Synthetic Methods

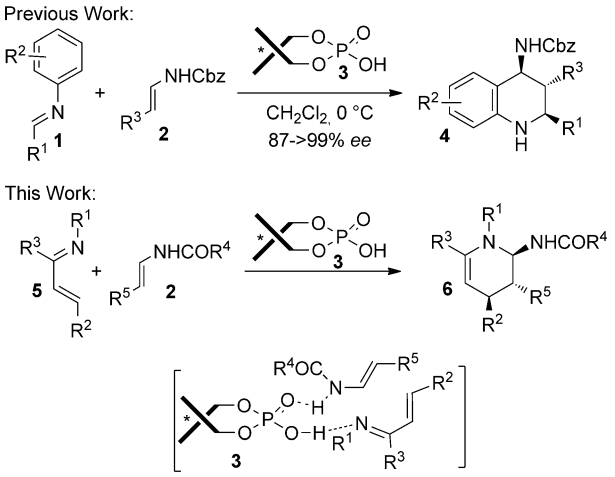
DOI: 10.1002/ange.201304969

Highly Enantioselective Aza-Diels–Alder Reaction of 1-Azadienes with Enecarbamates Catalyzed by Chiral Phosphoric Acids**

*Long He, Gregory Laurent, Pascal Retailleau, Benoît Folléas, Jean-Louis Brayer, and Géraldine Masson**

Chiral tetrahydropyridine frameworks represent a privileged six-membered azacycle commonly found within a wide variety of biologically active natural products and synthetic compounds of medicinal interest.[1] Among the synthetic approaches to access these valuable heterocycles, the inverse-electron-demand aza-Diels–Alder (IEDADA) reaction of 1-azadienes with electron-rich alkenes is one of the most convergent methods, thus resulting in the one-pot formation of a C–C and C–N bond and up to three new stereocenters.[2] Nevertheless, this IEDADA reaction suffers from drawbacks such as a low reactivity and stability of 1-azadienes, drawbacks which could be responsible for the slow development of its corresponding enantioselective version.[3] The introduction of strong electron-withdrawing groups (N-acyl, N-sulfonyl)[4,5] on the 1-aza-1,3-butadiene, thus enhancing its inherent electron-deficient character as well as its stability, have paved the way towards success in catalytic enantioselective IEDADA reaction.[3] The first example was disclosed by Bode et al.,[6] who reacted N-sulfonyl-1-aza-butadienes with β-activated aldehydes in the presence of catalytic amounts of a chiral N-heterocyclic carbene catalyst. One year later, Esquivias, Arrayás, and Carretero[7] reported that a DBFOX-Ph/Ni^{II} complex was able to catalyze the asymmetric IEDADA reaction of N-heteroarylsulfonyl α,β-unsaturated imines with vinyl ethers. Afterward, other examples of organocatalysis, relying on covalent attachment of the catalyst were used, thus leading to significant advances in the enantioselective IEDADA reaction of N-sulfonyl-1-aza-dienes.[8] To the best of our knowledge, no example of Brønsted acid catalyzed[9] IEDADA reactions of 1-azadienes has been reported, although Brønsted acids have been used successfully as catalysts in the cycloaddition of 2-azadienes.[10]

Recently, we described that chiral phosphoric acids were efficient catalysts for the asymmetric IEDADA reaction of N-arylimines (**1**) and enecarbamates (**2**) as dienophiles in a highly diastereo- and enantioselective manner (Scheme 1).[10b,f,g] A study of the mechanism indicated that the simultaneous dual activation through hydrogen-bonding interactions of the bifunctional phosphoric acid with both **1** and the NH donor group of **2** was critical for achieving high enantioselectivity.[11–13] Based on these results, we reasoned that **2** and the N-aryl-1-azadiene **5** could be well adapted as dienophile and diene, respectively, to develop an enantioselective IEDADA reaction catalyzed by a chiral phosphoric acid. Indeed, the simultaneous dual activation of the two reacting partners by the phosphoric acid catalyst might ensure high reactivity and stereoselectivity. As shown in our previous work, the cycloaddition with non-α-substituted N-aryl-azadiene ($R^3 = H$) gave solely the Povarov products **4**.[10b,f] We spectulated that the use of α,β-unsaturated ketoimines (**5**) might change the regioselectivity of the IEDADA reaction to lead to valuable 6-amino-1,4,5,6-tetrahydropyridine derivatives (**6**). This latter structural motif is found in natural products such as siastatin B, a potent neuraminidase inhibitor,[1c,e,f] or in synthetic compounds exhibiting significant in vitro antimicrobial activities.[1m]



Scheme 1. Bifunctional catalyst for the enantioselective IEDADA reaction.[10b,f] Cbz = benzyloxycarbonyl.

