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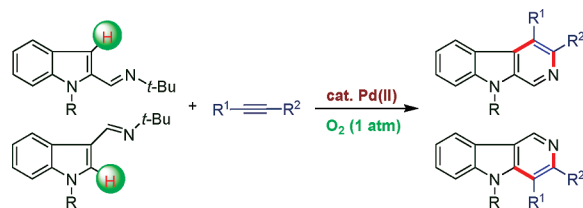
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ABSTRACT



A palladium-catalyzed iminoannulation of internal alkynes via direct C–H bond cleavage was developed. Dioxygen was employed as a clean oxidant in this kind of catalysis. Carbolines were synthesized from *tert*-butylimines of *N*-substituted indole-2-carboxaldehydes or indole-3-carboxaldehydes.

Pyrido[3,4-*b*]indoles¹ and pyrido[4,3-*b*]indoles,² commonly known as β - and γ -carbolines, are of great importance in the areas of pharmaceuticals and are also versatile building blocks for natural products, bioactive compounds, and drugs.³ Compounds containing the β -caroline units have been found

to exhibit a wide range of biological activities, such as possessing potent and varied CNS and antitumor properties, acting as inhibitors of I κ B kinase and PDE5, etc.⁴ γ -Carbolines have also been investigated as antitumor agents.^{3g,5} Their importance has stimulated considerable attention from

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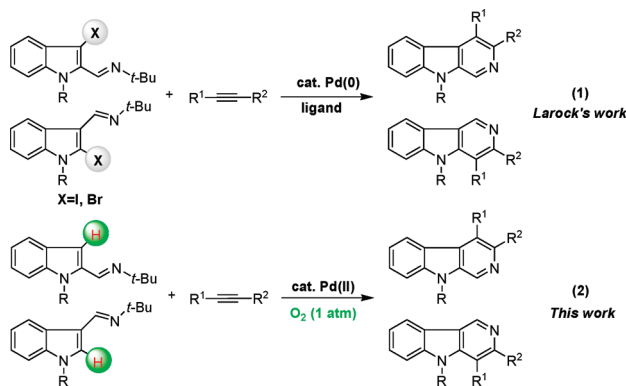
[‡] Chinese Academy of Sciences.

(1) (a) Inman, W. D.; Brat, W. M.; Gassner, N. C.; Lokey, R. S.; Tenney, K.; Suh, T.; Crews, P. *J. Nat. Prod.* **2010**, *73*, 255–257. (b) Till, M.; Prinsep, M. R. *J. Nat. Prod.* **2009**, *72*, 796–798. (c) Takahashi, Y.; Kubota, T.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2009**, *11*, 21–24. (d) Wang, W.; Nam, S.-J.; Lee, B.-C.; Kang, H. *J. Nat. Prod.* **2008**, *71*, 163–166. (e) Kearns, P. S.; Rideout, J. A. *J. Nat. Prod.* **2008**, *71*, 1280–1282. (f) Teichert, A.; Schmidt, J.; Porzel, A.; Arnold, N.; Wessjohann, L. *J. Nat. Prod.* **2007**, *70*, 1529–1531. (g) Costa, E. V.; Pinheiro, M. L. B. *J. Nat. Prod.* **2006**, *69*, 292–294. (h) Becher, P. G.; Beuchat, J.; Gademann, K.; Jüttner, F. *J. Nat. Prod.* **2005**, *68*, 1793–1795. (i) Iinuma, Y.; Kozawa, S.; Ishiyama, H.; Tsuda, M.; Fkushi, E.; Kawabata, J.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 1109–1110. (j) Youssef, D. T. A. *J. Nat. Prod.* **2005**, *68*, 1416–1419. (2) (a) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 889–925. (b) Butin, A. V.; Pilipenko, A. S.; Milich, A. A.; Finko, A. V. *Chem. Heterocycl. Compd.* **2009**, *45*, 613–614.

