EDGE ARTICLE

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 is 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 a single H-bond donor performs 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 enzyme catalysis, the strategy of hydrogen bonding has been elaborated and successfully applied in numerous cases of organocatalysis in the past two decades, which provides the synthetic community with many solutions for organic synthesis.[1] Among the 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] Their effective bonding with neutral functional groups, potent binding affinity, and high tunability make thiourea catalysts versatile for many types of organic reactions.[3] Herein, using ferrocene–thiourea chiral bisphosphine ligands (ZhaoPhos series) and a combination of transition metal catalysis and organocatalysis, we focus on whether two hydrogen bonds from the thiourea group are essential in the transformation of β-cyanocinnamic esters, which are very challenging substrates. When the asymmetric hydrogenation of β-cyanocinnamic esters was carried out, the catalyst (**L1**) with only one H-bond donor in a precise position performed better than ZhaoPhos (possesses two H-bond donors) in both reactivity and enantioselectivity. This novel discovery provides new

insight for the design of catalysts in the areas of organocatalysis and metalorganocatalysis.

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] and Baclofen[8] (Fig. 1). In addition, many chiral GABA derivatives are common motifs in numerous drugs, such as Rolipram,[9] Brivaracetam,[10] Vernakalant[11] and Enablex[12] (Fig. 1). Thus, the synthesis of chiral GABA and their derivatives has attracted a great deal of interest; however, very limited approaches have been developed. The methods for their synthesis 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, the transition metal catalyzed asymmetric hydrogenation of functionalized olefins has emerged as

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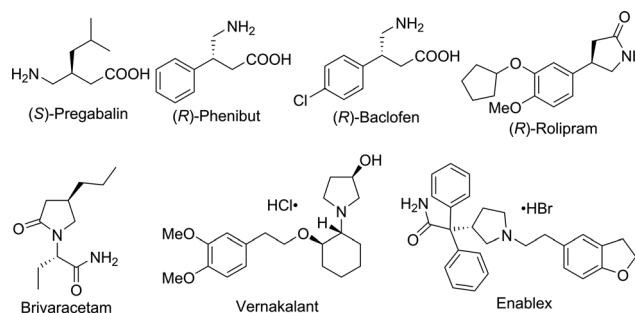
Fig. 1 Chiral GABA derivatives in pharmaceuticals.

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 and activities. However, the asymmetric hydrogenation of β-cyanocinnamic esters has not been reported, which is due to two reasons: (1) the electron-withdrawing ester group and nitrile group, which can sharply reduce the electron density of the C=C bond, are disadvantageous for the C=C bond coordination to the metal center, which leads to the low reactivity of these substrates and (2) the linearity of the nitrile group, which is not suitable for assisting the coordination between the C=C bond and metal catalyst, makes it very difficult to achieve high enantioselectivities.[20a,b] As a result, it is a very difficult task to achieve satisfactory results from the asymmetric hydrogenation of β-cyanocinnamic esters with the classical bidentate diphosphine/Rh system, as summarized in Table 1.

Methyl (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, which gave low to even trace conversions and almost racemic products. This 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 has been made.[22] Therefore, 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 ZhaoPhos-bearing H-bond donors. Although the

preliminary result was moderate (entry 11, 28% conversion with 84% ee), it inspired us for further exploration.

In order to obtain the optimal reaction conditions, a serious of solvents were screened (summarized in the ESI†). 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.

To obtain insight into this catalytic system, three other chiral ligands **L1–L3** were employed and the results are summarized in Table 2. To our surprise, the N methylation of ZhaoPhos led to an increase in enantioselectivity (entry 2, 98% ee), which is quite different from the previous results we reported.[18f,23] In comparison, when both N–H groups 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 the thiourea group showed very low activity and enantioselectivity (entry 4). These results show that the thiourea motif efficiently activates the carbonyl group through hydrogen-bonding interaction and works as an excellent directing agent. 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 was compared (Scheme 1). We thought that enhancement of the steric hindrance of the ester would influence this transformation; however, the results indicate that the changes in the substrate have a slight impact on the reaction (**2a–2c**). Many functional groups, such as methyl

