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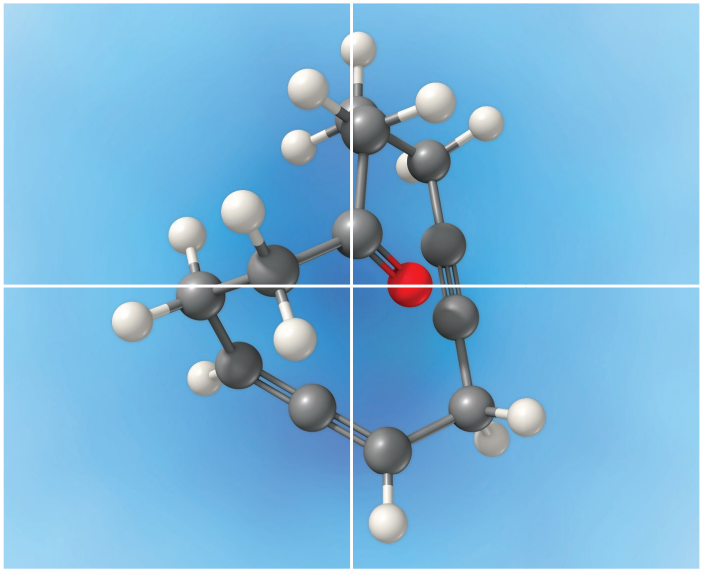

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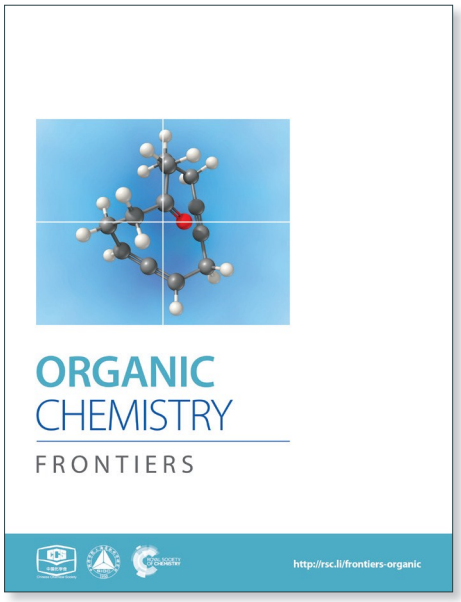

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Diastereo- and enantioselective construction of cyclohexanone-fused spirospyrazolones containing four consecutive stereocenters through asymmetric sequential reactions

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The diastereo- and enantioselective synthesis of cyclohexanone-fused spirospyrazolones containing four consecutive chiral centers has been successfully developed through an asymmetric Michael/Michael/aldol cascade reaction catalyzed by the combination of the bifunctional squaramide and diphenylprolinol silyl ether, followed by a sequential oxidation with pyridinium chlorochromate. This protocol affords the cyclohexanone-fused spirospyrazolones in moderate to high yields, moderate to good diastereoselectivities and perfect enantioselectivities.

Pyrazolone scaffolds which have been known for more than one century,[1] have been proved to be a kind of important structural units. For example, the pyrazolone phenazone[2] is the first synthetic antipyretic and analgesic drug. And metamizole, is considered to be the strongest antipyretic.[3] The pyrazolone edaravone is a neuroprotective agent.[4] Meanwhile, the pyrazolone derivatives could also be used as HIV integrase inhibitors,[5] antibacterial agent.[6] Owing to the excellent biological properties, the synthesis of new, potentially bioactive enantiopure pyrazolone derivatives has attracted considerable research interest from synthetic chemists.[7] Especially, the synthesis of the cyclohexane-fused spiropyrazolones or cyclohexene-fused spiropyrazolones was one of the most attractive topics for researchers, and different ways have been explored.[8] At the same time, Wang[9] and Wang[10] groups reported the synthesis of the cyclohexanone-fused spiropyrazolones with three consecutive stereocenters through a double Michael reaction of α,β-unsaturated ketones to α,β-unsaturated pyrazolones respectively. In 2015, Biju and coworkers reported the enantioselective synthesis of the pyrazolone-fused spirocyclohexdienones with one stereocenter by the reaction of α,β-unsaturated aldehydes with α-arylidene pyrazolinones under oxidative *N*-heterocyclic carbine (NHC) catalysis.[11] Considering the potential biological activities of the cyclohexanone-fused spiropyrazolones, we were fascinated by synthesis of cyclohexanone-fused spiropyrazolones with more stereocenters. Recently, the application of the relay catalysis have been widely used in the organic synthesis, which offers the promise to incorporate more substrates and reaction types to design novel cascade reactions, which are very attractive for building up molecular complexity from simple materials.[12] In addition, the combination of hydrogen-bond donating catalyst with aminocatalyst has been widely employed in one-pot reactions between substrates with different functional groups, when the multi-component reaction could not be catalyzed by only hydrogen-bond donating catalyst or aminocatalyst.[13] Many incredible reactions containing specific groups could be catalyzed smoothly by sequential addition of reagents and catalysts throughout the course of the reaction. In these cases, the hydrogen-bond donating catalyst can catalyze the first step of multi-component reaction to obtain the intermediates, and the intermediates could be catalyzed by the aminocatalyst to reaction with aldehyde compounds to complete the reactions, which was not feasible for a single catalyst system.

