

Organocatalysis

International Edition: DOI: 10.1002/anie.201604201
German Edition: DOI: 10.1002/ange.201604201Brønsted Acid Catalyzed Addition of Enamides to *ortho*-Quinone Methide Imines—An Efficient and Highly Enantioselective Synthesis of Chiral Tetrahydroacridines

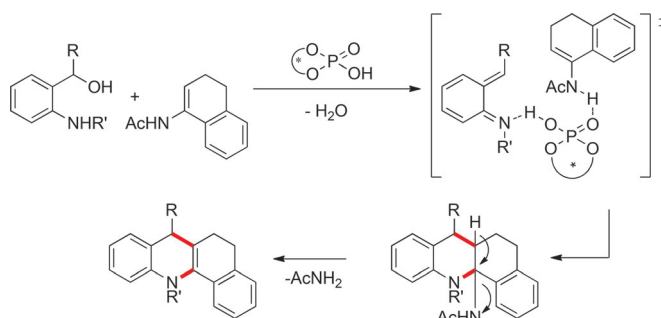
Martin Kretzschmar, Tomáš Hodík, and Christoph Schneider*

Abstract: The direct and highly enantioselective synthesis of tetrahydroacridines was achieved through the phosphoric acid catalyzed addition of enamides to in situ generated *ortho*-quinone methide imines and subsequent elimination. This novel one-step process constitutes a very efficient, elegant, and selective synthetic approach to valuable *N*-heterocycles with a 1,4-dihydroquinoline motif. By subsequent highly diastereoselective hydrogenation and *N*-deprotection the reaction products were easily converted into free hexahydroacridines with a total of three new stereogenic centers.

An essential goal of modern synthetic organic chemistry is the efficient and selective synthesis of complex, enantiomerically pure compounds that exhibit significant biological activity. In this respect catalytic, enantioselective processes that ideally form several bonds in a single step are distinguished through high levels of efficiency and are becoming increasingly important.^[1]

Due to their high biological activity 1,4-dihydroquinolines are privileged structural motifs in the field of medicine and biology, exhibiting anticancerogenic, HIV integrase inhibiting, and antimicrobial properties amongst others.^[2] Hydroacridines also play an important role in treatment of Alzheimer's disease and have already been approved as reversible inhibitors of acetylcholinesterase.^[3] Despite this huge potential only a few direct syntheses of this class of substances are currently known, and even these have a limited substrate scope.^[4] A direct and broadly applicable synthetic approach towards this important structural motif without these limitations would be very desirable.

We herein report a conceptually novel, one-step synthetic strategy comprising a highly enantioselective, phosphoric acid catalyzed formal cycloaddition of enamides with in situ generated *ortho*-quinone methide imines as the key step (Scheme 1). Additionally, the tetrahydrobenzo[*c*]acridines thus formed can be hydrogenated with full control of diastereoselectivity to provide saturated hexahydroacridines with two new stereogenic centers. The hexahydroacridines structural motif, which closely resembles the tetrahydroquinolines, is also well known for its versatile biological activities.^[5]



Scheme 1. Concept behind this *N*-heterocycle synthesis.

Ortho-quinone methide imines are transient synthetic intermediates which readily react with electron-rich 2π components in hetero-Diels–Alder reactions and with nucleophiles in conjugate 1,4-additions, both with reconstitution of the aromatic π-system.^[6] They can be generated by various methods ranging from thermolysis and photolysis to acid- or base-mediated eliminations.^[7] However, currently only very few catalytic, asymmetric examples exist that fully exploit the synthetic potential of *ortho*-quinone methide imines.^[8] Tunge and Wang developed a palladium-catalyzed, formal [4+2]-cycloaddition of alkylidene malononitriles leading to tetrahydroquinolines.^[8a] Scheidt et al. revealed that azolium enolates generated by *N*-heterocyclic carbene (NHC) catalysis react with *ortho*-quinone methide imines in a highly enantioselective fashion to form dihydroquinolones.^[8b] A Brønsted acid catalyzed transfer hydrogenation of 1,2-dihydroquinolines with Hantzsch esters was described by Li et al.^[8c]

