JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Highly Enantioselective Electrophilic α-Bromination of Enecarbamates: Chiral Phosphoric Acid and Calcium Phosphate Salt Catalysts

Aurélien Alix,† Claudia Lalli,† Pascal Retailleau, and Géraldine Masson*

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

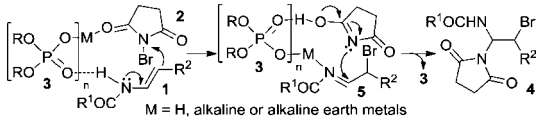
Supporting Information

ABSTRACT: Metal-free chiral phosphoric acids and chiral calcium phosphates both catalyze highly enantio- and diastereoselective electrophilic α-bromination of enecarbamates to provide an atom-economical synthesis of enantioenriched vicinal haloamines. Either enantiomer can be formed in good yield with excellent diastereo- and enantioselectivity simply by switching the catalyst from a phosphoric acid to its calcium salt.

Vicinal haloamines are a versatile structural motif for the synthesis of various biologically active compounds and can serve as key intermediates for further transformations.[1−3] To date, however, only a few examples of their asymmetric synthesis have been described.[4] Among the reported syntheses, electrophilic halofunctionalization of enamides represents one of the most convenient and straightforward approaches to obtain chiral vicinal haloamine compounds in a regio- and stereoselective manner.[5] Despite recent advances in the catalytic asymmetric halogenation of carbonyl,[4c,d,6] acyl chloride,[7] 1,3-dicarbonyl,[8] oxindole,[9] and enyne compounds,[10] no example of an enantioselective α-halogenation of enamides is extant.[11]

Chiral phosphoric acids[12,13] and chiral phosphate metal salts[9d,14] were found to be effective in catalyzing enantioselective additions of enamide compounds[15] to various electrophiles, such as carbonyl,[16c] imine,[16a,b,d−g,j] azodicarboxylate,[16i] and nitroso compounds.[16h] A recent report described the activation of *N*-halogenosuccinimide toward highly enantioselective reactions catalyzed by chiral phosphoric acid or chiral sodium phosphate.[9d,17] Inspired by the successful employment of these catalysts and our interest in enantioselective transformations,[16e−g,i,j] we envisioned that chiral phosphoric acids or their metal salts (**3**) could catalyze enantioselective electrophilic α-halofunctionalization of enamide compounds (Scheme 1). Moreover, the electrophile *N*-bromosuccinimide (NBS, **2**), which includes a masked nucleophilic component, could be incorporated into the electrophilic iminium intermediate **5** (Scheme 1), leading to a valuable aminal **4**[18] for retro-inverso synthesis of peptide mimics.[19] Herein we report the first enantioselective α-bromofunctionalization of enecarbamates through a domino bromination/nucleophilic addition. This approach also led to the discovery that the chiral phosphoric acid (**3**, M = H) and its calcium salt (**3**, M = Ca) give access to both enantiomers of the vicinal haloamine product.

