Organocatalysis

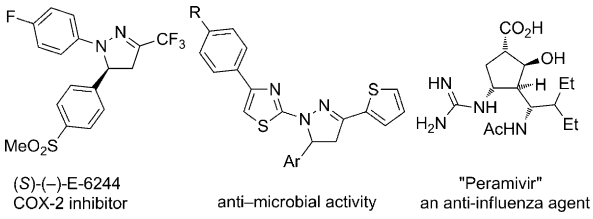
DOI: 10.1002/anie.201205813

Asymmetric Brønsted Acid Catalyzed Cycloadditions—Efficient Enantioselective Synthesis of Pyrazolidines, Pyrazolines, and 1,3-Diamines from *N*-Acyl Hyrazones and Alkenes**

Magnus Rueping, Modhu Sudan Maji, Hatice Başpınar Küçük, and Iuliana Atodiresei*

Dedicated to Prof. Dieter Seebach on the occasion of his 75th birthday

Nitrogen-containing heterocycles constitute common structural motifs in a wide range of complex natural products. Among them, pyrazoline and pyrazolidine derivatives are highly important organic molecules because of their broad spectrum of biological activity and widespread natural occurrence.[1] They are often used as anticancer, antidepressant, anti-inflamatory, antiviral, and antibacterial agents as well as acyltransferase inhibitors.[2] Apart from these impressive biological properties, which make them privileged structures in medicinal chemistry and pharmacology, these structures recently also attracted attention in materials science.[3] Moreover, differently substituted enantiopure pyrazolidine derivatives can be used as precursors for the preparation of chiral 1,3-diamine derivatives through cleavage of the N–N bond of the pyrazolidine moiety. In addition to their broad application as chiral ligands in asymmetric synthesis,[4] 1,3-diamines are also significant for the preparation of cytostatic cisplatin analogues for cancer therapy.[5] Furthermore, they are also used as anti-influenza agents (Scheme 1).[6]



(*S*)-(–)-E-6244
COX-2 inhibitor

anti–microbial activity

"Peramivir"
an anti-influenza agent

Scheme 1. Bioactive molecules based on pyrazolines and 1,3-diamines.

The [3+2] cycloaddition between hydrazones and alkenes represents a convenient access to pyrazolidines.[7–14] These cycloadditions are generally achieved by using stoichiometric amounts of achiral Brønsted acids[8] with strong heating,[9] or employ Lewis acid catalysts.[10–14] Given the usefulness of this class of compounds, considerable effort has been devoted to the development of improved methods for their synthesis. To date, several efficient protocols are available for their formation in a diastereoselective fashion.[10] In contrast, the enantioselective synthesis of pyrazolidines from hydrazones is a great challenge and there are only a few reports of this. Kobayashi et al. showed that chiral zirconium/binol complexes are efficient Lewis acid catalysts for both the intramolecular as well as intermolecular [3+2] cycloaddition of hydrazones with alkenes.[11] Leighton and co-workers later reported a related intermolecular cycloaddition between enol ethers and acylhydrazones by using 1.5 equivalents of a chiral silane Lewis acid.[12] Zamfir and Tsogoeva reported an interesting approach, wherein a chiral silane derived from a binol phosphate acted as the Lewis acid, and good enantioselectivity was obtained for one example.[13] The authors also described an example in which a chiral phosphoric acid diester was used.

Herein we describe a general and highly enantioselective Brønsted acid catalyzed cycloaddition[15,16] between various alkenes and *N*-benzoylhydrazones that leads to valuable optically active pyrazolidine derivatives.

We started our investigation with the examination of different binol phosphoric acid catalysts. However, low yields of product were observed, irrespective of the reaction conditions used. The low acidity of phosphoric acid (pK_a 13–14 in MeCN) accounted for this low reactivity. Recent studies showed that binol-based *N*-triflylphosphoramides are not only more acidic (pK_a 6–7 in MeCN), but also more reactive catalysts.[17] From the various *N*-triflylphosphoramides tested, **4** turned out to be the best catalyst for the [3+2] cycloaddition of hydrazones with cyclopentadiene (Table 1). The use of hydrazones with different acyloyl protecting groups **1a**–**3a** had an impact on the enantioselectivity of the cycloaddition (Table 1, entries 1–3). The best result was obtained with benzoyl-protected hydrazone **3a**, with pyrazolidine **7a** being isolated in a quantitative yield and with excellent enantioselectivity (99%, 92% *ee*; Table 1, entry 3).

