100 Gram Scale Synthesis of a Key Intermediate of Matrix Metalloproteinase Inhibitor in a Continuous-Flow System Based on a Copper-Free Sonogashira Reaction Using an Ionic Liquid as a Catalyst Support

Takahide Fukuyama,*[a] Md. Taifur Rahman,[a] Yukihito Sumino,[b] Ilhyong Ryu*[a]

[a] Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

[b] Quality, Safety and Regulatory Affairs Management Division, SHIONOGI & Co., LTD., Osaka, Osaka 541-0045, Japan
Fax +81(72)2549695; E-mail: fukuyama@c.s.osakafu-u.ac.jp

Received: 30.05.2012; Accepted after revision: 28.06.2012

Abstract: The key intermediate of matrix metalloproteinase (MMP) inhibitor was synthesized using a flow microreactor for a copper-free Sonogashira coupling reaction in an ionic liquid. The ionic liquid [emim]NTf_2 was used as a solvent and a catalyst support. A 100 g scale synthesis was achieved in combination with a flow-extraction/catalyst-recycling system, in which the ionic liquid containing the palladium catalyst was continuously recycled.

Key words: microreactor, flow reaction, ionic liquids, palladium, Sonogashira coupling, matrix metalloproteinase inhibitor

In the last decade, rapidly evolving microreaction technology based on tiny microchannels, typically tens to hundreds of μm wide and/or deep, has attracted broad attention in organic synthesis, because of its great potential as a reaction apparatus for chemical reactions, since it allows efficient mixing, efficient heat and mass transfer, precise residence time control, and high operational safety.[1,2] Microreaction systems when coupled with a continuous-flow system have good potentials as a tool for chemical production.[3] We recently reported the synthesis of matrix metalloproteinase (MMP) inhibitor **1**[4] (Figure 1) via a Pd/Cu-catalyzed Sonogashira coupling reaction in DMF using an automated microreactor system (Scheme 1).[5] Time-saving optimization of flow-reaction conditions was accomplished using our home-made automated microreactor system, and the optimal conditions could be immediately applied to a 100 gram scale production. In this system, however, the recovery and the reuse of the Pd/Cu catalysts has yet to be realized, since the used solvent DMF, created a homogeneous solution.

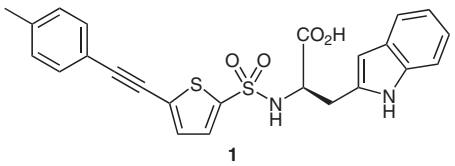
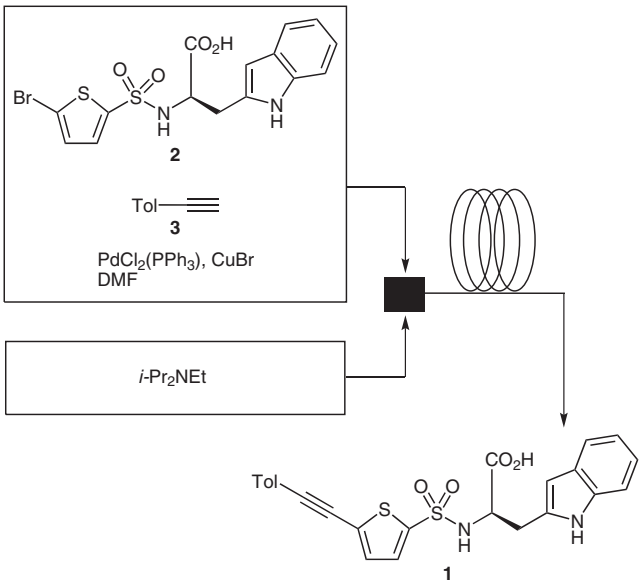
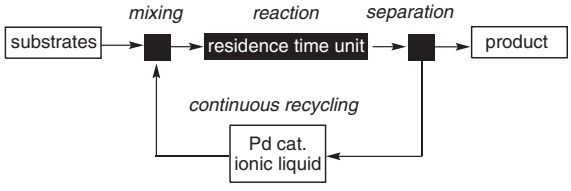


