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Palladium-Catalyzed Oxidative Cyclization of Tertiary Enamines for Synthesis of 1,3,4-Trisubstituted Pyrroles and 1,3-Disubstituted Indoles

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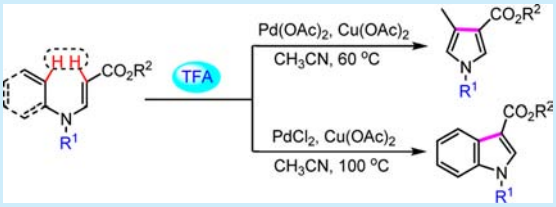
Supporting Information

ABSTRACT: A novel and efficient palladium-catalyzed intramolecular oxidative cyclization of tertiary enamines for the synthesis of 1,3,4-trisubstituted pyrroles and 1,3-disubstituted indoles has been developed. Trifluoroacetic acid plays an important role in the reaction. A series of pyrroles and indoles with substitution patterns that are not easily accessible by traditional routes were synthesized in good yields under mild conditions.

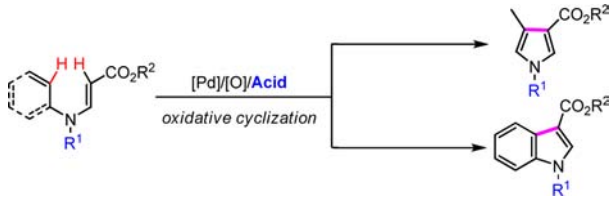


Nitrogen-containing aromatic heterocycles, such as pyrroles and indoles, are ubiquitous scaffolds in numerous bioactive natural and synthetic compounds, pharmaceuticals, and functional materials.[1] Therefore, novel and efficient methods for the synthesis of these heterocycles have been and continue to be a very active area of research.[2] Over the past decades, a number of protocols have been developed for the synthesis of various pyrroles.[3] However, 1,3,4-trisubstituted pyrroles, especially those containing three different substituents, are still one of the most challenging compounds in organic synthesis[4] because (1) conventional methods are mainly suitable for the synthesis of 2,5-disubstituted or polysubstituted pyrroles[5] and (2) the functionalization of simple pyrroles usually suffers from a lack of selectivity and polymerization.[6]

Recently, a novel palladium-catalyzed oxidative cyclization of *N*-aryl enamines to synthesize substituted indoles has been developed by Glorius and co-workers.[7] Palladium-catalyzed aerobic oxidative cyclization of *N*-aryl imines or *N*-allyl imines for the synthesis of 2-arylindoles or 2-arylpyrroles has emerged.[8,9] The secondary enamines or *N*-substituted imines was employed as the readily available starting materials, thus making these reactions promising for NH indoles or NH pyrroles synthesis.[7−10]

The cross-coupling reactions of tertiary enamines are very rare,[11] and it has been noted that tertiary enamines, unlike their secondary enamine homologues, are generally inactive in palladium-catalyzed C−H activation reactions.[12] We hypothesized that oxidative cyclization of the 2-fold C−H bond of tertiary enamines for the synthesis of pyrroles or indoles may be achieved by improving the electrophilicity of palladium catalysts under acidic conditions (Scheme 1).[13] In this paper, we describe the development of a palladium-catalyzed intramolecular oxidative cyclization of tertiary enamines for the synthesis of 1,3,4-trisubstituted pyrroles and 1,3-disubstituted indoles under mild conditions.

Scheme 1. Palladium-Catalyzed Oxidative Cyclization of Tertiary Enamines



We commenced our study by investigating the palladium-catalyzed oxidative cyclization of (*E*)-ethyl 3-(allyl(phenyl)-amino)acrylate **1a** (Table 1). Only a trace of pyrrole **2a** was observed in the presence of the $Pd(OAc)_2$ catalyst and stoichiometric $Cu(OAc)_2$ in CH_3CN at 60 °C (Table 1, entry 1). Then, various acids were screened as additives to improve the reaction efficiency. Expectedly, a 22% yield of pyrrole product **2a** was obtained when 1.0 equiv of *p*-TsOH was used, while acetate acid shows no reactivity (Table 1, entries 2−3). Indeed, the yield of **2a** was dramatically improved to 61% when PivOH was used as an additive (Table 1, entry 5). Further improvement was made by using TFA, in which case a 70% yield of pyrrole **2a** was obtained (Table 1, entry 6). Optimization of different palladium catalyst precursors and solvents revealed that $Pd(OAc)_2$ and CH_3CN was the most suitable catalyst and solvent respectively for this reaction (Table 1, entries 7−12). Finally, the reaction temperature was also varied, and 60 °C gave the best result (Table 1, entries 13−14).