We^[9] and other groups^[10] recently reported phosphoric acid catalyzed, highly enantioselective, conjugate additions of different π-nucleophiles to the related *ortho*-quinone methides which were obtained in situ from the corresponding benzhydryl alcohols by dehydration. Pursuing this strategy we were able to gain access to a broad range of benzoannulated oxygen heterocycles with a high level of enantiocontrol. Independently, Rueping and co-workers successfully transferred this concept to *ortho*-quinone methide imines in conjugate addition reactions of alcohols and indoles recently.^[11]

On the basis of our previous work we envisioned the synthesis of tetrahydroacridines starting from *N*-protected amino benzhydryl alcohols and enamides.^[12] The benzhydryl alcohols were to be transformed in situ to hydrogen-bonded *ortho*-quinone methide imines by a chiral phosphoric acid,^[13] which in a bifunctional catalysis mode would also form a hydrogen bond to the enamide (Scheme 1). In an ensuing

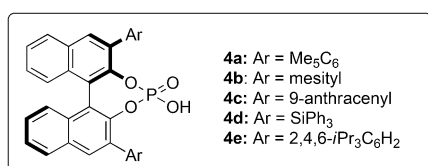
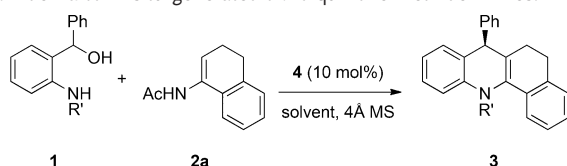
[*] M. Sc. M. Kretzschmar, M. Sc. T. Hodík, Prof. Dr. C. Schneider
Institut für Organische Chemie, Universität Leipzig
Johannisallee 29, 04103 Leipzig (Germany)
E-mail: schneider@chemie.uni-leipzig.de

Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201604201>.

formal cycloaddition two new σ -bonds would eventually form and upon elimination of acetamide a tetrahydrobenzo[*c*]acridine would emerge as the product of the reaction.

First experiments were carried out using the *N*-allyl-protected *ortho*-aminobenzhydriyl alcohol **1a**, tetralone-based enamide **2a**, and 10 mol % of chiral BINOL-based phosphoric acid **4a** in chloroform at room temperature for 3 days giving rise to tetrahydrobenzo[*c*]acridine **3a** with 72 % yield and 96:4 e.r. (Table 1, entry 1). While handling the products in

Table 1: Optimization of the phosphoric acid catalyzed addition of enamide **2a** to in situ generated *ortho*-quinone methide imines.^[a]



Entry	Solvent	R' (product)	Cat.	Yield[%] ^[b]	e.r. ^[c]
1	CHCl ₃	allyl (3a)	4a	72	96:4
2	CHCl ₃	PMP (3b)	4a	61	85:15
3	CHCl ₃	benzyl (3c)	4a	73	96:4
4	CHCl ₃	PMB (3d)	4a	75	97:3
5	CHCl ₃	PMB (3d)	4b	65	96:4
6	CH ₂ Cl ₂	PMB (3d)	4b	74	95:5
7	toluene	PMB (3d)	4b	50	93:7
8	CH ₃ CN	PMB (3d)	4b	34	73:27
9	CHCl ₃	PMB (3d)	4c	45	89:11
10	CHCl ₃	PMB (3d)	4d	51	65:35
11	CHCl ₃	PMB (3d)	4e	68	89:11
12	CHCl ₃	PMB (3d)	4a	79 ^[d]	97:3

[a] Reaction conditions: 0.10 mmol (1.0 equiv) *ortho*-aminobenzhydriyl alcohol **1**, 0.12 mmol (1.2 equiv) enamide **2a**, catalyst **4** (10 mol %), 4 Å molecular sieves (powdered, 25 mg), solvent (1 mL), RT, 3 d. [b] Yield of isolated product after purification by flash column chromatography [c] Enantiomeric ratio determined by HPLC on a chiral stationary phase (see the Supporting Information). [d] Reaction time 4 d.

