Title: Stereoselective synthesis of highly-congested tetralin-fused spirooxindoles with hydroxyl group: net oxygen atom induced hydride shift/cyclization process

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Abstract

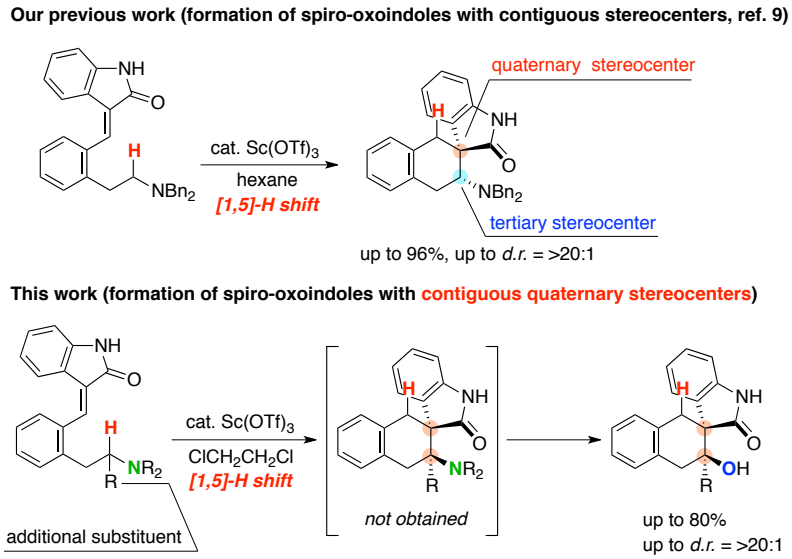
Highly stereoselective synthesis of tetralin-fused spirooxindoles with two contiguous stereogenic centers. In the present reaction, not only [1,5]-hydride shift/cyclization process, but also replacemnt of nitrogen atom to oxygen atom ocurred smoothly to give target structure with hydroxy grop in good chemical yields with good to excellent diastereoselectivities (up to *d.r.* = >20:1). Investigation of the reaction mechanism suggested that this "atom-replacement" event ocurred via the iminium cation intermediates.

Main text

Hybrid molecule, which contains two or more number of pharmacore, is an important class of compound in the pharmaceutical and agrochemical fields. Because of the significant improvement of biological activity compared to the compound with single pharmacore and their structural complexity, much effort has been devoted to the development of synthetic method.[1] Among the hybrid compounds, spirooxindoles having tetralin core is expected to be an useful organic molecules because each structure itself exhibits potent biological activities.[2-4] But surprisingly, the efficient method leading to this class of skeleton was quite limited.[5-8] In this context, we recently reported the highly diastereoselective synthesis of tetralin-fused spirooxindoles with two contiguous (quaternary/tertiary) stereogenic centers via hydride shift triggered C(sp^3)–H bond functionalization (internal redox reaction, upper part of Scheme 1).[9–15] Application of the

construction of related structure with two contiguous quaternary stereogenic centers is not a trivial issue from the following two viewpoints: (1) difficulty of the stereoselective construction of fused-structure with two contiguous quaternary stereogenic centers, and (2) their potent biological activity.

Herein we report the realization of the target reaction (lower part of Scheme 1). Interestingly, the replacement of nitrogen atom to oxygen atom in the target structure with two contiguous quaternary stereogenic centers could be accomplished under the optimized reaction conditions, and corresponding adducts were obtained in good chemical yields with excellent diastereoselectivities (up to *d.r.* = >20:1). This transformation realized net oxygen atom induced hydride shift/cyclization process, which is sometimes difficult in the substrate with low reactive electrophilic portion.



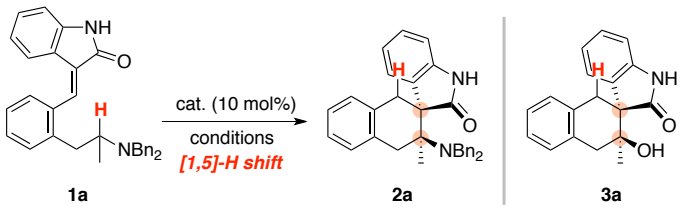
Scheme 1. Stereoselective synthesis of tetralin-fused spirooxindoles with two contiguous quoternaty stereoters.

