ORGANIC LETTERS

2012
Vol. 14, No. 4
1130–1133

Au(I)-Catalyzed Intramolecular Hydroamination of the Fluorinated *N*′-Aryl-*N*-Propargyl Amidines: Mild Conditions for the Synthesis of 2-Fluoroalkyl Imidazole Derivatives

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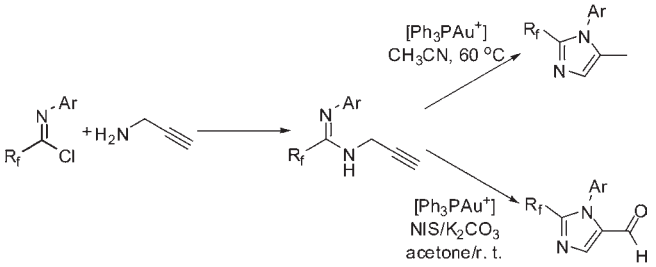
Received January 11, 2012

ABSTRACT



The gold(I)-catalyzed synthesis of 2-fluoroalkyl imidazole derivatives was developed. Catalyzed by gold(I), propargyl amidines underwent a 5-*exo*-*dig* cyclization to afford 2-fluoroalkyl-5-methyl imidazoles. Also, 2-fluoroalkyl imidazole-5-carbaldehydes were obtained in the presence of NIS. A mechanism investigation manifested the probable process and the carbonyl oxygen derived from O_2.

Reactions catalyzed by gold have attracted much attention.[1−3] Compared to other transition-metal catalyzed reactions, these reactions are more economical and mild. Among them, the most important reaction pattern is the addition of nucleophiles to C−C multiple bonds.[4] In 1987, Utimoto reported the first evidence of intramolecular hydroamination of 5-yn-1-amine, which delivered tetrahydropyridines by isomerization from enamine.[5] Since then, investigation in this area has been growing rapidly. In 2000, Hashmi demonstrated that even carbonyl oxygen can serve as a nucleophile.[6] Based on these findings, we wish to report our work on cyclization of fluorinated *N*′-aryl-*N*-propargyl amidines catalyzed by gold(I) to synthesize 2-fluoroalkyl imidazole derivatives.

Hacksell reported that when bases were used as a catalyst, propargyl amides might be cyclized to the

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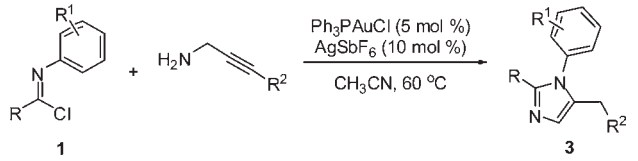
(1) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (c) Li, Z.; Brown, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (d) Jiménez-Núñez, E.; Echavarren, E. *Chem. Rev.* **2008**, *108*, 3326–3350. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (f) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (g) Hashmi, A. S. K.; Rudolp, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (h) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782.

(2) (a) Thompson, D. T. *Top. Catal.* **2006**, *38*, 231–240. (b) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386–388. (c) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem.—Eur. J.* **2008**, *14*, 11310–11313. (d) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112–3115. (e) Zhang, G.; Cui, L.; Wang, L.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475. (f) Brenzovich, W. E.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5519–5522. (g) Melhado, A. D.; Brenzovich, W. E.; Lackner, J. A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885–8887. (h) Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4450–4454. (i) Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 14293–14300.

10.1021/ol3000525
Published on Web 02/03/2012

corresponding oxazoles.[7] However, fluorinated propargyl amidines were unstable under strong basic conditions, which often resulted in low yield. This cyclization also could be accomplished by using a Brønsted acid;[8] the yield of 2-fluoroalkyl imidazoles was only 30%, but both long reaction times and high temperatures were required. To our delight, an excellent yield was obtained under mild conditions by gold(I) catalysis via 5-*exo*-*dig* cyclization. We envisioned that 2-fluoroalkyl imidazoles can be obtained in one pot from fluorinated imidoyl chlorides.[9] With $Ph_3PAuCl/AgSbF_6$ as the catalyst and CH_3CN as the solvent, an optimized yield of 87% was obtained when the reaction was carried out at 60 °C (see Table S1 in the Supporting Information (SI)).

