DOI: 10.1002/adsc.201100447

Cinchona Alkaloid-Catalyzed Enantioselective Amination of α,β-Unsaturated Ketones: An Asymmetric Approach to Δ^2-Pyrazolines

Nathaniel R. Campbell,[a] Bingfeng Sun,[a] Ravi P. Singh,[a] and Li Deng[a,*]

[a] Department of Chemistry, Brandeis University, 415 South St., Waltham, MA 02454-9110, USA
Fax: (+1)-781-736-2516; e-mail: deng@brandeis.edu

Received: May 31, 2011; Revised: July 21, 2011; Published online: November 16, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100447.

Abstract: Δ^2-Pyrazolines are of significant medicinal and synthetic interest due to their therapeutic properties and utility in the synthesis of 1,3-diamines, yet few asymmetric methods exist to prepare them. An unprecedented and highly enantioselective organocatalytic synthesis of 2-pyrazolines was achieved through an asymmetric conjugate addition catalyzed by 9-*epi*-amino *Cinchona* alkaloids followed by deprotection-cyclization, which furnished chiral 2-pyrazolines in 46–78% yield and 59–91% *ee*. This bifunctional catalytic methodology thus provides easy access to a considerable range of optically active 3,5-dialkyl 2-pyrazolines.

Keywords: asymmetric catalysis; *Cinchona* alkaloids; conjugate addition reaction; cyclization; enones; Δ^2-pyrazolines

Δ^2-Pyrazolines and their derivatives have been reported to possess antimicrobial,[1] immunosuppressive,[2] anticancer,[3] antidepressant,[4] and central nervous system effects.[5] More recently, compounds with a 2-pyrazoline (4,5-dihydropyrazole) backbone have been targeted as potent CB_1 receptor antagonists (Figure 1), which have exhibited antiobesity activity (Ibipinabant **1**[6]). Also 2-pyrazolines have demonstrated potential activity in several biological screens,[7] e.g., optimized 2-pyrazoline **2** has shown excellent activity ($IC_{50}=26$ nM) against kinesin spindle protein; inhibitors of this protein constitute a unique strategy in cancer treatment.[8] Apart from their medicinal significance, 2-pyrazolines have also been shown as useful intermediates in the synthesis of various amines including pyrazolidines,[9] azaprolines,[10] and 1,3-diamines.[11]

To date, however, only a few examples have been reported for the asymmetric synthesis of chiral 2-pyrazolines, and optically pure 2-pyrazolines are commonly obtained by resolution of their racemic counterparts.[12] In 2000, the first asymmetric catalytic synthesis of 2-pyrazolines through the 1,3-dipolar cycloaddition of acrylamides was reported utilizing a chiral Lewis acid catalyst.[13] In 2005 an indirect strategy to synthesize chiral 2-pyrazoline **3** (Figure 1) was reported where chirality was introduced by enantioselective organocatalytic thia-Michael addition to enones. However, 2-pyrazolines obtained by further transformation of the thia-adduct showed low *ee*s, and were found to readily undergo racemization.[14] Alternatively, organometallic approaches which cover asymmetric [3+2]cycloadditions of 1,3-dipoles such as diazoesters,[15] nitrile imine dipole precussors[16] to α,β-

