JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Chiral Organic Contact Ion Pairs in Metal-Free Catalytic Asymmetric Allylic Substitutions

Magnus Rueping,* Uxue Uria, Ming-Yuan Lin, and Iuliana Atodiresei

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

Supporting Information

ABSTRACT: Chiral contact ion-pair catalysis with particular focus on metal-free processes is gaining in interest. As a result, new perspectives are opened, and highly stereoselective transformations, traditionally performed under metal catalysis, can be realized. Herein, we report the development of an unprecedented asymmetric Brønsted acid-catalyzed allylic alkylation. The concept relies on chiral contact ion-pair catalysis, in which the chiral organic counteranion of an allylic carbocation induces high enantioselectivities and allows access to biologically relevant chromenes in good yields and with excellent enantioselection.

Chiral ion-pair catalysis has emerged as a powerful tool for asymmetric organic synthesis. Inspired by nature, researchers have designed efficient catalysts and protocols to attain highest enantioselectivities in a variety of different reactions involving ion pairing. Today's strategies mainly involve the use of cationic phase transfer catalysts,[1] chiral anion receptors,[2] and self-assembled supramolecular catalysts,[3] as well as Brønsted acids.[4] Depending on the nature of the catalyst the chiral intermediary ion pairs formed consist of either chiral cations[1] or chiral anions.[5] In this context, the recently introduced chiral Brønsted acids,[4] in particular BINOL-phosphoric acids and derivatives,[6,7] have successfully been employed in the activation of various substrates through formation of a chiral contact ion pair between the phosphate/phosphoramide anion X^- and cations including iminium,[7] oxocarbenium,[8] and episulfonium ions.[9] So far, no catalytic asymmetric process in which an intermediate of type **A**, comprising a carbocation and a chiral counteranion, has ever been described (Figure 1).[10−12]

One of the well-established methods for the construction of carbon−carbon and carbon−heteroatom bonds involving carbocations is the allylic alkylation. The development of asymmetric allylic alkylation reactions[13] has played a significant role in allowing synthetic access to biologically important complex organic molecules. Yet the field is dominated by metal-catalyzed processes, which have been extensively studied with a wide spectrum of metals, including Pd, Mo, Ir, W, Ni, Rh, Ru, Pt, and Cu complexes. The most common one, palladium, has been used with considerable success owing to its generally high and predictable levels of chemo-, regio-, and stereoselectivity. In contrast, the development of metal-free asymmetric versions constitutes a significant challenge in organic synthesis, and in spite of the exciting developments in the field of Brønsted acid catalysis, metal-free allylic alkylations involving chiral ion pairs have remained elusive.

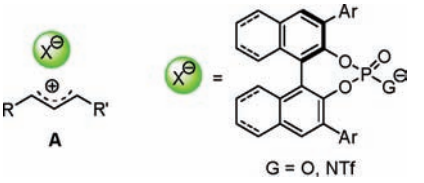


Figure 1. Potential chiral ion pairs based on carbocations and BINOL-phosphoric acids and derivatives.

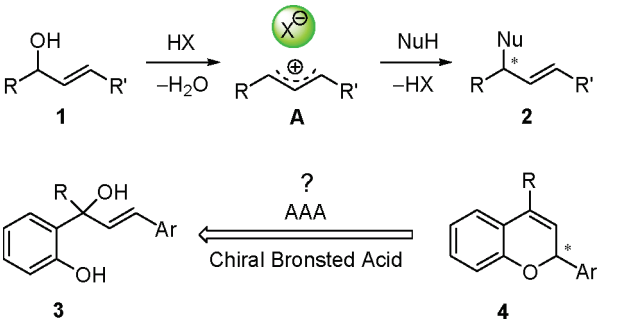


Figure 2. Potential chiral Brønsted acid catalyzed asymmetric allylic substitution.

On the basis of our experience in asymmetric ion-pair and hydrogen-bond catalysis,[14,15] we decided to examine a Brønsted acid-catalyzed enantioselective allylic alkylation reaction, as it would not only be the first example of such a reaction but would also open new avenues in asymmetric ion-pair catalysis. When designing our reaction, we assumed that the alkylation of allylic alcohol **1** may proceed under chiral Brønsted acid catalysis with initial formation of a carbocation in the form of a chiral ion pair A (Figure 2).[16] We further anticipated that the activation by the Brønsted acid would accelerate the subsequent allylic substitution, providing the desired optically active product **2** with regeneration of the chiral Brønsted acid catalyst HX. With these considerations in mind, our attention has been drawn to 2H-1-benzopyran derivatives **4** (2H-chromenes) which might retrosynthetically be obtained from allylic alcohol **3**, via an intramolecular asymmetric allylic substitution.[17]