Table 1. Au(I)-Catalyzed the Formation of 2-Fluoroalkyl Imidazoles[a]



entry	R	R^1	R^2	yield/%[b]
1	$-CF_3$	H	H	**3a/78**
2	$-CF_3$	*p*-OCH_3	H	**3b/87**
3	$-CF_3$	*o*-CH_3	H	**3c/89**
4	$-CF_3$	*p*-NO_2	H	**3d/72**
5	$-CF_3$	*p*-COOEt	H	**3e/68**
6	$-CF_3$	Naphthyl	H	**3f/85**
7	$-CF_3$	*m*-CF_3	H	**3g/68**
8	$-CF_3$	*o*-Cl	H	**3h/85**
9	$-CF_2Br$	*p*-CH_3	H	**3i/74**
10	$-CF_2Br$	*m*-CH_3	H	**3j/79**
11	$-CF_2Br$	*o*-CH_3	H	**3k/79**
12	$-CF_2Br$	*p*-CF_3	H	**3l/65**
13	$-CF_2Br$	*p*-CN	H	**3m/63**
14	$-CF_2Br$	*p*-Cl	H	**3n/60**
15	$-CF_2Br$	*o*-Br	H	**3o/76**
16	$-CF_2H$	H	H	**3p/87**
17	$-CF_2CF_3$	H	H	**3q/62**
18	$-CF_3$	*p*-OCH_3	Ph	**3r/73**[c]
19	-COOEt	H	H	**3s/67**
20	$-CF_3$	*p*-OCH_3	$AuPPh_3$	**3t**

[a] Reaction conditions: Ph_3PAuCl (5 mol %)/$AgSbF_6$ (10 mol %), fluoronated imidoyl chlorides (1.0 mmol), propargyl imine (2.5 mmol), CH_3CN (3.5 mL), 60 °C. [b] Isolated yield. [c] The product is 1,4-dihydropyrimidine.

Under the optimized conditions, a variety of fluorinated imidoyl chlorides were tested (Table 1). This reaction has good compatibility to various functional groups, and most of them offered the expected products in good yields. Substrates with electron-donating groups on the benzene ring gave good yields (Table 1, entry 2). Electron-withdrawing groups would lead to lower yields (Table 1, entries 4, 5, 7). Compared to the electronic effect, steric hindrance of the substituents had little influence on the yield (Table 1, entries 3, 6, 8). The effect of fluoroalkyl (R_f) was also examined; substrates with $-CF_2Br$ often had lower yields, and the corresponding products decomposed easily (Table 1, entries 9–15). With 3-phenyl propargyl amine as the starting material, the reaction intermediate of propargyl amidine underwent a 6-*endo*-*dig* cyclization to generate 1,4-dihydropyrimidine **3r** in 73% yield (Table 1, entry 18). As we expected, nonfluorinated imidazole **2s** was obtained in moderate yield when a nonfluorinated substrate was used (Table 1, entry 19).

In this reaction, cationic Au(I) is thought to be coordinated with C–C triple bonds to form a vinyl-gold intermediate. We tried to prepare this intermediate, and an alkylgold(I) species **3t** that differed from Hashmi's work was obtained.[10,11] Treated **3t** with protontic acid solvent failed to generate imidazole **3b**, but decomposed.

We speculated that a gold(I) intermediate in the reaction may be a zwitterionic species. Coordinated with cationic Au(I), C–C triple bonds accept the attack of amidinonyl nitrogen to afford intermediate **A**. Affected by R_f, **A** isomerizes to the more stable imidazole **B** by an H-1,3 shift first. In this process, the nitrogen atom in imidazole is protonated all the way, which favors H–Au (I) exchange to give the final product imidazole **3** which is accomplished in one pot (Scheme 1).

(3) (a) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927–7930. (b) Hopkinson, M. N.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Synlett* **2010**, *18*, 2737–2742. (c) de Haro, T.; Nevado, C. *Adv. Synth. Catal.* **2010**, *352*, 2767. (d) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 7247–7252. (e) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220–4223. (f) de Haro, T.; Nevado, C. *Chem. Commun.* **2011**, *47*, 248–249.

