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Cinchona Alkaloid Amide Catalyzed Enantioselective Formal [2+2] Cycloadditions of Allenoates and Imines: Synthesis of 2,4-Disubstituted Azetidines**

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Chiral azetidines[1] represent an important class of four-membered nitrogen heterocycles that have a wide range of synthetic applications,[1–3] remarkable biological activities,[1,4] and are prevalent in natural products.[1,5] However, in contrast to the homologous small-ring saturated nitrogen heterocycles such as aziridines, pyrrolidines, and piperidines, the synthetic approaches to enantiomerically enriched azetidines are few in number and are generally multistep processes.[1,6,7] Among the different synthetic routes, the formal [2+2] cycloaddition[8] is certainly one of the most powerful methods for the construction of the strained four-membered ring. However, only a few catalytic enantioselective methods have been developed for a one-step synthesis of azetidines in spite of the great number of synthetic efforts dedicated to this field.[9]

Recently, an elegant synthesis of 2,4-disubstituted azetidines involving a new DABCO-catalyzed regioselective [2+2] cycloaddition of N tosylimines with allenoates was described by Shi and co-workers.[10] While the synthetic potential of this transformation is self-evident, its enantioselective version remains, to the best of our knowledge, unknown to date.[11] Indeed, the diverse reactivity of allenoates[10–16] and the complexity of the mechanism make the development of the asymmetric version particularly challenging. In connection with our ongoing project that deals with the catalytic potential of the cinchona-alkaloid-derived amides,[17–19] we became interested in examining the reaction of allenoates with imines in the presence of a chiral tertiary amine catalyst. Herein, we report the first examples of the catalytic enantioselective [2+2] cycloaddition between allenoates and N sulfonylimines to give enantioenriched 2-alkylideneazetidines.[20]

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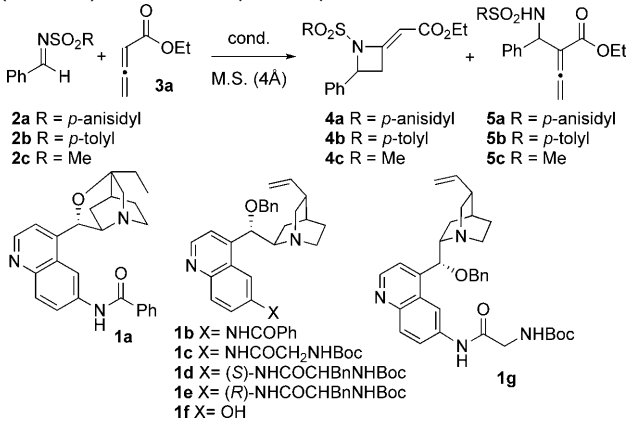
We began our studies by examining the reaction of (*E*)-*N*-benzylidene-4-methoxybenzene sulfonamide (**2a**) with ethyl 2,3-butadienoate (**3a**) in the presence of 6′-deoxy-6′-benzamido-β-isocupreidine (**1a**; 10 mol%)[17] and molecular sieves (4 Å) in CH_2Cl_2 (Table 1). Although the *E*-azetidine **4a** was formed as a major product, no enantioselectivity was observed (Table 1, entry 1).[21,22] Interestingly, the less-rigid 6′-

Table 1: Enantioselective [2+2] versus the aza-Morita–Baylis–Hillman (aza-MBH) reaction: Survey of catalytic reaction conditions.[a]



Entry	2	Cat.	Solvent	4	Yield [%][b]	*ee* [%][c,d]	5	Yield [%][b]	*ee* [%][c,d]
1	**2a**	**1a**	CH_2Cl_2	**4a**	57	<5	**5a**	8	29
2	**2a**	**1b**	CH_2Cl_2	**4a**	71	89	**5a**	5	0
3	**2a**	**1c**	CH_2Cl_2	**4a**	77	94	**5a**	5	25
4	**2a**	**1c**	CH_2Cl_2	**4a**	60[e]	94	**5a**	18[e]	25
5	**2a**	**1d**	CH_2Cl_2	**4a**	72	80	**4a**	3	14
6	**2a**	**1e**	CH_2Cl_2	**4a**	57	74	**5a**	13	15
7	**2a**	**1f**	CH_2Cl_2	**4a**	31	63	**5a**	15	5
8	**2a**	**1c**	THF	**4a**	41	90	**5a**	15	28
9	**2a**	**1c**	toluene	**4a**	57	95	**5a**	8	25
10	**2a**	**1c**	benzene	**4a**	93	95	**5a**	<5	n.d.
11	**2a**	**1c**	benzene	**4a**	41[f]	94	**5a**	5	n.d.
12	**2a**	**1c**	$CF_3C_6H_5$	**4a**	52	90	**5a**	5	15
13	**2b**	**1c**	benzene	**4b**	75	91	**5b**	<5	n.d.
14	**2c**	**1c**	benzene	**4c**	81	91	**5c**	<5	n.d.
15	**2a**	**1g**	benzene	**4a**	69	−92[g]	**5c**	<5	n.d.