Figure 1 Matrix metalloproteinase (MMP) inhibitor **1**

Ionic liquids (IL) can act as excellent supports for transition-metal NHC complexes, and we have reported a continuous microflow system for carrying out a copper-free Sonogashira coupling reaction,[6] the Mizoroki–Heck reaction,[7] and a carbonylative Sonogashira reaction[8] using low viscosity IL such as [bmim]NTf_2 as a reaction medium and a palladium N-heterocyclic carbene complex (Pd–NHC) as a catalyst, in which IL can serve as a catalyst support.[9,10] We also developed a continuous catalyst-recycling system by connecting with a microextraction system, which allowed the 100 g scale synthesis of butyl cinnamate via the Mizoroki–Heck reaction.[7] Then, we embarked on the construction of a bench-top production facility to synthesize 100 grams of **1** using such a catalyst-/medium-recycling protocol (Scheme 2).



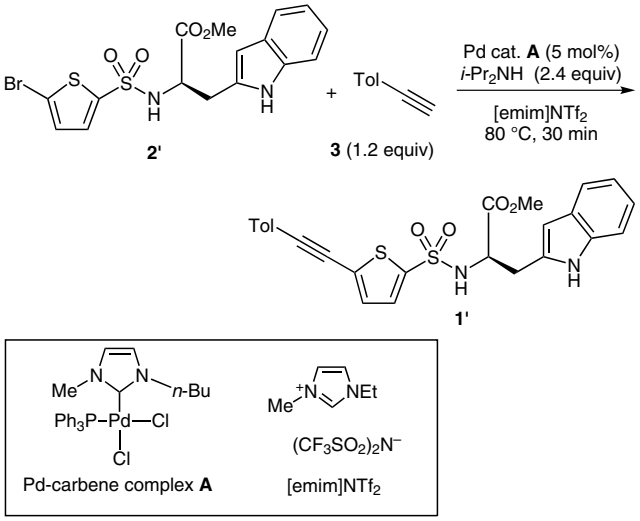
Scheme 1 Microflow synthesis of MMP inhibitor **1**[5]



Scheme 2 Concept of a continuous catalyst-recycling system using an IL as a reaction medium

SYNLETT 2012, 23, 2279–2283
Advanced online publication: 14.08.2012
DOI: 10.1055/s-0031-1290456; Art ID: ST-2012-U0463-L

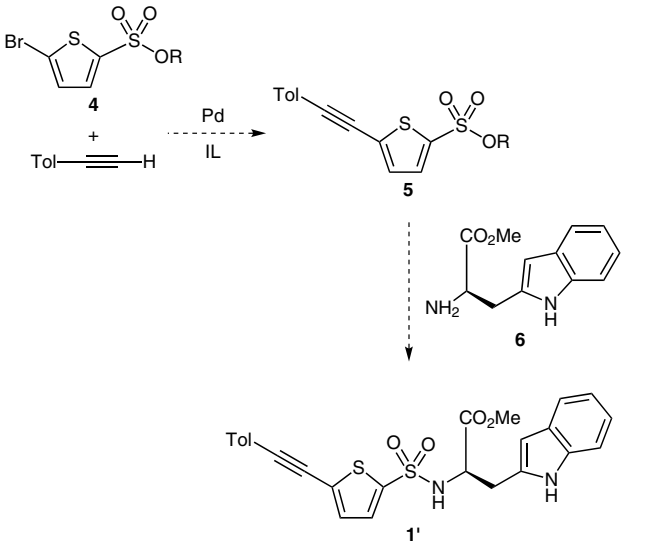
To investigate the viability of a microflow version of the above-mentioned step using IL as a solvent, we initially checked a batch reaction (Scheme 3). Methyl ester **2′** was used as the Sonogashira precursor, which was prepared by the reaction of 5-bromo-2-thiophenesulfonyl chloride and methyl ester of tryptophan. The batch reaction was carried out using [emim]NTf_2 as a reaction medium and Pd–NHC complex **A** as a catalyst. Although the reaction was completed within 30 minutes to give the desired product **1′**, this reaction was unsuitable as a flow system for the following reasons: (i) the solubility of **2′** in a [emim]NTf_2 solution containing (*p*-tolyl)acetylene (**3**) and diisopropylamine was quite low, and (ii) the product could not be extracted efficiently from a polar IL layer by a nonpolar solvent such as cyclohexane.



