

## A Convenient Synthesis of Imidazolidin-4-ones *via* Domino Reactions

by Xueming Chen, Hui Wei, Yunyun Chen, and Xingshu Li\*

School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510006, P. R. China  
(phone: + 86-20-39943050; fax: + 86-20-39943050; e-mail: lixsh@mail.sysu.edu.cn)

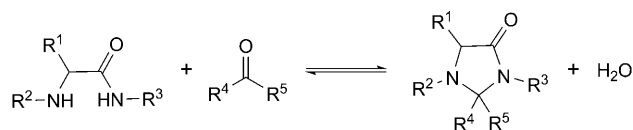
A series of imidazolidin-4-one derivatives was synthesized *via* a domino reaction of aldminoesters and dialkylzinc. Chiral ligands were also examined in this reaction to obtain optically active products.

**Introduction.** – Domino reactions, which can rapidly generate complex molecules in a controlled and predictable manner, have attracted great attention in organic synthesis because of the formation of two or more C–C bonds without isolation or purification of any intermediates [1]. Especially, the novel ways of proceeding for the synthesis of heterocyclic systems have been well explored [2]. *Padwa's* rhodium carbenoid-initiated dipolar cycloadditions [3], *Denmark's* nitroalkene [4 + 2]/[3 + 2]-cycloadditions [1d][4], *Overman's* aza-*Cope/Mannich* cascade [5], and *Grubbs's* ring-closing metathesis chemistry [6] have all matured into significant synthetic tools.

Imidazolidin-4-one derivatives are found in a large spectrum of biological activities, ranging from essential antibacterial activity [7a], cell inhibitor [7b–d], antimalarial agents [7e–l], antiproliferative activity for melanoma [7m], selective inhibitor of the glycine transporter 1 (GlyT1) [7n], and anticancer activity [7o–s]. They were also used as efficient organocatalysts by *MacMillan* and co-workers for a variety of asymmetric reactions [8][9].

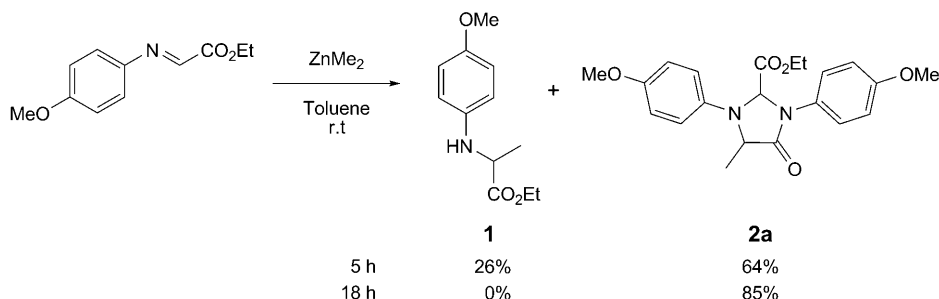
Consequently, several synthetic methodologies have been developed for the synthesis of imidazolidin-4-one and its derivatives in the past decades. The main method toward these target products is the condensation of  $\alpha$ -amino amide and CO compounds (*Scheme 1*) [8–10]. The other well-established procedure for imidazolidines are dipolar cycloadditions between azomethine ylides and imines [11]. However, to the best of our knowledge, there have been limited reports in the literature on the formation of imidazolidin-4-ones by domino reactions [12]. Herein, we report a convenient procedure for the synthesis of imidazolidin-4-ones *via* condensation of  $\alpha$ -aldiminoesters and dialkylzinc reagents.

Scheme 1. Main Method toward the Synthesis of Imidazolidin-4-ones



**Results and Discussion.** – In our study of the alkylation of PMP (*para*-methoxyphenyl)-protected aldimino ester with  $\text{ZnMe}_2$ , we found that the reaction gave two products after a period of 5 h, namely, minor amounts of 1,2-addition product **1** (26% yield) and the major product, imidazolidin-4-one **2a** (64% yield). However, the 1,2-addition product **1** was fully converted to imidazolidin-4-one in 85% yield (after isolation) when the reaction was continued at room temperature for 18 h (Scheme 2).

Scheme 2. Reaction of PMP-Protected Aldiminoester with Dimethylzinc



The single crystal of imidazolidin-4-one **2a** was obtained, and the structure was characterized by X-ray diffraction analysis (Fig. 1)<sup>1)</sup>. This results was much different from the literature reports, which revealed that Zn-mediated additions of iminoester mainly produced 1,2-addition products [12][13]. On the other hand, the *cis* configuration of **2a** was proved by crystallographic analysis, which is in coincidence with the results in literature [12].

