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Pd-Catalyzed Oxidative Coupling of Enamides and Alkynes for Synthesis of Substituted Pyrroles

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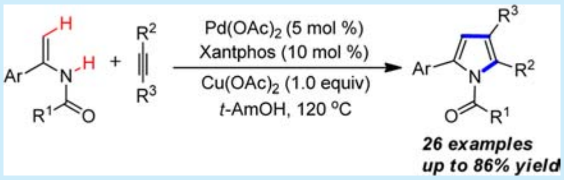
Ⓢ *Supporting Information*

ABSTRACT: A novel and efficient palladium(II)-catalyzed alkenyl C−H activation oxidative annulation of enamides with alkynes for the synthesis of substituted pyrroles has been developed. The reaction tolerates a wide range of functional groups and is a reliable method for the synthesis of triaryl-substituted pyrroles in high yields.

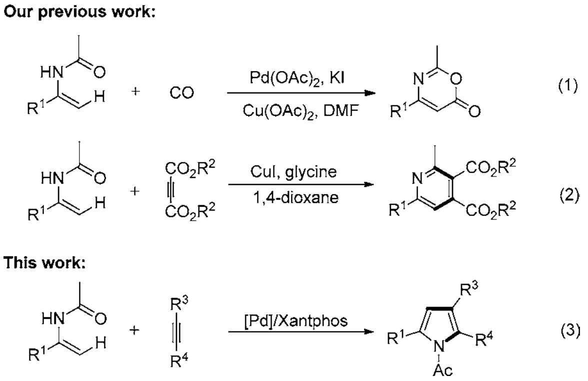


Pyrroles are some of the most important monocyclic heterocycles which are prevalent in many pharmaceutical drugs, biological compounds, and functional materials.[1] Over the past decades, many efforts have been devoted to the synthesis of various substituted pyrroles.[2] Very recently, elegant strategies, such as multicomponent reactions,[3] dehydrogenative cyclization reactions,[4] and oxidative cyclization of *N*-allylimines,[5] have been developed for the synthesis of pyrroles. Despite these advances, the development of new methodologies for the synthesis of substituted pyrroles remains one of the hottest topics in synthetic chemistry.[6]

Recently, transition-metal-catalyzed oxidative annulations of the C−H/N−H bond with alkynes have emerged as an efficient strategy to synthesize various heterocycles[7] such as indoles,[7e] carbolines,[7f] isoquinolines,[7i] and benzothiazines.[7j] Enamides which are a class of versatile building blocks have been widely applied in asymmetric hydrogenations,[8] Lewis acid catalyzed nucleophilic addition reactions,[9] and transition-metal-catalyzed cross-coupling reactions.[10,11] As one of the C−H/N−H bond annulation reaction precursor, Rh-catalyzed oxidative annulation of enamides with internal alkynes for the synthesis of substituted pyrroles has been developed by the groups of Glorius[12] as well as Stuart and Fagnou.[13] Ru-catalyzed annulation of enamides with alkynes has also been developed independently by the groups of Wang[14] and Ackermann.[15] However, these reactions are restricted to electron-deficient enamides which display an electron-withdrawing ester group on the alkenyl moiety. The electron-rich enamides such as aryl-substituted enamides are still challenging substrates for Rh- or Ru-catalyzed annulation reactions.[12−15]

Very recently, we have developed a series of Pd- or Cu-catalyzed cross-coupling of enamides for the synthesis of azaheterocycles (Scheme 1, eqs 1 and 2).[16] We hypothesized that the Pd-catalyzed oxidative annulation of enamides with internal alkynes may be tolerated a broad substrate scope and show an efficient approach for the synthesis of pyrroles. Herein, we describe the development of a Pd-catalyzed oxidative coupling of aryl enamides with internal alkynes for the synthesis of substituted pyrroles (Scheme 1, eq 3).

Scheme 1. Transition-Metal-Catalyzed Couplings of Enamides



We began our study by investigating the palladium-catalyzed oxidative coupling of enamide **1a** and diphenylacetylene **2a**. We were pleased to find that pyrrole **3aa** was obtained in 37% yield in the presence of $Cu(OAc)_2$ (1 equiv) in CH_3CN at 120 °C (Table 1, entry 1). Screening of various solvents, such as DCE, toluene, *t*-AmOH, and 1,4-dioxane, suggested that *t*-AmOH was the most suitable solvent for this reaction (Table 1, entries 2−5). Further experiments showed that $Pd(OAc)_2$ was the first choice for catalyst precursor; other palladium salts, such as $PdCl_2$, $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(dba)_2$, were inferior (Table 1, entries 6−9). Indeed, no reaction occurred in the absence of a palladium catalyst (Table 1, entry 10). However, the best yield was 42% at this stage.