Scheme 3

To circumvent such limitations, we had to reconsider another strategy suitable for the microflow system using an IL. We planned to use sulfonyl ester derivatives **4** (Scheme 4), since the sulfonyl ester **4** should meet the following requirements: (i) sulfonyl ester derivatives **4** would be soluble with **3** and amine to give a homogeneous solution; (ii) the copper-free Sonogashira reaction would be successful in IL; (iii) the coupling product **5** would be separated from the IL layer by an extraction using nonpolar or less polar solvent; and, (iv) the coupling product **5** would react readily with a methyl ester of tryptophan **6** to give the desired precursor **1′**.

Several sulfonyl esters were tested, and we found pentafluorophenyl ester **4a** to have the most potential as a substrate. Thus, we examined the reaction of **4a** with **3** in [emim]NTf_2 in the presence of *i*-Pr_2NEt as a base. When these compounds were mixed at room temperature, a homogeneous solution resulted. During and after the reaction (80 °C to r.t.), the mixture remained homogeneous. The coupling product **5** could be extracted by 30% diethyl ether in cyclohexane. After silica gel chromatography, compound **5** was obtained in 70% yield (Scheme 5). The



Scheme 4 Modified protocol for synthesis of MMP inhibitor's precursor **1′**

obtained coupling product **5** reacted with compound **6** in the presence of bases at 90 °C for 18 hours to give a 78% yield of **1′** (Scheme 6).

Other sulfonyl esters, such as ethyl ester **4b** and neopentyl ester **4c**, were found unsuitable for this protocol (Figure 2). The Sonogashira coupling reaction of **4b** with **3** gave a complex mixture. In the case of **4c**, while the coupling product was obtained in good yield, the reaction with **6** was very sluggish.

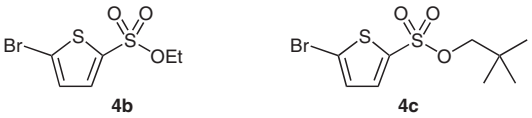
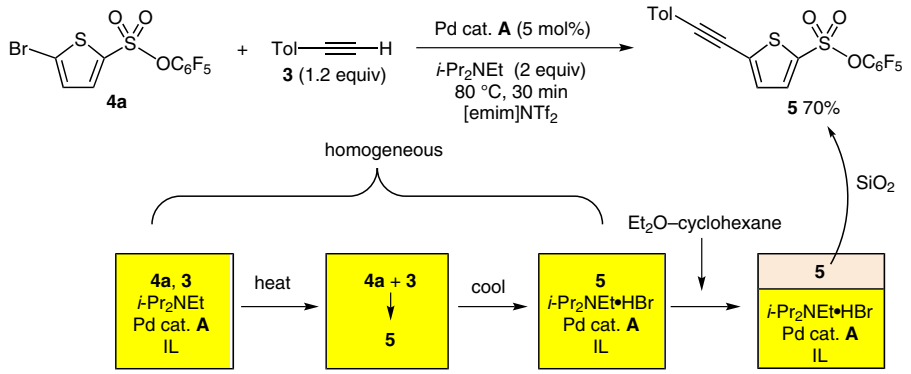