Scheme 1. Working Hypothesis



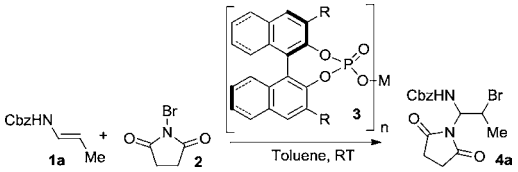
To validate our hypothesis, we began our studies by examinating the reaction of *O*-benzyl *N*-(*E*)-prop-1-en-1-yl carbamate (**1a**) with **2** in the presence of a 10 mol % loading of chiral phosphoric acids **3** at room temperature. As shown in Table 1, both the reactivity and enantioselectivity were dramatically affected by the structure of the chiral phosphoric acid. The highest diastereo- and enantioselectivity were obtained when (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid (**3e**) was used (9:1 dr, 88% ee; entry 5).[20] Additionally, it was found that a significant reduction of the catalyst loading to only 1 mol % under more concentrated conditions (*c* = 0.1 M) improved the reaction diastereo- and enantioselectivity (>95:5 dr, 98% ee, 99% yield; entry 9 vs 5). Comparable enantioselectivity was obtained when the catalyst loading was reduced to 0.1 mol %, although this gave a reduced yield (entry 11). Reducing the amount of **1a** to 1.2 equiv relative to **2** gave **4a** in lower yield (entry 13). The absolute configuration of the major isomer *cis*-**4a** was unambiguously determined to be 1*R*,2*S* by X-ray analysis [see the Supporting Information (SI)]. As the stereochemical outcome of electrophilic bromination can depend on the enecarbamate geometry, the reaction with the *Z* isomer of enecarbamate **1a** was investigated, and it gave the same enantiomer of **4a** as the major product, albeit with lower yield (entry 12). However, to our surprise, reversal of the enantioselectivity of product **4a** to supply (1*S*,2*R*)-*cis*-**4a** was observed when the catalyst was changed from **3e** to its corresponding metal salt **3f** (M = Li) or **3g** (M = Ca), still with excellent ee and dr values (entries 14 and 15).[21] Thus, both enantiomers of **4a** could be prepared efficiently.[14a,b,21]

We next examined the scope of the enecarbamate component in this enantioselective domino process catalyzed by chiral phosphoric acid **3e** or its calcium salt **3g**. Representative results are summarized in Table 2. In general, the **3e**-catalyzed reaction (entries 1−13) proceeded smoothly with high diastereo- and enantioselectivity in excellent yield

Received: May 3, 2012
Published: June 11, 2012

dx.doi.org/10.1021/ja304095z | J. Am. Chem. Soc. 2012, 134, 10389−10392

Table 1. Optimization of Enantioselective α-Bromination of Enecarbamates[a]



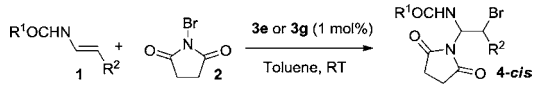
entry	3 (R/M)	mol % 3	yield (%)[e]	*ee* (%)[f]/dr[g]
1	**3a** (C_6H_5/H)	10[a]	33	51/(75:25)[h]
2	**3b** (4-ClC_6H_4 [H8]/H)	10[a]	39	52/(75:25)[h]
3	**3c** (2-naphthyl/H)	10[a]	44	62/(85:25)[h]
4	**3d** (1-naphthyl/H)	10[a]	39	64/(85:25)[h]
5	**3e** (2,4,6-iPr$_3$$C_6H_2$/H)	10[a]	87	88/(90:10)[h]
6	**3e**	5[a]	87	88/(90:10)[h]
7	**3e**	2[a]	87	90/(>95:5)[h]
8	**3e**	1[b]	89	94/(>95:5)[h]
9	**3e**	1[b]	99	98/(>95:5)[h]
10	**3e**	0.5[b]	75	94/(>95:5)[h]
11	**3e**	0.1[b]	56	92/(>95:5)[h]
12	**3e**	1[b,c]	67	86/(>95:5)[h]
13	**3e**	1[b]	64	98/(>95:5)[h,i]
14	**3f** (2,4,6-^{i}Pr$_3$$C_6H_2$/Li)	1[b,d]	74	−96/(>95:5)[j]
15	**3g** (2,4,6-^{i}Pr$_3$$C_6H_2$/Ca)	1[b,d]	78	−98/(>95:5)[j]