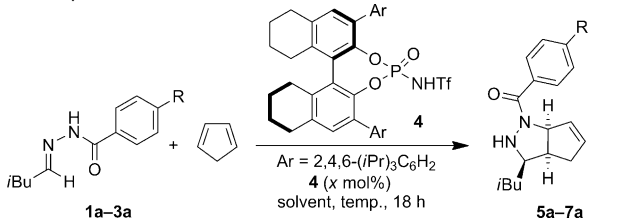
To improve the reaction further, we studied the effect of different solvents and catalyst loadings. Chlorinated solvents were generally found to be superior for our reaction (Table 1, entries 3–6), with 1,2-dichloroethane giving the best results in terms of both yield and selectivity (99%, 95% *ee*; Table 1, entry 6). Furthermore, the reaction can be performed by using

[*] Prof. Dr. M. Rueping, M. S. Maji, H. B. Küçük, I. Atodiresei
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: magnus.rueping@rwth-aachen.de

[**] M.S.M. thanks the Alexander von Humboldt Foundation, and H.B.K. thanks The Council of Higher Education of Turkey for a fellowship.

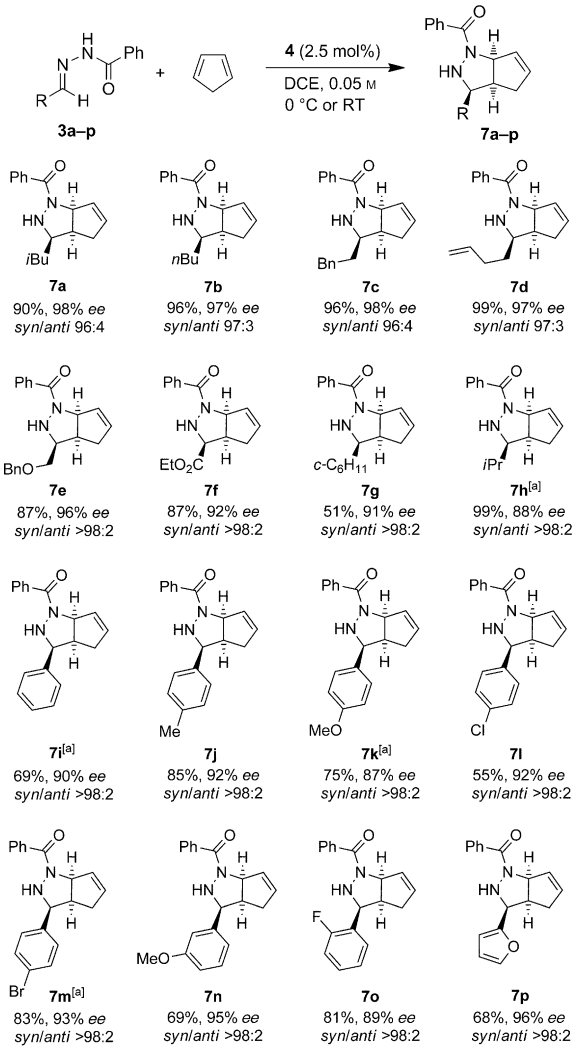
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205813.