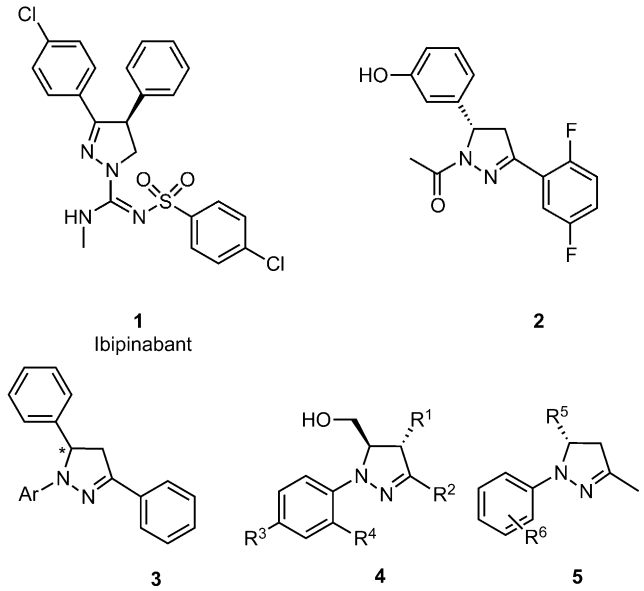
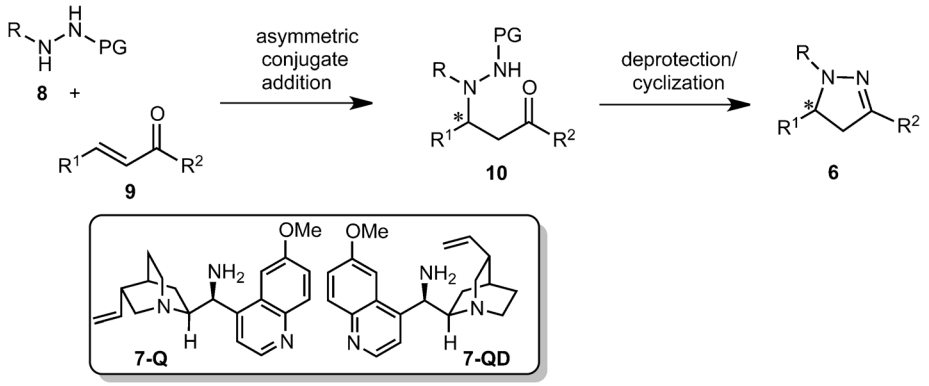


Figure 1. 2-Pyrazolines with valuable biological activities.



Scheme 1. Synthetic route to 3,5-disubstituted pyrazolines **6** and 9-amino-*Cinchona* alkaloid catalysts **7-Q** and **7-QD**.

enones provide trisubstituted 3,5-dialkyl-2-pyrazolines **4** in high *ee* and yield. More recently List and Müller disclosed the use of chiral phosphoric acid catalysis to obtain 2-pyrazolines **5** in high enantioselectivity and yield through a 6π electrocyclization,[17] however, dialkylpyrazolines (R^1 = alkyl) proved challenging, and only one example was reported with low *ee* and yield. Building upon this work, Briére and co-workers employed a *Cinchona* alkaloid-derived phase-transfer catalyst to arrive at 3,5-diarylpyrazolines with good *ee* and yield.[18]

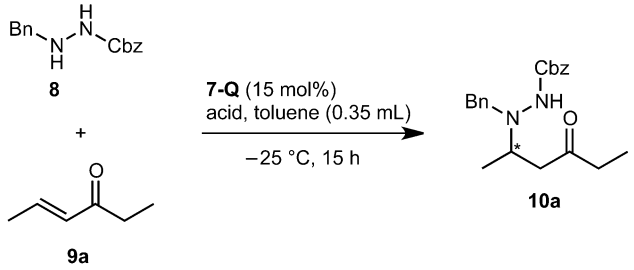
However, the substrate scope was restricted to aryl-substituted α,β-unsaturated enones making it of limited use. Thus, development of an asymmetric method which can use the alkyl-substituted α,β-unsaturated enones to provide the chiral 3,5-dialkylpyrazolines in useful yield and enantioselectivity will afford a complementary way to bridge this gap and allow direct access to important classes of pyrazoline heterocycles (Scheme 1).[9a]

First reported in 1968,[19] 9-*epi*-amino-*Cinchona* alkaloids (**7**, Scheme 1) were found to serve as highly enantioselective organic catalysts during the last several years. To date, they have demonstrated high enantioselectivity in the promotion of a series of asymmetric conjugate additions of carbon,[20] sulfur,[21] nitrogen,[22] and oxygen[23] nucleophiles to α,β-unsaturated carbonyl compounds, as well as of other nucleophilic additions[24] and Diels–Alder reactions.[25] Following our recent success in the development of **7**-catalyzed aminations[22b] and peroxidations[23d] of aliphatic α,β-enones, we became interested in developing the efficient enantioselective conjugate addition of hydrazide nucleophile **8** to aliphatic α,β-enones **9** followed by a deprotection-cyclization of the 1,4-adduct **10** as a catalytic asymmetric access to 2-pyrazolines **6** (Scheme 1).