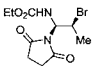
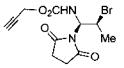
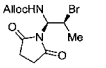
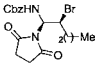
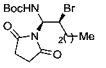
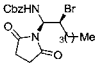
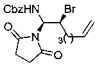
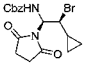
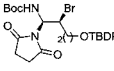
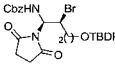
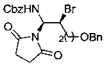
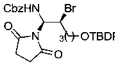
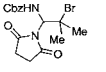
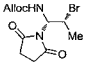
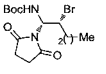
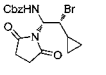
[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.05 mmol), and **3** in 1 mL of toluene for 14 h. [b]Same conditions as in footnote *a* except with 0.5 mL of toluene. [c]The *Z* isomer of **1a** was used. [d]The reaction was performed for 48 h. [e]Yields of the chromatographically pure major diastereoisomer. [f]Determined by chiral HPLC analysis. [g]Determined by ^{1}H NMR analysis of the crude material. [h](1*R*,2*S*)-enriched **4a**. [i]1.2 equiv of **1a** (0.6 mmol) was used. [j](1*S*,2*R*)-enriched **4a**.

(>90%). This reaction worked well for a broad range of substituted enecarbamates bearing a linear or branched alkyl group or a heteroalkyl substituent. Introduction of steric hindrance at the α-position of the ene moiety resulted in a slight decrease in the yield without affecting the enantioselectivity of the process (entry 8). Even the β,β-disubstituted enecarbamate **1n** afforded the corresponding bromoaminal product **4n** containing a quaternary center with 96% ee (entry 13). In contrast, vinyl carbamates substituted with aryl groups at the β-position failed to participate in this electrophilic α-bromination, probably because of their lower nucleophilicity.[22] Modification of the carbamate moiety from benzyl to ethyl, propargyl, allyl, or *tert*-butyl carbamate afforded the bromoaminal products (**4b**−**f**, entries 1−5) with similar diastereo- and enantioselectivities. It is noteworthy that no bromination of unsaturated bonds present in the enecarbamate was observed, whether in the carbamate moiety (entries 2 and 3) or the lateral chain (entry 7), thus demonstrating the high chemo- and regioselectivity of this reaction.[17] We also investigated enantioselective electrophilic α-bromination using the optimized reaction conditions with calcium salt **3g** (entries 14−16). A variety of selected enecarbamates **1** reacted with good enantioselectivity in all cases affording the opposite enantiomer of the products formed using the corresponding phosphoric acid **3e**. We also found that, contrary to our previous studies, the N-protecting group of **1** had an influence on the enantiomeric excess, as diminished enantioselectivity was observed when Boc or Alloc was used (entries 14 and 15).

We then became interested in pursuing experiments designed to test the mechanistic hypothesis outlined in Scheme

Table 2. Enantioselective Direct α-Bromination of Enecarbamates: Substrate Scope[a]



entry	structure and configuration of 4		yield (%)[b]	ee (%)[d]
1		(1*R*,2*S*)-**4b**	90	91[e]
2		(1*R*,2*S*)-**4c**	75	91[e]
3		(1*R*,2*S*)-**4d**	81	86[e]
4		(1*R*,2*S*)-**4e**	92	90[e]
5		(1*R*,2*S*)-**4f**	99	94[e]
6		(1*R*,2*S*)-**4g**	93	96[e]
7		(1*R*,2*S*)-**4h**	90	97[e]
8		(1*R*,2*S*)-**4i**	77	92[e]
9		(1*R*,2*S*)-**4j**	46	92[e]
10		(1*R*,2*S*)-**4k**	72	91[e]
11		(1*R*,2*S*)-**4l**	94	84[e]
12		(1*R*,2*S*)-**4m**	94	98[e]
13		**4n**	66	96[f]
14		(1*S*,2*R*)-**4d**[c]	62	-88[g]
15		(1*S*,2*R*)-**4f**[c]	67	-81[g]
16		(1*S*,2*R*)-**4i**[c]	74	-86[g]

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.1 mmol), and **3e** (entries 1−13) or **3g** (entries 14−16) (1 mol %) in toluene (1.0 mL) at room temperature for 14 h. [b]Yields of chromatographically pure product. [c]The reaction was performed for 48 h. [d]Determined by chiral HPLC analysis. [e](1*R*,2*S*)-enriched **4**. [f]The absolute configuration was not determined. [g](1*S*,2*R*)-enriched **4**.