(4) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (b) Kang, J. E.; Lee, E. S.; Park, S. I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431–7433. (c) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023–5026. (d) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325–328. (e) Lee, E. S.; Yeom, H. S.; Hwang, J. H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503–3507. (f) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (g) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482. (h) Belting, V.; Krause, N. *Org. Biomol. Chem.* **2009**, *7*, 1221–1225. (i) Garcia, P.; Malacria, M.; Aubert, C.; Gandon, V.; Fensterbank, L. *ChemCatChem* **2010**, *2*, 493.

(5) (a) Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297–300. (b) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975–978.

(6) (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285–2288. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590–3593.

(7) (a) Nilsson, B. M.; Hacksell, U. J. *Heterocycl. Chem.* **1989**, *26*, 269–275. (b) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. J. *J. Med. Chem.* **1992**, *35*, 285.

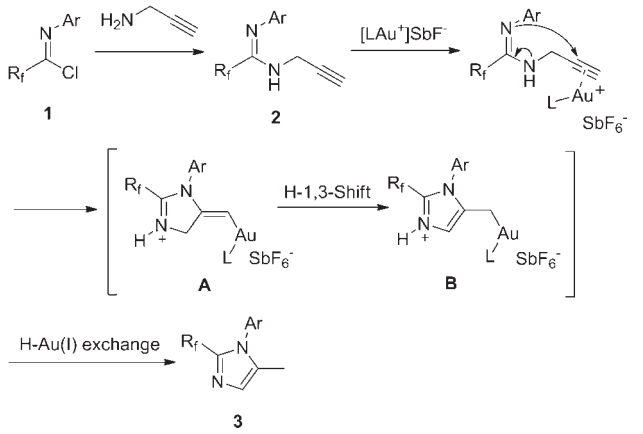
(8) (a) Eloy, A. D. *Chim. Ther.* **1973**, *8*, 437. (b) Street, L. J.; Baker, R.; Castro, J. L.; Chambers, M. S.; Guiblin, A. R.; Hobbs, S. C.; Matassa, V. G.; Reeve, A. J.; Beer, M. S. *J. Med. Chem.* **1993**, *36*, 1529. (c) Pan, Y. M.; Zheng, F. J.; Lin, H. X.; Zhan, Z. P. *J. Org. Chem.* **2009**, *74*, 3148–3151. (d) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075–5087.

(9) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58* (1), 32–35.

(10) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391–4394. (b) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763–1766. (c) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudoiph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2010**, *16*, 956–963.

(11) (a) Hashmi, A. S. K.; Schuster, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8247–8249. (b) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 8243–8246.

Scheme 1. Proposed Mechanism for the Formation of 2-Fluoroalkyl Imidazoles



In order to functionalize 2-fluoroalkyl imidazoles, we next investigated the possibility of coupling fluorinated propargyl amidines with electrophiles.[12] In the presence of $Ph_3PAuCl/AgBF_4$, propargyl amidine **2b** was treated with NIS. To our surprise, imidazole-5-carbaldehyde formed instead of the expected product 5-iodomethyl imidazole. An excellent yield of 98% was obtained with 1.0 equiv of K_2CO_3 added in acetone at room temperature (see Table S2 in the SI).

The transformations with NIS proceeded without any difficulty to afford the desired products in good to excellent yields (Table 2). Both electron-rich and -poor propargyl amidines are reactive. Functional groups, including ester and cyano (Table 2, entries 6, 8), as well as sterically hindered ones (Table 2, entries 4, 5, 7) are tolerated. However, substrates with $-CF_2Br$ were found to be inefficient because of its instability (Table 2, entries 8, 9). This method is also suitable for nonfluorinated substrates. Nonfluorinated aldehyde **4l** was obtained in good yield under similar conditions (Table 2, entry 12). Unfortunately, our method is only suitable for substrates with a terminal alkyne group. The substrate that possesses a group of Ph at an alkyne terminus converted to 5-iodo-1,4-dihydropyrimidine **4m** in moderate yield (Table 2, entry 13).