With the optimized conditions established, the scope of the reaction was investigated (Scheme 2). This new palladium-catalyzed oxidative cyclization reaction displayed good functional-group tolerance and proved to be a general method for

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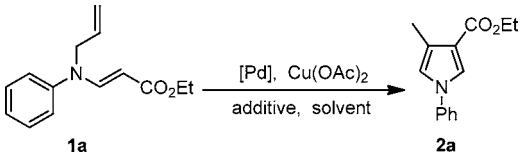
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	catalyst	additive	solvent	t (°C)	yield (%)
1	$Pd(OAc)_2$	–	CH_3CN	60	3
2	$Pd(OAc)_2$	HOAc	CH_3CN	60	5
3	$Pd(OAc)_2$	*p*-TsOH	CH_3CN	60	22
4	$Pd(OAc)_2$	TCA	CH_3CN	60	20
5	$Pd(OAc)_2$	PivOH	CH_3CN	60	61
6	**$Pd(OAc)_2$**	**TFA**	**CH_3CN**	**60**	**70**
7	$PdCl_2$	TFA	CH_3CN	60	40
8	$Pd(TFA)_2$	TFA	CH_3CN	60	36
9	$Pd(OAc)_2$	TFA	DMSO	60	52
10	$Pd(OAc)_2$	TFA	DMF	60	12
11	$Pd(OAc)_2$	TFA	DMA	60	7
12	$Pd(OAc)_2$	TFA	toluene	60	14
13	$Pd(OAc)_2$	TFA	CH_3CN	100	58
14	$Pd(OAc)_2$	TFA	CH_3CN	40	24

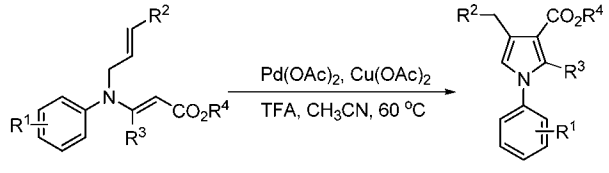
[a]Reaction conditions: **1a** (0.2 mmol), [Pd] (5 mol %), $Cu(OAc)_2$ (2.2 equiv), acid (1.0 equiv) in CH_3CN (2 mL) at 60 °C, 12 h, in air; isolated yield.

facile construction of 1,3,4-trisubstituted pyrroles that have not been easily accessible. *N*-Allyl aryl tertiary enamines with electron-donating groups, such as methyl and methoxyl, or electron-withdrawing groups, such as fluoro, chloro, and bromo, on the aryl rings reacted smoothly and resulted in the corresponding 1,3,4-trisubstituted pyrroles **2b**–**2j** in good yields, thus indicating that the electronic nature of the substrates has little influence on the cyclization reaction. Ethyl 4-methyl-1-(*o*-tolyl)-1*H*-pyrrole-3-carboxylate **2e** was obtained in a slightly lower yield which may be due to the steric effect of the *ortho*-methyl group on the aryl ring. *β*-Naphthyl substituted tertiary enamine **1k** was also tolerated and afforded the corresponding **2k** in 45% yield.