the presence of light and oxygen we noticed a rapid aromatization to acridine **8**. Therefore all further work was done under the utmost exclusion of light to prevent this undesired side reaction. Reaction of the *N*-unsubstituted starting material (R' = H) did not yield the desired unsubstituted product but instead acridine **8** was obtained again directly. In screening various *N*-substituents we found that electron-rich, aliphatic *N*-groups gave the best results with regard to yield and selectivity. Based on these results and for the ease of later deprotection we decided to use the *N*-*p*-methoxybenzyl- (PMB)-protected substrate **1d** for further studies (entries 1–4). A short solvent screen revealed that chloroform was superior to other solvents (entries 5–8). Among the BINOL-based phosphoric acids **4a–e** that we tested for this reaction, phosphoric acid **4a** carrying 3,3'-pentamethylphenyl groups proved to be optimal (entries 9–12). Furthermore, a prolon-

gation of reaction time also led to an increase of yield (entry 12). The absolute configuration of the products was unambiguously determined by X-ray crystallography of tetrahydrobenzo[*c*]acridine **3d** (Figure 1).^[14]

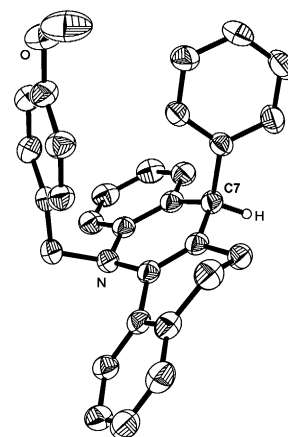
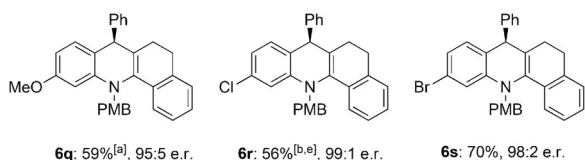
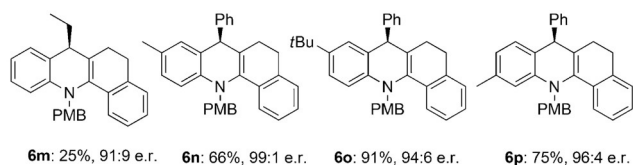
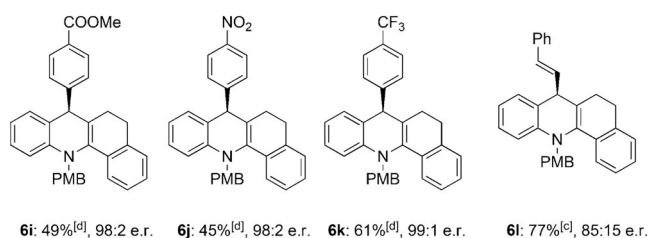
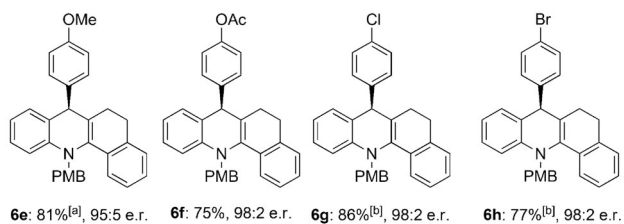
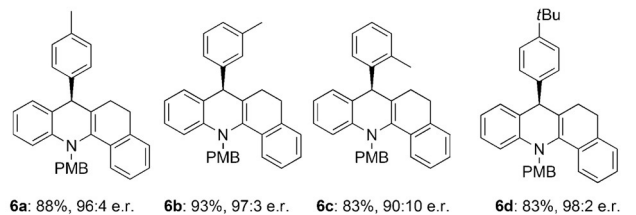
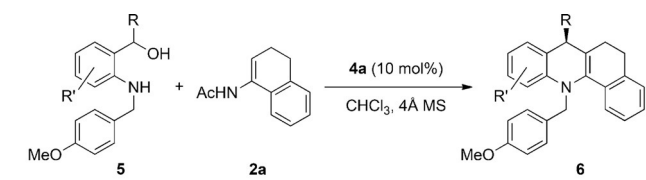


Figure 1. Crystal structure of tetrahydrobenzo[*c*]acridine **3d**. Thermal ellipsoids at the 50 % probability level.^[14]