We began our studies by selecting the appropriate hydrazide **8**, which was critical for the desired transformation, as the observed instability of **10** required mild deprotection conditions. Protecting the hydrazine with benzyl carbamate (Cbz) provided both the required regioselectivity and allowed the use of mild deprotection through hydrogenolysis. Benzyl substitution at the other hydrazine nitrogen made possible the cleavage of this group under hydrogenolysis conditions to form **6**.

For the promotion of the conjugate addition of an amine nucleophile *via* iminium catalysis, selection of an appropriate acid co-catalyst is crucial for achieving optimal reaction rate and enantioselectivity. Accordingly, a screening of several acids of varying acidity and steric properties was performed (Table 1) utilizing **9a** as a model substrate. As expected, there was no reaction observed after 15 h without any acid co-catalyst

Table 1. Acid co-catalyst screening.[a]



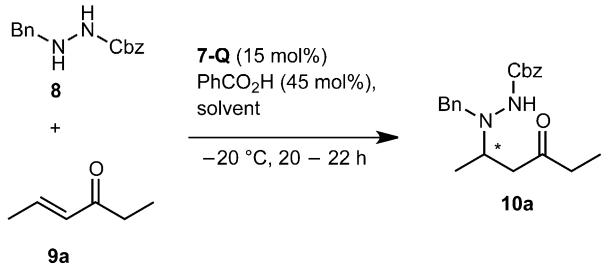
Entry	Acid	Equiv. *vs.* **7-Q**	Conversion [%][b]	*ee* **10a** [%]
1	–	–	0	–
2	CH_3CO_2H	3	3	85
3	$ClCH_2CO_2H$	3	3	37
4	Cl_2CHCO_2H	3	33	7
5	CF_3CO_2H	3	15	racemic
6	Ph_2CHCO_2H	3	12	76
7	Ph_3CCO_2H	3	3	86
8	$PhCO_2H$	3	12	90
9	$PhCO_2H$	2	9	91
10	$PhCO_2H$	1	2	–

[a] **8** (0.05 mmol) and **9a** (0.1 mmol).
[b] For comparative purposes only, determined by relative integration of **8** and **10a** on GC.

(entry 1, Table 1). Acetic acid (entry 2), and several halogenated derivatives (entries 3–5) revealed a trend of decreasing *ee* with increasing acidity; however, acceptable levels of conversion could not be obtained in conjunction with high *ee*. Two sterically hindered acetic acid derivatives (entries 6 and 7) were investigated next, both of which afforded 76% and 86% *ee*, though not at a useful level when coupled with an acceptable reaction rate. Finally, benzoic acid (entry 8) was used, giving an optimal combination of enantioselectivity and reaction rate. Lowering the equivalents of benzoic acid *versus* catalyst (entries 9 and 10) decreased the reaction rate without decreasing selectivity, indicating that 3 equivalents of benzoic acid gave the best combination of *ee* and conversion.

We next screened the effect of solvent on the reaction (Table 2). Toluene, although a poor solvent for dissolving hydrazide **8**, proved to be one of the best for the asymmetric conjugate addition (entry 1). Halogenated solvents, while fully dissolving all substrates, resulted in only moderate *ee* and conversion (entries 2–4). Ethers, which also allowed full dissolution, gave generally moderate to high *ee*; however, conversions were significantly lower than with toluene (entries 5–7). Following these results, and with the poor solubility of **8** in toluene in mind, several mixtures with chloroform (entries 8–10) were investigated, all of which improved solubility; however, with decreased conversion. A mixed solvent of toluene and ether (entry 11) maintained both excellent *ee* and good substrate solubility; however, the rate was slower in toluene. Finally, a mixture of toluene and 1,2-dichloroethane (entry 12) provided improved substrate solubility along with a slight improvement in *ee* compared to pure toluene, while sacrificing a negligible level of conversion.

