DOI: 10.1002/adsc.200800584

Copper(II)-Catalyzed C−C Bond-Forming Reactions of α-Electron-Withdrawing Group-Substituted Ketene *S,S*-Acetals with Carbonyl Compounds and a Facile Synthesis of Coumarins

Hong-Juan Yuan,[a] Mang Wang,[a,*] Ying-Jie Liu,[a] and Qun Liu[a,*]

[a] Department of Chemistry, Northeast Normal University, Changchun, 130024, People's Republic of China
Fax: (+86)-431-8509-9759; e-mail: wangm452@nenu.edu.cn

Received: September 21, 2008; Published online: December 19, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800584.

Abstract: A new catalytic C−C bond-forming reaction has been developed. Catalyzed by cheap and commercially available copper(II) bromide ($CuBr_2$; 10 mol%), the reactions of α-electron-withdrawing group (EWG)-substituted ketene *S,S*-acetals with aldehydes or ketones in acetonitrile at room temperature gave a variety of densely functionalized coupling products in excellent yields (80–98%). Based on this catalytic process, coumarin derivatives were efficiently synthesized when salicylaldehydes were selected as the carbonyl components.

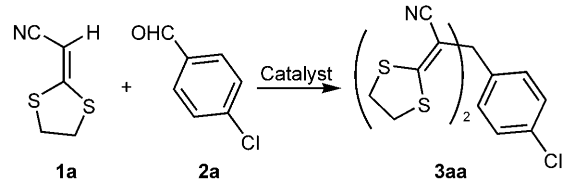
Keywords: carbonyl compounds; C−C bond formation; copper catalysis; coumarins; α-electron-withdrawing group (EWG)-substituted ketene *S,S*-acetals

Functionalized ketene *S,S*-acetals are versatile intermediates in organic synthesis.[1–4] With the recent advances in the wide applications of these intermediates for the construction of a diverse array of polysubstituted carbo- and heterocyclic compounds,[1–6] some efforts have focused on the design and synthesis of new ketene *S,S*-acetal-based synthons via α-functionalization of α-EWG-substituted ketene *S,S*-acetals (EWG = electron-withdrawing group).[7–9] In this context, the C−C bond forming reactions at the nucleophilic α-carbon atom of these β,β-dialkylthio-activated alkenes have been found to be reliable and incorporate a wide variety of carbon electrophiles.[7,8] Our previous research revealed that the reactions of Lewis acid-activated aldehydes,[7a–d,g] simple ketones,[7d] or enones[7e] with α-EWG-substituted ketene *S,S*-acetals were accessible in the presence of over stoichiometric amounts of $TiCl_4$. Taking consideration of the importance of the C−C bond construction and with the aim of making the above reactions more efficient for further applications, we are interested in the catalytic version of these processes. Transition metal catalysts are widely used in the C−C coupling reactions.[10] Among them, copper catalysts have received much attention due to their low cost, easily handling, and good functional tolerance.[11] Herein, we report a copper(II) salt-catalyzed C−C bond forming reaction between nucleophilic α-EWG-substituted ketene *S,S*-acetals **1** and electrophilic aldehydes/ketones **2**, which leads to the formation of 2:1 adducts **3** or coumarin derivatives **4** in high to excellent yields under very mild conditions.

Initially, a series of simple copper salts, including $CuBr_2$, $CuCl_2$, $Cu(OAc)_2$ and CuBr were evaluated in the model reaction of α-cyanoketene cyclic *S,S*-acetal **1a** with 4-chlorobenzaldehyde **2a** as depicted in Table 1. After extensive experiments, the best results were obtained with $CuBr_2$ as the catalyst. Under the optimized conditions, i.e., the mixture of **1a** (1.0 mmol), **2a** (0.5 mmol), and $CuBr_2$ (0.05 mmol) reacted at room temperature in acetonitrile (4.0 mL) for 12 h, the 2:1 adduct **3aa**[7d] was obtained in excellent yield (Table 1, entry 2).