Figure 2

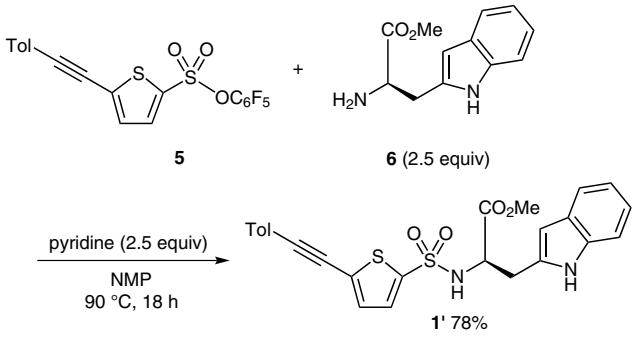
We then investigated the reaction of **4a** with **3** in a microflow system using a T-shaped mixer (1000 μm i.d.) and a stainless steel tube (1000 μm i.d. × 50 cm) under varied conditions. These results are summarized in Scheme 7. The reaction at 80 °C with two minutes residence time gave a 17:83 mixture of **4a** and **5**. A higher reaction temperature (95 °C) resulted in complete conversion. A similar result was obtained with a shorter residence time (1.75 min), while a 1.5 minutes residence time resulted in a remaining portion of the starting substrate **4a**. In all cases, the reaction mixture obtained had a higher viscosity because of the formation of an ammonium salt byproduct. Since a high viscous IL solution might not flow smoothly and could overburden the pumps, we tested the reaction in a mixed-flow system, in which 1.5 M potassium carbonate aqueous solution was mixed with the reaction mixture to remove the ammonium salt quickly from the IL layer. Fortunately, prior addition of an aqueous solution to the reaction mixture did not interfere with the formation of **5**.



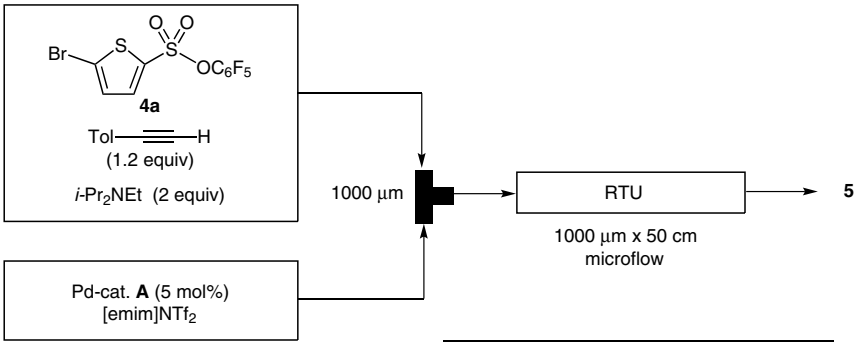
Scheme 5 Batch synthesis of **5**

With these promising results in hand, we then constructed a continuous production system (Scheme 8). For the production, a 2000 μm i.d. tube was used as a residence time unit to increase productivity. Thus, a homogeneous mixture of **4a**, **3**, and *i*-Pr_2NEt was mixed with the IL containing the Pd–NHC complex using a T-shaped mixer (600 μm i.d.), followed by mixing with 1.5 M potassium carbonate aqueous solution. The resulting mixture was introduced into a 2000 μm i.d. tube that was heated at 95 °C for 1.75 minutes (residence time). The reaction mixture was removed from the residence time unit after 1.75 minutes and mixed with 30% diethyl ether in cyclohexane using another T-shaped mixer (400 μm i.d.). The entire mixture was then passed through another tube (2000 μm i.d. × 25 cm, 40 °C) to ensure extraction. The exiting reaction mixture was collected by a Y-shaped container where it was partitioned in three distinct phases: an IL layer (bottom), an aqueous layer (middle), and an organic layer containing the product (top). The IL layer was continuously fed into the reaction system using another pump. The process was run for 5.5 hours, and consumed 269 mmol of the starting material **4a**. After workup, 103 g of the desired compound **5** was obtained (86% yield).

In summary, the key intermediate of matrix metalloproteinase (MMP) inhibitor was successfully synthesized via a flow copper-free Sonogashira reaction in [emim]NTf_2 as a solvent. Sulfonyl ester **4a** was found to be a suitable substrate for the present continuous-microflow synthesis. A 100 gram scale synthesis of **5**, the precursor for matrix metalloproteinase (MMP) inhibitor **1**, was achieved using the continuous catalyst-recycling system.



