ORGANIC LETTERS

2007
Vol. 9, No. 23
4821−4824

Gold-Catalyzed Hydroarylation of Allenes: A Highly Regioselective Carbon–Carbon Bond Formation Producing Six-Membered Rings

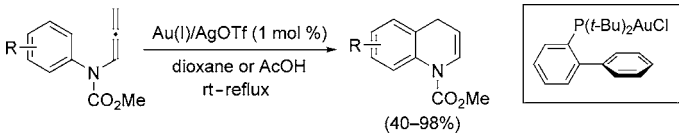
Toshiaki Watanabe, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

hohno@pharm.kyoto-u.ac.jp; nfujii@pharm.kyoto-u.ac.jp

Received September 5, 2007

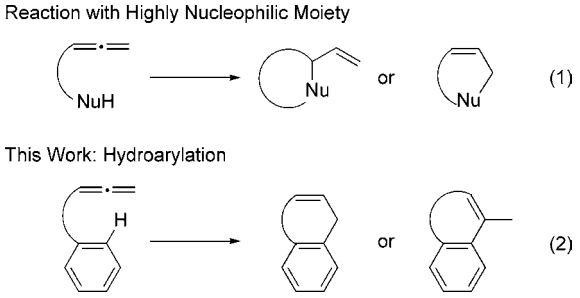
ABSTRACT



Gold-catalyzed intramolecular hydroarylation of allenic anilines and phenols offers an efficient route to dihydroquinoline and chromene derivatives under mild reaction conditions. The hydroarylation takes place at the terminal or central allenic carbon depending on the substrate structure, leading to a highly selective formation of six-membered rings.

Transition-metal-catalyzed cycloisomerization of allenes has received considerable attention as an atom-economical transformation.[1] Compared to the well-documented cyclization reactions with a highly nucleophilic functionality such as nitrogen, oxygen, or active methylene (Scheme 1, eq 1), cycloisomerization through functionalization of an aromatic C−H bond (hydroarylation; eq 2) has scarcely been investigated. Nagao and co-workers reported endo-mode hydroarylation of allenic ketones promoted by Lewis acids such as BF_3·OEt_2 or $TiCl_4$.[2] Cycloisomerization of aryl allenic ethers mediated by a stoichiometric amount of mercury(II) trifluoroacetate to form regioisomeric six-membered rings has also been shown.[3−5]

Scheme 1. Transition-Metal-Catalyzed Reaction of Allenic Compounds



As a part of a program directed toward the development of novel methods for cyclization of allenic compounds,[6] we

(1) For recent reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (c) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (d) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (e) Hashmi, A. S. K. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 877−923.

(2) (a) Nagao, Y.; Lee, W.-S.; Kim, K. *Chem. Lett.* **1994**, 389. (b) Nagao, Y.; Lee, W. S.; Komaki, Y.; Sano, S.; Shiro, M. *Chem. Lett.* **1994**, 597. (c) Nagao, Y.; Lee, W. S.; Jeong, I.-Y.; Shiro, M. *Tetrahedron Lett.* **1995**, *36*, 2799. (d) Lee, W. S.; Jeong, I.-Y.; Shiro, M.; Sano, S.; Nagao, Y. *Tetrahedron Lett.* **1997**, *38*, 611.

(3) Balasubramanian, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 6641.

(4) For related intermolecular reactions, see: (a) De Renzi, A.; Panunzi, A.; Saporito, A.; Vitagliano, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 993. (b) Kido, Y.; Yonehara, F.; Yamaguchi, M. *Tetrahedron* **2001**, *57*, 827.

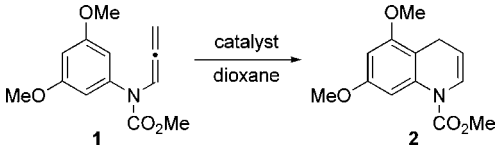
(5) For related electrocyclization, see: (a) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 3274. (b) Brandsma, L.; Nedolya, N. A.; Verkruijsse, H. D.; Owen, N. L.; Li, D.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 6905. (c) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 5295.