Table 1 Ligand screening for the Rh-catalyzed asymmetric hydrogenation of **1a**[a]
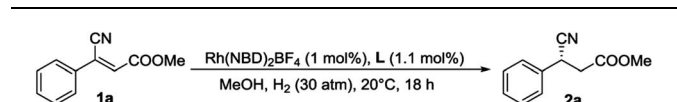
Entry	Ligand	Conv.[b] [%]	ee[c] [%]
1	(Rc,Sp)-DuanPhos	19	rac
2	(S)-Binapine	Trace	—
3	(S,S)–Me-DuPhos	Trace	—
4	(R,R)-QuinoxP*	23	rac
5	(S)-BINAP	Trace	—
6	(S)-SegPhos	Trace	—
7	(S)-DTBM-SegPhos	Trace	—
8	(R,S)-tBu-JosiPhos	25	rac
9	(R)-TaniaPhos	35	−7
10	(R)-WalPhos	Trace	—
11	ZhaoPhos	28	84

[a] All reactions were carried out with an [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.

Table 2 Evaluation of a series of bisphosphine–thiourea ligands[a]
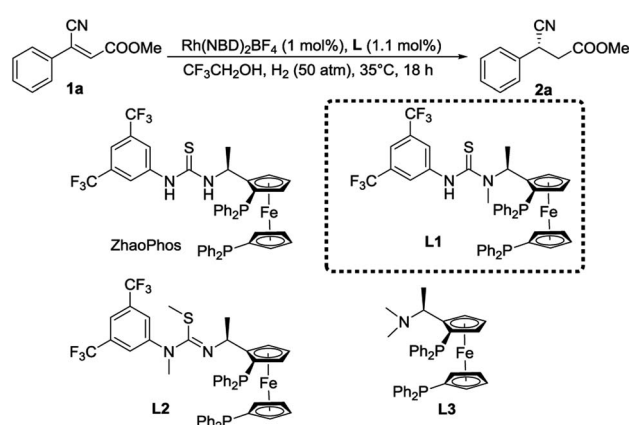
Entry	Ligand	Conv.[b] [%]	ee[c] [%]
1	ZhaoPhos	99	95
2	**L1**	**99**	**98**
3	**L2**	Trace	—
4	**L3**	5	7

[a] All reactions were carried out with an [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.
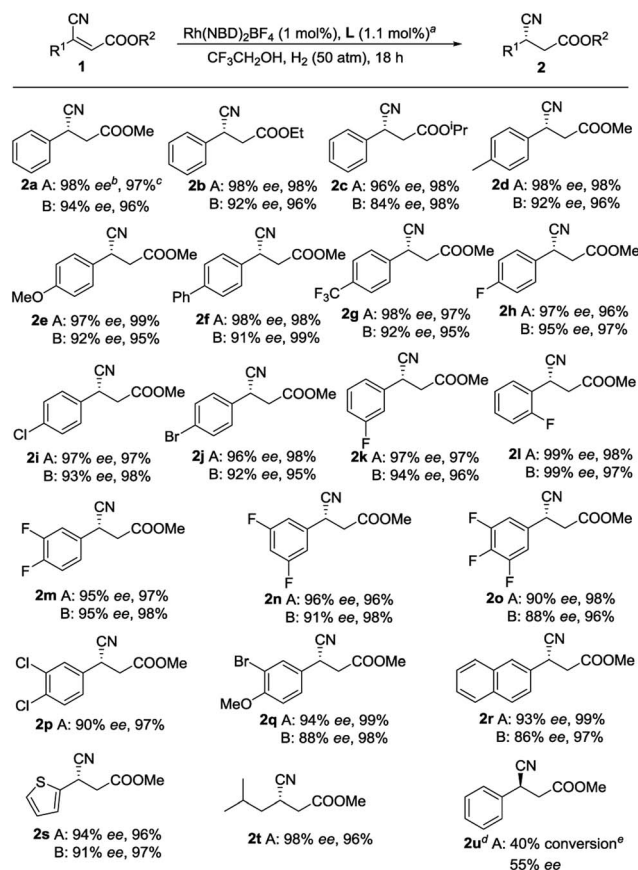
Scheme 1 Substrate scope. Condition A: L = L1, 20 °C. Condition B: L = ZhaoPhos, 35 °C. [a]All reactions were carried out with an [Rh(NBD)$_2$]BF$_4$/L/substrate ratio of 1 : 1.1 : 100, in 1 mL of trifluoroethanol, under hydrogen (50 atm) for 18 h. [b]Determined by HPLC analysis using a chiral stationary phase. [c]Isolated yield. [d](E)-1a was used. [e]Determined by ^{1}H NMR spectroscopy.