(3) (a) Wang, Y.-H.; Tang, J.-G.; Wang, R.-R.; Yang, L.-M.; Dong, Z.-J.; Du, L.; Shen, X.; Liu, J.-K.; Zheng, Y.-T. *Biochem. Biophys. Res. Commun.* **2007**, *355*, 1091–1095. (b) Liu, J.; Wu, G.; Cui, G.; Wang, W.-X.; Zhao, M.; Wang, C.; Zhang, Z.; Peng, S. *Bioorg. Med. Chem.* **2007**, *15*, 5672–5693. (c) Wu, J.-P.; Wang, J.; Abeywardane, A.; Andersen, D.; Emmanuel, M.; Gautschi, E.; Goldberg, D. R.; Kashem, M. A.; Lukas, S.; Wang, M.; Martin, L.; Morwick, T.; Moss, N.; Pargellis, C.; Patel, U. R.; Patnaude, L.; Peet, G. W.; Skow, D.; Snow, R. J.; Ward, Y.; Werneburg, B.; White, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4664–4669. (d) Moura, D. J.; Richter, M. F.; Boeira, J. M.; Henriques, J. A. P.; Saffi, J. *Mutagenesis* **2007**, *22*, 293–302. (e) Herraiz, T. *J. Agric. Food. Chem.* **2007**, *55*, 8534–8540. (f) Li, Y.; Liang, F.; Jiang, W.; Yu, F.; Cao, R.; Ma, Q.; Dai, X.; Jiang, J.; Wang, Y.; Si, S. *Cancer Biol. Ther.* **2007**, *6*, 1193–1199. (g) Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780–3790. (h) Deveau, A. M.; Costa, N. E.; Joshi, E. M.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3522–3525. (i) Cao, R.; Yi, W.; Wu, Q.; Guan, X.; Feng, M.; Ma, C.; Chen, Z.; Song, H.; Peng, W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6558–6561.

organic chemists and encouraged the development of new synthetic strategies to construct carbolines.⁶ Recently, Larock and co-workers developed a palladium-catalyzed annulation between internal alkynes and *tert*-butylimines of N-substituted 3-iodoindole-2-carboxaldehydes or 2-haloindole-3-carboxaldehydes (eq 1, Scheme 1).^{6a,d} However, aryl halides

Scheme 1. Pd-Catalyzed Approaches to Carboline



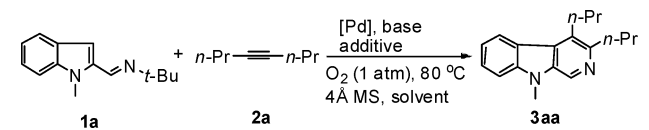
were required and halide byproducts were produced via these methods. With the development of chemical science, C–H functionalization has received substantial attention, because of its sustainable and environmentally benign features.⁷ Herein, we describe a Pd(II)-catalyzed iminoannulation of internal alkynes and *tert*-butylimines of N-substituted indole-carboxaldehydes via direct C–H bond activation using dioxygen as a clean oxidant (eq 2, Scheme 1).

We recently developed direct-dehydrogenative annulation (DDA) reactions of simple anilines⁸ or biaryls⁹ with internal alkynes to generate indoles and carbazole derivatives,

respectively, using O₂ as the oxidant.¹⁰ On the basis of these results, we envisioned a direct-dehydrogenative annulation (DDA) of internal alkynes and *tert*-butylimines of N-substituted indole-carboxaldehydes to generate carboline derivatives (eq 2).

The initial iminoannulation of internal alkynes was examined by the reaction of the *tert*-butylimine of 1-methylindole-2-carboxaldehyde (**1a**) with 4-octyne (**2a**) in DMF in the presence of Pd(OAc)₂ (10 mol %), K₂CO₃, and 4 Å MS (150 mg) under O₂ (1 atm). The expected product β-carboline **3aa** was successfully obtained in 48% yield (entry 1, Table 1). The yield was slightly improved to 55%

