JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

An Asymmetric Synthesis of 1,2,4-Trioxane Anticancer Agents via Desymmetrization of Peroxyquinols through a Brønsted Acid Catalysis Cascade

David M. Rubush,[†] Michelle A. Morges,[‡] Barbara J. Rose,[‡] Douglas H. Thamm,[‡] and Tomislav Rovis[†,*]

[†]Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States
[‡]Animal Cancer Center, Department of Clinical Sciences, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information

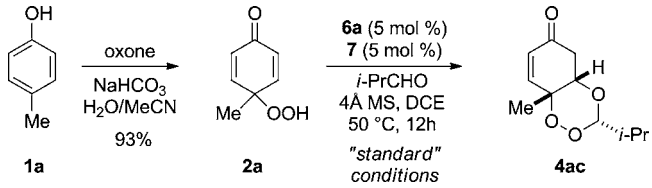
ABSTRACT: The desymmetrization of *p*-peroxyquinols using a Brønsted acid-catalyzed acetalization/oxa-Michael cascade was achieved in high yields and selectivities for a variety of aliphatic and aryl aldehydes. Mechanistic studies suggest that the reaction proceeds through a dynamic kinetic resolution of the peroxy hemiacetal intermediate. The resulting 1,2,4-trioxane products were derivatized and show potent cancer cell-growth inhibition.

Trioxanes are important scaffolds that appear in molecules exhibiting antimalarial, anticancer, and antibacterial activities.[1] In particular, artemisinin, administered as a part of a combination therapy for the frontline treatment of malaria, contains a 1,2,4-trioxane as the key pharmacophore. The recent emergence of an artemisinin-resistant malaria strain[2] combined with the fact that artemisinin's mode of action remains under debate[3] has increased the difficulty of treating malaria and makes the pursuit of novel therapeutic agents more urgent. One potential solution has been the development of new synthetic endoperoxides.[4] Enantiomers of a few synthetic trioxanes have shown similar antimalarial activities,[5] but stereochemistry has a demonstrated impact on anticancer activity.[6] Current methods for the enantioselective synthesis of trioxanes are lengthy and use chiral starting materials or reagents.[5−8]

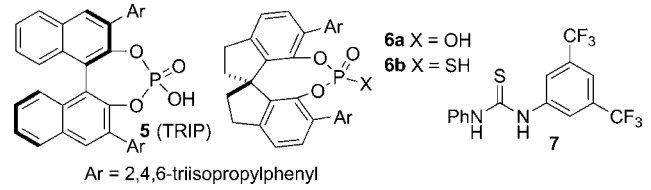
We envisioned that enantioenriched trioxanes could be accessed quickly and enantioselectively through a desymmetrization of *p*-peroxyquinols via an acetalization/oxa-Michael cascade first reported by Jefford.[9,10] Cascade catalysis[11−13] and desymmetrizations[14] are powerful methods utilized by our group and others to construct complex molecules containing multiple stereocenters in a rapid and efficient manner. Both enantioselective acetalization[15] and oxa-Michael[16] reactions are relatively unsolved problems. We were cognizant of the potential difficulties in this approach due to the inherent reversibility of both transformations, particularly under acidic conditions. Nevertheless, we were emboldened by recent successes in this area.[17]

We began our investigation by studying the desymmetrization of *p*-peroxyquinol **2a**, trivially accessed from cresol, using chiral Brønsted acid catalyst **5** (TRIP), which afforded the desired trioxane in good yield as a single diastereomer with 86% ee (Table 1, entry 5). Switching to bis(2,4,6-triisopropylphenyl)spirobiindane phosphoric acid **6a** developed by List[15e,18] improved the enantioselectivity to 96%. Other biindane Brønsted acids were screened, but the parent acid **6a** gave the best results. Lowering the catalyst loading from 10 mol % gave decreased reactivity, which could be restored through the use of thiourea **7** as a cocatalyst. A catalyst loading as low as 2 mol % could be used at the expense of a longer reaction time (Table 1, entry 7). The use of thiourea **7** alone led to no product.