(2d), methoxy (2e), phenyl (2f), trifluoromethyl (2g), and halides (2h, 2i and 2j), at the *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,

respectively). Generally, polyfluorinated compounds exist in drug molecules,[24] thus 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, respectively). In comparison, when the 3,4,5-trifluoro compound 1o was employed, the adduct 2o was produced with slightly 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, respectively). 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 the fact that L1 bearing a single H-bond donor is more suitable than ZhaoPhos for this reaction. Moreover, when (E)-1a was employed, much lower reactivity and enantioselectivity were obtained, but the configuration of 2u supports our assumption that the enantioselectivity is inducted by the ester group of the substrates.

To gain a better understanding of the performance of ZhaoPhos and L1, the free energies (kcal mol^{-1}) of the hydrogen bonds between different ligands with 2a (ΔG_{HB}) were evaluated using the B3LYP-GD3BJ/6-31G** method,[25] as summarized in Table 3. To our surprise, the free energy of 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 perform better than two H-bonds in this reaction, thus we proposed that the stronger hydrogen bond is important in making L1 a more selective catalyst. Both the L1 and Zhao-Phos systems 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, the reduction of 1a was performed using L1 of varying ee. As shown in Fig. 2a, a linear correlation between the ee of the ligand and that of the product was observed, which indicates that a 1 : 1 ratio of

Table 3 The comparison of ZhaoPhos and L1[a]

Ligand		T (°C)			
		0	20	35	60
ZhaoPhos	ΔG_{HB} (kcal mol^{-1})	−13.4	−12.2	−11.4	−10.0
	ee	97[b] (20[c])	95 (94)	95 (99)	92 (99)
L1	ΔG_{HB} (kcal mol^{-1})	−16.4	−15.3	−14.5	−13.2
	ee	99 (60)	98 (99)	98 (99)	93 (99)

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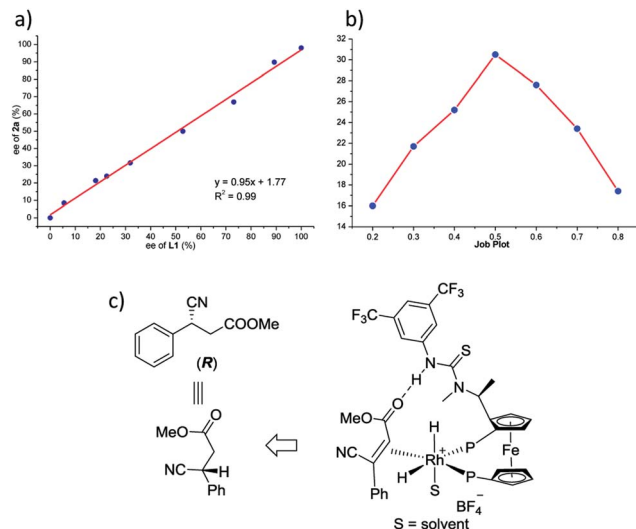
Fig. 2 (a) Hydrogenation of **1a** using **L1** of varying ee, the line corresponds to the least-squares linear regression of the data with slope = 0.95, intercept = 1.77, and r^2 = 0.99; (b) Job plot, $x = c(\mathbf{L1})/[c(\mathbf{L1}) + c(\mathbf{1a})]$, $y = \Delta\delta \times 10^4 \times c(\mathbf{L1})/[c(\mathbf{L1})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

ligand to metal is present in the catalytic complex.[26] Moreover, a Job plot was drawn and the curve suggests a 1 : 1 binding pattern between **L1** and **1a** (Fig. 2b), and a 1 : 1 binding pattern

Scheme 2 Synthetic transformations.

between ZhaoPhos and **1a** was also suggested (summarized in the ESI†). These experimental data validate our hypothesis, and the catalytic model was illustrated, as shown in Fig. 2c.

In order to further demonstrate the synthetic utility of this methodology, several gram-scale transformations were achieved, as summarized in Scheme 2. First, 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, with a 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). Thus far, this may be the most concise way to synthesize chiral Pregabalin, Phenibut and Baclofen. Next, 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 exhibits an efficient approach for 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 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 the synthesis of chiral GABA derivatives. This transformation exhibits excellent enantioselectivities (up to 99% ee) under mild reaction conditions with low catalyst loadings. Furthermore, this method provides a concise route for the synthesis of (S)-Pregabalin, (R)-Phenibut, (R)-Baclofen, chiral δ-amino alcohols, chiral γ-lactam and chiral pyrrolidines, which demonstrates the high synthetic utility of the current methodology. Notably, in our ferrocene–thiourea chiral bisphosphine ligand (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 mechanisms of the proposed key hydrogen bonds and the applications of the asymmetric hydrogenation strategy in organic synthesis are in progress in our lab.