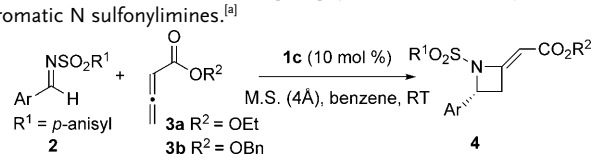
[a] Reaction conditions: imine (**2a**; 0.1 mmol), ethyl 2,3-butadienoate (**3a**; 0.2 mmol), **1** (0.01 mmol), $c = 0.25$ M, RT, 48 h. [b] Yield of the isolated product after purification by column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral stationary phase. [d] *R*-enriched **4a**. See the Supporting Information for the structure determination by X-ray crystallographic analysis. [e] Catalyst was used without drying. [f] Reaction carried out at 0°C. [g] *S*-enriched **4a**. Boc = *tert*-butyloxycarbonyl, Bn = benzyl, M.S. = molecular sieves, n.d. = not determined, THF = tetrahydrofuran.

deoxy-6′-benzamido quinidine (**1b**) gave much better enantioselectivity than **1a** (Table 1, entries 1 and 2). Catalyst **1c**, which contains the N-Boc glycinamide unit at C6′, afforded adduct **4a** with even better enantioselectivity (Table 1, entry 3). However, when the catalyst **1c** was not anhydrous,[23] the proportion of the aza-Morita–Baylis–Hillman (MBH) product **5a** increased (Table 1, entry 4). In contrast, catalysts **1d** and **1e**, which contain the N-Boc L- and D-phenylalanine units, respectively, provided inferior results relative to **1c** (Table 1, entries 5 and 6). That the quinidine amides (**1b**–**1e**) provided higher regio- and enantioselectivities than the O-demethyl quinidine **1f** (Table 1, entry 7) demonstrated the superiority of the N–H of the amide over the O–H group in this process.[17] The solvent effect was next examined, and benzene was found to be the best reaction medium. In this solvent, the formation of the aza-MBH product **5a** was minimized and the azetidine **4a** was isolated in 93% yield with 95% *ee* (Table 1, entry 10).[10] Lowering the reaction temperature reduced significantly the yield of **4a** and did not have a positive impact on the enantioselectivity (Table 1, entry 11). The N-substituent effect was also examined, and it was found that both N-tosyl and N-mesyl imines were suitable substrates (Table 1, entries 13 and 14) and led to the corresponding cycloadducts **4b** and **4c** with slightly lower enantioselectivities and yields. As expected, the enantiomer of **4a** was formed with the same efficiency when the quinine-derived catalyst **1g** was employed as a catalyst (Table 1, entry 15).[22]

Having established the optimal reaction conditions for the formation of the azetidine, we surveyed the scope of the reaction by varying the structure of sulfonylimines **2** and allenoates **3**. As shown in Table 2, the reaction of ethyl 2,3-butadienoate (**3a**) with N-sulfonylimines **2**, which are derived from aromatic aldehydes, afforded cleanly the corresponding *R*-configured azetidines in moderate to high yields and excellent enantioselectivities (entries 1–11). The electronic properties of the substituents on the phenyl ring did not affect the enantioselectivity much, but did impact the yield. For instance, imines bearing both electron-withdrawing and weak electron-donating substituents afforded the desired products in excellent yields (Table 2, entries 1–8), while strong electron-donating substituents, such as the methoxy group, led to diminished yields (Table 2, entry 9). *Ortho*, *meta,* and *para* substituents were all well tolerated. The α,β-unsaturated imine was also a suitable substrate and afforded the corresponding cycloadduct **4m** with excellent enantioselectivity (Table 2, entry 10). Similarly, benzyl 2,3-butadienoate (**3b**) reacted with various sulfonylimines under identical reaction conditions to give the corresponding *R*-configured azetidines with excellent enantioselectivities (>96% *ee*; Table 2, entries 12–15).