Under the conditions described in Table 1, entry 2, the scope of the reaction was studied and some representative results are listed in Table 2. It was found that a wide range of electrophiles, including benzaldehyde (entry 2), aromatic aldehydes having both electron-withdrawing (entries 1 and 3) and electron-donating (entry 4) substituents, heteroaromatic aldehydes (entry 5), α,β-unsaturated aldehydes (entry 6), aliphatic aldehydes (entry 7), and ketones (entries 8 and 9), reacted smoothly with **1a** to give the corresponding 2:1 adducts **3aa**–**3ai** in excellent yields. The tolerance of substrates **1** was then investigated by varying the EWG and SR groups. It is clear from Table 2 that the reactions of **1b**–**1d** with **2a** could give the desired products **3ba**–**3da** in 82–94% yields, re-

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



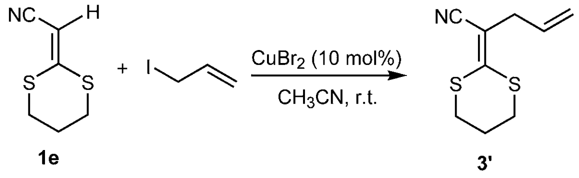
Entry	Cat. [equiv.][b]	Solvent	Time [h]	Yield [%][c]
1	$CuBr_2$ (1.0)	CH_3CN	8.0	98
2	$CuBr_2$ (0.1)	CH_3CN	12	98
3	$CuBr_2$ (0.05)	CH_3CN	48	42
4	$CuCl_2$ (1.0)	CH_3CN	23	90
5	$CuCl_2$ (0.1)	CH_3CN	48	45
6	$Cu(OAc)_2$ (0.1)	CH_3CN	24	–[d]
7	CuBr (1.0)	CH_3CN	72	–[d]
8	$CuBr_2$ (0.1)	CH_2Cl_2	14	95

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (0.5 mmol), solvent (4.0 mL), room temperature.
[b] Equivalents based on **2a**.
[c] Isolated yield.
[d] No reaction.

spectively (entries 10–12). In particular, the reaction of **1d** with **2a** was much faster and was complete within 3.0 h (entry 12). Similarly, when cyclic substrate **1e** was subjected to identical reaction conditions, **3ea** was obtained in 95% yield in a short time (entry 13). In addition, this reaction can also tolerate the acyclic alkylthio functionality of **1**. Upon treatment with 4-chlorobenzaldehyde **2a**, the acyclic analogues **1f** and **1g** afforded the corresponding **3fa** and **3ga** in 95% and 94% yields, respectively, under $CuBr_2$ catalysis (entries 14 and 15).

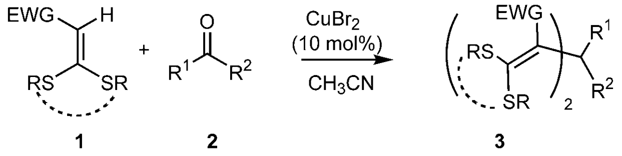
Compared with the results mentioned above and our previous reports,[7] a different reaction process of this new catalytic C–C bond-forming reaction is predictable. Although the mechanism is not yet clear at this stage, the reaction of **1e** with allyl iodide (10 equiv.) in the presence of 10 mol% of $CuBr_2$ (Scheme 1) to deliver the C–C coupling product 2-(1,3-dithian-2-ylidene)pent-4-enenitrile **3′** (70% isolated yield) might indicate that $CuBr_2$ plays a duplicate role and results in the activation not only of the carbonyl electrophiles,[7] but also of the β,β-dialkylthio-activated alkenes **1**.[12,13]

Attracted by the advantages, such as cheap catalyst, broad scope of carbonyl compounds and α-EWG-substituted ketene *S,S*-acetals, high product yields, and



Scheme 1. Coupling of **1e** with allyl iodide catalyzed by $CuBr_2$.

