ORGANIC LETTERS

2007
Vol. 9, No. 7
1387−1390

Highly Efficient and Stereoselective N-Vinylation of Oxiranecarboxamides and Unprecedented 8-*endo*-Epoxy-arene Cyclization: Expedient and Biomimetic Synthesis of Some *Clausena* Alkaloids

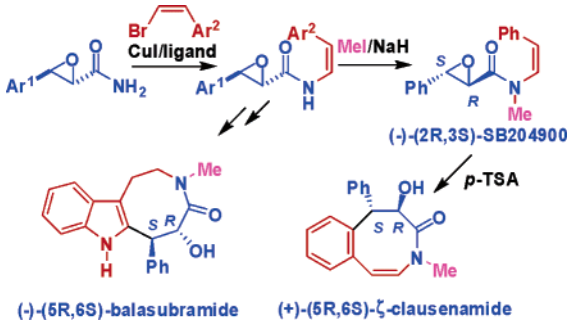
Luo Yang,[†] Gang Deng,[†] De-Xian Wang,[†] Zhi-Tang Huang,[†] Jie-Ping Zhu,[‡] and Mei-Xiang Wang*,[†]

Beijing National Laboratory for Molecular Sciences, Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China, and Institut de Chimie des Substances Naturelles, UPR 2301, CNRS, Gif-sur-Yvette, France

mxwang@iccas.ac.cn

Received February 5, 2007

ABSTRACT



Catalyzed by CuI/*N,N*-dimethylglycine, oxiranecarboxamides underwent a highly efficient and stereoselective N-vinylation reaction with (*Z*)-1-aryl-2-bromoethenes to afford the corresponding enamides. The method has been applied to a straightforward synthesis of (–)-(2*R*,3*S*)-SB204900, the enantiomer of the natural product. Following a hypothetic biomimetic pathway, both (+)-(5*R*,6*S*)-ξ-Clausenamide and (–)-(5*R*,6*S*)-balasubramide have been efficiently synthesized for the first time through the unprecedented intramolecular 8-*endo*-epoxy-arene cyclization of (*Z*)-*N*-(phenylvinyl)oxiranecarboxamides.

Rutaceae *Clausena lansium* (Lour.) Skeels is a fruit tree widely distributed in southern China, and its fruits and leaves are used for the treatment of influenza, gastrointestinal disorders, viral hepatitis, and dermatological diseases in folk medicine. The investigation of the hot-water extract of the leaves in the mid 1980s resulted in the isolation of a number of natural products,[1a−d] and among them, the (±)-ξ-Clausenamide **1** is especially intriguing because of its eight-membered lactam structure and efficacious liver-protecting and antiamnesia effects.[1b−e] About 10 years ago, another eight-membered lactam-containing alkaloid (+)-balasubramide **2** was isolated from *Clausena indica* which grows in the central montane rainforests in Sri Lanka,[2] whereas (*Z*)-*N*-methyl-*N*-phenylvinyl-3-phenyloxirane-2-carboxamide (+)-

[†] Chinese Academy of Sciences.
[‡] Institut de Chimie des Substances Naturelles.

(1) (a) Chen, Y.-R.; Yang, M.-H.; Huang, L.; Liu, G.-T.; Benz, U. Ger. Offen. DE 3,431,257, 1986; *Chem. Abstr.* **1986**, *105*, 7269r. (b) Yang, M.-H.; Chen, Y.-Y.; Huang, L. *Phytochemistry* **1988**, *27*, 445. (c) Yang, M.-H.; Chen, Y.-Y.; Huang, L. *Chin. Chem. Lett.* **1991**, *2*, 291. (d) Ji, X.; ver der Helm, D. *Acta Cryst.* **1992**, *C48*, 1082. (e) Yang, M.-H.; Chen, Y.-R.; Liu, G.-T.; Huang, L. Ger. Offen. DE 3,700,706, 1987; *Chem. Abstr.* **1988**, *108*, 37514v.
(2) Riemer, B.; Hofer, O.; Greger, H. *Phytochemistry* **1997**, *45*, 337.