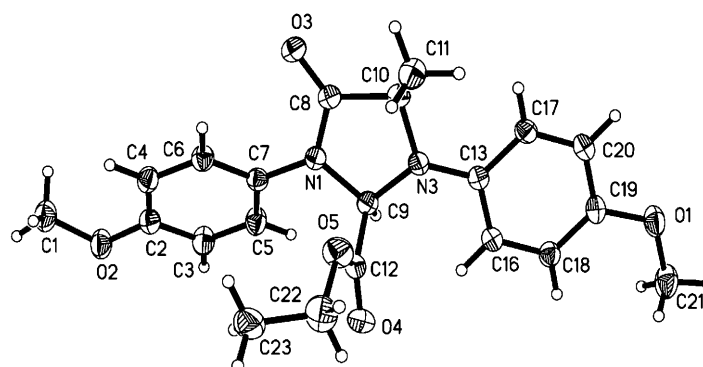


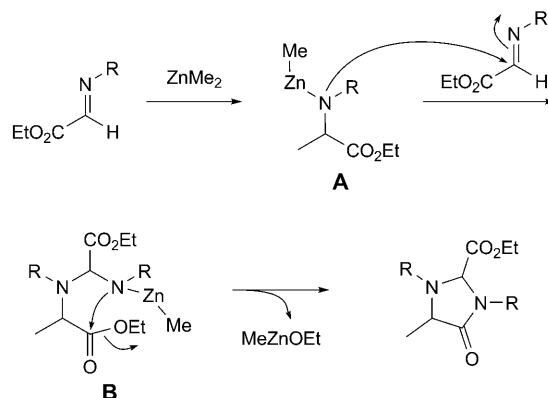
Fig. 1. ORTEP Presentation of Imidazolidin-4-one **2a** at 50% Probability

The possible mechanism for the formation of imidazolidin-4-ones is shown in Scheme 3. A first molecule of the aldimino ester reacts with  $\text{ZnMe}_2$  to give the 1,2-addition product **A**. The subsequent reaction of **A** with another molecule of the

<sup>1)</sup> CCDC-707059 contains the supplementary crystallographic data for this work. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

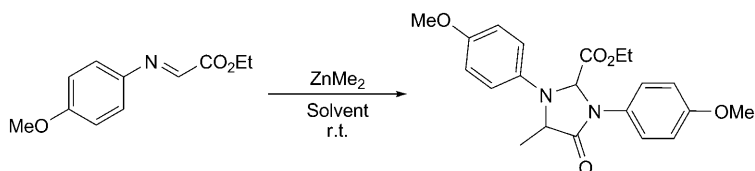
aldiminoester gives the intermediate **B**. Finally, the intramolecular cyclization leads to the imidazolidin-4-one products.

Scheme 3. Possible Mechanism for the Formation of Imidazolidin-4-ones



Other solvents, such as  $\text{CH}_2\text{Cl}_2$  or THF for the domino reaction were also investigated, and the results indicated that toluene was the best solvent for the reaction (Table 1).

Table 1. Synthesis of Imidazolidin-4-ones via Domino Reactions in Various Solvents



| Entry | Solvent                  | Yield [%] <sup>a) b)</sup> |
|-------|--------------------------|----------------------------|
| 1     | Toluene                  | 85                         |
| 2     | $\text{CH}_2\text{Cl}_2$ | 80                         |
| 3     | THF                      | 35                         |
| 4     | $\text{Et}_2\text{O}$    | 50                         |

<sup>a)</sup> Yield of isolated material. <sup>b)</sup> Single diastereoisomer, as determined by  $^1\text{H-NMR}$  and HPLC.

The reactions of a variety of aldimino esters and  $\text{ZnMe}_2$  under the optimal reaction conditions are summarized in Table 2. It was clearly observed that both the electronic and steric effects of the substrate were substantially important for the yield of imidazolidin-4-ones. For example, the aldimino esters derived from 4-methoxy- or 4-methylaniline gave products with higher yields than those from 4-chloro- or 4-bromoaniline; on the other hand, besides the aldiminoester derived from 3-methylaniline, which gave moderate yield, the aldiminoesters derived from 3-chloro- and 3-methoxyaniline only gave precipitated by-products which could not be dissolved in organic solvents and  $\text{H}_2\text{O}$ . Diethylzinc was also used for the domino reaction with the

