JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Asymmetric Olefin Isomerization of Butenolides via Proton Transfer Catalysis by an Organic Molecule

Yongwei Wu, Ravi P. Singh, and Li Deng*

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States

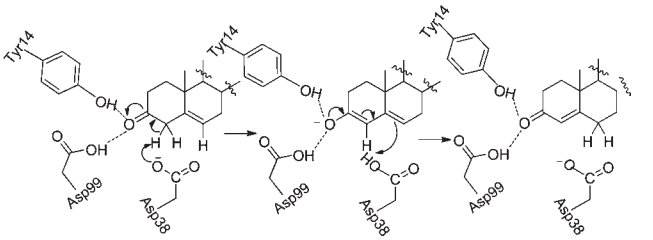
Supporting Information

ABSTRACT: An unprecedented enantioselective and general olefin isomerization was realized via biomimetic proton transfer catalysis with a new chiral organic catalyst. A broad range of mono- and disubstituted β,γ-unsaturated butenolides were transformed into the corresponding chiral α,β-unsaturated butenolides in high enantioselectivity and yield in the presence of as low as 0.5 mol % catalyst. Mechanistic studies have revealed the protonation as the rate-determining step.

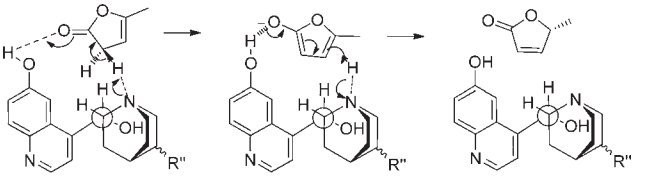
As exemplified by the Δ^5-3-ketosteroid isomerase (KSI)-catalyzed conversion of β,γ- to α,β-unsaturated steroidal ketones (Scheme 1), enzyme-mediated olefin isomerization via a proton transfer from one carbon atom to another in the same substrate molecule constitutes a common and important class of chemical reactions in biology.[1] In contrast, only metal-mediated hydride transfer catalysis has been employed in small molecule-catalyzed asymmetric olefin isomerizations, which include enantioselective olefin isomerizations of allylic amines by a chiral Rh^+/BINAP complex[2] and isomerization of allylic alcohols with a Rh^+/planar-chiral phosphaferrocene complex.[3] Although substrate-directed diastereoselective olefin isomerizations with either achiral acids or bases have been applied in natural product synthesis,[4] only a single example of olefin isomerization by enantioselective proton transfer catalysis, mediated by a bimetallic gadolinium complex, was reported in the literature.[5] Herein, we wish to report the realization of a general and highly enantioselective olefin isomerization with a chiral organic catalyst.

Although the KSI-catalyzed olefin isomerization does not generate a stereocenter, the mechanism underlying the enzymatic proton transfer catalysis is illuminating (Scheme 1). It involves the deprotonation of the C4-β-proton of steroidal ketone by Asp38, while Tyr14 and Asp99 serve as acidic catalytic residues by providing hydrogen bonds to the ketone group. With the oxyanion engaging in hydrogen bonding interactions with Tyr14 and Asp99, the γ-carbon of the dienolate intermediate undergoes a protonation by Asp38 from the β-face. As illustrated in Scheme 2, a 6′-OH cinchona alkaloid in a gauche-open conformation also has a *syn*-arrangement of acidic and basic active sites, which is similar to how Tyr14 and Asp38 are arranged in the active site of KSI. This observation in combination with the ability of 6′-OH cinchona alkaloids to serve as an acid−base bifunctional catalyst and as a chiral proton donor for asymmetric protonation[6−9] led us to envision the possibility of 6′-OH cinchona alkaloids as a catalyst for an enantioselective isomerization via proton transfer catalysis (Scheme 2).[10]

Scheme 1. Isomerization of Steroidal Ketones Catalyzed by KSI



Scheme 2. Proposed Isomerization Pathway of Butenolides Catalyzed by Cinchona Alkaloids