Table 1: Optimization of the reaction conditions.[a]



Entry	R	Solvent	*T* [°C]	**4** [mol%]	Yield [%][b]	*ee* [%][c]
1	NO_2, **1a**	CH_2Cl_2	RT	5	95	73
2	CF_3, **2a**	CH_2Cl_2	RT	5	44	77
3	H, **3a**	CH_2Cl_2	RT	5	99	92
4	H, **3a**	toluene	RT	5	99	81
5	H, **3a**	$CHCl_3$	RT	5	99	91
6	H, **3a**	$(CH_2Cl)_2$	RT	5	99	95
7	H, **3a**	$(CH_2Cl)_2$	RT	2.5	99	95
8	H, **3a**	$(CH_2Cl)_2$	RT	1	94	93
9	H, **3a**	$(CH_2Cl)_2$	0	5	99	98
10[d]	H, **3a**	$(CH_2Cl)_2$	0	2.5	90	98
11[e]	H, **3a**	CH_2Cl_2	RT	0	0	–

[a] Unless otherwise noted, the reactions were carried out for 18 h in the presence of 5 mol% catalyst in a 0.05 M solution of hydrazone using the solvent and the temperature as indicated; **5a**: R = NO_2, **6a**: R = CF_3, **7a**: R = H. [b] The *syn* product was isolated along with its *anti* diastereomer in a 96:4 ratio, as determined by ^{1}H NMR spectroscopy. [c] The enantioselectivity was determined by HPLC analysis on a chiral stationary phase. [d] Reaction time 48 h. [e] Without any catalyst.



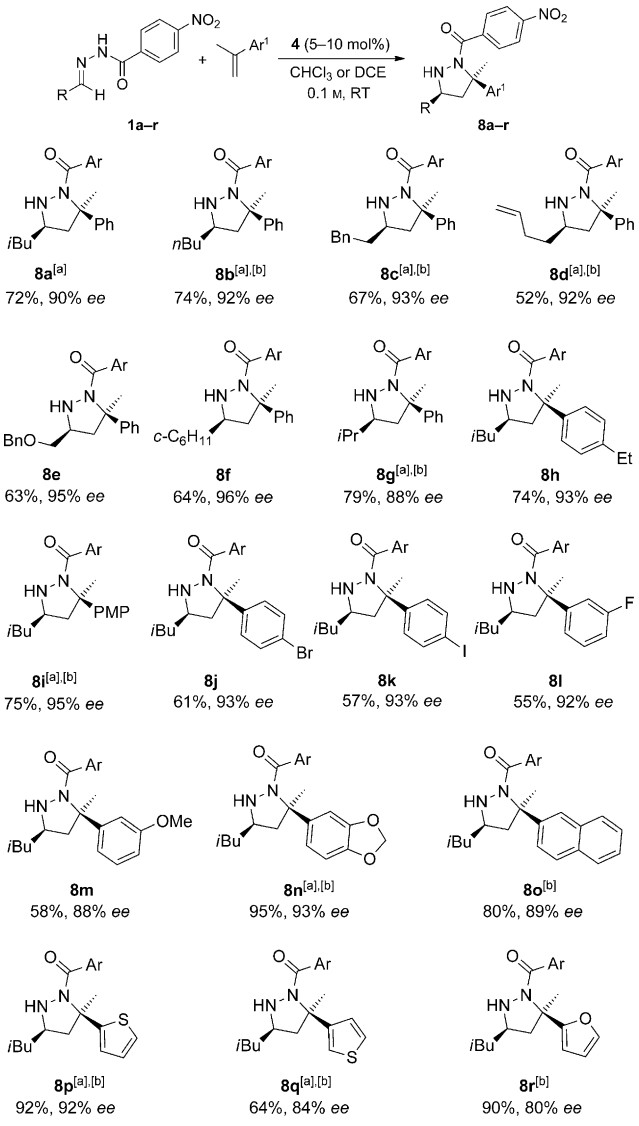
Scheme 2. Substrate scope of the organocatalytic enantioselective [3+2] cycloaddition with cyclopentadiene. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy when the minor diastereomer was observed in the ^{1}H NMR spectrum; otherwise it is reported as >98:2. The enantiomeric excess was determined by HPLC analysis. [a] Reaction was performed with a 5 mol% catalyst loading.

