DOI: 10.1002/adsc.201100608

Synthesis of Oxazolidin-2-ones *via* a Copper(I)-Catalyzed Tandem Decarboxylative/Carboxylative Cyclization of a Propiolic Acid, a Primary Amine and an Aldehyde

Huangdi Feng,[a,b] Denis S. Ermolat′ev,[a,*] Gonghua Song,[b] and Erik V. Van der Eycken[a,*]

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium
Fax: (+32)-16-327-990; phone: (+32)-16-327-406; e-mail: denis.ermolatev@chem.kuleuven.be or erik.vandereycken@chem.kuleuven.be

[b] Shanghai Key Laboratory of Chemical Biology, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China

Received: August 1, 2011; Revised: September 18, 2011; Published online: January 19, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100608.

Abstract: A facile approach to polysubstituted oxazolidin-2-ones is presented *via* a copper(I)-catalyzed tandem decarboxylative/carboxylative cyclization of a propiolic acid, a primary amine and an aldehyde (PA^2-coulpling). This new multicomponent coupling constitutes an efficient methodology to provide the corresponding oxazolidin-2-ones in good yields.

Keywords: carboxylative cyclization; decarboxylative coupling; oxazolidinones; three-component coupling

Introduction

Oxazolidin-2-ones are largely utilized as latent 1,2-amino alcohols and as chiral auxiliaries in enantioselective synthesis.[1] Moreover, oxazolidin-2-ones have also a wide application in pharmaceutical science: for example, Linezolid has been reported as the first member of a new class of antibacterial agents that possess potent activity against Gram-positive bacteria, and an array of various oxazolidin-2-ones have been described as antibacterial compounds (Figure 1).[2] Therefore, the development of an efficient and green method for the synthesis of oxazolidin-2-ones has attracted much attention in the chemical community.

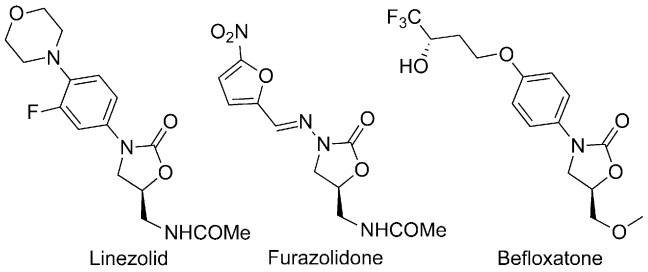
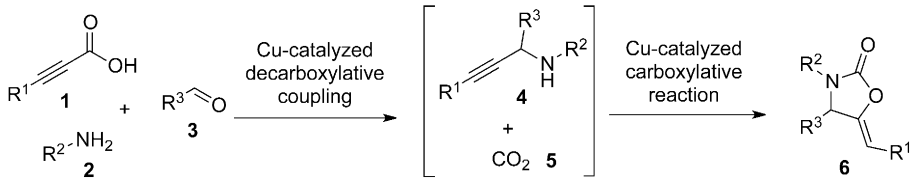


Figure 1. Examples of biologically active oxazolidin-2-ones.

In the past decades, a variety of protocols has been reported for the syntheses of oxazolidin-2-ones including the cyclization of carbonyl compounds with α-amino acids or 1,2-amino alcohols,[3] the [2+3] coupling between heterocumulenes and oxiranes or aziridines,[4] cyclocarbamations[5] and Au-catalyzed cyclization of N-Boc-propargylic amines.[6] The cycloaddition procedure of propargylic amines with CO_2 is a very attractive alternative as CO_2 is an easily available, renewable and environmentally benign substrate.[7] Although a variety of methods for these carboxylation reactions has been developed, high CO_2 pressure or/and noble metal catalyst are required, and most protocols are limited to the use of terminal alkynes.[8]

Results and Discussion

Following the success of the tandem A^3-coupling/carboxylative cyclization for the synthesis of oxazolidin-2-ones[9] and the C–C and C–N bond formation *via* decarboxylative coupling of propiolic acids,[10] we were wondering whether it would be possible to generate the oxazolidin-2-one framework in a one-pot fashion *via* reaction of a propiolic acid, an aldehyde and a primary amine (PA^2-coupling) in which the car-

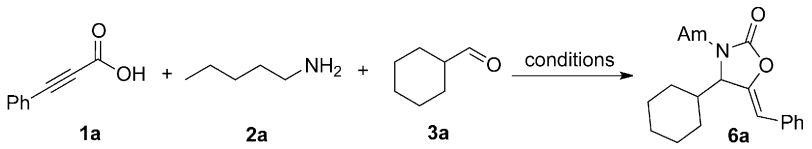


Scheme 1. One-pot synthesis of oxazolidin-2-ones.

boxylic acid should serve as the source of CO_2 (Scheme 1).

