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Strain-Promoted Oxidative Annulation of Arynes and Cyclooctynes with Benzamides: Palladium-Catalyzed C−H/N−H Activation for the Synthesis of *N*-Heterocycles

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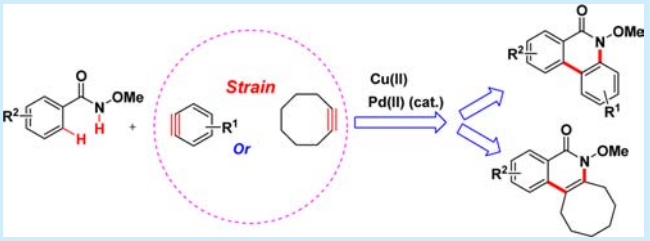
Supporting Information

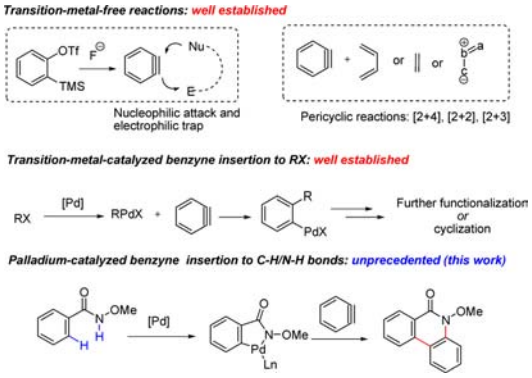
ABSTRACT: Strained alkynes include arynes and cyclooctynes reacted with *N*-methoxyamides through palladium-catalyzed C−H/N−H activation for the first time. A variety of important N-heterocycles such as phenanthridinones and isoquinolones were constructed in one step with high efficiency.



Arynes are reactive transient intermediates. Inherent strain makes them great energy reservoirs and defines their unusually high reactivity toward nucleophiles. Thus, arynes have emerged as powerful synthons widely used in synthesis of heterocycles and complex natural products.[1] Well-established aryne transformations include nucleophilic addition, followed by electrophilic trap cascade reactions and pericyclic reactions such as [4 + 2]- and [2 + 2]-cycloadditions.[2] Recently, transition metals such as palladium and nickel were introduced into benzyne chemistry, and many unprecedented transformations such as [2 + 2 + 2]-cycloaddition have been developed. Larock,[3a−d] Greaney,[3e,f] Cheng,[3g−j] Zhu,[3k] and others demonstrated that the benzynes could insert into the organopalladium species RPdX to produce the arylpalladium intermediate. Subsequent intramolecular cyclization gave polyaromatics and heterocycles, and coupling with a third component gave 1,2-difunctionalized benzene (Scheme 1).[3] Transition-metal-catalyzed C−H functionalization has emerged as a powerful synthetic strategy avoiding the preactivation of substrates. Palladium-catalyzed one-pot C−H activation, subsequent benzyne insertion and cyclization sequence is a very attractive synthetic strategy to build up structural complex molecules with great atom and step economy. However, to the best of our knowledge, this type of transformation has never been reported before. One possible reason is that the unstable and highly reactive intermediate arynes undergo many side reactions under the relatively harsh C−H activation conditions such as strong acid additive or high temperature. Herein, we report the first example of such a process which leads to the rapid construction of important N-heterocycles including phenanthridinones and isoquinolones (Scheme 1).

Recently, transition-metal-catalyzed C−H/N−H activation and cyclization have been developed as a very important approach for the synthesis of nitrogen-containing heterocycles. In particular, the Rh(III)-catalyzed cyclization of benzamide has been extensively explored in recent years. A series of five-, six-, or seven-membered N-heterocycles could be achieved by the direct annulation of benzamides with alkenes, alkynes, and other molecules.[4] Recently, ruthenium[5] and palladium[6] catalysts have also been employed in such processes.[7] Extention of this strategy to the coupling of benzamides with arynes and cycloalkynes is very attractive but also very challenging. The highly reactive benzyne intermediate is prone to many undesired side reactions such as trimerization in the presence of transition metal under the relative harsh C−H activation conditions. To avoid this compatibility issue, Larock[8] and Jiao[6a] used an elegant one-pot, two-step procedure to synthesize carbazoles. The mechanism involves a nucleophilic attack of anilines to the benzyne intermediate generating diarylamines, which subsequently undergoes palladium-catalyzed direct arylation or C−H/C−H coupling without isolation. To overcome this problem, we

Scheme 1. Synthetic Design on Benzyne Chemistry



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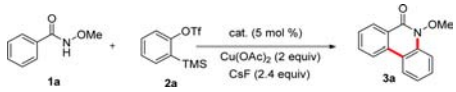
envision that, first, a mild basic C−H activation condition compatible to benzyne must be developed, and second, to reduce the undesired side reactions of the active benzyne intermediate, we must keep it at very low concentration or slow down its formation rate to synchronize with the slow turnover of C−H activation.