First trial was conducted with **1a** having methyl-group adjacent to nitrogen atom (Table 1). When **1a** was treated with 10 mol% of $Sc(OTf)_3$ in $ClCH_2CH_2Cl$ at 50 °C, starting material **1a** was mostly consumed after 12 h. But surprisingly, the resulting product was not the desired adduct **2a**, but tertiary alcohol **3a**, whose structure was determined by X-ray analysis (57%, entry 1).[16] This unexpected result is quite impressive for us. One of the limitation of the internal redox reaction, especially using benzylidene oxindole as a

substrate,[9,12] is the requirement of nitrogen atom; that is, high electron donating ability of nitrogen was essential to promote the key hydride shift process, and the reaction with corresponding oxygen analogue did not proceed completely. From this viewpoint, the present reaction realized the net oxygen atom induced hydride shift/cyclization process, and hence, would open the new door of the related reaction. Stimulated by this result, our attention turned to tertiary alcohol **3a** as a target. Further studies suggested that $Sc(OTf)_3$ was the catalyst of choice. Although $Yb(OTf)_3$ and $Gd(OTf)_3$ also promoted the reaction, the chemical yields reached only low level (entries 2 and 3). Same situation hold for other catalysts such as $Mg(OTf)_2$, $Zn(OTf)_2$, $Al(OTf)_3$, and BF_3•OEt_2 (entries 4–7).

Solvent screening offered promising information for improving the chemical yield. Although the starting material **1a** was mostly consumed in CH_2Cl_2 as in the case of $ClCH_2CH_2Cl$, amine product **2a** was solely observed (ca. 70%, entry 8). This result was specific in CH_2Cl_2, *i.e.*, the reaction in CH_3CN resulted in exclusive formation of **3a** (58%, entry 9), and the reaction did not proceed when MeOH and Benzene were employed (entries 10 and 11). Synthesis of alcohol **3a** was also possible even in the CH_2Cl_2 by the additional heating for 3 h in the presence of H_2O (solvent amount) after the formation of amine **2a**. Gratifyingly, the chemical yield of **3a** was significantly improved to 80% (entry 12). Scale-up reaction was also attainable in this sequential system in CH_2Cl_2, and satisfactory chemical yield (71%) was achieved (entry 13).

Table 1. Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Catalyst	Solvent	Yield/ %[b]	
			3a	**2a**[c]
1	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	52 (>20:1)	0
2	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	4 (>20:1)	0 (80)
3	$Gd(OTf)_3$	$ClCH_2CH_2Cl$	16 (>20:1)	0 (65)

4	$Mg(OTf)_2$	$ClCH_2CH_2Cl$	26 (>20:1)	0 (74)
5	$Zn(OTf)_2$	$ClCH_2CH_2Cl$	trace	0 (98)
6	$Al(OTf)_3$	$ClCH_2CH_2Cl$	18 (>20:1)	0 (63)
7	BF_3•OEt_2	$ClCH_2CH_2Cl$	5 (>20:1)	0 (73)
8	$Sc(OTf)_3$	CH_2Cl_2	0	ca. 70 (0)
9	$Sc(OTf)_3$	CH_3CN	58 (>20:1)	0 (30)
10	$Sc(OTf)_3$	MeOH	0	0 (98)
11	$Sc(OTf)_3$	Benzene	8 (>20:1)	0 (62)
12[d]	$Sc(OTf)_3$	CH_2Cl_2	80 (>20:1)	0 (0)
13[e]	$Sc(OTf)_3$	CH_2Cl_2	72 (>20:1)	0 (0)

[a] Unless otherwise noted, all reactions were conducted with 0.10 mmol of 1a in the presence of an acid catalyst (10 mol %) in solvent (1.0 mL) at 50 °C. [b] Isolated yield. [c] Recovery of 1a was shown in parenthesis. [d] H_2O (1.0 mL, solvent amount) was added after 12 h, then heated for 3 h at refluxing temperature. [e] 2.53 mmol scale.