Table 2. Synthesis of Imidazolidin-4-ones via Domino Reactions

| Entry | ZnR <sub>2</sub>  | R <sup>1</sup>                     | Product   | Yield [%] <sup>a) b)</sup> |
|-------|-------------------|------------------------------------|-----------|----------------------------|
| 1     | ZnMe <sub>2</sub> | 4-MeOC <sub>6</sub> H <sub>4</sub> | <b>2a</b> | 85                         |
| 2     | ZnMe <sub>2</sub> | 4-MeC <sub>6</sub> H <sub>4</sub>  | <b>2b</b> | 72                         |
| 3     | ZnMe <sub>2</sub> | 4-ClC <sub>6</sub> H <sub>4</sub>  | <b>2c</b> | 68                         |
| 4     | ZnMe <sub>2</sub> | 4-BrC <sub>6</sub> H <sub>4</sub>  | <b>2d</b> | 58                         |
| 5     | ZnMe <sub>2</sub> | Ph                                 | <b>2e</b> | 75                         |
| 6     | ZnMe <sub>2</sub> | 3-MeC <sub>6</sub> H <sub>4</sub>  | <b>2f</b> | 63                         |
| 7     | ZnMe <sub>2</sub> | 3-MeOC <sub>6</sub> H <sub>4</sub> | <b>2g</b> | by-product                 |
| 8     | ZnMe <sub>2</sub> | 3-ClC <sub>6</sub> H <sub>4</sub>  | <b>2h</b> | by-product                 |
| 9     | ZnMe <sub>2</sub> | PhCH <sub>2</sub>                  | <b>2i</b> | by-product                 |
| 10    | ZnEt <sub>2</sub> | 4-MeOC <sub>6</sub> H <sub>4</sub> | <b>2j</b> | 76                         |

<sup>a)</sup> Yield of isolated material. <sup>b)</sup> Single diastereoisomer as determined by <sup>1</sup>H-NMR and HPLC.

aldiminoester derived from 4-methoxyaniline as the substrate, and the results showed that it was not as favorable as dimethylzinc for the reaction.

We also investigated the asymmetric synthesis of chiral imidazolidin-4-ones in the presence of a series of readily available chiral ligands **3–12** in toluene at room temperature. The results are shown in Fig. 2. Among the various chiral ligands tested, the amide ligand **9**, which is derived from camphor-10-sulfonic acid, gave the target product with 21% ee; BINOL (**10**), the versatile chiral ligand in many asymmetric catalytic reactions, provided 13% ee in this reaction.

The enantioselectivity of the reaction with the ratio of chiral ligand to substrate was examined. With ligand **9**, there was not much difference in enantioselectivity when the amount of the ligand was increased (Table 3, Entries 1–3). On the other hand, when BINOL was used as ligand, the ee value increased as the molar ratio of the ligand increased. When the ligand/substrate ratio reached about 40%, the product ee values came to a plateau (Table 3, Entries 4–7).

The temperature effect was insignificant in the range of 0° to room temperature. When the reaction was carried out at 0° with BINOL as ligand, the enantioselectivity was not improved. These results indicated that the use of chiral ligands presents a possibility for the performance of asymmetric domino reactions, but the modification of the ligands has still to be improved for better enantioselectivities.

**Conclusions.** – In conclusion, a series of imidazolidin-4-ones was synthesized via a domino reaction of aldimino esters and dialkylzinc. Asymmetric induction with chiral ligands was also explored but gave only low enantioselectivity. The development of more stereoselective catalysts for the simple domino reactions is currently underway.

We thank the financial support from the Science & Technology Foundation of Guangzhou (07A8206031) and the National Science Foundation of China (20472116).

