ORGANIC LETTERS

2012
Vol. 14, No. 8
2046–2049

# The Regioselective Switch for Amino-NHC Mediated C–H Activation of Benzimidazole via Ni–Al Synergistic Catalysis

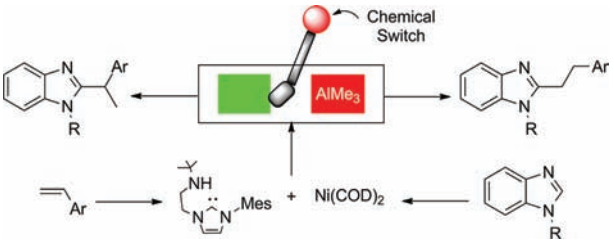
**Wei-Chun Shih,[†] Wen-Ching Chen,[†] Ying-Chieh Lai,[†,‡] Ming-Shiuan Yu,[†,§] Jhao-Jhe Ho,[†,‡] Glenn P. A. Yap,[∥] and Tiow-Gan Ong*[,†]**

*Institute of Chemistry, Academia Sinica, Nangang, Taipei, Taiwan, Republic of China, Department of Chemistry and Biochemistry, National Chung Cheng University, Taiwan, Republic of China, Taipei Municipal University of Education, Taiwan, Republic of China, and Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States*

*tgong@chem.sinica.edu.tw*

**Received March 6, 2012**

## ABSTRACT




**We have disclosed a new mode of a chemically regioselective switch for C–H bond functionalization of benzimidazole derivatives via a cooperative effect invoked by Ni–Al bimetallic catalysis to create a steric requirement for obtaining the linear product of styrene insertion. Yet, excluding the $AlMe_3$ cocatalyst switches the reaction toward branch selectivity.**

The past decade has witnessed the rapid rise of C–H activation and functionalization, which would obviate the additional steps and limitations associated with the preparation of functionalized substrates in the catalytic coupling process.[1] From the perspective of synthetic and catalytic applications, the next conceptual hurdle would be a facile ability to control the site selectivity. Yu and Gaunt have addressed this challenge by relying on specific directing groups on arenes to facilitate the site selectivity.[2] Alternatively, the design and preparation of the ligand based on steric and electronic modulation can be deployed to achieve the targeted selectivity in a spatially precise manner.[3] However, these strategies may have their Achilles' heel, as both methods required myriads of functional group additions and laborious synthetic manipulations.

[†] Academia Sinica.
[‡] National Chung Cheng University.
[§] Taipei Municipal University of Education.
[∥] University of Delaware.

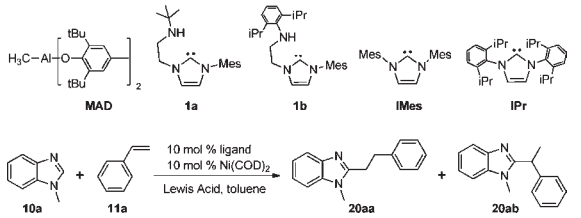
(1) Selected review papers: (a) Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J. Q. *Science* **2010**, *327*, 315–319. (b) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (f) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca, N.; Maestri, G. *Coord. Chem. Rev.* **2010**, *254*, 456–469. (g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (i) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (j) Albrecht, M. *Chem. Rev.* **2010**, *110*, 576–623. (k) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (h) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205.

(2) (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (b) Ciana, C. L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458–462. (c) Wang, X.; Leow., D.; Yu, J.-Q. J. A. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.

(3) (a) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964–6967. (b) Sanford, M. S.; Lyons, T. W.; Hull, K. L. *J. Am. Chem. Soc.* **2011**, *133*, 4455–4464. (c) Sanford, M. S.; Hickman, A. H. *ACS Catal.* **2011**, *1*, 170–174. (d) Yoshikai, N.; Gao, K. *J. Am. Chem. Soc.* **2011**, *133*, 400–402.