Figure 1 shows the plausible mechanism of the present reaction. At first, [1,5]-H shift/cyclization process proceeds to give NBn_2-substituted compound **2a**. Importantly, because of the high electron donating ability of nitrogen atom, there is ring opening/closing equilibrium between **2a** and **A**. After above events, two pathways could be assumed for the formation of **3a**: (1) hydrolysis of iminium species **A** to ketone moiety **B** followed by the intramolecular aldol reaction (path I), and (2) acid induced liberation of NBn_2 group followed by the nucleophilic addition of H_2O to the resulting tertiary carbocation **D** (path II). By considering the chelation model **C** and hydrogen bonded transition state structure **E**, stereochemical outcome could be well rationalized in both cases. As for the high stereoselectivity, thermodynamic control after the hydrolysis (interconversion between **3a** and **3a'**) was another possible phenomena.

To gain insight into the reaction mechanism, some additional experiments were conducted (Figure 2). When NBn_2-substituted spirocompound **2a** was treated with 10 equiv. of $NaBH_4$ in the presence of 10 mol% of $Sc(OTf)_3$, tertiary amine **4** and secondary alcohol **5** were detected (60% combined yield), and alkane-type product **6** was not obtained at all. This result strongly suggests that path I would be a main pathway. Subjection of

the each diastereomers **3c** and **3c'** to the reaction conditions (10 mol% of $Sc(OTf)_3$, $ClCH_2CH_2Cl$, 50 °C) resulted in no production of another diastereomer, which implies the stereochemistry is determined in kinetically.

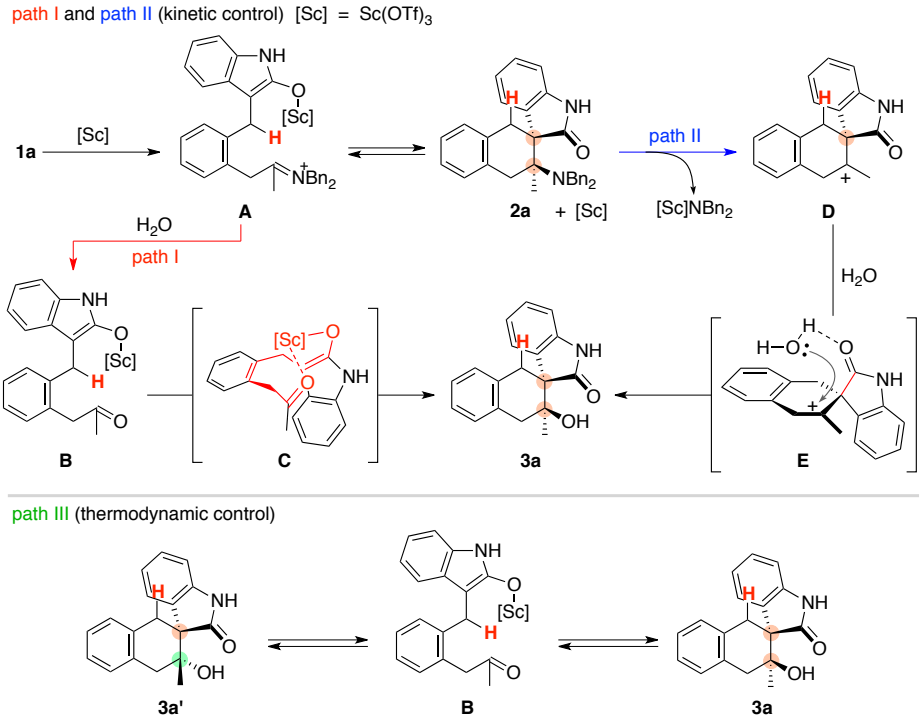


Figure 1. Possible reaction mechanisms.

