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$FeCl_3$-Catalyzed Stereoselective Construction of Spirooxindole Tetrahydroquinolines via Tandem 1,5-Hydride Transfer/Ring Closure

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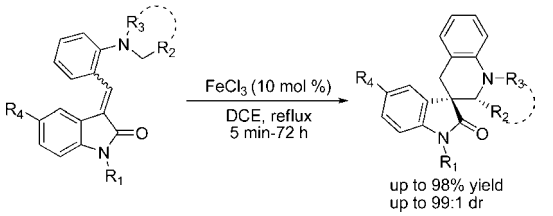
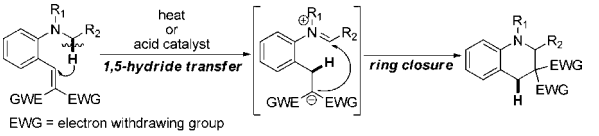
ABSTRACT



An efficient $FeCl_3$-catalyzed stereoselective intramolecular tandem 1,5-hydride transfer/ring closure reaction was developed. The method allows for the formation of structurally diverse spirooxindole tetrahydroquinolines in high yields (up to 98%) with good to excellent levels of diastereoselectivity (up to 99:1 dr). The catalytic enantioselective variant of this process was also investigated preliminarily with a chiral BINOL-derived phosphoric acid.

Because of their highly remarkable biological activities, heterocyclic spiro compounds occupy a key place among the various classes of organic molecules.[1] Particularly, spirocyclic-3,3′-oxindoles have emerged as attractive synthetic targets because of their prevalence in a number of biologically active compounds and natural products.[2] The defined three-dimensional spatial shape of spirooxindoles is an attractive target to complement the flat heterocyclic compounds encountered in many drug discovery programs, since it greatly influences the related biological activity.[2e] In the past few years, many diverse methods to access structure-diversity spirocyclic oxindoles have been reported, including metal-based and organocatalytic methods.[3] Undoubtedly, each of the developed strategies results in a different class of spirocycle that may show promise as biologically active compounds. In this regard, new methods to afford spirocyclic oxindoles

Scheme 1. Functionalization of $C(sp^3)$–H Bond via 1,5-Hydride Transfer/Ring Closure Sequence



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(1) (a) Chen, M.-H.; Pollard, P. P.; Patchett, A. A.; Cheng, K.; Wei, L.; Chan, W. W.-S.; Butler, B.; Jacks, T. M.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1261. (b) Behera, R. K.; Behera, A. K.; Pradhan, R.; Pati, A.; Patra, M. *Synth. Commun.* **2006**, *36*, 3729.

(2) For selected reviews, see: (a) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (e) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (f) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (g) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758. (h) Zhou, F.; Liu, Y. L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. For selected examples, see: (i) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. (j) Shangary, S.; Wang, S. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 223.

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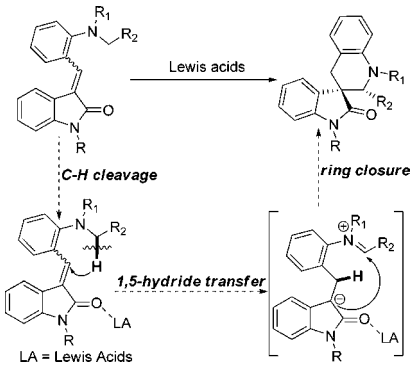
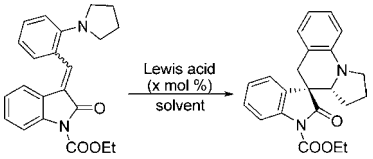
Scheme 2. Plan for the Construction of Spiro[tetrahydroquinoline-3,3′-oxindoles] via 1,5-Hydride Transfer/Ring Closure Sequence



with structural diversity are highly desirable. More important, such methods will probably provide a certain synthetic platform for library-based medicinal evaluation of the spirooxindoles and their analogues. However, to the best of our knowledge, the methodology for the construction of a new class of spirooxindoles in which the oxindole core is fused with a tetrahydroquinoline[4] moiety at the C3-position still remains elusive. Herein, we wish to report a $FeCl_3$-catalyzed protocol for the stereoselective synthesis of spiro[tetrahydroquinoline-3,3′-oxindoles] via a tandem 1,5-hydride transfer and subsequent ring closure reaction.

