Organic LETTERS

Letter

pubs.acs.org/OrgLett

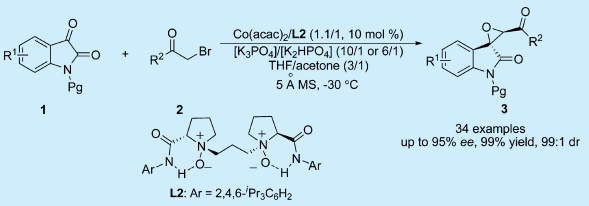
Asymmetric Synthesis of Spiro-epoxyoxindoles by the Catalytic Darzens Reaction of Isatins with Phenacyl Bromides

Yulong Kuang, Yan Lu, Yu Tang, Xiaohua Liu, Lili Lin, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

Supporting Information

ABSTRACT: The asymmetric Darzens reaction between phenacyl bromides and *N*-protected isatins was developed to synthesize potentially bioactive spiro-epoxyoxindoles. The optically active products were obtained in moderate to good yields and enantioselectivities catalyzed by chiral *N*,*N*′-dioxide-Co(acac)$_2$ complexes. A retro-aldol process accompanying the ring-closure step was observed in the process. A chiral control step was determined to be the initial aldol addition.



Spiro-epoxyoxindoles and their closest derivatives have been identified as a kind of privileged skeleton with important biological activities.[1] Benzoyl-substituted oxiranes are particularly noticeable as antifungal and antitubercular agents (Figure 1). For instance, *trans*-**3a** is against *Rhizoctonia solani*; *cis*-**3b** and *trans*-**3d** have anti-*Fusarium oxysporum* activity, and *trans*-**3a** and *cis*-**3d** even have higher antitubercular activity than the standard drug rifampicin.[2] Compound **3c** (NSC 621179) is also found to be significant against both melanoma and leukemia at $p < 0.05$.[3] As a consequence, synthesis of optically active spiro-epoxyoxindoles is interesting and valuable. However, there are sparse reports related to accessing to chiral spiro-epoxyoxindoles via catalytic asymmetric reactions.[1b,k,p,4] In 2007, Brière and co-workers first attempted a stereoselective Darzens reaction using stoichiometric enantiopure sulfides, although only 30% ee was achieved.[1p] The Gasperi group succeeded in asymmetric organocatalytic epoxidation of α-ylideneoxindoles with a terminal ester substituent to obtain spiro-oxirane.[1k] Very recently, the Xiao group reported an asymmetric synthesis of epoxyoxindoles by employing chiral sulfur ylides generated in situ from camphor-derived sulfonium salts.[1b] Nevertheless, highly enantioselective synthesis of a series of benzoyl-substituted targets remains elusive.[1d] The catalytic asymmetric Darzens reaction[5] between phenacyl bromide and isatins gives a straightforward route to benzoyl-substituted spiro-oxirane-oxindoles.

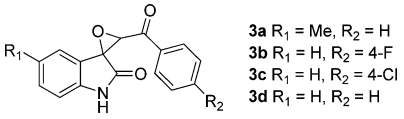


Figure 1. Representative biologically active benzoyl-substituted spiro-epoxyoxindoles.

The catalytic asymmetric Darzens reaction continues to be a challenge among tremendously developed asymmetric transformations. It may be due to the conflict demand of electronic properties of nucleophilic species between enolization and the ring-closure step under basic conditions, for which the electron-withdrawing group can facilitate the enolization and the electron-donor group is in favor of the cyclization step.[6] On the other hand, ketones were less used as electrophiles in the asymmetric Darzens reaction because the steric hindrance of the substrates might hamper both the nucleophilic addition and the ring-closure step.[7] Additionally, competitive reactions, retro-aldol processes, as well as epimerization of the halohydrin intermediate under strong basic conditions have prevented the development of the highly efficient and enantioselective Darzens reaction.[8] We envisioned that chiral Lewis acids could mediate the first addition process wherein the initial stereochemistry of the reaction is established. The subsequent intramolecular S_N2 reaction step proceeds to give enantiomerically enriched epoxides. Herein, we report the Co(acac)$_2$-*N*,*N*′-dioxide-catalyzed[9] asymmetric Darzens reaction of phenacyl bromides with *N*-methyl-protected isatins. The method allows diastereo- and enantioselective construction of *trans*-spiro-epoxyoxindoles in moderate to good yields and stereoselectivities.