10.1021/ol702179n CCC: $37.00
Published on Web 10/09/2007

planned to investigate the catalytic hydroarylation of allenes in the presence of a gold salt. Gold-catalyzed reaction is of current interest for various transformations[7] including nucleophilic cyclization of allenes shown in eq 1.[8−10] Although 6-*exo* cyclization of allenes with a highly nucleophilic indole[11a] or pyrrole ring[11b] and 5-*endo* indene formation from acetoxy-substituted allenes[12] have been already reported, there have been no precedents for gold-catalyzed 6-*endo* hydroarylation of allenes that can be applied to a variety of allenes and aromatic rings.[13] Herein we report hydroarylation of allenes derived from anilines and phenols, leading to dihydroquinolines and chromenes, which are widely found as core structures of natural products and other biologically active compounds.[14,15]

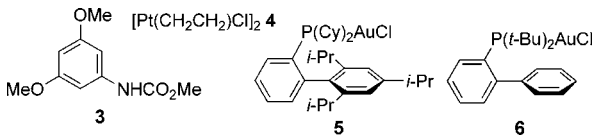
First, screening of transition-metal catalysts for the hydroarylation of allenes was performed by use of *N*-allenylaniline **1**, which was easily prepared by propargylation of *N*-protected 3,5-dimethoxyaniline followed by *t*-BuOK-mediated isomerization.[16,17] Results are summarized in Table 1 (for more details, see Supporting Information). Whereas $Pd(OAc)_2$, $CuBr_2$, and AgOTf afforded a mixture of undesired products such as **3** as well as the recovered starting material (entries 1−3), AuCl, $AuCl_3$, and $PtCl_2$ gave the desired cyclization product **2** in low to good yields (29−77%, entries 4−6). The reaction with a platinum complex **4**/*p*-$(CF_3C_6H_4)_3P$[11a] completed in only 5 min, affording **2** in 57% yield (entry 7). While the reaction with $(Ph_3P)AuCl$/AgOTf gave **2** in moderate yield (56%, entry 8), a gold complex **5**[18] in the presence of AgOTf gave a more promising result (86% yield, entry 9). Among the catalysts investigated, gold complex **6**[18] with AgOTf was most effective in producing the desired product **2** in 98% yields (entry 10). By lowering the catalyst loading to 1 mol %, a comparable result was obtained (96% yield, entry 11). Considering that combination of the gold and silver salts is important (compare entries 3 and 11), a cationic gold complex would be the reactive species for this transformation.

Table 1. Screening of Transition-Metal Catalysts[a]



entry	catalyst (mol %)	temp (°C)	time (min)	yield[b] 2	yield[b] 3
1	$Pd(OAc)_2$ (5)	80	360		14
2	$CuBr_2$ (5)	80	60		12
3	AgOTf (5)	25	720	trace	
4	AuCl (5)	80	90	29[d]	
5	$AuCl_3$ (5)	25	30	58	
6	$PtCl_2$ (5)	80	360	77	
7	**4**/P(*p*-$CF_3C_6H_4)_3$ (5)	25	5	57	
8	$(Ph_3P)AuCl$/AgOTf (5)	25	10	56	
9	**5**/AgOTf (5)	25	10	86	
10	**6**/AgOTf (5)	25	5	98	
11	**6**/AgOTf (1)	25	5	96	

[a] Reactions were carried out in dioxane at room temperature. [b] Yields based on ^1H NMR. [c] 13% of **1** was recovered.



We next investigated the cyclization of various *N*-allenylaniline derivatives based on the optimized conditions (Table 1, entry 11) for the allenylaniline **1**. Results are summarized in Table 2. Disubstituted electron-rich aniline derivatives **7** and **9** gave the desired products **8** and **10**, respectively (both in 88% yield after hydrogenation; entries 2 and 3). While the reaction of monomethoxyaniline derivative **11** provided **12** as the sole product (90% yield after

(6) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. (b) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904. (c) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255. (d) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647. (e) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749. (f) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744. (g) Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113.