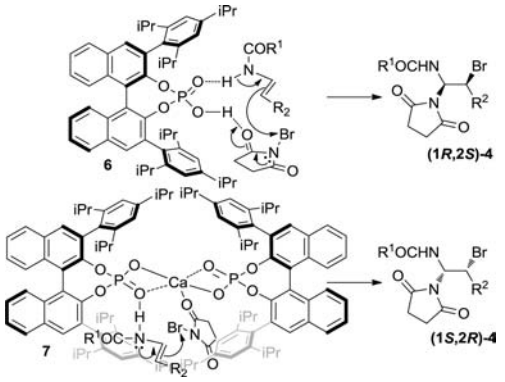
1. Different modes of activation of NBS by **3** could be proposed, such as hydrogen bonding, metallic bonding, or proton transfer with formation of a chiral bromonium ion intermediate.[9d,17] Inspired by the elegant work of Denmark and Burk,[17c] we investigated the addition of the achiral Lewis base $Ph_3P{=}S$, which is known to favor the ion-pairing mechanism. Under these conditions, the two catalysts **3e** and **3g** gave

dx.doi.org/10.1021/ja304095z | J. Am. Chem. Soc. 2012, 134, 10389−10392

similar results in terms of reaction rate, yield and ee (see the SI). The phenomenon of enantioselectivity reversal by phosphate salt **3g** was preserved, whereas the same enantiomer should have been observed with a mechanism involving a chiral bromonium ion intermediate. We also carried out a control experiment with a two-component catalyst composed of TRIP phosphoric acid **3e** and $Ca(iPrO)_2$, which furnished the desired product in 95% ee with the same selectivity as **3e**. It can therefore be suggested that **3e** would activate NBS through either hydrogen bonding or ion pairing. At this stage, it is not possible to distinguish these two activation modes. On the other hand, an alkaline-earth-metal bonding interaction between **3g** and NBS would be evoked. Next, we carried out a nonlinear effect (NLE) experiment to gain further insight into the structure of the active calcium phosphate salt catalyst. We observed a positive NLE in the **3g**-catalyzed α-bromination of enecarbamates (see the SI), indicating that the active catalyst is a dimeric species rather than a Ca^{II}-free phosphoric acid or monophosphate salt.[14,23] In addition, it is worth noting that secondary enecarbamates gave no reaction in the presence of **3e** or **3g**, suggesting that activation of NBS alone is not sufficient to achieve effective α-bromination.

On the basis of these observations, we assumed that **3e** and **3g** act as bifunctional catalysts activating both NBS and the enecarbamate via hydrogen bonding and metal chelation, respectively. While a precise understanding of the origin of the enantioselectivity reversal awaits further study, two different transition state models, **6** and **7**, were postulated (Scheme 2).

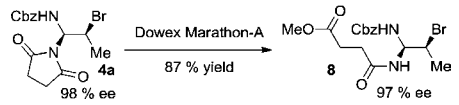
Scheme 2. Proposed Transition State Model



Phosphoric acid **3e** with the sterically bulky 2,4,6-triisopropylphenyl group efficiently hinders the *Re* face of NBS, and the enecarbamate can attack only the *Si* face of NBS, leading to the (*S*)-imine intermediate. In contrast, the other face (*Re* face) is fully accessible with calcium bis(phosphate) complex **3g**, furnishing the *R* isomer.[14] In both cases, a highly diastereoselective nucleophilic addition reaction of the imide to the (*S*)- or (*R*)-imine would then furnish the observed *cis*-bromoaminal (1*R*,2*S*)-**4a** or (1*S*,2*R*)-**4a**, respectively.