just 2.5 mol% catalyst at room temperature without affecting either the yield or the enantioselectivity (Table 1, entry 7). More pleasingly, the catalyst loading could be decreased remarkably to 1 mol%, with product **7a** being isolated in only a slightly lower yield and enantiomeric excess (94%, 93% *ee*; Table 1, entry 8). Finally, the effect of temperature on the reaction outcome was also investigated. Cycloadduct **7a** was isolated in quantitative yield and with an improved enantioselectivity of 98% *ee* when the reaction was conducted at 0°C by using 5 mol% of the catalyst (Table 1, entry 9). Decreasing the catalyst loading to 2.5 mol% at 0°C resulted in the product being isolated with the same enantioselectivity (Table 1, entry 10). Hence, we decided to apply these conditions (Table 1, entry 10) to reactions involving reactive hydrazones. Reactions involving less-reactive hydrazones were performed under the conditions described in Table 1, entry 7.

To investigate the scope of this newly developed protocol we prepared several hydrazones derived from aliphatic, aromatic, and heteroaromatic aldehydes and evaluated them under the optimized reaction conditions. The results are summarized in Scheme 2. The reaction generally occurred with excellent diastereoselection and the major *syn* diastereomer was isolated along with the minor *anti* diastereomer. Firstly, several hydrazones prepared from different aliphatic aldehydes were tested. Excellent results were obtained with the α-methylene-substituted hydrazones **3a**–**e**, and adducts **7a**–**e** were isolated in excellent yields and enantioselectivities (87–99%, 96–98% *ee*; Scheme 2). Ethyl glyoxalate derived hydrazone **3f** underwent a smooth reaction with cyclopentadiene to afford cycloadduct **7f** as a single diastereomer in 87% yield and 92% *ee*. Hydrazones **3g**,**h** with alkyl substitutents are also suitable substrates for the reaction, with products **7g**,**h** isolated in good to high yields and *ee* values. Next we turned our attention to hydrazones **3i**–**p**, which are derived from aromatic aldehydes. We were pleased to find that these hydrazones are also appropriate substrates for our cycloaddition. Cycloadduct **7i** was isolated from the reaction of benzaldehyde-derived hydrazone **3i** in 69% yield and 90% *ee*. Hydrazones bearing either electron-donating or -withdrawing substituents on the benzene ring reacted efficiently, and products **7j**–**o** were isolated in good to high yields and enantioselectivities. Importantly, substrate **3p** bearing a heteroaromatic ring also furnished the corresponding adduct **7p** in good yield and with an excellent enantiomeric excess of 96% *ee*. The absolute configuration of product **7l** was determined as *S*,*S*,*S* by single-crystal X-ray analysis (see the Supporting Information).[22]

To show the synthetic applicability of our newly developed method, we carried out a reaction on a 0.3 g scale by employing a catalyst loading of only 1 mol%. Pleasingly, the reaction was highly efficient, and product **7a** was isolated in 95% yield with 93% *ee* after 1 day. Thus, scaling-up of this procedure is feasible.

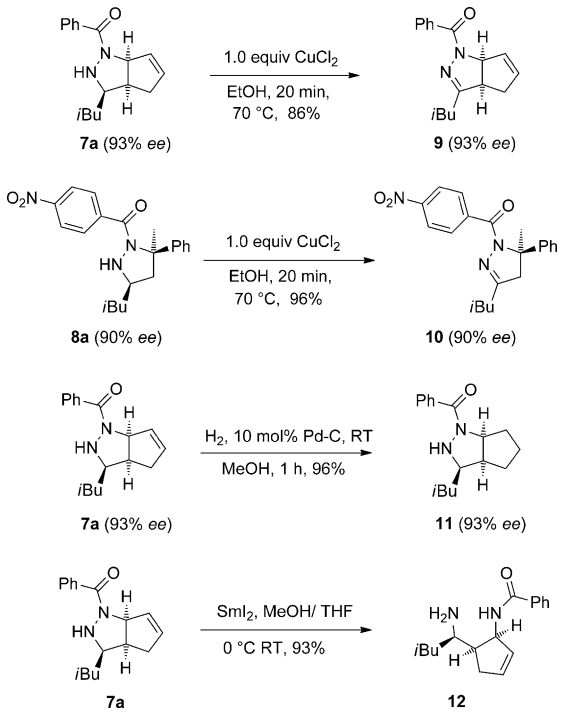
After proving the wide substrate scope with regard to the structure of the hydrazone in the reaction with cyclopentadiene, our attention turned to different alkenes for the [3+2] cycloaddition with hydrazones, and we examined the use of α-methylstyrenes (Scheme 3). To the best of our knowledge, the asymmetric [3+2] cycloaddition of α-methylstyrene with hydrazones has not been reported, although valuable pyrazolidine derivatives bearing a quaternary and a tertiary stereocenter at the 3- and 5-positions would be obtained.