Herein, we will present a diastereo- and enantioselective synthesis of cyclohexanone-fused spirospyrazolones containing four consecutive stereocenters through an asymmetric relay catalysis of Michael/Michael/aldol cascade reaction catalyzed by the combination of the bifunctional squaramide and diphenylprolinol silyl ether, followed by a sequential oxidation with pyridinium chlorochromate. This protocol affords the highly functionalized cyclohexanone-fused spiropyrazolones in moderate to high yields (30–78% yield), moderate to good diastereoselectivities (60:40–25:1 dr) and perfect enantioselectivities (up to > 99% ee).

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† Electronic Supplementary Information (ESI) available: [Copies of ^{1}H and ^{13}C NMR spectra of new compounds, and HPLC chromatograms]. See DOI: 10.1039/b000000x/

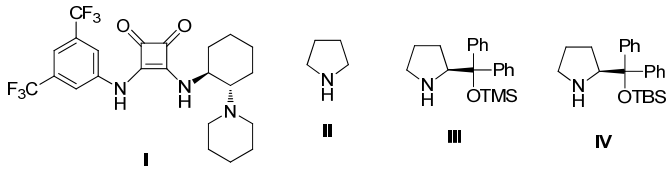
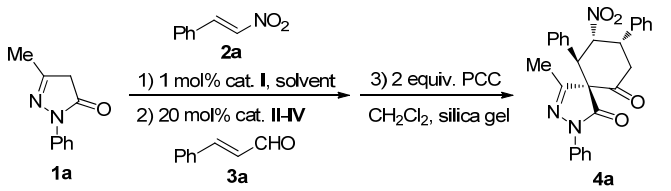


Figure 1. The structures of screened organocatalysts.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield (%)[b]	d.r.[c]	ee (%)[c]
1	**II**	$CHCl_3$	30	70:30	91
2	**III**	$CHCl_3$	44	50:50	>99
3	**IV**	$CHCl_3$	54	45:55	>99
4	**IV**	CH_2Cl_2	55	66:34	>99
5	**IV**	$ClCH_2CH_2Cl$	57	58:42	>99
6	**IV**	Toluene	64	63:37	99
7	**IV**	THF	59	76:24	>99
8[d]	**IV**	THF	59	74:26	>99
9[e]	**IV**	THF	55	74:26	99
10[f]	**IV**	THF	55	75:25	99

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol) and catalyst **I** (1 mol%) in solvent (1 mL) was reacted for 2 h, then **3a** (0.3 mol) and catalyst **II**–**IV** (20 mol%) was added and reacted for further 46 h. Then the intermediate product was isolated and oxidized with PCC (0.4 mmol) and silica gel (86.2 mg) in CH_2Cl_2 (3 ml) for 36 h at r.t. [b] Isolated yield after purification by silica gel column chromatography. [c] Determined by HPLC analysis. [d] $PhCO_2H$ (0.04 mmol) was added. [e] AcOH (0.04 mmol) was added. [f] NaOAc (0.02 mmol) was added.

