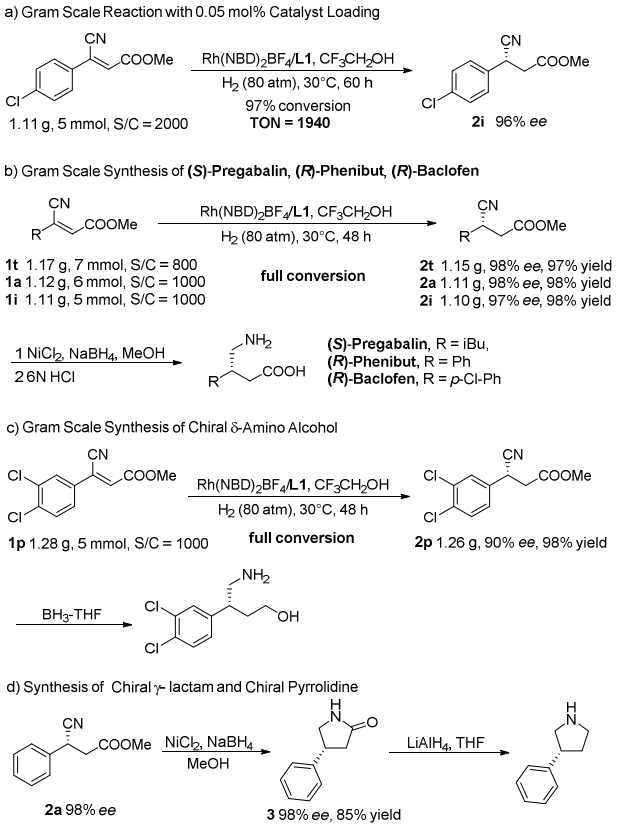
bond is important in making L1 a more selective catalyst. Both **L1** system and ZhaoPhos system are sensitive to the reaction temperature due to their weaker hydrogen-bonding interaction with substrates at higher temperature.

To verify the accuracy of the catalytic model we assumed, the reduction of **1a** was performed using **L1** of varying ee. As shown in figure 2a, a linear correlation between the ee of the ligand and that of the product was observed, indicating that a 1:1 ratio of ligand to metal is present in the catalytic complex.[26] Moreover, Job plot was drawn and the curve suggested a 1:1 binding pattern between **L1** and **1a** (figure 2b), and a 1:1 binding pattern between ZhaoPhos and **1a** was also suggested (summarized in SI). These experimental data validate our hypothesis, and the catalytic model was sketched out as shown in figure 2c.



Scheme 2. Synthetic transformations.

In order to further demonstrate the synthetic utility of this methodology, several gram-scale transformations were achieved, as summarized in Scheme 2. Firstly, upon decreasing the catalyst loading to 0.05 mol%, the asymmetric reaction was conducted on a gram scale, and 97% conversion (TON = 1940) with unchanged enantioselectivity was obtained (Scheme 2a). Then, a high-efficiency synthetic route for (*S*)-Pregabalin,[13b] (*R*)-Phenibut and (*R*)-Baclofen[14a] was developed. As shown in Scheme 2b, upon 0.1-0.125 mol% catalyst loading, three key intermediates were obtained on a gram scale with high yields (97-98% yield) and excellent ee values (97-98% ee). So far, this may be the most concise way to synthesize chiral Pregabalin, Phenibut and Baclofen. Next, a gram-scale **2p**, which can be readily converted to a chiral δ-amino alcohol whose enantiomer can be used in the synthesis of NK1 antagonists directly,[27] was produced (Scheme 2c). Scheme 2d exhibited an efficient approach to the establishment of chiral pyrrolidines. The asymmetric hydrogenation product **2a** was reduced by $NiCl_2/NaBH_4$ in MeOH and afforded the corresponding lactam **3** in high yield without any loss in the enantioselectivity. By treating the lactam with lithium aluminium hydride (LAH) in THF, the chiral pyrrolidine can be readily obtained.[28]