Table 1. Optimization of Pd-Catalyzed Annulation Conditions^a



| entry | [Pd] | base | additive | solvent | yield (%) ^b |
|-----------------|---------------------------------------|---------------------------------|-------------|--------------------|------------------------|
| 1 | Pd(OAc) ₂ | K ₂ CO ₃ | | DMF | 48 |
| 2 | Pd(OAc) ₂ | K ₂ CO ₃ | TBAB | DMF | 55 |
| 3 | Pd(OAc) ₂ | Na ₂ CO ₃ | TBAB | DMF | 58 |
| 4 | Pd(OAc) ₂ | HCOONa·2H ₂ O | TBAB | DMF | 30 |
| 5 | Pd(OAc) ₂ | pyridine | TBAB | DMF | 35 |
| 6 | Pd(OAc)₂ | NaHCO₃ | TBAB | DMF | 71 |
| 7 | Pd(OAc) ₂ | NaHCO ₃ | TBAC | DMF | 45 |
| 8 | Pd(OAc) ₂ | NaHCO ₃ | TBAF | DMF | 28 |
| 9 | Pd(OAc) ₂ | NaHCO ₃ | TBAB | DMA | 31 |
| 10 | Pd(OAc) ₂ | NaHCO ₃ | TBAB | DMSO | 62 |
| 11 | Pd(OAc) ₂ | NaHCO ₃ | TBAB | CH ₃ CN | 49 |
| 12 | Pd(OAc) ₂ | NaHCO ₃ | TBAB | toluene | 22 |
| 13 | Pd(OAc) ₂ | NaHCO ₃ | TBAB | THF | 18 |
| 14 | PdCl ₂ | NaHCO ₃ | TBAB | DMF | 55 |
| 15 | Pd(PhCN) ₂ Cl ₂ | NaHCO ₃ | TBAB | DMF | 59 |
| 16 ^c | Pd(OAc) ₂ | NaHCO ₃ | TBAB | DMF | 54 |
| 17 ^d | Pd(OAc) ₂ | NaHCO ₃ | TBAB | DMF | 38 |

^a **1a** (0.20 mmol), **2a** (0.40 mmol), [Pd] (10 mol %), base (0.40 mmol), additive (0.20 mmol), 4 Å MS (150 mg), and solvent (2 mL) were heated in a sealed tube under O₂ (1 atm), 80 °C, 24 h. ^b Isolated yields. ^c 5 mol % Pd(OAc)₂ was employed. ^d The reaction was carried out under air.

when TBAB (1 equiv) was added (entry 2, Table 1). As other bases such as Na₂CO₃, HCOONa·2H₂O, pyridine, and NaHCO₃ (entries 3–6, Table 1) were tested in the reaction,

(7) For recent reviews on C–H activation, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (c) Whited, M. T.; Grubbs, R. H. *Acc. Chem. Res.* **2009**, *42*, 1607–1616. (d) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (g) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714. (h) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, *41*, 1512–1522. (i) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 7, 949–957.

(8) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572–4576.

(9) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895–7898.

(4) (a) Wernike, C.; Schott, Y.; Enzensperger, C.; Schulze, G.; Lehmann, J.; Rommelspacher, H. *Biochem. Pharmacol.* **2007**, *74*, 1065–1077. (b) Hanson, S. M.; Czajkowski, C. *J. Neurosci.* **2008**, *28*, 3490–3499. (c) Herráiz, T.; Guillén, H.; Arán, V. J. *Chem. Res. Toxicol.* **2008**, *21*, 2172–2180. (d) Mansoor, T. A.; Ramalho, R. M.; Mulhovo, S.; Rodrigues, C. M. P.; Ferreira, M. J. U. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4255–4258.

(5) (a) Chen, J.; Dong, X.; Liu, T.; Lou, J.; Jiang, C.; Huang, W.; He, Q.; Yang, B.; Hu, Y. *Bioorg. Med. Chem.* **2009**, *17*, 3324–3331. (b) Ivachtchenko, A. V.; Frolv, E. B.; Mitkin, O. D.; Kysil, V. M.; Khvat, A. V.; Okun, I. M.; Tkachenko, S. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3183–3187. (c) Bonjoch, J.; Diaba, F.; Pages, L.; Perez, D.; Soca, L.; Miralpeix, M.; Vilella, D.; Anton, P.; Puig, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4299–4302.