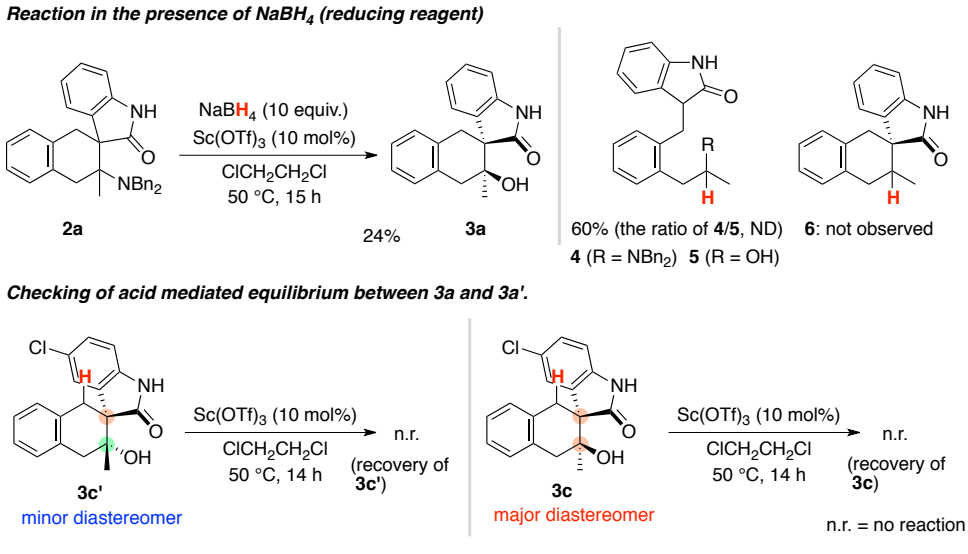


Figure 2. Additional experiments for clarification of the mechanism.

Having the optimal reaction conditions and reaction mechanism, substrate scope was examined (Figure 3). This reaction was applicable to various substituted-oxindole moieties, and corresponding adducts **3a–c** were obtained in good chemical yields with good to excellent diastereoselectivities (up to 80%, *d.r.* = >20:1). Further studies revealed that the substituent effect on mother aromatic ring was almost negligible. Tetralin-fused spirooxindoles **3d–h** having electron donating groups (methyl and methoxy) and electron withdrawing group (fluoro), and naphthyl-type product **3i** were obtained good chemical yields and diastereoselectivities (45–69%, *d.r.* = 7.7–>20:1).

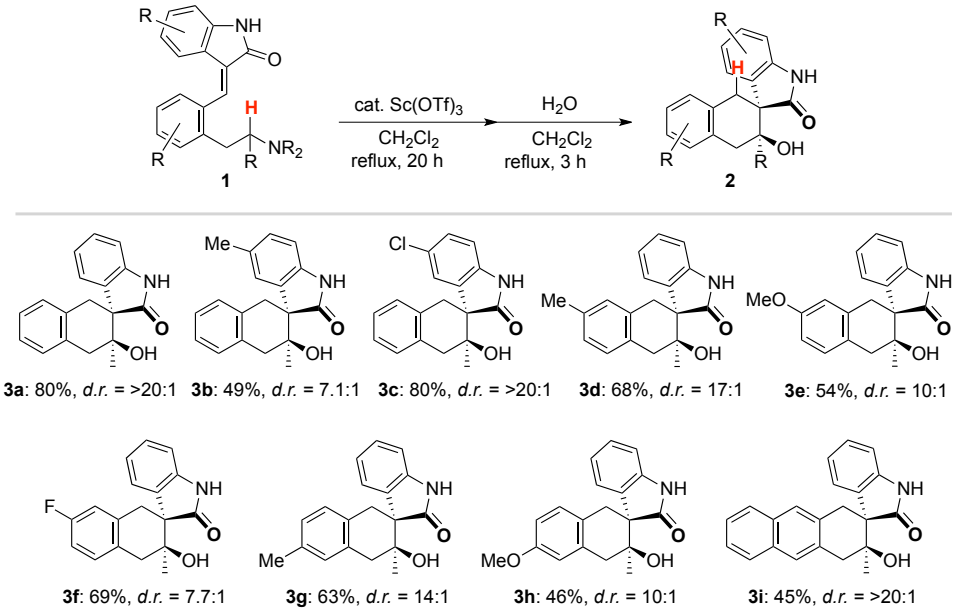


Figure 3. Substrate cope.