10.1021/ol300570f 
**Published on Web 04/05/2012**

**Table 1.** Screening and Optimization of Hydroheteroarylation of Styrene with Benzimidazole (**10a**)[a]




| entry | ligand | Lewis acid (mol %) | time (h) | temp (°C) | yield (%) | ratio (**20aa:20bb**) |
|---|---|---|---|---|---|---|
| 1 | **1a** | $AlMe_3$ (20) | 15 | 130 | 80 | 12:1 |
| 2 | **1a** | Alls (20) | 15 | 130 | 4 | 0:100 |
| 3 | **1a** | $AlCl_3$(20) | 15 | 130 | 63 | 4:1 |
| 4 | **1a** | MAD (20) | 15 | 130 | 61 | 3:1 |
| 5 | **1a** | $ZnEt_2$ (20) | 15 | 130 | 58 | 1:2 |
| 6 | **1a** | $ZnCl_2$ (20) | 15 | 130 | 42 | 2:5 |
| 7 | **1a** | $AlMe_3$ (10) | 15 | 100 | 85 | 100:0 |
| 8 | **1a** | $AlMe_3$ (10) | 2 | 100 | 85 | 100:0 |
| 9 | **1a** | $AlMe_3$ (10) | 15 | 70 | 46 | 100:0 |
| 10 | **1b** | $AlMe_3$ (10) | 15 | 100 | 70 | 100:0 |
| 11 | **IMes** | $AlMe_3$ (10) | 15 | 100 | 77 | 100:0 |
| 12 | **IPr** | $AlMe_3$ (10) | 15 | 100 | 68 | 100:0 |

[a] The reactions were carried out using **10a** (0.5 mmol) and **11a** (0.75 mmol) and determined by GC yield with $^1$H NMR analysis based on **10a** as the limiting reagent.

Tandem cooperative Lewis acid/transition metal catalysis has attracted more interest in recent years[4−7] for its unique ability to enhance the rate or to control selectivity when compared with its respective transition metal catalyst. For instance, Hartwig[4a] and Nolan[4b] et al. have uncovered Lewis acid like $AlCl_3$ and $BEt_3$ accelerating Pd-mediated reductive elimination reactions. Similarly, Knochel reported the direct Pd-catalyzed arylation of methyl-substituted pyridine promoted by $ZnCl_2$, $Sc(OTf)_3$, and $BF_3\cdot OEt_2$ with regioselectivity.[4c]

The use of nickel, a benign and low-cost transition metal, to mediate the functionalization of C−H bonds is less common compared to its palladium counterpart.[5−8] More recently, our group[7] and Nakao, Hiyama[5c] utilized more benign and economical bifunctional catalysts consisting of Ni and a Lewis acid to derivatize the C−H bond of pyridine in a *para* selective manner. Encouraged by our previous results, we proceeded to explore new types of Ni−Al catalytic reactions involving the C−H bond functionalization of heterocyclic substrates. At this juncture, we envisage that addition of $AlMe_3$ would act cooperatively in a tandem fashion with nickel to invoke a new selectivity. Herein we describe the development of a reactivity strategy for Ni-catalyzed heteroaromatic C−H bond functionalization based on using a chemical switch like $AlMe_3$ that selectively generates linear or branched adducts.

We begin our screening process by examining the C−H bond functionalization of 1-methylbenzimidazole **10a** with styrene **11a** involving the catalytic mixture of amino-NHC **1a**,[7,9] $Ni(COD)_2$, and various Lewis acids in toluene as outlined in Table 1. We first probed a range of Lewis acids (entries 1−6), and among those examined, $AlMe_3$ was highly effective in yield with high linear selectivity. For example, the addition of a 20% loading of $AlMe_3$ in toluene at 130 °C afforded a 80% yield of hydroheteroarylation products with a major linear isomer **20aa** (entry 1). Employing a very bulky (2,6-*t*-$Bu_2$-4-Me-$C_6H_2O)_2AlMe$ (MAD)[10] as a Lewis acid gave a lower yield (61%) and linear selectivity (**20aa:20ab** = 3:1, entry 4). Finally, use of other zinc-based Lewis acids including $ZnEt_2$ and $ZnCl_2$ resulted disappointing outcomes with poor yields and regioselectivities (entries 5−6).

To our delight, an excellent yield of reaction (85%) could also be achieved with a 10% loading of $AlMe_3$ at a lower temperature of 100 °C with no detection of the other branched regioisomeric product **20ab** (entry 7). More importantly, the reaction time could be reduced to 2 h without compromising the yield of the reaction (entry 8). It should be noted that **IMes** and **IPr** NHC ligands could also perform in a similar mode of reaction with yields of 77% and 68% (entries 11−12), respectively. Lastly, a control experiment with no carbene ligand was also performed, obtaining no detectable amount of coupling adduct.