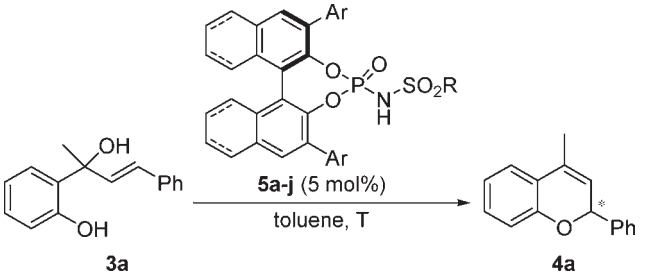
Our interest in this particular class of compounds has also been raised by the fact that **4** constitutes a family of privileged

Received: November 20, 2010
Published: February 28, 2011

ACS Publications © 2011 American Chemical Society

dx.doi.org/10.1021/ja110213t | J. Am. Chem. Soc. 2011, 133, 3732–3735

Table 1. Catalyst and Temperature Effect on the Asymmetric Allylic Substitution[a]



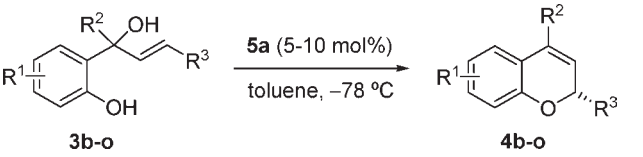
entry	Ar	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	phenyl [H_8] (**5a**)	0	13	77	56
2	*p*-FC_6H_4 [H_8] (**5b**)	0	15	87	31
3	*p*-$MeOC_6H_4$ [H_8] (**5c**)	0	16	79	42
4	2,4,6-$Me_3C_6H_2$ [H_8] (**5d**)	0	13	81	46
5	phenyl [H_8] (**5e**)[c]	0	17	94	55
6	phenyl (**5f**)	0	20	76	50
7	methyl (**5g**)	0	16	54	16[d]
8	phenanthryl (**5h**)	0	24	82	12
9	1-naphthyl (**5i**)	0	19	97	22
10	*p*-ClC_6H_4 (**5j**)	0	17	92	22
11	phenyl [H_8] (**5a**)	−48	24	80	73
12	phenyl [H_8] (**5a**)	−78	24	76	88
13[e]	phenyl [H_8] (**5a**)	−78	20	92	92

[a] Unless otherwise noted, the reactions were performed with 5 mol % of catalyst (R = CF_3) in toluene (0.08 M) at the temperature indicated in the table. [b] Enantiomeric excesses were determined by chiral supercritical fluid chromatography (SFC). [c] The catalyst **5e** with R = C_4F_9 was used. [d] The opposite enantiomer was obtained. [e] Reaction was performed with 10 mol % of catalyst.

structural motifs,[18] being present in many biologically active natural products which exhibit antioxidant, antiviral, antifungal, cytotoxic, and anti-inflammatory activities. In addition, closely related chiral chromans[19] are also a class of valuable compounds, e.g. vitamin E, which is an efficient lipophilic antioxidant, or rhododaurichromanic acid A, which shows potent anti-HIV activity. Therefore, it is desirable to develop improved methodologies for the synthesis of chiral chromenes, which could potentially lead to natural products or their analogues with enhanced pharmacological features.

In order to validate our proposal, we selected phenol **3a** as model substrate and performed a preliminary evaluation of Brønsted acid nature, catalyst loading and temperature.[20] Promising results (77%, 56% ee) were obtained by employing the highly acidic *N*-triflylphosphoramide **5a** at 0 °C in toluene.[15,21−23] These results confirmed that chiral Brønsted acids do indeed promote the intramolecular allylic alkoxylation in a selective manner and provided the starting point for the development of an enantioselective catalytic process. Subsequently, the influence of solvent on the catalytic activity of our system was investigated.[20] Although the reaction proceeded with excellent yields in almost all solvents tested, the enantioselectivity dropped compared to that of the reaction performed in toluene. Use of molecular sieves had a negative effect on both yield and selectivity. Next, in order to evaluate the influence of the catalyst structure on the reaction outcome, a small library of chiral *N*-triflylphosphoramides **5a**−**j** was examined (Table 1).