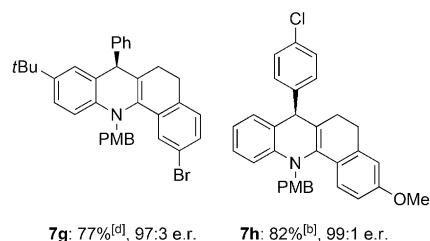
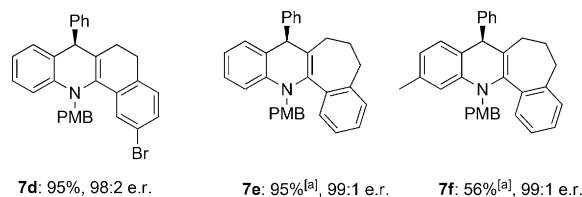
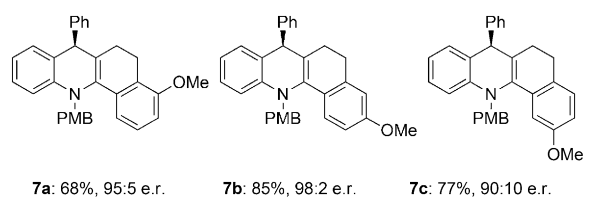
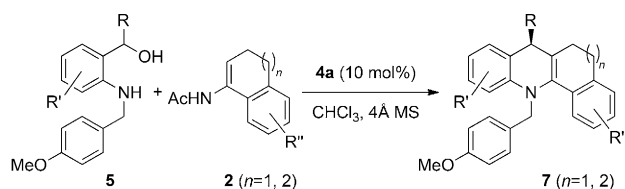
With optimized reaction conditions for this process established, its substrate scope was subsequently studied first by reacting various substituted *ortho*-aminobenzhydriyl alcohols **5** with enamide **2a** (Scheme 2). Quite a number of different aryl groups were tolerated in the 7-position of the acridine backbone yielding the desired products with constantly excellent selectivities of up to 99:1 e.r. and moderate to very good yields. Acridines **6a–f** containing electronically neutral or electron-rich 7-aryl groups were obtained in typically fast reactions with very good yields and mostly outstanding enantioselectivities. In this category of substrates only the introduction of a substitution in *ortho*-position caused a slight drop in selectivity to 90:10 e.r. (see **6c**). *para*-Halogen-substituted products **6g,h** were also obtained in good yields and with excellent selectivities but required longer reaction times, supposedly due to the negative inductive effect. Products **6i–k** with electron-poor 7-aryl substituents were again obtained with excellent selectivity but only with moderate yields and also required an increase of the reaction temperature to 40 °C. These observed substituent effects suggest that the formation of the *ortho*-quinone methide imine, which is readily stabilized by electron-rich substituents, was the rate-determining step of the entire reaction cascade.^[15] Alkenyl- and alkyl-substituted products **6l** and **6m** were obtained with good enantioselectivities of up to 91:9 e.r. as well. Probably due to the diminished stability of the in situ formed *ortho*-quinone methide imine product **6m** was isolated in only moderate yield. Structural variations in the acridine backbone were also investigated by employing the corresponding *ortho*-aminobenzhydriyl alcohols **5**. Thus, alkyl, alkoxy, and halogen substituents were easily introduced in positions 9 and 10 of the acridine and the products **6n–s** were obtained with good yields and with up to 99:1 e.r.

In order to further expand the diversity of available scaffolds, additional enamides **2b–f** were studied under the established reaction conditions (Scheme 3). Alkoxy and



Scheme 2. Substrate scope of the phosphoric acid catalyzed synthesis of 5,6,7,12-tetrahydrobenzo[c]acridines **6**. Reaction conditions: 0.10 mmol (1.0 equiv) PMB-protected *ortho*-aminobenzhydryl alcohol **5**, 0.12 mmol (1.2 equiv) enamide **2a**, catalyst **4a** (10 mol%), 4 Å molecular sieves (powdered, 25 mg), solvent (1 mL), RT, 4 d. [a] Reaction time 24 h. [b] Reaction time 6 d. [c] Temperature: 0°C. [d] Temperature: 40°C. [e] Very high sensitivity towards light.

bromo substituents on the aromatic ring of the tetralone backbone were tolerated very well and the products **7a–d** were obtained in good yields and with excellent enantioselectivity throughout.^[16] A ring expansion as in enamide **2f** ($n=2$) was possible without any difficulty and gave product **7e** in almost quantitative yield and with 99:1 e.r. after a short reaction time. Finally, reactions of enamides **2c**, **2e**, and **2f** with *ortho*-aminobenzhydryl alcohols **5g**, **5o**, and **5p** yielded