Our initial study applied phenylpropiolic acid in combination with cyclohexanecarbaldehyde and amylamine. The feasibility of this tandem reaction was investigated under microwave irradiation, employing different catalysts and solvents (Table 1, entries 1–7). To our great satisfaction the desired oxazolidin-2-one **6a** was formed in each case together with the propargylic amine. The best result was obtained when 30 mol% of CuI was used in EtOH under microwave irradiation at a ceiling temperature of 85 °C and a maximum power of 80 W for 80 min (Table 1, entry 7). However, as the irradiation time was already long (Table 1, compare entries 2 and 7) we decided to switch to conventional heating. Applying the same conditions we could isolate the desired compound **6a** in an excellent yield of 92% after 22 h of oil bath heating (Table 1, entry 8). Switching to other Cu catalysts resulted in noticeably lower yields (Table 1, entries 8–14). A relatively high amount of CuI was required with an optimum of 30 mol% (Table 1, entries 8, 15 and 16). Further increasing the catalyst loading did not result in a higher yield (Table 1, entry 17). In addition, we found that the reaction time and temperature were important parameters for this tandem reaction. When decreasing the reaction time to 6 h, the yield was drastically reduced (Table 1, entry 18). This could not be fully compensated by an increase of the reaction temperature to 100 °C (Table 1, entry 19).

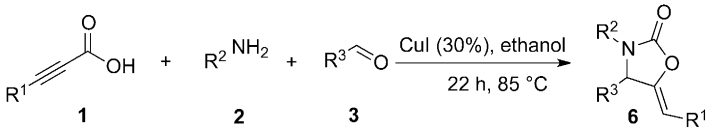
Table 1. Optimization of the conditions.[a]



Entry	Catalyst (mol%)	Solvent	Temperature [°C]	Time	Yield[b] [%]
1	CuI (30)	toluene	100	40 min	trace[c]
2	CuI (30)	EtOH	85	40 min	37[c]
3	CuI (30)	THF	80	40 min	5[c]
4	CuI (30)	EtOAc	75	40 min	9[c]
5	CuBr (30)	EtOH	85	40 min	15[c]
6	$AgNO_3$ (10)	EtOH	85	40 min	8[c]
7	CuI (30)	EtOH	85	80 min	57[c]
8	CuI (30)	EtOH	85	22 h	92
9	CuBr (30)	EtOH	85	22 h	52
10	CuCl (30)	EtOH	85	22 h	23
11	CuOAc (30)	EtOH	85	22 h	6
12	$Cu(MeCN)_4PF_6$ (30)	EtOH	85	22 h	16
13	CuOTf (30)	EtOH	85	22 h	11
14	CuTc (30)	EtOH	85	22 h	5
15	CuI (10)	EtOH	85	22 h	78
16	CuI (20)	EtOH	85	22 h	83
17	CuI (40)	EtOH	85	22 h	87
18	CuI (30)	EtOH	85	6 h	61
19	CuI (30)	EtOH	100	6 h	77
20	CuI (30)	EtOH	70	22 h	73

[a] Reactions were performed using phenylpropiolic acid (2 mmol), amylamine (1.5 mmol), cyclohexanecarbaldehyde (1 mmol) and solvent (1.5 mL) under conventional heating conditions.
[b] Isolated yields based on cyclohexanecarbaldehyde.
[c] Microwave irradiation, 80 W.