Studies were undertaken to explore a feasible mechanism. When **3t** was treated with NIS in acetone, no aldehyde **4b** was detected. When the reaction was carried out in anhydrous acetonitrile under a nitrogen atmosphere, 5-iodomethyl imidazole **4n**, the probable intermediate, was not detected, but **4b** formed in lower yield.

Gold(I) catalyst was considered to just act as a Lewis acid to active C−C triple bonds promoting the reaction with NIS; no gold(I) intermediate formed in the reaction. Further investigation revealed that this transformation can take place in the absence of gold(I) catalyst with a low

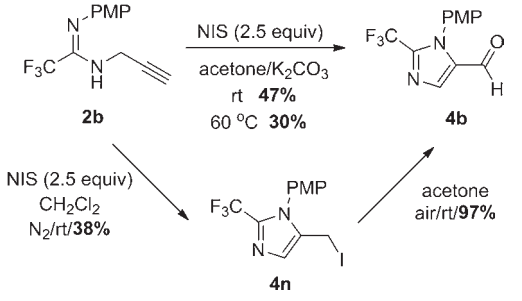
(12) (a) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147–2150. (b) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592–597.

Table 2. Au (I)-Catalyzed Synthesis of Imidazole-5-carbaldehyde[a]

entry	R	R^1	R^2	yield/%[b]
1	$-CF_3$	H	H	**4a/98**
2	$-CF_3$	*p*-OCH_3	H	**4b/94**
3	$-CF_3$	*p*-Cl	H	**4c/82**
4	$-CF_3$	*o*-CH_3	H	**4d/89**
5	$-CF_3$	*o*-I	H	**4e/87**
6	$-CF_3$	*p*-COOEt	H	**4f/95**
7	$-CF_3$	*o*-Ph	H	**4g/90**
8	$-CF_2Br$	*p*-CN	H	**4h/57**
9	$-CF_2Br$	*o*-CF_3	H	**4i/60**
10	$-CF_2H$	H	H	**4j/81**
11	$-CF_2CF_3$	H	H	**4k/93**
12	-COOEt	H	H	**4l/86**
13	$-CF_3$	*p*-OCH_3	Ph	**4m/74**[c]

[a] Reaction conditions: Ph_3PAuCl (5 mol %)/$AgBF_4$ (10 mol %), fluorinated propargyl amidines (1.0 mmol), NIS (2.5 mmol), K_2CO_3 (1.0 mmol), acetone (10 mL), rt, in the absence of light. [b] Isolated yield. [c] The product is 5-iodo-1,4-dihydropyrimidine.

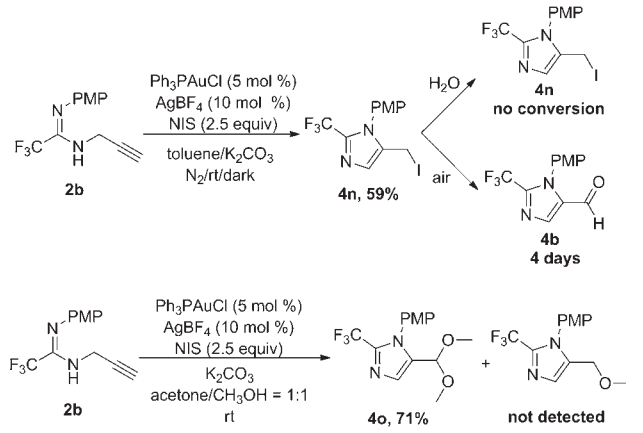
Scheme 2. Reactions without Au(I) Catalyst



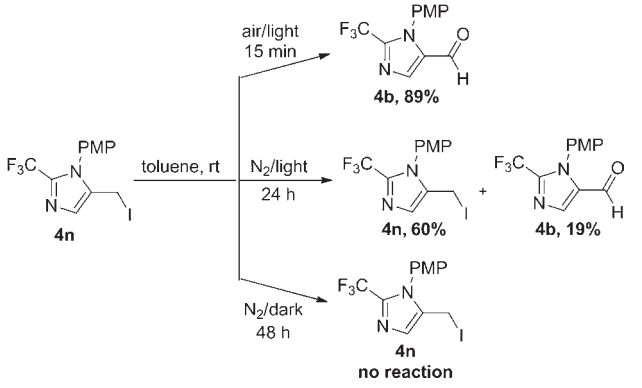
yield. **4n** was found to convert to **4b** in excellent yield (Scheme 2). Based on these above-mentioned observations, we understood the plausible pathway for this transformation.