The phosphine ligand is generally air-sensitive due to it being easily oxidized. Therefore, phosphine ligand has rarely been used in palladium-catalyzed oxidative coupling reactions. Huang and co-workers reported an elegant palladium-catalyzed oxidative carbonylation reaction using Xantphos as the ligand.[17] Herein, we found that phosphine ligands can improve the

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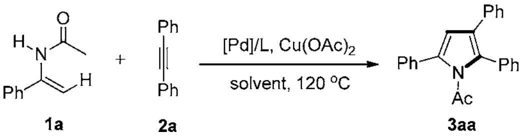
Table 1. Optimization of Reaction Conditions[a]

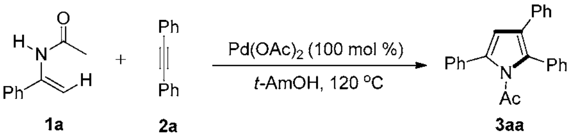


entry	catalyst	ligand	solvent	yield (%)
1	$Pd(OAc)_2$		CH_3CN	37
2	$Pd(OAc)_2$		DCE	19
3	$Pd(OAc)_2$		toluene	15
4	$Pd(OAc)_2$		*t*-AmOH	42
5	$Pd(OAc)_2$		1,4-dioxane	30
6	$PdCl_2$		*t*-AmOH	34
7	$Pd(TFA)_2$		*t*-AmOH	27
8	$Pd(PPh_3)_2Cl_2$		*t*-AmOH	32
9	$Pd(dba)_2$		*t*-AmOH	24
10			*t*-AmOH	0
11	$Pd(OAc)_2$	PPh_3	*t*-AmOH	36
12	$Pd(OAc)_2$	dppf	*t*-AmOH	50
13	$Pd(OAc)_2$	dppe	*t*-AmOH	52
14	$Pd(OAc)_2$	dppp	*t*-AmOH	48
15	$Pd(OAc)_2$	Xantphos	*t*-AmOH	86
16	$Pd(OAc)_2$	Xantphos oxide	*t*-AmOH	20

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (5 mol %), ligand (10 mol %), $Cu(OAc)_2$ (1 equiv), solvent (3 mL), 12 h; isolated yields.

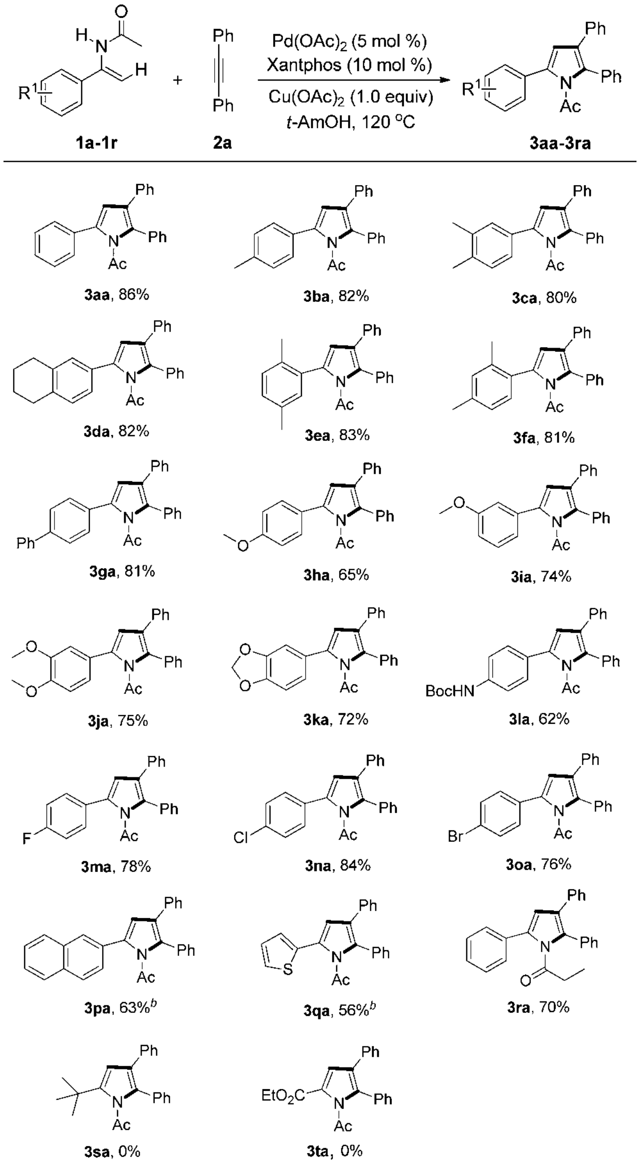
conversion of our palladium-catalyzed oxidative reactions. A series of bisphosphine ligands show positive effect for the reaction (Table 1, entries 11–15). In particular, Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl xanthene) was found to be the most effective ones to give pyrrole **3aa** in 86% yield (Table 1, entry 15). Although the ^{31}P NMR spectrum of the crude reaction mixture indicated that most of the Xantphos has been oxidized in the reaction,[18] the oxidized Xantphos ((9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine oxide)) did not promote the reaction (Table 1, entry 16). And the stoichiometric reaction also confirmed that the Xantphos indeed promoted the reaction (Scheme 2). Therefore, Xantphos should be the real ligand in the reaction.

