Tetrahedron Letters 53 (2012) 6650–6653

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile organocatalyzed Michael addition of pyrazolines to α,β-unsaturated carbonyl compounds

Chen Xie, Zhijin Lu, Wei Zhou, Jianlin Han *, Yi Pan *

School of Chemistry and Chemical Engineering, Nanjing University, State Key Laboratory of Coordination, Nanjing 210093, China

ARTICLE INFO

Article history:
Received 1 August 2012
Revised 4 September 2012
Accepted 21 September 2012
Available online 5 October 2012

Keywords:
Cascade
Organocatalyst
Pyrazolone
Michael
Deprotection

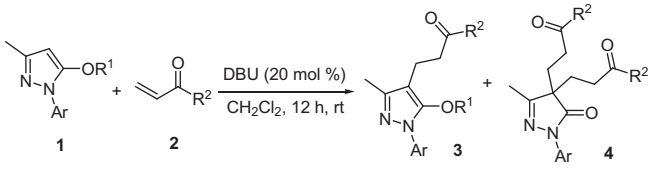
ABSTRACT

A new highly efficient cascade reaction of pyrazolines with α,β-unsaturated carbonyl compounds catalyzed by DBU was reported. The process underwent the first deprotection/Michael addition reaction to give 4-substituted pyrazoline derivatives, which were further converted into 4,4-di-substituted pyrazolone derivatives through the second deprotection/Michael reaction. The mechanism for this reaction was also studied.

In the past decade, organocatalysis has become a rapidly growing area in organic chemistry due to its operational simplicity, mild reaction conditions, and environmental benignity.[1,2] The development of cascade reactions in which an adduct is generated in a single operation from three or more reactants with high atom economy is a new hot topic in organocatalysis. Using these methods, chemists are able to reduce the purification steps and thereby optimize synthesis time, costs, and minimize chemical waste.[3]

Pyrazolone derivatives are an important class of aza-heterocycles, which have exhibited a variety of applications as pharmaceutical candidates and biologically important structural components.[4,5] Recently, a new pyrazolone compound, edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, also known as MCI-186), has been developed as a medical drug for brain ischemia[6] and has also been reported to be effective for myocardial ischemia.[7] Accordingly, the synthesis of different kinds of pyrazolone derivatives has been a hot point in modern organic chemistry. Some examples have been documented for the synthesis of pyrazolone derivatives.[8,9] However, a careful survey of the relevant literature reveals that the synthesis of double 4-substituted pyrazolone derivatives by the organocatalytic cascade reaction has not been well explored before.[10] In this context, searching for a method to synthesizing a new kind of pyrazolone derivatives by organocatalytic cascade reaction should be valuable and strongly desired. Herein, we wish to report a new method to synthesize pyrazolone derivatives starting from pyrazolines **1** and α,β-unsaturated carbonyl compounds **2** (Scheme 1). The mono- substituted product **3** was generated through the first deprotection/Michael sequence, which underwent the second deprotection/Michael process to form the final double substituted pyrazolone derivatives **4**.

Initially, 3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate **1a** and methyl vinyl ketone **2a** were chosen as the model substrates for optimizing the cascade reaction conditions (Table 1). Several regular organic bases were tried for the reaction (entries 1–3 and 5), which can promote this reaction and provide the desired products in moderate yields. Almost no desired product was obtained at all when DABCO was used (entry 4). NaOH as an inorganic base, was also tired in this reaction, but no reaction was observed even after 48 h (entry 6). No obvious improvement on yields was observed when 50 mol % catalyst was used (entries 7 and 9). When 1 equiv of catalysts (DBU or TMG) were used (entries 8 and 10), the reaction mixtures darkened quickly, mostly because the substrate **1a** decomposed and **2a** dimerized.[11] Next, further optimization with DBU as a catalyst was focused on the screening of solvents (entries 11–15), which was found to play an important role in the current