The functionalization of a C(sp^3)−H bond via intramolecular 1,5-hydride transfer/ring closure sequences (Scheme 1) represents an important and creative goal in synthetic organic chemistry.[5] The intramolecular tandem 1,5-hydride transfer/ring closure sequence (Scheme 1) is characterized by an internal redox process comprising a 1,5-hydride shift from the carbon atom (α to the nitrogen atom) to the electrophilic position of the vinyl group followed by a cyclization.[6] Much effort has been exerted to intensively study this tandem transformation and employ it for the construction of tetrahydroquinoline derivatives.[6] Inspired by these related studies, and as part of our research program on the development of synthetic methods to access various spirocyclic oxindoles,[7,8] we speculated that a methodology, in which the initial cleavage of a C(sp^3)−H bond in the context of a 1,5-hydride transfer and subsequent ring closure utilizing corresponding

Table 1. Evaluation of Various Reaction Conditions[a]



entry	solvent	Lewis acid	x	time (h)	dr[b]	yield (%)[c]
1	DCE	$Cu(OTf)_2$	30	3	91:9	95
2	DCE	$FeCl_3$	30	3	92:8	94
3	DCE	$Sc(OTf)_3$	30	1	91:9	90
4	DCE	$Zn(OTf)_2$	30	48	91:9	87
5	DCE	$Mg(ClO_4)_2$	30	2	91:9	82
6	DCE	$NiCl_2$	30	48	91:9	97
7	DCE	$FeCl_3$	20	4	92:8	94
8	DCE	$FeCl_3$	10	5	93:7	93
9	DCE	$FeCl_3$	5	48	–	trace
10	THF	$FeCl_3$	10	5	–	trace
11	MeCN	$FeCl_3$	10	5	–	trace

[a] Reaction conditions: **1a** (0.11 mmol) in refluxing solvent (2.0 mL) with the catalyst, its loading and the reaction time as indicated. [b] Diastereomeric ratios were determined by ^1H NMR spectra of purified product. Diastereomers were inseparable by column chromatography. [c] Isolated yield.

(3) For selected examples, see: (a) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schurmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735. (b) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (c) Jiang, K.; Jia, Z.-J.; Yin, X.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 2766. (d) Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 2852. (e) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12541. (f) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328. (g) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473. (h) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584. (i) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (j) Lan, Y.-B.; Zhao, H.; Liu, Z.-M.; Liu, G.-G.; Tao, J.-C.; Wang, X.-W. *Org. Lett.* **2011**, *13*, 4866. (k) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (l) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (m) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (n) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354. (o) Liu, Y.-K.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (p) Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas, C. F., III; Zhong, G. *Chem.—Eur. J.* **2012**, *18*, 63.

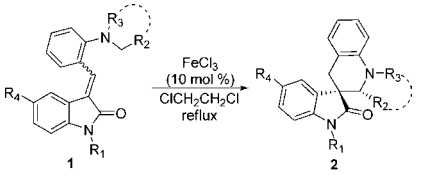
(4) For a leading review on the diverse array of biological activities of tetrahydroquinolines, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(5) For selected reviews, see: (a) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(6) For recent examples on the intramolecular 1,5-hydride transfer/ring closure sequences, see: (a) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (b) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129. (c) Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419. (d) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. (e) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (f) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (g) Yang, S.; Li, Z.; Jian, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999. (h) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (i) Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16626. (j) Mori, K.; Kawasaki, T.; Sueoka, S.; Akiyama, T. *Org. Lett.* **2010**, *12*, 1732. (k) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798. (l) Deb, I.; Seidel, D. *Tetrahedron Lett.* **2010**, *51*, 2945. (m) Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 3543. (n) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593. (o) Haibach, M. C.; Deb, I.; Kanta De, C.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100. (p) Zhang, C.; Das, D.; Seidel, D. *Chem. Sci.* **2011**, *2*, 233. (q) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 2424. (r) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. (s) Mori, K.; Kawasaki, T.; Akiyama, T. *Org. Lett.* **2012**, *14*, 1436. (t) Vadola, P. A.; Carrera, I.; Sames, D. *J. Org. Chem.* **2012**10.1021/jo300635m. (u) Chen, L.; Zhang, L.; Lv, J.; Cheng, J.-P.; Luo, S. *Chem.—Eur. J.* **2012**, *18*, 8891.