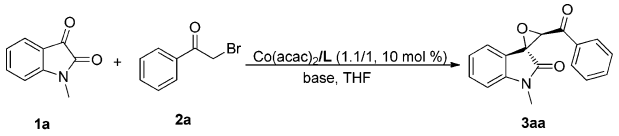
Initially, *N*-methyl-protected isatin **1a** was employed to react with phenacyl bromide to prevent the generation of *N*-alkylated byproduct.[1d] Racemic *trans*-spiro[indoline-3,2′-oxiran]-2-one **3aa** could be exclusively obtained in the K_2CO_3/EtOH system with 99% yield.[10] We commenced the catalytic asymmetric reaction with various metal salts as the catalyst in combination with chiral *N*,*N*′-dioxide ligand **L1** (see Supporting Information for details). It was found that the less expensive metal salt of Co(acac)$_2$ was better in terms of yield, diastereoselectivity, and enantioselectivity than Mg(OTf)$_2$, In(OTf)$_3$, and Ni(Tfacac)$_2$.[10] However, the enantioselective induction was

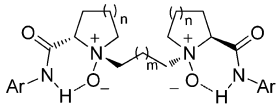
Received: July 4, 2014
Published: August 4, 2014

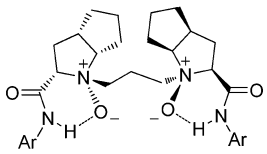
dx.doi.org/10.1021/ol501941n | *Org. Lett.* 2014, 16, 4244−4247

poor (28% ee; Table 1, entry 1). To improve the enantioselectivity, we modified the amide and amino acid backbone of

Table 1. Optimization of the Reaction Conditions[a]







L1 n = 1, m = 1, Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$
L2 n = 1, m = 1, Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
L3 n = 1, m = 0, Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$
L4 n = 2, m = 1, Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

L5 Ar = 2,4,6-^{i}Pr$_3$C$_6$H$_2$

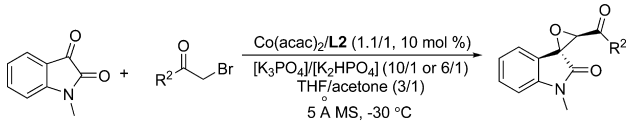
entry	L	base	yield [%][b]	ee [%][c]
1	**L1**	K_2CO_3	89	28
2	**L2**	K_2CO_3	95	37
3	**L3**	K_2CO_3	99	29
4	**L4**	K_2CO_3	82	33
5[d]	**L2**	K_2CO_3	81	40
6[d,e]	**L2**	K_2CO_3	16	85
7[d,e]	**L2**	Cs_2CO_3	49	60
8[d,e]	**L2**	Ag_2CO_3	13	84
9[d,e]	**L2**	^{i}Pr$_2$NEt	18	77
10[d,e]	**L2**	[K_3PO_4]	41	89
11[d−f]	**L2**	[K_3PO_4]/[K_2HPO_4]	20	96
12[d−g]	**L2**	[K_3PO_4]/[K_2HPO_4]	43	94
13[d,e,g,h]	**L2**	[K_3PO_4]/[K_2HPO_4]	60	95

[a]Unless otherwise noted, reactions were performed with **1a** (0.1 mmol), **2a** (0.11 mmol), and base (0.1 mmol) in THF (0.2 mL) at 30 °C for 24 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase (chiralcel IB). [d]5 Å MS (30 mg) was added. [e]At −30 °C for 48 h. [f][K_2HPO_4] (0.01 mmol) was added. [g]The mixed solvent THF/acetone (3/1, 0.2 mL) was used. [h][K_3PO_4] (0.06 mmol)/[K_2HPO_4] (0.01 mmol) was added. After 2 days, [K_3PO_4] (0.04 mmol) was added and the mixture stirred continuously for 4 h. [K_3PO_4] = $K_3PO_4{\cdot}7H_2O$; [K_2HPO_4] = $K_2HPO_4{\cdot}3H_2O$.