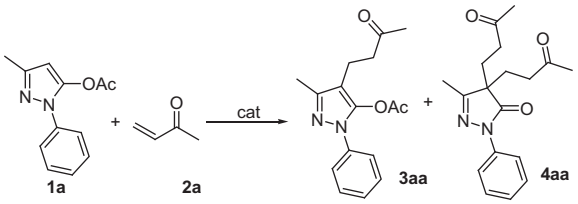


Scheme 1. Reaction of pyrazolin-5-one **1** with α,β-unsaturated carbonyl compounds **2.**

* Corresponding authors. Tel.: +86 25 83592846; fax: +86 25 83593153.
E-mail addresses: hanjl@nju.edu.cn (J. Han), yipan@nju.edu.cn (Y. Pan).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.096

Table 1
Optimization of reaction conditions[a]



Entry	Base (mol %)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	
					3aa	**4aa**
1	DMAP (20)	CH_2Cl_2	20	12	21	26
2	DBU (20)	CH_2Cl_2	20	12	31	38
3	TMG (20)	CH_2Cl_2	20	12	25	37
4	DABCO (20)	CH_2Cl_2	20	48	Trace	
5	PBu_3 (20)	CH_2Cl_2	20	12	25	18
6	NaOH (20)	CH_2Cl_2	20	48	NR[c]	
7	DBU (50)	CH_2Cl_2	20	12	31	37
8	DBU (100)	CH_2Cl_2	20	12	Mixture	
9	TMG (50)	CH_2Cl_2	20	12	27	41
10	TMG (100)	CH_2Cl_2	20	12	Mixture	
11	DBU (20)	$CHCl_3$	20	12	23	18
12	DBU (20)	DMF	20	48	Trace	
13	DBU (20)	THF	20	48	Trace	
14	DBU (20)	CH_3CN	20	48	Trace	
15	DBU (20)	H_2O	20	48	NR[c]	
16	DBU (20)	CH_2Cl_2	40	12	33	37
17	DBU (20)	CH_2Cl_2	60	12	28	35

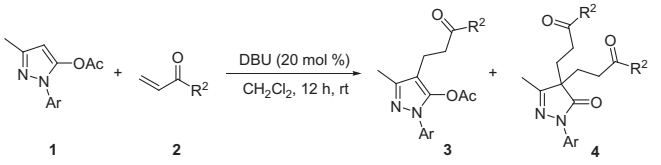
[a] Reaction conditions: **1a** (0.5 mmol), methyl vinyl ketone **2a** (1.0 mmol), solvent (2 mL).
[b] Isolated yields.
[c] No reaction was observed.

system. Only CH_2Cl_2 and $CHCl_3$ as a solvent could give the desired products and CH_2Cl_2 was the best choice in which the reaction gave the desired products **3aa** in 31% yield and **4aa** in 38% yield. When the temperature of the reaction was elevated to 40 °C or 60 °C (entries 16–17), no dramatic effect in yields happened.

After having established the optimal reaction conditions, we began to investigate the scope of pyrazoline derivatives by using methyl vinyl ketone **2a** as the reaction partner (Table 2). Initially, we examined the pyrazol-5-yl acetates bearing different substituents on the aryl ring (entries 1–8). Generally, the reactions proceeded smoothly to generate the desired products **3** and **4** in moderate yields. For all the probed substituted-phenyl ring pyrazol-5-yl acetates, the electronic factor of aromatic ring showed almost no dramatic effect on the yields (entries 2–8). Then, the protecting group on the pyrazol-5-yl derivatives (R^1) was changed into Boc, Cbz, etc., to check the substrates scope. We found that the reaction also proceeded well to give the corresponding products in moderate yields (entries 9–15). When the protecting group was Boc, the desired product **3ia** was obtained with an obvious decrease in the yield (21%), and no obvious decrease happened in the yield for product **4ia** (entry 9). Furthermore, these mono and bis-substituted products could be easily separated by column chromatography.