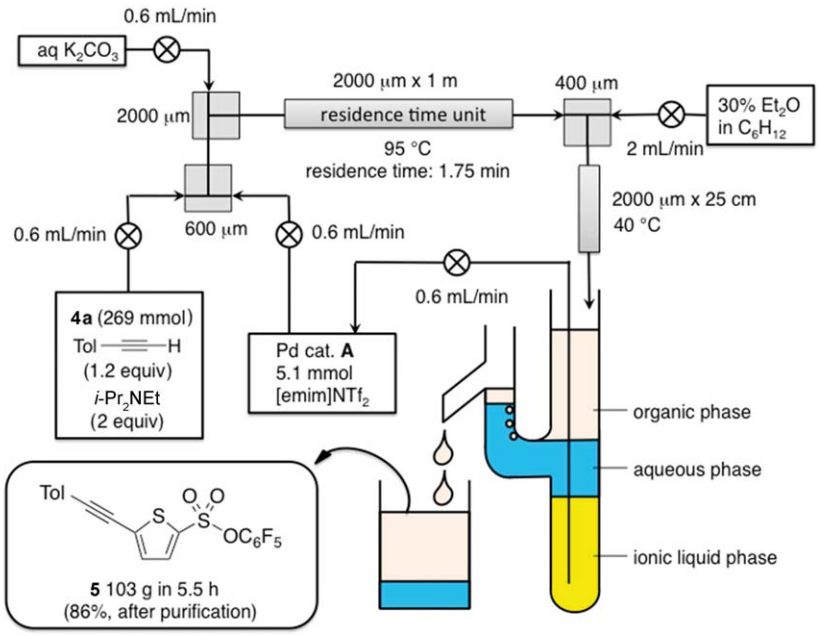
Scheme 6



temp	residence time	4/5[a]
80 °C	2 min	17:83
95 °C	2 min	0:100
95 °C	1.75 min	0:100
95 °C	1.5 min	5:95

[a] determined by ^{1}H NMR analysis

Scheme 7 Microflow synthesis of **5**



Scheme 8 Synthesis of **5** on a 100 gram scale using a continuous-flow and catalyst-/solvent-recycling system

Procedure for the 100 Gram Scale Synthesis of 5

A mixture of **4a** (332.9 mmol, 136.2 g), (*p*-tolyl)acetylene (**3**, 400 mmol, 46.5 g), and *i*-Pr_2NEt (674 mmol, 87.1 g) was loaded into a container. The Pd catalyst **A** (5.1 mmol, 3.0 g) in [emim]NTf_2 (75 mL) was loaded into another container. The flow rates were adjusted to 0.6 mL/min for both the substrates and the Pd-catalyst solution, and the two solutions were mixed in a T-shaped micromixer (MiChS α-600, 600 μm i.d.). The mixture was mixed with 5 M K_2CO_3 aq solution in a T-shaped mixer with a 2000 μm i.d., and the mixture was then fed into the residence time unit (2000 μm i.d. × 1 m, residence time: 1.75 min), which was heated at 95 °C. The reaction mixture was mixed with 30% Et_2O in cyclohexane in another T-shaped mixer (MiChS α-400, 400 μm i.d.), and the entire mixture was passed through another tube (2000 μm i.d. × 25 cm, 40 °C) for extraction. The exiting reaction mixture was collected in a Y-shaped flask, where it was partitioned in three distinct phases. The IL layer containing the Pd catalyst was pumped to the catalyst solution. This system was operated for 5.5 h and consumed 269 mmol of the sulfonyl ester **4a**. The organic phase was separated from the aqueous phase and dried over $MgSO_4$. After evaporation, a light brown solid was obtained. The solid was washed with 10% Et_2O–hexane to remove any remaining **3** to give 90 g of **5** (mp 116–118 °C, ^{1}H NMR analysis indicates a purity of >95%.). The washing (Et_2O + hexane) was evaporated, and the resulting residue was purified by SiO_2 column chromatography (Et_2O) providing another 13 g of pure **5** (mp 119–119.5 °C) (combined weight of **5** = 103 g, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 4.1 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 7.68 (d, *J* = 4.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 79.8, 99.2, 118.3, 129.5, 131.4, 131.8, 132.3, 135.2, 136.2, 136.9 (m), 139.0 (m), 140.3, 141.4 (m), 143.4 (m). IR (neat): 2253.4, 1520 cm^{-1}. MS (EI): *m/z* = 408 [M$^+$]. HRMS: *m/z* calcd for $C_{10}H_2BrF_5O_3S_2$ [M$^+$]: 407.8549; found: 407.8540.