(6) (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083–3086. (b) Zhang, H.; Larock, R. C. *Org. Lett.* **2002**, *4*, 3035–3038. (c) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048–7056. (d) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318–9330. (e) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5132–5138. (f) Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495–4498. (g) Batanova, O. V.; Dubovitskii, S. V. *Tetrahedron Lett.* **2004**, *45*, 1299–1300. (h) Golovko, T. V.; Soloveva, N. P.; Anisimova, O. S.; Smirnova, O. B.; Evstratova, M. I.; Kiselev, S. S.; Granik, V. G. *Russ. Chem. Bull., Int. Ed.* **2008**, *57*, 177–185. (i) Smirnova, O. B.; Golovko, T. V.; Alekseeva, L. M.; Shashkov, A. S.; Granik, V. G. *Russ. Chem. Bull.* **2008**, *57*, 2410–2417. (j) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485–3488. (k) Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2009**, 6211–6216. (l) Kulkarni, A.; Abid, M.; Huang, X. D. *Tetrahedron Lett.* **2009**, *50*, 1791–1794. (m) Chiba, S.; Xu, Y.-J.; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886–12887.

it was revealed that NaHCO_3 is the most effective base for this transformation (71% yield, entry 6, Table 1). Under these conditions, different phase-transfer catalysts (entries 7 and 8, Table 1), solvents (entry 9–13, Table 1), and Pd catalysts (entries 14 and 15, Table 1) were investigated but gave lower efficiencies. β -Carboline **3aa** was produced in 38% yield when this reaction was carried out under air (entry 17, Table 1).

Under the optimal conditions, we then investigated the scope of this transformation by different N-substituted *tert*-butylimines of indole-carboxaldehydes (Table 2). Using

Table 2. $\text{Pd}(\text{OAc})_2$ -Catalyzed DDA Reaction of **1** with **2a**^a

| entry | imine | product | yield (%) ^b |
|-------|-------|---------|------------------------|
| 1 | | | 71 |
| 2 | | | 0 |
| 3 | | | 51 |
| 4 | | | 64 |
| 5 | | | 37 |
| 6 | | | 40 |

^a Conditions: **1** (0.40 mmol), **2a** (0.80 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), TBAB (0.40 mmol), NaHCO_3 (0.80 mmol), and 4 Å MS (300 mg) in 4 mL of DMF under O_2 (1 atm), 80 °C, 36 h. ^b Isolated yield.

N-substituted *tert*-butylimines of indole-2-carboxaldehydes led to good yields of the corresponding β -carboline (entries 1, 3, and 4, Table 2). Moreover, when the N-substituted *tert*-butylimines of indole-3-carboxaldehydes were allowed to react with 4-octyne, the C–H bond at C-2 could also be cleaved, generating the corresponding γ -carboline with moderate yields (entries 5 and 6, Table 2). However, the *tert*-butylimine of indole-2-carboxaldehyde **1b** did not work under these conditions (entry 2, Table 2).

Table 3. $\text{Pd}(\text{OAc})_2$ -Catalyzed DDA Reaction of **1a** with Internal Alkynes **2a**^a

| entry | alkyne | product | yield (%) ^b |
|-------|--------|---------|-------------------------|
| 1 | | | 69 |
| 2 | | | 42 |
| 3 | | | 45 |
| 4 | | | 45 |
| 5 | | | 41 |
| 6 | | | 52 |
| 7 | | | 57 |
| 8 | | | 52 (1:2.5) ^c |
| 9 | | | 64 (1:3.8) ^c |
| 10 | | | 56 (1.3:1) ^c |
| 11 | | | 37 (1:2) ^c |

^a Conditions: **1a** (0.40 mmol), **2** (0.80 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), TBAB (0.40 mmol), NaHCO_3 (0.80 mmol), and 4 Å MS (300 mg) in 4 mL of DMF under O_2 (1 atm), 80 °C, 36 h. ^b Isolated yield. ^c The ratio was determined by ¹HNMR.