Table 2. Substrate Scope of the Organocatalytic Enantioselective Allylic Substitution



entry	R^1	R^2	R^3	4	yield (%)	ee[a] (%)
1	H	Me	4-Me-Ph	**4b**	84	93
2	H	Me	4-MeO-Ph	**4c**	91	90
3	H	Me	4-Br-Ph	**4d**	80	94
4	H	Me	4-Cl-Ph	**4e**	86	94
5	H	Me	4-F-Ph	**4f**	81	94
6[b]	H	Me	3-Cl-Ph	**4g**	95	84
7	5-Me	Me	4-F-Ph	**4h**	82	90
8	4-MeO	Me	4-Cl-Ph	**4i**	83	84
9	5-Me	Me	4-Me-Ph	**4j**	87	84
10	5-F	Me	4-Me-Ph	**4k**	94	92
11	H	Me	2-thiophen	**4l**	94	90
12	H	Et	Ph	**4m**	88	91[c]
13	H	Et	4-Cl-Ph	**4n**	71	96
14	H	Et	4-Br-Ph	**4o**	61	93

[a] Enantiomeric excesses were determined by chiral supercritical fluid chromatography (SFC). [b] Reaction was performed at −48 °C. [c] 98% ee after crystallization.

The selectivity proved to be highly dependent on the substituents at the 3,3′-positions of the BINOL framework. Among all catalysts tested, comparable results were obtained with the BINOL and H_8BINOL derivatives bearing phenyl groups at the 3,3′ positions (Table 1, entries 1, 5, 6). Furthermore, a considerable improvement in the selectivity was obtained by lowering the temperature (Table 1, entries 12, 13).

With an effective protocol for the enantioselective intramolecular allylic substitution in hands, the scope and generality of the method with regard to the substrate were examined (Table 2).

The Brønsted acid-catalyzed process exhibits compatibility with the presence of a wide range of substituted aromatic rings in the substrate. For example, electron-donating and electron-withdrawing groups in the para position of the aryl ring conjugated to the olefin led to the isolation of the corresponding adducts **4b**−**f** with excellent results (Table 2, entries 1−5). In contrast, when an electron-withdrawing Cl-group was introduced in the meta position, no reaction occurred at −78 °C. Nevertheless, an excellent yield and good enantiomeric excess could be obtained in a short time by performing the reaction at −48 °C (Table 2, entry 6). Higher substituted compounds gave similar results, employing the optimal conditions (Table 2, entries 7−10), as did a hetereoaromatic ring-bearing substrate (Table 2, entry 11). Good to high yields and excellent enantioselectivities were also obtained when the methyl group present in the starting compound was exchanged with the bulkier ethyl group (Table 2, entries 12−14). These results revealed that catalyst **5a** is an efficient promoter for the metal-free allylic substitution, allowing entry to a broad range of optically enriched chromenes.

By means of different techniques, e.g. single-crystal X-ray analysis combined with CD-spectroscopy and theoretical calculations, the absolute configuration of enantioenriched **4m** was assigned as R.[20]

dx.doi.org/10.1021/ja110213t | *J. Am. Chem. Soc.* 2011, 133, 3732–3735

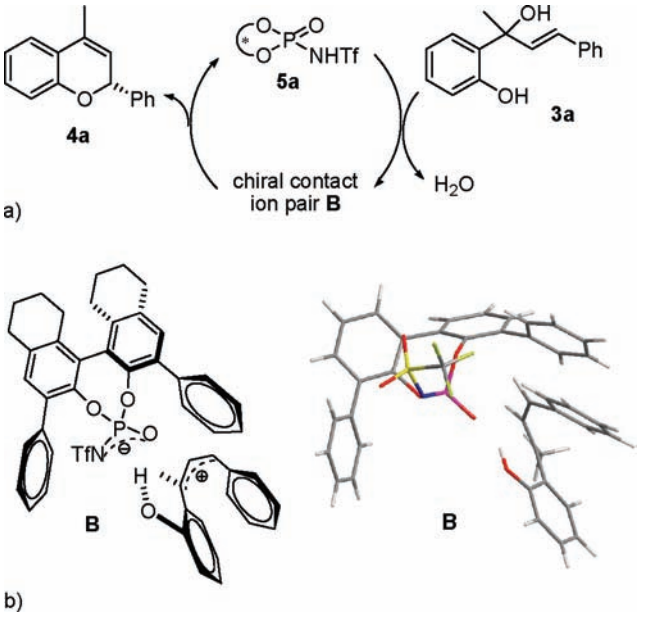


Figure 3. (a) Proposed mechanism for the metal-free, chiral Brønsted acid-catalyzed allylic alkylation. (b) Simplified stereochemical models of the contact ion pair **B**. In the three-dimensional model (bottom, right) the $(-CH_2-)_4$ groups of the catalyst backbone have been omitted for clarity.