In summary, we developed the highly diastereoselective synthesis of tetralin-fused spirooxindoles with two contiguous quaternary stereogenic centers via hydride shift triggered C(sp^3)–H bond functionalization. The unique feature of the present reaction is the replacement of nitrogen atom to oxygen atom. Some additional experiments revealed that this replacement occurred in the meanwhile ring-opening/closing equilibrium. Furthers studies of this "atom-replacement" strategy for the construction of another hybrid structure is under way in our laboratory.

Acknowledgments

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References and notes

1. Some reviews on hybrid-type natural products, see: (a) K. C. Nicolaou, C. R. H. Hale, C. Nilewski, H. A. Loannidou, *Chem. Soc. Rev.* **2012**, *41*, 5185; (b) K. Kitamura, Y. Ando, T. Matsumoto, K. Suzuki, *Chem. Rev.* **2018**, *118*, 1495; (c) K. Ma, B. S. Martin, X. Yin, M. Dai, *Nat. Prod. Rep.* **2019**, *36*, 174; (d) L. A. Morrill, R. B. Susick, J. V. Chari, N. K. Garg, *J. Am. Chem. Soc.* **2019**, *141*, 12423; (e) Y.-J. Hu, L.-X. Li, J. C. Han, L. Min, C.-C. Li, *Chem. Rev.* **2020**, *120*, 5910.
2. For recent reviews on the synthesis of spirooxindoles, see: (a) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.,* **2007**, *46*, 8748; (b) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; (c) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381. d) N. R. Ball-Jones, J. J. Badillo A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; (e) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023; (f) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743.
3. (a) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H. P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler, T. T. Diagana, *Science*, **2010**, *329*, 1175; (b) S. Y. Leong, P. W. Smith, B. Zou, *Chin. J. Chem.* **2014**, *32*, 1217; (c) S. Wang, W. Sun, Y. Zhao, D. McEachern, I. Meaux, C. Barrière, J. A. Stuckey, J. L. Meagher, L. Bai, L. Liu, C. G. Hoffman-Luca, J. Lu, S. Shangary, S. Yu, D. Bernard, A. Aguilar, O. Dos-Santos, L. Besret, S. Guerif, P. Pannier, D. Gorge-Bernat, L. Debussche, *Cancer Res.* **2014**, *74*, 5855.
4. For some natural products and pharmaceuticals containing tetralin scaffold, see: (a) O. Pinto, J. Sardinha, P. D. Vaz, F. Piedade, M. J. Calhorda, R. Abramovitch, N. Nazareth, M. Pinto, M. S. J. Nascimento, A. P. Rauter, *J. Med. Chem.* **2011**, *54*, 3175; (b) M. Kvasnica, L. Rarova, J. Oklestkova, M. Budesinsky L. Kohout, *Bioorg. Med. Chem.* **2012**, *20*, 6969; (c) J. H. Soper, S. Sugiyama, K. Herbst-Robinson, M. J. James, X. Wang, J. Q. Trojanowski, A. B. Smith III, V. M. Y. Lee, C. Ballatore, K. R. Brunden, *ACS Chem. Neurosci.* **2012**, *3*, 928; (d) M. J. Hatfield, L. G. Tsurkan, J. L. Hyatt, C. C.

Edwards, A. Lemoff, C. Jeffries, B. Yan, P. M. Potter, *J. Nat. Prod.* **2013**, *76*, 36; (e) Gamal-Eldeen, M.; Hamdy, N. A.; Abdel-Aziz, H. A.; El-Hussieny, E. A.; Fakhr, I. M. I. *Eur. J. Med. Chem.* **2014**, *77*, 323.