Scheme 3. Substrate scope of the organocatalytic enantioselective [3+2] cycloaddition with α-methylstyrenes. Ar = 4-NO_2-Ph. The enantiomeric excess was determined by HPLC analysis. Bn = benzyl, PMP = *p*-methoxyphenyl. [a] Reactions were conducted with a 5 mol% catalyst loading. [b] Reactions were performed at different temperatures (see the Supporting Information).

After optimization of the reaction conditions, we found that α-methylstyrene and analogues are also suitable substrates for our cycloaddition, and we were able to isolate product **8a** in 72% yield and 90% *ee* as a single diastereomer (Scheme 3). In general, different alkyl-, aryl-, and heteroaryl-substituted styrene derivatives as well as *para*-nitrobenzoyl-protected hydrazones could be applied in this new Brønsted acid catalyzed [3+2] cycloaddition, and the desired pyrazolidines **8a–r** were obtained in good yields and with excellent enantioselectivities. The absolute configurations of products **8j** and **8p** were determined as *R*,*R* by X-ray crystal structure analysis (see the Supporting Information).[22]

The cycloaddition products obtained can be further functionalized to afford synthetically valuable products. To demonstrate their usefulness, we performed several functionalization reactions by using products **7a** and **8a** as model substrates. As shown in Scheme 4, oxidation of the C–N bond



Scheme 4. Derivatization of the [3+2] cycloaddition products.

is of interest, as products having a pyrazoline core structure show diverse biological activities.[1,2] Treatment of **7a** with a stoichiometric amount of cupric chloride resulted in the oxidation occurring smoothly, and product **9** was isolated without any loss of enantiopurity.[18] In a similar fashion, pyrazolidine **8a** was also smoothly oxidized to **10**.[19] Hydrogenation was also easily performed, and product **11** was isolated in 96% yield without affecting the *ee* value. Finally, we focused on the more important N–N bond cleavage reaction, as it provides valuable 1,3-diamine derivatives. When a methanolic solution of **7a** was treated with SmI_2 at room temperature, N–N bond cleavage occurred smoothly and product **12** with a core structure similar to that of the anti-influenza agent peramivir (Scheme 1) was isolated.[20,21]

In conclusion, we have developed a general metal-free highly enantioselective cycloaddition between hydrazones and alkenes that affords pyrazolidine and pyrazoline derivatives, which are valuable compounds with important biological activity. In contrast to the less acidic binol-derived phosphoric acids, the much more acidic *N*-triflylphosphoramide Brønsted acids proved to be very effective catalysts and promoted the highly enantioselective cycloaddition. The reaction can be performed with a broad range of hydrazones and alkenes and leads to high yields and excellent diastereo- and enantioselectivities. Notably, the resulting optically active pyrazolidines can undergo many chemical transformations, including the enantioselective synthesis of valuable 1,3-diamines.

Received: July 23, 2012
Published online: November 19, 2012

Keywords: heterocycles · homogeneous catalysis · hydrazones · hydrogen bonding · ion pairs

[1] L. C. Behr, R. Fusco, C. H. Jarboe, *Pyrazoles*, *Pyrazolines*, *Pyrazolidines*, *Indazoles and Condensed Rings*, *The Chemistry of Heterocyclic Compounds 22*, Interscience Publishers, New York, **1967**.