the *N*,*N*′-dioxide ligand. It showed that the backbone of *N*,*N*′-dioxide greatly affected the enantioselectivity of the reaction (Table 1, entries 1−4). In the presence of $Co(acac)_2$ and ligand **L2** derived from L-proline and 2,4,6-^{i}Pr$_3$aniline, the desired product could be given in 37% ee with 95% yield (Table 1, entry 2). The addition of 5 Å molecular sieves (MS) enhanced the enantiomeric excess to 40% (Table 1, entry 5). To minimize base-mediated background reaction, the reaction temperature and various bases were screened (Table 1, entries 6−10). When K_3PO_4 was used instead of K_2CO_3 and the reaction temperature was decreased to −30 °C, Darzens reaction proceeded with maintaining exclusive diastereoselectivity and higher enantioselectivity (89% ee) but delivered the desired product in 41% isolated yield (Table 1, entry 10). When K_2HPO_4 was added to adjust the basicity of the system, the enantioselectivity increased to 96% ee but with decreasing yield (Table 1, entry 11). However, the yield of the reaction increased from 20 to 43% in the presence of a mixed solvent of THF/acetone without obviously compromising the enantioselectivity (Table 1, entry 12 vs entry 11). When basic additive K_3PO_4 was subjected in batch and the reaction time was prolonged, the spiro-epoxyoxindole **3aa** was obtained in 60% yield and 95% ee (Table 1, entry 13). Thus, the optimized condition is $Co(acac)_2$/**L2** (1.1/1, 10 mol %), 5 Å MS (30 mg), and batch addition of K_3PO_4/K_2HPO_4 (10/1, 1.0 equiv) in THF/acetone (3/1) at −30 °C.

With the optimized reaction conditions, we next examined the scope of substituted phenacyl bromides and analogues. As summarized in Table 2, various bromopropanone derivatives

Table 2. Catalytic Asymmetric Darzens Reaction of *N*-Me Isatin (1a) with Substituted *α*-Bromoketones[a]



entry	R^2	3	yield [%][b]	*ee* [%][c]
1	C_6H_5 (**2a**)	**3aa**	60 (80)[d]	95 (95)[d]
2	 (**2b**)	**3ab**	72	85
3	*p*-MeOC_6H_4 (**2c**)	**3ac**	71	82
4	*p*-MeC_6H_4 (**2d**)	**3ad**	78	81
5	*m*-MeC_6H_4 (**2e**)	**3ae**	74	78
6	*p*-FC_6H_4 (**2f**)	**3af**	44	81 (99)[e]
7	*m*-FC_6H_4 (**2g**)	**3ag**	70	70
8	*p*-ClC_6H_4 (**2h**)	**3ah**	73	71
9	*m*-ClC_6H_4 (**2i**)	**3ai**	61	51
10	*o*-ClC_6H_4 (**2j**)	**3aj**	40	47
11[f]	*p*-BrC_6H_4 (**2k**)	**3ak**	68	80
12	*p*-C$F_3C_6H_4$ (**2l**)	**3al**	64	58
13	 (**2m**)	**3am**	45	79
14	 (**2n**)	**3an**	35	81
15	^{i}Pr (**2o**)	**3ao**	35	78
16	^{t}Bu (**2p**)	**3ap**	90	78
17	1-adamyl (**2q**)	**3aq**	81	80

[a]Unless otherwise noted, reactions were performed with **1a** (0.1 mmol), **2** (0.11 mmol), $Co(acac)_2$/**L2** (1.1/1, 10 mol %), 5 Å MS (30 mg), and [K_3PO_4]/[K_2HPO_4] (10/1, 0.10 mmol; 6/1, 0.06 mmol) in THF/acetone (3/1, 0.2 mL) at −30 °C for 48−72 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. [d]Data in parentheses were obtained from ligand **L5** instead of **L2**. [e]Data in parentheses were obtained after recrystallization. [f]Absolute configuration of **3ak** was determined to be (2′*R*,3′*R*) by X-ray crystallographic analysis.

