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Diastereodivergent and Enantioselective Access to Spiroepoxides via Organocatalytic Epoxidation of Unsaturated Pyrazolones

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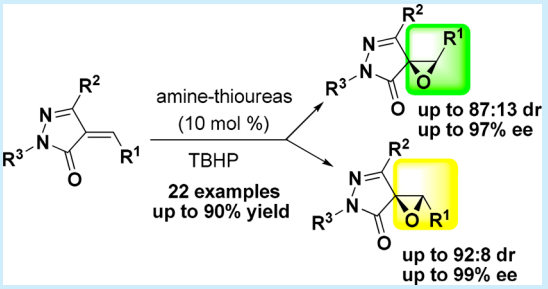
Supporting Information

ABSTRACT: Readily available chiral amine−thioureas are effective catalysts for the first diastereo- and enantioselective epoxidation of unsaturated pyrazolones. The *trans*- or *cis*-spiroepoxides are preferentially obtained in good yield and high to excellent enantioselectivity using an appropriate organocatalyst and *tert*-butyl hydroperoxide as the oxidant. The epoxidation appears applicable to highly challenging *β*,*β*′-substituted unsaturated pyrazolones, giving access to spiroepoxides bearing two vicinal quaternary stereocenters. The reaction represents a unique example of Weitz−Scheffer epoxidation, where the catalyst-controlled ring-closure step is usefully exploited to prepare both enantioenriched diastereomeric epoxides.



The asymmetric construction of spirocyclic centers is a formidable challenge and a fascinating task in synthetic chemistry.[1] Enantioenriched spirocyclics are biologically active compounds and common motifs in nature but also serve as ligands in metal-based catalysis and promoters in organocatalysis.[2] New stereoselective methodologies to synthesize these rigid molecular scaffolds have rapidly flourished in recent years, remarkably in the realm of organocatalysis.[3] Five- and six-membered spirocyclic compounds, bearing different heteroatoms and stereocenters, are now obtainable with a high level of diastereo- and enantioselectivity, exploiting domino reactions.[4] Concerning spiroepoxides, only a few examples for their asymmetric synthesis have been developed so far, although representative natural spiroepoxides are important compounds; examples include fumagillin,[5] lumacinin D,[6] and FR901464,[7] which show potent antibiotic, antiangiogenic, and anticancer activities, respectively. The few protocols reported are based on chiral substrates or auxiliary tools.[8] Only recently, the catalytic metal-based Darzens reaction,[9] organocatalyzed epoxidation,[10] and kinetic resolution tool[11] emerged as viable routes to access spiro-epoxyoxindoles in modest to high stereoselectivities. 4-Spiro-5-pyrazolones are heterocycles of great interest as agrochemicals and in medicinal chemistry, showing biological activities as phosphodiesterase inhibitors, antitumor, and antibacterial agents and have become the subject of intense research.[3] Surprisingly, to the best of our knowledge, examples of asymmetric synthesis of spiropyrazolone epoxides are not known, and we planned to address this issue.[12] These compounds can be potentially ring-opened to prepare scaffolds of interest as functionalized 4-hydroxypyrazolones, bearing a quaternary stereocenter.[13] Given the good reactivity displayed by unsaturated pyrazolones in organocatalyzed Michael type reactions[3b] and based on our previously disclosed research,[14] we envisioned that bifunctional organocatalysts would promote their nucleophilic asymmetric epoxidation. Here, we report our findings on the asymmetric epoxidation of unsaturated pyrazolones catalyzed by an easily available amine−thiourea/TBHP system. We demonstrate that either *cis*- or *trans*-spiroepoxides can be preferentially obtained with high to excellent enantioselectivity. Moreover, preliminary findings showed that this oxidative system would be applicable to *β*,*β*′-substituted alkylidene pyrazolones to give optically active spiroepoxides bearing two vicinal quaternary stereocenters.

Literature precedents[15] on the epoxidation of (*Z*)-unsaturated pyrazolones showed that (i) the $NaOH/H_2O_2$ system afforded the *trans*-spiroepoxide as major product, whereas (ii) the employment of *m*-CPBA led to a mixture of *cis*-and *trans*-spiroepoxides due to in situ alkene isomerization.[16] Hence, the control of the diastereoselectivity is not a trivial task, which essentially relies on the nature of the oxidative system used and ultimately on the mechanism of epoxidation as a two-step (i) or concerted pathway (ii) (Scheme 1). The formation of *trans*-epoxide from the (*Z*)-alkene suggests that, under Weitz−Scheffer conditions (i),[17] the *cis*/*trans* ratio might be affected by a bifunctional catalyst, as it would drive the ring-closure step of a relatively stable peroxy enolate intermediate (iii).