To validate this concept, the Kobayashi precursor **2a** was chosen as the coupling partner because the rate of benzyne generation can be controlled by varying the concentration of fluoride ion in solution. At the outset, *N*-methoxybenzamide **1a** and benzyne precursor **2a** were subjected to this reaction by using $Cu(OAc)_2$ as the oxidant in the presence of Rh(III), Ru(II), and Pd(II) catalysts. After many trials, we found that the mostly used Rh(III) and Ru(II) catalysts were not effective and the starting material **1a** was recovered (Table 1, entries 1−3).

Table 1. Optimization of Reaction Conditions[a]



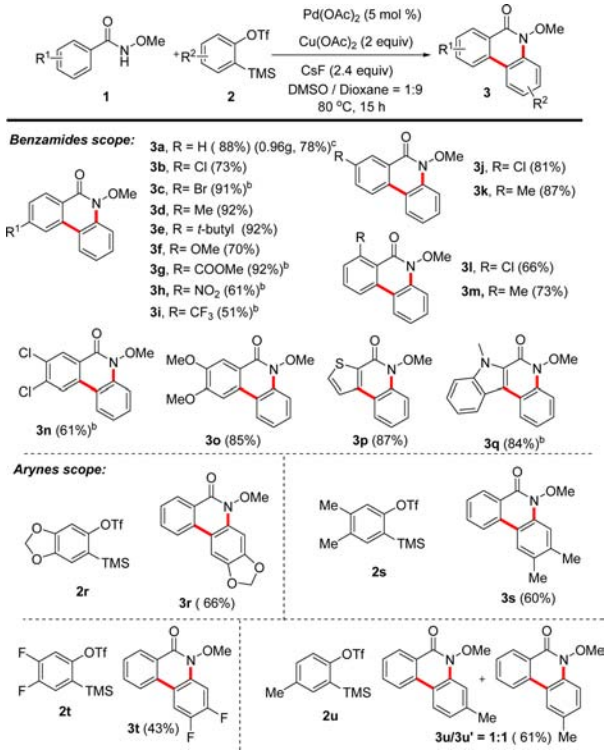
entry	cat.	additive	solvent	temp (°C)	yield[e] (%)
1	$[Cp^*RhCl_2]_2$		DMF	60	0
2	$[RuCl_2(p\text{-cymene})]_2$		DMF	60	0
3	$Pd(OAc)_2$		DMF	60	0
4	$Pd(OAc)_2$	TBAB	DMF	60	11
5	$Pd(OAc)_2$	TBAB	THF	60	43
6	$Pd(OAc)_2$	TBAB	CH_3CN	60	31
7	$Pd(OAc)_2$	TBAB	toluene	60	35
8	$Pd(OAc)_2$	TBAB	CH_3COOH	60	0
9	$Pd(OAc)_2$	TBAB	DMSO	60	trace
10	$Pd(OAc)_2$	TBAB	NMP	60	trace
11	$Pd(OAc)_2$	TBAB	CH_3CN	80	52
12	$Pd(OAc)_2$	TBAB	dioxane	80	60
13[b]	$Pd(OAc)_2$	TBAB	dioxane	80	67
14[b]	$Pd(OAc)_2$	TBAB	dioxane	90	48
15[b,c]	$Pd(OAc)_2$	TBAB	dioxane	80	41
16[b,d]	$Pd(OAc)_2$	TBAB	dioxane	80	**88**
17[b,d]		TBAB	dioxane	80	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (5 mol %), $Cu(OAc)_2$ (0.2 mmol), CsF (0.24 mmol), TBAB (0.1 mmol), solvent (1 mL), 15 h. [b]4 Å molecular sieves (100 mg) were added. [c]TBAF (0.24 mmol) was used to replace CsF. [d]DMSO (0.1 mL), dioxane (0.9 mL). [e]isolated yield. TBAB = tetra-*n*-butylammonium bromide, TBAF = tetra-*n*-butylammonium fluoride.

