ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

Rhodium-Catalyzed Annulation of Tertiary Aniline *N*-Oxides to *N*-Alkylindoles: Regioselective C−H Activation, Oxygen-Atom Transfer, and *N*-Dealkylative Cyclization

Bin Li,*[,†] Hong Xu,[†] Huanan Wang,[†] and Baiquan Wang*[,†,‡,§]

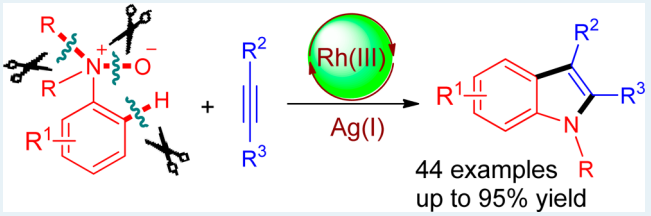
[†]State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Supporting Information

ABSTRACT: [Cp*Rh^{III}]-catalyzed annulation of tertiary aniline *N*-oxides with alkynes was reported to achieve the challenging *ortho* C−H functionalization of tertiary anilines via N−O bond acting as a traceless directing group. More significantly, this system represents the first example which integrates C−H activation, oxygen-atom transfer, and *N*-dealkylative cyclization in one reaction. This unprecedented coupling reaction has allowed the construction of *N*-alkylindole derivatives in high efficiency with broad substrate scope and good functional group tolerance.



KEYWORDS: *C−H activation, C−N bond cleavage, cyclization, oxygen-atom transfer, tertiary aniline N-oxides*

As a powerful tool for synthetic innovation, transition-metal-catalyzed direct functionalization of C−H bonds led to a more step-economical and waste-reducing synthetic route compared with classical organic synthesis.[1] During the past decades, this new strategy has been intensively studied and well-identified for organic synthesis, medicinal chemistry, and materials science.[2] Despite the fact that the direct C−H transformation of various compounds has been established, tertiary anilines remain a big challenge for transition-metal-catalyzed *ortho*-selective aromatic C−H functionalization, partly due to the steric hindrance of tertiary amino groups. Up to now, only a few examples have been reported for this purpose.[3] Lei and co-workers demonstrated the first palladium/copper-catalyzed oxidative *ortho* C−H alkenylation/*N*-dealkylative carbonylation of tertiary anilines.[3a] Later, the group of You developed a rhodium-catalyzed *ortho* C−H alkenylation of tertiary aniline *N*-oxides to form 2-alkenylated tertiary anilines.[3b] Very recently, Zhou et al. disclosed a rhodium-catalyzed *ortho* C−H functionalization of tertiary aniline *N*-oxides with diazomalonates to access aminomandelic acid derivatives.[3c] Given that tertiary anilines are important synthetic building blocks for pharmaceuticals, agrochemicals, and organic functional materials,[4] the development of new transformation of tertiary anilines through *ortho*-selective C−H activation is highly desirable. On the other hand, C−N bond activation is one of the central topics in organic chemistry which provides nitrogen and/or carbon sources for the synthesis of the desired product,[5] and transformation of C−N bond has become a hot area in organic synthesis over the past years. In this context, however, C−N bond cleavage of tertiary anilines has been less investigated, especially the employment of tertiary anilines as nitrogen nucleophiles after cleavage of C−N bond.[3a,6]

Meanwhile, it is known that the integration of C−H activation and O atom transfer (OAT) has been realized by the utilization of [Cp*Rh^{III}] catalyst recently.[3c,7] In this regard, the elegant contributions from the research groups of Li, Chang, Wang, Liu and Lu, and Zhou have disclosed that the catalytic OAT took place in the redox-neutral coupling of quinoline *N*-oxides and arylnitrones with alkynes, and tertiary aniline *N*-oxides with diazomalonates. The N−O bonds served as both directing groups for C−H activation and as oxygen-atom donors in these processes.

Despite these impressive advances, we envisioned that combination of C−H activation, OAT, and C−N bond cleavage in one transformation would be highly interesting and attractive to form nitrogen-containing heterocycles when readily available tertiary anilines *N*-oxides and internal alkynes are used as common starting materials. In line with our interest in heterocycle synthesis via metal-catalyzed C−H coupling with alkynes,[8] we here present our new development of rhodium-catalyzed oxidative annulation of tertiary anilines *N*-oxides with alkynes through *N*-oxide behaving as a traceless directing group and *N*-alkyl as leaving group to provide an efficient and straightforward access for the preparation of *N*-alkyl substituted indole derivatives (Scheme 1). Importantly, the resulting indole

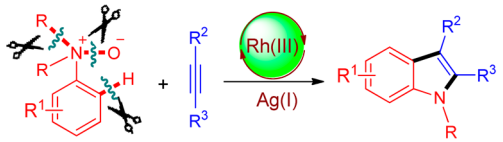
Received: January 30, 2016
Revised: April 15, 2016

© XXXX American Chemical Society

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862

products are widely found as core structural units in both biologically active natural products and pharmaceutical products.[9−11]