Table 2. $CuBr_2$-catalyzed C–C bond forming reactions of α-EWG-substituted ketene *S,S*-acetals **1** with aldehydes/ketones **2**.[a]

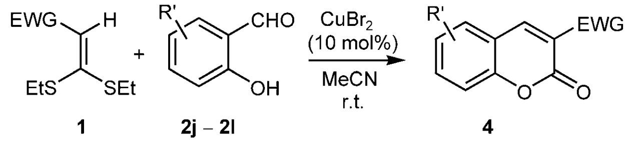


Entry	1	EWG	R or R,R	2	R^1	R^2	3	Time [h]	Yield [%][b]
1	**1a**	CN	$(CH_2)_2$	**2a**	$4\text{-}ClC_6H_4$	H	**3aa**	12	98
2	**1a**	CN	$(CH_2)_2$	**2b**	C_6H_5	H	**3ab**	12	93
3	**1a**	CN	$(CH_2)_2$	**2c**	$4\text{-}NO_2C_6H_4$	H	**3ac**	18	96
4	**1a**	CN	$(CH_2)_2$	**2d**	$4\text{-}MeOC_6H_4$	H	**3ad**	15	97
5	**1a**	CN	$(CH_2)_2$	**2e**	2-furyl	H	**3ae**	9.0	88
6	**1a**	CN	$(CH_2)_2$	**2f**	*E*-$C_6H_5CH{=}CH$	H	**3af**	14	90
7	**1a**	CN	$(CH_2)_2$	**2g**	Me	H	**3ag**	24	86
8	**1a**	CN	$(CH_2)_2$	**2h**	Me	Me	**3ah**	35	85
9	**1a**	CN	$(CH_2)_2$	**2i**	$(CH_2)_5$		**3ai**	18	85
10	**1b**	MeCO	$(CH_2)_2$	**2a**	$4\text{-}ClC_6H_4$	H	**3ba**	22	82
11	**1c**	PhCO	$(CH_2)_2$	**2a**	$4\text{-}ClC_6H_4$	H	**3ca**	24	80
12	**1d**	CO_2Et	$(CH_2)_2$	**2a**	$4\text{-}ClC_6H_4$	H	**3da**	3.0	94
13	**1e**	CN	$(CH_2)_3$	**2a**	$4\text{-}ClC_6H_4$	H	**3ea**	3.0	95
14	**1f**	CN	Me	**2a**	$4\text{-}ClC_6H_4$	H	**3fa**	19	95
15	**1g**	CN	Et	**2a**	$4\text{-}ClC_6H_4$	H	**3ga**	16	94

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (0.5 mmol), $CuBr_2$ (0.05 mmol), CH_3CN (4.0 mL), room temperature.
[b] Isolated yield.

mild reaction conditions, of the above catalytic C–C bond-forming reactions, efforts were then focused on developing a facile synthesis of coumarin derivatives. Thus, salicylaldehydes **2j**–**2l** were selected as the electrophiles to react with acyclic ketene *S,S*-acetals **1g**–**1j** catalyzed by $CuBr_2$. As expected, all the reactions proceeded smoothly to afford coumarins **4** in good to high yields in a single operation (Table 3). As a comparison, **4gj** was obtained only in 35% isolated yield along with the recovery of **1g** (in 30% yield) by reacting **1g** with **2j** for 24 h under identical conditions, but mediated with overstoichiometric amounts of $TiCl_4$ (1.2 equiv.).

Table 3. Synthesis of coumarins *via* the reaction of **1** and **2** catalyzed by $CuBr_2$.[a]