Consequently, by exploiting a nucleophilic pathway of epoxidation, a diastereodivergent and enantioselective process can in principle be developed starting from the same alkene and a proper choice of the organocatalyst. This is an important yet highly challenging and general goal in asymmetric synthesis and drug discovery; i.e, the selective synthesis of all enantioenriched

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Scheme 1. Diastereoselective Epoxidation of (*Z*)-Unsaturated Pyrazolones

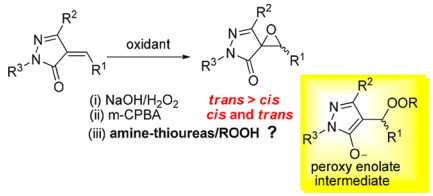
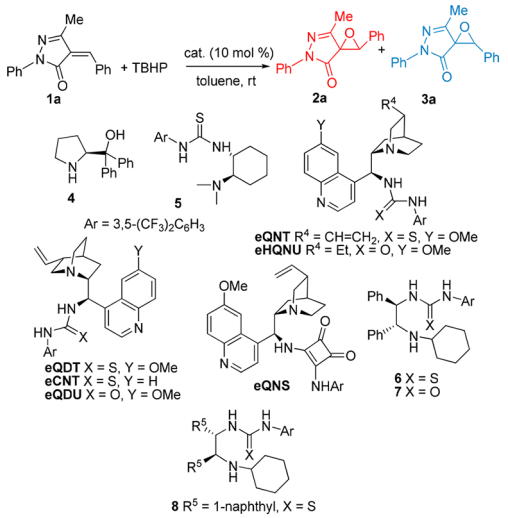


Table 1. Catalyst Screening in the Epoxidation of Alkene 1a[a]



entry	cat.	time (h)	yield[b] (%)	2a/3a[c]	ee 2a/3a[d] (%)
1	**4**	7	98	85/15	−32/−64
2[e]	**QN**	24	85	30/70	33/8
3	**5**	28	60	65/35	−13/35
4	**eQNT**	16	85	30/70	37/−98
5	**eQDT**	6	90	22/78	−29/94
6	**eCNT**	6	97	25/75	−23/92
7	**eHQNU**	2	97	33/67	59/−98
8	**eQDU**	4	93	40/60	−46/96
9[e]	**eQNS**	21	84	57/43	−11/−45
10	**6**	5	95	56/44	91/36
11	**7**	24	75	75/25	40/55
12	**8**	1	98	80/20	−95/−56

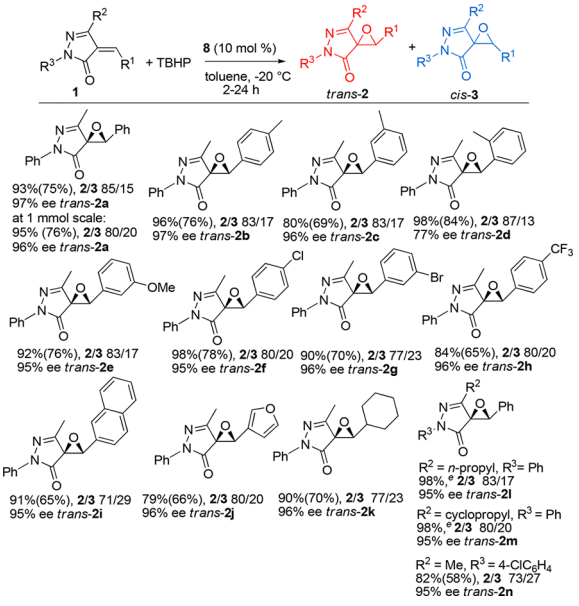
[a]Reactions were performed at on an 0.08 mmol scale of **1a** (*c* 0.2 M) using TBHP (1.2 equiv). [b]Determined by ^{1}H NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as an internal standard. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by chiral HPLC analysis. Negative sign indicates enantiomeric excess for the opposite enantiomer. [e]5 mol % of catalyst was used.

diastereoisomers from the same reagents using chiral catalytic systems.[18]

The epoxidation of model alkene **1a** was first investigated by using 10 mol % of a variety of bifunctional organocatalysts, TBHP in toluene at room temperature (Table 1).