With the optimized reaction conditions in hand, we examined the scope of the reaction with several styrene derivatives (Table 2). High linear regioselectivities and excellent yields were observed for 4-methyl styrene (**11b**), 4-methoxy styrene (**11c**), 4-fluoro styrene (**11d**), and 4-phenyl-styrene (**11h**) derivatives (entries 2−4, 8), illustrating the nonsensitivity of the reaction toward the electronic perturbation.

Likewise, introduction of a methyl substitution at different positions of the styrene (para, meta, and ortho,

(4) (a) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734–7735. (b) Huang, J. K.; Haar, C. M.; Nolan, S. P.; Marcone, J. E.; Moloy, K. G. *Organometallics* **1999**, *18*, 297–299. (c) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686–7690.

(5) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996–7. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449. (c) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666–13668. (d) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070–1. (e) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267. (f) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451–4454. (g) Kanyiva, K. S.; Loberm, F.; Nakao, Y.; Hiyama, T. *Tetrahedron Lett.* **2009**, *50*, 3463–3466.

(6) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071.

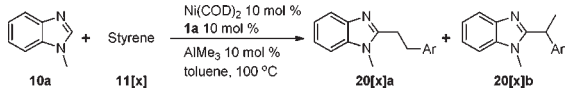
(7) Tsai, C. C.; Shih, W. C.; Fang, C. H.; Li, C. Y.; Ong, T.-G.; Yap, G. P. A *J. Am. Chem. Soc.* **2010**, *132*, 11887–11889.

(8) Recent representative literatures related to Ni mediated C−H bond activation: (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169–172. (b) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061–3064. (c) Ogata, K.; Atsuumi, Y.; Shimada, D.; Fukuzawa, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5896–5899. (d) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955. (e) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775–779. (f) Kumar, P.; Louie, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10768–1−769. (g) Qu, G. R.; Xin, P. Y.; Niu, H. Y.; Wang, D. C.; Ding, R. F.; Guo, H. M. *Chem. Commum.* **2011**, 11140–11142. (h) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113–10122.

(9) Li, C.-Y.; Kuo, Y.-Y; Tsai, J.-H.; Yap, G. P. A; Ong, T.-G. *Chem.—Asian J.* **2011**, *6*, 1520–1524.

(10) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.

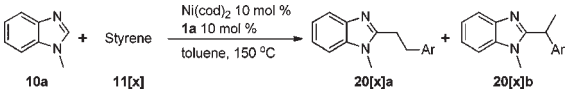
**Table 2.** Hydroheteroarylation of Various Styrenes with Benzimidazole in Presence of $AlMe_3$ Additive[a]




| entry | 11[x] | time (h) | major product | isolate yield of 20[x]a+20[x]b (%) | linear/brach |
|---|---|---|---|---|---|
| 1 | 11a | 2 | 20aa | 85 | 100:0 |
| 2 | 11b | 2 | 20ba | 88 | 100:0 |
| 3 | 11c | 15 | 20ca | 96 | 100:0 |
| 4 | 11d | 2 | 20da | 93 | 100:0 |
| 5 | 11e | 15 | 20eb | 66 | 45:55 |
| 6 | 11f | 2 | 20fa | 70 | 93:7 |
| 7 | 11g | 2 | 20ga | 87 | 100:0 |
| 8 | 11h | 15 | 20ha | 90 | 96:4 |

[a] The reactions were carried out using **10a** (0.5 mmol) and styrene (0.75 mmol) and determined by $^1$H NMR analysis with isolated yield based on **10a** as the limiting reagent. Method: 10 mol % $AlMe_3$, 10 mol % $Ni(COD)_2$, 10 mol % **1a** ligand.

**Table 3.** Hydroheteroarylation of Various Styrenes with Benzimidazole without $AlMe_3$ Additive[a]




| entry | 11[x] | time (h) | product | isolate yield of 20[x]b (%) | linear/brach |
|---|---|---|---|---|---|
| 1 | 11a | 15 | 20ab | 70 | 0:100 |
| 2 | 11b | 15 | 20bb | 50 | 0:100 |
| 3 | 11c | 15 | 20cb | 69 | 0:100 |
| 4 | 11d | 15 | 20db | 67 | 0:100 |
| 5 | 11e | 15 | 20eb | 72 | 0:100 |
| 6 | 11f | 15 | 20fb | 98[b] | 0:100 |
| 7 | 11g | 15 | 20gb | 93[b] | 0:100 |
| 8 | 11h | 15 | 20hb | 97[b] | 0:100 |