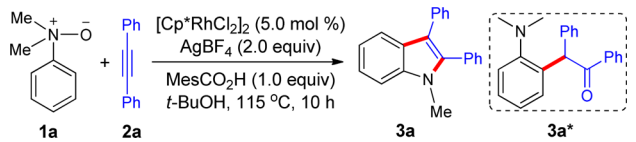
Scheme 1. Rhodium-Catalyzed Oxdative Coupling of Tertiary Anilines *N*-Oxides with Alkynes



- Combination of C-H activation, OAT, and C-N cleavage
- *ortho* C-H functionalization of tertiary anilines
- *N*-oxide as traceless directing group
- High regioselectivity and broad substrate scope

We initiated our optimization experiments with *N*,*N*-dimethylaniline *N*-oxide (**1a**) and diphenylacetylene (**2a**) as model substrates for the cyclization reaction (Table 1). After many trials, we were pleased to find that the reaction indeed did proceed leading to annulation product in the presence of a rhodium catalyst. Under the standard reaction conditions, *N*-methyl-2,3-diphenylindole (**3a**) was isolated in 80% yield (entry 1). Interestingly, good to high yields of **3a** were obtained in alcohol solvents and *t*-BuOH was found to be most optimal (entries 1−3), whereas the reactions were totally inactive when MeCN and DMF were employed as solvents (entries 4 and 5). The reaction efficiency was also sensitive to the reaction temperatures (entry 7). Notably, the addition of $AgBF_4$ (2 equiv) is crucial for this transformation (entry 8), which provided higher yields than other metal salts such as $AgClO_4$, $AgNO_3$, AgOAc or $Cu(BF_4)_2{\cdot}6H_2O$ (entries 9−12). It was observed that the omission of $MesCO_2H$ dramatically affects the reaction efficiency (entry 13), while a relative lower yield of **3a** was obtained by increasing the loading of $MesCO_2H$ (entry 14). Other carboxylic acids, for instance, PivOH or 1-$AdCO_2H$, are inferior to $MesCO_2H$ as an additive (entries 15 and 16). The efficiency of the reaction was not improved with addition of CsOAc[12] as additive (entry 17) or changing the ratio of **1a**:**2a** (from 3:1 to 2:1 or 1:2) (entries 18 and 19). No desired product was obtained in the absence of rhodium catalyst (entry 20), and a decrease in the amount of catalyst resulted in lower conversion (entry 21). Finally, further experiments revealed that other metal catalysts like $[Cp^*IrCl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ displayed very low catalytic activity under the present reaction conditions (entries 22 and 23). It should be noted that complex **3a***, characterized as an OAT product, was isolated in several studies during the course of optimization process (entries 8, 10, and 11). This observation is noteworthy providing a hint for mechanistic understanding (vide infra).

Table 1. Optimization Studies[a]



1a 2a 3a 3a*

entry	change from the standard conditions	yield (%)[b] 3a	3a*[c]
1	standard conditions	80	0
2	*t*-AmOH instead of *t*-BuOH	65	0
3	*i*-PrOH instead of *t*-BuOH	62	0
4	MeCN instead of *t*-BuOH	0	0
5	DMF instead of *t*-BuOH	<5	0
6	130 °C	80	0
7	100 °C	74	0
8	1.0 equiv of $AgBF_4$	34	15
9	2.0 equiv of $AgClO_4$ instead of $AgBF_4$	74	0
10	2.0 equiv of $AgNO_3$ instead of $AgBF_4$	22	16
11	2.0 equiv of AgOAc instead of $AgBF_4$	6	18
12	2.0 equiv of $Cu(BF_4)_2{\cdot}6H_2O$ instead of $AgBF_4$	<5	0
13	without $MesCO_2H$	57	<5
14	2.0 equiv of $MesCO_2H$	70	0
15	1.0 equiv of PivOH instead of $MesCO_2H$	60	<5
16	1.0 equiv of 1-$AdCO_2H$ instead of $MesCO_2H$	64	0
17	add 20 mol % of CsOAc	78	0
18	0.40 mmol of **1a**	71	0
19	0.20 mmol of **1a** with 0.40 mmol of **2a**	67	0
20	without $[Cp^*RhCl_2]_2$	0	0
21	2.5 mol % of $[Cp^*RhCl_2]_2$	32	0
22	5.0 mol % of $[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	<5	0
23	5.0 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ instead of $[Cp^*RhCl_2]_2$	0	0