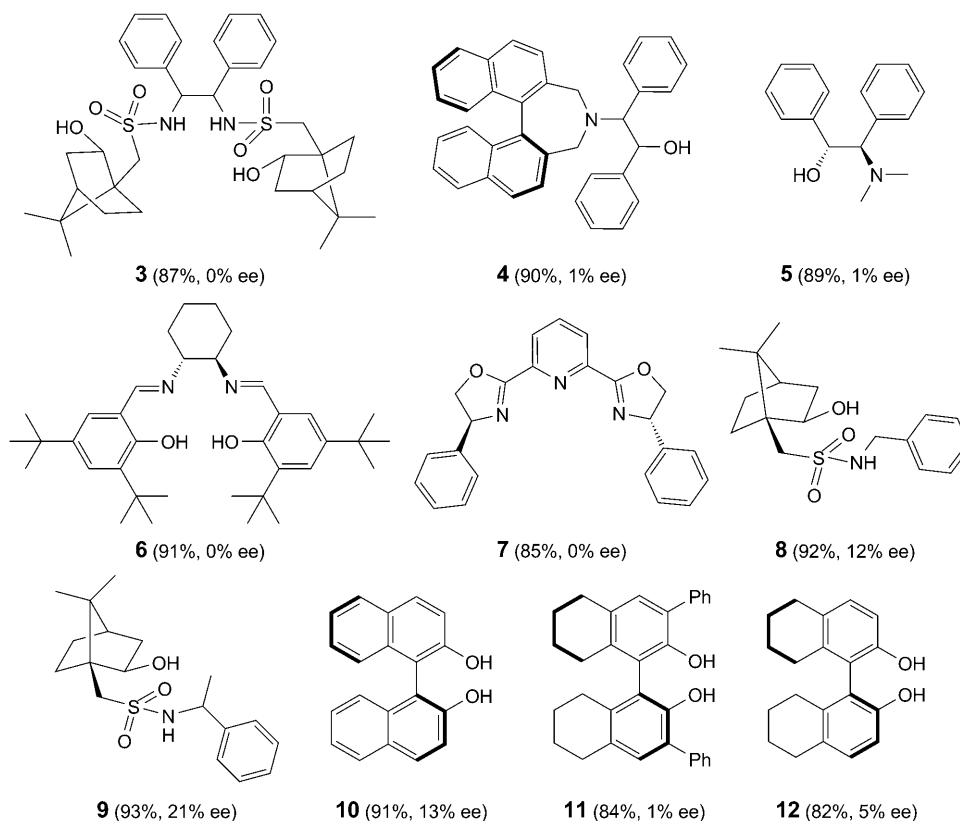


Fig. 2. Asymmetric Induction in Imidazolidin-4-one Formation

### Experimental Part

**General Procedure for the Preparation of Imines.** To a flask containing amine (10 mmol) and anh.  $\text{Na}_2\text{SO}_4$  (50 mmol) in 20 ml of toluene was added ethyl glyoxalate (12 mmol) slowly with stirring at r.t. The stirring was continued for 1 h until the reaction was completed (monitored by TLC).  $\text{Na}_2\text{SO}_4$  was removed by filtration, and toluene was distilled off under reduced pressure to get the crude imine (95% yield) which was used for the next step without purification.

**General Procedure for the Synthesis of Imidazolidine Derivatives.** To a flask containing imine (1.0 mmol) in toluene (2 ml) was added  $\text{Me}_2\text{Zn}$  soln. (1.2 mmol, 1.2M in toluene) at r.t. After completion of the reaction (18 h, monitored by TLC),  $\text{H}_2\text{O}$  (5 ml) was added. The mixture was diluted with AcOEt and filtered through *Celite*. The collected phases were separated, and the aq. phase was extracted with AcOEt ( $3 \times 3$  ml). The combined org. phases were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (FC; AcOEt/petroleum ether (PE) 1:5) to afford the desired imidazolidin-4-one products. All the products were characterized by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR, and selected data as follows.

**General Procedure for the Asymmetric Synthesis of Imidazolidin-4-one (2a).** To a flask containing imine (1.0 mmol) and chiral ligand (0.1 mmol) in toluene (2 ml) was added  $\text{Me}_2\text{Zn}$  soln. (1.2 mmol, 1.2M in toluene) at r.t. After completion of the reaction (monitored by TLC),  $\text{H}_2\text{O}$  (5 ml) was added. The mixture was diluted with AcOEt and filtered through *Celite*. The collected phases were separated, and the aq. phase was extracted with AcOEt ( $3 \times 3$  ml). The combined org. phases were washed with brine

Table 3. Asymmetric Synthesis of Imidazolidin-4-one **2a** via Domino Reactions

**2a**

| Entry | Ligand    | Ligand Ratio [%] | Yield [%] <sup>a)</sup> | ee [%] <sup>b)</sup> |
|-------|-----------|------------------|-------------------------|----------------------|
| 1     | <b>9</b>  | 5                | 93                      | 18                   |
| 2     | <b>9</b>  | 10               | 91                      | 21                   |
| 3     | <b>9</b>  | 20               | 90                      | 22                   |
| 4     | <b>10</b> | 10               | 89                      | 13                   |
| 5     | <b>10</b> | 20               | 96                      | 18                   |
| 6     | <b>10</b> | 40               | 91                      | 31                   |
| 7     | <b>10</b> | 50               | 92                      | 26                   |

<sup>a)</sup> Yield of material. <sup>b)</sup> Enantiomeric excesses were determined using an Agilent 1100 HPLC with UV detection at 254 nm and Daicel Chiralpak OD column.

and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent under reduced pressure, the crude product was purified by FC (AcOEt/PE 1:5) to afford imidazolidin-4-one **2a**. Enantiomeric excesses were measured using an Agilent 1100 HPLC system with UV detection at 254 nm and a Daicel Chiralpak OD column.