(7) (a) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472. (b) Han, Y.-Y.; Chen, W.-B.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490. (c) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132.

Table 2. Scope of the Tandem 1,5-Hydride Transfer/Ring Closure Reaction[a]



entry	1	2	time	dr[b]	yield (%)[c]
1	1b	2b	5 h	97:3	96
2	1c	2c	5 h	91:9	92
3	1d	2d	3 h	91:9	93
4	1e	2e	5 h	91:9	98[d]
5	1f	2f	3 h	91:9	94
6	1g	2g	3 h	86:14	92
7	1h	2h	3 h	91:9	87
8	1i	2i	4 h	91:9	94
9	1j	2j	72 h	99:1	97
10	1k	2k	4.5 h	99:1	90
11	1l	2l	10 h	86:14	93
12	1m	2m	4.5 h	91:9	88
13	1n	2n	1 h	91:9	89
14	1o	2o	20 min	90:10	95
15	1p	2p	30 min	91:9	97
16	1q	2q	5 min	91:9	94
17	1r	2r	5 min	91:9	92

[a] Reaction conditions: **1** (0.33 mmol) and $FeCl_3$ (10 mol %) in $ClCH_2CH_2Cl$ (6.0 mL) at 85 °C for the time as indicated. [b] Diastereomeric ratios were determined by ^1H NMR spectra of purified product. Diastereomers are inseparable by column chromatography. [c] Isolated yield. [d] The structure of product **2e** was characterized by X-ray crystallography.[10]

methyleneindolinone derivatives as substrates and Lewis acids as catalysts, would ultimately lead to the formation of a series of spirooxindole tetrahydroquinolines (Scheme 2). Admittedly, if the above-mentioned strategy was successfully realized, it will provide a highly attractive and convergent approach toward the complex spiro[tetrahydroquinoline-3,3′-oxindole] derivatives.

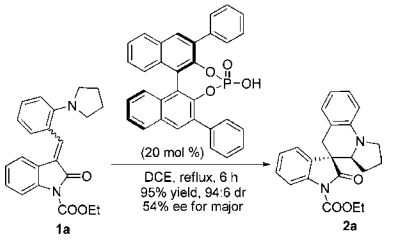
We commenced our investigation with compound **1a** as the substrate in 1,2-dichloroethane (DCE) for the screening of various potential catalysts. As shown in Table 1, with 30 mol % $Cu(OTf)_2$, **1a** could be smoothly converted into the expected product **2a** after 3 h in 95% yield with 91:9 dr (Table 1, entry 1). To our delight, the same reaction could complete even with inexpensive $FeCl_3$ (30 mol %) after 3 h, affording **2a** in 94% yield with 92:8 dr (Table 1, entry 2). Additionally, we found that some other Lewis acids, such as $Sc(OTf)_3$, $Zn(OTf)_2$, $Mg(ClO_4)_2$, and $NiCl_2$, also promoted the transformation of **1a** to **2a** well with acceptable results (Table 1, entries 3–6). Therefore, in light of multiple factors including the price of the catalyst,

(8) (a) Chen, W.-B.; Liao, Y.-H.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Green Chem.* **2009**, *11*, 1465. (b) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, *66*, 1441. (c) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896. (d) Liu, X.-L.; Liao, Y.-H.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2010**, *75*, 4872. (e) Liu, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron Lett.* **2011**, *52*, 903. (f) Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2011**, *76*, 4008. (g) Han, Y.-Y.; Wu, Z.-J.; Chen, W.-B.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 5064. (h) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Chem.—Eur. J.* **2012**, *18*, 6679.

reactivity, and stereoselectivity, we decided to use $FeCl_3$ as the best catalyst for further investigation of other reaction conditions. We were delighted to discover that the reaction could proceed well in the presence of 20 or 10 mol % $FeCl_3$ (Table 1, entries 7–8). Disappointedly, in the presence of 5 mol % $FeCl_3$, only a trace amount of **2a** was obtained after 48 h (Table 1, entry 9). Additionally, a simple survey of solvents revealed that DCE was significantly superior to THF and acetonitrile (Table 1, entry 8 vs entries 10–11). Therefore, these studies provided the optimal reaction conditions: the reaction was conducted with 10 mol % $FeCl_3$ as the catalyst in refluxing DCE.