When we carried out this reaction with 1 equiv of TBAB as additive[7b] in the presence of 5 mol % palladium acetate at 60 °C in DMF solution, the desired phenanthridinone **3a** could be isolated in 11% yield (Table 1, entry 4). A detailed screening of different solvents revealed that the yield could be improved to 60% in dioxane at 80 °C (Table 1, entry 12). When CsF was replaced by more soluble TBAF, which could generate benzyne instantly, a much lower yield was observed (Table 1, entry 15). To our delight, when 0.1 mL of DMSO[9] was added into the reaction system, the highest yield 88% was achieved (Table 1, entry 16). A blank test indicated that no product was formed without palladium catalyst (Table 1, entry 17). When the protecting group on the nitrogen atom was switched to Ph, CH_2Ph, *n*-propyl, or OAc, no desired products were observed, which highlighted the importance of the methoxyl group.[10] In addition, the produced heterocycles could be easily deprotected by cleavage of the N−OMe bond.[6c,e]

With the optimized conditions in hand, the scope of oxidative coupling of various benzamides with different benzyne precursors was extensively investigated. As summarized in Table 2, a large variety of phenanthridinone derivatives[3d,4y,6d,e,11]

Table 2. Annulation of Various Benzamides with Benzyne Precursors[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (0.4 mmol), CsF (0.48 mmol), TBAB (0.2 mmol), 4 Å molecular sieves (100 mg), solvent (1 mL), 15 h, isolated yield. [b]$Pd(OAc)_2$ (10 mol %). [c]Gram-scale experiments.

were synthesized in good to excellent yields with very wide scope. For the *para*-substituted substrates **1b−i**, the reaction afforded the desired products in good to excellent yields (**3b−i**). A series of functional groups such as chloro, bromo, methoxyl, ester, nitro, and trifluoromethyl were well tolerated under these reaction conditions, thus allowing further functionalization if needed. Substitution at the *meta* position delivered the C−H activation at the less hindered position, and the corresponding products could be isolated in very good yields (**3j,k**). Benzamides with a chloro or methyl group at the *ortho* position were also suitable for this transformation, giving the corresponding phenanthridinones in 66% and 73% yields (**3l,m**). Multi-substituted benzamides also reacted efficiently to furnish the sterically favored polysubstituted phenanthridinones as the single products in good yields (**3n,o**). In addition, thiophene-2-caboxamides and indolyl-2-carboxamides were also applicable in this transformation and gave the corresponding poly-heterocycles in 87% and 84% yield (**3p,q**). To further test the practicality of this methodology, a gram-scale experiment was carried out, and the desired product was isolated in 78% yield (0.96 g).

Then the scope of various functionalized arynes was examined. Pleasingly, all arynes bearing both electron-donating and

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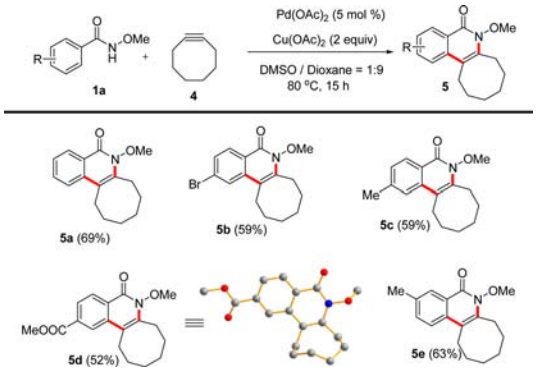
electron-withdrawing groups were compatible with the standard conditions, and the corresponding N-heterocycles could be obtained in reasonable yield. When unsymmetrical ayne **2u** was used in this reaction, equal amounts of two regioisomers were obtained (**3u**/**3u**′ = 1:1). These results clearly indicated the formation of aryne intermediates in the reaction.

Cyclooctynes are another type of strained alkynes used in strain-promoted click reaction with azides or nitrones for the bioorthogonal labeling and imaging of living cells.[12] Incorporation of cyclooctynes with benzamides represents an interesting method to construct isoquinolone derivatives bearing an eight-membered ring, which is difficult to access by using other methods. Cyclooctyne **4** was prepared in advance, and the reaction of **4** with benzamide **1a** under the above optimal conditions failed to give the desired product; only starting **1a** was recovered. To mimic the previous slow formation of the benzyne intermediate, the cyclooctyne was diluted and was slowly injected into the reaction system in 15 h via syringe pump. Gratefully, the target isoquinolone **5a** was isolated in 69% yield. Then the substrate scope of this reaction was explored, and various benzamides were reacted with cyclooctyne **4** smoothly, achieving diverse novel isoquinolone derivatives in respectable yields (Table 3). The structure of isoquinolone **5d** was unambiguously characterized by single X-ray analysis, and interestingly, the eight-membered ring takes a boat conformation in solid state.