Conflicts of interest

There are no conflicts to declare.

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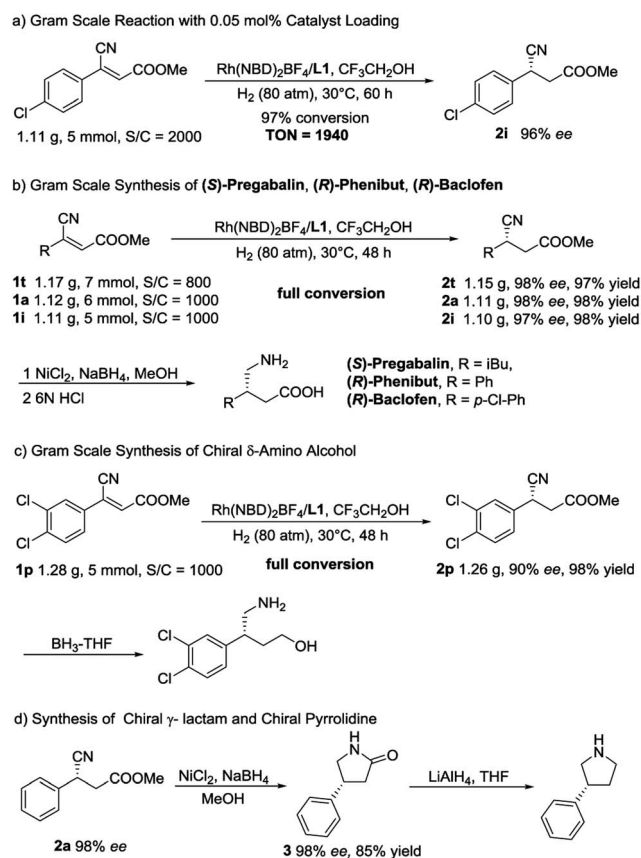
Notes and references

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

2 Recent studies on thiourea in electrophile activation: (a) P. R. Schreiner and 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 and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2012, **134**, 15621; (d) R. R. Walvoord, P. N. H. Huynh and 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 and C. J. Wang, *Chem. Commun.*, 2015, **51**, 1185.

4 R. L. Macdonald and R. W. Olsen, *Annu. Rev. Neurosci.*, 1994, **17**, 569.

5 A. G. Malykh and 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 and M. S. Carey, *Arch. Neurol.*, 1977, **34**, 422.

9 J. Zhu, E. Mix and 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 and P. Michel, *J. Med. Chem.*, 2004, **47**, 530.

11 D. R. Boyd, N. D. Sharma, H. Dalton and D. A. Clarke, *Chem. Commun.*, 1996, 45.

12 P. E. Cross and A. R. MacKenzie, *US Pat.*, 005096890 A, 1992.

13 (a) H. Mukherjee and C. A. Martinez, *ACS Catal.*, 2011, **1**, 1010; (b) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher and L. Tully, *Org. Process Res. Dev.*, 2008, **12**, 392.

14 (a) A. Fryszkowska, K. Fisher, J. M. Gardiner and 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 and 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 and J. D. Stewartc, *Adv. Synth. Catal.*, 2015, **357**, 1849.

15 Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2010, **132**, 10070.

16 (a) P. García-García, A. Ladépêche, R. Halder and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 4719; (b) A. Leyva-Pérez, P. García-García and A. Corma, *Angew. Chem., Int. Ed.*, 2014, **53**, 8687; (c) T. Tsubogo, Y. Yamashita and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9117; (d) T. Tsubogo, H. Oyamada and S. Kobayashi, *Nature*, 2015, **520**, 329; (e) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (f) K. Akagawa and K. Kudo, *Angew. Chem., Int. Ed.*, 2012, **51**, 12786; (g) J. H. Sim and C. E. Song, *Angew. Chem., Int. Ed.*, 2017, **56**, 1835; (h) O. V. Maltsev, A. S. Kucherenko, I. P. Beletskaya, V. A. Tartakovsky and S. G. Zlotin, *Eur. J. Org. Chem.*, 2010, 2927; (i) K. G. Lewis, S. K. Ghosh, N. Bhuvanesh and J. A. Gladysz, *ACS Cent. Sci.*, 2015, **1**, 50; (j) D. A. Evans, S. Mito and D. Seidel, *J. Am. Chem. Soc.*, 2007, **129**, 11583.