Having established the optimum reaction conditions, we next examined the scope of the tandem transformation with a series of substrates **1b**–**r** (Table 2).[9] First, an unprotected methyleneindolinone derivative **1b** as substrate was investigated, it was found that the expect intramolecular tandem 1,5-hydride transfer/ring closure process proceeded smoothly, giving the corresponding spirooxindole tetrahydroquinoline **2b** in 96% yield with 97:3 diastereoselectivity ratio (Table 2, entry 1). Substitution on the oxindole aromatic ring was well tolerated regardless of the electronic nature of the substituent, leading to the desired ring-fused spirooxindole tetrahydroquinoline in high yield (92–98%) with high dr values (Table 2, entries 2–4). The exact structure and relative configuration of the major isomer of **2e** was characterized by single-crystal X-ray analysis.[10] Nevertheless, the relative configuration of the major isomer of **2i** could be determined by NOE NMR experiment. Therefore, the relative configurations, not absolute configurations, of the major isomer of other products in this paper were tentatively assigned by analogy. In addition, the reactions with the piperidine derived substrates **1f**–**i** showed very good reactivity and stereoselectivity under the optimal reaction conditions (Table 2, entries 5–8). The related morpholine compound **1j**, with an unprotected oxindole core, also could rearrange efficiently to product **2j** in 97% yield and up to 99:1 dr with a longer reaction time (72 h, Table 2, entry 9). However, some other morpholine-derived substrates **1k**–**m**, with a *N*-ethoxy carbonyl protected oxindole core, participated readily and delivered the corresponding products **2k**–**m** with satisfactory results (Table 2, entries 10–12). We observed the tetrahydroisoquinoline **1n** rapidly rearranged to **2n** under the standard conditions after 1 h in 89% yield with a 91:9 dr (Table 2, entry 13). Gratifyingly, some other substrates **1o**–**r** incorporating tetrahydroisoquinoline into the unprotected oxindole core also smoothly rearranged to the expected products even in no more than 30 min (Table 2, entries 14–17). Moreover, these cases demonstrate that various amine donors, such as pyrrolidine, piperidine, morpholine, and tetrahydroisoquinoline, are well-tolerated (Table 2).

Scheme 3. Catalytic Asymmetric Variant of this Process[a]



[a] The relative configuration of the major isomer of **2a** was determined by NOE NMR,[10] but the absolute configuration was not determined.

We also attempted to develop a catalytic asymmetric version of this process for access to enantioenriched spirooxindole tetrahydroquinolines. After a series of efforts, we found that the use of some chiral ligands[11] in combination with various metal salts, including $FeCl_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $Zn(OTf)_2$, $Mg(ClO_4)_2$, and $NiCl_2$, gives rise to the product **2a** in very poor enantioselectivity (no more than 11% ee; results not shown). However, to our delight, we discovered that a promising result of the catalytic asymmetric process could be obtained by using 20 mol % chiral BINOL-derived phosphoric acid[12] to afford product **2a** in 95% yield with 94:6 dr and 54% ee (Scheme 3).[13] Notably, this example indicates the process is able to be realized without metal.

In conclusion, we have developed a highly stereoselective intramolecular tandem 1,5-hydride transfer/ring closure reaction for the synthesis of a new class of spirocyclic oxindole tetrahydroquinolines using $FeCl_3$ as the catalyst. With this tandem strategy, biologically interesting and structurally diverse spirooxindole tetrahydroquinolines are able to be smoothly obtained in excellent yield (up to 98%) and diastereoselectivity (up to 99:1 dr). A preliminary experiment for the catalytic enantioselective variant of this process with a chiral BINOL-derived phosphoric acid as the catalyst[12] could deliver the corresponding product in 95% yield with 94:6 dr and 54% ee. Efforts to realize the highly enantioselective version of this reaction and use this new methodology to synthesize interesting biologically active compounds are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(9) For the synthesis of substrates **1**, see the Supporting Information.

(10) For details, see the Supporting Information.

(11) Chiral diamine, salen, diphosphine, and bisoxazoline ligands were tested.

(12) For leading reviews of asymmetric catalysis using chiral phosphoric acids, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Terada, M. *Synthesis* **2010**, 1929. (d) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

(13) For the enantiomeric excess analysis of chiral **2a**, see the Supporting Information.