Table 2. Solvent screening for the addition of **8** to **9a**.[a]



Entry	Solvent	Conv. [%][b]	*ee* **10a** [%]
1	toluene	51	88
2	$CHCl_3$	13	76
3	1,2-dichloroethane	22	77
4	CH_2Cl_2	13	82
5	THF	8	82
6	TBME	21	88
7	Et_2O	24	91
8[c]	toluene/$CHCl_3$ (7/3)	40	87
9[c]	mesitylene/$CHCl_3$ (7/3)	33	89
10[c]	Et_2O/$CHCl_3$ (7/3)	35	89
11	toluene/Et_2O (1/1)	31	91
12[c]	tolene/1,2-DCE	47	90

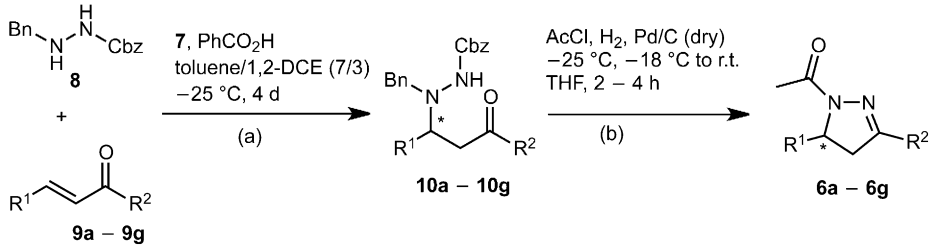
[a] *Reaction conditions:* **8** (0.05 mmol) and **9a** (0.1 mmol), and solvent (0.18 mL).
[b] For comparative purposes only, determined by relative integration of **8** and **10a** on GC.
[c] Solvent (0.2 mL).

With optimized reaction conditions for the asymmetric conjugate addition, we decided to explore the deprotection-cyclization step. It was observed that due to the oxidative decomposition of N^1-benzylated 2-pyrazolines (cyclized product) the enantioselectivity was lower in comparision to aza-Michael adduct **10a**. We chose to stabilize 2-pyrazolines **6** by adding an electron-withdrawing acetyl group to the 1-position during cyclization. When subjected to deprotection-cyclization after acetyl substitution, the model substrate **9a** furnished 2-pyrazoline **6a** in 72% yield in two steps with no loss of *ee* compared to **10a** (Table 3, entry 1 *vs.* Table 2, entry 12).

We then investigated the scope of the reaction with regard to α,β-unsaturated enones **9** (Table 3). We found that a variety of alkyl substituents (R^1 and R^2) with or without a functional group could be tolerated. Substrates with a methyl group as R^1, and R^2 either as ethyl (**9a**, entries 1 and 2) or methyl group (**9b**, entries 3 and 4) afforded good yield and selectivity, though enone **9b** showed slightly lower levels of *ee* than **9a**. Fixing R^1 as a methyl group, a variety of straight-chain aliphatic substrates were successfully applied in high *ee*. In addition to R^1 as *n*-propyl (**9c**, entries 5 and 6) and *n*-pentyl (**9d**, entries 7 and 8), the substrate scope included R^1 groups with a terminal chloride (**9e**, entries 9 and 10), and a SEM-protected alcohol (**9f**, entries 11 and 12), indicating compatibility with the use of protecting groups. Additionally, the methodology could be extended to enone **9g**, with straight-chain alkyl substituents at both R^1 and R^2 (entries 13 and 14). Furthermore, the enantiomer of **6a** was obtained in 83% *ee* by using catalyst **7-QD** (Table 3, entry 2). This deprotection protocol could be applied to intermediates **10** to obtain 3,5-disubstituted 2-pyrazolines **6** in synthetically useful *ee*s and yields (Table 3). For all substrates, we observed similar isolated yields with both **7-Q-** and **7-QD**-catalyzed reactions; however, the *ee* of the product obtained with the **7-QD** pseudoenantiomer was consistently lower by 4 to 23% compared with that of the **7-Q**-catalyzed product. Importantly, in all cases either enantiomer could still be obtained in useful overall yield and enantiomeric excess.

In the presence of an acid co-catalyst, the 9-amino-*Cinchona* alkaloid **7** was postulated to activate the