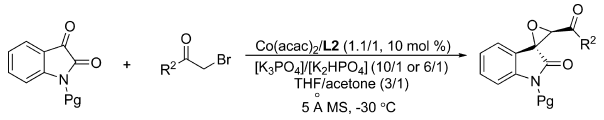
smoothly reacted with *N*-methyl isatin **1a** to afford the corresponding *trans*-spiro-epoxyoxindoles in moderated to good results (47−85% ee). The substituent on phenacyl group had a great effect on both the reactivity and the enantioselectivity. The *para*-substituted one was a better candidate than the *meta*- and *ortho*-substituted ones (Table 2, entries 8−10). Electron-donating groups were prior to electron-withdrawing groups (Table 2, entries 2−5 vs 6−12). Besides, 2-thiophenyl- and 2-naphthyl-substituted bromopropanones produced the epoxylated targets in moderate enantioselectivities, albeit in lower yields (Table 2, entries 13 and 14). It should be noted that the strategy could also be extended to aliphatic-substituted *α*-bromoketones, which afforded the corresponding products with good yields and moderate ee values (Table 2, entries 15−17). Additionally, an improved result (95% ee and 80% yield) was observed when the reaction

dx.doi.org/10.1021/ol501941n | *Org. Lett.* 2014, 16, 4244−4247

of isatin **1a** and phenacyl bromide **2a** was performed with the cobalt complex of *N*,*N*′-dioxide **L5** (Table 2, entry 1, data in parentheses), but it is not good for the other substrates compared with **L2**. Moreover, the absolute configuration of the product **3ak** was determined to be (2′*R*,3′*R*) by X-ray crystallographic analysis[11] (Scheme 2). The others exhibited a similar Cotton effect in their CD spectras.[10] The reaction can be carried out on a gram scale with higher yield and slightly decreased enantioselectivity, and optically active **3af** could be achieved by recrystallization (99% ee).[10]

Next, we evaluated the effect of altering the *N*-protecting group of isatins and the substituent on phenacyl bromide (Table 3, entries 1−6). The enantioselectivity of the reaction

Table 3. Scope of *N*-Protecting Groups of Isatins[a]



entry	Pg	2	3	yield [%][b]	ee [%][c]
1	Et (**1b**)	**2b**	**3bb**	64	89
2	Et (**1b**)	**2a**	**3ba**	18	81
3	^{i}Pr (**1c**)	**2b**	**3cb**	60	89
4	^{i}Pr (**1c**)	**2a**	**3ca**	24	78
5	Mom (**1d**)	**2b**	**3db**	54	81
6	Bn (**1e**)	**2b**	**3eb**	69	73

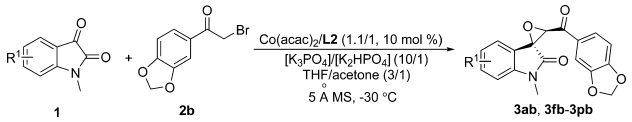
[a]Unless otherwise noted, reactions were performed with **1** (0.1 mmol), **2a** or **2b** (0.11 mmol), 5 Å MS (30 mg), Co(acac)$_2$/**L2** (1.1/1, 10 mol %), and [K_3PO_4]/[K_2HPO_4] (10/1, 1.0 equiv) in THF/acetone (3/1, 0.2 mL) at −30 °C for 72 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. Mom = methoxy methyl.

was obviously affected by the *N*-substituent of isatin, and the sterically hindered group diminished the ee value (Table 3, entries 2 and 4). However, *N*-Mom- and *N*-Bn-substituted isatins, which could easily be removed, also obtained moderate yields and ee values (Table 3, entries 5 and 6). When we compared the data in entries 1−4, it showed that the electron-donating 3,4-dioxylmethene-substituted group at the phenacyl bromide displayed better results in terms of both yield and ee.