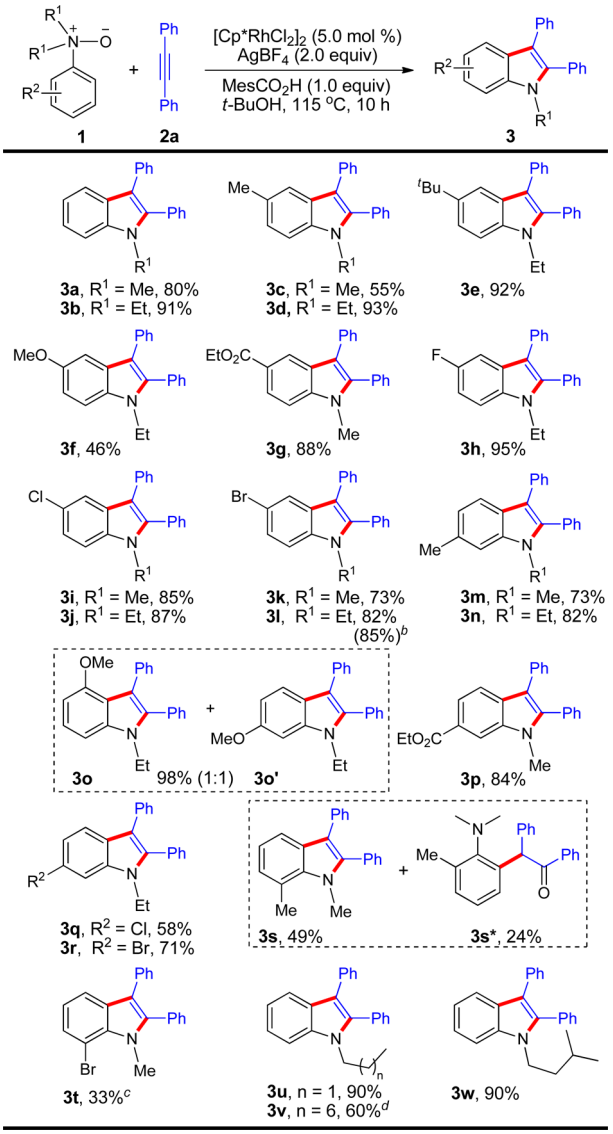
[a]Standard reaction conditions: **1a** (0.60 mmol), **2a** (0.20 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgBF_4$ (2.0 equiv), $MesCO_2H$ (1.0 equiv), *t*-BuOH (2.0 mL), sealed tube under Ar atmosphere, 115 °C, 10 h. [b]Yields of isolated products. Cp* = pentamethylcyclopentadienyl, Mes = 2,4,6-trimethylphenyl, DMF = *N*,*N*-dimethylformamide, *t*-Am = *tert*-amyl, Piv = pivaloyl, Ad = adamantyl. [c]Characterized as an OAT product.

With the promising optimal conditions, the reaction scope with respect to the tertiary aniline *N*-oxides in reaction with **2a** was investigated (Scheme 2). The annulation proceeded smoothly with tertiary aniline *N*-oxides bearing diverse arene substituents to provide the corresponding indole derivatives in moderate to excellent yields. For *para*-substituted substrates, electron-donating groups resulted in relative lower reaction efficiency, as exemplified by **3c** (55%) and **3f** (46%). The examination of the *meta*-substituted aniline *N*-oxides scope showed that cyclization commonly occurred at the less steric hindered aromatic C−H bond with exclusive regioselectivity (**3m**, **3n**, **3p**, **3q**, and **3r**). The structures of **3p** and **3r** were unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information).[13] In comparison, two regioisomers **3o** and **3o′** were obtained in a nearly 1:1 ratio from *m*-OMe substituted substrate. It was found that 2-bromo-*N*,*N*-dimethylaniline *N*-oxide was less reactive, giving rise to 7-bromo-indole **3t** (33%) along with small amount of debrominated product **3a**. However, when 2-methylaniline derived *N*-oxide was subjected to the standard conditions, not only the corresponding indole product **3s** but also an OAT complex **3s*** were isolated.[14] Note that various functional groups, such as methoxy (**3f** and **3o**), ester (**3g** and **3p**), fluoro (**3h**), chloro (**3i**, **3j**, and **3q**), and bromo (**3k**, **3l**, and **3r**) substituents, were strongly compatible with the present reaction conditions, thus allowing further functionalization to construct more complicated molecules. Moreover, the reaction could be conducted on a gram scale with good performance (1.28 g of **3l**, 85% yield).

To our satisfaction, the cyclization approach was successfully applied to a wide range of *N*,*N*-diethylaniline *N*-oxides, which were demonstrated not suitable for C−H olefiantion in previous report,[3b] even exhibited higher reactivity than the

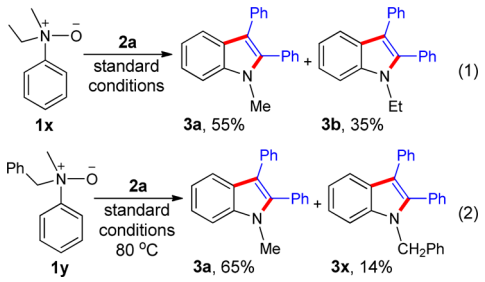
DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862

Scheme 2. Tertiary Aniline *N*-Oxides Substrate Scope[a]



[a]**1** (0.60 mmol), **2a** (0.2 mmol, 1.0 equiv), yields of isolated products. Unless otherwise noted, the corresponding OAT complex for each reaction is not detected (for most cases) or isolated in <5% yield. [b]4.0 mmol scale reaction. [c]5.0% of **3a** was also isolated. [d]The difficulty in separating **3v** and *N*,*N*-dihexylaniline leads to the low isolated yield of pure **3v**.