10.1021/ol070292+ CCC: $37.00
Published on Web 03/03/2007

SB204900 **3**[3] was isolated from a hexane extract of the *Clausena lansium* leaves. Surprisingly, the synthesis of **1**−**3** (Figure 1) has been largely unexplored.[4] Our recent study[5]

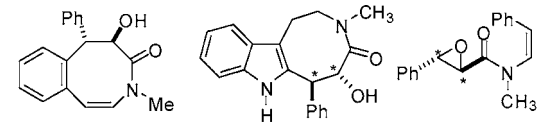


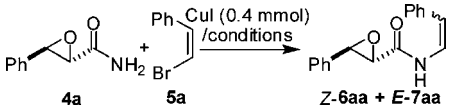
Figure 1. Structures of SB204900, ξ-Clausenamide, and balasubramide

of nitrile biotransformations for the preparation of enantiopure oxiranecarboxamides led us to address the synthesis of optically active SB204900, ξ-Clausenamide, and balasubramide. We envisioned that, in nature, ξ-Clausenamide **1** is most likely constructed from SB204900 **3** via an intramolecular epoxide-arene cyclization, whereas enamide **3** might be synthesized from cross-coupling reaction of *trans*-3-phenyloxirane-2-carboxamide with a vinyl halide.

A number of methods have been reported[6] for the preparation of enamides; however, they are not compatible with epoxide-containing molecules such as **3**. Having considered the easy availability of enantiomerically pure oxiranecarboxamides from both nitrile biotransformations[5] and asymmetric syntheses[7] and the emerging powerful cross-coupling reactions between amides and vinyl halides,[8] we decided to explore the vinylation of oxiranecarboxamides with a vinyl halide.

As we expected, the CuI-catalyzed cross-coupling reaction of *trans*-3-phenyloxirane-2-carboxamide **4a** with (*Z*)-2-bromo-1-phenylethene **5a** appeared challenging because of the low reactivity of amide **4a** and the lability of the epoxide ring. The use of ligands such as *N*,*N*′-dimethylethylenediamine (A), *trans*-*N*,*N*′-dimethylcyclohexyldiamine (B), and proline (C) that have been successfully employed in C−N bond-forming reactions[8] gave desired enamide **6aa** only in very low yields, along with the formation of an epoxide ring-opening byproduct (entries 1−5, Table 1). Further reaction

Table 1. CuI-Catalyzed N-Vinylation of **4a** with **5a**



entry	4a/5a[a]	ligand[b] (0.8 mmol)/ base (2 mmol)/ solvent/temp, time (h)	6aa+7aa (%)[c]	6aa/7aa
1	1:1	A/Cs_2CO_3/dioxane/rt, 20	3	100/−
2	1.2:1	A/Cs_2CO_3/dioxane/60 °C, 20	12	nd[d]
3	1:3	A/Cs_2CO_3/dioxane/reflux, 3	15	nd[d]
4	1:3	B/Cs_2CO_3/dioxane/60 °C, 4	trace	nd[d]
5	1:3	C/K_2CO_3/DMSO/100 °C, 22	trace	nd[d]
6	1:1	D/Cs_2CO_3/dioxane/reflux, 5	21	92:8
7	2:1	D/Cs_2CO_3/dioxane/reflux, 8	38	nd[d]
8	2:1	D/Cs_2CO_3/dioxane/reflux, 20	32	nd[d]
9	2:1	D/Cs_2CO_3/toluene/reflux, 8	-	-
10	2:1	D/^{t}BuOK/dioxane/reflux, 8	-	-
11	1:2	D/Cs_2CO_3/dioxane/reflux, 5	58	nd[d]
12	1:3	D/Cs_2CO_3/dioxane/reflux, 5	82	93:7

[a] Molar ratio (mmol/mmol). [b] Ligand: A, *N*,*N*′-dimethylethylenediamine; B, *trans*-*N*,*N*′-dimethylcyclohexyldiamine; C, proline; D, *N*,*N*-dimethylglycine hydrochloride. [c] Determined by ^{1}H NMR. [d] nd = not determined.

screenings revealed that the combination of CuI and *N*,*N*-dimethylglycine (D) was effective to catalyze the vinylation of **4a** with **5a** (entries 6−12, Table 1). As indicated by Table 1, under the optimal conditions, such as refluxing **4a** with an excess amount of **5a** in 1,4-dioxane using Cs_2CO_3 as a base, an efficient CuI−*N*,*N*-dimethylglycine-catalyzed cross-coupling reaction yielded 82% of enamide product (entry 12, Table 1). Importantly, the reaction proceeded in a highly stereoselective manner, giving *Z*-isomer **6aa** and *E*-isomer **7aa** in a ratio of 93:7.

As summarized in Table 2, the cross-coupling reaction was generally applicable to oxiranecarboxamides **4** and vinyl bromides **5** that contain either an electron-donating or an electron-withdrawing group. All reactions proceeded efficiently to afford enamide products in 49−82% yield (entries 1−8, Table 2). Tri- and tetrasubstituted oxiranecarboxamides **4d** and **4e** reacted equally well with **5a** to furnish the corresponding enamides in 91% and 79% yield, respectively

(3) Milner, P. H.; Coates, N. J.; Gilpin, M. L.; Spear, S. R. *J. Nat. Prod.* **1996**, *59*, 400.