**Ethyl 1,3-Bis(4-methoxyphenyl)-4-methyl-5-oxoimidazolidine-2-carboxylate (2a)**. White solid. M.p. 97–98°. HPLC (Chiralpak OD; 1.0 ml/min, hexane/i-PrOH 95:5): *t<sub>R</sub>* (*R,R*) = 45 min, *t<sub>R</sub>* (*S,S*) = 60 min; the configuration was assigned by comparing the retention time of its homologue, ethyl 4-ethyl-1,3-bis(4-methoxyphenyl)-5-oxoimidazolidine-2-carboxylate [12]. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.18 (*t*, *J* = 6.9, 3 H); 1.68 (*d*, *J* = 6.0, 3 H); 3.79 (*s*, 3 H); 3.82 (*s*, 3 H); 4.15 (*q*, *J* = 6.9, 2 H); 4.35 (*q*, *J* = 6.6, 1 H); 5.67 (*s*, 1 H); 6.75 (*d*, *J* = 9.0, 2 H); 6.93 (*d*, *J* = 9.0, 4 H); 7.39 (*d*, *J* = 9.0, 2 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.36; 18.07; 55.79; 56.11; 57.15; 62.42; 76.94; 113.05; 114.80; 115.56; 125.30; 128.90; 138.61; 153.21; 159.92; 169.42; 171.88. HR-MS: 407.1580 ([*M* + Na]<sup>+</sup>, C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>5</sub><sup>+</sup>; calc. 407.1583).

**Ethyl 4-Methyl-1,3-bis(4-methylphenyl)-5-oxoimidazolidine-2-carboxylate (2b)**. White solid. M.p. 107–108°. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.18 (*t*, *J* = 6.9, 3 H); 1.71 (*d*, *J* = 6.0, 3 H); 2.33 (*s*, 3 H); 2.38 (*s*, 3 H); 4.15 (*q*, *J* = 6.9, 2 H); 4.42 (*q*, *J* = 6.6, 1 H); 5.79 (*s*, 1 H); 6.76 (*d*, *J* = 9.0, 2 H); 7.05–7.24 (*m*, 4 H); 7.41 (*d*, *J* = 6.0, 2 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.40; 17.93; 20.78; 21.52; 56.99; 62.52; 76.95; 111.81; 123.01; 128.48; 130.19; 130.49; 132.69; 137.01; 141.91; 169.35; 171.84. HR-MS: 375.1680 ([*M* + Na]<sup>+</sup>, C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>5</sub><sup>+</sup>; calc. 375.1685).

**Ethyl 1,3-Bis(4-chlorophenyl)-4-methyl-5-oxoimidazolidine-2-carboxylate (2c)**. Yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.25 (*t*, *J* = 5.1, 3 H); 1.45 (*d*, *J* = 6.0, 3 H); 4.16 (*q*, *J* = 5.1, 2 H); 4.35 (*q*, *J* = 6.6, 1 H); 5.74 (*s*, 1 H); 6.49 (*d*, *J* = 9.0, 2 H); 6.72 (*d*, *J* = 9.0, 1 H); 7.08 (*d*, *J* = 9.0, 2 H); 7.25 (*d*, *J* = 9.0, 2 H); 7.35 (*d*, *J* = 9.0, 1 H); 7.52 (*d*, *J* = 9.0, 1 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.38; 17.61; 61.62; 62.94; 75.96; 113.01; 114.66; 122.92; 123.48; 124.36; 129.34; 129.73; 129.84; 132.27; 133.92; 142.37; 145.39; 168.68; 174.50.

**Ethyl 1,3-Bis(4-bromophenyl)-4-methyl-5-oxoimidazolidine-2-carboxylate (2d)**. White solid. M.p. 149–150°. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.15 (*t*, *J* = 4.5, 3 H); 1.64 (*d*, *J* = 6.0, 3 H); 4.15 (*q*, *J* = 4.5, 2 H); 4.32 (*q*, *J* = 5.1, 1 H); 5.74 (*s*, 1 H); 6.42 (*d*, *J* = 9.0, 2 H); 7.19 (*d*, *J* = 9.0, 2 H); 7.47 (*m*, 4 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.37; 17.52; 56.87; 62.90; 75.74; 111.55; 113.51; 115.14; 120.02; 123.55; 132.62; 134.53; 142.77; 168.57; 171.22.