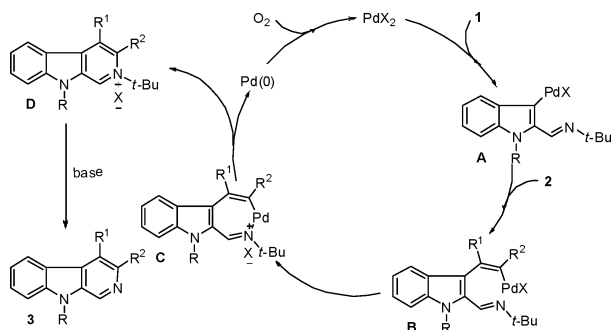
The scope of the direct-dehydrogenative annulation (DDA) reaction was further expanded to a variety of internal alkynes (Table 3). The results in Table 3 demonstrate that this transformation has a high degree of functional group tolerance in the internal alkyne partners. Alkyl groups, aryl

(10) For some reviews, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329–2364. For some Pd-catalyzed examples, see: (c) Stahl, S. S. *Science* **2005**, *309*, 1824–1826. (d) Nielsen, R. J.; Goddard, W. A., III *J. Am. Chem. Soc.* **2006**, *128*, 9651–9660. (e) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355. (f) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (g) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733–4736. (h) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191. (i) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753–5762. For some of our recent works, see: (j) Chen, A.; Lin, R.; Liu, Q.; Jiao, N. *Chem. Commun.* **2009**, 6842–6844. (k) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28–29.

groups, and esters are well tolerated, generating the corresponding carbolines in moderate yields. But-2-yne-1,4-diyl diacetate (**2c**) smoothly underwent cyclization with **1a**, leading to **3ac** in 42% yield (entry 2, Table 3). It is particularly noteworthy that with unsymmetrical alkynes with an ester group and an aryl group, such as 3-phenylpropiolates, a single carboline isomer was obtained with high regioselectivity (entries 6 and 7, Table 3). However, other unsymmetrical alkynes, such as 1-phenylpropyne, 1-phenylhexyne, phenylcyclopropylacetylene, and but-2-ynyl acetate, produced two regioisomers.

A plausible mechanism for the DDA reaction of **1** with alkyne **2** is illustrated in Scheme 2. The initiated electrophilic

Scheme 2. Plausible Mechanism for the DDA Reaction



aromatic palladation¹¹ affords a Pd^{II} intermediate **A**. The resulting intermediate **A** subsequently inserts into **2** to produce a vinylic palladium(II) intermediate **B**, followed by reaction with the neighboring imine substituent to form a seven-membered palladacyclic immonium salt **C**. Subsequent reductive elimination generates a *tert*-butylcarbolinium salt

D as well as a Pd⁰ complex, which can be reoxidized to a Pd^{II} species for a new catalytic cycle by O₂ (1 atm). As previously suggested by Heck¹² and Larock,^{6a,d} the *tert*-butyl group of the *tert*-butylcarbolinium salt **D** apparently fragments to produce carbolines **3** (Scheme 2).

In summary, we have demonstrated a novel Pd(II)-catalyzed direct-dehydrogenative annulation (DDA) of internal alkynes and *tert*-butylimines of *N*-substituted indole-carboxaldehydes via direct C–H bond activation leading to carboline derivatives. Use of dioxygen (1 atm) as the oxidant and the absence of ligands make this approach very easy to handle. Further efforts to expand the scope of this transformation and the synthetic applications are ongoing in our laboratory.

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (b) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174. (c) Beck, E. M.; Hatley, B. R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529. (d) Grimster, N. P.; Gauntlett, C.; Godfrey, C. M. R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125–3129. (e) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579. (f) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; Deboef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (g) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339–1342.

(12) (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941–1946. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238–3241.