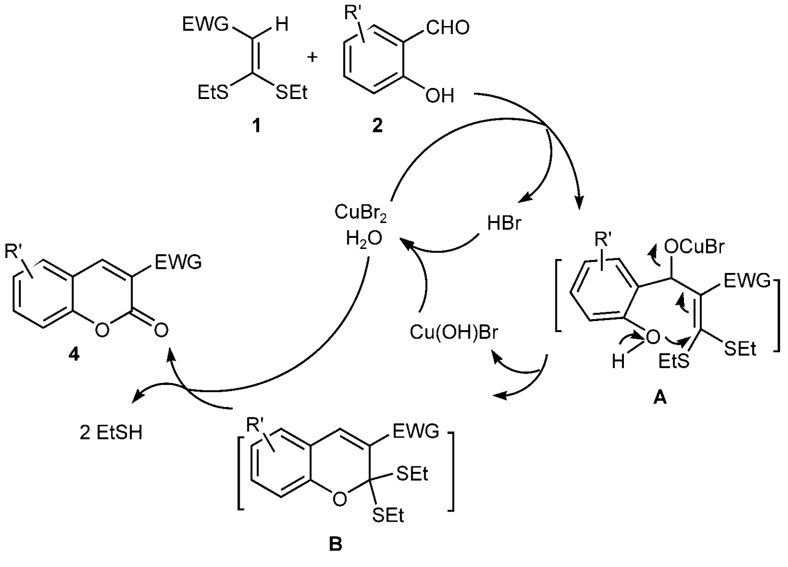


Entry	1	EWG	2	R′	Time [h]	4	Yield [%][b]
1	**1g**	CN	**2j**	H	3.0	**4gj**	82
2	**1h**	MeCO	**2j**	H	6.0	**4hj**	50
3	**1i**	PhCO	**2j**	H	4.0	**4ij**	84
4	**1j**	CO_2Et	**2j**	H	2.0	**4jj**	86
5	**1g**	CN	**2k**	5-MeO	3.5	**4gk**	70
6	**1h**	MeCO	**2k**	5-MeO	3.0	**4hk**	86
7	**1i**	PhCO	**2k**	5-MeO	4.0	**4ik**	82
8	**1j**	CO_2Et	**2k**	5-MeO	2.0	**4jk**	74
9	**1g**	CN	**2l**	5-Cl	5.0	**4gl**	79
10	**1h**	MeCO	**2l**	5-Cl	5.0	**4hl**	77
11	**1i**	PhCO	**2l**	5-Cl	3.0	**4il**	76
12	**1j**	CO_2Et	**2l**	5-Cl	1.0	**4jl**	90

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (1.0 mmol), $CuBr_2$ (0.1 mmol), CH_3CN (4.0 mL), room temperature.

[b] Isolated yield.

Coumarins are important heterocycles widely present in natural products exhibiting a broad range of biological and therapeutic activities.[14] A number of classical approaches for accessing coumarins are available and novel synthetic routes are attracting much attention in organic chemistry.[15] Recently, Pd-catalyzed coumarin syntheses presented a new promising strategy.[16] In 2006, Rao and Sivakumar reported a route to the synthesis of 3-aroylcoumarins by the condensation of α-aroylketene *S,S*-acetals and salicylaldehydes in the presence of catalytic amount of piperidine at reflux temperature.[8a] It is noteworthy that our method for the synthesis of coumarins represents a general route using a wide range of α-EWG-substituted ketene *S,S*-acetals, including α-aroyl, acetyl, cyano, ethoxycarbonyl groups and the reactions can be carried out under very mild conditions (Table 3). Thus, this new protocol allows the more effective synthesis of a combinatorial library of coumarins. The proposed mechanism is described in Scheme 2. The reaction begins with the addition of **1** to **2** catalyzed by $CuBr_2$ to give intermediate **A** along with the loss of a molecule of HBr. Then, an intramolecular conjugate displacement leads to the formation of intermediate **B** and Cu(OH)Br. Finally, coumarin **4** is formed by hydrolysis of **B**. In the course of this reaction, catalyst $CuBr_2$ can be recycled by the reaction of Cu(OH)Br with HBr. Clearly, this novel procedure for the synthesis of coumarin derivatives has the advantages of mild reaction conditions and a broad scope of substrates.[8a,15,16]



Scheme 2. Proposed mechanism for the synthesis of coumarins from **1** and salicylylaldehydes **2j**–**2l** catalyzed by $CuBr_2$.

In summary, we have developed a new Cu(II)-catalyzed C–C bond forming reaction. A wide range of densely functionalized double-coupling products **3** were obtained in excellent yields by reacting the readily available α-EWG-substituted ketene *S,S*-acetals with a variety of aldehydes and ketones under very mild reaction conditions. Based on this catalytic process, coumarin derivatives were synthesized in high yields. The efficiency and convenience of the coumarin syntheses along with a broad range of EWG groups at the 3-position make this synthetic strategy very attractive for practical applications. Further studies on the reaction mechanism and synthetic potential of this catalytic reaction are in progress.

