Diversity-Oriented Construction of Highly Substituted Indolizinones

Kyungsun Kim and Ikyon Kim*

Medicinal Chemistry Research Center, Korea Research Institute of Chemical Technology, Daejeon 305-600, Republic of Korea

Received January 26, 2010

Rapid generation of a small library of highly functionalized indolizonones was realized by exploiting three palladium-catalyzed cross-coupling reactions of 2-iodoindolizinones which in turn were readily accessed via sequential iodine-mediated cyclization/1,2-shift reactions of propargylic alcohols.

Introduction

In the context of drug discovery, halogenated heterocyclic compounds serve as a useful platform for increasing molecular diversity.[1] This is particularly true as enormous progress has been made in the modern transition-metal catalyzed cross-coupling technology, which enables a number of functional groups to be installed at the halogen site.[2] In this regard, the reactions incorporating halogens into the molecular framework of interest in a regioselective manner have been increasingly gaining attention. Among these, halocyclization[3,4] is highly valuable because of its ability to introduce halide(s) as a functional handle for further synthetic elaboration as well as to form new ring(s) under relatively mild reaction conditions.

We recently established the novel approach to 2-iodoindolizinones **3** based on *5-endo-dig* iodocyclization and subsequent 1,2-migration strategy (Scheme 1).[5] Thus, a wide range of 2-iodoindolizinones were easily prepared in excellent yields under very mild conditions. As indolizines constitute an important class of heterocycles with diverse biological activities, many efforts have been devoted to search for new drugs bearing an indolizine moiety.[6] For example, indolizine oxalylamide **A** was reported to exhibit antifungal activity whereas indolizine acetic acid **B** was known to be a ligand of the CRTH2 receptor useful for the treatment of inflammatory respiratory diseases (Figure 1).[7] Thus, a number of synthetic methods toward this skeleton have been developed.[8]

Indolizinones, however, have not been evaluated as a pharmacophore to our knowledge. As part of our medicinal research program, we decided to construct a focused molecular library based on an indolizinone core. Particularly, we envisioned that at least three positions are available in this scaffold for diversification (Scheme 1). Herein we report an expedient route to highly substituted indolizinones using Pd-catalyzed cross-coupling reactions of 2-iodoindolizinones.

Results and Discussion

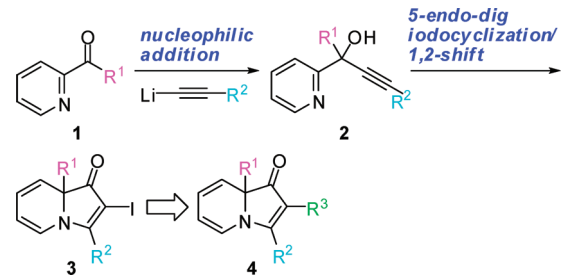
We began this study with the preparation of 2-iodoindolizinones **3** by following the procedure reported by us (Scheme 2).[5] Nucleophilic addition of the appropriate terminal acetylide to 2-acylpyridine **1** provided tertiary propargylic alcohol **2** which was converted to the corresponding 2-iodoindolizinone **3** via a sequential iodocyclization/1,2-shift. By using this protocol, the requisite 2-iodoindolizinones in which two diversity points are occupied by different groups were rapidly synthesized in excellent overall yields.

Having secured diverse 2-iodoindolizinones in hand, we next focused our attention on introduction of new functional groups at the third diversity point. To this end, we planned to employ three Pd-catalyzed cross-coupling reactions, namely, Heck,[9] Sonogashira,[10] and Suzuki−Miyaura reactions[11] (Scheme 3).

As shown in Figure 2, methyl acrylate was used as a coupling partner for the Heck reaction. For the Sonogashira and Suzuki−Miyaura reactions, small sets of terminal acetylenes and boronic acids were chosen as reacting partners. Heck coupling was conducted under the Jeffery's ligandless conditions.[12] Two reaction conditions (**methods C** and **D**) were employed for Suzuki-Miyaura coupling reactions.

As outlined in Table 1, three palladium-catalyzed cross-couplings of **3** enabled us to synthesize a wide range of highly functionalized indolizinones **4** in good to excellent yields, displaying good functional group tolerance. Both Heck and Sonogashira reactions proceeded well to give the desired products in good yields for all 2-iodoindolizinones tested except for the thiophene-containing one **3{7}**. Although modest yields were obtained in some cases (for example, entries 9, 12, 18, 47, 49, 50, and 59), Suzuki−Miyaura

Scheme 1. Our Strategy for the Synthesis of Poly-Substituted Indolizinones



* To whom correspondence should be addressed. E-mail: ikyon@krict.re.kr. Phone: +82 42 860 7177. Fax: +82 42 860 7160.

10.1021/cc100015k
Published on Web 03/31/2010

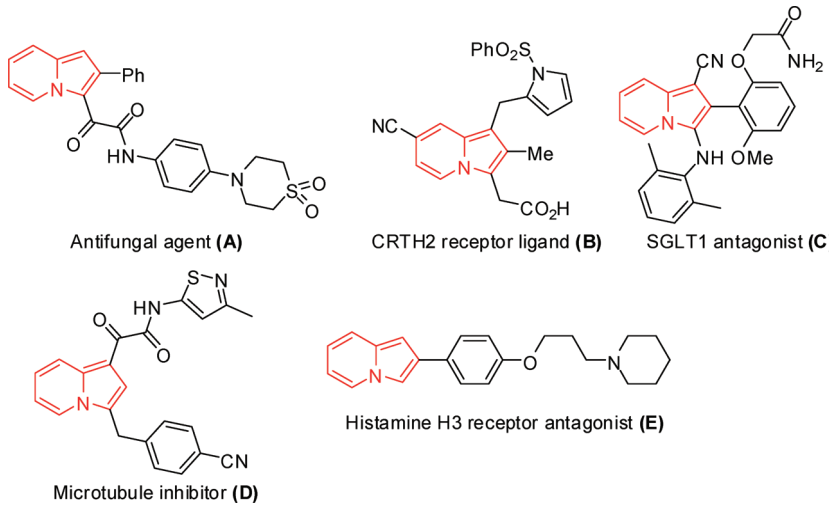
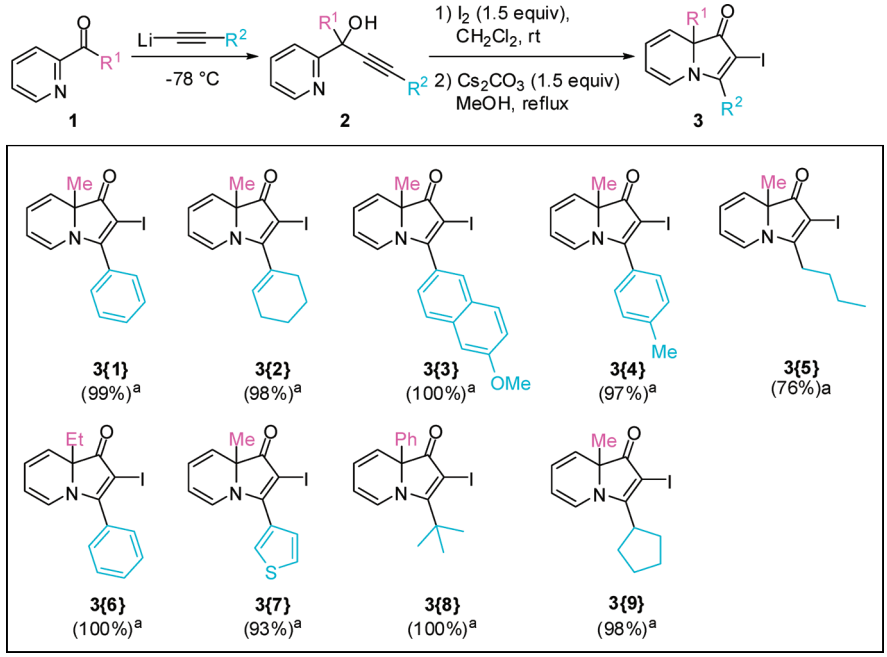


Figure 1. Selected molecular structures bearing an indolizine core.

Scheme 2. Preparation of 2-Iodoindolizinones



[a] Overall yield from **1**.

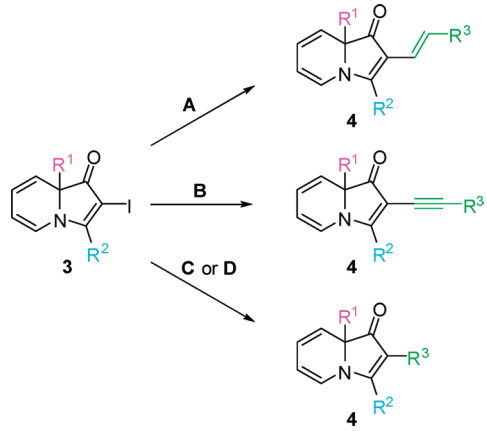
coupling of **3** generally provided the corresponding products in good to excellent yields. Preliminary biological screening of these compounds in several cancer cell lines indicated that some are capable of killing cancer cells selectively although the mode of action is not clear at this point.

In summary, diversity-oriented construction of poly substituted indolizinones was accomplished from three simple building blocks in a highly efficient manner. Nucleophilic addition of lithium acetylides to 2-acylpyridines provided propargylic alcohols which underwent smooth iodocyclization/1,2-shift to afford 2-iodoindolizinones in excellent overall yields. Finally, Pd-catalyzed cross-coupling reactions with alkenes, alkynes, and boronic acids delivered a variety of highly substituted indolizinones. Biological evaluation of these compounds is currently ongoing and will be reported soon.

Experimental Section

General Procedure for the Synthesis of 3. To a stirred solution of terminal alkyne (1.2 equiv) in tetrahydrofuran (THF) was added *n*-BuLi (1.1 equiv, 1.6 M solution in hexanes) at −78 °C. After 5 min, a solution of ketone **1** (1.0 equiv) in THF was slowly added to this mixture at −78 °C. After 15 min at −78 °C, the reaction mixture was quenched with saturated NH_4Cl. The reaction mixture was diluted with ethyl acetate and washed with aqueous NH_4Cl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a crude mixture which was purified by silica gel column chromatography (hexane:ethyl acetate:dichloromethane) to afford the propargylic alcohol **2**. To a solution of propargylic alcohol **2** (1.0 equiv) in CH_2Cl_2 was added iodine (1.5 equiv) at room temperature. After being stirred at room temperature (rt) for 5 h, the reaction mixture was quenched by the addition of excess aqueous $NaHSO_3$ solution. The solid (indolizinium salt) was filtered, washed with dichloromethane, and dried. A mixture of indolizinium salt (1.0 equiv) and Cs_2CO_3 (1.5 equiv) in MeOH was heated to reflux for 1 h. After being cooled to rt, the reaction mixture was concentrated in vacuo. The residue was diluted

Scheme 3. Pd-Catalyzed Cross-Coupling Reactions of **3**[a]



[a] **Method A:** $Pd(OAc)_2$ (0.1 equiv), methyl acrylate (4.1 equiv), *n*-Bu_4NCl (1 equiv), $NaHCO_3$ (2 equiv), DMF, 100 °C; **Method B:** terminal alkyne (2 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), CuI (0.1 equiv), Et_3N (3 equiv), DMF, rt; **Method C:** boronic acid (1.5 equiv), 10% Pd/C (0.1 equiv), Na_2CO_3 (3 equiv), DME/H_2O (1:1), 100 °C; **Method D:** boronic acid (1.5 equiv), $Pd(Ph_3P)_4$ (0.1 equiv), K_2CO_3 (2 equiv), toluene/EtOH/H_2O (4:2:1), 100 °C.

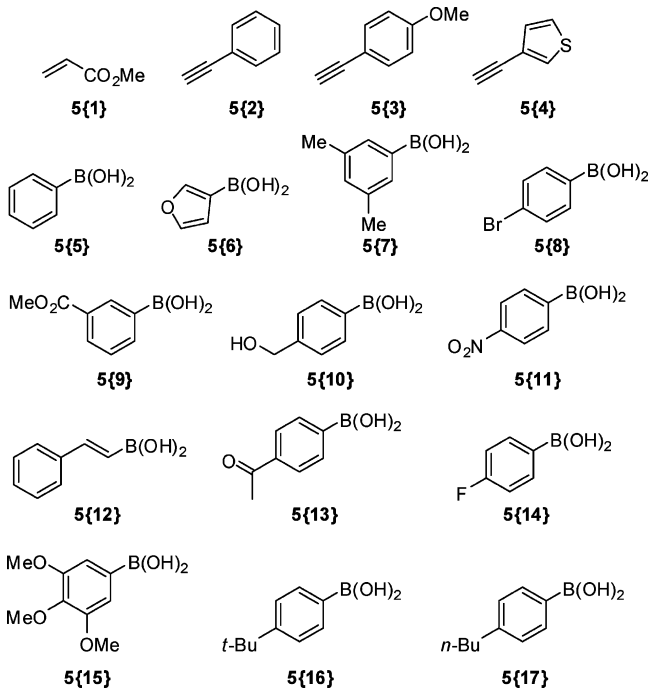


Figure 2. Coupling partners for Pd-catalyzed reactions.

with ethyl acetate and washed with H_2O. The water layer was extracted with ethyl acetate one more time. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 7:1:2) to give 2-iodoindolizinone **3**.