17 For reviews, see: (a) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (b) J. H. Xie, S. F. Zhu and Q. L. Zhou, *Chem. Rev.*, 2011, **111**, 1713; (c) J. H. Xie and Q. L. Zhou, *Acta Chim. Sin.*, 2012, **70**, 1427; (d) S. F. Shou and Q. L. Zhou, *Acc. Chem. Res.*, 2017, **50**, 988; (e) Z. Zhang, N. A. Butt and W. Zhang, *Chem. Rev.*, 2016, **116**, 14769; (f) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557; (g) S. J. Roseblade and A. Pfaltz, *Acc. Chem. Res.*, 2007, **40**, 1402; (h) G. Erre, S. Enthaler, K. Junge, S. Gladiali and M. Beller, *Coord. Chem. Rev.*, 2008, **252**, 471; (i) T. L. Church and P. G. Andersson, *Coord. Chem. Rev.*, 2008, **252**, 513; (j) J. J. Verendel, O. Pàmies, M. Diéguez and P. G. Andersson, *Chem. Rev.*, 2014, **114**, 2130.

18 (a) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel and P. G. Andersson, *J. Am. Chem. Soc.*, 2008, **130**, 7208; (b) J. Mazuela, P.-O. Norrby, P. G. Andersson, O. Pàmies and 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 and P. J. Chirik, *J. Am. Chem. Soc.*, 2016, **138**, 3562; (d) W. Tang, W. Wang and 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 and X. Zhang, *ACS Catal.*, 2016, **6**, 6214; (g) P. Li, X. Hu, X.-Q. Dong and X. Zhang, *Chem. Commun.*, 2016, **52**, 11677; (h) J. Wen, J. Jiang and X. Zhang, *Org. Lett.*, 2016, **18**, 4451; (i) Y. Liu and W. Zhang, *Angew. Chem., Int. Ed.*, 2013, **52**, 2203; (j) Y. Liu, I. D. Gridnev and W. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1901; (k) X. Liu, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2014, **53**, 1978; (l) J. Shang, Z. Han, Y. Li, Z. Wang and K. Ding, *Chem. Commun.*, 2012, **48**, 5172.

19 (a) T. Zhou, B. Peters, M. F. Maldonado, T. Govender and 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 and P. G. Andersson, *J. Am. Chem. Soc.*, 2014, **136**, 16557.

20 (a) M.-A. Müller and A. Pfaltz, *Angew. Chem., Int. Ed.*, 2014, **53**, 8668; (b) Q. Yan, D. Kong, M. Li, G. Hou and G. Zi, *J. Am. Chem. Soc.*, 2015, **137**, 10177; (c) X. Li, C. You, Y. Yang, F. Wang, S. Li, H. Lv and X. Zhang, *Chem. Commun.*, 2017, **53**, 1313.

21 (a) S. Li, K. Huang, B. Cao, J. Zhang, W. Wu and X. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8573; (b) Q. Zhao, S. Li, K. Huang, R. Wang and X. Zhang, *Org. Lett.*, 2013, **15**, 4014.

22 (a) P.-A. R. Breuil, F. W. Patureau and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2009, **48**, 2162; (b) J. Daubignard, R. J. Detz, A. C. H. Jans, B. Bruin and J. N. H. Reek, *Angew. Chem., Int. Ed.*, 2017, **56**, 13056; (c) P. Dydio, C. Rubay, T. Gadzikwa, M. Lutz and J. N. H. Reek, *J. Am. Chem. Soc.*, 2011, **133**, 17176; (d) L. Pignataro, M. Boghi, M. Civera, S. Carboni, U. Piarulli and 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 and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 8467; (b) J. Wen, R. Tan, S. Liu, Q. Zhao and 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 and 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 and R. E. Carson, *Sci. Transl. Med.*, 2016, **8**, 348ra96.

25 See computational details in ESI.†

26 C. Girard and 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 and 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 and G. Poli, *Chem.– Eur. J.*, 2011, **17**, 2885.