(4) (a) The synthesis of racemic SB-204900 was reported from the epoxidation of Lansiumamide. Stefanuti, B. I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735. (b) In a communication, synthesis of racemic ξ-clausenamide in 21.6% yield was reported from BF_3·Et_2O-mediated reaction of an enamide. Ma, N. C.; Wu, K. M.; Huang, L. *Chin. Chem. Lett.* **1996**, *7*, 706.

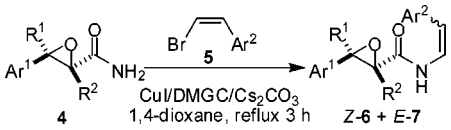
(5) (a) Wang, M.-X.; Lin, S.-J.; Liu, C.-S.; Zheng, Q.-Y.; Li, J.-S. *J. Org. Chem.* **2003**, *68*, 4570. (b) Wang, M.-X.; Deng, G.; Wang, D.-X.; Zheng, Q.-Y. *J. Org. Chem.* **2005**, *70*, 2439.

(6) (a) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (b) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 6643. (c) Zezza, C. A.; Smith, M. B. *Synth. Commun.* **1987**, *17*, 729. (d) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227. (e) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413. (f) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185. (g) Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841. (h) Palomo, C.; Aizpurua, J. M.; Legido, M.; Picard, J. P.; Dunogues, J.; Constantieux, T. *Tetrahedron Lett.* **1992**, *33*, 3903. (i) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479.

(7) (a) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (b) Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 417; *Angew. Chem.* **2004**, *116*, 321. (c) Tosaki, S.-y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 2147. (d) Ohshima, T.; Nemoto, T.; Tosaki, S.-y.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 10485.

(8) For leading references, see: (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (c) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650. (d) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (e) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 111. (f) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (g) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (h) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (i) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (j) Nishikawa, T.; Kajii, S.; Isobe, M.; *Chem. Lett.* **2004**, *33*, 440. (k) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035.

Table 2. Stereoselective N-Vinylation of Oxanecarboxamides **4** with (*Z*)-1-Aryl-2-bromoethenes **5**



entry	4	Ar^1	5	Ar^2	R^1	R^2	6+7 (%)	6/7
1	**4a**	C_6H_5	**5a**	C_6H_5	H	H	82	**6aa/7aa** (93:7)
2	**4a**	C_6H_5	**5b**	4-Cl-C_6H_4	H	H	64	**6ab/7ab** (84:16)
3	**4a**	C_6H_5	**5c**	4-CF_3-C_6H_4	H	H	62	**6ac/7ac** (78:22)
5	**4a**	C_6H_5	**5d**	4-Me-C_6H_4	H	H	54	**6ad/7ad** (88:12)
4	**4a**	C_6H_5	**5e**	3-Me-C_6H_4	H	H	62	**6ae/7ae** (92:8)
6	**4a**	C_6H_5	**5f**	2-Me-C_6H_4	H	H	49	**6af/7af** (84:16)
7	**4b**	4-Cl-C_6H_4	**5a**	C_6H_5	H	H	54	**6ba/7ba** (93:7)
8	**4c**	4-Me-C_6H_4	**5a**	C_6H_5	H	H	74	**6ca/7ca** (87:13)
9	**4d**	C_6H_5	**5a**	C_6H_5	H	Me	91	**6da/7da** (87:13)[a]
10	**4e**	C_6H_5	**5a**	C_6H_5	Me	Me	79	**6ea/7ea** (95:5)[b]

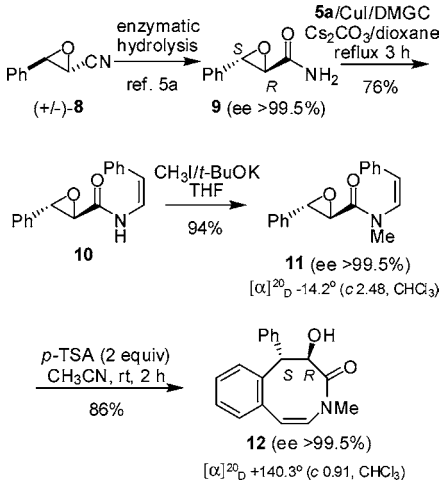
[a] Reaction time was 8 h. [b] Reflux for 6 h. When the reaction was stopped after 10 h, a quantitative yield was obtained with the ratio of **6fa/7fa** being 53:47.