Scheme 2. Stoichiometric Reactions



Xantphos (0 mol %): 53% yield
Xantphos (200 mol %): 84% yield

Scheme 3. Pd-Catalyzed Oxidative Coupling Enamides 1 with Diphenylacetylene 2a for the Synthesis of Substituted Pyrroles[a]

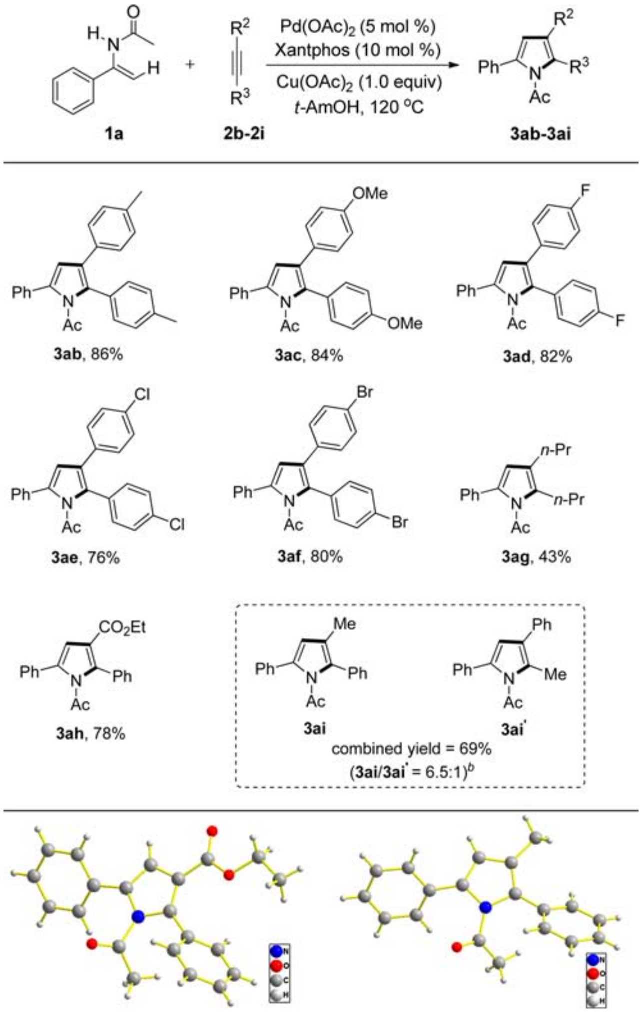


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), $Cu(OAc)_2$ (1 equiv), *t*-AmOH (3 mL), 12 h; isolated yields. CH_3CN was used as solvent.

With the optimized reaction conditions established, a series of enamides **1** was investigated for extending the substrate scope (Scheme 3). This transformation displayed high functional group tolerance and proved to be a quite general methodology for preparation of triaryl-substituted pyrroles. Enamides with electron-neutral or electron-donating groups on aryl rings, such as alkyl, phenyl, methoxyl, [1,3]dioxolyl, and amino, all gave the corresponding *N*-acetyl-substituted pyrroles **3ba–la** in good to high yields. *o*-Methyl substituted enamides **1e** and **1f** were transformed efficiently into corresponding pyrroles **3ea** and **3fa** in 81–83% yields implying that the transformation was insensitive to steric hindrance of the enamides. Enamides with an electron-withdrawing group such as fluoro, chloro and bromo, were well tolerated and afforded the corresponding pyrroles **3ma–oa** in 76%-84% yields. 2-Naphthyl enamide **1p** and thienyl enamide **1q** proceeded smoothly as well to give the desired pyrroles **3pa–qa** in 63%, 56% yield respectively when acetonitrile was used as the solvent. In addition, the *N*-propionyl enamide **1r** shows similar reactivity with **1a** to give the corresponding *N*-propionyl pyrrole **3ra** in 70% yield. However, no reaction occurred when the aliphatic enamides and electron-deficient enamides such as **1s,t** were used as the substrates.