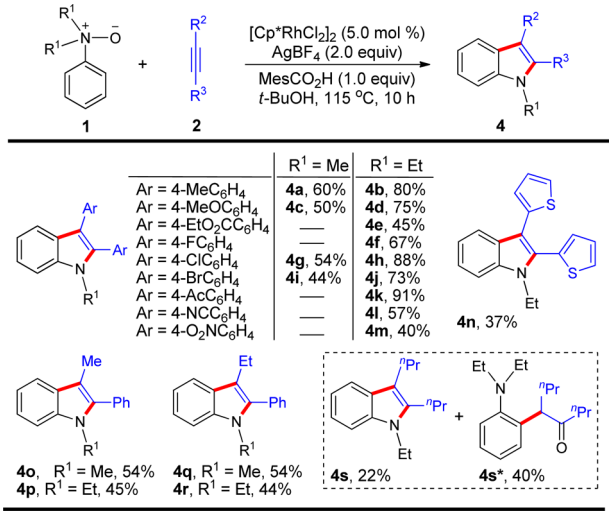
N,*N*-dimethyl counterparts (Scheme 2). Similarly, the introduction of dipropyl, dioctyl, and diisobutyl as *N*-substituents of aniline *N*-oxides minimally affected the outcome of reactivity to furnish the desired products **3u**–**3w** in high yields without difficulty. On the other hand, treatment of *N*-ethyl-*N*-methylaniline *N*-oxides (**1x**) with **2a** led to the formation *N*-ethyl and *N*-methyl cleaved products **3a** and **3b** in 55% and 35% yields, respectively (eq 1). *N*-benzyl-*N*-methylaniline *N*-oxide (**1y**) was also reacted to afford *N*-benzyl cleaved product **3a** in major (65%) with a small amount of *N*-methyl cleaved product **3x** (14%) (eq 2). These results were in contrast to previous report that the C–N cleavage commonly occurred at the less sterically hindered alkyl group, which provides a mechanistic implication of a different C–N bond activation process (vide infra). In addition, *N*-oxides derived from *N*,*N*-dimethyl 4-nitroaniline, 4-cyanoaniline, 1-naphthyl-



amine, 2-naphthylamine, *N*-methyldiphenylamine, and 1-ethyl-1,2,3,4-tetrahydroquinoline failed to work under the current reaction conditions.[15−17]

Furthermore, the reaction showed broad substrate tolerance with internal alkynes. As illustrated in Scheme 3, a variety of

Scheme 3. Alkynes Substrate Scope[a]

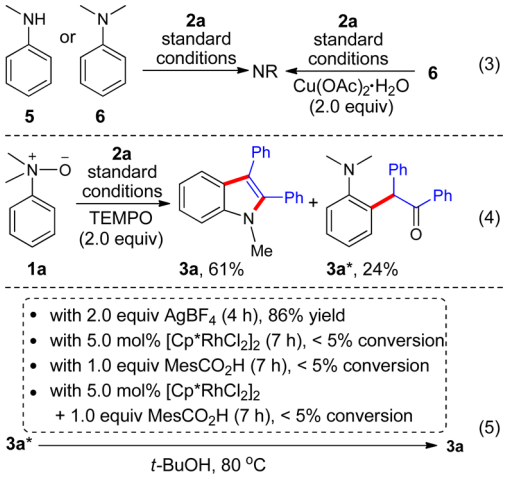


[a]**1** (0.60 mmol), **2a** (0.2 mmol, 1.0 equiv), yields of isolated products. Unless otherwise noted, the corresponding OAT complex for each reaction is not detected (for most cases) or isolated in <5% yield.

symmetric diarylacetylenes were all readily employed in reactions with **1a** and **1b**. Many important functional groups (for example, OMe, CO_2Et, F, Cl, Br, Ac, CN, and NO_2) were well-tolerated, and the resulting indole products were isolated in moderate to high yields (**4a**–**4m**). Heteroaryl-substituted alkyne was also suitable for the present annulation protocol but generated the desired product **4n** in relatively low yield. In the cyclization with unsymmetrical aryl alkyl-disubstituted alkynes, the complete regioselective coupling took place albeit in moderate reactivity (**4o**–**4r**). To our surprise, when 4-octyne was allowed to react, a mixture of indole **4s** and OAT product **4s*** was isolated.[14]

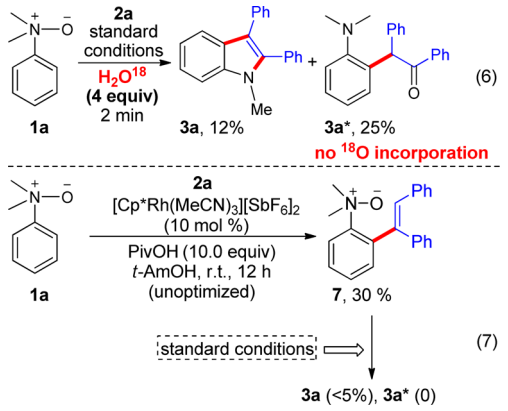
Subsequently, a series of experiments were carried out to unveil the reaction mechanistic pathway. First, *N*-methylaniline (**5**) and *N*,*N*-dimethylaniline (**6**) were tested as the substrates under the standard conditions or with additional oxidant (2.0 equiv of $Cu(OAc)_2·H_2O$ for **6**) (eq 3). No products were detected for all reactions, which reveals the necessity of N–O bond for the present transformation. With addition of 2.0 equiv of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, a radical inhibitor), the OAT complex **3a*** could be isolated in 24% yield along with **3a** (61%) when **1a** annulated with **2a** under the standard reaction conditions (eq 4). To our surprise, the