5. F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* **2014**, *53*, 2628.
6. B. Wang, H.-J. Leng, X.-Y. Yang, B. Han, C.-L. Rao, L. Liu, C. Peng, W. Huang, *RSC. Adv.* **2015**, *8*, 88272.
7. H.-R. Wu, L. Cheng, D.-L. Kong, H.-Y. Huang, C.-L. Gu, L. Liu, D. Li, Wang, C.-J.. *Org. Lett.* **2016**, *18*, 1382.
8. K. Lokesh, V. Kesavan, *Eur. J. Org. Chem.* **2017**, 5689.
9. M. Machida, K. Mori, *Chem. Lett.* **2018**, *47*, 868
10. For the internal redox reaction developed by our group, see: (a) K. Mori, Y. Ohshima, K. Ehara, T. Akiyama, *Chem. Lett.* **2009**, *38*, 524; (b) K. Mori, T. Kawasaki, S. Sueoka, T. Akiyama, *Org. Lett.* **2010**, *12*, 1732; (c) K. Mori, S. Sueoka, T. Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 2424; (d) K. Mori, S. Sueoka, T. Akiyama, *Chem. Lett.* **2011**, *40*, 1386; (e) K. Mori, K. Ehara, K. Kurihara, T. Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 6166; (f) K. Mori, T. Kawasaki, T. Akiyama, *Org. Lett.* **2012**, *14*, 1436; (g) K. Mori, K. Kurihara, T. Akiyama, *Chem. Commun.* 2014, **50**, 3729; (h) K. Mori, N. Umehara, T. Akiyama, *Adv. Synth. Catal.* **2015**, *357*, 901; (i) T. Yoshida, K. Mori, *Chem. Commun.* **2017**, *53*, 4319; (j) K. Yokoo, K. Mori, *Chem. Commun.* **2018**, 54, 6927; (k) N. Hisano, Y. Kamei, Y. Kansaku, M. Yamanaka, K. Mori, *Org. Lett.* **2018**, *20*, 4223; (l) T. Yoshida, K. Mori, K. *Chem. Commun.* **2018**, 54, 12686; (m) R. Tamura, E. Kitamura, R. Tsutsumi, M. Yamanaka, T. Akiyama, K. Mori, *Org. Lett.* **2019**, *21*, 2383; (n) Y. Otawa, K. Mori, *Chem. Commun.* **2019**, *55*, 13856; (o) K. Yokoo, K. Mori, *Org. Lett.* **2020**, *22*, 244; (p) D. Hoshino, K. Mori, *Org. Bioomol. Chem.* **2020**, *18*, 6602.
11. For the double C(sp^3)–H bond functionalization by sequential utilization of the internal redox reaction developed by our group, see: (a) K. Mori, K. Kurihara, S. Yabe, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2014**, *136*, 3744; (b) K. Mori, N. Umehara, T. Akiyama, *Chem. Sci.* **2018**, *9*, 7327; (c) K. Mori, R. Isogai, Y. Kamei, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2018**, *140*, 6203; (d) M. Kataoka, Y. Otawa, N. Ido, K. Mori, *Org. Lett.* **2019**, *21*, 9334. (e) K. Yokoo, D. Sakai, K. Mori, *Org. Lett.* **2020**, *22*,

5801.