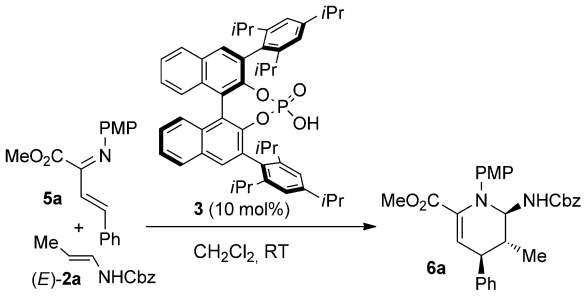
In our initial study, we chose the *N*-aryl β,γ-unsaturated α-iminoester **5a**[14] and benzylprop-1-enylcarbamate [(*E*)-**2a**] in the presence of the chiral phosphoric acid catalyst as the model reaction (Scheme 2). To our delight, *syn*- and *anti*-methyl (*E*)-2-(*p*-methoxyphenyl)-4-phenyliminobut-3-enoate[11b,15] led to desired 6-amino-1,4,5,6-tetrahydropyridine **6a** with an excellent all-*trans* diastereoselectivity. After a brief

[*] Dr. L. He, G. Laurent, Dr. P. Retailleau, Dr. G. Masson
Centre de Recherche de Gif
Institut de Chimie des Substances Naturelles, CNRS
91198 Gif-sur-Yvette Cedex (France)
E-mail: geraldine.masson@cnrs.fr
Dr. B. Folléas, Dr. J.-L. Brayer
Diverchim, ZAC du Moulin
6 rue du Noyer, 95700 Roissy-en-France (France)

[**] We wish to thank the ICSN and CNRS for financial support and Pascal Retailleau in ICSN for the X-ray crystallographic analysis. H.L. also acknowledges ANR for post-doctoral fellowships. G.L. thanks Diverchim for a CIFRE grant.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304969.

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



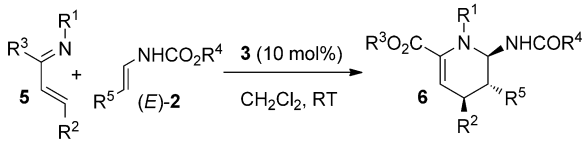
Scheme 2. Chiral phosphoric acid (**3**)-catalyzed enantioselective IEDADA reaction of 1-azadienes. PMP = *para*-methoxyphenyl.

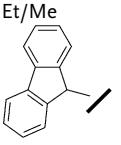
survey of reaction conditions (catalysts, the solvents, the temperatures, and the stoichiometries), we found that the reaction performed at room temperature in dichloromethane with 10 mol% of (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-binol (TRIP) phosphoric acid (**3**; see the Supporting Information) furnished the desired product in 71% yield with 93% *ee*.

With the optimal reaction conditions outlined above, a range of N-aryl-1-azabutadienes (**5**) was subjected to the enantioselective IEDADA cycloaddition. As summarized in Table 1, various β,γ-unsaturated α-iminoesters bearing electron-donating and electron-withdrawing groups at the γ-position reacted smoothly to afford the 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines **6c–j** in good yields with excellent diastereo- and enantioselectivities (entries 1–8). The presence of heteroaromatic rings such as furyl (entry 7) and thiophenyl (entry 8) is well tolerated in the cycloaddition as well. Additionally, enantioselectivities of products resulting from the reaction of N-substituted arylimines were generally high, independent of the electronic character of the aromatic ring (entry 13–17). Several 1-azadienes bearing various ester moieties such as ethyl, isopropyl, propyl, and *tert*-butyl esters were investigated. In all the cases, chiral tetrahydropyridines were obtained with the same range of yields and *ee* values (entries 9–12). The catalytic system also proved to be efficient for various carbamates, thus affording the highly substituted tetrahydropyridines **6t–y** with excellent diastereomeric (all *trans*) and *ee* values (entries 18–22). The enecarbamate **2g** participated smoothly in the cycloaddition but with a lower *ee* value (entry 23). Finally, the current cycloaddition was extended to other 1-azadienes bearing phenyl group at the α-position of the β,γ-unsaturated imines and the cycloadditions with (*E*)-**2a** proceeded with complete regioselectivity, thus affording the desired products **6z** and **6aa** with high enantioselectivities, albeit with slightly moderate yields (entries 24 and 25). The absolute configuration of **6c** was unambiguously determined to be 4*S*,5*R*, and 6*R* by single-crystal X-ray analysis (see the Supporting information).