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862



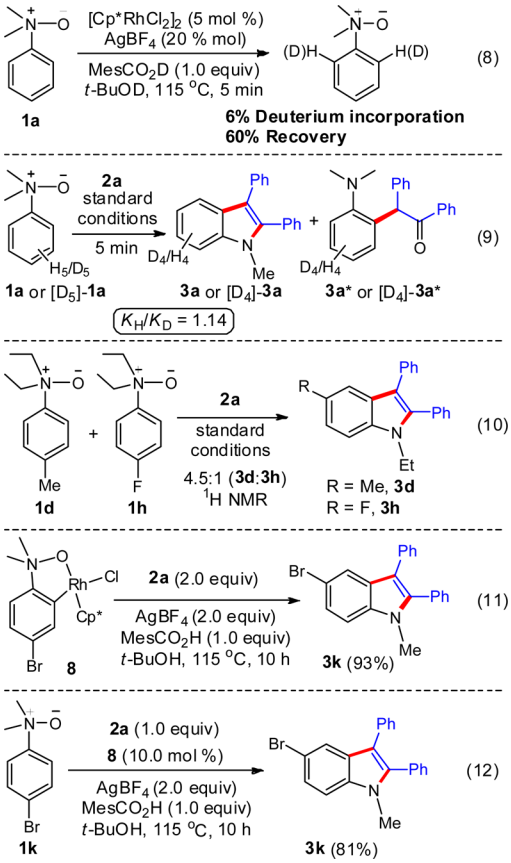
OAT complex **3a*** was efficiently converted into indole **3a** just with the aid of $AgBF_4$ (2.0 equiv) in *t*-BuOH at 80 °C. However, **3a*** was stable in the presence of $[Cp^*RhCl_2]_2$ and $MesCO_2H$ (eq 5). These results suggest that (i) the OAT complex might probably be the reaction intermediate; (ii) the whole transformation consists of a [Cp*Rh]-catalyzed C−H activation/oxygen-atom transfer and a Ag-mediated *N*-dealkylative cyclization; and (iii) a radical process might be involved in the latter step (*N*-dealkylative cyclization).

To understand the O atom transfer process, a reaction of **1a** with **2a** was conducted in the presence of H_2O^{18} (4.0 equiv) (eq 6]). No ^{18}O incorporation was detected in the isolated **3a***,



indicating that water is not involved in the OAT step and an intramolecular OAT is most likely to occur. Moreover, an alkenylated *N*,*N*-dimethylaniline *N*-oxide **7** was synthesized following a modified method of Rh(III)-catalyzed intermolecular hydroarylation of alkynes (eq 7).[18] The resulting olefin **7** was then subjected to the standard conditions, and very low transformation from **7** to **3a** was observed (eq 7). Therefore, the *ortho*-olefination intermediate can be ruled out.

To gain more insight into the mechanism of this reaction, the following experiments were also conducted. The H/D exchange experiment of **1a** suggested that the *ortho* C−H bond cyclometalated step is an irreversible process (eq 8). In the intermolecular isotopic study of two parallel competition reactions between 1a and $[D_5]$-**1a**, a kinetic isotope effect (KIE) of k_H/k_D = 1.14 was observed (eq 9), thus demonstrating that the cleavage of the C−H bond is not involved in the rate-determining step.[19] It was found that the preferential formation of product **3d** with an electron-rich substituent (**3d**:**3h** = 4.5:1)



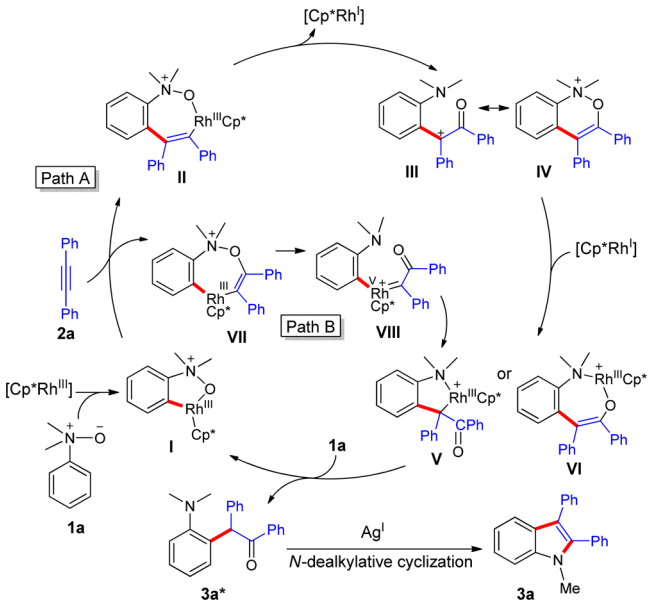
in the competition reactions between **1d** (4-Me) and **1h** (4-F) with **2a** (eq 10), which indicates that the C−H activation step might be an electrophilic aromatic substitution process.[3b,20] Additionally, the cyclization was smooth in the stoichiometric reaction of the isolated five-membered rhodacycle **8**[3b] with alkyne **2a** to furnish the desired product **3k** in 93% yield (eq 11). In a catalytic reaction, complex **8** also exhibited comparable efficiency for the coupling of **1k** with **2a** (eq 12). These results supported that rhodacycle **8** might probably be an active species in the catalytic cycle.