12. For the synthesis of tetrahydroquinoline fused-spirooxindoles by internal redox reaction, see: a) Y.-Y. Han, W.-Y. Han, X. Hou, X.-M. Zhang, W.-C. Yuan. *Org. Lett.* **2012**, *14*, 4054. Asymmetric version, see: b) W. Cao, X. Liu, J. Guo, L. Lin, X. Feng, *Eur. Chem. J.* **2015**, *21*, 1632.
13. For recent reviews on internal redox process, see: (a) M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2006**, *45*, 168; (b) S. C. Pan, *Beilstein J. Org. Chem.* **2012**, *8*, 1374; (c) M. Wang, *ChemCatChem* **2013**, *5*, 1291. d) B. Peng, N. Maulide, *Chem, Eur. J.* **2013**, *19*, 13274; (e) L. Wang, J. Xiao, *Adv. Synth. Catal.* **2014**, *356*, 1137; (f) M. C. Haibach, D. Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5010; (g) S. J. Kwon, D. Y. Kim, *Chem. Rec.* **2016**, *16*, 1191; (h) X.-D. An, J. Xiao, *Org. Chem. Front.* **2021**, *8*, 1364.
14. For selected recent examples of the internal redox reactions, see: (a) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180; (b) S. J. Pastine, D. Sames, *Org. Lett.* **2005**, *7*, 5429; (c) C. Zhang, C. Kanta De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416; (d) K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2009**, 131, 402; (e) K. M. McQuaid, J. Z. Long, D. Sames, *Org. Lett.* **2009**, *11*, 2972; (f) S. Yang, Z. Li, X. Jian, C. He, *Angew. Chem. Int. Ed.* **2009**, *48*, 3999; (g) P. A. Vadola, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 16525; (h) I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 1950; (i) D.-F. Chen, Z.-Y. Han, Y.-P. He, J. Yu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 12307; (j) Y.-Z. Li, M.-L.; Zhao, W.-F. Chang, X. Wen, H. Sun, Q.-L. Xu, *J. Org. Chem.* **2015**, *80*, 9620; (k) K. Eamakumar, T. Maji, J. J. Partridge, J. A. Tunge, *Org. Lett.* **2017**, *19*, 4014; (l) S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu, J. Xiao, *Org. Lett.* **2018**, *20*, 138; (m) S. Wang, X. D. An, S. S. Li, X. Liu, Q. Liu, J. Xiao, *Chem. Commun.* **2018**, *54*, 13833; (n) S.-S. Li, S. Zhu, C. Chen, K. Duan, Q. Liu, J. Xiao, *Org. Lett.* **2019**, *21*, 1058; (o) S. Zhao, X. Wang, P. Wang, G. Wang, W. Xhao, X. Tang, M. Guo, *Org. Lett.* **2019**, *21*, 3990; (p) A. Paul, D. Seidel, *J. Am. Chem. Soc.* **2019**, *141*, 8788; (q) L. Zhou, Y.-B. Shen, X.-D. An, X.-J. Li, S.-S. Li, Q. Liu, J. Xiao, *Org. Lett.* **2019**, *21*, 8543; (r) L. Zhou, X.-D. An, S. Yang, X.-J. Li, C.-L. Shao, Q. Liu, J. Xiao, *Org. Lett.* **2020**, *22*, 776; (s) K. Duan, X.-D. An, L.-F. Li, L.-L. Sun, B. Qiu, X.-J. Li, C.-L. Shao, Q. Liu, J.

Xiao, *Org. Lett.* **2020**, *22*, 2537.

15. For examples of the enantioselective internal redox reactions, see: (a) S. Murarka, I. Deb, C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226; (b) Y. K. Kang, S. M. Kim, D. Y. Kim, *J. Am. Chem. Soc.* **2010**, *132*, 11847; (c) W. Cao, X. Liu, W. Wang, L. Lin, X. Feng, *Org. Lett.* **2011**, *13*, 600; (d) G. Zhou, F. Liu, J. Zhang, *Chem. Eur. J.* **2011**, *17*, 3101; (e) Y.-P. He, Y.-L. Du, S.-W. Luo, L. Z. Gong, *Tetrahedron Lett.* **2011**, *52*, 7064; (f) L. Chen, L. Zhang, Z. Lv, J.-P. Cheng, S. Luo, *Chem. Eur. J.* **2012**, *18*, 8891; (g) Z.-W. Jiao, S.-Y. Zhang, C. He, Y.-Q. Tu, S.-H. Wang, F.-M. Zhang, Y.-Q. Zhang, H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 8811; (h) Y. K. Kang, D. Y. Kim, *Adv. Synth. Catal.* **2013**, *355*, 3131; (i) Y. K. Kang, D. Y. Kim, *Chem. Commun.* **2014**, *50*, 222; (j) C. W. Suh, D. Y. Kim, *Org. Lett.* **2014**, *16*, 5374; (k) W. Cao, X. Liu, J. Guo, L. Lin, X. Feng, *Chem. Eur. J.* **2015**, *21*, 1632. See also, refs 10e and 11c.
16. CCDC-2081088 contains the supplementary crystallographic data of **3a** (See SI for details). This data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request.