On the basis of previous work,[2,16] we proposed two mechanism pathways for the cycloaddition: a) a concerted mechanism between the 1-azadiene and the enecarbamate or b) a two-step mechanism consisting first of the enecarbamate attacking the β,γ-unsaturated α-iminoester through a Michael reaction with subsequent intramolecular aminalization of the formed anion into an iminium ion.[2g,17] To distinguish between the two mechanisms, we evaluated the influence of the substitution at the N- and Cγ-positions in β,γ-unsaturated α-iminoesters. Here, we observed that the presence of an electron-donating or electron-withdrawing group on the nitrogen atom has an influence on reaction times (see the Supporting Information). Likewise, reaction rates are influenced by the electronic nature of aryl substituents in the γ-position. These findings seem consistent with a concerted mechanism. In addition, when EtOH (3 to 10 equivalents or as solvent) was added to the reaction to trap the iminium

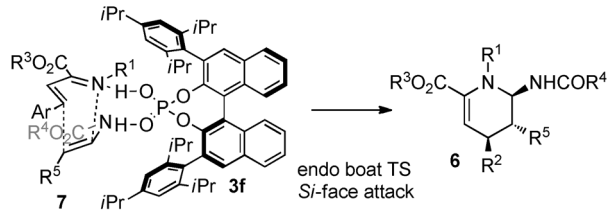
Table 1: Substrate scope of the enantioselective synthesis of 4,5,6-trisubstituted-1,4,5,6-tetrahydropyridines.[a]



Entry	$R^1/R^2/R^3$	R^4/R^5	**6**	Yield [%][b]	*ee* [%][c]
1	PMP/4-ClC_6H_4/CO_2Me	Bn/Me	**6c**	75	95[d]
2	PMP/4-MeC_6H_4/CO_2Me	Bn/Me	**6d**	72	90[d]
3	PMP/4-$OMeC_6H_4$/CO_2Me	Bn/Me	**6e**	63	86
4	PMP/4-$NO_2C_6H_4$/CO_2Me	Bn/Me	**6f**	63	86
5	PMP/3-ClC_6H_4/CO_2Me	Bn/Me	**6g**	74	91
6	PMP/3-BrC_6H_4/CO_2Me	Bn/Me	**6h**	76	91
7		Bn/Me	**6i**	72	94[e]
8		Bn/Me	**6j**	63	91
9	PMP/Ph/CO_2Et	Bn/Me	**6k**	76	93[d]
10	PMP/Ph/CO_2nPr	Bn/Me	**6l**	62	91
11	PMP/Ph/CO_2iPr	Bn/Me	**6m**	72	92
12	PMP/Ph/CO_2tBu	Bn/Me	**6n**	61	94
13	4-ClC_6H_4/Ph/CO_2Me	Bn/Me	**6o**	72	94[e]
14	4-MeC_6H_4/Ph/CO_2Me	Bn/Me	**6p**	82	92
15	2-$MeOC_6H_4$/Ph/CO_2Me	Bn/Me	**6q**	68	92[d]
16	Ph/Ph/CO_2Me	Bn/Me	**6r**	75	92
17	4-BrC_6H_4/Ph/CO_2Me	Bn/Me	**6s**	74	92
18	PMP/Ph/CO_2Me	Et/Me	**6t**	78	90[d]
19	PMP/Ph/CO_2tBu		**6u**	66	94
20	Ph/Ph/CO_2Me	4-$CF_3C_6H_4CH_2$/Me	**6v**	84	91[f]
21	Ph/Ph/CO_2Me	4-$BrC_6H_4CH_2$/Me	**6w**	73	92[g]
22	Ph/Ph/CO_2Me	$C_6F_5CH_2$/Me	**6x**	68	93[f]
23	PMP/Ph/CO_2iPr	tBu/n-C_3H_7	**6y**	61	70[e]
24	PMP/Ph/Ph	Bn/Me	**6z**	59	93
25	PMP/Ph/4-BrC_6H_4	Bn/Me	**6aa**	57	88

[a] Reaction conditions: 1-azadiene **5** (0.1 mmol), enecarbamate (*E*)-**2** (0.2 mmol), **3f** (0.01 mmol) in CH_2Cl_2 (1.0 mL) at RT. [b] Yield of chromatographically pure product, all *trans* isomer (d.r. = 95:5). [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reaction at 0°C. [e] d.r. = 7:1. [f] d.r. = 9:1. [g] d.r. = 12:1.