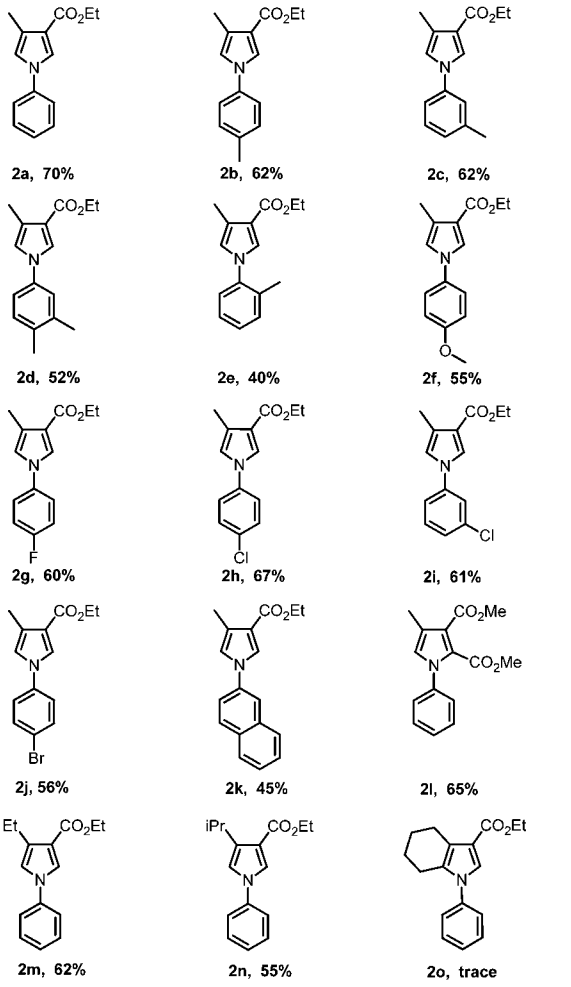
In addition, phenyl tertiary enamines with a difference in vinyl or allyl groups, such as dimethyl 2-(allyl(phenyl)amino)-maleate **1l**, (*E*)-ethyl 3-(but-2-en-1-yl(phenyl)amino)acrylate **1m**, and (*E*)-ethyl 3-((3-methylbut-2-en-1-yl)(phenyl)amino)-acrylate **1n**, show good reactivity, producing the corresponding pyrroles **2l**–**2n** in 55–65% yields. However, no reaction occurred when (*E*)-ethyl 3-(cyclohex-2-en-1-yl(phenyl)amino)-acrylate **1o** was employed as the substrate.

Encouraged by the aforementioned results, we envision that the palladium-catalyzed intramolecular oxidative coupling reaction may occur at a vinyl C–H bond and an aryl C–H bond to afford 1,3-disubstituted indoles when *N*-alkyl aryl tertiary enamines were used as the substrates. After a brief survey of reaction conditions,[14] a 68% yield of butyl 1-methyl-1*H*-indole-3-carboxylate **4a** was obtained in the presence of $PdCl_2$, $Cu(OAc)_2$, and TFA in CH_3CN at 100 °C (Table 2, entry 1). Therefore, a series of *N*-alkyl indole-3-carboxylate **4a**–**4h** were synthesized (Table 2). It should be noted that 1,7-annulated indole-3-carboxylate **4i** which was an important synthetic precursor for a high-affinity 5-HT3 receptor antagonist was easily synthesized in 51% yield,[15] thus implying that our method is of synthetic utility (Table 2, entry 9). However, when (*E*)-ethyl 3-(diphenylamino)acrylate **3j** was employed as the substrate, the corresponding ethyl 1-phenyl-

Scheme 2. Palladium-Catalyzed Oxidative Cyclization of *N*-Allyl Aryl Tertiary Enamines for Synthesis of 1,3,4-Trisubstituted Pyrroles[a]



1 2



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (2.2 equiv), TFA (1.0 equiv) in CH_3CN (2 mL) at 60 °C, 8–12 h, in air; isolated yields.

1*H*-indole-3-carboxylate **4j** was obtained only in 15% yield, along with 41% of diphenylamine as the byproduct.

On the basis of the above results and previous reports, a tentative mechanism for the reaction is proposed in Scheme 3. The reaction begins with an electrophilic palladation of the vinyl C–H bond of tertiary enamine **1** under acidic conditions to give a vinylpalladium intermediate **A**.[11,13] Intramolecular 5-exo-trig cyclization of **A** affords the intermediate **B**, which undergoes *β*-hydride elimination and tautomerization to form the 1,3,4-trisubstituted pyrrole **2** (Cycle I).[9] Alternatively, intramolecular aryl C–H activation of the vinylpalladium intermediate **A**′ gives the intermediate **D**.[8,11,16] Then, reductive elimination of intermediate **D** produces the 1,3-disubstituted indole **4** (Cycle II). In these catalytic cycles, the Pd(0) was