Table 1. Reaction Optimization[a]



entry	variation from "standard" conditions	yield (%)[b]	ee (%)[c]
1	none	92	96
2	no 4 Å MS	90	88
3	no **7**	46	95
4	no **6a**	<5	–
5	10 mol% **5** instead of **6a**, no **7**	93	86
6	no **7**, **6a** (10 mol %)	93	96
7	**6a** (2 mol %), 72 h	88	95
8	**6b** instead of **6a**	65	95
9	23 °C, 48 h instead of 50 °C, 24 h	85	96



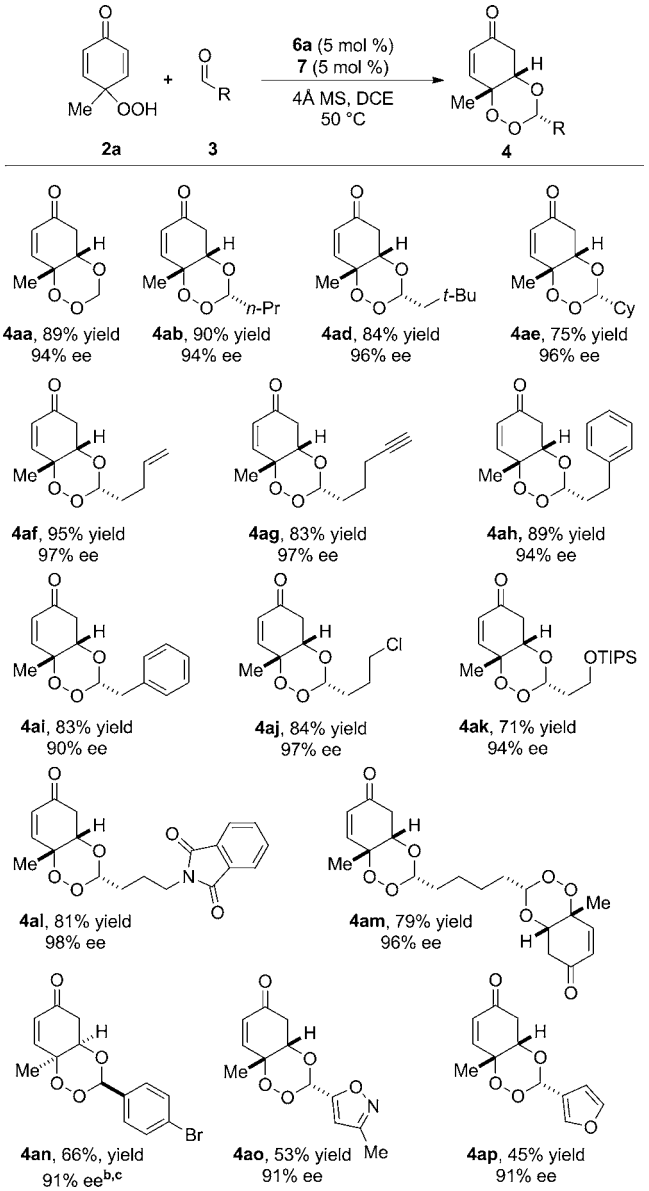
[a]Reactions were performed on a 0.1 mmol scale (0.25 M solution). [b]Isolated yields of analytically pure material. [c]Determined by HPLC using a chiral stationary phase.

With our optimized reaction conditions in hand, we explored the aldehyde scope of the reaction (Table 2). Paraformaldehyde and a variety of sterically hindered aliphatic aldehydes work well. Aldehydes containing alkyl halides, protected alcohols, and protected amines are tolerated, affording trioxanes with

Received: May 30, 2012
Published: August 7, 2012

   dx.doi.org/10.1021/ja3052427 | J. Am. Chem. Soc. 2012, 134, 13554−13557

Table 2. Aldehyde Substrate Scope[a]



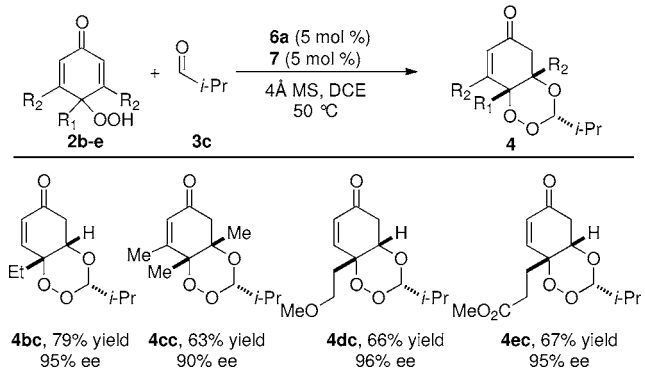
[a]Conditions: **2a** (0.3 mmol), **3** (1.25 equiv). All products formed as single diastereomers (>20:1). Enantiomeric excess determined by HPLC using a chiral stationary phase. [b]The absolute configuration of **4an** was established by X-ray analysis. The rest were assigned by analogy. [c]*ent*-**6a** was used as the catalyst.

excellent selectivities. Aromatic aldehydes also participate in the reaction with high enantioselectivities but slightly decreased yields (Table 2).