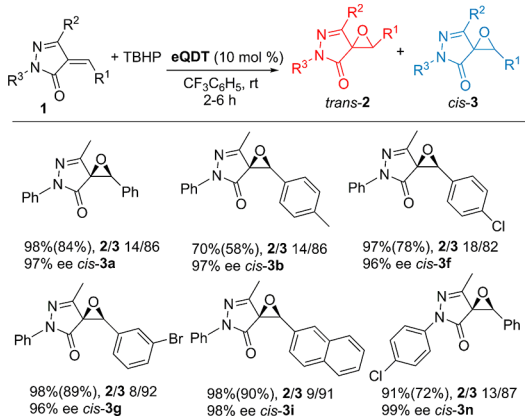
Amino alcohols such as L-diphenylprolinol **4** and quinine (entries 1 and 2) catalyzed the epoxidation with minimal enantiocontrol, but in a diastereodivergent manner, attesting the crucial role played by the organocatalyst in directing the ring-closure step. This prompted us to check double H-bonding donors, amine−thioureas, as more pertinent promoters. Takemoto's catalyst **5** proved to be less effective (entry 3), but when **eQNT**, **eQDT**, and **eCNT** cinchona alkaloids derived thioureas were used, good conversions to *cis*-spiroepoxide **3a** in up to 78/22 dr and high enantioselectivity were observed (entries 4−6). **eHQNU** and **eQDU** cinchona alkaloid-derived ureas proved to

Scheme 2. Substrate Scope for the Asymmetric Epoxidation of Alkenes 1 with 8/TBHP System[a−e]



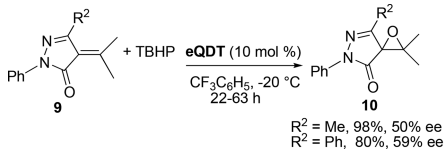
[a]Reactions were performed on a 0.1 mmol scale of **1** (*c* 0.1 M) using TBHP (1.2 equiv). [b]Isolated yield of both epoxides; yield of **2** in parentheses. [c]Epoxide **2**/**3** ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [d]ee determined by chiral HPLC analysis. [e]Unseparable mixture of **2** and **3**.

Scheme 3. Asymmetric Epoxidation of Alkenes 1 with eQDT/TBHP System[a−d]



[a]Reactions were performed on a 0.1 mmol scale of **1** (*c* 0.1 M) using TBHP (1.2 equiv). [b]Isolated yield of both epoxides; yield of **3** in parentheses. [c]Epoxide **2**/**3** ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [d]ee determined by chiral HPLC analysis.

Scheme 4. Enantioselective Epoxidation of Alkenes 9 with eQDT/TBHP System



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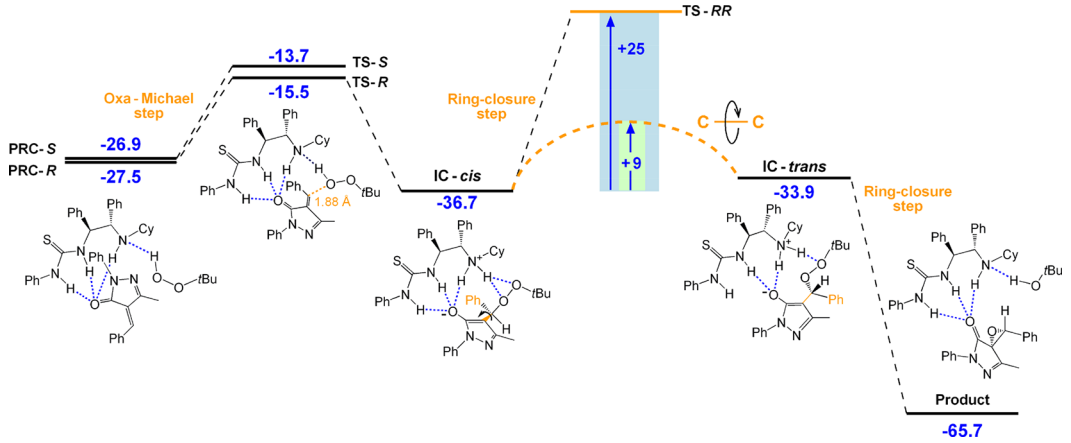