Mechanistically, the reaction of imines **2** with allenoates **3** in the presence of a Lewis base catalyst can take place through different pathways, which include the aza-MBH reaction as well as [3+2] and [2+2] cycloadditions.[24] Therefore to be synthetically meaningful, the catalytic reaction conditions should not only be able to determine the enantioselectivity but also be able to direct the reaction toward a single pathway.[10–15] Two competitive pathways that lead to

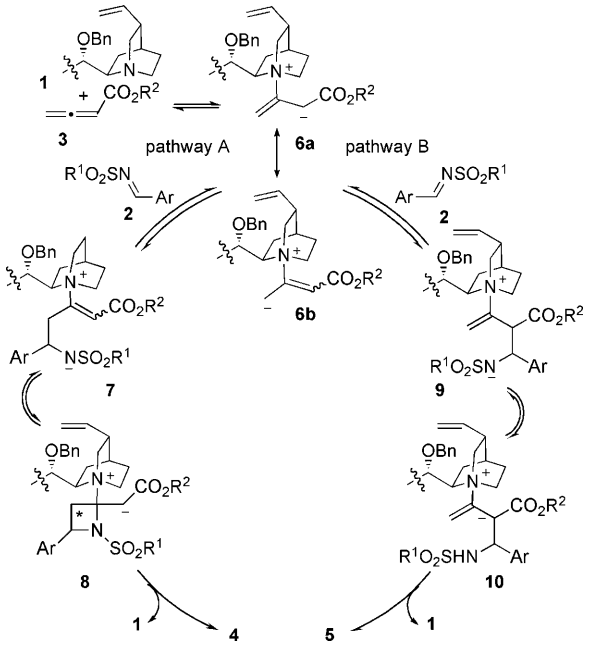
Table 2: Enantioselective formal [2+2] cycloaddition with representative aromatic N sulfonylimines.[a]



Entry	Ar	3	Yield [%][b]	*ee* [%][c,d]
1	*p*-ClC_6H_4 (**2d**)	**3a**	85	92
2	*p*-CNC_6H_4 (**2e**)	**3a**	75	85
3	*p*-$NO_2C_6H_4$ (**2f**)	**3a**	74	92
4	*p*-$CF_3C_6H_4$ (**2g**)	**3a**	79	86
5	naphthyl (**2h**)	**3a**	59	90
6	*p*-MeC_6H_4 (**2i**)	**3a**	65	92
7	*m*-MeC_6H_4 (**2j**)	**3a**	80	94
8	*o*-BrC_6H_4 (**2k**)	**3a**	86	90
9	*p*-$MeOC_6H_4$ (**2l**)	**3a**	46	95
10	PhCH=CH (**2m**)	**3a**	58	94
11	*m*-BrC_6H_4 (**2n**)	**3a**	56	96
12	C_6H_5 (**2o**)	**3b**	58	98
13	*m*-BrC_6H_4 (**2p**)	**3b**	72	97
14	*p*-MeC_6H_4 (**2q**)	**3b**	67	98
15	*p*-CNC_6H_4 (**2r**)	**3b**	76	96

[a] Reaction conditions: imine (**2**; 0.1 mmol), alkyl 2,3-butadienoate (**3**; 0.2 mmol), **1c** (0.01 mmol), benzene (0.4 mL), RT, 48 h. [b] Yield of the isolated product after purification by column chromatography on silica gel. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The **1g**-catalyzed reaction between **2a** and **3a** gave the product with the *S* configuration.

the azetidine and the aza-MBH adduct are shown in Scheme 1. Addition of the catalyst **1** to the allenoate **3** would afford the zwitterionic intermediate **6**, which might react with the imine **2** according to two different pathways. In pathway A, the addition of γ-carbanion **6b** to the imine would afford the intermediate **7**, which upon a 4-*exo*-trig cyclization



Scheme 1. Competitive reaction pathways leading to azetidines and aza-MBH adducts.