[2] a) A. Gürspy, S. Demirayak, G. Capan, K. Erol, K. Vural, *Eur. J. Med. Chem.* **2000**, *35*, 359 – 364; b) Y. J. Prasad, A. L. Rao, L. Prasoona, K. Murali, P. R. Kumar, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030 – 5034; c) T.-S. Jeong, K. S. Kim, S.-J. An, K.-H. Cho, S. Lee, W. S. Lee, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2715 – 2717; d) A. Özdemir, G. Turan-Zitouni, Z. A. Kaplancıkli, G. Revial, K. Guven, *Eur. J. Med. Chem.* **2007**, *42*, 403 – 409; e) Z. Brzozowski, F. Saczewski, M. Gdaniec, *Eur. J. Med. Chem.* **2000**, *35*, 1053 – 1064; f) Z. Özdemir, H. B. Kandilci, B. Gumusel, U. Calis, A. A. Bilgin, *Eur. J. Med. Chem.* **2007**, *42*, 373 – 379; g) X. Zhang, X. Li, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen, Z. Sui, *J. Med. Chem.* **2007**, *50*, 3857 – 3869; h) M. E. Camacho, J. Leon, A. Entrena, G. Velasco, M. D. Carrion, G. Escames, A. Vivo, D. Acuna-Castroviejo, M. A. Gallo, A, Espinosa, *J. Med. Chem.* **2004**, *47*, 5641 – 5650; i) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi, D. M. Ferguson, *J. Med. Chem.* **2006**, *49*, 2127 – 2137.

[3] a) X. C. Gao, H. Cao, L. Q. Zhang, B. W. Zhang, Y. Cao, C. H. Huang, *J. Mater. Chem.* **1999**, *9*, 1077 – 1080; b) H. B. Fu, J. N. Yao, *J. Am. Chem. Soc.* **2001**, *123*, 1434 – 1439; c) S. W. Oh, D. R. Zhang, Y. S. Kang, *Mater. Sci. Eng. C* **2004**, *24*, 131 – 134.

[4] For the application of 1,3-diamines in asymmetric catalysis, see a) W. P. Hems, M. Groarke, A. Zanotti-Gerosa, G. A. Grasa, *Acc. Chem. Res.* **2007**, *40*, 1340 – 1347; b) K. Kodama, K. Sugawara, T. Hirose, *Chem. Eur. J.* **2011**, *17*, 13584 – 13592; c) T. Kano, Y. Yamaguchi, K. Maruoka, *Angew. Chem.* **2009**, *121*, 1870 – 1872; *Angew. Chem. Int. Ed.* **2009**, *48*, 1838 – 1840; d) Y. Yamashita, K. Odashima, K. Koga, *Tetrahedron Lett.* **1999**, *40*, 2803 – 2806; e) Y. Yamashita, Y. Emura, K. Odashima, K. Koga, *Tetrahedron Lett.* **2000**, *41*, 209 – 213; f) E. Vedejs, A. W. Kruger, *J. Org. Chem.* **1998**, *63*, 2792 – 2793; g) D. Pini, A. Mastantuono, G. Uccello-Barretta, *Tetrahedron* **1993**, *49*, 9613 – 9624; h) Q. J. Yao, Z. M. A. Judeh, *Tetrahedron* **2011**, *67*, 4086 – 4092.

[5] a) J. E. Shurig, W. T. Brandner, J. B. Huflutalen, G. J. Doyle, J. A. Gylys, *Cisplatin*, Academic Press, New York, **1980**, 227; b) W. L. Armarego, T. Kobayashi, *J. Chem. Soc.* **1970**, 1597 – 1600.

[6] a) C. M. Bromba, J. W. Mason, G. M. Brant, T. Chan, M. D. Lunke, M. Petric, M. J. Boulanger, J. E. Wulff, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7137 – 7141; b) D. M. Andrews, P. C. Cherry, D. C. Humber, P. S. Jones, S. P. Kelling, P. F. Martin, C. D. Shaw, S. Swanson, *Eur. J. Med. Chem.* **1999**, *34*, 563 – 574; c) P. Chand, P. L. Kotian, A. Dehghni, Y.-E. Kattan, T.-H. Lin, T. L. Hutchison, Y. S. Babu, S. Bantia, A. J. Elliot, J. A. Montgomery, *J. Med. Chem.* **2001**, *44*, 4379 – 4392.