Figure 1. Energy profile of the epoxidation catalyzed by simplified *ent*-**6**; relative energy (kcal/mol) refers to reactants (Cy = cyclohexyl).

be active in the process, leading to the *cis*-spiroepoxide **3a** with a comparable level of enantioselectivity but slightly decreased diastereoisomeric ratios (entries 7 and 8). Conversely, the quinine-derived squaramide (**eQNS**) displayed low activity and stereoselectivity (entry 9). Easily available amine−thiourea **6**, developed by our group as an effective catalyst in a sulfa-Michael reaction,[19] gave only a slight preference of *trans*-spiroepoxide **2a**, which was recovered with 91% ee (entry 10). The corresponding urea **7** was less efficient in terms of enantiocontrol (entry 11). Gratifyingly, more sterically hindered amine−thiourea **8** rapidly converted the alkene into a 80/20 *trans*/*cis* mixture of epoxides, with the *trans*-**2a** being recovered with 96% ee (entry 12).

Further optimization of the reaction parameters using catalysts **8** and **eQDT** enabled identification of the best reaction conditions to preferentially access enantioenriched *trans*-[20] or *cis*-spiroepoxides from unsaturated pyrazolones.[21] To assess the scope of the epoxidation, alkenes **1** were reacted with catalyst **8** and TBHP in toluene at −20 °C (Scheme 2). Alkenes bearing electron-donating or -withdrawing groups at the *para*, *meta* positions of the aromatic R^1 group were rapidly converted in good to high yield, satisfactory diastereocontrol, and high ee values into *trans*-spiroepoxides **2a**−**h**. A somewhat lower enantioselectivity was observed with the *ortho*-substituted epoxide *trans*-**2d**. More sterically demanding 2-naphthyl or heteroaromatic groups were tolerated, achieving comparable results in terms of stereocontrol (**2i**,**j**). The *β*-alkyl-substituted alkene **1k** gave the *trans*-spiroepoxide **2k** in good yield, somewhat lower diastereocontrol, and 96% ee.

Unsaturated pyrazolones differently substituted at positions 1 or 3 of the heterocycle were smoothly transformed into epoxides with similar *trans*-diastereocontrol and excellent level of asymmetric induction. The absolute configuration of spiroepoxide **2f** was determined to be (2*R*,3*S*) by X-ray crystallographic analysis (Flack parameter = −0.00(3)), and the configurations of the other epoxides were assigned by analogy.[21]

Then, epoxidation to obtain *cis*-spiroepoxides **3** using **eQDT** as the organocatalyst in trifluorotoluene at room temperature was studied (Scheme 3).[21] As a general remark, the reactions proceeded to give *cis*-spiroepoxides **3** in good to high yield, a good level of diastereocontrol (up to 92/8 dr), and excellent enantioselectivity.[22] The absolute configuration of spiroepoxide **3g** was determined to be (2*S*,3*S*) by X-ray crystallographic analysis (Flack parameter = −0.023(17)), and the configurations of the other epoxides were assigned by analogy.[21] The *trans*-**2** and *cis*-**3** spiroepoxides, preferentially enriched in the opposite enantiomers, can be eventually obtained by using catalysts *ent*-**8** and ***e*HQNU** (see Table 1).

Finally, we were intrigued by the possibility to perform a more ambitious reaction of *β*,*β*′-substituted alkylidene pyrazolones to obtain spiroepoxides bearing vicinal quaternary stereocenters. To this end, symmetrically *β*-disubstituted 4-alkylidenepyrazolones **9a**,**b** were treated under conditions reported in Scheme 3 at −20 °C (Scheme 4). Interestingly, epoxides **10a**,**b** were isolated in high yield and with an encouranging level of enantioselectivity.