(7) For recent reviews, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, *2*, 167. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (e) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

(8) For the reaction with oxygen nucleophiles, see: (a) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (b) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485. (c) Widenhoefer, R. A.; Zhang, Z. *Angew. Chem., Int. Ed.* **2007**, *46*, 283. (d) Piera, J.; Krumlinde, P.; Strübing, D.; Bäckwall, J.-E. *Org. Lett.* **2007**, *9*, 2235. (e) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868.

(9) For the reaction with nitrogen nucleophiles, see: (a) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (b) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (c) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. See also ref 11a.

(10) For the reaction with sulfur nucleophiles, see: Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897.

(11) (a) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (b) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (c) Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935.

(12) Marion, N.; Díez-González, S.; de Frémont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647.

(13) For hydroarylation of other related substrates, see: (a) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (b) Hashmi, A. S. K.; Grundl, L. *Tetrahedron* **2005**, *61*, 6231. (c) Hashmi, A. S. K.; Blanco, M. C. *Eur. J. Org. Chem.* **2006**, 4340.

(14) (a) Hamann, L. G.; Higuchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X. N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 623. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939.

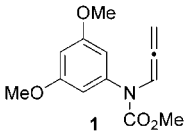
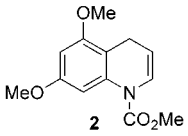
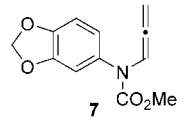
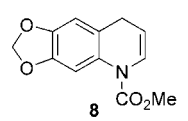
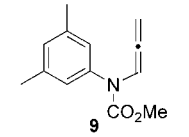
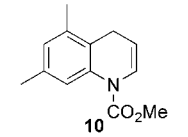
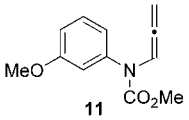
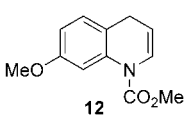
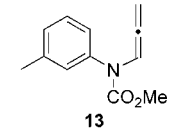
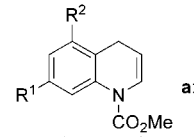
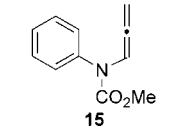
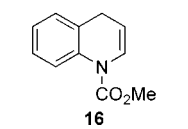
(15) (a) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894. (b) Shezad, N.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **2001**, *42*, 323. (c) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (d) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435. (e) Bennasar, M. L.; Roca, T.; Monerris, M.; Garcia-Diaz, D. *J. Org. Chem.* **2006**, *71*, 7028.

(16) (a) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

(17) Unfortunately, synthesis of internal allenes by this approach was difficult.

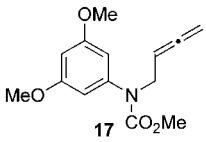
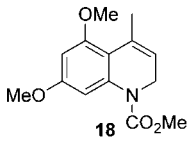
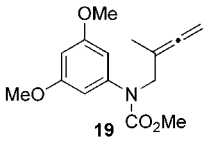
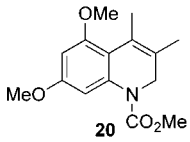
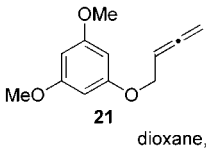
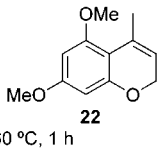
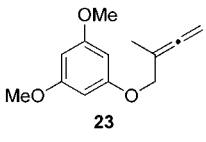
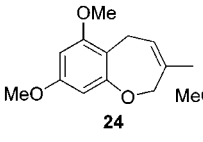
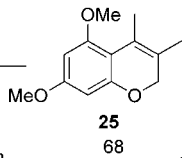
(18) Complexes **5** and **6** were prepared according to Lopez, S.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