[7] For achiral Brønsted acid mediated [3+2] cycloadditions, see a) K.-D. Hesse, *Justus Liebigs Ann. Chem.* **1970**, *743*, 50 – 56; b) G. Le Fevre, S. Sinbandhit, J. Hamelin, *Tetrahedron* **1979**, *35*, 1821 – 1824; c) B. Fouchet, M. Joucla, J. Hamelin, *Tetrahedron Lett.* **1981**, *22*, 1333 – 1336; d) T. Shimizu, Y. Hayashi, Y. Kitora, K. Teramura, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2450 – 2455; e) T. Shimizu, Y. Hayashi, M. Miki, K. Teramura, *J. Org. Chem.* **1987**, *52*, 2277 – 2285; f) L. O. Davis, W. F. M. Daniel, S. L. Tobey, *Tetrahedron Lett.* **2012**, *53*, 522 – 525.

[8] For recent reviews on 1,3-dipolar cycloadditions, see a) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235 – 3285; b) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247 – 12275.

[9] For [3+2] cycloadditions under thermal conditions, see a) R. Grigg, J. Kemp, N. Thompson, *Tetrahedron Lett.* **1978**, *19*, 2827 – 2830; b) G. Le Fevre, J. Hamelin, *Tetrahedron Lett.* **1979**, *20*, 1757 – 1760; c) B. B. Snider, R. S. E. Conn, S. Sealfon, *J. Org. Chem.* **1979**, *44*, 218 – 221; d) R. Grigg, M. Dowling, M. W. Jordan, V. Sridharan, *Tetrahedron* **1987**, *43*, 5873 – 5886; e) V. V. Khau, M. J. Martinelli, *Tetrahedron Lett.* **1996**, *37*, 4323 – 4326.

[10] For Lewis acid catalyzed [3+2] cycloadditions with hydrazones, see a) S. Kobayashi, R. Hirabayashi, H. Shimizu, H. Ishitani, Y. Yamashita, *Tetrahedron Lett.* **2003**, *44*, 3351 – 3354; b) E. Frank, Z. Mucsi, I. Zupko, B. Rethy, G. Falkay, G. Schneider, J. Wolfling, *J. Am. Chem. Soc.* **2009**, *131*, 3894 – 3904; c) A. Zamfir, S. Schenker, W. Bauer, T. Clark, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2011**, 3706 – 3709; d) H. Xie, J. Zhu, Z. Chen, S. Li, Y. Wu, *Synthesis* **2011**, 2767 – 2774.

[11] a) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani, J. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13678 – 13679; b) Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 11279 – 11282.

[12] S. Shirakawa, P. J. Lombardi, J. L. Leighton, *J. Am. Chem. Soc.* **2005**, *127*, 9974 – 9975.

[13] A. Zamfir, S. B. Tsogoeva, *Synthesis* **2011**, 1988 – 1992.

[14] For recent catalytic asymmetric syntheses of pyrazolines and pyrazolidines, see a) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem.* **2010**, *122*, 608 – 611; *Angew. Chem. Int. Ed.* **2010**, *49*, 598 – 601; b) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu, K. Maruoka, *J. Am. Chem. Soc.* **2010**, *132*, 4076 – 4077; c) T. Hashimoto, M. Omote, K. Maruoka, *Angew. Chem.* **2011**, *123*, 3551 – 3554; *Angew. Chem. Int. Ed.* **2011**, *50*, 3489 – 3492; d) M. Fernández, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, *Adv. Synth. Catal.* **2012**, *354*, 371 – 376; e) T. Hashimoto, H. Kimura, Y. Kawamata, K. Maruoka, *Nat. Chem.* **2011**, *3*, 642 – 646; f) L. Deiana, G.-L. Zhao, H. Leijonmarck, J. Sun, C. W. Lehmann, A. Córdova, *ChemistryOpen* **2012**, *1*, 134 – 139.