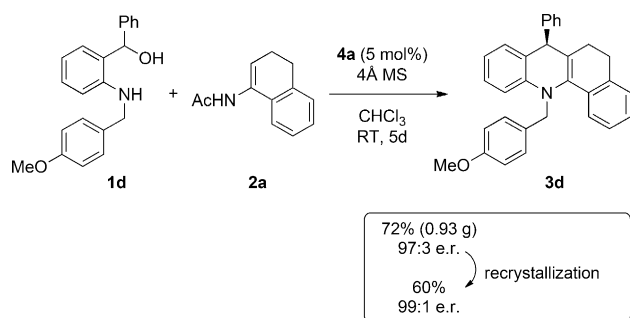


Scheme 3. Expansion of the substrate scope towards more highly substituted enamides **2**. Reaction conditions: 0.10 mmol (1.0 equiv) PMB-protected *ortho*-aminobenzhydryl alcohol **5**, 0.12 mmol (1.2 equiv) enamide **2**, catalyst **4a** (10 mol%), 4 Å molecular sieves (powdered, 25 mg), solvent (1 mL), RT, 4 d. [a] Reaction time 24 h. [b] Reaction time 6 d. [c] Temperature: 0°C. [d] Very high sensitivity towards light.

highly substituted 1,4-dihydroquinoline systems **7f–h**, respectively, with good yields and > 97:3 e.r. respectively. In control experiments with *N*-alkyl-*N*-acetyl enamides, which do not carry a free NH proton, no product formed, underlining the importance of an additional hydrogen-bond activation of the nucleophile in this reaction.

To demonstrate the applicability of our process a large-scale synthesis of tetrahydrobenzo[c]acridine **3d** was conducted (Scheme 4). In doing so we were able to further lower the catalyst loading to only 5 mol% while retaining a good yield of 72% and an excellent selectivity of 97:3 e.r. The product **3d**, which we obtained in an amount of 0.93 g, could be optically further enantiomerically enriched to 99:1 e.r. by one recrystallization.

Mechanistically, the title reaction may occur either as a concerted [4+2]-cycloaddition or as a stepwise process initiated by a conjugate addition followed directly by cyclization to the amination.^[17] We currently assume that both the *ortho*-quinone methide imine and the enamide are bound through hydrogen bonds to the chiral phosphoric acid in the transition state of this reaction (Figure 2). In our proposed



Scheme 4. Synthesis of tetrahydrobenzo[*c*]acridine **3d** on a gram scale.

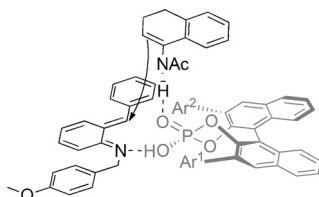


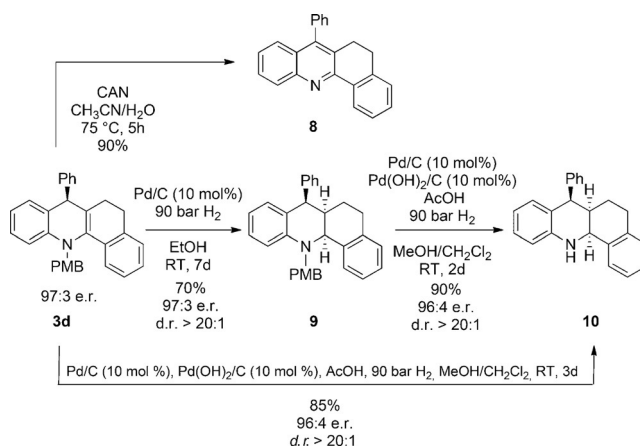
Figure 2. Proposed transition state of the reaction.

transition-state assembly the bottom face of the *ortho*-quinone methide imine is effectively blocked by the aryl group Ar² of the catalyst which is closer to the reaction center thereby directing the enamide to attack from the top face. This arrangement would also explain the observed decrease in selectivity for substrates with *ortho*-substituted β -aryl groups.