(entries 9 and 10, Table 2). The stereoselectivity of the reaction was good to excellent with the ratio of *Z*-isomer over *E*-isomer ranging roughly from 85:15 to 95:5, except trifluoromentyl-substituted vinyl bromide **5f** which gave a decreased selectivity (entry 3, Table 2).

The successful coupling reaction established for oxirane-carboxamides allowed us to attempt the synthesis of natural products **1**−**3**. Starting with enantiopure 2*R*,3*S*-3-phenyl-oxirane-2-carboxamide **9**, obtained from the biotransformation of racemic *trans*-3-phenyloxirane-carbonitrile **8** using a *Rhodococcus erythropolis* AJ270 whole-cell catalyst,[5a] catalytic N-vinylation with **5a** led to **10** in 76% yield. Treatment of **10** with methyl iodide in the presence of a strong base afforded an almost quantitative yield of **11** with $[\alpha]_D^{20}$ −14.2° (Scheme 1). Because product **11** has an opposite optical rotation to **2** ($[\alpha]_D^{25}$ +14°),[3] compound **11** is therefore the enantiomer of the natural product, and the absolute configuration of (+)-SB204900 **2** was assigned as 2*S*,3*R*.

To test our hypothetical synthetic pathway of ξ-Clausenamide **1** from enamide **2**, the 8-*endo*-aryl-epoxide cyclization reaction of the racemic SB204900 (±)-**11** was investigated under a variety of conditions (Table 3). Lewis acids such as $SnCl_4$ and $BF_3{\cdot}Et_2O$ did not promote intramolecular cyclization reaction. Instead, a mixture of epoxide ring-opening products by halides were formed (entries 1 and 2). Amberlyst and *p*-toluenesulfonic acid (*p*-TSA) were found to effect the desired reaction in refluxing dichloromethane, albeit in low yields (entries 3 and 4). When (±)-**11** was treated with 2 equiv of *p*-TSA in acetonitrile at ambient temperature, racemic ξ-Clausenamide (±)-**1** was produced

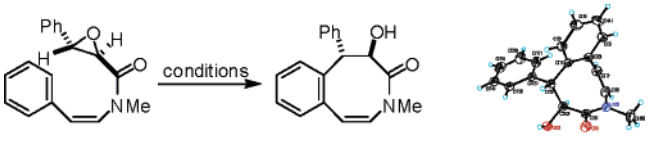
Scheme 1. Synthesis of (−)-(2*R*,3*S*)-**11** and (+)-(5*R*,6*S*)-ξ-Clausenamide **12**



exclusively in high yield (entry 5). The use of a smaller amount of *p*-TSA (entries 6 and 7) and of trifluoroacetic acid (entry 9) can also promote the reaction to give (±)-**1** after a longer period of time. Acetic acid, however, was proved not to be effective at all in the transformation of (±)-**11** into (±)-**1** (entry 8). Applying the optimal conditions for intramolecular aryl-epoxide cyclization to SB204900 (−)-(2*R*,3*S*)-**11** led to the highly efficient synthesis of enantiopure (+)-(5*R*,6*S*)-ξ-Clausenamide **12** as the sole product in 86% yield (Scheme 1).

The highly efficient and stereospecific 8-*endo*- rather than 7-*exo*-epoxy-arene cyclization of **11** is remarkable. Though epoxy-arene cyclizations to yield six- and seven-membered rings have been well documented, to our knowledge, the formation of an eight-membered ring is not known.[9] The exclusive formation of **12** is most probably due to the

Table 3. 8-*endo*-Aryl-epoxide Cyclization of Racemic SB204900



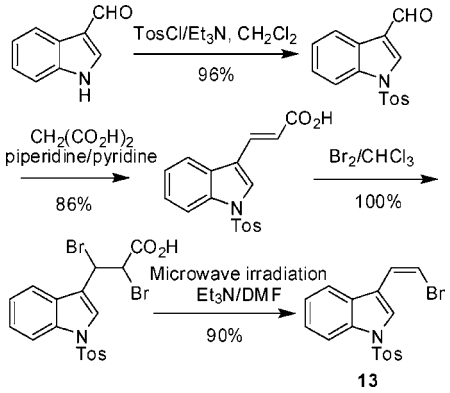
entry	acid (equiv)	solvent, temp, time (h)	yield (%)[a]
1	$SnCl_4$ (2)	CH_2Cl_2, reflux, 3	0[b]
2	$BF_3{\cdot}Et_2O$ (2)	CH_2Cl_2, reflux, 12	0[b]
3	amberlyst (2)	CH_2Cl_2, reflux, 12	37
4	*p*-TSA (2)	CH_2Cl_2, reflux, 18	44
5	*p*-TSA (2)	CH_3CN, rt, 2	86
6	*p*-TSA (0.2)	CH_3CN, rt, 24	46[c]
7	*p*-TSA (1)	CH_3CN, rt, 24	76
8	CH_3CO_2H (2)	CH_3CN, rt, 24	0[d]
9	CF_3CO_2H (2)	CH_3CN, rt, 24	80

[a] Isolated yield. [b] Ring-opening product was formed. [c] Starting material was recovered. [d] No reaction was observed.