would afford **8**. Hydride elimination from **8** would produce the azetidine **4** with concurrent regeneration of the catalyst **1**. In pathway B, the addition of the α-carbanion **6a** to the imine would provide the aza-MBH-type product **5** via intermediates **9** and **10**. On the basis of earlier reports[10] and our own investigations, we believed that the rigidity of the catalyst structure[18] and the presence of a protic additive can in part modulate the regiochemical outcome.[25] As the proton-transfer step of the aza-MBH reaction is known to be favored in the presence of a protic additive,[10,26] the equilibrium favors pathway A, thus leading to **4** under anhydrous reaction conditions because of the reduced rate of the aza-MBH reaction (Table 1, entries 4 and 3). To gain an insight into the influence of the protic additives on the regioselectivity of the reaction pathways additional control experiments were carried out. When the reaction of **2a** and **3a** was performed in the presence of **1c** (0.1 equiv) and a Brønsted acid (β-naphthol, 2-pyridone, and *p*-nitrophenol; 0.1 equiv), the yield of the product **4a** decreased (70%→46%) and there was concurrent formation of the aza-MBH adduct **5a** (see the Supporting Information). Likewise, the same reaction catalyzed by **1a** in the presence of β-naphthol and trifluorethanol afforded the adduct **5a** as the major (β-naphthol) and even as the only product (trifluorethanol; see the Supporting Information).[27]

A possible transition-state model (**11**) using **1c** as the catalyst is shown in Figure 1. We hypothesized that the imine would be activated by both CONH and BocNH through two hydrogen bonds, which could in turn be stabilized by a π–π interaction between the arylsulfonyl group and quinoline. Then the zwitterion homoenolate may preferentially add to the imine from the *Re* face in a pseudo-intramolecular manner, thus leading to **12**, which after cyclization and elimination events would provide the *R*-azetidine **4**.

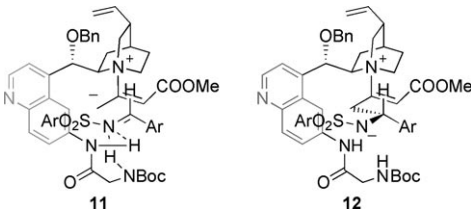


Figure 1. Possible transition state.

In summary, we developed the first asymmetric organocatalytic formal [2+2] cycloaddition of N sulfonylimines and allenoates using the novel bifunctional 6′-deoxy-6′-acylaminoquinidine (**1c**) as a catalyst. A variety of aromatic N sulfonylimines underwent cycloaddition with allenoates to afford *R*-configured azetidines in good yields and excellent regio- and enantioselectivities. When the quinine-derived catalyst **1g**, a pseudoenantiomer of **1c**, was used as a catalyst the *S*-configured azetidine compounds were produced with similar efficiency.

Experimental Section

General protocol: Catalyst **1c** (2.6 mg, 0.005 mmol, 0.1 equiv), and alkyl 2,3-butadienoate (**3**; 0.1 mmol, 2.0 equiv) were added to a solution of N sulfonylimine (**2**; 0.05 mmol, 1.0 equiv) in anhydrous benzene (0.2 mL) at room temperature. The reaction mixture was stirred under an argon atmosphere at room temperature for 48 h. The reaction was stopped by passing the mixture through a short pad of silica gel using dichloromethane as the eluent. The filtrate was concentrated in vacuo and the residue was purified by preparative thin-layer chromatography (silica gel; eluent: *n*-heptane/ethyl acetate = 3:2) to afford the corresponding pure azetidine.

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[1] For a recent review on the synthesis of azetidines and azetidinones, see: a) A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988–4035; b) F. Couty, E. Gwilherm, *Synlett* **2009**, *19*, 3053–3064.