To further functionalize the reaction products we first intended to cleave the PMB protecting group which can be achieved either hydrogenolytically or oxidatively. Treatment with ceric ammonium nitrate, however, led to almost quantitative formation of acridine **8**, formation of which was previously observed under the influence of light. Therefore, we chose to use a hydrogenolytic approach for deprotection. Initially, using 10 mol % of palladium on activated charcoal and a hydrogen pressure of 90 bar, we were able to selectively hydrogenate the enamine double bond and obtain the PMB-protected hexahydrobenzo[*c*]acridine **9** with good yield and complete diastereoselectivity (Scheme 5). The relative configuration of **9** was determined through NOESY NMR measurements (see the Supporting Information) and is consistent with the observation that the bottom face of **3d** is much more easily accessible (see the X-ray crystal structure in Figure 1).

Subsequently, by combining palladium on activated charcoal and the Pearlman catalyst, and adding acetic acid in methanol^[18] we obtained the free hexahydrobenzo[*c*]acridine **10** with good yield and selectivity. This sequence of enamine hydrogenation and PMB cleavage was also easily achieved in one step by simultaneously using palladium and Pd(OH)₂ on activated charcoal in acetic acid/methanol. Thus, we were able to obtain the free hexahydrobenzo[*c*]acridine **10** directly from **3d** in 85 % yield and as a single diastereomer with 96:4 e.r.

In conclusion, we have developed a broadly applicable phosphoric acid catalyzed, enantioselective addition of



Scheme 5. Further functionalization of tetrahydrobenzo[*c*]acridine **3d**.

enamides to in situ generated *ortho*-quinone methide imines which delivers highly valuable tetrahydroacridines in typically very good yields and with excellent enantioselectivities. The applicability of our process was demonstrated by a large-scale experiment. Furthermore, the products were subsequently converted into saturated hexahydroacridines with two new stereogenic centers and very high diastereoselectivity. The extension of this method to other nucleophiles as well as further functionalizations of the reaction products are subjects of our current investigations.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SCHN 441/11-1) for the generous financial support of this work. M. Kretzschmar and T. Hodik are grateful for doctoral fellowships from the Deutsche Bundesstiftung Umwelt (DBU) and the DAAD, respectively. We thank Prof. D. Sieler (Universität Leipzig) for conducting the X-ray crystallography and Evonik and BASF for the donation of chemicals.

Keywords: asymmetric synthesis · chiral phosphoric acids · nitrogen heterocycles · organocatalysis · *ortho*-quinone methide imines

How to cite: *Angew. Chem. Int. Ed.* **2016**, 55, 9788–9792
Angew. Chem. **2016**, 128, 9941–9946

- [1] Representative reviews: a) D. Enders, C. Grondal, M. R. M. Huettl, *Angew. Chem. Int. Ed.* **2007**, 46, 1570–1581; *Angew. Chem.* **2007**, 119, 1590–1601; b) E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley, New York, **2009**; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, 2, 167–178; d) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, 51, 314–325; *Angew. Chem.* **2012**, 124, 320–332; e) H. Pellissier, *Adv. Synth. Catal.* **2012**, 354, 237–294; f) H. Pellissier, *Organocatalysis in Domino Processes* (Ed.: L. F. Tietze) Wiley-VCH, Weinheim, **2014**, pp. 325–358; for a general overview concerning domino reactions see: g) L. F. Tietze, *Chem. Rev.* **1996**, 96, 115–136; h) *Domino Reactions: Concepts for Efficient Organic Synthesis* (Ed.: L. F. Tietze), Wiley-VCH, Weinheim, **2014**.
- [2] a) J. Y. Nagasawa, J. Song, H. Chen, H.-W. Kim, J. Blazel, S. Ouk, B. Groschel, V. Borges, V. Ong, L.-T. Yeh, et al., *Bioorg. Med.*