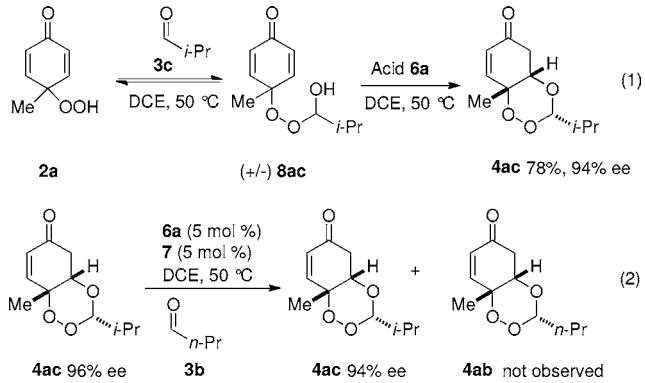
The reaction also proved tolerant of substitution on the *p*-peroxyquinol. Products with esters, ethers, and multiple tetrasubstituted stereocenters all were isolated in good yields and selectivities (Table 3).

The enantiodetermining step is likely the oxa-Michael event, in view of the high enantioselectivity of the product formed from paraformaldehyde.[19] We propose that the reaction proceeds via a dynamic kinetic resolution of peroxy hemiacetal (±)-**8a** (eq 1). As a further test of this hypothesis, racemic peroxyhemiacetal **8ac** was formed by heating *p*-peroxyquinol **2a** with isobutyraldehyde. After excess aldehyde was removed, unpurified (±)-**8ac** was reacted with chiral acid **6a**. To our

Table 3. Peroxyquinol Substrate Scope[a]



[a]See Table 2, footnote *a*.



delight, trioxane **4ac** was formed in good yield as a single diastereomer with 94% ee. This suggests that peroxyhemiacetal **8ac** is resolved through a dynamic kinetic resolution (eq 1). Additionally, when we monitored the reaction under the standard conditions with catalyst **6a** by HPLC, we noted that the peroxyhemiacetal remained as a racemate throughout the course of the reaction. A crossover experiment in which **4ac** was reacted with *n*-butyraldehyde showed that the oxa-Michael step is not reversible under the reaction conditions (eq 2).[20]

The 1,2,4 trioxane products of the desymmetrization have a variety of synthetic handles for subsequent derivatization. Luche reduction of **4ac** formed the allylic alcohol in 4:1 dr, and subsequent directed epoxidation delivered highly oxygenated cyclohexane **9** (Figure 1). Bromination of **4ac** followed by elimination formed vinyl bromide **10**, allowing the incorporation of a variety of functional groups though cross-coupling. Chemoselective reduction of the olefin in the presence of the

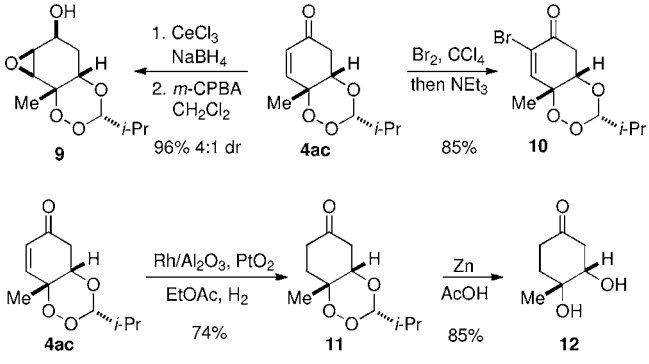
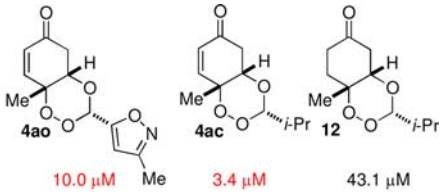


Figure 1. Trioxane derivatizations.

dx.doi.org/10.1021/ja3052427 | J. Am. Chem. Soc. 2012, 134, 13554−13557

peroxide was achieved under the aegis of Rh/Al_2O_3 and Adams' catalyst. This product was further reduced under acidic conditions to reveal the previously unreported diol **12**.