The chiral *N*,*N*′-dioxide cobalt(II)-catalyzed Darzens reaction was further applied to a range of substituted isatins. 5-Substituted isatins could be readily transformed into the desired spiro-epoxyoxindoles in obviously high yields (92−99%), but the enantioselectivities decreased significantly (Table 4, entries 2−4). The corresponding products of 6- or 7-substituted isatins could be obtained in relatively higher ee values under optimal conditions (Table 4, entries 5−9 vs 2−4). Benzoindole-2,3-dione **1p** and its analogue **1o** could be converted to the desired spiro-epoxides in moderate enantioselectivities (67% ee; Table 4, entries 11 and 12).

To elucidate the varied yield and enantioselectivity of the reactions, an intermediate of the aldol reaction, **4a**, was isolated from the standard procedure for preparation of **3aa** (Table 1, entry 13). Unfortunately, enantioselectivity of bromohydrin **4a** could not be determined as a result of the instability under HPLC analysis conditions. The diastereomeric ratio of intermediate **4a** was determined to be 5:1 by ^{1}H NMR spectroscopy. The relative configuration of the major diastereomer was defined as (*S*′,*S*′) by X-ray crystallographic

Table 4. Catalytic Asymmetric Darzens Reaction of Substituted *N*-Me Isatin 1[a]

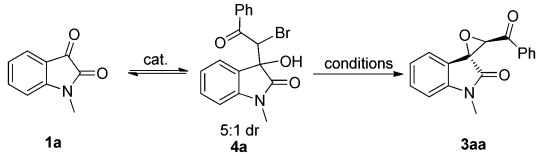


entry	R^1	3	yield [%][b]	*ee* [%][c]
1	H (**1a**)	**3ab**	72	85
2	5-MeO (**1f**)	**3fb**	99	74
3	5-Me (**1g**)	**3gb**	92	67
4	5-F (**1h**)	**3hb**	99	55
5	6-Br (**1i**)	**3ib**	55	77
6	7-F (**1j**)	**3jb**	77	73
7	7-Cl (**1k**)	**3kb**	55	70
8	7-Br (**1l**)	**3lb**	55	81
9	7-Me (**1m**)	**3mb**	78	78
10	5,7-Me$_2$ (**1n**)	**3nb**	80	55
11	 (**1o**)	**3ob**	96	67
12	 (**1p**)	**3pb**	66	67

[a]The reactions were performed with **1** (0.1 mmol), **2b** (0.11 mmol), 5 Å MS (30 mg), Co(acac)$_2$/**L2** (1.1/1, 10 mol %), and [K_3PO_4]/[K_2HPO_4] (10/1, 1.0 equiv) in THF/acetone (3/1, 0.2 mL) at −30 °C for 72 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

analysis,[11] which could be converted to the desired *trans*-spiro-epoxyoxindole through the S_N2 reaction (Scheme 2). Subsequently, we carried out the cyclization reaction from isolated bromohydrin intermediates of an asymmetric catalytic reaction (Scheme 1). Upon addition of TBAF, spiro-epoxide

Scheme 1. Control Experiments from Bromohydrin



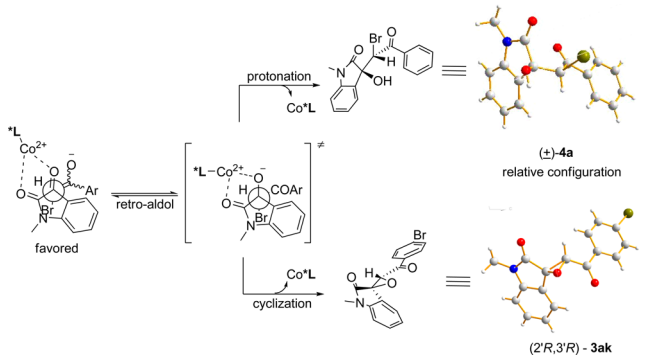
4a	condition	3aa
(-)-4a	TBAF (1N in THF, 1.0 equiv), rt, 30 min	99% yield, 57% *ee*
(-)-4a	**L2**/Co(II) (10 mol %), [K_3PO_4]/[K_2HPO_4], -30 °C	54% yield, 91% *ee*
(±)-4a	**L2**/Co(II) (10 mol %), [K_3PO_4]/[K_2HPO_4], -30 °C	78% yield, 8% *ee*