Table 2. Au-Catalyzed Cyclization of *N*-Allenylaniline Derivatives[a]

entry	substrate	conditions	product	yield(%)[b]
1	 **1**	25 °C, 5 min	 **2**	92
2	 **7**	60 °C, 1 h	 **8**	88
3	 **9**	60 °C, 1 h	 **10**	88
4	 **11**	100 °C, 1 h	 **12**	90
5	 **13**	reflux, 3 h	 **14a** (R^1 = Me, R^2 = H) **14b** (R^1 = H, R^2 = Me)	72 **a**:**b** = 61:39[c]
6	 **15**	reflux, 3 h[d]	 **16**	40

[a] Conditions: 1 mol % of **6**/AgOTf in dioxane. [b] Isolated yields after hydrogenation since most of the cyclized products with a 1,4-dihydroquinoline moiety were relatively unstable and gradually decomposed during isolation. [c] Ratio was determined by ^{1}H NMR. [d] 3 mol % of **6**/AgOTf was used.

Table 3. Au-Catalyzed Cyclization of *N*-(Buta-2,3-dienyl)aniline Derivatives and Their Phenol Analogues

entry	substrate	conditions[a]	product	yield (%)[b]
	 **17**		 **18**	
1		dioxane, 3 mol %, 60 °C, 1.5 h		63
2		AcOH, 3 mol %, 25 °C, 1 h		82
3		AcOH, 1 mol %, 60 °C, 1 h		85
	 **19**		 **20**	
4		AcOH, 3 mol %, 25 °C, 4 h		75
5		AcOH, 1 mol %, 60 °C, 1 h		74
	 **21**		 **22**	
6		dioxane, 1 mol %, 60 °C, 1 h		98[c]
	 **23**		 **24**  **25**	
7		dioxane, 1 mol %, 60 °C, 4 h		68 (**24**:**25** = 59:41)[d]
8		dioxane/AcOH (4:1), 1 mol %, 60 °C, 3.5 h		99 (**24**:**25** = 48:52)[d]

[a] Solvent, loading of **6**/AgOTf, reaction temperature, and reaction time. [b] Isolated yield. [c] Isolated yield after hydrogenation. [d] Ratios were determined by ^{1}H NMR.

hydrogenation) by regioselective cyclization at the less hindered aromatic carbon (entry 4), 3-methylaniline derivative **13** afforded **14** as a mixture of regioisomers (**14a**:**14b** = 61:39, entry 5). As anticipated, unsubstituted derivative **15** showed lower reactivity; however, ca. 40% yield of the desired product **16** was obtained by refluxing in dioxane with 3 mol % of the catalyst. In all cases examined, reaction at the terminal allenic carbon resulted solely in formation of a six-membered ring.

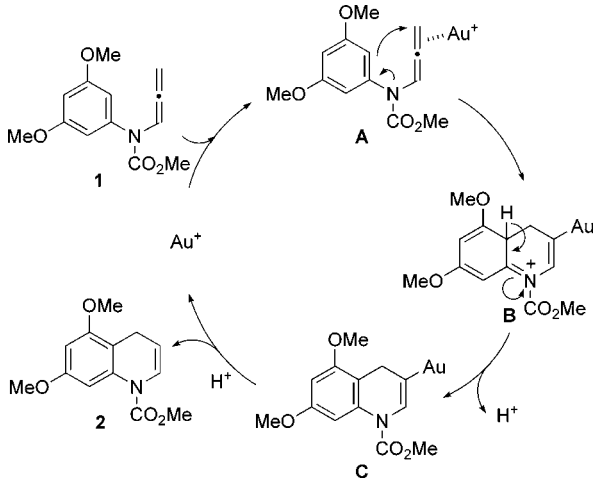
We proceeded to explore the scope of this cyclization (Table 3). Although the reactivity of *N*-(buta-2,3-dienyl)-aniline derivative **17** was relatively low even with 3 mol % of the catalyst at 60 °C (entry 1), use of AcOH[8d] instead of dioxane dramatically enhanced its reactivity to afford **18** in 82% yield at room temperature (entry 2).[19] When the reaction was performed in AcOH at 60 °C, 85% yield of **18** was obtained with 1 mol % of the catalyst (entry 3). A similar result was obtained with disubstituted allene derivative **19** (entries 4 and 5). Phenol derivative **21** has a sufficient reactivity in dioxane, affording **22** in 98% yield (after hydrogenation) with 1 mol % of the catalyst (entry 6). These are remarkable examples of transition-metal-catalyzed hydroarylation of unactivated allenes at the central carbon.[20] Interestingly, the reaction of phenol-derived methylated allene **23** in dioxane slightly favors seven-membered ring formation to give dihydrobenzo[*b*]oxepine derivative **24**, produced by hydroarylation at the terminal allenic carbon, as well as the six-membered ring **25** (**24**:**25** = 59:41, entry 7). Although the reaction of **23** in AcOH as the sole solvent gave a mixture of unidentified products, addition of a small amount of AcOH to dioxane gave **24** and **25** in 99% combined yield (entry 8).