[15] For reviews on Brønsted acid catalysis, see a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550 – 1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520 – 1543; d) H. Yamamoto, N. Payette, in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 73 – 140; e) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112; f) M. Terada, *Synthesis* **2010**, 1929 – 1982; g) M. Terada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101 – 119; h) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262 – 5276; i) D. Kampen, C. M. Reisinger, B. List, *Top Curr. Chem.* **2010**, *291*, 395 – 456; j) M.

Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852 – 865; k) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539 – 4549.

[16] For other Brønsted acid catalyzed 1,3-dipolar cycloadditions, see a) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 2445 – 2447; *Angew. Chem. Int. Ed.* **2008**, *47*, 2411 – 2413; b) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652 – 5653; c) W.-J. Liu, X.-H. Chen, L.-Z. Gong, *Org. Lett.* **2008**, *10*, 5357 – 5360; d) J. Yu, L. He, X.-H. Chen, J. Song, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4946 – 4949; e) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819 – 13825; f) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 13504 – 13518.

[17] For pioneering work in the field of chiral binol-based *N*-triflylphosphoramides, see a) S. A. Yamamoto, D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627; for an overview, see b) M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, I. Atodiresei, *Angew. Chem.* **2011**, *123*, 6838 – 6853; *Angew. Chem. Int. Ed.* **2011**, *50*, 6706 – 6720; for further examples, see c) M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143 – 2146; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097 – 2100; d) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603 – 606; *Angew. Chem. Int. Ed.* **2008**, *47*, 593 – 596; e) M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903 – 6906; *Angew. Chem. Int. Ed.* **2008**, *47*, 6798 – 6801; f) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem.* **2008**, *120*, 5744 – 5748; *Angew. Chem. Int. Ed.* **2008**, *47*, 5661 – 5665; g) M. Zeng, Q. Kang, Q.-L. He, S.-L. You, *Adv. Synth. Catal.* **2008**, *350*, 2169 – 2173; h) M. Rueping, W. Ieawsuwan, *Adv. Synth. Catal.* **2009**, *351*, 78 – 84; i) M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116 – 13126; j) M. Rueping, M.-Y. Lin, *Chem. Eur. J.* **2010**, *16*, 4169 – 4172; k) M. Rueping, B. J. Nachtsheim, *Synlett* **2010**, 119 – 122; l) M. Rueping, E. Merino, R. M. Koenigs, *Adv. Synth. Catal.* **2010**, *352*, 2629 – 2634; m) C. H. Cheon, H. Yamamoto, *Org. Lett.* **2010**, *12*, 2476 – 2479; n) M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732 – 3735; o) T. Hashimoto, H. Nakatsu, K. Yamamoto, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 9730 – 9733; p) M. Rueping, W. Ieawsuwan, *Chem. Commun.* **2011**, *47*, 11450 – 11452.

[18] M. A. Badawy, S. A. El-Bahaie, A. M. Kadry, Y. A. Ibrahim, *Heterocycles* **1988**, *27*, 7 – 10.

[19] For the enantioselective synthesis of 3,5-disubstituted pyrazolines, see a) S. Müller, B. List, *Angew. Chem.* **2009**, *121*, 10160 – 10163; *Angew. Chem. Int. Ed.* **2009**, *48*, 9975 – 9978; b) O. Mahé, I. Dez, V. Levacher, J.-F. Brière, *Angew. Chem.* **2010**, *122*, 7226 – 7229; *Angew. Chem. Int. Ed.* **2010**, *49*, 7072 – 7075; c) O. Mahé, I. Dez, V. Levacher, J.-F. Brière, *Org. Biomol. Chem.* **2012**, *10*, 3946 – 3954; d) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres, C. Bolm, *J. Am. Chem. Soc.* **2012**, *134*, 6924 – 6927.

[20] M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266 – 6267.

[21] For reviews on organocatalysis in the synthesis of natural products and bioactive compounds, see a) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138; b) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575.

[22] CCDC 909012 (**7l**), 909013 (**8j**) and 909014 (**8p**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