In addition to serving as a frontline antimalarial agent, artemisinin is cytotoxic toward cancer cells, and the 1,2,4-trioxane is believed to play an important role.[1] Our products and their derivatives were screened for cytotoxicity against a variety of cancer cell lines. Compounds **4ac**, **4ao**, and **11** showed promising activity toward bone and lung cancer cell lines with in vitro IC_{50} values of 3.4−25 μM (Figure 2). Importantly, the significant antitumor activity of the semi-reduced trioxane **12** demonstrates that their activity is not due solely to the presence of the Michael acceptor.



D17 Canine osteosarcoma	10.0 μM	3.4 μM	43.1 μM
M21 Human melanoma	-	26.3 μM	~100 μM
MDA human breast carcinoma	-	> 100 μM	> 100 μM
A549 Human lung carcinoma	-	5.7 μM	25 μM
PC3 Human prostate carcinoma	-	11.1 μM	~100 μM

Figure 2. Anticancer activity of 1,2,4-trioxane products.

In conclusion, we have reported the first catalytic enantioselective synthesis of trioxanes using a desymmetrization of *p*-peroxyquinols via an acetalization/oxa-Michael cascade. We propose that the reaction proceeds via a dynamic kinetic resolution of a peroxyhemiacetal intermediate. The 1,2,4-trioxane products are easily derivatized and show promising cancer growth inhibition. Further development of this reaction, antimalarial testing of these trioxanes, and investigation of the mode of antineoplastic action are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, crystallographic data for **4an** (CIF), and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

rovis@lamar.colostate.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NIGMS (GM72586) for support and Kevin Oberg for X-ray analysis of **4an**. T.R. thanks Amgen and Roche for unrestricted support.

■ REFERENCES

(1) (a) Efferth, T. *Curr. Drug Targets* **2006**, *7*, 407. (b) Chaturvedi, D.; Goswami, A.; Saikia, P. P.; Barua, N. C. *Chem. Soc. Rev.* **2010**, *39*, 435. (c) Morrissey, C.; Gallis, B.; Solazzi, J. W.; Kim, B. J.; Gulati, R.; Vakar-Lopez, F.; Goodlett, D. R.; Vessella, R. L.; Sasaki, T. *Anti-Cancer Drugs* **2010**, *21*, 423.

(2) (a) Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; An, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P. J.; Lindegardh, N.; Socheat, D.; White, N. J. *New Engl. J. Med.* **2009**, *361*, 455. (b) O'Brien, C.; Henrich, P. P.; Passi, N.; Fidock, D. A. *Curr. Opin. Infect. Dis.* **2011**, *24*, 570.

(3) (a) Jefford, C. W. *Curr. Med. Chem.* **2001**, *8*, 1803. (b) Golenser, J.; Waknine, J. H.; Krugliak, M.; Hunt, N. H.; Grau, G. E. *Int. J. Parasitol.* **2006**, *36*, 1427. (c) O'Niell, P. M.; Barton, V. E.; Ward, S. A. *Molecules* **2010**, *15*, 1705.

(4) (a) Tang, Y.; Dong, Y.; Vennerstorm, J. L. *Med. Res. Rev.* **2004**, *24*, 425. (b) Kumar, N.; Sharma, M.; Rawat, D. S. *Curr. Med. Chem.* **2011**, *18*, 3889. (c) Jefford, C. W. *Drug Discovery Today* **2012**, *12*, 487. (d) Jefford, C. W. *Curr. Top. Med. Chem.* **2012**, *12*, 373. (e) Slack, R. D.; Jacobine, A. M.; Posner, G. H. *Med. Chem. Commun.* **2012**, *3*, 281.

(5) O'Niell, P. M.; Rawe, S. L.; Borstnik, K.; Miller, A.; Ward, S. A.; Bray, P. G.; Davies, J.; Oh, C. H.; Posner, G. H. *ChemBioChem* **2005**, *6*, 2048.