According to our previous report,[14] we initiated our investigation by using 1,2-diaminocyclohexane-derived squaramide **I** (1 mol%) to catalyze the Michael addition of 3-methyl-1-phenyl-2-pyrazolin-5-one (**1a**) to (*E*)-β-nitrostyrene (**2a**) in chloroform. After 2 h, the cinnamaldehyde (**3a**) and pyrrolidine **II** (20 mol%) were added sequentially. When the reaction was completed, the intermediate product was obtained by silica gel column chromatography, followed by the oxidation using pyridinium chlorochromate in dichloromethane. This sequence was conducted as a three-step asymmetric relay catalysis procedure and the desired product **4a** was obtained in moderate yield and diastereoselectivity with good enantioselectivity (Table 1, entry 1). Because the polarity of the intermediate product **E** was close to the raw material, only crude intermediate product was obtained. Additionally, the one-pot three-step reaction was also tried, but the yield of the product in the oxidation step was too low, except in the solvent of dichloromethane. In order to increase the yield and the stereoselectivity of the final product, appropriate organocatalysts which can coordinate and activate the cinnamaldehyde in the second step were also screened (Table 1, entries 2–3). As can be seen from the results, when catalyst **IV** was used, both of the yield and enantioselectivity were improved (Table 1, entry 3). To further increase the yield and diastereoselectivity of this reaction, the solvents and additives were also evaluated. The solvent evaluation (Table 1, entries 4–7) revealed that THF was a optimal solvent for this reaction, and the product was obtained in good yield (59%) and good diastereoselectivity (76:24) with excellent enantioselectivity (>99%). Further efforts for screening of additives such as $PhCO_2H$, AcOH, and NaOAc did not result in any improvement in the product yield and diastereoselectivity (Table 1, entries 8–10).

With the optimal reaction conditions established, a diverse array of substituted substrates was evaluated, and the results are summarized in Table 2. In general, most of the reactions proceeded well to afford the desired products in good yields, perfect enantioselectivities and moderate to good diastereoselectivities.

First, the R^1 and R^2 group of the pyrazolone were evaluated, and all of the desired spiropyrazolones (**4b**–**4e**) were efficiently obtained in good yields, moderate to good diastereoselectivities and excellent enantioselectivities. Then different aromatic nitroalkenes bearing electron-withdrawing as well as electron-donating substituents were also explored. Generally, all of the products (**4f**–**4h**, **4j** and **4k**) were obtained in perfect enantioselectivities (≧99% *ee*). When the electron-withdrawing or electron-donating ability of the substituents were gentle, good yields were obtained (**4f**–**4h**). Otherwise, if the electron-withdrawing or electron-donating ability of the substituents were too strong, the yields of the product became lower (**4j** and **4k**). Specifically, when the nitroalkene was substituted by nitro group on *meta*-position, excellent diastereoselectivity but lower yield was obtained (**4k**), which demonstrate that the strong electron-withdrawing group influence the reaction, and only one diastereomer was formed. The heteroaromatic nitroalkene was also tested, a moderate yield (53%) with good diastereoselectivity (89:11 *dr*) and perfect enantioselectivity (99% *ee*) was obtained for **4i**. Next, different cinnamaldehydes were explored, and the similar results were obtained for corresponding products (**4j**–**4n**). To evaluate the synthetic potential of this asymmetric relay catalysis system, substituents variations on different substrates at the same time were also evaluated, and the excellent enantioselectivities were also obtained (**4o** and **4p**).