The γ-substituted α,β-unsaturated butenolides constitute a structural motif shared by many biologically interesting natural and synthetic products. Furthermore, they are versatile chiral building blocks for asymmetric synthesis. Thus, the preparation of optically active γ-alkyl α,β-unsaturated butenolides have been a topic of interest. Accordingly, several approaches utilizing easily accessible intermediates from the chiral pool[11] or synthetic chiral precursors have been developed.[12] Among these only two were catalytic approaches, which involved the Os-mediated asymmetric dihydroxylation of β,γ-unsaturated esters,[12f,h] and the Cu-catalyzed heteroallylic asymmetric alkylation, respectively, as the asymmetric induction step.[12j,k] Thus, an efficient and general catalytic enantioselective isomerization of γ-substituted β,γ-butenolides to the corresponding α,β-unsaturated butenolides could provide a complementary method that may also expand the scope of chiral butenolides accessible by catalytic asymmetric synthesis (Scheme 2).

Guided by these considerations we investigated a series of existing 6′-OH cinchona alkaloids and other structurally distinct

Received: June 18, 2011
Published: July 18, 2011

dx.doi.org/10.1021/ja205674x | *J. Am. Chem. Soc.* 2011, 133, 12458–12461

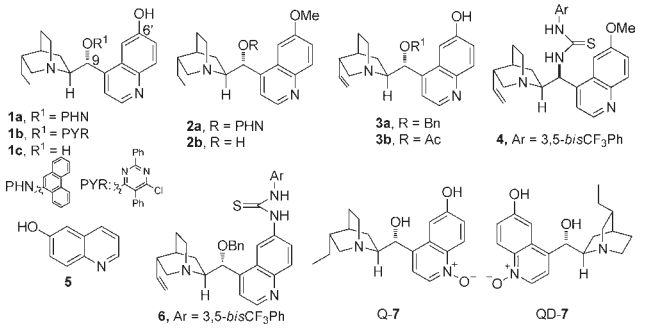
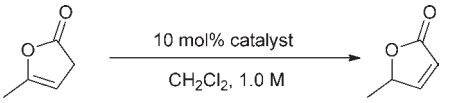


Figure 1. Structure of cinchona alkaloids and achiral acids.

cinchona alkaloids (Figure 1) reported in the literature for their ability to promote the enantioselective isomerization of the commercially available γ-methyl β,γ-butenolide **8a** to the corresponding γ-methyl α,β-unsaturated butenolide **9a** in dichloromethane at room temperature (Table 1). To our surprise, the catalytic activity of these cinchona alkaloids for this olefin isomerization was found to be critically dependent on not only whether a hydrogen bond donor is presented but also where it is located in the cinchona alkaloid skeleton. Specifically, while 6′-OH cinchona alkaloids **1a** afforded promising activity, cinchona alkaloid **2a**, which bears no hydrogen bond donor, was found to be inactive as a catalyst. Although hydroquinine (**2b**), a 9-OH cinchona alkaloid, was active, its activity was significantly lower than that of **1a** (entry 3 vs 1, Table 1). Moreover, the 9-thiourea cinchona alkaloid **4** failed to catalyze this reaction. Even in the presence of both cinchona alkaloid **2a** and 6′-OH quinoline **5**, no isomerization occurred. These data indicated that the specific spatial relationship between the hydrogen bond donor and acceptor is largely responsible for the outstanding activity of **1a** toward this isomerization.