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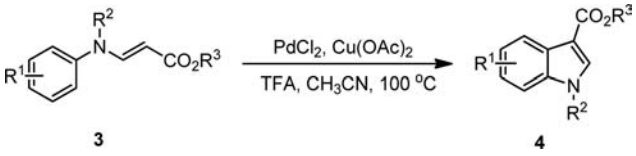
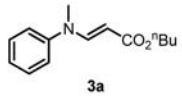
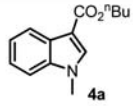
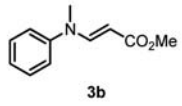
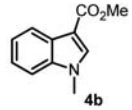
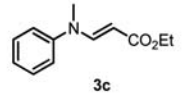
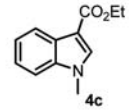
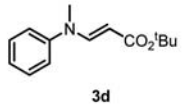
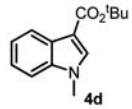
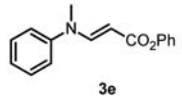
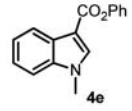
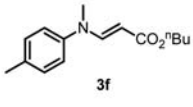
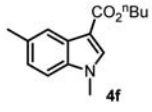
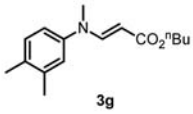
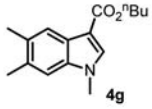
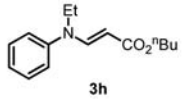
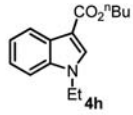
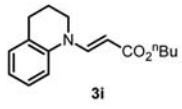
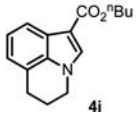
Table 2. Palladium-Catalyzed Oxidative Cyclization of *N*-Alkyl Aryl Tertiary Enamines for Synthesis of 1,3-Disubstituted Indoles[a]



3 4

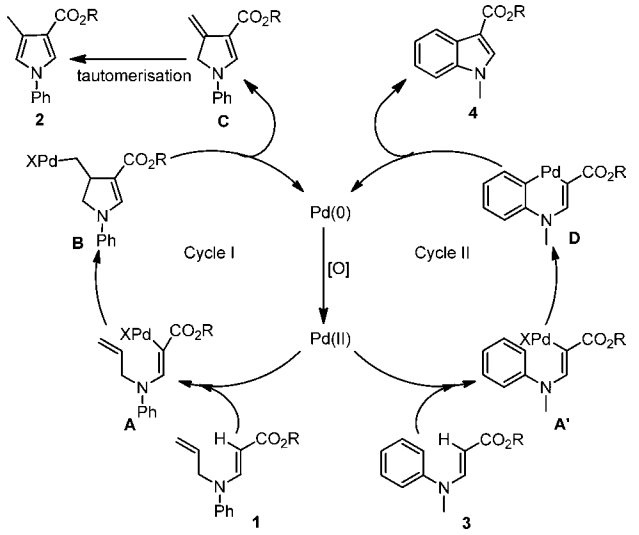
entry	substrate	product	yield (%)
1	 3a	 4a	68 (61)[b]
2	 3b	 4b	55
3	 3c	 4c	55
4	 3d	 4d	61
5	 3e	 4e	50
6	 3f	 4f	60
7	 3g	 4g	52
8	 3h	 4h	65
9	 3i	 4i	51

[a]Reaction conditions: **3** (0.2 mmol), $PdCl_2$ (5 mol %), $Cu(OAc)_2$ (2.0 equiv), TFA (1.0 equiv) in CH_3CN (2 mL) at 100 °C, 12−16 h, in air; isolated yield. [b]The reaction was carried in 0.5 mmol scale.

assumed to be oxidized by $Cu(OAc)_2$ to regenerate the active Pd(II) catalyst.

In summary, we have developed a novel palladium-catalyzed intramolecular oxidative cyclization of tertiary enamines for the synthesis of substituted pyrroles and indoles. Palladium-catalyzed vinyl C−H activation of a tertiary enamine sequence of intramolecular oxidative cyclization was achieved by employing trifluoroacetic acid as an additive. The reaction shows a good method for the rapid elaboration of readily available tertiary enamines into a variety of substituted 1,3,4-trisubstituted pyrroles and 1,3-disubstituted indoles. Further studies on the substrate scope and mechanism of the reaction are underway in our laboratory.