[a] The reactions were carried out using **10a** (0.5 mmol) and styrene (0.75 mmol) and determined by $^1$H NMR analysis with isolated yield based on **10a** as the limiting reagent. Method: 10 mol % $Ni(COD)_2$, 10 mol % **1a** ligand. [b] 10 mol % **IMes** was used instead of **1a**.

entries 2, 6−7) did not affect the rate or selectivity of the reaction. 2-Vinylnapthalene **11e** also participated in the hydroheteroarylation reaction to give a moderate yield (66%) of an equal amount of linear and branched isomers. We attributed the lack of selectivity in **11e** to a more effective $\pi$-conjugated stabilization invoked by the naphthalene ring. Finally, the most striking demonstration of this utility is that exclusion of $AlMe_3$ completely switches the selectivity back to the branched product as shown in Table 3, albeit with a lower average yield in comparison to the reaction containing Lewis acid addition. Interestingly, Bergman and Ellman also reported that the linear product from styrene was afforded for the C−H bond functionalization of benzimidazole via cooperative catalysis of Rh/Brønsted acid, albeit in low yield.[11] In addition, Yoshikai has also employed different ligands to modulate cobalt-mediated regioselective switchable hydroarylation of styrenes on 2-phenyl-pyridine.[3d]

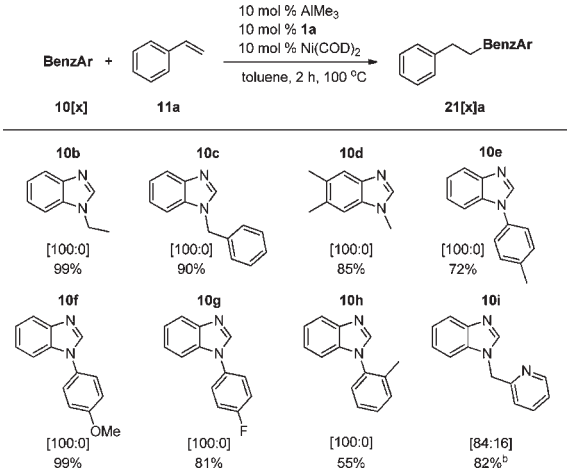
As illustrated in Scheme 1, we can also expand the utility of this catalytic manifold to other benzimidazole derivatives. High levels of linear selectivity and yield were consistently observed with benzimidazole bearing ethyl (**10b**) and benzyl (**10c**) groups at the nitrogen side arm or methyl groups on the aryl ring (**10d**). Such a method can also be extended to other aryl benzimidazole derivatives with high efficiency and selectivity (**10e**−**g**), but 1-(*o*-tolyl) benzimidazole (**10h**) gave a moderate yield (55%), which is perhaps due to an unfavorable steric hindrance at the *ortho* position. Finally, omitting the $AlMe_3$ additive in the reaction mixture switches the selectivity toward the branched isomer (see Scheme 2).

At this stage, the reaction pathway of each basic step remains to be ascertained by detailed mechanistic studies. Based on the previous literature precedent,[3d,5,12] we postulate that the preliminary hydroarylation mechanism proceeds through the following steps: (1) oxidative addition of the C−H bond to the Ni center to afford Ni−H species **4**, (2) insertion of styrene into the Ni−H bond,

(11) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964–13965. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202–3203.

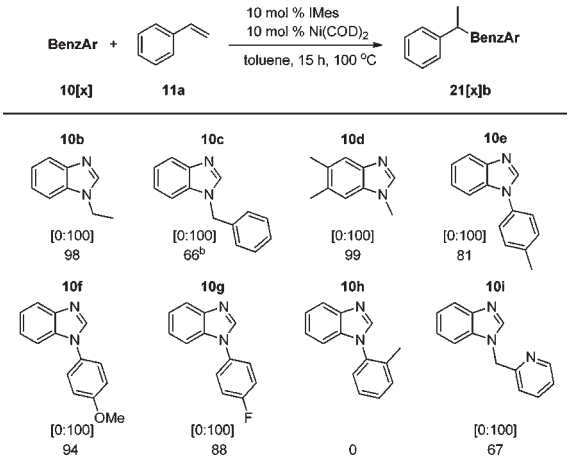
(12) A preliminary crystallographic study on **3**, representing the best of several trials, yielded poor data coverage but established molecular connectivity. See Supporting Information.