Conclusions

In conclusion, the first asymmetric hydrogenation of β-cyanocinnamic esters has been reported, which provides an efficient approach for synthesizing chiral GABA derivatives. This transformation exhibits excellent enantioselectivities (up to 99% *ee*) under mild reaction conditions with low catalyst loading. This method provides a concise route to the synthesis of (*S*)-Pregabalin, (*R*)-Phenibut, (*R*)-Baclofen, chiral δ-amino alcohols, chiral γ-lactam and chiral pyrrolidines, demonstrating the high synthetic utility of the current methodology. Notably, in our ferrocene-thiourea chiral bisphosphine ligands (ZhaoPhos series) system, the catalyst with a single H-bond donor in a precise position performed better than that with double H-bond donors, which is a novel discovery in the metalorganocatalysis area. This novel discovery provides a new way to design catalysts. Further investigations on the detailed mechanistic studies on the proposed key hydrogen bonds and the applications of the asymmetric hydrogenation strategy in organic synthesis are in progress in our lab.

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Notes and references

1 (a) P. M. Pihko, *Hydrogen Bonding in Organic Synthesis*; Wiley, 2009; (b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.,* 2006, **45**, 1520; (d) P. Dydio, J. N. H. Reek, *Chem. Sci.*, 2014, **5**, 2135; (e) H. J. Davis, R. J. Phipps, *Chem. Sci.*, 2017, **8**, 864.

2 Recent studies on thiourea in electrophile activation: (a) P. R. Schreiner, A. Wittkopp, *Org. Lett.,* 2002, **4**, 217; (b) P. M. Pihko, *Angew. Chem., Int. Ed.,* 2004, **43**, 2062; (c) P. N. H. Huynh, R. R. Walvoord, M. C. Kozlowski, *J. Am. Chem. Soc.,* 2012, **134**, 15621; (d) R. R. Walvoord, P. N. H. Huynh, M. C. Kozlowski, *J. Am. Chem. Soc.*, 2014, **136**, 16055.

3 Reviews for recent advances on thiourea small-molecule catalysis: (a) S. J. Connon, *Chem. -Eur. J.,* 2006, 12, 5418; (b) S. J. Connon, *Chem. Commun.,* 2008, 2499; (c) X. Fang, C. J. Wang, *Chem. Commun.,* 2015, **51**, 1185.