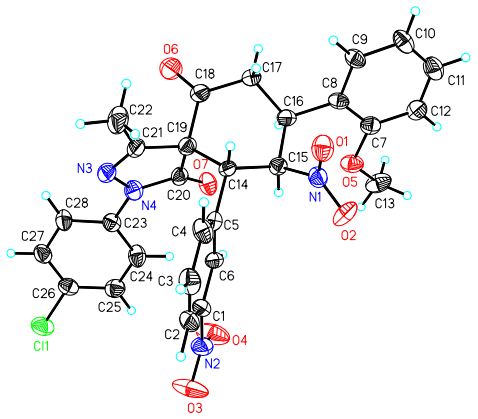
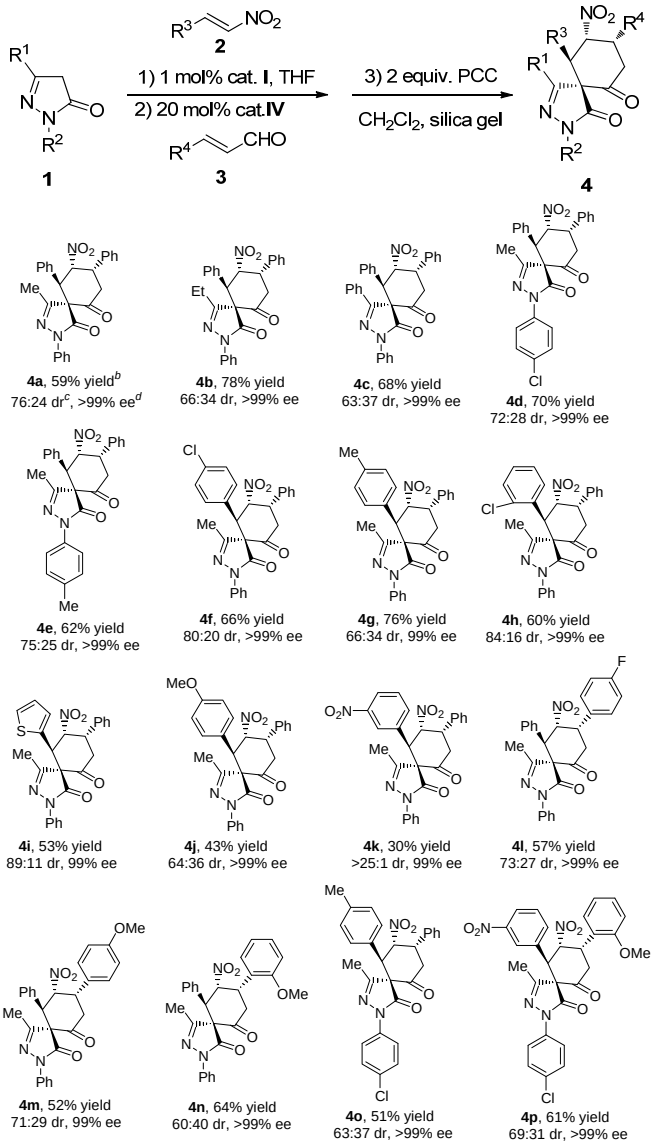


Figure 2. The crystal structure of compound **4p**.

Table 2 Substrate scope of the asymmetric relay reaction[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol) and catalyst **I** (1 mol%) in solvent (1 mL) was reacted for 2 h, then **3** (0.3 mmol) and catalyst **IV** (20 mol%) was added and reacted for further 46 h. Then the intermediate product was isolated and oxidized with PCC (0.4 mmol) and silica gel (86.2 mg) in CH_2Cl_2 (3 ml) for 36 h at r.t. [b] Isolated yield after purification by silica gel column chromatography. [c] Determined by NMR analysis. [d] Determined by HPLC analysis.

The absolute configuration of **4p** was determined to be 5*R*,8*S*,9*R*,10*R* by X-ray crystallographic analysis (Figure 2).[15] The absolute configurations of other products were assigned by analogy.

On the basis of the absolute configuration of **4p** and the previous theoretical study on the mechanism of similar reactions,[13c,14] a plausible mechanism was proposed, as shown in Scheme 1. Firstly, the pyrazolone **1a** is deprotonated by the basic nitrogen atom of the tertiary amine via tautomerization, Meanwhile the nitroalkene is activated by the squaramide moiety through double hydrogen bonding between the NH groups and the nitro group to form the transition state **A**. The deprotonated pyrazolone attacks the activated nitroalkene to afford the Michael adducts. Then, the coordination of the squaramide catalyst to the nitro group allows the tertiary amine to deprotonate the α-proton to generate the nitronate (**B**), followed by an iminium-catalyzed nitro-Michael addition (**C**) to form the intermediate product **D**. Next, an intramolecular aldol reaction is carried out to afford the cyclohexanol-fused spirospyrazolone **E**. Finally, the oxidation reaction with pyridinium chlorochromate to provide the desired cyclohexanone-fused spirospyrazolone **4a**.

In conclusion, we have developed an efficient cascade reaction for the construction of highly functionalized cyclohexanone-fused spirospyrazolones contain four consecutive stereocenters, including one quaternary spirocarbon center, through an asymmetric Michael/Michael/aldol cascade reaction catalyzed by the combination of the bifunctional squaramide and diphenylprolinol silyl ether and a sequential oxidation with pyridinium chlorochromate. This protocol affords the corresponding spiropyrazolones in moderate to high yields (30-78% yield) with moderate to good diastereoselectivities (60:40–25:1 dr) and perfect enantioselectivities (up to >99% ee). We anticipate that this cascade transformation sequence will be valuable for catalyst development, structural diversity of spiropyrazolones and in the identification of new medicinal agents. Further studies on the organocatalytic enantioselective synthesis of potential bioactive heterocycles are ongoing in our laboratory.