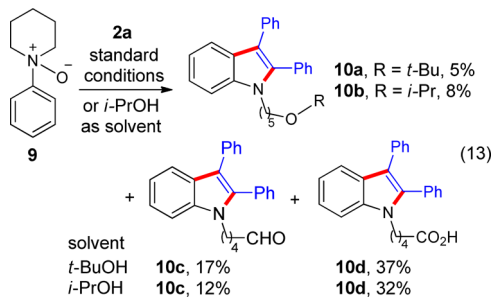
On the basis of the above observations and precedent literatures,[3,6,7] a plausible mechanism is proposed (Scheme 4). The reaction initiates the formation of five-membered cyclometalated species **I** via *ortho* C−H activation of **1a**, which is followed by alkyne insertion into the Rh−C bond to generate a seven-membered rhodacycle intermediate (**II**) (Path A). After reductive elimination of C−O bond of **II**, the resulting intermediate **III** or **IV** (tautomerization from **III** through OAT) undergoes oxidative addition to afford enolate intermediate **V** or **VI**. Then, the transformation from enolate intermediate **V** or **VI** to the OAT complex **3a*** occurs by cyclometalation of an incoming substrate **1a**. The subsequent silver-mediated C−N bond cleavage of **3a*** and further intramolecular nucleophilic cyclization could give the final product **3a**. On the other hand, the alkyne insertion into the Rh−O bond which leads to intermediates **VII**, **VIII**, and **V** (Path B) cannot be completely ruled out at the present stage.

To further understand the C−N bond cleavage process, the reactions of cyclic amine *N*-oxide were examined [eq 13]. Under the standard conditions, 1-phenylpiperidine *N*-oxide **9** coupled with **2a** to afford complex products. Fortunately, *N*-5-*t*-butoxypentyl indole **10a** (5%), 5-indol-1-yl pentanal **10c**

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862

Scheme 4. Proposed Mechanism for the Coupling Reaction between *N*,*N*-Dimethylaniline *N*-Oxide 1a with Diphenylacetylene 2a

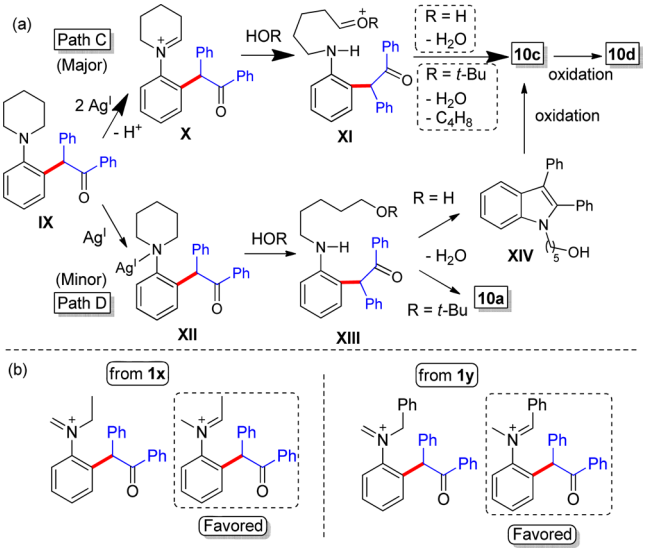




(17%), and 5-indol-1-yl pentanoic acid **10d** (37%) were successfully isolated and fully characterized. Similar results were obtained when the reaction was conducted in *i*-PrOH, from which *N*-5-isopropoxypentyl indole **10b** as well as **10c** and **10d** were isolated in 8%, 12%, and 32% yields, respectively.

On the basis of these experiments, two possible pathways of C−N bond cleavage starting from OAT intermediate **IX** have been proposed in Scheme 5a. As a major pathway (Path C), iminium ion **X** is generated via one-electron oxidation of nitrogen, deprotonation, and a second one-electron oxidation with the aid of silver salt acting as an oxidant.[5] Then hydrolysis (or alcoholysis) of **X** affords amine **XI**, which undergoes an intramolecular nucleophilic cyclization to give product **10c**. After further oxidation, acid **10d** is formed from **10c**. The above proposal on C−N cleavage is in well agreement with the reaction results of **1x** and **1y** (eq1 and eq 2): iminium ions generated by deprotonation at Et and Bn group are more favored than that deprotonated at Me group (Scheme 5b) according to their relative stability, which result in the cleavage N−Et and N−Ph bonds proceeds favorably to form *N*-methyl complex **3a** as major product for both reactions. Although the process of hydrolysis of **X** is postulated to be more favored, the alcoholysis process cannot be fully ruled out as evidenced by the formation of **3a** and **3a*** (in relative lower yield) by addition of 4 Å molecular sieve to the model reaction (see the Supporting Information). Alternatively, in Path D (minor