3aa was obtained in complete conversion and 57% ee. When bromohydrin **4a** was resubjected into the asymmetric catalytic system, product **3aa** was obtained in 91% ee and only 54% yield, accompanying the detection of **1a**. It was in keeping with the facts that bromohydrin **4** and isatin **1** existed in the most catalytic reaction (Tables 2−4). The comparison implied that epimerization happened in the presence of TBAF, and a retro-aldol process accompanied the ring-closure process, which might account for the moderate yield achieved in most asymmetric catalytic cases. Furthermore, if racemic bromohydrin generated from the non-asymmetric catalyzed reaction was employed under the optimal condition, the epoxide was obtained in 78% yield and only 8% ee. It turned out that the enantiocontrol step of this Darzens reaction was the initial nucleophilic addition.

Based on the above observations, a plausible induction model is proposed (Scheme 2). First, the chiral *N*,*N*′-dioxide ligand was chelated with the cobalt(II) precursor to form the chiral catalytic species.[9] Isatin **1a** coordinated with the metal in a

dx.doi.org/10.1021/ol501941n | *Org. Lett.* 2014, 16, 4244−4247

Scheme 2. Possible Induction Model and X-ray Structure of the Bromohydrin Intermediate 4a and Spiro-epoxyoxindole 3ak



bidentate manner. The addition of an enolate (*Z* or *E*) generated from phenacyl bromide with its *Si*-face preferably attacked the *Re*-face of isatin to form the (*S*,*S*)-bromohydrin which could be identified after protonation. After cyclization, the desired (2′*R*,3′*R*)-spiro-epoxyoxindole was released.

In summary, we have addressed a catalytic asymmetric synthesis of benzoyl-substituted spiro-epoxyoxindoles based on the Darzens reaction between phenacyl bromides and *N*-protected isatins. A diverse range of spiro-epoxyoxindoles were prepared with moderate to good results. Benzoyl-substituted spiro-epoxyoxindoles **3aa** and **3af**, which can be used as potential antifungal and antitubercular agents, were obtained in high optical purity. Studies of the mechanism illustrated that the chiral control step was the aldol addition step. The occurrence of a retro-aldol process stunted the efficient generation of epoxide products to some extent. Further improvement of the efficiency of the related reaction is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xmfeng@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21321061, 21290182, and 21172151), the Ministry of Education (20110181130014), and the Basic Research Program of China (973 Program: 2010CB833300) for financial support.