Scheme 3. A Tentative Mechanism for Palladium-Catalyzed Oxidative Cyclization of Tertiary Enamines



■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all products. 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.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Fan, H.; Peng, J. M.; Hamann, T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (c) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787. (d) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Chem. Rev.* **2003**, *103*, 17.

(2) For reviews on methods for the synthesis of pyrroles and indoles, see: (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. For some recent indole syntheses, see: (g) Shan, D.; Jia, Y. *Chin. J. Org. Chem.* **2013**, *33*, 1144. (h) Huestis, M. P.; Chan, L. N.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (i) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (j) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. (k) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. (l) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int.*

Ed. **2009**, *48*, 4572. (m) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056.
(3) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433. For some recent pyrrole syntheses, see: (d) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (e) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146. (f) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (g) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012. (h) Iida, K.; Miura, T.; Ando, J.; Saito, S. *Org. Lett.* **2013**, *15*, 1436. (i) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (j) Toh, K. K.; Biswas, A.; Wang, Y.-F.; Tan, Y. Y.; Chiba, S. *J. Am. Chem. Soc.* **2014**, *136*, 6011. (k) Du, W.; Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2014**, DOI: 10.1039/C4CC03129F. (l) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Green Chem.* **2014**, *16*, 112.
(4) (a) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, *12*, 4066. (b) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046. (c) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926. (d) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (e) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873. (f) Zhu, R.; Xing, L.; Liu, Y.; Deng, F.; Wang, X.; Hu, Y. *J. Organomet. Chem.* **2008**, *693*, 3897. (g) Tanaka, K.; Otake, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 3953. (h) Aoyagi, Y.; Mizusaki, T.; Shishikura, M.; Komine, T.; Yoshinaga, T.; Inaba, H.; Ohta, A.; Takeya, K. *Tetrahedron* **2006**, *62*, 8533.
(5) (a) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (b) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (c) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (d) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (e) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (f) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136. (g) Xu, Y.-H.; He, T.; Zhang, Q.-C.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 2784. (h) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608. (i) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem.—Eur. J.* **2014**, *20*, 1839. (j) Guan, Z.-H.; Li, L.; Ren, Z.-H.; Li, J.; Zhao, M.-N. *Green Chem.* **2011**, *13*, 1664.
(6) (a) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811. (b) Ragaini, F.; Cenini, S.; Brignoli, D.; Gasperini, M.; Gallo, E. *J. Org. Chem.* **2003**, *68*, 460. (c) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977.
(7) (a) Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (b) Neumann, J. J.; Rakshit, S.; Droge, T.; Wurtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298.
(8) (a) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098. (b) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220.
(9) (a) Shi, Z.; Suri, M.; Glouris, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 4892. (b) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (c) Li, M.; Wu, K.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, *49*, 5853.
(10) (a) Jia, Z.; Nagano, T.; Li, X.; Chan, A. S. C. *Eur. J. Org. Chem.* **2013**, 858. (b) He, Z.; Liu, W.; Li, Z. *Chem.—Asian J.* **2011**, *6*, 1340. (c) He, Z.; Li, H.; Li, Z. *J. Org. Chem.* **2010**, *75*, 4636. (d) Guan, Z.-H.; Yan, Z.-Y.; Ren, Z.-H.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2010**, *46*, 2823.
(11) (a) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708. (b) Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7333. (c) Pankajakshan, S.; Xu, Y.-H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5701.
(12) (a) Wang, X.; Turunen, B. J.; Leighty, M. W.; Georg, G. I. *Tetrahedron Lett.* **2007**, *48*, 8811. (b) Kranke, B.; Kunz, H. *Org. Biomol. Chem.* **2007**, *5*, 349. (c) Comins, D. I.; Joseph, S. P.; Chen, X. *Tetrahedron Lett.* **1995**, *36*, 9141.
(13) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (c) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (d) Oyamada, J.; Kitamura, T. *Chem. Commun.* **2008**, 4992. (e) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (f) Ji, X.; Huang, H.; Wu, W.; Li, X.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 11155.
(14) For optimization of reaction conditions, see Supporting Information.
(15) van Wijngaarden, I.; Hamminga, D.; van Hes, R.; Standaar, P. J.; Tipker, J.; Tulp, M. T. M.; Mol, F.; Oliver, B.; de Jonge, A. *J. Med. Chem.* **1993**, *36*, 3693.
(16) (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.