Scheme 5. (a) Proposed Mechanism for C−N Cleavage Process and (b) Iminium Ions Derivated from 1x and 1y



pathway), coordination of Ag^I to *N*-atom of **IX** followed by alcoholysis and intramolecular nucleophilic cyclization is assumed to occur, thus giving rise to indole **10a**. If hydrolysis happens, it would lead to the formation of intermediate **XIV**, which could be oxidized by *N*-oxide to form **10c**. As can be seen in both pathways, alcohol acts as an important role for the transformation from OAT intermediate to the final indole product, especially in the early stage of reaction system when the water content is low. This is in line with the solvent effect found in optimization studies that the formation of indole was favored in alcohol solvent (Table 1, entries 1−5).

In summary, we have developed a rhodium(III)-catalyzed oxidative coupling reaction of tertiary aniline *N*-oxides with internal alkynes, which has allowed the construction of *N*-alkylindole derivatives in high efficiency. A broad substrate scope for both tertiary aniline *N*-oxides and alkynes are strongly compatible with this catalytic process. The challenging *ortho* C−H functionalization of tertiary anilines has been achieved by the utilization of N−O bond as a traceless directing group. More significantly, the present protocol represents the first example which integrates C−H activation, oxygen-atom transfer, and *N*-dealkylative cyclization in one reaction. Further studies on catalytic C−H activation and transformation of C−N bond of tertiary aniline are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00311.

Full experimental procedures, additional experimental data, analytical data, and characterization of new compounds (^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF)
Crystallographic data for **3p** (CIF)
Crystallographic data for **3r** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail for B.L.: nklibin@nankai.edu.cn.
*E-mail for B.W.: bqwang@nankai.edu.cn.

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the grants of the National Natural Science Foundation of China (21372121 and 21421062).

■ REFERENCES

(1) For selected recent reviews, see: (a) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007−1020. (b) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155−1171. (c) Kuhl, N.; Schroder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (d) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814−825. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918. (g) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (h) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (i) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588−5598. (j) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (k) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936−946. (l) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (m) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215−1292. (n) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (o) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931.

(2) For selected reviews, see: (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369−375. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.

(3) (a) Shi, R.; Lu, L.; Zhang, H.; Chen, B.; Sha, Y.; Liu, C.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10582−10585. (b) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12970−12974. (c) Zhou, B.; Chen, Z.; Yang, Y.; Ai, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 12121−12126.

(4) (a) Liang, M.; Chen, J. *Chem. Soc. Rev.* **2013**, *42*, 3453−3488. (b) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem. - Eur. J.* **2011**, *17*, 1388−1408. (c) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595−6663. (d) Chen, C.-T. *Chem. Mater.* **2004**, *16*, 4389−4400. (e) Wermuth, C.-G. *The Practice of Medicinal Chemistry*, 3rd ed., Academic Press: London, 2008.

(5) For selected reviews, see: (a) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. *Chem. Rev.* **2015**, *115*, 12045−12090. (b) Wang, R.; Falck, J. R. *RSC Adv.* **2014**, *4*, 1062−1066. (c) Li, Y.; Ma, L.; Li, Z. *Youji Huaxue* **2013**, *33*, 704−714. (d) Turner, N. J. *Chem. Rev.* **2011**, *111*, 4073−4087. (e) Krüger, K.; Tillack, A.; Beller, M. *ChemSusChem* **2009**, *2*, 715−717.

(6) For selective examples, see: (a) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098−6099. (b) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173−176. (c) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176−4179. (d) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 942−945. (e) Kuninobu, Y.; Nishi, M.; Takai, K. *Chem. Commun.* **2009**, *46*, 8860−8862. (f) Xia, X.-F.; Zhang, L.-L.; Song, X.-R.; Niu, Y.-N.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 1410−1412. (g) Zhang, X.; Yang, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 3649−3654. (h) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12992−12996. (i) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 3200−3203. (j) Chen, X.; Chen, T.; Li, Q.; Zhou, Y.; Han, L.-B.; Yin, S.-F. *Chem. - Eur. J.* **2014**, *20*, 12234−12238. (k) Pan, X.; Luo, Y.; Kuang, Y.; Li, G. *Org. Biomol. Chem.* **2014**, *12*, 5861−5865. (l) Sheng, J.; Li, S.; Wu, J. *Chem. Commun.* **2014**, *50*, 578−580. (m) Bao, Y.-S.; Zhaorigetu, B.; Agula, B.; Baiyin, M.; Jia, M. *J. Org. Chem.* **2014**, *79*, 803−808. (n) Ha, T. M.; Yao, B.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1750−1753.