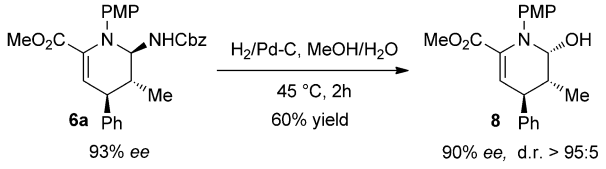
 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Activation model via a putative transition state. TS = transition state.

intermediate, neither the expected adduct nor the tetrahydropyridine were detected.[18] Even though we cannot definitely rule out a possible stepwise mechanism, this supports a highly asynchronous concerted mechanism. Based on these observations, we propose a transition state to explain the observed (absolute) stereochemical outcome of the enantioselective IEDDA reaction (Scheme 3). In this system, the chiral phosphoric acid may serve as a bifunctional catalyst: the OH group activates the 1-azadiene as a Brønsted acid and the phosphoryl oxygen atom activates the enecarbamates as a Lewis base. The IEDADA reaction might take place with *endo* selectivity, via a transition state in which the *Si* face of the azadiene would be attacked, thus affording the (4*S*,5*R*,6*R*)-cycloadduct **6**. The importance of the hydrogen atom on **2** was supported by the moderate yield and enantioselectivity of the reaction with a tertiary endocyclic enecarbamate (see the Supporting Information). This indicates that the presence of the NH group is crucial for both reactivity and enantioselectivity.

With the successful construction of tetrahydropyridines, we turned our attention to transforming **6** into valuable compounds. As illustrated in Scheme 4, removal of the Cbz



Scheme 4. Synthetic transformation of the tetrahydropyridine.

group in **6a** by a Pd/C-catalyzed hydrogenolysis produced the hemiaminal adduct **8** (a key precursor of a variety of chiral piperidines as described by other authors)[8a–b] in 60% yield with a very subtle erosion of enantioselectivity.

In summary, we have developed the first catalytic enantioselective IEDADA reaction of N-aryl α,β-unsaturated ketimines (**5**) and β-substituted enecarbamates (**2**) using a chiral bifunctional phosphoric acid catalyst. This cycloaddition employs easily accessible starting materials to construct densely functionalized 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines (**6**) having three contiguous stereogenic centers (with up to 84% yield, 95:5 d.r. and 95% *ee*). Early mechanistic studies seem to indicate that the reaction proceeds by an asynchronous concerted mechanism. Further studies regarding the applications of this IEDADA reaction are ongoing and will be reported in due course.

Received: June 10, 2013
Revised: July 5, 2013
Published online: August 28, 2013

Keywords: cycloaddition · dienes · heterocycles · organocatalysis · synthetic methods

[1] a) J. P. Michael in *The Alkaloids*, *Vol. 55* (Ed.: G. A. Cordell), Academic Press, San Diego, **2001**; b) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633–640; c) Y. Nishimura, T. Satoh, H. Adachi, S. Kondo, T. Takeuchi, M. Azetaka, H. Fukuyasu, Y. Lizuka, *J. Med. Chem.* **1997**, *40*, 2626–2633; d) P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679–3681; e) S. Knapp, D. Zhao, *Org. Lett.* **2000**, *2*, 4037–4040; f) E. Shitara, Y. Nishimura, K. Nerome, Y. Hiramoto, T. Takeuchi, *Org. Lett.* **2000**, *2*, 3837–3840; g) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; h) V. H. Lillelund, H. H. Jensen, X. F. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553; i) M. Amat, N. Llor, J. Hidalgo, C. Escolano, J. Bosch, *J. Org. Chem.* **2003**, *68*, 1919–1928; j) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; k) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; l) F.-X. Felpin, J. Lebreton, *Curr. Org. Synth.* **2004**, *1*, 83–109; m) N. Zanatta, L. da S. Fernandes, F. M. Nachtigall, H. S. Coelho, S. S. Amaral, A. F. C. Flores, H. G. Bonacorso, M. A. P. Martins, *Eur. J. Org. Chem.* **2009**, 1435–1444, and references therein; n) X. G. Huang, A. Q. Zhang, D. L. Chen, Z. H. Jia, X. S. Li, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2859–2863.