*Ethyl 4-Methyl-5-oxo-1,3-diphenylimidazolidine-2-carboxylate (2e)*. White solid. M.p. 94–95°. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.14 (t, *J* = 6.9, 3 H); 1.72 (d, *J* = 6.0, 3 H); 4.15 (q, *J* = 6.9, 2 H); 4.45 (q, *J* = 6.6, 1 H); 5.84 (s, 1 H); 6.87–6.92 (*m*, 3 H); 7.27–7.44 (*m*, 5 H); 7.56 (d, *J* = 9.0, 2 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.37; 17.82; 56.93; 62.65; 76.39; 111.80; 119.31; 122.73; 127.06; 129.64; 130.03; 135.34; 143.98; 169.12; 171.73.

*Ethyl 4-Methyl-1,3-bis(3-methylphenyl)-5-oxoimidazolidine-2-carboxylate (2f)*. White solid. M.p. 189–190°. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.18 (t, *J* = 7.2, 3 H); 1.71 (d, *J* = 6.6, 3 H); 4.17 (q, *J* = 7.2, 2 H); 4.42 (q, *J* = 6.6, 1 H); 5.83 (s, 1 H); 6.61 (d, *J* = 6.9, 2 H); 6.71 (d, *J* = 7.5, 1 H); 7.09 (d, *J* = 7.2, 1 H); 7.21–7.35 (*m*, 3 H); 7.44 (s, 1 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 14.34; 17.84; 21.90; 22.30; 56.94; 62.46; 77.01; 109.05; 112.55; 119.83; 120.17; 123.55; 127.84; 129.34; 129.85; 135.35; 139.54; 139.88; 144.15; 169.22; 171.74. HR-MS: 375.1680 ([*M* + Na]<sup>+</sup>, C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>3</sub><sup>+</sup>; 375.1685).

*Ethyl 4-Ethyl-1,3-bis(4-methoxyphenyl)-5-oxoimidazolidine-2-carboxylate (2j)*. White solid. M.p. 110–111°. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 1.12–1.18 (*m*, 6 H); 2.08–2.12 (*m*, 2 H); 3.78 (s, 3 H); 3.80 (s, 2 H); 4.14 (q, *J* = 7.2, 2 H); 4.26 (t, *J* = 5.1, 1 H); 5.63 (s, 1 H); 6.82–6.92 (*m*, 6 H); 7.37 (d, *J* = 9.0, 2 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): 9.85; 14.37; 25.48; 55.79; 62.09; 62.45; 76.97; 114.19; 114.72; 115.33; 125.39; 127.99; 129.85; 139.91; 153.55; 158.42; 169.39; 171.15. HR-MS: 398.1830 (*M*<sup>+</sup>, C<sub>22</sub>H<sub>26</sub>O<sub>5</sub>N<sub>2</sub><sup>+</sup>; 398.1841).