Table 2. Scope and limitations of the protocol.[a]

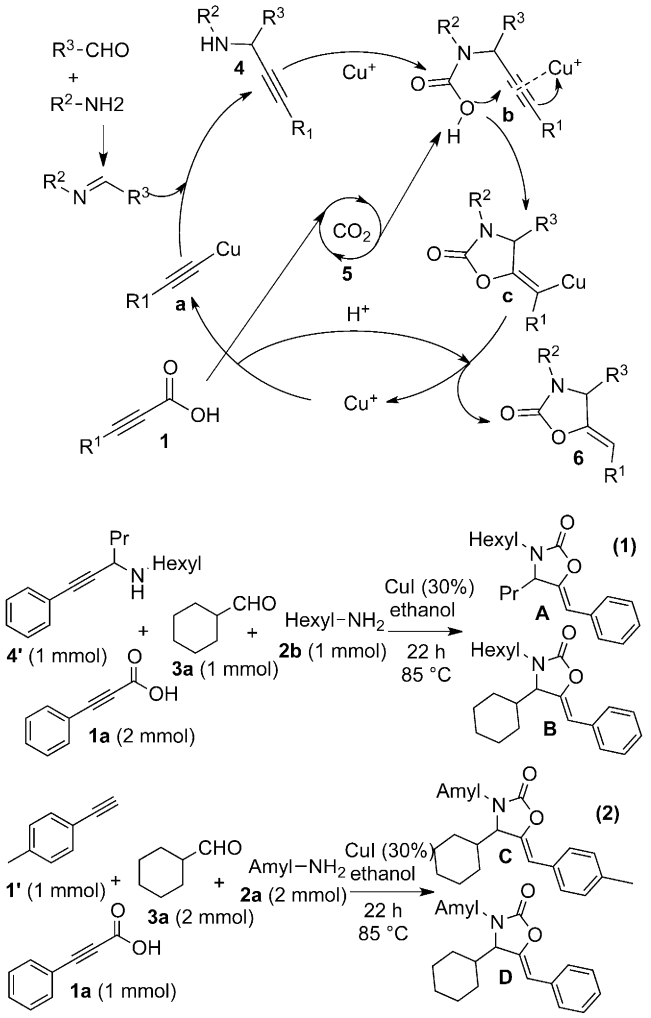


Entry	R^1	R^2	R^3	Product	Yield[b] [%]
1	phenyl	amyl	cyclohexyl	**6{1}**	92
2	phenyl	hexyl	cyclohexyl	**6{2}**	89
3	phenyl	heptyl	cyclohexyl	**6{3}**	91
4	phenyl	nonyl	cyclohexyl	**6{4}**	93
5	phenyl	undecyl	cyclohexyl	**6{5}**	89
6	phenyl	cyclohexylmethyl	cyclohexyl	**6{6}**	88
7	phenyl	3,4-dimethoxyphenethyl	cyclohexyl	**6{7}**	87
8	phenyl	3-methoxylphenyl	cyclohexyl	**6{8}**	0
9	phenyl	amyl	hexyl	**6{9}**	73
10	phenyl	amyl	decyl	**6{10}**	67
11	phenyl	amyl	*i*-butyl	**6{11}**	70
12	phenyl	amyl	Ph	**6{12}**	62
13	phenyl	amyl	4-methylphenyl	**6{13}**	65
14	phenyl	octyl	*i*-butyl	**6{14}**	68
15	phenyl	PMB	*i*-butyl	**6{15}**	65
16	phenyl	cyclopentyl	*i*-butyl	**6{16}**	36
17	phenyl	heptyl	*i*-propyl	**6{17}**	85
18	phenyl	heptyl	3-ethylpropyl	**6{18}**	71
19	phenyl	octyl	cyclopropyl	**6{19}**	84
20	Me	amyl	cyclohexyl	**6{20}**	39
21	ethyl	amyl	cyclohexyl	**6{21}**	41
22	isopropyl	amyl	cyclohexyl	**6{22}**	51
23	amyl	amyl	cyclohexyl	**6{23}**	55
24	hexyl	amyl	cyclohexyl	**6{24}**	54
25	naphthyl-2-	amyl	cyclohexyl	**6{25}**	57
26	4-methylphenyl	amyl	cyclohexyl	**6{26}**	85
27	4-methoxyylphenyl	amyl	cyclohexyl	**6{27}**	83

[a] Reactions were performed using propiolic acid (2 mmol), amine (1.5 mmol), aldehyde (1 mmol) and ethanol (1.5 mL) under conventional heating at 85 °C for 22 h.
[b] Isolated yields based on cyclohexanecarbaldehyde.