[2] For examples, see: a) M. K. Ghorai, A. Kumar, D. P. Tiwari, *J. Org. Chem.* **2010**, *75*, 137–151; b) B. Drouillat, F. Couty, V. Razafimahaléo, *Synlett* **2009**, 3182–3186; c) B. Drouillat, F. Couty, O. David, G. Evano, J. Marrot, *Synlett* **2008**, 1345–1348; d) M. K. Ghorai, A. Kumar, K. Das, *Org. Lett.* **2007**, *9*, 5441–5444; e) M. Vargas-Sanchez, S. Lakhdar, F. Couty, G. Evano, *Org. Lett.* **2006**, *8*, 5501–5504; f) W. Van Brabandt, R. Van Landeghem, N. De Kimpe, *Org. Lett.* **2006**, *8*, 1105–1108; g) M. Vargas-Sanchez, F. Couty, G. Evano, D. Prim, J. Marrot, *Org. Lett.* **2005**, *7*, 5861–5864; h) J. A. Vanecko, F. G. West, *Org. Lett.* **2005**, *7*, 2949–2952; i) V. K. Yadav, V. Sriramurthy, *J. Am. Chem. Soc.* **2005**, *127*, 16366–16367; j) B. A. B. Prasad, A. Bisai, V. K. Singh, *Org. Lett.* **2004**, *6*, 4829–4831; k) J. Jiang, H. Shah, R. J. De Vita, *Org. Lett.* **2003**, *5*, 4101–4103; l) B. Alcaide, P. Almendros, C. Aragoncillo, N. R. Salgado, *J. Org. Chem.* **1999**, *64*, 9596–9604.

[3] For the application of azetidines as ligands in metal-catalyzed transformations and as chiral auxiliaries, see: a) G. S. Singh, M. D′Hooghe, N. De Kimpe in Comprehensive Heterocyclic Chemistry III, *Vol. 2* (Ed.: C. V. Stevens), Elsevier, Oxford, **2008**, pp. 1–110; b) F. Couty in *Science of Synthesis*, *Vol. 40a* (Eds.: E. Schaumann, D. Enders), Thieme, Stuttgart, **2009**, pp. 773–816; c) Z. Zhang, X. Bai, R. Liu, G. Zi, *Inorg. Chim. Acta* **2009**, *362*, 1687–1691; d) F. Couty, D. Prim, *Tetrahedron: Asymmetry* **2002**, *13*, 2619–2624; e) P. J. Hermsen, J. G. O. Cremers, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **2001**, *42*, 4243–4245; f) G. Guanti, R. Riva, *Tetrahedron: Asymmetry* **2001**, *12*, 605–618; g) J. Wilken, S. Erny, S. Wassmann, J. Martens, *Tetrahedron: Asymmetry* **2000**, *11*, 2143–2148; h) M. Shi, J.-K. Jiang, *Tetrahedron: Asymmetry* **1999**, *10*, 1673–1679; i) W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. de Gelder, J. M. M. Smits, B. Zwanenburg, *Tetrahedron* **1998**, *54*, 4991–5004.

[4] For examples, see: a) G. B. Evans, R. H. Furneaux, B. Greatrex, A. S. Murkin, V. L. Schramm, P. C. Tyler, *J. Med. Chem.* **2008**, *51*, 948–956; b) K.-I. Fuhshuku, N. Hongo, T. Tashiro, Y. Masuda, R. Nakagawa, K.-I. Seino, M. Taniguchi, K. Mori, *Bioorg. Med. Chem.* **2008**, *16*, 950–964; c) U. Iserloh, Y. Wu, J. N. Cumming, J. Pan, L. Y. Wang, A. W. Stamford, M. E. Kennedy, R. Kuvelkar, X. Chen, E. M. Parker, C. Strickland, J. Voigt, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 414–418; d) Y. Ikee, K. Hashimoto, M. Nakashima, K. Hayashi, S. Sano, M. Shiro, Y. Nagao, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 942–945; e) J. Slade, J. Bajwa, H. Liu, D. Parker, J. Vivelo, G. P. Chen, J. Calienni, E. Villhauer, K. Prasad, O. Repic, T. J. Blacklock, *Org. Process Res. Dev.* **2007**, *11*, 825–835; f) C. H. Yeh, S. J. Wu, Y. F. Tsai, H. Y. Chen, C. Y. Lin, *Plant Sci.* **2007**, *172*, 1124–1130; g) N. Kolocouris, G. Zoidis,

G. B. Foscolos, G. Fytas, S. R. Prathalingham, J. M. Kelly, L. Naesens, E. De Clercq, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4358 – 4362; h) L. Provins, B. Christophe, P. Danhaive, J. Dulieu, M. Gillard, L. Quere, K. Stebbins, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3077 – 3080; i) G. Zoidis, C. Fytas, I. Papanastasiou, G. B. Foscolos, G. Fytas, E. Padalko, E. D. Clercq, L. Naesens, J. Neyts, N. Kolocouris, *Bioorg. Med. Chem.* **2006**, *14*, 3341 – 3348; j) H. Bräuner-Osborne, L. Bunch, N. Chopin, F. Couty, G. Evano, A. A. Jensen, M. Kusk, B. Nielsen, N. Rabasso, *Org. Biomol. Chem.* **2005**, *3*, 3926 – 3936.