## REFERENCES

- [1] a) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; b) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; d) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137; e) J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167; f) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; g) M. H. Schmitt, S. Blechert, *Angew. Chem., Int. Ed.* **1997**, *36*, 1474; h) H.-J. Knölker, E. Baum, R. Graf, P. G. Jones, O. Spiess, *Angew. Chem., Int. Ed.* **1999**, *38*, 2583; i) S. A. A. El Bialy, H. Braun, L. F. Tietze, *Angew. Chem., Int. Ed.* **2004**, *43*, 5391; j) A. Goeke, D. Mertl, G. Brunner, *Angew. Chem., Int. Ed.* **2005**, *44*, 99; k) V. K. Yadav, N. V. Kumar, M. Parvez, *Chem. Commun.* **2007**, 2281; k) H. Li, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2008**, *130*, 3521; l) 'Domino Reactions in Organic Synthesis', Eds. L. F. Tietze, G. Brasche, K. M. Gericke, Wiley-VCH, Weinheim, Germany, 2006; m) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267.
- [2] A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341.
- [3] G. W. Gribble, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products', Eds. A. Padwa, W. H. Pearson, John Wiley and Sons, Hoboken, New Jersey, NJ, 2003, pp. 681–753; M. P. Doyle, R. J. Pieters, J. Taunton, H. Q. Pho, A. Padwa, D. L. Hertzog, L. Precedo, *J. Org. Chem.* **1991**, *56*, 820; D. L. Hertzog, D. J. Austin, W. R. Nadler, A. Padwa, *Tetrahedron Lett.* **1992**, *33*, 4731; A. Padwa, M. A. Brodney, J. P. Marino Jr., M. H. Osterhout, A. T. Price, *J. Org. Chem.* **1997**, *62*, 67; A. Padwa, A. T. Price, *J. Org. Chem.* **1995**, *60*, 6258; J. M. Mejía-Oneto, A. Padwa, *Org. Lett.* **2006**, *8*, 3275.
- [4] S. E. Denmark, A. R. Hurd, *J. Org. Chem.* **1998**, *63*, 3045; S. E. Denmark, A. R. Hurd, *J. Org. Chem.* **2000**, *65*, 2875; S. E. Denmark, D. S. Middleton, *J. Org. Chem.* **1998**, *63*, 1604; S. E. Denmark, A. Thorarensen, *J. Am. Chem. Soc.* **1997**, *119*, 125; S. E. Denmark, J. A. Dixon, *J. Org. Chem.* **1997**, *62*, 7086; S. E. Denmark, A. Thorarensen, D. S. Middleton, *J. Am. Chem. Soc.* **1996**, *118*, 8266; S. E. Denmark, L. Gomez, *Org. Lett.* **2001**, *3*, 2907.
- [5] E. J. Jacobsen, J. Levin, L. E. Overman, *J. Am. Chem. Soc.* **1988**, *110*, 4329; L. E. Overman, M.-A. Kakimoto, *J. Am. Chem. Soc.* **1979**, *101*, 1310; L. E. Overman, G. M. Robertson, A. J. Robichaud, *J. Am. Chem. Soc.* **1991**, *113*, 2598; J. M. Fevig, R. W. Marquis Jr., L. E. Overman, *J. Am. Chem. Soc.* **1991**, *113*, 5085; L. E. Overman, J. Shim, *J. Org. Chem.* **1991**, *56*, 5005; Z. D. Aron, L. E. Overman, *Org. Lett.* **2005**, *7*, 913.
- [6] R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446; A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; M. J. Bassindale, P. Hamley, A. Leitner, J. P. A. Harrity, *Tetrahedron Lett.* **1999**, *40*, 3247; R. A. J. Wybrow, L. A. Johnson, B. Auffray, W. J. Moran, H. Adams, J. P. A. Harrity, *Tetrahedron Lett.* **2002**, *43*, 7851; T.-L. Choi, R. H. Grubbs, *Chem. Commun.* **2001**, 2648; W. J.

- Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 6634; N. Buschmann, A. Rückert, S. Blechert, *J. Org. Chem.* **2002**, *67*, 4325.
- [7] a) N.-J. Hong, J.-K. Chang, J.-W. Lim, *Korean J. Med. Chem.* **1998**, *8*, 44; b) T. A. Kelly, D. D. Jeanfavre, D. W. McNeil, J. R. Woska Jr., P. L. Reilly, E. A. Mainolfi, K. M. Kishimoto, G. H. Nabozny, R. Zinter, B.-J. Bormann, R. J. Rothlein, *J. Immunol.* **1999**, *163*, 5173; c) J. R. Woska Jr., M. M. Morelock, D. D. Jeanfavre, B.-J. Bormann, *J. Immunol.* **1996**, *156*, 4680; d) N. K. Yee, L. J. Nummy, R. P. Frutos, J. J. Song, E. Napolitano, D. P. Byrne, P.-J. Jones, V. Farina, *Tetrahedron: Asymmetry* **2003**, *14*, 3495; e) G. J. Rasmussen, H. Bundgaard, *Int. J. Pharm.* **1991**, *71*, 45; f) G. J. Rasmussen, H. Bundgaard, *Int. J. Pharm.* **1991**, *76*, 113; g) A. Bak, M. Fich, B. D. Larsen, S. Frokjaer, G. J. Friis, *Eur. J. Pharm. Sci.* **1999**, *7*, 317; h) S. W. Larsen, M. Sidenius, M. Ankersen, C. Larsen, *Eur. J. Pharm. Sci.* **2003**, *20*, 233; i) P. Chambel, R. Capela, F. Lopes, J. Iley, J. Morais, L. Gouveia, J. R. B. Gomes, P. Gomes, R. Moreira, *Tetrahedron* **2006**, *62*, 9883; j) P. Gomes, M. J. Araújo, M. Rodrigues, N. Vale, Z. Azevedo, J. Iley, P. Chambel, J. Morais, R. Moreira, *Tetrahedron* **2004**, *60*, 5551; k) N. Vale, J. Matos, J. Gut, F. Nogueira, V. do Rosário, P. J. Rosenthal, R. Moreira, P. Gomes, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4150; l) M. J. Araújo, J. Bom, R. Capela, C. Casimiro, P. Cambel, P. Gomes, J. Iley, F. Lopes, J. Morais, R. Moreira, E. de Oliveira, V. do Rosário, N. Vale, *J. Med. Chem.* **2005**, *48*, 888; m) J. Chen, Z. Wang, Y. Lu, J. T. Dalton, D. D. Miller, W. Li, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3183; n) E. Pinard, S. M. Ceccarelli, H. Stalder, D. Alberati, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 349; o) R. H. Jiao, S. Xu, J. Y. Liu, H. M. Ge, H. Ding, C. Xu, H. L. Zhu, R. X. Tan, *Org. Lett.* **2006**, *8*, 5709; p) B. K. S. Yeung, Y. Nakao, R. B. Kinnel, J. R. Carney, W. Y. Yoshida, P. J. Scheuer, M. Kelly-Borges, *J. Org. Chem.* **1996**, *61*, 7168; q) Y. Nakao, J. Kuo, W. Y. Yoshida, M. Kelly, P. J. Scheuer, *Org. Lett.* **2003**, *5*, 1387; r) B. B. Snider, X. Wu, *Org. Lett.* **2007**, *9*, 4913; s) B. B. Snider, H. Zeng, *J. Org. Chem.* **2003**, *68*, 545.
- [8] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32; M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108; S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192; N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894; J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.
- [9] M. T. H. Fonseca, B. List, *Angew. Chem., Int. Ed.* **2004**, *43*, 3958; H. Adolfsson, *Angew. Chem., Int. Ed.* **2005**, *44*, 3340; W. Wang, H. Li, J. Wang, *Org. Lett.* **2005**, *7*, 1637; Y. Zhang, L. Zhao, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 2027.
- [10] U. Zehavi, D. Ben-Ishai, *J. Org. Chem.* **1961**, *26*, 1097; C. A. Panetta, M. Pesh-Imam, *J. Org. Chem.* **1972**, *37*, 302; P. M. Hardy, D. J. Samworth, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954; U. Klíxbüll, H. Bundgaard, *Int. J. Pharm.* **1985**, *23*, 163; M. Rinnová, A. Vidal, A. Nefzi, R. A. Houghton, *J. Comb. Chem.* **2002**, *4*, 209.
- [11] A. Padwa, *Top. Curr. Chem.* **1997**, *189*, 121; K. Amornraksa, D. Barr, G. Donegan, R. Grigg, P. Ratananukul, V. Sridharan, *Tetrahedron* **1989**, *45*, 4649; Y. Nagao, K. Kim, Y. Komaki, S. Sano, M. Kihara, M. Shiro, *Heterocycles* **1994**, *38*, 587; J. Chastanet, G. Roussi, *J. Org. Chem.* **1988**, *53*, 3808; A. Szöllösy, T. Tischer, I. Kádas, L. Tőke, G. Tóth, *Tetrahedron* **1999**, *55*, 7279; R. Grigg, G. Donegan, H. Q. Nimal Gunaratne, D. A. Kennedy, J. F. Malone, V. Sridharan, S. Thianpatanagul, *Tetrahedron* **1989**, *45*, 1723; J. M. Lerestif, J. P. Bazureau, J. Hamelin, *Tetrahedron Lett.* **1993**, *29*, 4639; A. Padwa, D. C. Dean, M. H. Osterhout, L. Precedo, M. A. Semones, *J. Org. Chem.* **1994**, *59*, 5347; G. Dallas, J. W. Lown, J. P. Moser, *J. Chem. Soc. C* **1970**, 2383; O. Tsuge, T. Hatta, H. Tashiro, H. Maeda, *Heterocycles* **2001**, *55*, 243; D. Alker, L. M. Harwood, C. E. Williams, *Tetrahedron Lett.* **1998**, *39*, 475.
- [12] S. Basra, M. W. Fennie, M. C. Kozlowski, *Org. Lett.* **2006**, *8*, 2659.
- [13] K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205; Y. Yamamoto, W. Ito, *Tetrahedron* **1988**, *44*, 5415, and refs. therein.

Received January 12, 2009