We next focused our attention toward the optimization of enantioselectivity by screening various 6′-OH cinchona alkaloids (**1** and **3**) already reported in the literature (Table 2). As the optical purity of chiral α,β-butenolide **9a** was found to gradually decrease at room temperature in the presence of catalyst **1a** (Table 1, footnote c), the enantioselectivity afforded by different catalysts was evaluated by the ee of **9a** obtained at 10 min after the initiation of the isomerization. To our disappointment, 6′-OH cinchona alkaloids bearing 9-aryl and alkyl groups of various bulk (**1a**, **1b**, **3a**, **3b**) afforded similarly modest selectivity (entries 1−5, Table 2). Interestingly, the enantioselectivity was improved with cupreidine **1c** (entry 3, Table 2), albeit not to a synthetically useful level. We also investigated a 6′-thiourea cinchona alkaloid **6**. In contrast to the completely inactive 9-thiourea cinchona alkaloid **4**, **6** proved to be remarkably active but furnished only a modest enantioselectivity. Following the hypothesis that a perturbation of the acidity of the 6′-OH might improve the catalytic activity and enantioselectivity of the 6′-OH cinchona alkaloids,[13] we prepared a novel cinchona alkaloid derivative Q-7 in which the quinoline ring was oxidized into the corresponding *N*-oxide analogue as 6-hydroxyquinoline-*N*-oxide was determined to be more acidic than 6-hydroxyquinoline.[14] To our delight, it was shown to be a more active as well as selective catalyst in comparison to 6′-OH cinchona alkaloids **1** and **3** (entry 7 vs entries 1−5, Table 2). Importantly, QD-7 afforded even higher activity and selectivity while providing the expected opposite sense of asymmetric induction (entry 8, Table 2). By

Table 1. Isomerization of 8a to 9a Catalyzed by Cinchona Alkaloids[a]

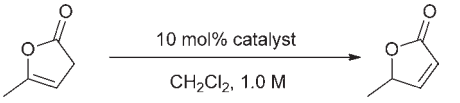


8a **9a**

entry	catalyst	T (°C)	Time	conv (%)[b]	ee (%)[b]
1	**1a**	rt	4 h	80	47[c]
2	**2a**	rt	4 h	0	–
3	**2b**	rt	4 h	20	32
4	**4**	rt	4 h	0	–
5	**5**	rt	4 h	0	–
6	**2a** + **5**	rt	4 h	<5	0

[a] Unless noted, reactions were run with 0.05 mmol of **8a** in 0.05 mL of CH_2Cl_2 with 10 mol % catalyst. See Supporting Information for details. [b] Determined by HPLC analysis. [c] 10 min, 20% conv, 67% ee.

Table 2. Asymmetric iIsomerization of 8a to 9a by a Cinchona Alkaloid Bearing a 6′ Hydrogen Bonding Donor[a]



8a **9a**

entry	catalyst	T (°C)	Time	conv (%)[b]	ee (%)[b]
1	**1a**	rt	10 min	20	67
2	**1b**	rt	10 min	16	60
3	**1c**	rt	10 min	12	74
4	**3a**	rt	10 min	5	60
5	**3b**	at	10 min	5	63
6	**6**	rt	10 min	55	64
7	Q-7	rt	10 min	33	84
8	QD-7	rt	10 min	17	−86
9	QD-7	−20	24 h	36	−92
10	QD-7	−20	72 h	80	−90

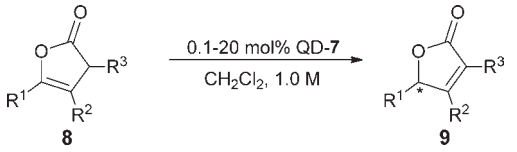
[a] Unless noted, reactions were run with 0.05 mmol of **8a** in 0.05 mL of CH_2Cl_2 with 10 mol % catalyst. See Supporting Information for details. [b] Determined by HPLC analysis.

decreasing the reaction temperature to −20 °C, the QD-7-mediated isomerization of **8a** afforded **9a** in 92% ee (entry 9, Table 2). At this temperature, the racemization of **9a** was found to be minimal, if not completely suppressed (entry 10 vs 9, Table 2).