[5] For examples of natural products, see: a) E. Rubenstein, H. Zhou, K. M. Krasinska, A. Chien, C. H. Becker, *Phytochemistry* **2006**, *67*, 898 – 903; b) Y. Hamada, T. Shioiri, *J. Org. Chem.* **1986**, *51*, 5489 – 5490; c) K. Miyakoshi, J. Oshita, T. Kitahara, *Tetrahedron* **2001**, *57*, 3355 – 3360; d) Y. Aoyagi, *Phytochemistry* **2006**, *67*, 618 – 621; e) D. Schummer, E. Forche, V. Wray, T. Domke, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1996**, 971 – 978; f) K. Isono, K. Asahi, S. Suzuki, *J. Am. Chem. Soc.* **1969**, *91*, 7490 – 7505; g) K. Ohshita, H. Ishiyama, Y. Takahashi, J. Ito, Y. Mikami, J. Kobayashi, *Bioorg. Med. Chem.* **2007**, *15*, 4910 – 4916; h) H. Yoda, T. Uemura, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 977 – 979; i) M. Kitajima, N. Kogure, K. Yamaguchi, H. Takayama, N. Aimi, *Org. Lett.* **2003**, *5*, 2075 – 2078; j) H. Hayashi, K. Takiuchi, S. Murao, M. Arai, *Agric. Biol. Chem.* **1988**, *52*, 2131 – 2133.

[6] *Asymmetric Synthesis of Nitrogen Heterocycles* (Ed.: J. Royer), Wiley-VCH, Weinheim, **2009**.

[7] a) L. Albrecht, H. Jiang, G. Dickmeiss, B. Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 9188 – 9196; b) S. Guo, Y. Xie, X. Hu, C. Xia, H. Huang, *Angew. Chem.* **2010**, *122*, 2788 – 2791; *Angew. Chem. Int. Ed.* **2010**, *49*, 2728 – 2731; c) D. M. Hodgson, J. Kloesges, *Angew. Chem.* **2010**, *122*, 2962 – 2965; *Angew. Chem. Int. Ed.* **2010**, *49*, 2900 – 2903; d) Y. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 3403 – 3406; *Angew. Chem. Int. Ed.* **2009**, *48*, 3353 – 3356; e) M. Medjahdi, J. González-Gómez, F. Foubelo, M. Yus, *J. Org. Chem.* **2009**, *74*, 7859 – 7865; f) T. Kawabata, K. Moriyama, S. Kawakami, K. Tsubaki, *J. Am. Chem. Soc.* **2008**, *130*, 4153 – 4157; g) K. Moriyama, H. Sakai, T. Kawabata, *Org. Lett.* **2008**, *10*, 3883 – 3886; h) E. Banide, V. Lemau de Talancé, G. Schmidt, H. Lubin, S. Comesse, L. Dechoux, L. Hamon, C. Kadouri-Puchot, *Eur. J. Org. Chem.* **2007**, 4517 – 4524; i) R. M. De Figueiredo, R. Fröhlich, M. Christmann, *J. Org. Chem.* **2006**, *71*, 4147 – 4154; j) F. Couty, G. Evano, M. Vargas-Sanchez, G. Bouzas, *J. Org. Chem.* **2005**, *70*, 9028 – 9031; k) R. Pedrosa, C. Andrés, J. Nieto, S. del Pozo, *J. Org. Chem.* **2005**, *70*, 1408 – 1416; l) V. Lemau de Talancé, E. Banide, B. Bertin, S. Comesse, C. Kadouri-Puchot, *Tetrahedron Lett.* **2005**, *46*, 8023 – 8025; m) A. C. B. Burtoloso, C. R. D. Correia, *Tetrahedron Lett.* **2004**, *45*, 3355 – 3358; n) F. Couty, G. Evano, D. Prim, J. Marrot, *Eur. J. Org. Chem.* **2004**, 3893 – 3897; o) M. Poch, X. Verdaguer, A. Moyano, M. A. Pericás, A. Riera, *Tetrahedron Lett.* **1991**, *32*, 6935 – 6938; p) A. Marinetti, P. Hubert, J.-P. Genêt, *Eur. J. Org. Chem.* **2000**, 1815 – 1820.