- Chem. Lett.* **2011**, 21, 760–763; b) P. Chidurala, V. Jetti, R. Pagadala, J. S. Meshram, S. B. Jonnalagadda, *J. Heterocycl. Chem.* **2015**, 52, 1302–1307; c) M. Hemmer, S. Krawczyk, I. Simon, H. Lage, A. Hilgeroth, *Bioorg. Med. Chem.* **2015**, 23, 5015–5021; d) M. Hemmer, S. Krawczyk, I. Simon, A. Hilgeroth, *Bioorg. Med. Chem. Lett.* **2015**, 25, 3005–3008.
- [3] G. R. Proctor, A. L. Harvey, *Curr. Med. Chem.* **2000**, 7, 295–302.
- [4] a) K. Namba, M. Kanaki, H. Suto, M. Nishizawa, K. Tanino, *Org. Lett.* **2012**, 14, 1222–1225; b) K.-Y. Park, J. Lee, S. J. Park, J.-N. Heo, H. J. Lim, *Adv. Synth. Catal.* **2015**, 357, 3917–3926; c) M.-L. Bannasar, T. Roca, M. Moneris, D. García-Díaz, *Tetrahedron Lett.* **2005**, 46, 4035–4038; d) S. Stokes, M. Bekkam, M. Rupp, K. Mead, *Synlett* **2012**, 23, 389–392; e) J. N. Kim, H. S. Kim, J. H. Gong, Y. M. Chung, *Tetrahedron Lett.* **2001**, 42, 8341–8344; f) G. Viault, D. Grée, T. Roisnel, S. Chandrasekhar, R. Grée, *Tetrahedron* **2009**, 65, 10149–10154; g) X. Zhang, X. Song, H. Li, S. Zhang, X. Chen, X. Yu, W. Wang, *Angew. Chem. Int. Ed.* **2012**, 51, 7282–7286; *Angew. Chem.* **2012**, 124, 7394–7398; h) Y. Lee, S. Heo, S.-G. Kim, *Adv. Synth. Catal.* **2015**, 357, 1545–1550; i) F. Rezgui, P. Mangeney, A. Alexakis, *Tetrahedron Lett.* **1999**, 40, 6241–6244; j) Y. Mikata, S. Aida, S. Yano, *Org. Lett.* **2004**, 6, 2921–2924; k) A. Suresh Kumar, T. Prabhakar Reddy, R. Madhavachary, D. B. Ramachary, *Org. Biomol. Chem.* **2016**, 14, 5494–5499.
- [5] a) P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, *J. Med. Chem.* **1992**, 35, 1954–1968; b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, 111, 7157–7259; c) R. N. Asolkar, D. Schröder, R. Heckmann, S. Lang, I. Wagner-Döbler, H. Laatsch, *J. Antibiot.* **2004**, 57, 17–23.
- [6] Review: K. Wojciechowski, *Eur. J. Org. Chem.* **2001**, 3587–3605.
- [7] a) H. Steinhagen, E. J. Corey, *Angew. Chem. Int. Ed.* **1999**, 38, 1928–1931; *Angew. Chem.* **1999**, 111, 2054–2056; b) R. D. Bowen, D. E. Davies, C. W. G. Fishwick, T. O. Glasbey, S. J. Noyce, R. C. Storr, *Tetrahedron Lett.* **1982**, 23, 4501–4504; c) M. T. Hovey, C. T. Check, A. F. Sipher, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2014**, 53, 9603–9607; *Angew. Chem.* **2014**, 126, 9757–9761; d) E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, 88, 1580–1581; e) K. Wojciechowski, *Tetrahedron* **1993**, 49, 7277–7286; f) J. M. Wiebe, A. S. Caillé, L. Trimble, C. K. Lau, *Tetrahedron* **1996**, 52, 11705–11724.
- [8] a) C. Wang, J. A. Tunge, *J. Am. Chem. Soc.* **2008**, 130, 8118–8119; b) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, 136, 10589–10592; c) G. Li, H. Liu, G. Lv, Y. Wang, Q. Fu, Z. Tang, *Org. Lett.* **2015**, 17, 4125–4127.
- [9] a) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti, C. Schneider, *Angew. Chem. Int. Ed.* **2014**, 53, 7923–7927; *Angew. Chem.* **2014**, 126, 8057–8061; b) S. Saha, C. Schneider, *Chem. Eur. J.* **2015**, 21, 2348–2352; c) S. Saha, C. Schneider, *Org. Lett.* **2015**, 17, 648–651; d) S. Saha, S. K. Alamsetti, C. Schneider, *Chem. Commun.* **2015**, 51, 1461–1464; e) S. K. Alamsetti, M. Spanka, C. Schneider, *Angew. Chem. Int. Ed.* **2016**, 55, 2392–2396; *Angew. Chem.* **2016**, 128, 2438–2442.
- [10] a) D. Wilcke, E. Herdtweck, T. Bach, *Synlett* **2011**, 1235–1238; b) C.-C. Hsiao, H.-H. Liao, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, 53, 13258–13263; *Angew. Chem.* **2014**, 126, 13474–13479; c) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, 54, 1910–1913; *Angew. Chem.* **2015**, 127, 1930–1933; d) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, *Angew. Chem. Int. Ed.* **2015**, 54, 5460–5464; *Angew. Chem.* **2015**, 127, 5550–5554; e) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, 137, 383–389; f) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, 54, 5762–5765; *Angew. Chem.* **2015**, 127, 5854–5857; g) Z. Lai, Z. Wang, J. Sun, *Org. Lett.* **2015**, 17, 6058–6061.