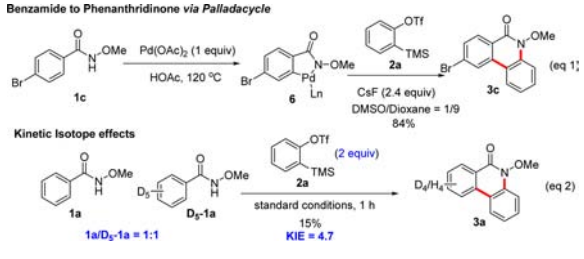
Table 3. Annulation of Benzamides with Cyclooctyne[a]



[a]Reaction conditions: **1a** (0.2 mmol), **4** (0.6 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (0.4 mmol), TBAB (0.2 mmol), solvent (2 mL), slow addition of the solution of **4** in 1.5 mL of solvent with syringe pump over 15 h, isolated yield.

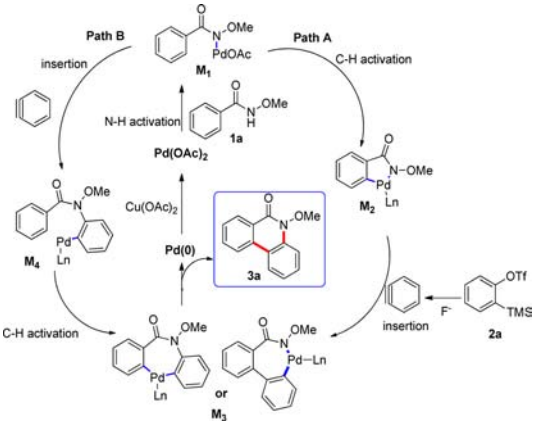
Several experiments were conducted to explore the reaction mechanism. The palladacycle **6**, which was prepared by refluxing in HOAc following Wang's method,[6d] was subjected to the standard conditions, and the target product **3c** was isolated in 84% yield (Scheme 2, eq 1). This experiment demonstrated the palladacycle is the possible reaction intermediate. Since C−H activation is involved in this reaction to form the palladacycle, an intermolecular kinetic isotope (KIE) effect experiment was conducted. A primary KIE value of 4.7 was observed and suggested the C−H activation step is the rate-determining step (Scheme 2, eq 2).

Scheme 2. Mechanism Studies



On the basis of the above results and previous reports, a tentative mechanism is proposed in Scheme 3. The reaction of **1a**

Scheme 3. Possible Pathways



with $Pd(OAc)_2$ through sequential N−H and C−H activation generated the five-membered palladacycle $\mathbf{M_2}$, and subsequent benzyne insertion formed the seven-membered intermediate $\mathbf{M_3}$. This intermediate went through reductive elimination to form the product **3a** and release Pd(0), which was reoxidized to Pd(II) by $Cu(OAc)_2$ (path A). However, another reaction pathway was also possible (path B): The N−H activation intermediate $\mathbf{M_1}$ reacted with benzyne to form the intermediate $\mathbf{M_4}$, which would also form the same seven-membered intermediate $\mathbf{M_3}$ through an intramolecular C−H activation.

In summary, we developed a novel palladium-catalyzed strain releasing oxidative annulation between benzamides with arynes and cyclooctynes, leading to the concise and flexible synthesis of different *N*-heterocycles.[13] Making the C−H activation and reactive aryne intermediate compatible is the determinant success of this reaction. This new method represents a new direction for transition-metal-involved benzyne chemistry and also C−H functionalization. Studies to elucidate the detailed mechanism and further applications of the current protocol to other heteroaynes are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. 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) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (b) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (c) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (e) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (f) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett* **2011**, 2599.

(2) For transition-metal-free reactions: (a) Chakrabarty, S.; Tebben, I. L.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2968. (b) Li, R.; Wang, X.; Wei, Z.; Wu, C.; Shi, F. *Org. Lett.* **2013**, *15*, 4366. (c) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10224. (d) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54. (e) Shen, C.; Yang, G.; Zhang, W. *Org. Lett.* **2013**, *15*, 5722. (f) Bunescu, A.; Piemontesi, C.; Wang, Q.; Zhu, J. *Chem. Commun.* **2013**, *49*, 10284. (g) Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 4620. (h) Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006. (i) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666. (j) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. (k) Cant, A. A.; Roberts, L.; Greaney, M. F. *Chem. Commun.* **2010**, *46*, 8671.