[2] a) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546; b) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902–923; c) P. R. Girling, T. Kiyoi, A. Whiting, *Org. Biomol. Chem.* **2011**, *9*, 3105–3121; d) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721–2750; e) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138.

[3] a) M. E. Jung, J. J. Shapiro, *J. Am. Chem. Soc.* **1980**, *102*, 7862–7866; for selected review, see: b) J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983**, 517–536; c) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**, chap. 2, pp. 34–70; chap. 9, pp. 239–299, and references therein; d) M. Behforouz, M. Ahmadian, *Tetrahedron* **2000**, *56*, 5259–5288; e) B. Groenendaal, E. Ruijter, R. V. A. Orru, *Chem. Commun.* **2008**, 5474–5489; f) J.-C. M. Monbaliu, K. G. R. Masschelein, C. V. Stevens, *Chem. Soc. Rev.* **2011**, *40*, 4708–4739.

[4] a) Y.-S. Cheng, A. T. Lupo, F. W. Fowler, *J. Am. Chem. Soc.* **1983**, *105*, 7696–7703; b) Y. C. Hwang, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 2719–2726; c) N. J. Sisti, I. A. Motorina, M.-E. Tran Huu Dau, C. Riche, F. W. Fowler, D. S. Grierson, *J. Org. Chem.* **1996**, *61*, 3715–3728.

[5] a) D. L. Boger, A. M. Kasper, *J. Am. Chem. Soc.* **1989**, *111*, 1517–1519; b) D. L. Boger, W. L. Corbett, J. M. Wiggins, *J. Org. Chem.* **1990**, *55*, 2999–3000; c) D. L. Boger, T. T. Curran, *J. Org. Chem.* **1990**, *55*, 5439–5442; d) D. L. Boger, W. L. Corbett, T. T. Curran, A. M. Kasper, *J. Am. Chem. Soc.* **1991**, *113*, 1713–1729; e) R. C. Clark, S. S. Pfeiffer, D. L. Boger, *J. Am. Chem. Soc.* **2006**, *128*, 2587–2593, and references therein.

[6] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[7] a) J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480 – 1481; b) J. Esquivias, I. Alonso, R. Gómez Arrayás, J. C. Carretero, *Synthesis* **2009**, 113 – 126.

[8] a) J.-P. Wan, C. C. J. Loh, F. Pan, D. Enders, *Chem. Commun.* **2012**, *48*, 10049 – 10051; b) B. Han, J.-L. Li, C. Ma, S.-J. Zhang, Y.-C. Chen, *Angew. Chem.* **2008**, *120*, 10119 – 10122; *Angew. Chem. Int. Ed.* **2008**, *47*, 9971 – 9974; c) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491 – 1500; d) J.-L. Li, S.-L. Zhou, B. Han, L. Wu, Y.-C. Chen, *Chem. Commun.* **2010**, *46*, 2665 – 2667; e) Z.-Q. He, B. Han, R. Li, L. Wu, Y.-C. Chen, *Org. Biomol. Chem.* **2010**, *8*, 755 – 757; f) S.-L. Zhou, J.-L. Li, L. Dong, Y.-C. Chen, *Org. Lett.* **2011**, *13*, 5874 – 5877; g) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5582 – 5585; *Angew. Chem. Int. Ed.* **2009**, *48*, 5474 – 5477; h) C. Simal, T. Lebl, A. M. Z. Slawin, A. D. Smith, *Angew. Chem.* **2012**, *124*, 3713 – 3717; *Angew. Chem. Int. Ed.* **2012**, *51*, 3653 – 3657; i) X. Jiang, X. Shi, S. Wang, T. Sun, Y. Cao, R. Wang, *Angew. Chem.* **2012**, *124*, 2126 – 2129; *Angew. Chem. Int. Ed.* **2012**, *51*, 2084 – 2087; j) Y. Deng, L. Liu, R. G. Sarkisian, K. Wheeler, H. Wang, Z. Xu, *Angew. Chem.* **2013**, *125*, 3448 – 3452; *Angew. Chem. Int. Ed.* **2013**, *52*, 3364 – 3667; k) Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun, *Angew. Chem.* **2013**, *125*, 2081 – 2085; *Angew. Chem. Int. Ed.* **2013**, *52*, 2027 – 2031; l) T.-Y. Jian, P.-L. Shao, S. Ye, *Chem. Commun.* **2011**, *47*, 2381 – 2383; m) P. Hu, J. Hu, J. Jiao, X. Tong, *Angew. Chem. Int. Ed.* **2013**, *125*, 5427 – 5430; *Angew. Chem.* **2013**, *52*, 5319 – 5322.