To illustrate the synthetic potential of this novel catalytic enantioselective domino bromination/succinimide addition, we developed conditions to open the succinimide ring. We were delighted to observe that such ring opening can be carried out by fast filtration on a basic resin, generating the valuable aminal **8**[18] with retention of enantiopurity (Scheme 3). Furthermore, the multifunctionality of the 1,2-bromoaminal products allows for few-step stereoselective syntheses of other useful chiral

Scheme 3. Ring Opening of the Succinimide Moiety



building blocks, such as aziridines,[5e,f,i] 1,2-ether/thioether-aminals,[5e,g,l] imidazolidin-2-ones,[5e] and pyrrolizidines.[24]

In conclusion, we have reported the first enantioselective chiral phosphoric acid-catalyzed electrophilic α-bromination of enecarbamates.[11] The efficiency of the system allows reactions to be run under mild conditions at room temperature with a modest amount of catalyst (1 mol %). We have also shown an unprecedented reversal of enantioselectivity for a catalytic bromination reaction when the corresponding chiral calcium phosphate salt is used. The high efficiency and operational simplicity of this procedure make it a practical protocol for synthesis of chiral vicinal haloamines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, HPLC enantiomer analysis, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

masson@icsn.cnrs-gif.fr.

Author Contributions

†A.A. and C.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the ICSN and CNRS for financial support and ANR for postdoctoral fellowships to A.A. and C.L. We also acknowledge Prof. Jieping Zhu for his generous support.

■ REFERENCES

(1) (a) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*; Wiley: New York, 1988. (b) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, U.K., 1991; Vol. 3, pp 469−513 and references therein. (c) Thomas, G. *Medicinal Chemistry: An Introduction*; Wiley: New York, 2000.

(2) For some representatives examples, see: (a) Barton, D. H. R.; Britten-Kelley, M. R.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1090. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811. (c) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863. (d) Qiu, J.; Silverman, R. B. *J. Med. Chem.* **2000**, *43*, 706. (e) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644. (f) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.

(3) For representative methods to prepare vicinal haloamines, see: (a) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745 and references therein. (b) Wu, X.-L.; Wang, G.-W. *Eur. J. Org. Chem.* **2008**, 6239. (c) Chen, Z.-G.; Wei, J.-F.; Li, R.-T.; Shi, X.-Y.; Zhao, P.-F. *J. Org. Chem.* **2009**, *74*, 1371. (d) Wei, J.-F.; Chen, Z.-G.; Lei, W.; Zhang, L.-H.; Wang, M.-Z.; Shi, X.-Y.; Li, R.-T. *Org. Lett.* **2009**, *11*, 4216. (e) Zhang, G.; An, G.; Zheng, J.; Pan, Y.; Yi, L.; Li, G. *Tetrahedron Lett.* **2010**, *51*, 987 and references therein.

(4) (a) Xu, X.; Kotti, S. R. S. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881. (b) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943. (c) Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W.

Org. Lett. **2010**, *12*, 3276. (d) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160. (e) Cai, Y. F.; Liu, X. H.; Jiang, J.; Chen, W. L.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2011**, *133*, 5636. (f) Shibatomi, K.; Narayama, A.; Soga, Y.; Muto, T. *Org. Lett.* **2011**, *13*, 2944. (g) Cai, Y. F.; Liu, X. H.; Li, J.; Chen, W. L.; Wang, W. T.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2011**, *17*, 14916.

(5) (a) Shin, C. G.; Sato, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1909. (b) Shin, C. G.; Nakano, T.; Sato, Y.; Kato, H. *Chem. Lett.* **1986**, 1453. (c) Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 1447. (d) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 4073. (e) Danion-Bougot, R.; Francis, G. *Tetrahedron Lett.* **1990**, *31*, 3739. (f) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813. (g) Matsumura, Y.; Terauchi, J.; Yamamoto, T. *Tetrahedron* **1993**, *49*, 8503. (h) Yamada, M.; Nakao, K.; Fukui, T.; Nunami, K.-I. *Tetrahedron* **1996**, *52*, 5751. (i) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088. (j) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205. (k) Le Corre, L.; Kizirian, J.-C.; Levraud, C.; Boucher, J.-L.; Bonnet, V.; Dhimane, H. *Org. Biomol. Chem.* **2008**, *6*, 3388. (l) Levraud, C.; Calvet-Vitale, S.; Bertho, G.; Dhimane, H. *Eur. J. Org. Chem.* **2008**, 1901. (m) Lina, D.; Cheng, K.; Lu, X.; Sun, J. *Synlett* **2009**, 2961.