Next, various internal alkynes **2** were investigated to extend the substrate scope, and the results are summarized in Scheme 4. Overall, this transformation showed broad substrate tolerance among internal alkynes. Symmetric diaryl-substituted

Scheme 4. Pd-Catalyzed Oxidative Coupling Enamide 1a with Alkynes 2 for the Synthesis of Substituted Pyrroles[a]

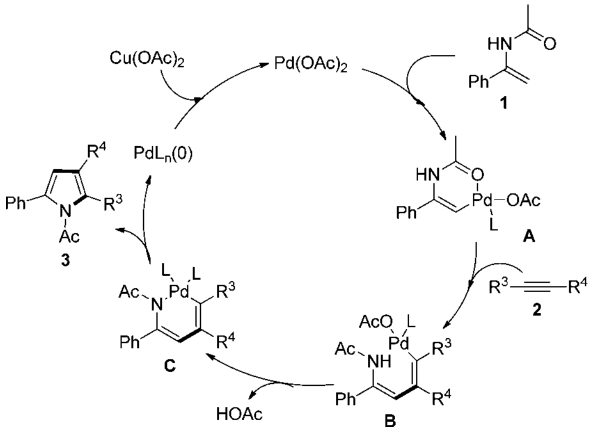


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), $Cu(OAc)_2$ (1 equiv), *t*-AmOH (3 mL), 12 h; isolated yields. [b] The regioisomeric ratio was determined by NMR analysis.

alkynes with either electron-donating or -withdrawing groups on the aromatic rings reacted efficiently to give the corresponding substituted pyrroles **3ab**–**af** in good to high yields (76–86%). Symmetrical aliphatic alkynes such as 4-octyne, underwent the desired reaction to give the corresponding pyrrole **3ag** in moderate yield. Unsymmetrical alkynes were also tolerated in the reaction. The pyrrole **3ah** was obtained as single regioisomer in 78% yield when ethyl 3-phenylpropiolate **2h** was employed as the substrate (see the X-ray diffraction structure of **3ah** in Scheme 4). Methyl phenyl alkyne **2i** underwent the reaction to give two regioisomers **3ai** and **3ai′** in total 69% yield with a 6.5:1 ratio.

On the basis of the aforementioned results and previous studies, a tentative mechanism for the reaction is proposed in Scheme 5. The alkenyl C–H bond of enamide **1a** is first activated by the $Pd(OAc)_2$ to form a palladium intermediate **A**.[11b,16a,19] Coordinative insertion of alkyne **2** into the Pd–C bond of intermediate **A** gives the intermediate **B**. Intramolecular deprotonated cyclization of intermediate **B** generates a six-membered palladacycle **C**. Finally, reductive elimination of intermediate **C** affords the *N*-acetyl-substituted pyrrole **3** and Pd(0) species. The Pd(0) was reoxidized by $Cu(OAc)_2$ to regenerate the active $Pd(OAc)_2$ catalyst. Since the C–H activation of enamide by $Pd(OAc)_2$ is fast step,[11b,16a] we assumed that the reductive elimination of Pd(II) from the vinylamido complexe **C** is the rate-determining step.[20] The Xantphos ligand is likely promoted reductive elimination of Pd(II) from intermediate **C** due to the wide bite-angle of bis-phosphine.[17c]

Scheme 5. Plausible Mechanism for Palladium-Catalyzed Oxidative Coupling of Enamides with Alkynes



In summary, we have developed a palladium-catalyzed alkenyl C–H activation annulation of aryl enamides with alkynes for the synthesis of triaryl- substituted pyrroles. This palladium-catalyzed oxidative annulation reaction tolerates a wide range of functional groups and is a reliable procedure for rapid elaboration of readily available aryl enamides into a variety of valuable substituted pyrroles in high yields. Further studies on the transition-metal-catalyzed transformations of enamides are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectral data for all products and X-ray data of **3ah** and **3ai** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Dipakranjan, M.; Brateen, S.; Bidyut, K. D. Pyrrole and Its Derivatives. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 187–220. (b) Wang, M.; Xu, H.; Liu, T.; Feng, Q.; Yu, S.; Wang, S.; Li, Z. *Eur. J. Med. Chem.* **2011**, *46*, 1463. (c) Fan, H.; Peng, J. N.; Hamann, M. T.; Hu, J. F. *Chem. Rev.* **2008**, *108*, 264.