[9] For recent reviews on Brønsted acid catalysis, see: a) H. Yamamoto, J. N. Payette in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 73 – 140; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; c) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516 – 532; d) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395 – 456.

[10] For Brønsted acid catalyzed IEDADA reactions, see: a) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070 – 13071; b) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598 – 4599; c) C. Wang, Z.-Y. Han, H.-W. Luo, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 2266 – 2269; d) G. Bergonzini, L. Gramigna, A. Mazzanti, M. Fochi, L. Bernardi, A. Ricci, *Chem. Commun.* **2010**, *46*, 327 – 329; e) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986 – 990; f) G. Dagousset, J. Zhu, G. Masson, *J. Am. Chem. Soc.* **2011**, *133*, 14804 – 14813; g) G. Dagousset, P. Retailleau, G. Masson, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 5869 – 5873; h) L. He, M. Bekkaye, P. Retailleau, G. Masson, *Org. Lett.* **2012**, *14*, 3158 – 3161; i) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* **2012**, *77*, 6970 – 6979; j) F. Shi, G.-J. Xing, R.-Y. Zhu, W. Tan, S. Tu, *Org. Lett.* **2013**, *15*, 128 – 131.

[11] For recent reviews on chiral phosphoric acid catalysis, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; c) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; d) M. Terada, *Synthesis* **2010**, 1929 – 1982; e) M. Terada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101 – 119; f) M. Terada, *Curr. Org. Chem.* **2011**, *15*, 2227 – 2256; g) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539 – 4549.

[12] Selected reviews dealing with enamides as nucleophiles, see: a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054 – 3131; b) R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292 – 301; c) D. R. Carbery, *Org. Biomol. Chem.* **2008**, *6*, 3455 – 3460; d) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753 – 819; e) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599 – 4657; f) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713 – 1760.

[13] Selected example of using enamides as nucleophiles in phosphoric acid catalyzed transformations: a) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312 – 2315; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254 – 2257; b) K. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336 – 10337; c) M. Terada, K. Soga, N. Momiyama, *Angew. Chem.* **2008**, *120*, 4190 – 4193; *Angew. Chem. Int. Ed.* **2008**, *47*, 4122 – 4125; d) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2009**, *121*, 2591 – 2594; *Angew. Chem. Int. Ed.* **2009**, *48*, 2553 – 2556; e) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620 – 4623; f) G. Dagousset, F. Drouet, G. Masson, J. Zhu, *Org. Lett.* **2009**, *11*, 5546 – 5549; g) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li, G. Zhong, *Angew. Chem.* **2010**, *122*, 8770 – 8774; *Angew. Chem. Int. Ed.* **2010**, *49*, 8588 – 8592; h) F. Drouet, C. Lalli, H. Liu, G. Masson, J. Zhu, *Org. Lett.* **2011**, *13*, 94 – 97; i) A. Alix, C. Lalli, P. Retailleau, G. Masson, *J. Am. Chem. Soc.* **2012**, *134*, 10389 – 10392.

[14] J. Vicario, D. Aparicio, F. Palacios, *Tetrahedron Lett.* **2011**, *52*, 4109 – 4111.

[15] 1-Azadienes were used as a *syn*/*anti* mixture of isomers: F. Palacios, J. Vicario, D. Aparicio, *J. Org. Chem.* **2006**, *71*, 7690 – 7696.

[16] a) J. Gonzalez, K. N. Houk, *J. Org. Chem.* **1992**, *57*, 3031 – 3037; b) L. R. Domingo, *Tetrahedron* **2002**, *58*, 3765 – 3774; c) R. G. Parr, L. von Szentpaly, S. Liu, *J. Am. Chem. Soc.* **1999**, *121*, 1922 – 1924.

[17] For stepwise mechanisms for polar Diels – Alder reactions, see: L. R. Domingo, J. A. Sáez, *Org. Biomol. Chem.* **2009**, *7*, 3576 – 3583.

[18] The majority of the unreacted 1-azadienes was recovered.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim