ORGANIC LETTERS

2010
Vol. 12, No. 16
3594−3597

Branch-Selective Synthesis of Oxindole and Indene Scaffolds: Transition Metal-Controlled Intramolecular Aryl Amidation Leading to C3 Reverse-Prenylated Oxindoles

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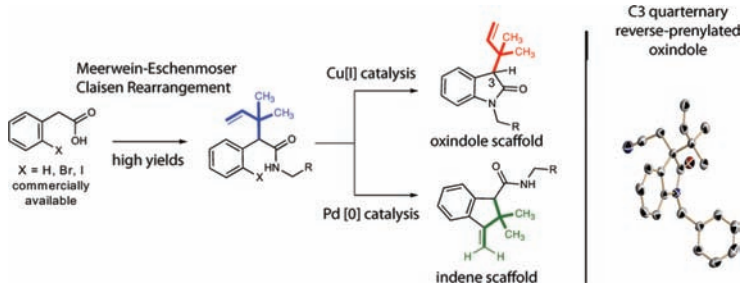
Received May 28, 2010

ABSTRACT



In an effort to access biologically important scaffolds, a concise branch-selective synthesis of C3 tertiary oxindoles by Cu(I)-catalyzed aryl amidation and 2,2-dimethyl indene by Pd(0)-catalyzed Heck cyclization has been accomplished from acyclic reverse-prenylated intermediates. Oxindole C3-enolate generation using NaH followed by alkylation in the presence of appropriate electrophiles provides a novel route to quaternary C3 reverse-prenylated oxindoles.

Direct synthetic access to privileged scaffolds is of crucial importance in the discovery and development of new drug candidates. Indole and oxindole scaffolds are common structural motifs in many therapeutic agents.[1−3] Indole alkaloids, which contain a reverse prenyl group at the C3 position, such as notoamide, roquefortine, amauromine, and ardeemin, have attracted the attention of the scientific community because of their significant biological activity. Nature has produced the welwitindolinone family of alkaloids that has challenged synthetic chemists by presenting this C3 reverse-prenyl signature embedded in addition to a highly dense arrangement of rings and functionalities (see Figure 1, reverse prenyl group highlighted).[4] Concurrently, the

(1) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, published ASAP April 9, 2010; DOI: 10.1021/cr900211p.

(2) de Sa Alves, F. R.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini-Rev.Med. Chem.* **2009**, *9*, 782.

(3) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(4) For ardeemins as a representative example, see: (a) Chou, T.-C.; Depew, K. M.; Zheng, Y.-H.; Safer, M. L.; Chan, D.; Helfrich, B.; Zatorska, D.; Zatorski, A.; Bornmann, W.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8369. For selected recent reports on synthetic approaches towards welwitindolinones, see: (b) Heidebrecht, R. W., Jr.; Gulledge, B.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2492. (c) Brailsford, J. A.; Lauchli, R.; Shea, K. J. *Org. Lett.* **2009**, *11*, 5330. (d) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782. (e) Tian, X.; Huters, A. D.; Douglas, G. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349. (f) For a potentially biomimetic approach, see: Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (g) Brown, L. E.; Konopelski, J. P. *Org. Prep. Proced. Int.* **2008**, *40*, 411. (h) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (I) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421. (j) For an example of early seminal report, see: Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovasaka, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270. (k) For a recent review, see Gademann, K.; Portmann, C. *Curr. Org. Chem.* **2008**, *12*, 326.

10.1021/ol1012372
Published on Web 07/27/2010

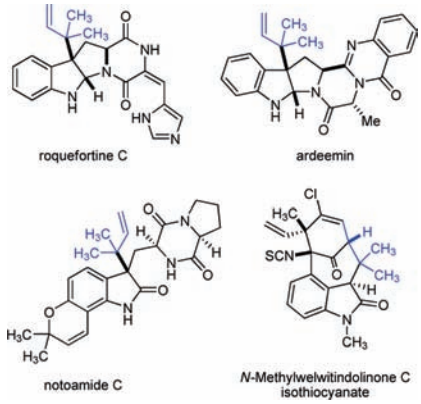


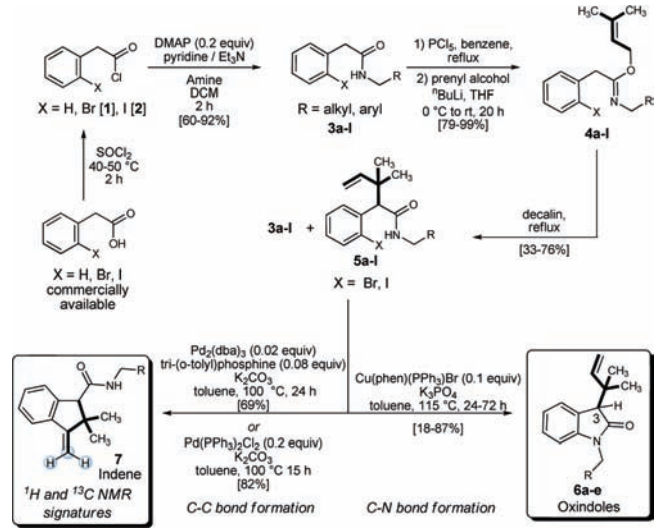
Figure 1. Representative examples with the highlighted portion showing a C3 reverse-prenyl scaffold in a prominent or in a cryptic fashion.

indene scaffold has been found in selective inhibitors of aldosterone synthase[5] and a series of serotonin receptor agonists.[6]

Oxindole derivatives containing a reverse prenyl group at C3 are challenging synthetic targets. Several approaches have been developed for the construction of reverse-prenylated quaternary C3 centers.[7] Despite the fact that some of them were applied to the syntheses of natural products, these strategies are limited by a narrow substrate scope, low-yielding protocols, arduous routes, or the use of highly toxic reagents (e.g., tin or selenium). Few methods exist for the synthesis of tertiary C3 reverse-prenylated oxindole scaffolds.[8] Although the corresponding C3 hydroxy product has been obtained in good yields, additional steps are required for the construction of complex and diverse C3 quaternary centers.

With the broad goal of synthesis and evaluation of biological activity for a series of C3 reverse-prenylated oxindoles and 2,2-dimethyl indenes, herein we report an elegant branch-selective syntheses of C3 tertiary oxindoles **6a**−**e** and indene **7** from the key intermediates **5a**−**l** simply by switching the transition metal catalyst for the corresponding coupling reactions (Scheme 1). Furthermore, the representative tertiary C3 reverse-prenylated oxindole **6a** has been shown to easily undergo the amide-enolate alkylation reaction to furnish quaternary C3 reverse-prenylated oxindoles **8** and **9** (*vide infra*).

Scheme 1. Divergent Synthetic Route to Reverse-Prenylated Oxindole (**6a**−**e**) and Indene (**7**) Scaffolds



Substituted phenylacetamides **3a**−**l** were obtained in a straightforward fashion from commercially available acids, in good yields by the reaction of the corresponding acid chlorides (X = H, Br [**1**] or I [**2**]) with an amine in the presence of DMAP (20 mol %) as a nucleophilic catalyst in DCM. Use of either pyridine (for **3a**−**e**) or triethylamine (for **3f**−**l**) as a base proved equally efficacious, while triethylamine proving superior with aliphatic amine substrates.

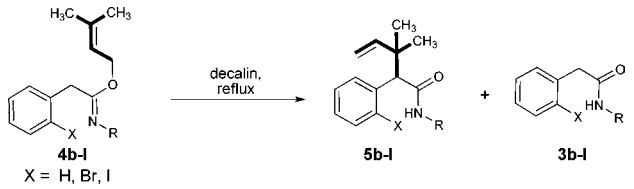
(5) Uimschneider, S.; Muller-Vieira, U.; Klein, C. D.; Antes, I.; Lengauer, T.; Hartmann, R. W. *J. Med. Chem.* **2005**, *48*, 1563.

(6) Alcalde, E.; Mesquida, N.; Lopez-Perez, S.; Frigola, J.; Merce, R. *J. Med. Chem.* **2009**, *52*, 675.

(7) For the construction of reverse-prenylated quaternary C3 centers, see the following. (a) Olefination followed by a tandem isomerization−Claisen rearrangement process: Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedron Lett.* **1996**, *37*, 7525. (b) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493. (c) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem.Commun.* **2006**, 420. (d) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959. (e) Preactivation of C3-substituted indoles with *N*-(phenylseleno)phthalimide followed by reaction with prenyl tributylstannane: Marsden, S.; Depew, K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (f) Depew, K.; Marsden, S.; Zatorska, D.; Zatorski, A.; Bornmann, W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953. (g) Chen, W.-C.; Joulie, M. M. *Tetrahedron Lett.* **1998**, *39*, 8401. (h) Schiavi, B.; Richard, D. J.; Joulie, M. M. *J. Org. Chem.* **2002**, *67*, 620. (i) Richard, D. J.; Schiavi, B.; Joulie, M. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11971. (j) Shangguan, N.; Hehre, W. J.; Ohlinger, W. S.; Beavers, M. P.; Joulie, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 6281. (k) Preactivation of C3-substituted indoles with NBS followed by reaction with prenyl tributylstannane: Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677. (l) Thio-Claisen rearrangement of 2-prenyl thioindole: Bycroft, B.; Landon, W. *Chem.Commun.* **1970**, 168. (m) Takase, S.; Iwami, M.; Ando, T.; Okamoto, M.; Yoshida, K.; Horiai, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1984**, *37*, 1320. (n) Takase, S.; Itoh, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron Lett.* **1985**, 847. (o) Takase, S.; Itoh, Y.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5887. (p) Takase, S.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5879. (q) Bhat, B.; Harrison, D. *Tetrahedron Lett.* **1986**, *27*, 5873. (r) Bhat, B.; Harrison, D.; Lamony, H. *Tetrahedron* **1993**, *49*, 10663. (s) Bhat, B.; Harrison, D. *Tetrahedron* **1993**, *49*, 10655. (t) Grignard reaction of an activated indoline with prenyl magnesium bromide: Morales-Rios, M.; Suarez-Castillo, O.; Joseph-Nathan, P. *J. Org. Chem.* **1999**, *64*, 1086. (u) Morales-Rios, M.; Suarez-Castillo, O.; Trujillo-Serrato, J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186. (v) Addition of prenyl alcohol to 3-chloro iminium ion followed by Claisen rearrangement: Booker-Milburn, K.; Fedouloff, M.; Paknoham, S.; Strachan, J.; Melville, J.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657. (w) For the singular report on catalytic enantioselective variant, see: Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162.

(8) For C3 reverse prenylation leading to isatin derivatives, see the following. (a) Enolate−Claisen rearrangement: Malapel-Andrieu, B.; Piroelle, S.; Merour, J.-Y. *Chem. Res., Synop.* **1998**, 594. (b) Barbier reaction of prenylindium reagents with isatin: Nair, V.; Ros, S.; Jayan, C.; Viji, S. *Synthesis* **2003**, *16*, 2542. (c) Transfer hydrogenation reaction of isatin with 1,1-dimethylallene as the prenyl donor: Skucas, E.; Bower, J.; Krische, M. *J. Am. Chem. Soc.* **2007**, *129*, 12678. (d) Grant, C. D.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4485. (e) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (f) For a review on the importance of this structural scaffold, see: Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20.

Table 1. Meerwein−Eschenmoser Claisen Rearrangement Leading to Major (**5b**−**l**) and Minor (**3b**−**l**) Product Formation



entry	R	X	time, h	ratio[a] **5**:**3**	yield[b] of **5**, %
1	benzyl	Br	2.5	6:1	71 (**5b**)
2	benzyl	I	2	1:1	45 (**5c**)
3	propyl	H	3	5:1	64 (**5d**)
4	propyl	Br	1	3:1	66 (**5e**)
5	propyl	I	1	6:1	71 (**5f**)
6	pentyl	Br	1	5:1	76 (**5g**)
7	pentyl	I	0.5	3:1	59 (**5h**)
8	isopropyl	Br	3	8:1	68 (**5i**)
9	isopropyl	I	0.5	3:1	54 (**5j**)
10	phenyl	H	1	1:1	41 (**5k**)
11	Phenyl	I	0.5	1:2	33 (**5l**)

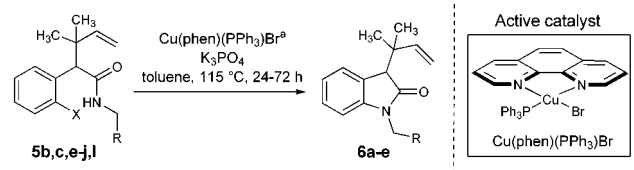
[a] Determined by ^{1}H NMR. [b] Isolated yield after flash chromatography.

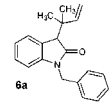
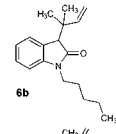
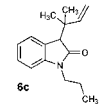
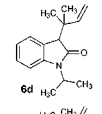
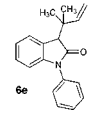
Indene scaffold **7** was synthesized from reverse-prenylated amide **5b** by a palladium (0)-catalyzed intramolecular 5-*exo*-*trig* Heck cyclization process. The use of tris(dibenzylideneacetone)dipalladium (0) with tri-*o*-tolyl phosphine as a ligand in toluene at 100 °C gave the desired product **7** in 69% yield after 24 h. Alternatively the use of bis(triphenylphosphine)palladium(II) chloride in toluene at 100 °C gave 2,2-dimethyl indene **7** in 82% yield after 15 h. Structurally rigid terminal olefin functionality was identified through distinct ^{1}H NMR signals at 4.92 and 5.41 ppm in addition to a characteristic ^{13}C NMR signal at 102.9 ppm that showed large coupling to the chemically distinct terminal olefinic protons (data not shown). The discovery of this synthetic route leading to **7** is important as it allows for derivatization of indene scaffold in previously intractable positions.

In midcourse to reverse-prenylated amides **5b**−**l**, the key intermediates in the synthesis of both target scaffolds, we applied the Meerwein−Eschenmoser Claisen rearrangement of allyl imidates[9] to substrates **4b**−**l**. Following this sequence, the amides **3b**−**l** were converted to intermediate imidochlorides by the means of phosphorus pentachloride in refluxing benzene. The crude imidochlorides were treated with lithium prenyloxide to form allyl imidates **4b-l,** which proved sufficiently pure for subsequent transformations. ^{1}H NMR signatures were observed for all of the precursors **4b**−**l**, however these imidates proved sensitive to storage and/or to further spectroscopic characterization. The Meerwein−Eschenmoser Claisen rearrangement under the contitions attempted caused a deprenylation event as a minor side reaction that led to formation of amides **3b**−**l**. Amides **3b**−**l** could be isolated from the reaction mixture and recycled as the starting material for the preparation of allylimidates **4b**−**l**, thereby rendering further efficiency to this sequence (Scheme 1). On our way to tertiary C3 reverse-prenylated oxindoles **6a**−**e**, we focused on copper(I)-catalyzed intramolecular Goldberg *N*-arylation reaction[10,11] of amides **5b,c,e**−**j,l**.

In order to avoid the standard protocol, which implies the use of high temperatures, highly polar solvents, and large amounts of copper(I) reagents, we have applied recent advances in aryl amidation chemistry to our substrates. For compound **6a**, we explored a set of two distinct conditions operating under Cu(I) catalysis. First, **5a** was subjected to the Aryl C−N bond-forming reaction according to the approach reported by Buchwald.[12] Use of copper(I) iodide as the source of transition metal, K_3PO_4 as a base, and *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand in toluene gave the desired product **6a** in only 55% yield (Table 2). Alternatively, substituting the amidation condi-

Table 2. Goldberg Aryl Amidation Reaction Leading to Tertiary C3 Reverse Prenylated Oxindoles **6a**−**e**



entry	X	product **6**	catalyst (equiv)	Yield, %[b]
1	Br		Cu(phen)(PPh$_3$)Br (0.1)	78
2	Br		CuI (0.1), DMEDA (0.2)	55
3	I		Cu(phen)(PPh$_3$)Br (0.1)	87
4	Br		Cu(phen)(PPh$_3$)Br (0.2)	43
5	I		Cu(phen)(PPh$_3$)Br (0.1)	85
6	Br		Cu(phen)(PPh$_3$)Br (0.1)	53
7	I		Cu(phen)(PPh$_3$)Br (0.1)	75
8	Br		Cu(phen)(PPh$_3$)Br (0.2)	18
9	I		Cu(phen)(PPh$_3$)Br (0.1)	79
10	I		Cu(phen)(PPh$_3$)Br (0.2)	72

[a] Except for entry 2. [b] Isolated yield after flash chromatography.

tions with structurally defined, air-stable copper(I) complex Cu(phen)(PPh$_3$)Br as reported by Venkataraman's group for

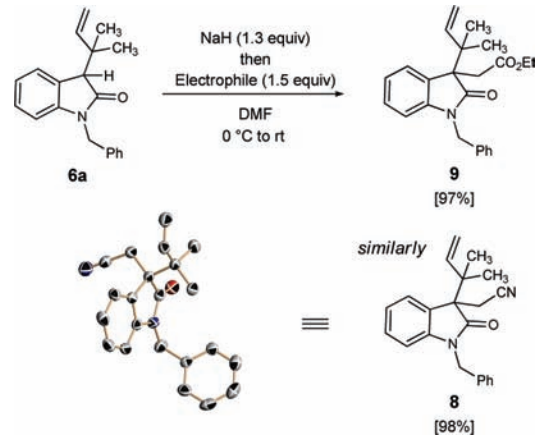
(9) (a) For a general discussion on this variant of the Claisen rearrangement, see: Gradl, S. N.; Trauner, D. In *Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; pp 367−396. (b) Metz, P.; Mues, C. *Tetrahedron* **1988**, *44*, 6841. (c) Metz, P.; Mues, C.; Schoop, A. *Tetrahedron* **1992**, *48*, 1071. (d) Metz, P.; Linz, C. *Tetrahedron* **1994**, *50*, 3951. (e) For chiral auxiliary-based enantioselection, see: Metz, P.; Hungerhoff, B. *J. Org. Chem.* **1997**, *62*, 4442. Hungerhoff, B.; Metz, P. *Tetrahedron* **1999**, *55*, 14941.

aryl-nitrogen bond formation proved superior.[13] Following this method, 10% Cu(phen)(PPh_3)Br, reverse-prenylated amide **5c**, and Cs_2CO_3 as a base in toluene gave desired cyclization product **6a** in 87% yield (Table 2) after 72 h. Using **6a** as a prototypical case, this amidation protocol was optimized for the catalyst, base, and duration of reaction (see Supporting Information). The use of K_3PO_4 as a base proved to be superior for the synthesis of the products **6b**−**e**, which were obtained in moderate to good yields following the same approach[14] (Table 2).

To illustrate the applicability of the developed synthetic method for the further derivatization of tertiary C3 reverse-prenylated oxindoles, we attempted an oxindole alkylation at the neopentyl C3 center. Because of the steric congestability caused by the C3 substitution, we anticipated this transformation to be challenging. Gratifyingly, formation of the corresponding enolate proved feasible upon treatment of **6a** with sodium hydride in DMF at room temperature, and the alkylation of the enolate with bromoacetonitrile and ethyl bromoacetate proceeded to completion at room temperature within 30 min to give the products **8** and **9** in 98% and 97% yield, respectively (Scheme 2). Oxindole **8** crystallized upon dissolving the purified compound in minimum amount of THF followed by vapor phase trituration with hexanes. The structure of oxindole **8** deduced from the X-ray diffraction data is shown below (Scheme 2). It is interesting to note that the C−N portion of the nitrile aligns, at least in the solid state, in an antiperiplanar orientation with the C═O π bond of the oxindole carbonyl group, understandably due to possible minimization of the dipole moment. As reverse-prenylated oxindoles occupy a significant chemical space in medicine, we anticipate the ease of crystallizability shown by oxindole **8** to bode well for ensuing ligand−receptor docking studies.

In conclusion, we have developed a novel, elegant branch-selective synthesis of oxindole and indene privileged scaffolds. 2,2-Dimethyl indene **7** has been obtained from intermediate **5b** by a 5-*exo-trig* Heck cyclization reaction. Conditions were studied for the conversion of acyclic reverse-prenylated amides **5** to tertiary C3 reverse-prenylated oxindoles **6a**−**e** via Cu(I)-catalyzed intramolecular aryl amidation. Finally, oxindole **6a** underwent enolate alkylation with corresponding electrophiles to give quaternary C3 reverse-prenylated adducts **8** and **9**. In addition to accessing stereodivergent ring skeletons from readily available precursors, the development of stereocontrolled syntheses of tertiary and quaternary C3 reverse-prenylated natural products is currently ongoing and will be reported in due course.

Scheme 2. Enolate Alkylation of **6a**; Direct Access to C3 Quaternary Oxindoles



Acknowledgment. Authors thank NSF (CHE 0541766) for funding provided for support of X-ray diffractometer. R.V. and V.A.I. deeply thank Prof. Gregory P. Tochtrop (CWRU) for highly insightful comments during the preparation of this work. R.V. thanks Dr. Jonathan Karty (IU) and Ms. Angela Hansen (IU) for ESI-MS data collection. Authors thank Ms. Deepti Sharma (CWRU) for efforts to collect X-ray of **8** and ESI-MS data collection and analysis. R.V. thanks Dr. Karthikeyan Thandavamurthy (CWRU) for proofing and editorial support. N.D. thanks the Republic of Turkey for a graduate fellowship.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

OL1012372

(10) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.
(11) For a review, se: e Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.
(12) (a) Klapars, A.; Antila, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (d) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78.
(13) (a) Gujadhur, R.; Bates, C.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791 The complex could be easily synthesized in good yield by a reported protocol (ref 15a) in two steps from copper (II) bromide, triphenylphosphine and 1,10-phenanthroline.
(14) Moriwaki, K.; Satoh, K.; Takada, M.; Ishino, Y.; Ohno, T. *Tetrahedron Lett.* **2005**, *46*, 7559.