With the optimized conditions at hand (Table 1, entry 8) we evaluated the scope of this PA^2 coupling protocol (Table 2). In general, moderate to good yields were obtained by reaction of a variety of propiolic acids, primary amines and aldehydes in the presence of 30 mol% CuI in ethanol. Primary aliphatic amines gave the corresponding products in good yields (Table 2, entries 1–7). However, no product was obtained when the aromatic 3-methoxyaniline was used (Table 2, entry 8). It was envisaged that aliphatic amines may increase the effective concentration of CO_2 in solution by the formation of the carbamic acids with CO_2.[11] To further investigate the scope of the reaction, we then investigated different aldehydes. Both aliphatic and aromatic aldehydes were explored in combination with various amines, and moderate to good yields were obtained (Table 2, entries 9–19). Finally, we evaluated the reaction of different propiolic acids. The desired oxazolidin-2-ones **6** were obtained in moderate to good yields (Table 2, entries 20–27). To the best of our knowledge, there are no literature examples describing a carboxylative cyclization to oxazolidin-2-ones when aliphatic propargylic amines or aliphatic alkynes are involved.

A tentative mechanism for this tandem decarboxylative/carboxylative cyclization is proposed in Scheme 2. In the first step, propiolic acid **1** undergoes a Cu(I)-catalyzed decarboxylation affording copper acetylide **a** and CO_2 (**5**). Then the copper acetylide **a** attacks the *in situ* formed imine resulting in the formation of the intermediate propargylamine **4**. After that, a Cu(I)-catalyzed addition of CO_2 **5** released from the propiolic acid to propargylic amine **4** gives the intermediate **b**, which undergoes a Cu(I)-catalyzed cyclization into **c**. Subsequent protonolysis delivers finally the desired product the oxazolidin-2-one **6**. In order to verify that the product **6** was formed *via* an intermolecular carbonylation of propargylic amine **4** and released CO_2, we set up two experiments (Scheme 2). Applying our optimized conditions, the



Scheme 2. Proposed mechanism for the PA^2 coupling.

addition of propargylic amine **4′** to the synthesis resulted in the mixture of products **A** and **B**, and the ratio of **A**/**B** was determined as 3/5 by GC-MS [Eq. (1)]. Further experiment using **1′** showed that both the products **C** and **D** were obtained in a 1:1 ratio as determined by GC-MS [Eq. (2)]. From these results, we are quite confident that the oxazolidin-2-one is generated *via* the formation of an intermediate propargylic amine **4/**intermolecular carboxylative cyclization.

Conclusions

In conclusion, the Cu(I)-catalyzed tandem decarboxylative/carboxylative cyclization of a propiolic acid, a primary amine and an aldehyde (PA^2 coupling) constitutes an efficient approach for the synthesis of oxazolidin-2-one under mild reaction conditions. Interestingly, this procedure is applicable to a wide variety of aldehydes, primary amines and propiolic acids.

Experimental Section

General Information

All solvents and reagents were purchased from commercial sources and were used without prior purification. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reactions were carried out in 10-mL glass tubes, sealed with a Teflon® septum and placed in the microwave cavity. The reaction mixture was irradiated at the required ceiling temperature using maximum power for the stipulated time, and the reaction mixture temperatures were measured by the external IR sensor. The reaction tube was cooled to ambient temperature with air jet cooling. TLC analysis was performed on aluminum backed plates SIL G/UV254. The products were purified by silica gel (200–300 mesh) column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz or 600 MHz NMR instrument. The ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane. High-resolution mass spectra were recorded by using an ion source temperature 150–250 °C as required. High-resolution EI-mass spectra were performed with a resolution of 10000.

General Procedure for the Synthesis of Oxazolidin-2-ones 6

Propiolic acid **1** (2.0 mmol) was dissolved in ethanol (1.5 mL) applying a vial along with a stirring bar, and then amine **2** (1.5 mmol), aldehyde **3** (1.0 mmol) and copper iodide (0.30 mmol) were added. The reaction vessel was sealed and heated in an oil-bath for 22 h at a temperature of 85 °C. The resulting reaction mixture was loaded on a column and flashed on silica gel (7–9% ethyl acetate-hexane mixture) to afford the desired product **6**

5-Benzylidene-4-cyclohexyl-3-pentyloxazolidin-2-one 6{1}: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 7.74$ Hz, 2H), 7.60 (t, $J = 15.09$, 2H), 7.20 (t, $J = 14.52$, 1H), 5.50 (s, 1H), 4.26 (s, 1H), 3.70–3.57 (m, 1H), 3.11–3.02 (m, 1H), 1.87–1.55 (m, 8H), 1.40–1.08 (m, 9H), 0.93 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.4$, 145.6, 133.7, 128.4, 126.7, 104.1, 63.4, 41.7, 40.7, 28.8, 27.9, 26.9, 26.4, 26.2, 26.1, 26.0, 22.3, 14.0; HR-MS (EI): $m/z = 327.2217$, calcd. for $C_{21}H_{29}NO_2$ [M+H]: 327.2198.