(7) (a) Zhang, X.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 10794−10798. (b) Sharma, U.; Park, Y.; Chang, S. *J. Org. Chem.* **2014**, *79*, 9899−9906. (c) Dateer, R. B.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4908−4911. (d) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 10613−10617. (e) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. *Adv. Synth. Catal.* **2015**, *357*, 2944−2950. (f) Kong, L.; Xie, F.; Yu, S.; Qi, Z.; Li, X. *Chin. J. Catal.* **2015**, *36*, 925−932.

(8) (a) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2011**, *17*, 12573−12577. (b) Tan, X.; Liu, B.; Li, X.; Li, B.; Xu, S.; Song, H.; Wang, B. *J. Am. Chem. Soc.* **2012**, *134*, 16163−16166. (c) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2012**, *18*, 12873−12879. (d) Wang, N.; Li, B.; Song, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2013**, *19*, 358−364. (e) Li, B.; Wang, N.; Liang, Y.; Xu, S.; Wang, B. *Org. Lett.* **2013**, *15*, 136−139. (f) Li, B.; Yang, J.; Xu, H.; Song, H.; Wang, B. *J. Org. Chem.* **2015**, *80*, 12397−12409.

(9) (a) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694−752. (b) Patil, S. A.; Patil, R.; Miller, D. D. *Future Med. Chem.* **2012**, *4*, 2085−2115. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489−4497. (d) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73−103. (e) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761−793. (f) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed., Wiley-VCH: Weinheim, 2003. (g) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996.

(10) For recent reviews on indole synthesis, see: (a) Guo, T.; Huang, F.; Yu, L.; Yu, Z. *Tetrahedron Lett.* **2015**, *56*, 296−302. (b) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29−41. (c) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508−3549. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215−PR283. (e) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469−6480. (f) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195−7210.

(11) For selective examples on indole synthesis via metal-catalyzed C−H activation/annulation with alkynes, see: (a) Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 2705−2709. (b) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 15400−15404. (c) Wu, J.-Q.; Yang, Z.; Zhang, S.-S.; Jiang, C.-Y.; Li, Q.; Huang, Z.-S.; Wang, H. *ACS Catal.* **2015**, *5*, 6453−6457. (d) Fan, Z.; Song, S.; Li, W.; Geng, K.; Xu, Y.; Miao, Z. H.; Zhang, A. *Org. Lett.* **2015**, *17*, 310−313. (e) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1577−1585. (f) Zhang, G.; Yu, H.; Qin, G.; Huang, H. *Chem. Commun.* **2014**, *50*, 4331−4334. (g) Zhou, B.; Yang, Y.; Tang, H.; Du, J.; Feng, H.; Li, Y. *Org. Lett.* **2014**, *16*, 3900−3903. (h) Zheng, L.; Hua, R. *Chem. - Eur. J.* **2014**, *20*, 2352−2356. (i) Cai, S.; Yang, K.; Wang, D. Z. *Org. Lett.* **2014**, *16*, 2606−2609. (j) Wang, C.; Sun, H.; Fang, Y.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5795−5798. (k) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625−16631. (l) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 12426−12429. (m) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764−767. (n) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338−1341. (o) Chen, J.; Pang, Q.; Sun, Y.; Li, X. *J. Org. Chem.* **2011**, *76*, 3523−3526. (p) Chen, J.; Song, G.; Pan, C. L.; Li, X. *Org. Lett.* **2010**, *12*, 5426−5429. (q) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326−18339. (r) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572−4576. (s) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474−16475 and references cited therein and also see refs 7d−f..

(12) CsOAc has been utilized as an additive in many Rh(III)-catalyzed C−H functionalization to facilitate C−H activation step, for selective examples, see: (a) Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2016**, *18*, 700−703. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254−258. (c) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367. (d) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033−6037. (e) Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421−3426. (f) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318−7322. (g) Zeng, R.; Fu, C.; Ma, S. *J.*

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862

Am. Chem. Soc. **2012**, *134*, 9597−9600. (h) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908−6909.
(13) CCDC 1449077 (**3p**) and 1449078 (**3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(14) As shown in eq 5, the OAT complex can be transformed into indole product via a Ag-mediated *N*-dealkylative cyclization. The steric effect of *ortho*-methyl in **3s*** might make it difficult to undergo the *N*-dealkylative cyclization step. However, in **4s***, the flexibility of ^{n}Pr substituent around ketone group might make it less favored in the *N*-dealkylative cyclization.
(15) It was reported that 4-nitro and 4-cyano *N*,*N*-dimethylaniline *N*-oxide readily underwent thermal rearrangement to *O*-arylhydroxylamine, see: Khuthier, A.-H.; Al-Kazzaz, A.-K. S.; Al-Rawi, J. M. A.; Al-Iraqi, M. A. *J. Org. Chem.* **1981**, *46*, 3634−3638.
(16) The reactions of *N*-oxides derived from 1-naphthylamine, 2-naphthylamine, and 1-ethyl-1,2,3,4-tetrahydroquinoline produced very complex mixtures.
(17) The reaction of *N*-methyldiphenylamine *N*-oxides met with failure might ascribed to the steric hindrance.
(18) Schipper, D.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910−6911.
(19) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.
(20) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492−3500. (b) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286−3289.

DOI: 10.1021/acscatal.6b00311
ACS Catal. 2016, 6, 3856−3862