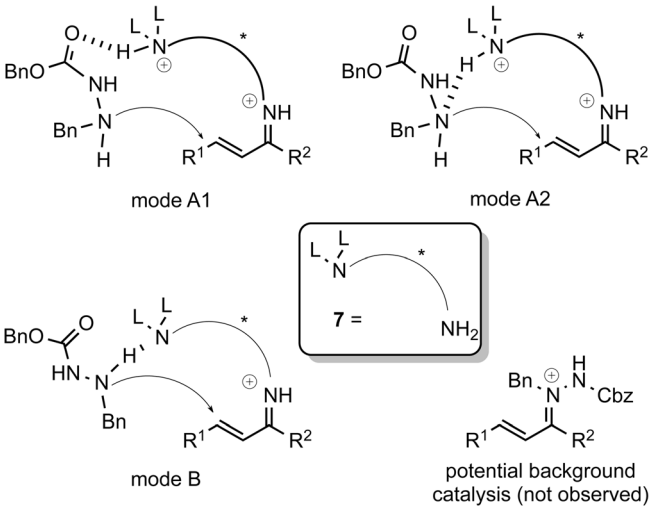
Table 3. Substrate scope for the addition of **8** to enones **9a–f**.[a]



Entry	R^1/R^2	9–6	7	Yield 6 [%] (2 steps)	*ee* 6 [%]
1	Me/Et	**9a–6a**	**7-Q**	72	90
2	Me/Et	**9a–6a**	**7-QD**	60	83
3	Me/Me	**9b–6b**	**7-Q**	57	82
4	Me/Me	**9b–6b**	**7-QD**	46	59
5	*n*-Pr/Me	**9c–6c**	**7-Q**	78	90
6	*n*-Pr/Me	**9c–6c**	**7-QD**	74	81
7	*n*-Pen/Me	**9d–6d**	**7-Q**	58	82
8	*n*-Pen/Me	**9d–6d**	**7-QD**	63	76
9	$Cl(CH_2)_3$/Me	**9e–6e**	**7-Q**	50	91
10	$Cl(CH_2)_3$/Me	**9e–6e**	**7-QD**	63	75
11	$SEMO(CH_2)_3$/Me	**9f–6f**	**7-Q**	64	91
12	$SEMO(CH_2)_3$/Me	**9f–6f**	**7-QD**	66	76
13	*n*-Pr/*n*-Bu	**9g–6g**	**7-Q**	66	90
14	*n*-Pr/*n*-Bu	**9g–6g**	**7-QD**	72	86

[a] *Reaction conditions* (a): **8** (0.1 mmol) **9** (0.2 mmol), 7 (15 mol%), $PhCO_2H$ (45 mol%), and solvent (0.35 mL); (b): AcCl (0.2 mmol), Pd/C (20 mg), and THF (2.0 mL).

α,β-unsaturated enone **9** *via* iminium catalysis while interacting with the hydrazide **8** through hydrogen bonding in the stereo-defining step. Due to the presence of benzoic acid in the reaction mixture, the catalyst could exist as both the ammonium salt and the free amine. Thus, two modes of nucleophile activation by the catalyst-substrate iminium salt could be proposed (Scheme 2), both based on the bifunctional nature of 9-amino-*Cinchona* alkaloid catalysts. Mode A involves hydrogen bonding of the ammonium salt to substrate **8**. Although this mode decreases the nucleophilicity of **8** electronically, it promotes catalysis through bringing both reactants close to each other,[26] facilitating the reaction while imparting stereocontrol. Three hydrogen bonding interactions are possible, involving the catalyst interacting with the carbonyl oxygen of the carbamate (mode A1), or with the nucleophilic nitrogen (mode A2). Additionally, the free amine catalyst can act as a base, activating nucleophile **8** via hydrogen bonding to the nucleophilic nitrogen (mode B). As has been postulated previously,[27] there exists the potential for nitrogen nucleophiles to compete with catalysts under iminium catalysis conditions through the formation of a nucleophile iminium salt; however, in this case no such background reaction was observed, indicating that the conjugate addition was promoted exclusively by the catalyst **7**.



Scheme 2. Proposed modes of substrate activation by catalyst **7**, and potential substrate-activated mode of background catalysis.

In conclusion, we have developed an efficient enantioselective organocatalytic approach, which provides an unprecedented asymmetric access to 3,5-dialkyl-2-pyrazolines **6** in useful yield and enantioselectivity. This methodology was tolerant of a variety of aliphatic α,β-unsaturated enones, using an easily accessible nitrogen nucleophile and catalyst. Additionally, both enantiomers of the chiral pyrazolines could be accessed by using the readily available bifunctional *Cin-*

chona alkaloid catalysts derived from quinine (**7-Q**) and quinidine (**7-QD**). Such a methodology should provide a useful asymmetric route to a variety of previously inaccessible asymmetric 3,5-dialkyl-2-pyrazolines and their derivatives.