General Procedure for the Heck Reaction of 3 with Methyl Acrylate (Method A). A mixture of 2-iodoindolizinone **3** (1 equiv), methyl acrylate (4.1 equiv), sodium bicarbonate (2 equiv), tetra-*n*-butylammonium chloride (1 equiv), palladium(II) acetate (0.1 equiv) in *N*,*N*-dimethylformamide (DMF) was heated at 100 °C for 18 h. After being cooled to rt, the reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water two times, and the aqueous layer was extracted with ethyl acetate one more time.

Table 1. Synthesis of Poly-Substituted Indolizinones

entry	3	5	method	product (4)	yield (%)[a]
1	3{1}	5{1}	A	4{1}	84
2	3{1}	5{2}	B	4{2}	99
3	3{1}	5{3}	B	4{3}	88
4	3{1}	5{4}	B	4{4}	90
5	3{1}	5{5}	C	4{5}	91
6	3{1}	5{6}	C	4{6}	83
7	3{1}	5{7}	C	4{7}	88
8	3{1}	5{8}	C	4{8}	63
9	3{1}	5{9}	C	4{9}	35
10	3{1}	5{10}	C	4{10}	93
11	3{1}	5{11}	C	4{11}	95
12	3{1}	5{12}	C	4{12}	30
13	3{1}	5{13}	C	4{13}	56
14	3{1}	5{14}	C	4{14}	76
15	3{2}	5{1}	A	4{15}	58
16	3{2}	5{2}	B	4{16}	77
17	3{2}	5{5}	C	4{17}	66
18	3{2}	5{6}	D	4{18}	33
19	3{2}	5{7}	C	4{19}	85
20	3{2}	5{8}	D	4{20}	77
21	3{2}	5{10}	D	4{21}	65
22	3{2}	5{11}	D	4{22}	68
23	3{2}	5{16}	D	4{23}	45
24	3{3}	5{2}	B	4{24}	70
25	3{3}	5{6}	C	4{25}	67
26	3{3}	5{7}	C	4{26}	82
27	3{3}	5{12}	C	4{27}	71
28	3{3}	5{15}	C	4{28}	69
29	3{4}	5{1}	A	4{29}	93
30	3{4}	5{2}	B	4{30}	73
31	3{4}	5{4}	B	4{31}	92
32	3{4}	5{6}	D	4{32}	55
33	3{4}	5{10}	D	4{33}	61
34	3{4}	5{11}	D	4{34}	55
35	3{4}	5{17}	D	4{35}	68
36	3{5}	5{1}	A	4{36}	76
37	3{5}	5{3}	B	4{37}	93
38	3{5}	5{6}	D	4{38}	66
39	3{5}	5{7}	C	4{39}	83
40	3{5}	5{10}	C	4{40}	78
41	3{5}	5{11}	C	4{41}	56
42	3{5}	5{16}	D	4{42}	52
43	3{5}	5{17}	D	4{43}	88
44	3{5}	5{15}	D	4{44}	48
45	3{6}	5{1}	A	4{45}	50
46	3{6}	5{4}	B	4{46}	63
47	3{6}	5{12}	D	4{47}	35
48	3{7}	5{1}	A	4{48}	45
49	3{7}	5{2}	B	4{49}	38
50	3{7}	5{6}	D	4{50}	36
51	3{7}	5{10}	D	4{51}	75
52	3{7}	5{11}	D	4{52}	46
53	3{7}	5{17}	D	4{53}	89
54	3{7}	5{9}	D	4{54}	49
55	3{8}	5{1}	A	4{55}	53
56	3{8}	5{2}	B	4{56}	48
57	3{9}	5{1}	A	4{57}	56
58	3{9}	5{2}	B	4{58}	71
59	3{9}	5{8}	D	4{59}	33
60	3{9}	5{11}	D	4{60}	89

[a] Isolated yield (%).

The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane =10:1:2) to give **4**.

General Procedure for the Sonogashira Coupling with 3 with Terminal Alkyne (Method B). A mixture of 2-iodoindolizinone **3** (1 equiv), terminal alkyne (2 equiv), copper(I) iodide (0.1 equiv), triethylamine (3 equiv), bis-(triphenylphosphine)palladium(II) dichloride (0.1 equiv) in DMF was stirred at rt for 18 h. The reaction mixture was

diluted with ethyl acetate and water. The organic layer was washed with water two times, and the aqueous layer was extracted with ethyl acetate one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 15:1:2) to give **4**.