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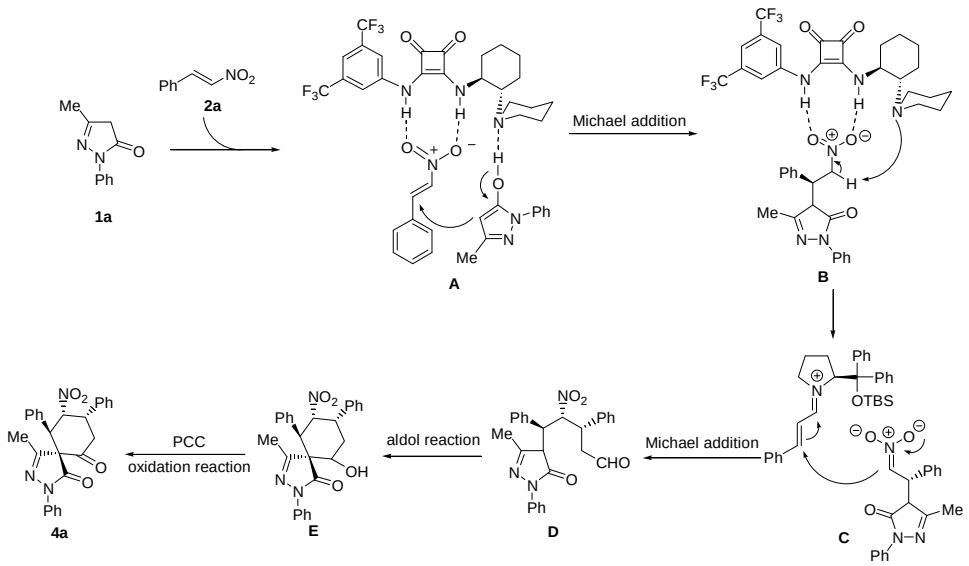

Scheme 1. Plausible Reaction Mechanism.

Notes and references

1 For selected reviews, see: (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (*b*) W. S. Hamama, H. G. El-Gohary, N. Kuhnert, and H. H. Zoorob, *Curr. Org. Chem.,* 2012*,* **16***,* 373.

2 (*a*) M. L. Tainter, *Ann. N. Y. Acad. Sci.*, 1948, **51**, 3; (*b*) K. Brune, *Acute Pain*, 1997, **1**, 33.

3 A. Brayfield, *Martindale: The Complete Drug Reference*, Pharmaceutical Press, 2014.

4 (*a*) H. Yoshida, H. Yanai, Y. Namiki, K. Fukatsu-Sasaki, N. Furutani and N. Tada, *CNS Drug Rev.*, 2006, **12**, 9; (*b*) W. Ji Yuan, T. Yasuhara, T. Shingo, K. Muraoka, T. Agari, M. Kameda, T. Uozumi, N. Tajiri, T. Morimoto, M. Jing, T. Baba, F. Wang, H. Leung, T. Matsui, Y. Miyoshi and I. Date, *BMC Neurosci.*, 2008, **9**, 75.

5 V. Hadi, Y.-H. Koh, T. W. Sanchez, D. Barrios, N. Neamati and K. W. Jung, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6854.

6 M. S. Chande, P. A. Barve and V. Suryanarayan, *J. Heterocycl. Chem.*, 2007, **44**, 49.

7 For review see: (*a*) P. Chauhan, S. Mahajan and D. Enders, *Chem. Commun.,* 2015, **51**, 12890; For selected examples see: (*b*) X. Bao, B. Wang, L. Cui, G. Zhu, Y. He, J. Qu and Y. Song, *Org. Lett.*, 2015, **17**, 5168; (*c*) D. Hack, A. B. Dürr, K. Deckers, P. Chauhan, N. Seling, L. Rübenach, L. Mertens, G. Raabe, F. Schoenebeck and D. Enders, *Angew. Chem. Int. Ed.*, 2016, **55**, 1797; (*d*) D. Hack, P. Chauhan, K. Deckers, Y. Mizutani, G. Raabea and D. Enders, *Chem. Commun.,* 2015, **51**, 2266; (*e*) W. Zheng, J. Zhang, S. Liu, C. Yua and Z. Miao, *RSC Adv.*, 2015, **5**, 91108; (*f*) S. Wang, C. Rodriguez-Escrich and M. A. Pericàs, *Org. Lett.*, 2016, **18**, 556; (*g*) N. Kumarswamyreddy and V. Kesavan, Org. Lett., DOI: 10.1021/acs.orglett.6b00287; (*h*)J.-H. Li, T.-F. Feng and D.-M. Du, *J. Org. Chem.*, 2015, **80**, 11369; (*i*) J.-H. Li and D.-M. Du, *Chem. Asian J.*, 2014, **9**, 3278.