Acknowledgment

T.F. thanks the Industrial Technology Research Grant Program from the New Energy and Industrial Technology Development Organization (NEDO) (05A33715d). I.R. acknowledges a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from the Ministry of Education, Culture, Sports, and Technology (MEXT) of Japan.

References

(1) (a) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, **2008**. (b) Hessel, V.; Renken, A.; Schouten, J. C.; Yoshida, J.-I. *Micro Process Engineering*; Wiley-VCH: Weinheim, **2009**. (c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (d) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem.–Eur. J.* **2008**, *14*, 7450. (e) Lin, W.-Y.; Wang, Y.; Wang, S.; Tseng, H.-R. *Nano Today* **2009**, *4*, 470. (f) McMullen, J. P.; Jensen, K. F. *Annu. Rev. Anal. Chem.* **2010**, *3*, 19. (g) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, 675. (h) Yoshida, J. *Chem. Rec.* **2010**, *10*, 332. (i) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583.

(2) For a review of our work, see: Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151.

(3) For selected examples, see: (a) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scheres, S.; Schönfeld, F.; Werner, B. *Org. Process Res. Dev.* **2004**, *8*, 511. (b) Wakami, H.; Yoshida, J. *Org. Process Res. Dev.* **2005**, *9*, 787. (c) Iwasaki, T.; Kawano, N.; Yoshida, J. *Org. Process Res. Dev.* **2006**, *10*, 1126. (d) Tanaka, K.; Motomatsu, S.; Koyama, K.; Tanaka, S.; Fukase, K. *Org. Lett.* **2007**, *9*, 299.

(4) Tamura, Y.; Watanabe, F.; Nakatani, T.; Yasui, K.; Fuji, M.; Komurasaki, T.; Tsuzuki, H.; Maekawa, R.; Yoshioka, T.; Kawada, K.; Sugita, K.; Ohtani, M. *J. Med. Chem.* **1998**, *41*, 640.

(5) Sugimoto, A.; Fukuyama, T.; Rahman, M. T.; Ryu, I. *Tetrahedron Lett.* **2009**, *50*, 6364.

(6) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.

(7) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477.

(8) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236.

(9) For recent reviews, see: (a) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, **2008**. (b) Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107, 21*, 83. (c) Plechkova, N. V.; Seddon, K. R. *Chem. Soc. Rev.* **2008**, *37*, 123. (d) Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508. (e) Isambert, N.; del Mar Sanchez Duque, M.; Plaquevent, J.-C.; Génisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347. (f) Petkovic, M.; Seddon, K. R.; Rebelo, L. P. N.; Pereira, C. S. *Chem. Soc. Rev.* **2011**, *40*, 1383.

(10) For our reports on coupling reactions using ionic liquids, see: (a) Liu, S. F.; Fukuyama, T.; Sato, M. *Synlett* **2004**, 1814. (b) Fukuyama, T.; Yamaura, R.; Ryu, I. *Can. J. Chem.* **2005**, *83*, 711. (c) Rahman, M. T.; Fukuyama, T.; Ryu, I.; Suzuki, K.; Yonemura, K.; Hughes, P. F.; Nokihara, K. *Tetrahedron Lett.* **2006**, *47*, 2703. (d) Fukuyama, T.; Inouye, T.; Ryu, I. *J. Organomet. Chem.* **2007**, *692*, 685. (e) Fukuyama, T.; Rahman, M. T.; Maetani, S.; Ryu, I. *Chem. Lett.* **2011**, *40*, 1027.