**Scheme 1.** Linear Selectivity: Hydroheteroarylation of Styrene with Various Benzimidazole Derivatives with $AlMe_3$[a]




[a] The reactions were carried out using **10x** (0.5 mmol) and styrene (0.75 mmol) and determined by $^1$H NMR analysis with the isolated yield based on **10x** as the limiting reagent. Selectivity in bracket [linear/branch]. [b] The amount of $AlMe_3$ was increased to 100 mol % (0.5 mmol).

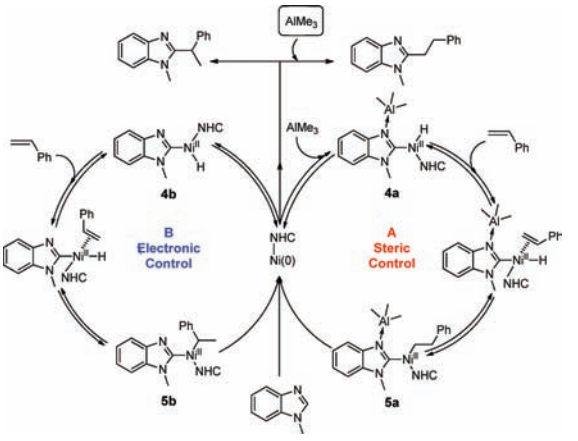
**Scheme 2.** Branch Selectivity: Hydroheteroarylation of Styrene with Various Benzimidazole Derivatives[a]




[a] The reactions were carried using **10x** (0.5 mmol) and styrene (0.75 mmol) determined by $^1$H NMR analysis with isolated yield based on **10x** as the limiting reagent. Selectivity in bracket [linear/branch]. [b] 10 mol % **1a** was used instead of **IMes**.

and (3) reductive elimination of **5a** (pathway A) and **5b** (pathway B) to afford linear and branched products, respectively (Scheme 3). Upon closer inspection via $^1$H NMR spectroscopy, it is clear that the generation of an Al-benzimidazole adduct (**3**) is observed, as the methyl signal of benzimidazole has moved upfield from 2.61 to

**Scheme 3.** Plausible Mechanism for Catalytic Ni−Al C−H Activation of Benzimidazole




2.20 ppm. Such a Lewis pair adduct **3** is further confirmed by X-ray crystallography in which $AlMe_3$ is datively coordinated to the benzimidazole nitrogen (Figure S1).[12] This positive result may indicate that the presence of $AlMe_3$ binding to the benzimidazole would impose a linear selectivity through a steric barricade as shown in reaction pathway A. In this respect, similar steric and mechanistic phenomena have been reported by the Cavell group for the Ni-mediated C−H activation/alkene insertion to produce linear 2-alkyl imidazolium.[13] In contrast to pathway B, adduct **4b** would electronically and thermodynamically favor hydride insertion at the $C_\beta$ position of vinylarene, resulting in branched selectivity.

In summary, without resorting to functional group manipulations on the substrate or ligand, we have disclosed a new mode of a chemically regioselective switch for C−H bond functionalization of benzimidazole derivatives. The catalytic method features a cooperative interaction between Ni and Al to create a steric requirement for obtaining the linear product. Exclusion of the $AlMe_3$ cocatalyst switches the reaction toward branched selectivity. Ongoing work seeks to gain a detailed mechanistic understanding of the synergism offered by Ni−Al bimetallic catalysis. Such mechanistic insights will be crucial for developing bimetallic catalysis on the scope of the reaction.

**Acknowledgment.** We thank Professor Jennifer Scott at Royal Military College of Canada for her insightful suggestion in our work and Dr. Mei-Chin Tseng's generous technical support for using the Mass Analysis facility at the Institute of Chemistry, Academia Sinica. We are also grateful to the Taiwan National Science Council (NSC: 97-2113-M-001-024-MY2) and Academia Sinica for their generous financial support.

**Supporting Information Available.** Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) (a) Clement, N. D.; Cavell, K. J.; Jones, C.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277–1278. (b) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845–3847. (c) Normand, A. T.; Hawkes, K. J.; Clement, N. D.; Cavell, K. J.; Yates, B. F. *Organometallics* **2007**, *26*, 5352. (d) Normand, A. T.; Yen, S. W.; Huynh, H. V.; Hor, T. S. A.; Cavell, K. J. *Organometallics* **2008**, *27*, 3153.