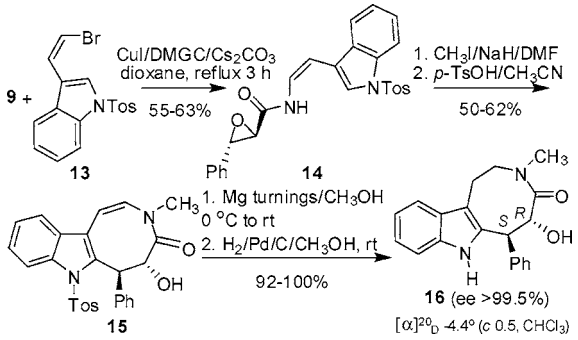
synergetic electronic and steric effects, i.e., the conjugation of an enamide with a benzene ring and the folded conformation of **11**.[3] In other words, both the delocalization of enamide electrons into the benzene ring and the perfectly predisposed conformational structure of **11** dictate the 8-*endo*-epoxy-arene cyclization.

Using the same strategy that comprises the cross-coupling reaction followed by the biomimetic 8-*endo*-epoxide-arene cyclization reaction, (−)-(5*R*,6*S*)-balasubramide **16**, the enantiomer of the natural balasubramide (+)-**3**, was synthesized very efficiently (Scheme 3). Thus, the reaction of enantiopure 2*R*,3*S*-3-phenyloxirane-2-carboxamide **9** with (*Z*)-3-(2-bromovinyl)-1-tosyl-1*H*-indole **13**, the synthesis of which was depicted in Scheme 2, afforded enamide intermediate **14** in 55−63% yield. N-Methylation using methyl iodide in the presence of sodium hydride and, without isolation and purification of the N-methylated intermediate, *p*-TSA-promoted 8-*endo*-indole-epoxide cyclization gave indole-fused eight-membered lactam **15** in 50−62% yield. Deprotection of the tosyl group in the presence of magnesium turnings followed by catalytic hydrogenation of **15** yielded an almost quantitative yield of (−)-(5*R*,6*S*)-balasubramide **16** (Scheme 3).

Scheme 2. Synthesis of (*Z*)-3-(2-Bromovinyl)-1-tosyl-1*H*-indole **13**



Scheme 3. Synthesis of (−)-(5*R*,6*S*)-Balasubramide **16**



In summary, we have developed a highly efficient and stereoselective CuI-catalyzed N-vinylation of *trans*-3-aryloxirane-2-carboxamides with (*Z*)-1-aryl-2-bromoethenes for the synthesis of functionalized enamides. With the use of an enantiopure 2*R*,3*S*-3-phenyloxirane-2-carboxamide, the method has been utilized for a straightforward synthesis of (−)-(2*R*,3*S*)-SB204900, the enantiomer of natural product (+)-SB204900. Following a hypothetic biomimetic intramolecular 8-*endo*-epoxide-arene cyclization reaction, we have achieved highly efficient synthesis of enantiopure (+)-(5*R*,6*S*)-ξ-Clausenamide and (−)-(5*R*,6*S*)-balasubramide for the first time. The easy availability of oxiranecarboxamides and vinyl bromides and the efficient cross-coupling reaction and biomimetic intramolecular epoxide-arene cyclization reaction should render the present protocols attractive for the synthesis of libraries of natural product-like compounds.

Acknowledgment. We thank the Ministry of Science and Technology (2003CB716005, 2006CB806106), the National Natural Science Foundation of China, and the Chinese Academy of Sciences for financial support.

Supporting Information Available: Detailed experimental procedures, full characterization of all products, and X-ray molecular structure of racemic ξ-Clausenamide (±)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070292+

(9) (a) For a review of epoxy-arene cyclizations, see: Taylor, S. K. *Org. Prep. Proceed. Int.* **1992**, *24*, 245. For recent examples, see: (b) Islas-González, G.; Benet-Buchholz, J.; Maestro, M. A.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2006**, *71*, 1537. (c) Kraus, G. A.; Kim, I. *Org. Lett.* **2003**, *5*, 1191. (d) Nagumo, S.; Miyoshi, I.; Akita, H.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 2223.