View Article Online
DOI: 10.1039/C7SC04639A

4 R. L. Macdonald, R. W. Olsen, *Annu. Rev. Neurosci.,* 1994, **17**, 569.
5 A. G. Malykh, M. R. Sadaie, *Drugs,* 2010, **70**, 287.
6 R. B. Silverman, *Angew. Chem. Int. Ed.,* 2008, **47**, 3500.
7 I. Lapin, *CNS Drug Rev.,* 2001, **7**, 471.
8 B. A. Sachais, J. N. Logue, M. S. Carey, *Arch. Neurol.,* 1977, **34**, 422.
9 J. Zhu, E. Mix, B. Winblad, *CNS Drug Rev.,* 2001, **7**, 387.
10 B. M. Kenda, A.C. Matagne, P. E. Talaga, P. M. Pasau, E. Differding, B. I. Lallemand, A. M. Frycia, F. G. Moureau, H. V. Klitgaard, M. R. Gillard, B. Fuks, P. Michel, *J. Med. Chem.,* 2004, **47**, 530.
11 D. R. Boyd, N. D. Sharma, H. Dalton, D. A. Clarke, *Chem. Commun.,* 1996, 45.
12 P. E. Cross, A. R. MacKenzie, U.S. Patent 005096890A, 1992.
13 (a) H. Mukherjee, C. A. Martinez, *ACS Catal.,* 2011, **1**, 1010; (b) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher, L.Tully, *Org. Process Res. Dev.,* 2008, **12**, 392.
14 (a) A. Fryszkowska, K. Fisher, J. M. Gardiner, G. M. Stephens, *Org. Biomol. Chem.*, 2010, **8**, 533; (b) C. K. Winkler, D. Clay, S. Davies, P. O'Neill, P. McDaid, S. Debarge, J. Steflik, M. Karmilowicz, J. W. Wong, K. Faber, *J. Org. Chem.,* 2013, **78**, 1525; (c) E. Brenna, M. Crotti, F. G. Gatti, D. Monti, F. Parmeggiani, R. W. Powell III, S. Santangelo, J. D. Stewartc, *Adv. Synth. Catal.,* 2015, **357**, 1849.
15 Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.,* 2010, **132**, 10070.
16 (a) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.,* 2008, **47**, 4719; (b) A. Leyva-Pérez, P. García-García, A. Corma, *Angew. Chem. Int. Ed.,* 2014, **53**, 8687; (c) T. Tsubogo, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.,* 2009, **48**, 9117; (d) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature,* 2015, **520**, 329; (e) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.,* 2005, **44**, 6367; (f) K. Akagawa, K. Kudo, *Angew. Chem. Int. Ed.,* 2012, **51**, 12786; (g) J.H. Sim, C. E. Song, *Angew. Chem. Int. Ed.,* 2017, **56**, 1835; (h) O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky, S.G. Zlotin, *Eur. J. Org. Chem.,* 2010, 2927; (i) K. G. Lewis, S. K. Ghosh, N. Bhuvanesh, J. A. Gladysz, *ACS Cent. Sci.,* 2015, **1**, 50; (j) D. A. Evans, S. Mito, D.Seidel, *J. Am. Chem. Soc.,* 2007, **129**, 11583.
17 For reviews, see: (a) W. Tang, X. Zhang, *Chem. Rev.,* 2003, **103**, 3029; (b) J. H. Xie, S. F. Zhu, Q. L. Zhou, *Chem. Rev.,* 2011, **111**, 1713; (c) J. H. Xie, Q. L. Zhou, *Acta Chim. Sin.* 2012, **70**, 1427; (d) S. F. Shou, Q. L. Zhou, *Acc. Chem. Res.* 2017, **50**, 988; (e) Z. Zhang, N. A. Butt, W. Zhang, *Chem. Rev.,* 2016, **116**, 14769; (f) D. -S. Wang, Q. -A. Chen, S. -M. Lu, Y.-G. Zhou, *Chem. Rev.,* 2012, **112**, 2557; (g) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.,* 2007, **40**, 1402; (h) G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *Coord. Chem. Rev.,* 2008, **252**, 471; (i) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.,* 2008, **252**, 513; (j) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.,* 2014, **114**, 2130.