(2) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084.

(3) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (b) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312. (c) Soleimani, E.; Zainali, M. *J. Org. Chem.* **2011**, *76*, 10306. (d) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916. (e) Hong, D.; Zhu, Y.; Li, Y.; Lin, X.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 4668. (f) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246. (g) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (h) Wu, G.; Su, W. *Org. Lett.* **2013**, *15*, 5278. (i) Hu, P.; Huang, S.; Xu, J.; Shi, Z.-J.; Su, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 9926.

(4) (a) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (b) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012. (c) Iida, K.; Miura, T.; Ando, J.; Saito, S. *Org. Lett.* **2013**, *15*, 1436.

(5) (a) Li, M.; Wu, K.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, *49*, 5853. (b) Shi, Z. Z.; Suri, M.; Glouris, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 4892. (c) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966.

(6) For selected examples, see: (a) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146. (b) Ngwerume, S.; Lewis, W.; Camp, J. E. *J. Org. Chem.* **2013**, *78*, 920. (c) Gao, M.; He, C.; Chen, H. Y.; Bai, R. P.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958. (d) Tang, X.; Huang, L.; Qi, C.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 9597. (e) Billedeau, R. J.; Klein, K. R.; Kaplan, D.; Lou, Y. *Org. Lett.* **2013**, *15*, 1421. (f) Liu, J. Q.; Fang, Z. X.; Zhang, Q.; Liu, Q.; Bi, X. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (g) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926. (h) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693.

(7) For selected reviews and examples, see: (a) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, DOI: 10.1021/ar3002798. (e) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (f) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. (g) Chen, J.; Pang, Q.; Sun, Y.; Li, X. *J. Org. Chem.* **2011**, *76*, 3523. (h) Ma, W.; Graczyk, K.; Ackermann, L. *Org. Lett.* **2012**, *14*, 6318. (i) Zhong, H.-B.; Yang, D.; Wang, S.-Q.; Huang, J.-H. *Chem. Commun.* **2012**, *48*, 3236. (j) Dong, W.; Wang, L.; Parthasarathy, K.; Pan, F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11573. (k) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768. (l) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12873. (m) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573. (n) Zhang, Y.; Chen, Z.; Wu, W.; Zhang, Y.; Su, W. *J. Org. Chem.* **2013**, *78*, 12494.

(8) (a) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (b) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (c) Guan, Z.-H.; Zhang, Z.-Y.; Ren, Z.-H.; Wang, Y.-Y.; Zhang, X. *J. Org. Chem.* **2011**, *76*, 339. (d) Tang, W.; Capacci, A.; Sarvestani, M.; Wei, X.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2009**, *74*, 9528.

(9) (a) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292 and references therein. (b) Chang, L.; Kuang, Y.; Qin, B.; Zhou, X.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2010**, *12*, 2214. (c) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708. (d) Tong, S.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2012**, *51*, 4417. (e) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390.

(10) (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. (b) Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7333. (c) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430.

(11) (a) Pankajakshan, S.; Xu, Y.-H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5701. (b) Xu, Y.-H.; Chok, Y. K.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1822. (c) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. (d) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355.

(12) Rakshit, S.; Patureau, F.-W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

(13) (a) Stuart, D.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (b) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338.

(14) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136.

(15) (a) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (b) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764.

(16) (a) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 14196. (b) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2012**, *48*, 8105. (c) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Green Chem.* **2014**, *16*, 112. (d) Zhao, M.-N.; Liang, H.; Ren, Z.-H.; Guan, Z.-H. *Adv. Synth. Catal.* **2013**, *355*, 221. (e) Guan, Z.-H.; Li, L.; Ren, Z.-H.; Li, J.; Zhao, M.-N. *Green Chem.* **2011**, *13*, 1664. (f) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem.—Eur. J.* **2014**, DOI: 10.1002/chem.201304565.

(17) (a) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (b) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, *15*, 3370. (c) Liu, H.; Laurenczy, G.; Yan, N.; Dyson, P. J. *Chem. Commun.* **2014**, *50*, 341.

(18) After the mixture was washed with dilute $NH_3\cdot H_2O$, Xantphos oxide and a trace of Xantphos were observed by TLC detection of the crude reaction mixture.

(19) (a) Sasano, K.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2013**, *135*, 10954. (b) Newkome, G. R.; Theriot, K. J.; Cheskin, B. K.; Evans, D. W.; Baker, G. R. *Organometallics* **1990**, *9*, 1375.

(20) Hartwig, J. F. *Nature* **2008**, *455*, 314 and references cited therein.