Experimental Section

General Procedure for the Enantioselcective Synthesis of Δ^2-Pyrazolines

Catalyst **7-Q** (4.9 mg, 15 μmol) or **7-QD** (4.9 mg, 15 μmol), benzoic acid (5.5 mg, 45 μmol), and **8** (25.6 mg, 0.1 mmol) were dissolved in toluene/1,2-dichloroethane (7/3, 0.35 mL) in an ultrasonic bath for 5 min. The reaction vial was placed in a −25 °C freezer for 20 min, at which point **9** (0.2 mmol) was added. After standing at −25 °C for 4 days, the reaction mixture was purified by flash chromatography to give a mixture of **10** and **6** (inseparable mixture). This mixture was concentrated under vacuum and used for the formation of **6**.

To an oven-dried Schlenk flask under N_2 were added Pd/C (20 mg, 0.2 mmol, dry support) and **10** in THF (2.0 mL). The flask was cooled to −78 °C, exchanged with H_2, and AcCl (14 μL, 0.2 mmol) was added. The bath was changed to −18 °C (dry ice in saturated aqueous NaCl) and allowed to warm slowly to room temperature until the full consumption of **10** was observed by TLC (2–4 h). The reaction was stopped by passing the suspension through a Celite® plug with $CHCl_3$. Solvent was removed under vacuum, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with excess aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2×1 mL), the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under vacuum. The basified residue was purified by flash chromatography to give **6a–g** as pale yellow oils.

Acknowledgements

We are grateful for financial support from the National Institute of Health (GM-61591 and ARRA 3R01M061591-09S1).

References

[1] a) K. Ramalingam, G. X. Thyvelikakath, K. D. Berlin, *J. Med. Chem.* **1977**, *20*, 847; b) P. K. Sharma, S. Kumar, P. Kumar, P. Kaushik, D. Kaushik, Y. Dhingra, K. R. Aneja, *Eur. J. Med. Chem.* **2010**, *45*, 2650.

[2] J. G. Lombardino, I. G. Otterness, *J. Med. Chem.* **1981**, *24*, 830.

[3] a) P. J. Coleman, J. D. Schreier, C. D. Cox, M. E. Fraley, R. M. Garbaccio, C. A. Buser, E. S. Walsh, K. Hamilton, R. B. Lobell, K. Rickert, W. Tao, R. E. Diehl, V. J. South, J. P. Davide, N. E. Kohl, Y. Yan, L. Kuo, T. Prueksaritanont, C. Li, E. A. Mahan, C. Fernandez-Metzler, J. J. Salata, G. D. Hartman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5390; b) M. Shaharyar, M. M. Abdullah, M. A. Bakht, J. Majeed, *Eur. J. Med. Chem.* **2010**, *45*, 114.

[4] Y. R. Prasad, A. L. Rao, L. Prasoona, K. Murali, P. R. Kumar, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030.

[5] A. Lévai, *J. Heterocycl. Chem.* **2002**, *39*, 1.

[6] a) J. H. M. Lange, H. H. v. Stuivenberg, W. Veerman, H. C. Wals, B. Stork, H. K. A. C. Coolen, A. C. McCreary, T. J. P. Adolfs, C. G. Kruse, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4794; b) B. K. Srivastava, A. Joharapurkar, S. Raval, J. Z. Patel, R. Soni, P. Raval, A. Gite, A. Goswami, N. Sadhwani, N. Gandhi, H. Patel, B. Mishra, M. Solanki, B. Pandey, M. R. Jain, P. R. Patel, *J. Med. Chem.* **2007**, *50*, 5951; c) J. H. M. Lange, H. K. A. C. Coolen, H. H. v. Stuivenberg, J. A. R. Dijksman, A. H. J. Herremans, E. Ronken, H. G. Keizer, K. Tipker, A. C. McCreary, W. Veerman, H. C. Wals, B. Stork, P. C. Verveer, A. P. d. Hartog, N. M. J. d. Jong, T. J. P. Adolfs, J. Hoogendoorn, C. G. Kruse, *J. Med. Chem.* **2004**, *47*, 627.

[7] J. Elguero, in: *Comprehensive Heterocyclic Chemistry*, (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, Vol. 5, p 167.