8 (*a*) X. Companyó, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano and R. Rios, *Chem. Commun.,* 2010, **46**, 6953; (*b*) A.-N. R. Alba, A. Zea, G. Valero, T. Calbet, M. Font-Bardía, A. Mazzanti, A. Moyano, and R. Rios, *Eur. J. Org. Chem.,* 2011, 1318; (*c*) A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano and R. Rios, *Org. Biomol. Chem.*, 2011, **9**, 6519; (*d*) P. Sun, C.-Y. Meng, F. Zhou, X.-S. Li, J.-W. Xie, *Tetrahedron*, 2014, **70**, 9330; (*e*) P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16**, 2954. (*f*) B. Han, W. Huang, W. Ren, G. He, J.-H. Wang and C. Peng, *Adv. Synth. Catal.*, 2015, **357**, 561.

9 J. Liang, Q. Chen, L. Liu, X. Jiang and R. Wang, *Org. Biomol. Chem.*, 2013, **11**, 1441.

10 (*a*) J.-X. Zhang, N.-K. Li, Z.-M. Liu, X.-F. Huang, Z.-C. Geng, and X.-W. Wang, *Adv. Synth. Catal.*, 2013, **355**, 797; (*b*) B. Wu, J. Chen, M.-Q. Li, J.-X. Zhang, X.-P. Xu, S.-J. Ji and X.-W. Wang, *Eur. J. Org. Chem.*, 2012, 1318.

11 S. R. Yetra, S. Mondal, S. Mukherjee, R. G. Gonnade, and A. T. Biju, *Angew. Chem. Int. Ed.*, 2016, **55**, 268.

12 For selected reviews, see: (*a*) J. Zhou, *Multicatalyst system in Asymmetric Catalysis*, John Wiley & Sons, New York, 2014; (*b*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.* 2005, **105**, 1001; (*c*) J. Zhou, *Chem. Asian J.* 2010, **5**, 422; (*d*) N. T. Patil, V. S. Shinde and B. Gajula, *Org. Biomol. Chem.*, 2012, **10**, 211; (*e*) H. Pellissier, *Tetrahedron* 2013, **69**, 7171; For selected examples, see: (*f*) X.-P. Yin, X.-P. Zeng, Y.-L. Liu, F.-M. Liao, J.-S. Yu, F. Zhou and J. Zhou, *Angew. Chem. Int. Ed.*, 2014, **53**, 13740; (*g*) Y. Wang, D.-F. Yu, Y.-Z. Liu, H. Wei, Y.-C. Luo, D. J. Dixon and P.-F. Xu, *Chem. Eur. J.,* 2010, **16**, 3922; (*h*) Z. Mao, Y. Jia, Z. Xu and R. Wang, *Adv. Synth. Catal.* 2012, 354, 1401; (i) Y.-L. Zhao, Z.-Y. Cao, X.-P. Zeng, J.-M. Shi, Y.-H. Yu and J. Zhou, *Chem. Commun.,* 2016, **52**, 3943; (*j*) Z.-Y. Cao, Y.-L. Zhao and J. Zhou, *Chem. Commun.,* 2016, **52**, 2537.

13 For seleted examples, see: (*a*) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, *Angew. Chem. Int. Ed.*, 2009, **48**, 9834; (*b*) S. Lin, L. Deiana, G.-L. Zhao, J. Sun and A. Córdova, *Angew. Chem. Int. Ed.*, 2011, **50**, 7624. (*c*) B. Zhou, Y. Yang, J. Shi, Z. Luo and Y. Li, *J. Org. Chem.*, 2013, **78**, 2897;
14 J.-H. Li and D.-M. Du, *Org. Biomol. Chem.*, 2013, **11**, 6215.
15 Cystallographic data for compound **4p** (CCDC-1470552) has been provided as CIF file in supporting information.