■ REFERENCES

(1) (a) Zhu, Y. G.; Wang, Q.; Cornwall, R. G.; Shi, Y. A. *Chem. Rev.* **2014**, DOI: 10.1021/cr500064w. (b) Boucherif, A.; Yang, Q. Q.; Wang, Q.; Chen, J. R.; Lu, L. Q.; Xiao, W. J. *J. Org. Chem.* **2014**, *79*, 3924. (c) Cheng, D. J.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal.* **2014**, *4*, 743. (d) Fu, Q.; Yan, C. G. *Beilstein J. Org. Chem.* **2013**, *9*, 918. (e) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (f) Muthusamy, S.; Karikalan, T. *Tetrahedron* **2012**, *68*, 1443. (g) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (h) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (i) Shmidt, M. S.; Perillo, I. A.; González, M.; Blanco, M. M. *Tetrahedron Lett.* **2012**, *53*, 2514. (j) Gasperi, T.; Loreto, M. A.; Migliorini, A.; Ventura, C. *Eur. J. Org. Chem.* **2011**, 385. (k) Palumbo, C.; Mazzeo, G.; Mazziotta, A.; Gambacorta, A.; Loreto, M. A.; Migliorini, A.; Superchi, S.; Tofani, D.; Gasperi, T. *Org. Lett.* **2011**, *13*, 6248. (l) Dandia, A.; Singh, R.; Bhaskaran, S. *Ultrason. Sonochem.* **2011**, *18*, 1113. (m) Muthusamy, S.; Karikalan, T.; Suresh, E. *Tetrahedron Lett.* **2011**, *52*, 1934. (n) Muthusamy, S.; Ramkumar, R.; Mishra, A. K. *Tetrahedron Lett.* **2011**, *52*, 148. (o) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Disc.* **2010**, *13*, 758. (p) Schulz, V.; Davoust, M.; Lemarié, M.; Lohier, J. F.; Santos, J. S. D.; Metzner, P.; Brière, J. F. *Org. Lett.* **2007**, *9*, 1745. (q) Kikumoto, R.; Kobayashi, T. *Tetrahedron* **1966**, 3337.

(2) Dandia, A.; Singh, R.; Saha, M.; Shivpuri, A. *Pharmazie* **2002**, *57*, 602.

(3) Marx, K. A.; O'Neil, P.; Hoffman, P.; Ujwal, M. L. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 1652.

(4) Chu, Y. Y.; Liu, X. H.; Li, W.; Hu, X. L.; Lin, L. L.; Feng, X. M. *Chem. Sci.* **2012**, *3*, 1996.

(5) Selected examples of catalytic asymmetric Darzens reaction to aldehyde: (a) Bakó, P.; Rapi, Z.; Keglevich, G. *Curr. Org. Synth.* **2014**, *11*, 361. (b) Novacek, J.; Waser, M. *Eur. J. Org. Chem.* **2013**, 637. (c) Liu, Y.; Provencher, B. A.; Bartelson, K. J.; Deng, L. *Chem. Sci.* **2011**, *2*, 1301. (d) Watanabe, S.; Hasebe, R.; Ouchi, J.; Nagasawa, H.; Kataoka, T. *Tetrahedron Lett.* **2010**, *51*, 5778. (e) He, L.; Liu, W. J.; Ren, L.; Lei, T.; Gong, L. Z. *Adv. Synth. Catal.* **2010**, *352*, 1123. (f) Liu, W. J.; Lv, B. D.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 6503. (g) Albanese, D. *Mini-Rev. Org. Chem.* **2006**, *3*, 195. (h) Li, L.; Zhang, Z. P.; Zhu, X. X.; Popa, A.; Wang, S. W. *Synlett* **2005**, 1873. (i) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J. C.; Cahard, D. *Synthesis-Stuttgart* **2001**, 1742.

(6) Bruckner, R. In *Organic Mechanisms Reactions, Stereochemistry and Synthesis*; Harmata, M., Ed.; Springer: Berlin, 2010, Vol. 2, pp 53−101.

(7) Examples of chiral auxiliary in asymmetric Darzens reaction to ketone: (a) Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. *J. Org. Chem.* **2000**, *65*, 9007. (b) Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. *Chem. Commun.* **1996**, 2411.

(8) Giubellina, N.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 5881.

(9) Selected examples of *N*,*N*′-dioxides in catalytic asymmetric reactions: (a) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574. (b) Liu, X. H.; Lin, L. L.; Feng, X. M. *Org. Chem. Front.* **2014**, *1*, 298. (c) Zheng, K.; Lin, L. L.; Feng, X. M. *Acta Chim. Sinica* **2012**, *70*, 1785. (d) Li, W.; Liu, X. H.; Hao, X. Y.; Cai, Y. F.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8644. (e) Zheng, K.; Yin, C. K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573.

(10) For more details, see the Supporting Information.

(11) CCDC 1006835 (**3ak**) and CCDC 1006842 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_requst/cif.