With **7** as the catalyst we explored the scope of the asymmetric olefin isomerization (Table 3). With either QD- or Q-7 the isomerization of **8a** produced **9a** in 90% ee. The conversion of this isomerization reached the maximum at near 80% due to a reverse isomerization. Importantly, the separation of **8a** and **9a** could be achieved via a standard chromatographic procedure, thereby allowing the isolation of optically active **9a** in moderate yields (entry 1, Table 3). The enantioselectivity of the reactions promoted by **7** was insensitive to the alteration of the steric bulk of the alkyl substituent (entries 2−4). Due to minimal racemization of **9d**, the isomerization of γ-isopropyl β,γ-butenolide **8d**

dx.doi.org/10.1021/ja205674x |*J. Am. Chem. Soc.* 2011, 133, 12458–12461

Table 3. Isomerization of 8 to 9 Catalyzed by QD-7 and Q-7[a,b]



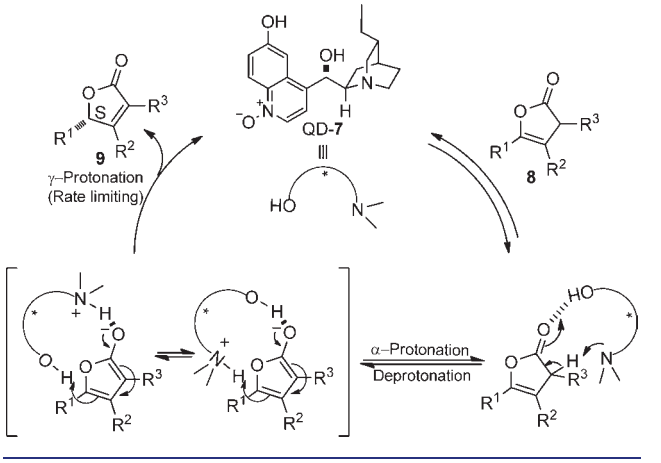
entry	8	T(°C)	t	Yield (%)[c]	ee (%)[d]
1	**8a**	-20	60h	63(56)	90[h](90)
2[e]	**8b**	-20	3d	69	91
3[e]	**8c**	-20	3d	64	90
4	**8d**	rt	1h	73(69)	90(88)
5	**8e**	-20	36h	64	87
6			1h	95(92)	90[h](90)
7	**8f**	rt	12h[f]	95	90
8			24h[g]	91	86
9[f]	**8g**	rt	12h	94	90
10[f]	**8h**	rt	12h	95	90
11[f]	**8i**	rt	12h	95	94
12[f]	**8j**	rt	12h	94	92
13[f]	**8k**	rt	12h	95	91
14	**8l**	-20	24h	95	81[h]
15	**8m**	-20	24h	83	82

[a] Unless noted, reactions were run with 0.10 mmol of **8** in 0.10 mL of CH_2Cl_2 with 10 mol % catalyst. [b] Results in parentheses were obtained with Q-7. [c] Isolated yield. [d] Determined by HPLC analysis. [e] Reaction was run with 20 mol % catalyst. [f] Reaction was run with 0.5 mol % catalyst. [g] Reaction was run with 0.10 mmol of **8f** in 20 μL of CH_2Cl_2 with 0.1 mol % catalyst. [h] Absolute configuration was determined to be *S*; see Supporting Information for details.

could be carried out at room temperature at which point the reaction proceeded rapidly (entry 4). Moreover, the isomerization of butenolide **8e**, which bears a free hydroxyl group on the alkyl chain, was also tolerated by QD-7 (entry 5, Table 3).