Regarding the reaction mechanism, several different pathways are possible. Although an oxa-6π electrocyclic reaction might be considered,[24] the low temperature (−78 °C) applied in the reaction allows us not to take into account this pathway. Furthermore, substrates lacking a vinyl *o*-quinone methide form undergo reaction under the given conditions.[25] Hence, an allylic alkylation has been considered. Concerning the mechanism of the allylic substitution, experiments have been conducted, and the results support a mechanism with an allylic cation intermediate, over a dynamic kinetic resolution through SN2′-type substitution. Subjection of optically pure substrates (*R*)- and (*S*)-**3a** (ee > 99%) to the reaction with achiral catalyst allowed formation of **4a** in a racemic form, indicating an intermediate which lost the chiral information. In addition, optically pure substrate **3a** (ee > 99%) reacted in the presence of chiral catalyst **5a** to give the product **4a** with 91% ee. If an SN2′ reaction would take place, the enantiomeric excess should be preserved during the reaction. Hence, the chiral substrate loses its chiral information, and the resulting allylic cation intermediate undergoes substitution reaction to afford the product **4a** with the same enantiomeric excess as in the case of the racemic substrate (ee = 92%). Under the given conditions the products are stable and do not undergo ring-opening reaction (racemic **4a** was isolated upon treating racemic **4a** with 2 equiv of H_2O and catalyst **5a**).

On the basis of these observations we propose that the Brønsted acid protonates the allylic alcohol which subsequently dehydrates to yield a carbocation which is associated with the phosphoramide anion in a chiral contact ion pair **B** (Figure 3). Furthermore, our model favors a carbocation with an anti,anti configuration that is stabilized through intramolecular $\pi-\pi$ stacking interactions as well as intermolecular electrostatic interaction with the catalyst. The two ions of the ion pair orientate in such a way that the positive charge of the cation is compensated by the negative charge delocalized on the OPNTf system. The HO phenolic group is subsequently deprotonated by the catalyst, enabling the intramolecular attack of the oxygen nucleophile and regenerating the effective catalyst. Cation−π interactions between the substrate and the catalyst are most likely responsible for the excellent enantioselection observed in the reaction (Figure 3).

In conclusion, we have developed a new organic ion-pair catalysis procedure for performing an enantioselective intramolecular allylic substitution catalyzed by a chiral Brønsted acid. The methodology presented herein has broad scope, providing the corresponding 2H-chromenes in good yields and with excellent enantioselectivities. These results highlight the potential of Brønsted acids in promoting highly stereoselective allylic reactions via a chiral contact ion pair. The present approach is particularly attractive as it avoids the use of often toxic metals and sensitive intermediates. We are thus confident that the concept of asymmetric ion-pair catalysis in which the chiral information is efficiently transferred from the Brønsted acid anions to the product will find broader application in reactions involving carbocationic intermediates.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and full characterization data for all new compounds. EDX spectrum of compound **5a**, crystal structure and CD-spectra of **4m**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
Magnus.Rueping@rwth-aachen.de

■ ACKNOWLEDGMENT

Financial support for this project was provided by the European Research Council. U.U. thanks "Eusko Jaurlaritza −Gobierno Vasco" for a postdoctoral fellowship.

■ REFERENCES

(1) Maruoka, K., Ed. *Asymmetric Phase Transfer Catalysis*; Wiley-VCH, Weinheim, Germany, 2008.

(2) (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. (b) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328–6331 and the references cited therein. (c) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986–990. (d) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060–17061. (e) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624–13626. (f) Thematic issue Supramolecular chemistry of anionic species. *Chem. Soc. Rev.* **2010**, *39*, issue 10.

(3) (a) van Leeuwen, P. W. N. M., Ed. *Supramolecular Catalysis*; Wiley-VCH, Weinheim, Germany, 2008. (b) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120–123.

(4) For reviews on Brønsted acid catalysis: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (e) Yamamoto, H.; Payette, N. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH, Weinheim, 2009, pp 73− 140. (f) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395–456.

(5) (a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373–382. (b) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073–7089.

(6) For pioneering work in the field of chiral BINOL-phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. For pioneering work in the field of chiral BINOL-based *N*-triflylphosphoramides, see: (c) Yamamoto, S. A.; Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627.