Experimental Section

General Procedure for the $CuBr_2$-Catalyzed C–C Bond-Forming Reactions of 1 with 2 (taking the Reaction of 1a and 2a as an Example)

To a solution of 2-(1,3-dithiolan-2-ylidene)acetonitrile **1a** (143 mg, 1.0 mmol) and 4-chlorobenzaldehyde **2a** (70 mg, 0.5 mmol) in dry acetonitrile (4.0 mL) was added $CuBr_2$ (11.2 mg, 0.05 mmol). The reaction mixture was stirred for 12 h at room temperature and monitored by TLC. After completion, the reaction mixture was poured into ice-water (20 mL). The precipitate was collected by filtration, washed with water (3×20 mL), and dried under vacuum to afford the product **3aa** as a white solid; yield: 199 mg (98%).

Acknowledgements

Financial support of this research by the National Natural Science Foundation of China (20672019 and 20872015), the Ministry of Education of China (108044), and the Training Fund of NENU's Scientific Innovation Fund are greatly acknowledged.

References

[1] For reviews on α-oxoketene *S,S*-acetals, see: a) R. K. Dieter, *Tetrahedron* **1986**, *42*, 3029–3096; b) H. Junjappa, H. Ila, C. V. Asokan, *Tetrahedron* **1990**, *46*, 5423–5506; c) G. H. Elgemeie, S. H. Sayed, *Synthesis* **2001**, 1747–1771.

[2] For synthesis and synthetic application of phosphonoketene *S,S*-acetals, see: a) T. Minami, T. Okauchi, H. Matsuki, M. Nakamura, J. Ichikawa, M. Ishida, *J. Org. Chem.* **1996**, *61*, 8132–8140; b) R. Kouno, T. Okauchi, M. Nakamura, J. Ichikawa, T. Minami, *J. Org. Chem.* **1998**, *63*, 6239–6246.

[3] For synthesis and synthetic applications of fluorinated ketene *S,S*-acetals, see: a) M. Muzard, C. Portella, *J. Org. Chem.* **1993**, *58*, 29–31; b) M. C. Pirrung, E. G. Rowley, C. P. Holmes, *J. Org. Chem.* **1993**, *58*, 5683–5689; c) E. Sotoca, J.-P. Bouillon, S. Gil, M. Parra, C. Portella, *Tetrahedron* **2005**, *61*, 4395–4402, and references cited therein.

[4] For the reactions and applications of silylketene *S,S*-acetals, see: a) T. Okauchi, T. Tanaka, T. Minami, *J. Org. Chem.* **2001**, *66*, 3924–3929; b) S. Yahiro, K. Shibata, T. Saito, T. Okauchi, T. Minami, *J. Org. Chem.* **2003**, *68*, 4947–4950.

[5] For selected examples, see: a) X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao, B. Li, *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579; b) F. Liang, J. Zhang, J. Tan, Q. Liu, *Adv. Synth. Catal.* **2006**, *348*, 1986–1990; c) X. Bi, J. Zhang, Q. Liu, J. Tan, B. Li, *Adv. Synth. Catal.* **2007**, *349*, 2301–2306; d) J. Liu, M. Wang, B. Li, Q. Liu, Y. Zhao, *J. Org. Chem.* **2007**, *72*, 4401–4405; e) J. Liu, D. Liang, M. Wang, Q. Liu, *Synthesis* **2008**, 3633–3638.

[6] a) S. Gill, P. Kocienski, A. Kohler, A. Pontiroli, Q. Liu, *Chem. Commun.* **1996**, 1743–1744; b) K. Panda, J. R. Suresh, H. Ila, H. Junjappa, *J. Org. Chem.* **2003**, *68*, 3498–3506; c) S. Peruncheralathan, T. A. Khan, H. Ila, H. Junjappa, *J. Org. Chem.* **2005**, *70*, 10030–10035.