General Procedure for the Suzuki−Miyaura Coupling of 3 with Boronic Acid (Method C). A mixture of 2-iodoindolizinone **3** (1 equiv), boronic acid (1.5 equiv), 10% Pd/C (0.1 equiv), Na_2CO_3 (3 equiv) in 1,2-dimethoxyethane: H_2O (1:1) was heated at 100 °C for 5 h. After being cooled to rt, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane) to give **4**.

General Procedure for the Suzuki−Miyaura Coupling of 3 with Boronic Acid (Method D). A mixture of 2-iodoindolizinone **3** (1 equiv), boronic acid (1.5 equiv), $Pd(Ph_3P)_4$ (0.1 equiv), K_2CO_3 (2 equiv) in toluene/EtOH/H_2O (4:2:1) was heated at 100 °C for 5 h. After being cooled to rt, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane) to give **4**.

Acknowledgment. This work was financially supported by Korea Research Institute of Chemical Technology.

Supporting Information Available. General synthetic procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Liao, Y.; Hu, Y.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem.* **2003**, *10*, 2285. (c) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (d) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (e) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48. (f) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149.

(2) For books and reviews, see: (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; John Wiley & Sons Ltd.: New York, 2000. (b) *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Chichester, U.K., 2004; Vols. 1 and 2. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (g) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(3) For reviews and recent examples, see: (a) Martins da Silva, F.; Jones, J., Jr.; de Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. (b) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377. (d) Barluenga, J.; Palomas, D.; Rubio, E.; González, J. M. *Org. Lett.* **2007**, *9*, 2823. (e) Knight, D. W.; Rost, H. C.; Sharland, C. M.; Singkhonrat, J. *Tetrahedron Lett.* **2007**, *48*, 7906. (f) Okitsu, T.; Nakazawa, D.; Taniguchi, R.; Wada, A. *Org. Lett.* **2008**, *10*, 4967. (g) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128.

(4) (a) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863. (b) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954. (c) Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976.

(5) Choi, J.; Lee, G. H.; Kim, I. *Synlett* **2008**, 1243.

(6) (a) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; King, F. D.; Miner, W. D.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 1924. (b) Gubin, J.; de Vogelaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425. (c) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (d) Sonnet, P.; Dallemagne, P.; Guillon, J.; Enguehard, C.; Stiebing, S.; Tanguy, J.; Bureau, R.; Rault, S.; Auvray, P.; Moslemi, S.; Sourdaine, P.; Seralini, G.-E. *Bioorg. Med. Chem.* **2000**, *8*, 945. (e) Millet, R.; Domarkas, J.; Rigo, B.; Goossens, L.; Goossens, J.-F.; Houssin, R.; Henichart, J.-P. *Bioorg. Med. Chem.* **2002**, *10*, 2905. (f) Teklu, S.; Gunderson, L.-L.; Larson, T.; Malterud, K. E.; Rise, F. *Bioorg. Med. Chem.* **2005**, *13*, 3127. (g) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59. (h) Gundersen, L.-L.; Charnock, C.; Negussie, A. H.; Rise, F.; Teklu, S. *Eur. J. Pharm. Sci.* **2007**, *30*, 26. (i) James, D. A.; Koya, K.; Li, H.; Liang, G.; Xia, Z.; Ying, W.; Wu, Y.; Sun, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1784.

(7) (a) Chai, W.; Bretenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767. (b) Li, H.; Xia, Z.; Chen, S.; Koya, K.; Ono, M.; Sun, L. *Org. Process Res. Dev.* **2007**, *11*, 246. (c) Mederski, W.; Beier, N.; Burgdorf, L.; Gericke, R.; Klein, M.; Tsaklakidis, C. DE 102006058236 A 12008. (d) Hynd, G.; Montana, J. G.; Finch, H. WO 2009044134 A 12009. (e) Birch, M.; Sibley, G. E. M.; Law, D.; Oliver, J. D. WO 2009144473 A 12009.

(8) For reviews and recent examples, see: (a) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209. (b) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 443. (c) Kaloko, J., Jr.; Hayford, A. *Org. Lett.* **2005**, *7*, 4305. (d) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (e) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (f) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (g) Zhu, L.; Vimolratana, M.; Brown, S. P.; Medina, J. C. *Tetrahedron Lett.* **2008**, *49*, 1768.

(9) Heck, R. F. *Org. React.* **1982**, *27*, 345.

(10) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(11) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Wolfe, J. P.; Buchwald, S. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153.

(12) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (d) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

CC100015K