To shed light on the mechanism of epoxidation, a preliminary DFT study was carried out with simplified catalyst *ent*-**6** (Figure 1).[23] In the prereactive complexes (**PRC-*R***), the carbonyl oxygen of the alkene was engaged in two strong H-bonds with the NH groups of the thiourea moiety and an additional hydrogen bond with the proton of the amino group, the latter playing an active role over the entire mechanism.[24] In the most stable PRCs, TBHP was strongly H-bonded to the amine nitrogen of the catalyst, ready to be deprotonated. The oxa-Michael reaction was calculated to be the enantioselectivity and rate-determining step. A moderate barrier (12 kcal/mol, **TS-*R***) was predicted for the formation of the **IC-*cis*** intermediate complex with the preferred *R*-configuration. Direct ring closure of the **IC-*cis*** intermediate complex to (2*R*,3*R*)-**3** would not be a feasible event due to the high barrier associated with the C−O bond formation (25 kcal/mol).[25] A much smaller barrier (9 kcal/mol) was predicted for the rotation about the C−C−C−O dihedral angle, converting the **IC-*cis*** into **IC-*trans*** intermediate. The latter would easily form the final (2*R*,3*S*)-spiroepoxide **2**, as experimentally observed, via a ring-closure step predicted to be a barrier less process. DFT computations are able to recover the experimental trends and give a rationale for the isomerization, although quantitative agreement with the outcome of the reaction carried out with catalyst **6** is only fair. Indeed, a too large energy difference between the ring closure step leading to (2*R*,3*R*)-product and the torsion step, leading to (2*R*,3*S*)-product is predicted, possibly due to the simplified nature of the model catalyst. Further theoretical studies employing real catalysts are thus needed for a definitive assessment of the mechanism.

In conclusion, we developed a first diastereodivergent and enantioselective epoxidation of unsaturated pyrazolones, which enabled successful preparation of *trans*- and *cis*-spiropyrazolone epoxides in high enantiocontrol by using readily accessible amine-thioureas. This study highlights an organocatalytic diastereodivergent asymmetric synthesis of epoxides that can

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be a suitable approach whenever stable peroxy enolates are involved in Weitz−Scheffer-type epoxidations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02189.

X-ray data for compound **2f** (CIF)
X-ray data for compound **3g** (CIF)
Experimental details, analytical data, NMR spectra, HPLC traces, optimized geometries, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. *ACS Catal.* **2013**, *3*, 540. (b) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (c) Nakazaki, A.; Kobayashi, S. *Synlett* **2012**, *23*, 1427.

(2) (a) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581. (b) Zhou, Q.-L. In *Privileged Chira Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011; p 137. For selected examples, see:. (c) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225. (d) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (e) Xing, C.-H.; Liao, Y.-X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q.-S. *Eur. J. Org. Chem.* **2012**, *2012*, 1115.

(3) For reviews, see: (a) Varvounis, G. Pyrazol-3-ones. Part IV: Synthesis and Applications. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 2009; Vol. *98*, p 143. (b) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890.

(4) For selected examples, see: (a) Companyó, X.; Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953. (b) Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Eur. J. Org. Chem.* **2012**, *2012*, 1318. (c) Liu, L.; Zhong, Y.; Zhang, P.; Jiang, X.; Wang, R. *J. Org. Chem.* **2012**, *77*, 10228. (d) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (e) Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J.-h.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561. (f) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem., Int. Ed.* **2016**, *55*, 268. (g) Hack, D.; Dîrr, A. B.; Deckers, K.; Chauhan, P.; Seling, N.; Rîbenach, L.; Mertens, L.; Raabe, G.; Schoenebeck, F.; Enders, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 1797.

(5) Eble, T. E.; Hanson, F. R. *Antibiot. Chemother.* **1951**, *1*, 54.

(6) (a) Shotwell, J. B.; Krygowski, E. S.; Hines, J.; Koh, B.; Huntsman, E. W. D.; Choi, H. W.; Schneekloth, J. S.; Wood, J. L.; Crews, C. M. *Org. Lett.* **2002**, *4*, 3087. (b) Bartlett, N.; Gross, L.; Péron, F.; Asby, D. J.; Selby, M. D.; Tavassoli, A.; Linclau, B. *Chem. - Eur. J.* **2014**, *20*, 3306.

(7) (a) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974. (b) Albert, B.; Sivaramakrishnan, J. A.; Naka, T.; Czaicki, N. L.; Koide, K. *J. Am. Chem. Soc.* **2007**, *129*, 2648.

(8) For a review, see: (a) Adam, W.; Zhang, A. *Synlett* **2005**, 1047. (b) Schulz, V.; Davoust, M.; Lemarié, M.; Lohier, J.-F.; Santos, J. S. O.; Metzner, P.; Brière, J.-F. *Org. Lett.* **2007**, *9*, 1745. (c) Švenda, J.; Myers, A. G. *Org. Lett.* **2009**, *11*, 2437. (d) Boucherif, A.; Yang, Q.-Q.; Wang, Q.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *J. Org. Chem.* **2014**, *79*, 3924.