Supporting Information

General experimental methods, spectroscopic characterization and copies of ^{1}H NMR and ^{13}C NMR spectra for all compounds are available in the Supporting Information.

Acknowledgements

The authors wish to thank the F.W.O. [Fund for Scientific Research – Flanders (Belgium)] and the Research Fund of the Katholieke Universiteit Leuven for financial support to the laboratory. D.S.E. is grateful to the F.W.O. for providing a postdoc fellowship. H. D. F. thanks the China Scholarship Council for financial support.

References

[1] a) D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, J. Bartroli, *Pure Appl. Chem.* **1981**, *53*, 1109–1127; b) D. A. Evans, *Aldrichimica Acta* **1982**, *15*, 23–32; c) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875; d) A. M. Slee, M. A. Wuonola, R. J. McRipley, I. Zajac, M. J. Zawada, P. T. Bartholomew, W. A. Gregory, M. Forbes, *Antimicrob. Agents Chemother.* **1987**, *31*, 1791–1797; e) M. A. Dyen, D. Swern, *Chem. Rev.* **1967**, *67*, 197–246; f) D. J. Ager, I. Prakash, D. R. Schaad, *Aldrichimica Acta* **1997**, *30*, 3–12.

[2] a) M. R. Barbachyn, C. W. Ford, *Angew. Chem.* **2003**, *115*, 2056–2070; *Angew. Chem. Int. Ed.* **2003**, *42*, 2010–2023; b) T.-J. Poel, R. C. Thomas, W. J. Adams, P. A. Aristoff, M. R. Barbachyn, F. E. Boyer, J. Brieland, R. Brideau, J. Brodfuehrer, A. P. Brown, A. L. Choy, M. Dermyer, M. Dority, C. W. Ford, R. C. Gadwood, D. Hanna, H.-L. Cai, M. D. Huband, C. Huber, R. Kelly, J.-Y. Kim, J. P. Martin, P. J. Pagano, D. Ross, L. Skerlos, M. C. Sulavik, T. Zhu, G. E. Zurenko, J. V. N. Vara Prasad, *J. Med. Chem.* **2007**, *50*, 5886–5889; c) V. B. Lohray, B. B. Lohray, B. K. Srivastava, *Pure Appl. Chem.* **2005**, *77*, 195–200; d) D. I. Diekema, R. N. Jones, *Drugs* **2000**, *59*, 7–16.

[3] a) G. Zappia, E. Gacs-Baitz, G. Delle Monache, D. Misiti, L. Nevola, B. Botta, *Curr. Org. Synth.* **2007**, *4*, 81–135; b) G. Bratulescu, *Synthesis* **2007**, 3111–3112; c) N. Alouane, A. Boutier, C. Baron, E. Vrancken, P. Mangeney, *Synthesis* **2006**, 860–864; d) B. B. Lohray, S. Baskaran, B. S. Rao, Y. Reddy, N. Rao, *Tetrahedron Lett.* **1999**, *40*, 4855–4856; e) B. Gabriele, R. Mancuso, G. Salerno, M. Costa, *J. Org. Chem.* **2003**, *68*, 601–604; f) M. A. Casadei, F. Micheletti, A. Inesi, G. Zappia, L. J. Rossi, *J. Org. Chem.* **1997**, *62*, 6754–6759; g) C. J. Dinsimore, S. Mercer, *Org. Lett.* **2004**, *6*, 2885–2888.