Both O_2 and H_2O could be the source of carbonyl oxygen. In order to determine which one deserves the credit, we carried out parallel experiments as follows: **4n** was prepared first and then divided into two portions; the first portion with distilled water added was inactive, while the second portion of **4n** was converted to **4b** when exposed to dry air. Moreover, acetal **4o** was obtained when CH_3OH was added to the standard system, no 5-methoxylmethyl imidazole was detected (Scheme 3). On the basis of these results, the carbonyl oxygen was considered to come from O_2.

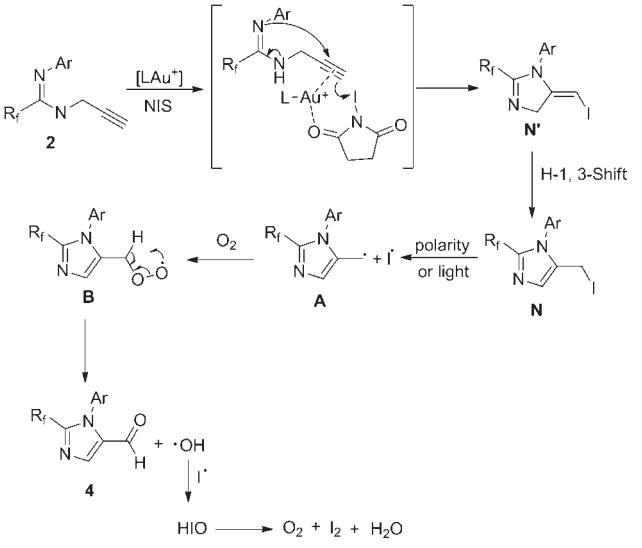
Scheme 3. Effect of O_2 and H_2O on Carbonylation



Scheme 4. Proposed Mechanism for Carbonylation



Scheme 5. Another Proposed Mechanism for Carbonylation



Light plays another significant role, when the reaction was carried out in nonpolar solvent. When exposed to light and air, **4n** was converted to **4b** efficiently in toluene. Under N_2, only a 19% yield of **4b** was formed (which might have resulted from the residual O_2 mixed in N_2), and 60% of **4n** was recovered after 24 h. In both experiments, I_2 was formed in the reaction. In the absence of light, **4n** was a relatively stable compound under N_2 in nonpolar solvent (Scheme 4).

Based on these results, a possible mechanism is proposed in Scheme 5. Two steps were involved in this transformation. The first step: propargyl amidine **2** activated by [Ph_3PAu^+] reacts with NIS to afford 5-iodomethyl imidazole **N**. The second step may be a radical process.[13] The C−I bond in **N** dissociates into radical intermediate **A** and an iodine radical. In the presence of O_2, **A** converts to peroxy-intermediate **B**. Aldehyde **4** forms by means of removal of a hydroxyl radical from **B**. The hydroxyl radical combines with the iodine radical to afford HIO, which decomposes into O_2, I_2, and H_2O.

In summary, we have developed a simple but efficient method for the synthesis of 2-fluoroalkyl imidazole derivatives. Catalyzed by Au(I), the substrates with a terminal alkyne group undergo a 5-*exo*-*dig* cyclization to afford imidazole derivatives. It is worth mentioning that this method is also suitable for nonfluorinated substrates. Also, 1,4-dihydropyrimidine was obtained from the substrates with a substituent at the alkyne terminus by 6-*endo*-*dig* cyclization. Research carried out on the reaction mechanism revealed the general process of these transformations and confirmed that carbonyl oxygen is derived from O_2.

Acknowledgment. This work was supported by the National Science Foundation of China (No. 21172239)

Supporting Information Available. Full experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Wang, H. H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678–5681.

The authors declare no competing financial interest.