[8] a) Y. Ye, H. Wang, R. Fan, *Org. Lett.* **2010**, *12*, 2803 – 2805; b) I. Nakamura, T. Nemoto, Y. Yamamoto, A. de Meijere, *Angew. Chem.* **2006**, *118*, 5300 – 5303; *Angew. Chem. Int. Ed.* **2006**, *45*, 5176 – 5179; c) T. Nishimura, Y. Yasuhara, T. Hayashi, *Angew. Chem.* **2006**, *118*, 5288 – 5290; *Angew. Chem. Int. Ed.* **2006**, *45*, 5164 – 5166; d) L.-G. Meng, P. Cai, Q. Guo, S. Xue, *J. Org. Chem.* **2008**, *73*, 8491 – 8496; e) R. W. M. Aben, R. Smit, J. W. Scheeren, *J. Org. Chem.* **1987**, *52*, 943 – 946; f) A. C. B. Burtoloso, C. R. D. Correia, *Tetrahedron Lett.* **2006**, *47*, 6377 – 6380.

[9] a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626 – 6635; b) S. France, M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth, T. Lectka, *J. Am. Chem. Soc.* **2005**, *127*, 1206 – 1215; c) T. Akiyama, K. Daidouji, K. Fuchibe, *Org. Lett.* **2003**, *5*, 3691 – 3693; for the enantioselective intramolecular Kinugasa reaction in the synthesis of β-lactam, see: R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216 – 4219; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082 – 4085.

[10] a) G.-L. Zhao, J.-W. Huang, M. Shi, *Org. Lett.* **2003**, *5*, 4737 – 4739; b) G.-L. Zhao, M. Shi, *J. Org. Chem.* **2005**, *70*, 9975 – 9984; c) X.-Y. Guan, Y. Wie, M. Shi, *J. Org. Chem.* **2009**, *74*, 6343 – 6346; for a review on the unusual aza-MBH reaction, see: d) G.-N. Ma, J.-J. Jiang, M. Shi, Y. Wei, *Chem. Commun.* **2009**, 5496 – 5514.

[11] Under Shi's reaction conditions (DABCO, molecular sieves), which favored the azetidine formation, the reaction between 2,3-allenoate bearing a chiral auxiliary on the ester moiety and N-tosyl imine afforded the aza-MBH adduct: B. S. Santos, A. L. Cardoso, A. M. Beja, M. R. Silva, J. A. Paixão, F. Palacios, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2010**, 3249 – 3256.

[12] a) L. B. Saunders, B. J. Cowen, S. J. Miller, *Org. Lett.* **2010**, *12*, 4800 – 4803; b) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2009**, *131*, 6105 – 6107.

[13] For reviews, see: a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811 – 891; b) V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511 – 4574; c) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1 – 48; d) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698 – 4712; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614 – 4628; e) Y. L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905 – 2916; f) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581 – 1585.

[14] For the chiral phosphoric acid catalyzed [3+2] cycloaddition of allenoates with azomethine ylides, see: J. Yu, L. He, X.-H. Chen, J. Song, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4946 – 4949.

[15] For representative examples of the phosphine-catalyzed enantioselective [3+2] cycloaddition of allenoates with imines, see: a) N. Pinto, N. Fleury-Brégeot, A. Marinetti, *Eur. J. Org. Chem.* **2009**, 146 – 151; b) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660 – 5661; c) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988 – 10989; d) N. Fleury-Brégeot, L. Jean, P. Retailleau, A. Marinetti, *Tetrahedron* **2007**, *63*, 11920 – 11927; e) A. Scherer, J. A. Gladysz, *Tetrahedron Lett.* **2006**, *47*, 6335 – 6337; f) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836 – 3837; g) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031 – 5041; for representative examples of the phosphine-catalyzed enantioselective [4+2] cycloaddition of allenoate with imines, see: h) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234 – 12235; for an example of phosphine-catalyzed [3+3] cycloaddition of allenoate with aziridines, see: H. Guo, Q. Xu, O. Kwon, *J. Am. Chem. Soc.* **2009**, *131*, 6318 – 6319.