18 (a) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P. G. Andersson, *J. Am. Chem. Soc.,* 2008, **130**, 7208; (b) J. Mazuela, P. -O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc,* 2011, **133**, 13634; (c) M. Shevlin, M. R. Friedfeld, H. Sheng, N. A. Pierson, J. M. Hoyt, L. -C. Campeau, P. J. Chirik, *J. Am. Chem. Soc.,* 2016, **138**, 3562; (d) W. Tang, W. Wang, X. Zhang, *Angew. Chem. Int. Ed.,* 2003, **42**, 943; (e) D. Rageot, D. H. Woodmansee, B. Pugin, and A. Pfaltz, *Angew. Chem. Int. Ed.,* 2011, **50**, 9598; (f) Z. Han, P. Li, Z. Zhang, C. Chen, Q. Wang, X. -Q. Dong, X. Zhang, *ACS Catal.,* 2016, **6**, 6214; (g) P. Li, X. Hu, X. -Q. Dong, X. Zhang, *Chem. Commun.,* 2016, **52**, 11677; (h) J. Wen, J. Jiang, X. Zhang, *Org. Lett.,* 2016, **18**, 4451; (i) Y. Liu, W. Zhang, *Angew. Chem. Int. Ed.,* 2013, **52**, 2203; (j) Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.,* 2014, **53**, 1901; (k) X. Liu, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.,* 2014, **53**, 1978; (l) J. Shang, Z. Han, Y. Li, Z. Wang, K. Ding, *Chem. Commun.,* 2012, **48**, 5172.
19 (a) T. Zhou, B. Peters, M. F. Maldonado, T. Govender, P. G. Andersson, *J. Am. Chem. Soc.,* 2012, **134**, 13592; (b) B. K. Peters, T. Zhou, J. Rujirawanich, A. Cadu, T. Singh, W. Rabten, S. Kerdphon, P. G. Andersson, *J. Am. Chem. Soc.,* 2014, **136**, 16557.
20 (a) M. -A. Müller, A. Pfaltz, *Angew. Chem. Int. Ed.,* 2014, **53**, 8668; (b) Q. Yan, D. Kong, M. Li, G. Hou, G. Zi, *J. Am. Chem. Soc.,* 2015, **137**, 10177; (c) X. Li, C. You, Y. Yang, F. Wang, S. Li, H. Lv, X. Zhang, *Chem. Commun.,* 2017, **53**, 1313.
21 (a) S. Li, K. Huang, B. Cao, J. Zhang, W. Wu, X. Zhang, *Angew. Chem. Int. Ed.,* 2012, **51**, 8573; (b) Q. Zhao, S. Li, K. Huang, R. Wang, X. Zhang, *Org. Lett.,* 2013, **15**, 4014.
22 (a) P. -A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem. Int. Ed.*, 2009, **48**, 2162; (b) J. Daubignard, R. J. Detz, A. C. H. Jans, B. Bruin, J. N. H. Reek, *Angew. Chem. Int. Ed.*, 2017, **56**, 13056; (c) P. Dydio, C. Rubay, T. Gadzikwa, M. Lutz, J. N. H. Reek, *J. Am. Chem. Soc.*, 2011, **133**, 17176; (d) L. Pignataro, M. Boghi, M. Civera, S. Carboni, U. Piarulli, C. Gennari, *Chem. Eur. J.* 2012, **18**, 1383.
23 (a) Q. Zhao, J. Wen, R. Tan, K. Huang, P. Metola, R. Wang, E. V. Anslyn, X. Zhang, *Angew. Chem. Int. Ed.,* 2014, **53**, 8467; (b) J. Wen, R. Tan, S. Liu, Q. Zhao, X. Zhang, *Chem. Sci.*, 2016, **7**, 3047.
24 (a) C. Warnier, C. Lemaire, G. Becker, G. Zaragoza, F. Giacomelli, J. Aerts, M. Otabashi, M. A. Bahri, J. Mercier, A. Plenevaux, A. Luxen, *J. Med. Chem.,* 2016, **59**, 8955; (b) S. J. Finnema, N. B. Nabulsi, T. Eid, K. Detyniecki, S.-f. Lin, M. -K. Chen, R. Dhaher, D. Matuskey, E. Baum, D. Holden, D. D. Spencer, J. Mercier, J. Hannestad, Y. Huang, R. E. Carson, *Sci. Transl. Med.,* 2016, **8**, 348ra96.
25 See computational details in Supporting Information.
26 C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.,* 1998, **37**, 2922.
27 C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik, D. Aharony, *Bioorg. Med. Chem.,* 2004, **12**, 2653.
28 X. Bantreil, G. Prestat, A. Moreno, D. Madec, P. Fristrup, P. -O. Norrby, P. S. Pregosin, G. Poli, *Chem. Eur. J.,* 2011, **17**, 2885.

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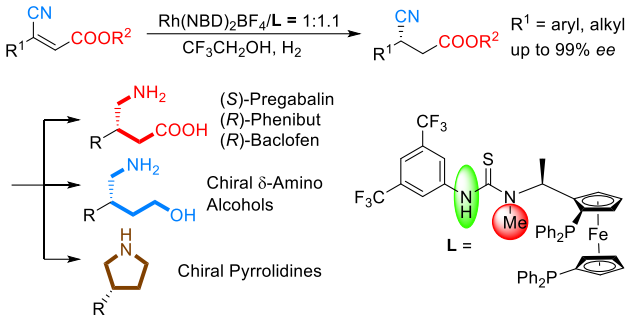

The first asymmetric hydrogenation of β-cyanoacrylate esters has been developed to furnish chiral β-cyano esters with excellent yields and excellent enantioselectivities (up to 99% yield, up to 99% ee), which provides an efficient approach to (*S*)-Pregabalin, (*R*)-Phenibut and (*R*)-Baclofen, chiral δ-amino alcohols, chiral γ-lactam and chiral pyrrolidines. Notably, the catalyst with a single H-bond donor in a precise position performed better than that with double H-bond donors. This novel discovery provides a new vision for the catalyst design.