[4] a) O. Ihata, Y. Kayaki, T. Ikariya, *Angew. Chem.* **2004**, *116*, 735–737; *Angew. Chem. Int. Ed.* **2004**, *43*, 717–719; b) B. M. Trost, A. R. Sudhakar, *J. Am. Chem. Soc.* **1988**, *110*, 7933–7935; c) Z.-Z. Yang, L.-N. He, S.-Y. Peng, A.-H. Liu, *Green Chem.* **2010**, *12*, 1850–1854; d) G. Bartoli, M. Bosco, A. Carloni, M. Locatelli, P. Melchiorre, L. Sambri, *Org. Lett.* **2005**, *7*, 1983–1985.

[5] a) H. W. Pauls, B. Fraiser-Reid, *J. Am. Chem. Soc.* **1980**, *102*, 3956–3957; b) T. Hayashi, A. Yamamoto, Y. Ito, *Tetrahedron Lett.* **1987**, *28*, 4837–4840; c) M. Hirama, T. Shigemoto, Y. Yamazaki, S. Ito, *J. Am. Chem. Soc.* **1985**, *107*, 1797–1798; d) H. M. L. Davies, M. S. Long, *Angew. Chem.* **2005**, *117*, 3584–3586; *Angew. Chem. Int. Ed.* **2005**, *44*, 3518–3520; e) D. N. Barman, K. M. Nicholas, *Eur. J. Org. Chem.* **2011**, 908–911; f) T. J. Donohoe, P. D. Johnson, M. Helliwell, M. Keenan, *Chem. Commun.* **2001**, 2078–2079; g) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 639–642; *Angew. Chem. Int. Ed.* **2000**, *39*, 625–628.

[6] a) R. Robles-Machín, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2006**, *71*, 5023–5026; b) E.-S. Lee, H.-S. Yeom, J.-H. Hwang, S. Shin, *Eur. J. Org. Chem.* **2007**, 3503–3507.

[7] a) M. Shi, Y.-M. Shen, *Curr. Org. Chem.* **2003**, *7*, 737–745; b) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387; c) H. Arakawa, M. Aresta, *Chem. Rev.* **2001**, *101*, 953–996; d) M. Aresta, A. Dibenedetto, I. Tommasi, *Energy Fuels*, **2001**, *5*, 269–273.

[8] a) T. Mitsudo, Y. Hori, Y. Yamakawa, Y. Watanabe, *Tetrahedron Lett.* **1987**, *28*, 4417–4418; b) M. Shi, Y. M. Shen, *J. Org. Chem.* **2002**, *67*, 16–21; c) M. Costa, G. P. Chiusoli, M. Rizzardi, *Chem. Commun.* **1996**, 1699–1700; d) M. Costa, G. P. Chiusoli, D. Taffurelli, G. J. Dalmonego, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1541–1546; e) Y. Kayaki, M. Yamamoto, T. Suzuki, T. Ikariya, *Green Chem.* **2006**, *8*, 1019–1021; f) M. Feroci, M. Orsini, G. Sotgiu, L. Rossi, A. Inesi, *J. Org. Chem.* **2005**, *70*, 7795–7798; g) S. Yoshida, K. Fukui, S. Kikuchi, T. Yamada, *Chem. Lett.* **2009**, *38*, 786–787.

[9] W.-J. Yoo, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 1503–1506.

[10] a) J. Moon, M. Jeong, H. Nam, J.-H. Ju, J. H. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2008**, *10*, 945–948; b) H. Kima, P. H. Lee, *Adv. Synth. Catal.* **2009**, *351*, 2827–2832; c) A. Park, K. Park, Y. Kim, S. Lee, *Org. Lett.* **2011**, *13*, 944–947; d) W. Jia, N. Jiao, *Org. Lett.* **2010**, *12*, 2000–2003; e) J. Moon, M. Jang, S. Lee, *J. Org. Chem.* **2009**, *74*, 1403–1406.

[11] a) E. R. PNrez, R. H. A. Santos, M. T. P. Gambardella, L. G. M. De Macedo, U. P. Rodrigues-Filho, J.-C. Launay, D. W. Franco, *J. Org. Chem.* **2004**, *69*, 8005–8011; b) D. J. Heldebrant, P. G. Jessop, C. A. Thomas, C. A. Eckert, C. L. Liotta, *J. Org. Chem.* **2005**, *70*, 5335–5338; c) D. B. Dell′Amico, F. Calderazzo, L. Labella, F. Marchetti, G. Pampaloni, *Chem. Rev.* **2003**, *103*, 3857–3897.