[8] a) C. D. Cox, M. Torrent, M. J. Breslin, B. J. Mariano, D. B. Whitman, P. J. Coleman, C. A. Buser, E. S. Walsh, K. Hamilton, M. D. Schaber, R. B. Lobell, W. K. Tao, V. J. South, N. E. Kohl, Y. W. Yan, L. C. Kuo, T. Prueksaritanont, D. E. Slaughter, C. Z. Li, E. Mahan, B. Lu, G. D. Hartman, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3175; b) C. D. Cox, M. J. Breslin, B. J. Mariano, P. J. Coleman, C. A. Buser, E. S. Walsh, K. Hamilton, H. E. Huber, N. E. Kohl, M. Torrent, Y. Yan, L. C. Kuo, G. D. Hartman, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041; c) C. D. Cox, M. J. Breslin, B. J. Mariano, *Tetrahedron Lett.* **2004**, *45*, 1489.

[9] a) J. M. d. L. Santos, Y. López, D. Aparicio, F. Palacios, *J. Org. Chem.* **2008**, *73*, 550; b) F. M. Guerra, M. R. Mish, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4265.

[10] M. R. Mish, F. M. Guerra, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, *119*, 8379.

[11] a) K. Weinhardt, M. B. Wallach, M. Marx, *J. Med. Chem.* **1985**, *28*, 694; b) P. Bielmeier, A. Kaiser, R. Gust, W. Wiegrebe, *Monatsh. Chem.* **1996**, *127*, 1073; c) A. Kaiser, P. Bielmeier, W. Wiegrebe, *Monatsh. Chem.* **1997**, *128*, 1247.

[12] M. J. Meyers, G. B. Arhancet, S. L. Hockerman, X. Chen, S. A. Long, M. W. Mahoney, J. R. Rico, D. J. Garland, J. R. Blinn, J. T. Collins, S. Yang, H.-C. Huang, K. F. McGee, J. M. Wendling, J. D. Dietz, M. A. Payne, B. L. Homer, M. I. Heron, D. B. Reitz, X. Hu, *J. Med. Chem.* **2010**, *53*, 5979.

[13] S. Kanemasa, T. Kanai, *J. Am. Chem. Soc.* **2000**, *122*, 10710.

[14] M. Zielinska-Błajet, R. Kowalczyk, J. Skarżewski, *Tetrahedron* **2005**, *61*, 5235.

[15] [3+2] Cycloadditions with diazoesters: a) T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2174; b) M. P. Sibi, L. M. Standley, T. Soeta, *Org. Lett.* **2007**, *9*, 1553; c) L. Gao, G.-S. Hwang, M. Y. Lee, D. H. Ryu, *Chem. Commun.* **2009**, 5460.

[16] [3+2] Cycloadditions with nitrilimines: a) M. P. Sibi, L. M. Stanley, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**,

127, 8276; b) M. P. Sibi, L. M. Stanley, T. Soeta, *Adv. Synth. Catal.* **2006**, *348*, 2371.
[17] S. Müller, B. List, *Angew. Chem.* **2009**, *121*, 10160; *Angew. Chem. Int. Ed.* **2009**, *48*, 9975.
[18] O. Mahé, I. Dez, V. Levacher, J.-F. Brière, *Angew. Chem.* **2010**, *122*, 7226; *Angew. Chem. Int. Ed.* **2010**, *49*, 7072.
[19] G. R. Pettit, S. K. Gupta, *J. Chem. Soc. C* **1968**, 1208.
[20] a) J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413; b) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, W. Yong, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; c) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816; d) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.
[21] P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49.
[22] a) F. Pesciaioli, F. D. Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703; b) X. Lu, L. Deng, *Angew. Chem.* **2008**, *120*, 7824; *Angew. Chem. Int. Ed.* **2008**, *47*, 7710; c) S. Gogoi, C.-G. Zhao, D. Ding, *Org. Lett.* **2009**, *11*, 2249.
[23] a) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112; b) A.; Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492; c) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070; d) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134.
[24] a) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; b) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671.
[25] R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422.
[26] R. B. Silverman, *The Organic Chemistry of Enzyme-Catalyzed Reactions*, Academic Press, San Diego, **2000**.
[27] D. Perdicchia, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3565.