- [11] a) H.-H. Liao, A. Chatupheeraphat, C.-C. Hsiao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, 54, 15540–15544; *Angew. Chem.* **2015**, 127, 15760–15765; b) A. Chatupheeraphat, H.-H. Liao, S. Mader, M. Sako, H. Sasai, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, 55, 4803–4807; *Angew. Chem.* **2016**, 128, 4882–4887.
- [12] Representative reviews: a) R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, 41, 292–301; b) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, 111, 4599–4657.
- [13] Reviews: a) T. Akiyama, *Chem. Rev.* **2007**, 107, 5744–5758; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, 107, 5713–5743; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, 8, 5262–5276; e) M. Terada, *Synthesis* **2010**, 1929–1982; f) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, 291, 395–456; g) T. Akiyama, in *Science of Synthesis: Asymmetric Organocatalysis, Vol. 2* (Ed. K. Maruoka), Thieme, Stuttgart, **2012**, pp. 169–217; h) M. Rueping, A. Kuenkel, I. Athdiresei, *Chem. Soc. Rev.* **2011**, 40, 4539–4549; i) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem. Int. Ed.* **2011**, 50, 6706–6720; *Angew. Chem.* **2011**, 123, 6838–6853; j) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, 114, 9047–9153; Pioneering work: k) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356–5357; l) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, 43, 1566–1568; *Angew. Chem.* **2004**, 116, 1592–1594.
- [14] CCDC 1455265 (**3d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. For details concerning the crystal structure of **3d** see the Supporting Information as well.
- [15] Similar effects were observed in reactions of the related *ortho*-quinone methides. S. Haseloff, C. Schneider, unpublished results.
- [16] At the current stage of development this reaction is limited to benzoannulated enamides because of their resonance stabilization.
- [17] Especially under Lewis and Brønsted acid activation, cycloadditions between heavily polarized dienes and dienophiles often proceed by a stepwise mechanism. a) S. J. Danishefsky, E. Larson, D. Ashkin, J. Kato, *J. Am. Chem. Soc.* **1985**, 107, 1246–1255; b) H. Kunz, W. Pfrengle, *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1067–1068; *Angew. Chem.* **1989**, 101, 1041–1042; c) H. Waldmann, M. Braun, M. Dräger, *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1468–1471; *Angew. Chem.* **1990**, 102, 1445–1447; d) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, 33, 6907–6910; e) G. E. Keck, X. Y. Li, D. Krishnamurthy, *J. Org. Chem.* **1995**, 60, 5998–5999; f) M. Roberson, A. S. Jepsen, K. A. Jørgensen, *Tetrahedron* **2001**, 57, 907–913; g) Y. Yamashita, S. Saito, H. Ishitani, S. Kobayashi, *J. Am. Chem. Soc.* **2003**, 125, 3793–3798; h) K. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed.* **2006**, 45, 4796–4798; *Angew. Chem.* **2006**, 118, 4914–4916; Representative reviews: i) H. Waldmann, *Synthesis* **1994**, 535–551; j) L. F. Tietze, G. Ketschau, *Top. Curr. Chem.* **1997**, 189, 1–120; k) K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, 39, 3558–3588; *Angew. Chem.* **2000**, 112, 3702–3733.
- [18] Y. Li, G. Manickam, A. Ghoshal, P. Subramaniam, *Synth. Commun.* **2006**, 36, 925–928.

Received: April 29, 2016

Revised: June 6, 2016

Published online: June 29, 2016