(6) For recent reviews of enantioselective halogenation of carbonyls, see: (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (b) Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005. For representative examples, see: (c) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (d) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507. (e) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (f) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (g) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706. (h) Kano, T.; Shirozu, F.; Maruoka, K. *Chem. Commun.* **2010**, *46*, 7590. (i) Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738.

(7) For a recent review, see: (a) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596. For a recent example, see: (b) Erb, J.; Paull, D. H.; Dudding, T.; Belding, L.; Lectka, T. *J. Am. Chem. Soc.* **2011**, *133*, 7536.

(8) For recent reviews, see: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147. (b) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2005**, 2065. (c) Russo, A.; De Fusco, C.; Lattanzi, A. *RSC Adv.* **2012**, 385. For recent examples, see: (d) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219. (e) Kano, T.; Ueda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 3728. (f) Cai, Y.; Wang, W.; Shen, K.; Wang, J.; Hu, X.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2010**, *46*, 1250.

(9) (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (b) Shibata, N.; Kohno, J.; Takai, K.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204. (c) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157. (d) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339.

(10) (a) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (b) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem.—Eur. J.* **2012**, *18*, 7296.

(11) During the submission of our manuscript, Toste reported fluorination of enamides. See: Phipps, R. J.; Hiramatsu, K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 8376.

(12) For seminal studies on the use of BINOL-derived phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(13) For recent reviews of chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Terada, M. *Chem. Commun.* **2008**, 4097. (d) Terada, M. *Synthesis* **2010**, 1929. (e) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (f) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (g) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.

(14) For selected examples, see: (a) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823. (b) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189. For examples of phosphoramide/calcium complexes, see: (c) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (d) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem.—Eur. J.* **2010**, *16*, 13116. (e) Terada, M.; Kanomata, K. *Synlett* **2011**, 1255. Also see: (f) Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

(15) For selected reviews dealing with enamides as nucleophiles, see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (c) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. (d) Nugenta, T. C.; El-Shazlya, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (e) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (f) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713.

(16) For selected examples, see: (a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (d) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553. (e) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (f) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546. (g) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804. (h) Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588. (i) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2010**, *13*, 94. (j) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem.—Eur. J.* **2012**, *18*, 5869.

(17) (a) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (b) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (c) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (d) Lia, G.-x.; Fu, Q.-q.; Zhang, X.-m.; Jiang, J.; Tang, Z. *Tetrahedron: Asymmetry* **2012**, *23*, 245. (e) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681.

(18) (a) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (b) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (c) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (d) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (e) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 908. (f) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749.

(19) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) Chorev, M.; Goodman, M. *Acc. Chem. Res.* **1993**, *26*, 266. (c) Chorev, M.; Goodman, M. *Trends Biotechnol.* **1995**, *13*, 438. (d) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* **1998**, *98*, 763.

(20) (*R*)-TRIP catalyst **3e** can easily be prepared from (*R*)-BINOL. See ref 14b and: Akiyama, T. U.S. Patent 0276329 A1, Dec 7, 2006.

(21) For a recent review, see: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663. For selected examples, see: (b) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776. (c) Lv, J.; Zhang, L.; Hu, J.-P.; Cheng, S.; Luo, S. *Chem.—Eur. J.* **2012**, *18*, 799.

(22) Only unreacted enecarbamate was recovered when the chiral phosphoric acid as well as its calcium salt were used as the catalyst.

(23) MALDI−TOF data for **3g** exhibited a peak at *m*/*z* 1543 corresponding to dimeric species.

(24) (a) Kraus, G. A.; Neuenschwander, R. *Tetrahedron Lett.* **1980**, *21*, 3841. (b) Quiroz, T.; Corona, D.; Covarruvias, A.; Avila-Zárraga, J. G.; Romero-Ortega, M. *Tetrahedron Lett.* **2007**, *48*, 1571.