(3) (a) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223. (c) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (d) Lu, C. A.; Dubrovskiy, V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 8648. (e) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (f) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *Org. Lett.* **2007**, *9*, 5589. (g) Jayanth, T. T.; Cheng, C.-H. *Chem. Commun.* **2006**, 894. (h) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5921. (i) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391. (j) Parthasarathy, K.; Han, H.; Prakash, C.; Cheng, C.-H. *Chem. Commun.* **2012**, *48*, 6580. (k) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572. (l) Dong, Y.; Liu, B.; Chen, P.; Liu, Q.; Wang, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3442. (m) Qiu, Z.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 5729. (n) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431.

(4) (a) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (b) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (c) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (d) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (e) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (f) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (g) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583. (h) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636. (i) Shi, Z.; Tang, C.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 2695. (j) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (k) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372. (l) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768. (m) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426. (n) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (o) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (p) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. (q) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (r) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (s) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896. (t) Du, Y.; Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 12074. (u) Zhu, C.; Xie, W.; Falck, J. R. *Chem.—Eur. J.* **2011**, *17*, 12591. (v) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5393. (w) Yu, D.; de Azambuja, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 2754. (x) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421. (y) Karthikeyan, J.; Haridharan, R.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12343. (z) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212.

(5) (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (c) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177. (d) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573. (e) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12873. (f) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136. (g) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(6) (a) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (b) Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 2908. (c) Zhong, H.; Yang, D.; Wang, S.; Huang, J. *Chem. Commun.* **2012**, *48*, 3236. (d) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380. (e) Karthikeyan, J.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 9880.

(7) (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895. (c) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (d) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10610. (e) He, G.; Zhao, Y.; Zhang, S.; Liu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (f) He, G.; Zhang, S.; Nack, W. A.; Li, Q.; Chen, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (g) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (h) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 8850. (i) Song, W.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638. (j) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 14196. (k) Tang, Q.; Xia, D.; Jin, X.; Zhang, Q.; Sun, X.-Q.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 4628. (l) Nan, J.; Zuo, Z.; Luo, L.; Bai, L.; Zheng, H.; Yuan, Y.; Liu, J.; Luan, X.; Wang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 17306. (m) He, R.; Huang, Z.-T; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950. (n) Muralirajan, K.; Cheng, C.-H. *Adv. Synth. Catal.* **2014**, *356*, 1571. (o) Mehta, V. P.; García-López, J.-A.; Greaney, M.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1529. (p) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608. (q) Manna, S.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7324. (r) Xu, Y.-H.; He, T.; Zhang, Q.-C.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 2784.

(8) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739.

(9) (a) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276. (b) Song, C.; Ju, L.; Wang, M.; Liu, P.; Zhang, Y.; Wang, J.; Xu, Z. *Chem.—Eur. J.* **2013**, *19*, 3584. (c) Song, C.; Dong, S.; Feng, L.; Peng, X.; Wang, M.; Wang, J.; Xu, Z. *Org. Biomol. Chem.* **2013**, *11*, 6258. (d) Song, C.; Sun, D.; Peng, X.; Bai, J.; Zhang, R.; Hou, S.; Wang, J.; Xu, Z. *Chem. Commun.* **2013**, *49*, 9167. (e) Song, C.; Wang, J.; Xu, Z. *Org. Biomol. Chem.* **2014**, *12*, 5802.

(10) For the first use of CONHOMe as a directing group, see: Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

(11) (a) Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 173. (b) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468. (c) Bhakuni, B. S.; Kumar, A.; Balkrishna, S. J.; Sheikh, J. A.; Konar, S.; Kumar, S. *Org. Lett.* **2012**, *14*, 2838. (d) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759.

(12) (a) Dommerholt, J.; Schmidt, S.; Temming, R.; Hendriks, L. J. A.; Rutjes, F. P. J. T.; van Hest, J. C. M.; Lefeber, D. J.; Friedl, P.; van Delft, F. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9422. (b) Chen, W.; Wang, D.; Dai, C.; Hamelberg, D.; Wang, B. *Chem. Commun.* **2012**, *48*, 1736. (c) Poole, T. H.; Reisz, J. A.; Zhao, W.; Poole, L. B.; Furdui, C. M.; King, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6167.

(13) During the preparation of the manuscript, a similar transformation was reported; see: Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 12116.