We then chose several other α,β-unsaturated carbonyl compounds **2** as substrates to further examine the reaction scope (Table 3). Ethyl vinyl ketone **2b**, which was similar to methyl vinyl ketone **2a**, reacted well with pyrazol-5-yl acetate under the same reaction condition, providing the products **3** in moderate yields (35% and 31%), and products **4** in dramatic higher yields (49% and 58%, entries 1 and 4). However, when the electrophiles were changed into acrylates (entries 2 and 5–8), the reaction proceeded very slowly and needed 24 h to consume all the starting materials, along with lower chemical yields of products **4** (8–15% yields). Interestingly, among the acrylates, phenyl acrylate showed the opposite activity to give the products **4** in obvious higher yields (47–48%, entries 3 and 9). Moreover, the steric features affected this reaction greatly and when we used *tert*-butyl acrylate as the electrophile, no reaction was observed even after 48 h (not shown in the Table 3). Unfortunately, acrylamide could not react with pyrazol-5-yl acetate **1** under this reaction condition (entry 10).

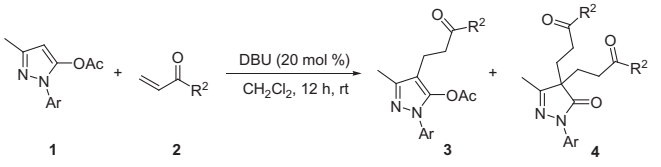
Table 2
Reaction scope of pyrazoline derivatives[a]



Entry	**1**	Ar	R^1	Yield[b] (%)	
				3	4
1	**1a**	C_6H_5	Ac	31 (**3aa**)	38 (**4aa**)
2	**1b**	2-ClC_6H_4	Ac	36 (**3ba**)	40 (**4ba**)
3	**1c**	3-ClC_6H_4	Ac	38 (**3ca**)	45 (**4ca**)
4	**1d**	4-ClC_6H_4	Ac	35 (**3da**)	43 (**4da**)
5	**1e**	4-BrC_6H_4	Ac	36 (**3ea**)	41 (**4ea**)
6	**1f**	4-FC_6H_4	Ac	29 (**3fa**)	38 (**4fa**)
7	**1g**	4-MeC_6H_4	Ac	26 (**3ga**)	35 (**4ga**)
8	**1h**	4-$MeOC_6H_4$	Ac	27 (**3ha**)	35 (**4ha**)
9	**1i**	C_6H_5	Boc	21 (**3ia**)	35 (**4ia**)[c]
10	**1j**	C_6H_5	Cbz	31 (**3ja**)	37 (**4ja**)[c]
11	**1k**	C_6H_5	COOEt	32 (**3ka**)	39 (**4ka**)[c]
12	**1l**	C_6H_5	COOAllyl	38 (**3la**)	33 (**4la**)[c]
13	**1m**	4-ClC_6H_4	Boc	27 (**3ma**)	38 (**4ma**)[d]
14	**1n**	4-ClC_6H_4	Cbz	34 (**3na**)	33 (**4na**)[d]
15	**1o**	4-ClC_6H_4	COOAllyl	32 (**3oa**)	37 (**4oa**)[d]

[a] Reaction conditions: **1** (0.5 mmol), methyl vinyl ketone **2a** (1.0 mmol), and DBU (0.1 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Isolated yields.
[c] The same with **4aa**.
[d] The same with **4da**.

Table 3
Reaction of **1** with different α,β-unsaturated carbonyl compounds **2**[a]



Entry	Ar	R^2	Time (h)	Yield[b] (%)	
				3	**4**
1	C_6H_5 (**1a**)	Et (**2b**)	12	35 (**3ab**)	49 (**4ab**)
2	C_6H_5 (**1a**)	OMe (**2c**)	24	33 (**3ac**)	15 (**4ac**)
3	C_6H_5 (**1a**)	OPh (**2g**)	24	28 (**3ag**)	47 (**4ag**)
4	4-ClC_6H_4 (**1d**)	Et (**2b**)	12	31 (**3db**)	58 (**4db**)
5	4-ClC_6H_4 (**1d**)	OMe (**2c**)	24	35 (**3dc**)	15 (**4dc**)
6	4-ClC_6H_4 (**1d**)	OEt (**2d**)	24	31 (**3dd**)	13 (**4dd**)
7	4-ClC_6H_4 (**1d**)	O^{n}Bu (**2e**)	24	28 (**3de**)	11 (**4de**)
8	4-ClC_6H_4 (**1d**)	O^{i}Bu (**2f**)	24	25 (**3df**)	8 (**4df**)
9	4-ClC_6H_4 (**1d**)	OPh (**2g**)	24	27 (**3dg**)	48 (**4dg**)
10	4-ClC_6H_4 (**1d**)	NH_2 (**2i**)	48	NR[c]	

[a] Reaction conditions: pyrazol-5-yl acetate **1** (0.5 mmol), α,β-unsaturated carbonyl compounds **2** (1.0 mmol), and DBU (0.1 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Isolated yields.
[c] No reaction was observed.