(9) Kuang, Y.; Lu, Y.; Tang, Y.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2014**, *16*, 4244.

(10) (a) Palumbo, C.; Mazzeo, G.; Mazziotta, A.; Gambacorta, A.; Loreto, M. A.; Migliorini, A.; Superchi, S.; Tofani, D.; Gasperi, T. *Org. Lett.* **2011**, *13*, 6248. (b) Mukaiyama, T.; Ogata, K.; Ono, T.; Hayashi, Y. *ChemCatChem* **2015**, *7*, 155.

(11) Zhu, G.; Bao, G.; Li, Y.; Sun, W.; Li, J.; Hong, L.; Wang, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 5332.

(12) For a single example of optically active spiropyrazolone epoxide, see: Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2014**, *356*, 2330.

(13) Kirschke, K.; Hübner, P.; Lutze, G.; Gründemann, E.; Ramm, M.; Xue, F.; Bao, X.; Zou, L.; Qu, J.; Wang, B. *Liebigs Ann. Chem.* **1994**, *1994*, 159. For asymmetric synthesis of 4-hydroxypyrazolones, see: Xue, F.; Bao, X.; Zou, L.; Qu, J.; Wang, B. *Adv. Synth. Catal.* **2016**, *358*, 3971.

(14) (a) Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem. - Eur. J.* **2012**, *18*, 6152. (b) Meninno, S.; Vidal-Albalat, A.; Lattanzi, A. *Org. Lett.* **2015**, *17*, 4348. (c) Meninno, S.; Zullo, L.; Overgaard, J.; Lattanzi, A. *Adv. Synth. Catal.* **2017**, *359*, 913. (d) Kobayashi, Y.; Li, S.; Takemoto, Y. *Asian J. Org. Chem.* **2014**, *3*, 403.

(15) Eğe, S. N.; Adams, A. D.; Gess, E. J.; Ragone, K. S.; Kober, B. J.; Lampert, M. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, *1*, 325.

(16) *cis*- and *trans*-epoxides were reported to occur from stereospecific *m*-CPBA epoxidation of the *E*/*Z*-alkene mixture present in solution; see: Lo Vecchio, G.; Gattuso, M.; Stagno d'Alcontres, G. *Gazz. Chim. Ital.* **1969**, *99*, 121.

(17) Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges. B* **1921**, *54*, 2327.

(18) For reviews, see: (a) Schindler, C. S.; Jacobsen, E. N. *Science* **2013**, *340*, 1052. (b) Oliveira, M. T.; Luparia, M.; Audisio, D.; Maulide, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 13149. (c) Bihani, M.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2017**, *359*, 534. (d) Lin, L.; Feng, X. *Chem. - Eur. J.* **2017**, *23*, 6464.

(19) Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.* **2013**, *15*, 3436.

(20) As a matter of comparison, the racemic epoxidation of representative alkenes **1a**,**g** performed at room temperature with the $NaOH/H_2O_2$ system (ref 15) afforded the corresponding epoxides **2a**,**g** in 75−80% yield and 90:10−91:9 *trans*/*cis* ratio, respectively.

(21) Detailed information can be found in the Supporting Information.

(22) The formation of the *cis*-epoxide might be explained by changed sterics or/and electronic requirements achieved in the different TS complex, leading to a more favorable ring closure of the first formed adduct before the C−C bond rotation occurred. This outcome has been frequently observed in stereoselective Weitz−Scheffer-type epoxidations.

(23) Calculations were performed at the PCM (toluene) M06-2X/6-311+G(2d,p) level of theory (see the Supporting Information).

(24) It is interesting to see the results obtained when using structurally similar Takemoto's catalyst (cat. **5**) bearing a tertiary amine portion, which preferentially afforded the *trans*-epoxide, but with lower diastereo- and enantiocontrol (see Table 1, entry 3) when compared to results provided by catalyst **8** (see Table 1, entry 12).

(25) It would be interesting to check the behavior of (*E*)-unsaturated pyrazolones, but their synthesis is not a trivial task, as (*Z*)-unsaturated pyrazolones are exclusively obtained in Knoevenagel-type reactions.

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