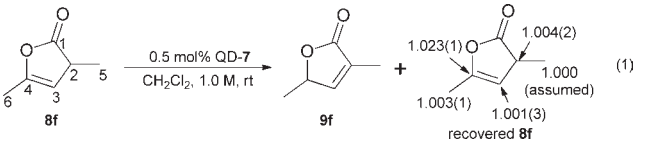
Interestingly, the isomerizations with α,γ-disubstituted β,γ-unsaturated butenolides (**8f**−**k**) proceeded readily to completion in a highly enantioselective fashion without detectable racemizations of the corresponding α,β-unsaturated butenolide (**9f**−**k**) even at room temperature. Consequently, rapid asymmetric isomerizations of high yield and enantioselectivity could be achieved. For example, with 10 mol % QD-7 the isomerization

Scheme 3. Proposed Catalytic Cycle for the Enantioselective Isomerization by QD-7



of **8f** was complete within 1.0 h to afford **9f** in 95% yield and 90% ee at room temperature (entry 6, Table 3). The catalyst loading could be reduced to as low as 0.5 mol % without sacrificing either the enantioselectivity or the yield (entry 7, Table 3), though a longer reaction time of 12 h was required. As exemplified with the isomerization of **8f**, a complete and high yielding reaction could still be attained even with 0.1 mol % catalyst, although the enantioselectivity was slightly decreased from 90% to 86% ee (entry 8, Table 3). Importantly, such catalytic efficiency could be extended to a series of substrates bearing various α- and γ-alkyl groups (entries 9−13, Table 3). The β,γ-disubstituted β,γ-unsaturated butenolides (**8l**−**m**) turned out to be a more challenging class of substrates. The isomerization of these butenolides proceeded with a lower yet still useful level of enantioselectivity. In light of the lack of an efficient approach toward optically active β,γ-disubstituted α,β-butenolides,[12f,i,15] the current isomerization represents a valuable access toward these chiral building blocks.

To gain insights into the reaction mechanism, we carried out a preliminary kinetic study of the QD-7-mediated isomerization of **8f**. The reaction was found to show first-order dependence on the QD-7 and **8f**, respectively.[16] In addition we measured the carbon isotope effect on carbons 2−6 of **8f** employing Singleton's NMR technique at natural abundance to discern the rate-limiting step of the olefin isomerization.[16,17] A pronounced carbon isotope effect was observed on the γ-carbon when the ^{13}C ratio of recovered **8f** at 71% conversion was compared to that of the virgin sample (^{13}C(recovered)/^{13}C(virgin) at C_γ = 1.023, average of three runs) (eq 1). This kinetic isotope effect indicates the γ-protonation step is the rate-limiting step of the isomerization reaction.



Based on these results from our mechanistic studies and the drastic difference in catalytic activity between 6′-OH cinchona alkaloid **1a** and the corresponding 6′-OMe congener **2a** (entry 1 vs 2, Table 1), we propose a catalytic cycle for this enantioselective isomerization reaction (Scheme 3). In this mechanism, the deprotonation of β,γ-butenolide **8** occurs after the hydrogen-

dx.doi.org/10.1021/ja205674x |*J. Am. Chem. Soc.* 2011, 133, 12458–12461

bond-based complexion of **8** with catalyst **7**, which is followed by the rate-determining γ-protonation. It should be noted that, in the protonation step, either the protonated quinuclidine or the 6′-OH could serve as the proton donor.

In summary, we have realized an unprecedented enantioselective olefin isomerization via biomimetic proton transfer catalysis with a new chiral organic catalyst. This asymmetric transformation is applicable to a broad range of β,γ-butenolides bearing one or more substituents. With a low catalyst loading and a simple experimental protocol, this reaction should provide a valuable method for the asymmetric synthesis of chiral α,β-butenolides. Mechanistic studies have revealed that the protonation step is the rate-determining step of this organocatalytic olefin isomerization. Interestingly, this stands in contrast to the enzyme-catalyzed olefin isomerizations, which feature a rate-determining deprotonation.[1a]

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
deng@brandeis.edu

■ ACKNOWLEDGMENT

We are grateful for financial support from the National Institute of Health (GM-61591). We thank Keith Bartelson for his assistance with the ^{13}C KIE study.