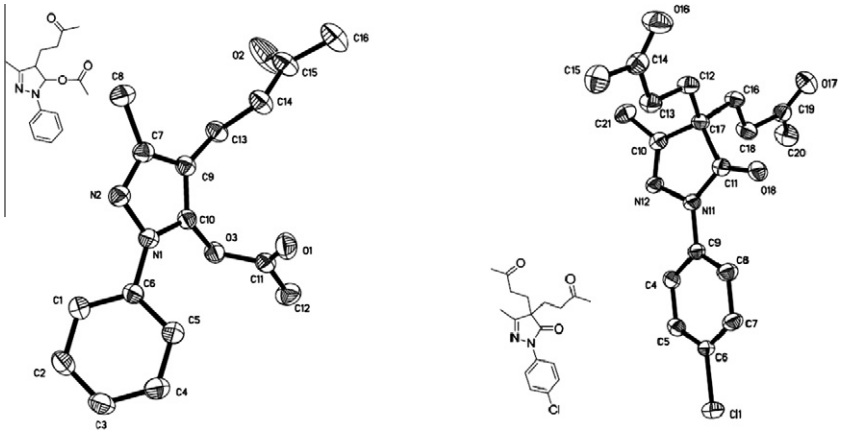
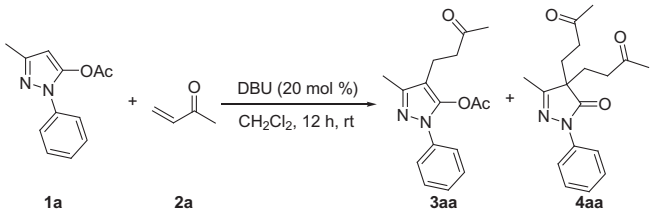


Figure 1. X-ray crystallography for **3aa** and **4da**.

Table 4
Different ratios of **1a** and methyl vinyl ketone **2a**[a]



1a **2a** **3aa** **4aa**

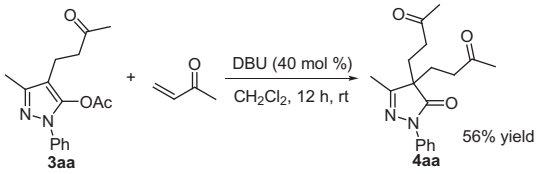
Entry	**1a** (mmol)	**2a** (mmol)	Ratio (**1a**:**2a**)	Yield[b] (%)	
				3aa	**4aa**
1	0.50	0.10	5:1	15	<5
2	0.50	0.25	2:1	18	<5
3	0.50	0.50	1:1	27	18
4	0.50	0.75	2:3	35	33
5	0.50	1.00	1:2	31	35
6	0.50	1.50	1:3	28	37
7	0.50	2.00	1:4	23	43
8	0.50	5.00	1:10	14	50

[a] Reaction conditions: 3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate **1a** (0.5 mmol), methyl vinyl ketone **2a,** and DBU (0.1 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Isolated yields.

To determine the absolute configurations of the products **3** and **4**, single crystals suitable for X-ray crystallographic analysis were fortunately obtained from the product **3aa** and product **4da** (Fig. 1). This confirmed the chemical structures of these newly formed mono- and bis-substituted pyrazoline derivatives.