[7] a) Y. Yin, M. Wang, Q. Liu, J. Hu, S. Sun, J. Kang, *Tetrahedron Lett.* **2005**, *46*, 4399–4402; b) S. Sun, Q. Zhang, Q. Liu, J. Kang, Y. Yin, D. Li, D. Dong, *Tetrahedron Lett.* **2005**, *46*, 6271–6274; c) W. Pan, D. Dong, S. Sun, Q. Liu, *Synlett* **2006**, 1090–1094; d) Q. Zhang, Y. Liu, M. Wang, Q. Liu, J. Hu, Y. Yin, *Synthesis* **2006**, 3009–3014; e) Y. Yin, Q. Zhang, J. Li, S. Sun, Q. Liu, *Tetrahedron Lett.* **2006**, *47*, 6071–6074; f) Q. Zhang, S. Sun, J. Hu, Q. Liu, J. Tan, *J. Org. Chem.* **2007**, *72*, 139–143; g) S. Sun, M. Wang, H. Deng, Q. Liu, *Synthesis* **2008**, 573–583; h) Z. Fu, M. Wang, Y. Ma, Q. Liu, J. Liu, *J. Org. Chem.* **2008**; *73*, 7625–7630.

[8] a) H. S. P. Rao, S. Sivakumar, *J. Org. Chem.* **2006**, *71*, 8715–8723; b) E. R. Anabha, C. V. A. Asokan, *Synthesis* **2006**, 151–155.

[9] a) M. Wang, X. X. Xu, Q. Liu, L. Xiong, B. Yang, L. Gao, *Synth. Commun.* **2002**, *32*, 3437–3443; b) Y.-L. Zhao, Q. Liu, R. Sun, Q. Zhang, X. X. Xu, *Synth. Commun.* **2004**, *34*, 463–469.

[10] a) C.-J. Li, *Acc. Chem. Res.* **2002**, *35*, 533–538; b) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067–2096; c) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

[11] a) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823.

[12] For selected examples on oxygen-directed Csp^2–H activations, see: a) B. M. Trost, K. Imi, I. W. Davies, *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372; b) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820–1822; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740–1742; c) K. Tsuchikama, Y. Kuwata, Y.-k. Tahara, Y. Yoshinami, T. Shibata, *Org. Lett.* **2007**, *9*, 3097–3099; d) K. Tanaka, Y. Otake, A. Wada, K. Noguchi, M. Hirano, *Org. Lett.* **2007**, *9*, 2203–2206.

[13] For selected examples on nitrogen-directed Csp^2–H activations, see: a) D. A. Colby, R. G. Bergman, J. A.

Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 5604–5605; b) Y. Kuninobu, Y. Nishina, C. Nakagawa, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 12376–12377; c) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791; d) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405; e) I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

[14] a) R. O. Kennedy, R. D. Tharnes, in: *Coumarins: Biology, Application and Mode of Action*, John Wiley and Sons, Chichester, **1997**; b) R. D. H. Murray, J. Mendez, S. A. Brown, in: *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*, John Wiley and Sons: New York, **1982**.

[15] a) J. R. Johnson, *Org. React.* **1942**, *1*, 210–266; b) R. L. Shriner, *Org. React.* **1942**, *1*, 1–37; c) T. Sugino, K. Tanaka, *Chem. Lett.* **2001**, 513–515; d) G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, *Heterocycles* **1996**, *43*, 1257–1266; e) I. Yavari, R. Hekmat-Shoar, A. Zonouzi, *Tetrahedron Lett.* **1998**, *39*, 2391–2392; f) D. C. Dittmer, Q. Li, D. V. Avilov, *J. Org. Chem.* **2005**, *70*, 4682–4686; g) V. M. Alexander, R. P. Bhat, S. D. Samant, *Tetrahedron Lett.* **2005**, *46*, 6957–6959.

[16] a) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, *J. Org. Chem.* **2000**, *65*, 7516–7522; b) P. Selles, U. Mueller, *Org. Lett.* **2004**, *6*, 277–279; c) K. Li, Y. Zeng, B. Neuenswander, J. A. Tunge, *J. Org. Chem.* **2005**, *70*, 6515–6518; d) S. Aoki, C. Amamoto, J. Oyamada, T. Kitamura, *Tetrahedron* **2005**, *61*, 9291–9297.