(7) Reviews on BINOL-phosphoric acids: (a) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (b) Terada, M. *Synthesis* **2010**, 1929–1982. (c) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, 101–119.

(8) (a) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431. For a process involving chiral ion pairs consisting of *N*-triflylthiophosphoramides and oxocarbenium ions, see: (b) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247. For thiourea-catalyzed additions to oxocarbenium ions, see: (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.

(9) Hamilton, G. L.; Kanai, T.; Toste, D. F. *J. Am. Chem. Soc.* **2008**, *130*, 14984–14986.

(10) We refer strictly to "pure" carbocations: structures with the positive charge located on carbon atoms regardless of the resonance structure written.

(11) For the generation of stabilized carbocations, see: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593–596. (b) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661–5665. (c) Sun, F. L.; Zeng, M.; Gu, Q.; You, S. L. *Chem.—Eur. J.* **2009**, *15*, 8709–8712. (d) Guo, Q. X.; Peng, Y. G.; Zhang, J. W.; Song, L.; Feng, Z.; Gong, L. Z. *Org. Lett.* **2009**, *11*, 4620–4623. (e) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685–9688.

(12) For a contact ion pair comprising a carbocation and a thiourea-bound halide complex, see: Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286–9288.

(13) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944. (b) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.

(14) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852–865 and the references cited therein.

(15) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem.—Eur. J.* **2010**, *16*, 13116–13126 and the references cited therein.

(16) For a chiral version with a dual achiral Lewis acid/chiral secondary amine catalytic system, see: (a) Capdevila, M. G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P. G. *Chem.—Eur. J.* **2010**, *16*, 11237–11241. For a chiral version with a dual achiral Brønsted acid/chiral primary amine catalytic system, see: (b) Qiao, Z.; Shafiq, Z.; Liu, L.; Yu, Z.-B.; Zheng, Q.-Y.; Wang, D.; Chen, Y.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7294–7298. For an achiral version with a dual achiral Brønsted acid/achiral secondary amine catalytic system: (c) Xu, L.-W.; Gao, G.; Gu, F.-L.; Sheng, H.; Li, L.; Lai, G.-Q.; Jiang, J.-X. *Adv. Synth. Catal.* **2010**, *352*, 1441–1445.

(17) For the acid-catalyzed cyclization of this type of substrates, see: Talley, J. J. *Synthesis* **1983**, 845–847.

(18) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953 and the references therein. (b) Ellis, G. P., Ed. *Chromenes, Chromanones, and Chromones*; The Chemistry of Heterocyclic Compounds; Wiley-Interscience: New York, 1977; Vol. 31.

(19) Ellis, G. P.; Lockhart, I. M., Eds. Chromans and Tocopherols. In *The Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1981; Vol. 36.

(20) For details see Supporting Information.

(21) Examples of *N*-triflylphosphoramide-catalyzed reactions from our group: (a) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100. (b) Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78–84. (c) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798–6801. (d) Rueping, M.; Lin, M.-Y. *Chem.—Eur. J.* **2010**, *16*, 4169–4172. (e) Rueping, M.; Nachtsheim, B. J. *Synlett* **2010**, 119–122. (f) Rueping, M.; Merino, E.; Koenigs, R. M. *Adv. Synth. Catal.* **2010**, *352*, 2629–2634.

(22) Further examples of *N*-triflylphosphoramides in enantioselective catalysis: (a) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411–2413. (b) Zeng, M.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 2169–2173. (c) Lee, S.; Kim, S. *Tetrahedron Lett.* **2010**, *50*, 3345–3348. For the application of *N*-triflylthiophosphoramides: (d) Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476–2479.

(23) The *N*-triflylphosphoramides employed in the reaction are free of metal impurities. For details see Supporting Information and ref 15.

(24) Recent examples of oxa-6π electrocyclic reactions in the synthesis of 2*H*-pyrans and derivatives: (a) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276–6283. (b) Lumb, J.-P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865–5868. (c) For a mechanistic study on the acid-catalyzed cyclization of a vinyl *o*-quinone methide, see: Bishop, L. M.; Winkler, M.; Houk, K. N.; Bergman, R. G.; Trauner, D. *Chem.—Eur. J.* **2008**, *14*, 5405–5408. (d) Jung, E. J.; Park, B. H.; Lee, Y. R. *Green Chem.* **2010**, *12*, 2003–2011. (e) Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. *J. Org. Chem.* **2009**, *74*, 8963–8973.

(25) A detailed study will be reported in due course.