To gain insight into the reaction mechanism, we investigated the relationship between the ratio of the two reactants and the yields of the two products (Table 4). As shown in Table 4, increasing the ratio of **1a** to **2a** could improve the chemoselectivity, and control the formation of product **4aa**. But the yield of **3aa** was decreased dramatically at the same time (entries 1–2). When the ratio of **1a** to **2a** was 1:1, both the products **3aa** and **4aa** were obtained (entry 3). As we expected, with the increase of the amount of methyl vinyl ketone **2a**, the yields of product **4aa** increased thereby. When the amount of methyl vinyl ketone **2a** was further increased to 10 equiv (entry 8), product **4aa** could be obtained in 50% yield while the yield of product **3aa** was relatively low (14% yield). The highest yield of product **3aa** (35% yield) was obtained when the ratio of the two reactants was 2:3 (entry 4).

The reaction mechanism for this reaction was still not clear at this stage. Then we used the product **3aa** as a starting material



Scheme 2. The reaction of **3aa** and methyl vinyl ketone with DBU as catalyst.

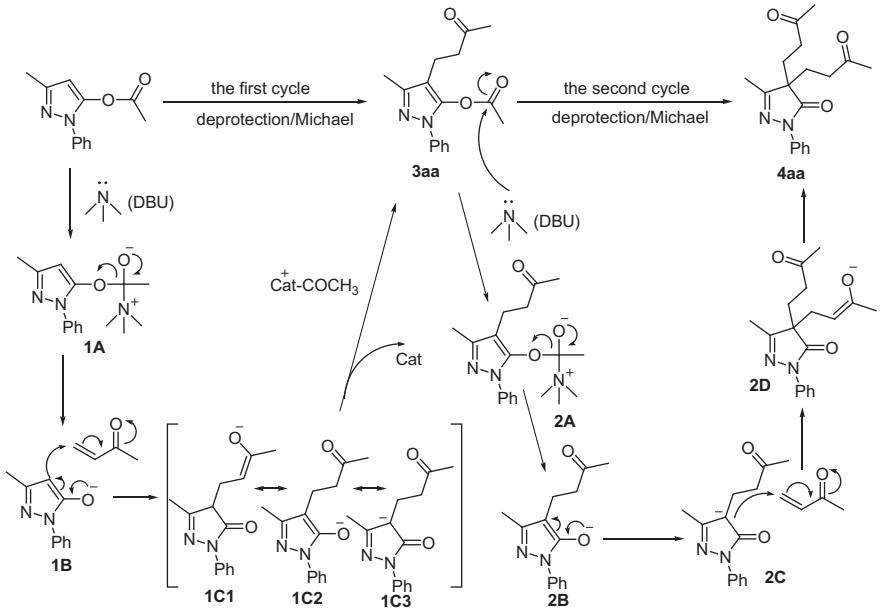
to react with methyl vinyl ketone under the similar reaction condition. To our delight, the **3aa** could be partly converted into **4aa** with 56% yield and the rest of **3aa** remained unreacted (Scheme 2). This result discloses that the **3aa** is probably the reaction intermediate.

On the basis of experimental results, a plausible reaction mechanism for this reaction was proposed in Scheme 3, which includes two deprotection/Michael reaction processes. In the first cycle, the starting material pyrazol-5-yl acetate is activated by DBU, giving intermediate **1A**. Then **1A** undergoes the deprotection step to result in intermediate **1B**, which is followed by Michael addition reaction with methyl vinyl ketone. The Michael adduct exists as tautomeric form **1C**. The similar tautomeric forms could be found in the reports from Fu's group.[12] Finally, the intermediate **1C1** reacts with Cat-$COCH_3^+$ to form the product **3aa**. Then, **3aa** acts as the substrate for the second deprotection/Michael cycle. Initially, **3aa** is activated to form **2A**, and **2A** is deprotected to give the intermediate **2B**, which is similar to the first cycle. Then is the Michael addition step to form the final adduct **4aa**. The reactions for the substrates with other protecting groups were believed to go through the similar processes.

In summary, we have developed a facile method to prepare different multiply 4-substituted-5-pyrazolone derivatives. This reaction could tolerate a wide scope of pyrazoline derivatives and α,β-unsaturated carbonyl compounds with moderate chemical yields. This organocatalytic cascade reaction proceeded through two deprotection/Michael steps, and gave mono- and bis-substituted pyrazoline derivatives at the same time. Further Studies applying pyrazolin-5-ones as reactants in asymmetric organic synthesis and exploring new organocatalytic tandem reactions are actively underway in our laboratory.