A proposed mechanism for the hydroarylation of allenes is shown in Scheme 2. The allene is activated by coordination to cationic gold and undergoes electrophilic aromatic substitution with the electron-rich arene to give vinyl-gold complex **B**, which is deprotonated to produce the neutral vinyl-gold intermediate **C**. Cleavage of the gold−carbon

(19) The reaction did not proceed in AcOH without using the gold catalyst.

(20) Such reactions with Hg(II) reagent have already been reported; see ref 3. For the reactions of activated allenes, see refs 2 and 4b.

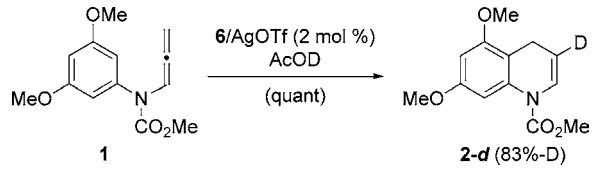
Scheme 2. Proposed Mechanism



bond by the proton generated in the previous step affords **2** and regenerates the cationic gold catalyst.

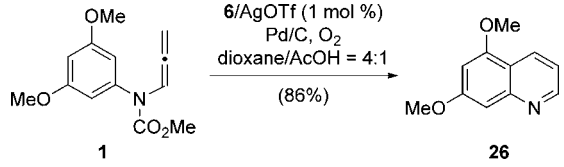
In order to reveal the role of AcOH as the activator of hydroarylation,[8d] we conducted deuterium experiments using AcOD (Scheme 3). As expected, the reaction of *N*-allenylaniline **1** in AcOD gave **2-*d*** (83%-d) in quantitative yield (Scheme 3). This result strongly suggests that the high reactivity in AcOH is attributed to acceleration of the protonation step from **C** (Scheme 2).

Scheme 3. Deuterium Experiment Using AcOD



Finally, one-pot synthesis of quinoline was investigated (Scheme 4).[21] When the reaction of the allenylaniline **1** was conducted in the presence of a catalytic amount of Pd/C under O_2, the desired quinoline **26** was obtained in 86% yield. This one-pot reaction clearly demonstrates the utility of the present hydroarylation of allenes as a convenient tool for construction of heterocycles.

Scheme 4. Synthesis of Quinoline by One-Pot Reaction



In conclusion, we have developed a novel efficient route from allenic compounds to dihydroquinolines and chromenes by means of gold-catalyzed intramolecular hydroarylation. We are now exploring ways to broaden the scope of the reaction, for example, to include various arenes.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists (A) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, 21st Century COE Program "Knowledge Information Infrastructure for Genome Science", and the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

Supporting Information Available: Representative experimental procedure, as well as ^{1}H and ^{13}C NMR spectra for the novel compounds. This material is available free of charge via Internet at http://pubs.acs.org.

OL702179N

(21) For a related reaction, see: Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *J. Org. Chem.* **2006**, *71*, 7028.