■ REFERENCES

(1) (a) Xue, L.; Talalay, P.; Mildvan, A. S. *Biochemistry* **1990**, *29*, 7491. (b) Austin, J. C.; Kuliopulos, A.; Mildvan, A. S.; Spiro, T. G. *Protein Sci.* **1992**, *1*, 259. (c) Hawkinson, D. C.; Pollack, R. M.; Ambulos, N. P. *Biochemistry* **1994**, *33*, 12172. (d) Zhao, Q.; Abeygunawardana, C.; Talalay, P.; Mildvan, A. S. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8220. (e) Zhao, Q. J.; Abeygunawardana, C.; Gittis, A. G.; Mildvan, A. S. *Biochemistry* **1997**, *36*, 14616. (f) Massiah, M. A.; Abeygunawardana, C.; Gittis, A. G.; Mildvan, A. S. *Biochemistry* **1998**, *37*, 14701.

(2) (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600. (b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208.

(3) (a) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870. (b) Tanaka, K.; Fu, G. C. *J. Org. Chem.* **2001**, *66*, 8177.

(4) (a) Suenaga, K.; Takayanagi, Y.; Yamaura, M.; Kigoshi, H. *Chem. Lett.* **2004**, *33*, 918. (b) Bao, G.; Zhao, L.; Burnell, D. J. *Org. Biomol. Chem.* **2005**, *3*, 3576. (c) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 5665.

(5) Saga, Y.; Motoki, R.; Makino, S.; Shimizu, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 7905.

(6) For a recent review on asymmetric protonation, see: Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359.

(7) For cinchona alkaloid-catalyzed asymmetric protonation, see: (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090.

(8) Selected references for other organocatalyzed asymmetric protonations: (a) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888. (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792. (c) Mitsuhashi, K.; Ito, R.; Arai, T.; Yanagisawa, A. *Org. Lett.* **2006**, *8*, 1721. (d) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (e) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641. (f) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860.

(9) Selected references for metal catalyzed asymmetric protonations: (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637. (c) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348. (d) Morita, M.; Drouin, L.; Motoki, R.; Kimura, Y.; Fujimori, I.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3858.

(10) (a) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* **2000**, 493. (b) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212. (c) Liu, H.; Feng, W.; Kee, C. W.; Leow, D.; Loh, W.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2010**, *352*, 3373.

(11) Camps, P.; Cardellach, J.; Corbera, J.; Font, J.; Ortuño, R. M.; Ponsatí, O. *Tetrahedron* **1983**, *39*, 395.

(12) Selected references: (a) Hanessian, S.; Hodges, P. J.; Murray, P. J.; Sahoo, S. P. *J. Chem. Soc., Chem. Commun.* **1986**, 754. (b) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912. (c) Bloch, R.; Gilbert, L. *J. Org. Chem.* **1987**, *52*, 4603. (d) Corbera, J.; Font, J.; Monsalvatje, M.; Ortuno, R. M.; Sanchez-Ferrando, F. *J. Org. Chem.* **1988**, *53*, 4393. (e) Hoye, T. R.; Humpal, P. E.; Jiménez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994**, *35*, 7517. (f) Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2750. (g) Harcken, C.; Bruckner, R. *New J. Chem.* **2001**, *25*, 40. (h) Braukmüller, S.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2110. (i) Kapferer, T.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2119. (j) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. (k) Mao, B.; Geurts, K.; Fañanás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948.

(13) (a) Vedejs, E.; Kruger, A. W.; Suna, E. *J. Org. Chem.* **1999**, *64*, 7863. (b) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748. (c) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194.

(14) Solntsev, K. M.; Clower, C. E.; Tolbert, L. M.; Huppert, D. *J. Am. Chem. Soc.* **2005**, *127*, 8534.

(15) For an example of preparing chiral **9l**, see: Bekish, A. V.; Prokhorevich, K. N.; Kulinkovich, O. G. *Eur. J. Org. Chem.* **2006**, 5069.

(16) See Supporting Information for details.

(17) (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357. (b) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748.