Acknowledgments

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (No. 21102071)



Scheme 3. Proposed Mechanism of the reaction.

and the Fundamental Research Funds for the Central Universities (No. 1107020522 and No. 1082020502). The Jiangsu 333 program (for Pan) and Changzhou Jin-Feng-Huang program (for Han) are also acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.096.

References and notes

1. For selected reviews on organocatalysis, see: (a) List, B. *Chem. Rev.* **2007**, *107*, 5413–5415; (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331; (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (d) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575–2600; (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171; (f) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; (g) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632–649; (h) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279.
2. (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308; (b) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807–810.
3. For the selected examples for discussion of the tandem reactions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581; (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; (e) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673.
4. For selected examples, see: (a) Field, J. B.; Dolendo, E. C.; Mireles, A.; Ershoff, B. H. *Cancer Res.* **1966**, *26*, 1371–1375; (b) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. *J. Pharm. Sci.* **1989**, *78*, 239–242; (c) Abass, M.; Mostafa, B. B. *Bioorg. Med. Chem.* **2005**, *13*, 6133–6144; (d) Chen, T.; Benmohamed, R.; Kim, J.; Smith, K.; Amante, D.; Morimoto, R. I.; Kirsch, D. R.; Ferrante, R. J.; Silverman, R. B. *J. Med. Chem.* **2012**, *55*, 515–527; (e) Norman, M. H.; Liu, L.; Lee, M.; Xi, N.; Fellows, I.; D'Angelo, N. D.; Dominguez, C.; Rex, K.; Bellon, S. F.; Kim, T. S.; Dussault, I. *J. Med. Chem.* **2012**, *55*, 1858–1867.
5. (a) Chantegrel, B.; Gelin, S. *Synthesis* **1985**, 548–550; (b) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G. *Tetrahedron Lett.* **1987**, *28*, 5165–5168; (c) Boeckman, R. K.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651–3653.
6. (a) Watanabe, T.; Yuki, S.; Egawa, M.; Nishi, H. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1597–1604; (b) Kawai, H.; Nakai, H.; Suga, M.; Yuki, S.; Watanabe, T.; Saito, K. I. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 921–927.
7. Wu, T. W.; Zeng, L. H.; Wu, J.; Fung, K. P. *Life Sci.* **2002**, *71*, 2249–2255.
8. (a) Liao, Y. H.; Chen, W. B.; Wu, Z. J.; Du, X. L.; Cun, L. F.; Zhang, X. M.; Yuan, W. C. *Adv. Synth. Catal.* **2010**, *352*, 827–832; (b) Wang, Z.; Yang, Z. G.; Chen, D. H.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4928–4932; (c) Yang, Z. G.; Wang, Z.; Bai, S.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2011**, *13*, 596–599; (d) Gogoi, S.; Zhao, C. G. *Tetrahedron Lett.* **2009**, *50*, 2252–2255; (e) Wang, Z.; Chen, Z. L.; Bai, S.; Li, W.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2776–2779.
9. (a) Luo, N.; Zheng, Z. Y.; Yu, Z. K. *Org. Lett.* **2011**, *13*, 3384–3387; (b) Wu, Y. H.; Yao, W. J.; Pan, L. J.; Zhang, Y. P.; Ma, C. *Org. Lett.* **2010**, *12*, 640–643; (c) Huang, Y. Y.; Lin, H. C.; Cheng, K. M.; Su, W. N.; Sung, K. C.; Lin, T. P.; Huang, J. J.; Lin, S. K.; Wong, F. F. *Tetrahedron* **2009**, *65*, 9592–9597.
10. (a) Alba, A. N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, 1318–1325; (b) Tu, X. C.; Feng, H.; Tu, M. S.; Jiang, B.; Wang, S. L.; Tu, S. J. *Tetrahedron Lett.* **2012**, *53*, 3169–3172.
11. (a) Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett.* **1987**, *28*, 4591–4592; (b) Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synth. Commun.* **1990**, *20*, 1915–1921.
12. Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.