[16] For reviews on allenoate chemistry, see: a) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102 – 3116; b) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174 – 194; c) G.-N. Ma, J.-J. Jiang, M. Shi, Y. Wei, *Chem. Commun.* **2009**, 5496 – 5514; d) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140 – 1152; e) S. Ma, *Chem. Rev.* **2005**, *105*, 2829 – 2872.

[17] a) N. Abermil, G. Masson, J. Zhu, *J. Am. Chem. Soc.* **2008**, *130*, 12596 – 12597; b) N. Abermil, G. Masson, J. Zhu, *Org. Lett.* **2009**, *11*, 4648 – 4651; c) N. Abermil, G. Masson, J. Zhu, *Adv. Synth. Catal.* **2010**, *352*, 656 – 660.

[18] For Hatakeyama's seminal paper on the β-isocupreidine-catalyzed enantioselective MBH reaction, see: Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219- 10220.

[19] a) H. M. R. Hoffmann, J. Frackenpohl, *Eur. J. Org. Chem.* **2004**, 4293; b) S. K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, pp. 621 – 631; c) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658 – 7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496 – 7504; d) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *8*, 1229 – 1279.

[20] For the synthesis and reactions of 2-alkylideneazetidines, see a) H. Lu, C. Li, *Org. Lett.* **2006**, *8*, 5365 – 5367; b) I. Martinez, A. R. Howell, *Tetrahedron Lett.* **2000**, *41*, 5607 – 5613; c) K. A. Tehrani, N. De Kimpe, *Tetrahedron Lett.* **2000**, *41*, 1975 – 1978; d) D. Crépin, J. Darwick, C. Aïssa, *Angew. Chem.* **2010**, *122*, 630 – 633; *Angew. Chem. Int. Ed.* **2010**, *49*, 620 – 623; for a review, see: e) K. A. Tehrani, N. De Kimpe, *Curr. Org. Chem.* **2009**, *13*, 854 – 877.

[21] The *E* configuration of azetidines **4** was determined by comparison of their spectroscopic data with those described in Ref. [10a] and [10b]. In addition, an X-ray crystal structure of **4n** corroborated with this assignment.

[22] The absolute configuration was determined by X-ray crystallographic analysis of an enantiomerically pure sample of **4n** (see the Supporting Information). CCDC 012011 (**4n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] Preparation of anhydrous catalysts: the catalysts were dissolved in THF and the volatiles were evaporated under reduced pressure at room temperature. This procedure was repeated three times.

[24] The presence of an internal nucleophilic center can further divert the reaction pathway, for examples, see: a) Y.-W. Sun, X.-Y. Guan, M. Shi, *Org. Lett.* **2010**, *12*, 5664 – 5667; b) Y.-L. Shi, M. Shi, *Org. Lett.* **2005**, *7*, 3057 – 3060; see also: c) X. Meng, Y. Huang, R. Chen, *Org. Lett.* **2009**, *11*, 137 – 140.

[25] Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470 – 3471.

[26] For accelerated MBH and aza-MBH reactions in the presence of protic solvents, see: a) V. K. Aggarwal, D. K. Dean, A. Mereu, R. Williams, *J. Org. Chem.* **2002**, *67*, 510 – 514; b) V. K. Aggarwal, I. Emme, S. Y. Fulford, *J. Org. Chem.* **2003**, *68*, 692 – 700 and references cited therein; c) F. Ameer, S. E. Drewes, S. Freese, P. T. Kaye, *Synth. Commun.* **1988**, *18*, 495 – 500; d) J. Augé, N. Lubin, A. Lubineau, *Tetrahedron Lett.* **1994**, *35*, 7947 – 7948; e) F. Rezgui, M. M. E. Gaied, *Tetrahedron Lett.* **1998**, *39*, 5965 – 5966; f) D. Basavaiah, M. Krishnamacharyulu, A. J. Rao, *Synth. Commun.* **2000**, *30*, 2061 – 2069; g) C. Yu, B. Liu, L. Hu, *J. Org. Chem.* **2001**, *66*, 5413 – 5418; h) J. Cai, Z. Zhou, G. Zhao, C. Tang, *Org. Lett.* **2002**, *4*, 4723 – 4725; i) Y. M. A. Yamada, S. Ikegami, *Tetrahedron Lett.* **2000**, *41*, 2165 – 2269.

[27] The control experiments in the presence of 2-pyridone and trifluoroethanol were suggested by one of the referees.