(6) Beekman, A. C.; Barentsen, A. R. W.; Woerdenbag, H. J.; Van Uden, W.; Pras, N.; Konings, A. W. T.; El-Feraly, F. S.; Galal, A. M.; Wikström, H. V. *J. Nat. Prod.* **1997**, *60*, 325.

(7) (a) Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timári, G.; Rossier, J.-C.; Rudaz, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G. *Helv. Chim. Acta* **1995**, *78*, 647. (b) Hamzaoui, M.; Provot, O.; Riche, C.; Chiaroni, A.; Gay, F.; Moskowitz, H.; Mayrargue, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2085. (c) Zouhiri, F.; Desmaële, D.; d'Angelo, J.; Riche, C.; Gay, F.; Cicéron, L. *Tetrahedron Lett.* **1998**, *39*, 2969.

(8) For the catalytic asymmetric synthesis of peroxides, see: (a) Lu, X.; Liu, Y.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (b) Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112. (c) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (d) Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6589.

(9) (a) Jefford, C. W.; Jaggi, D.; Kohmoto, S.; Boukouvalas, J.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 2254. (b) Jefford, C. W.; Rossier, J. C.; Kohmoto, S.; Boukouvalas, J. *Synthesis* **1985**, 29. (c) Redondo, M. C.; Ribagorda, M.; Carreño, M. C. *Org. Lett.* **2010**, *12*, 568. (d) Jefford, C. W.; Jaggi, D.; Boukouvalas, J.; Kohmoto, S. *J. Am. Chem. Soc.* **1983**, *105*, 6497. (e) Jefford, C. W.; Kohmoto, S.; Boukouvalas, J.; Burger, U. *J. Am. Chem. Soc.* **1983**, *105*, 6498.

(10) Two asymmetric acetalization/oxa-Michael reactions using γ-hydroxy aryl enones or γ-hydroxy-α,β-unsaturated thioesters and aldehydes as partners and catalyzed by a chiral thiourea have been reported; they proceed in excellent enantioselectivity but modest diastereoselectivity. See: (a) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620. (b) Okamura, T.; Asano, K.; Matsubara, S. *Chem. Commun.* **2012**, *48*, 5076.

(11) For reviews, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Grondal1, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (c) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (d) Albrecht, Ł.; Jiang, H.; Jørgensen, K.-A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (e) Peng, F.-Z.; Shao, Z.-H. *Curr. Org. Chem.* **2011**, *15*, 4144. (f) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237.

(12) For chiral Bronsted acid cascade examples, see: (a) Rueping, M.; Antonchik, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *44*, 3683. (b) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (c) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (d) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (e) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5662. (f) Rueping, M.; Antonchik, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836. (g) Cai, Q.; Zaho, Z.-A.; You, S.-L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7428. (h) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (i) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (j) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (k) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4204. (l) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org.*

Lett. **2010**, *12*, 4720. (m) He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490. (n) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804.

(13) (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (b) Filloux, C. M.; Lathrop, S. P.; Rovis, T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20666. (c) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835.

(14) (a) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623. (b) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184. (c) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (e) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404. (f) Gu, Q.; Rong, Z.-Q.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056. (g) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487. (h) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519. (i) Gu, Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 5192. (j) Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. *Org. Biomol. Chem.* **2011**, *9*, 7849. (k) Jia, M.-Q.; You, S.-L. *Chem. Commun.* **2012**, *48*, 6363.

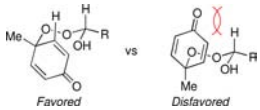
(15) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (c) Li, G.-L.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (d) Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536. (e) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370. (f) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (g) Čorić, I.; List, B. *Nature* **2012**, *483*, 315.

(16) (a) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (b) Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218. (d) Tokoroyama, T. *Eur. J. Org. Chem.* **2010**, 2009. (e) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.

(17) For recent contributions, see ref 15.

(18) For the synthesis of the diol (SPINOL), see: Birman, V. B.; Rheingold, A. L.; Lam, K.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 125.

(19) The high diastereoselectivity of the desymmetrizations can be explained by the reduced 1,3-diaxial interactions in the transition state leading to the favored product:



(20) While the yields were universally improved, the enantioselectivities were not appreciably impacted by the presence of the thiourea cocatalyst, suggesting that it is not involved in the enantioselectivity-determining event. Its exact role in this transformation is the subject of further investigations.