

Cyclization

Rhodium-Catalyzed Cyclization of Diynes with Nitrones: A Formal [2+2+5] Approach to Bridged Eight-Membered Heterocycles**

Chunxiang Wang, Dongping Wang, Hao Yan, Haolong Wang, Bin Pan, Xiaoyi Xin, Xincheng Li, Fan Wu, and Boshun Wan*

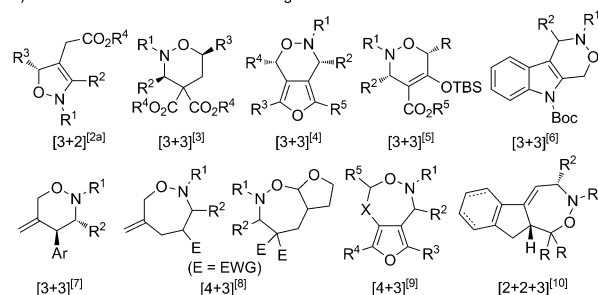
Abstract: *N*-aryl-substituted nitrones were employed as five-atom coupling partners in the rhodium-catalyzed cyclization with diynes. In this reaction, the nitron moiety served as a directing group for the catalytic C–H activation of the *N*-aryl ring. This formal [2+2+5] approach allows rapid access to bridged eight-membered heterocycles with broad substrate scope. The results of this study may provide new insight into the chemistry of nitrones and find applications in the synthesis of other heterocycles.

Combinations of various unsaturated coupling partners in cycloadditions have created new opportunities to access heterocycles of great complexity. In this regard, nitrones may serve as three-atom building units and can incorporate two heteroatoms into the frameworks in a single step.^[1] Recently, the metal-catalyzed cycloaddition of nitrones with various unsaturated hydrocarbons has proven to be an efficient tool to produce nitrogen-containing heterocycles. Although the reactivity of nitrones toward different synthons has been extensively studied, most attention has been given to [3+2],^[2] [3+3],^[3–7] [4+3],^[8,9] and [2+2+3]^[10] cycloadditions (Scheme 1a). In these intriguing studies, nitrones exclusively serve as 1,3-dipolar reagents to afford five-, six-, and seven-membered heterocycles. To the best of our knowledge, reactions using nitrones as five-atom building units in cycloadditions are unknown.

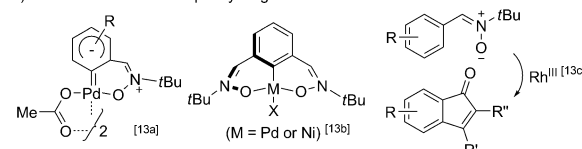
Cycloadditions involving diynes have been developed to enable the synthesis of various cyclic structures,^[11] including the formation of medium-sized heterocycles by using diynes as C₄ units. As part of our research in this area,^[12] we have recently reported the rhodium-catalyzed cycloaddition of diynes with oximes, in which the hydroxy group of the oxime plays a crucial role for the reactivity.^[12c] In view of the similarity between oximes and nitrones, we surmised that a nitron group could function as a directing group under rhodium catalysis and participate in a reaction with diynes to provide rapid access to the [2+2+3] cycloadduct. However, to our surprise, a bridged multicyclic skeleton was observed

Previous work:

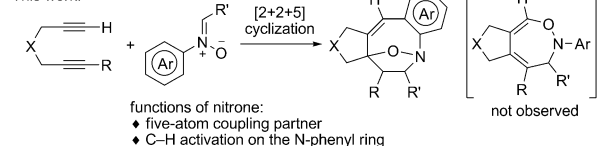
a) nitron serves as a three-atom building unit



b) C–H activation on the C-phenyl ring of the nitron



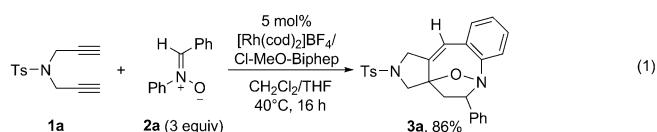
This work:



Scheme 1. Cycloadditions involving nitrones.

instead of the seven-membered ring (Scheme 1, this work). Five atoms of the nitron compound were incorporated into the product and a C–H activation step on the *N*-phenyl ring of nitron is likely to be involved. Indeed, C–H activation of nitrones has been recently reported by Yao and Li,^[13] but only focused on the C-phenyl ring (Scheme 1b). No C–H activation on the *N*-phenyl ring of nitrones has been reported. Herein, we report a formal [2+2+5] approach to bridged eight-membered heterocycles through the rhodium-catalyzed cyclization of diynes with nitrones.

At the outset of our investigation, diyne **1a** and nitron **2a** were selected as model substrates for the optimization of the reaction conditions (results summarized in Table S1 in the Supporting Information). After careful screening, we found that the use of [Rh(cod)₂]BF₄ as metal catalyst and Cl–MeO–Biphep (**L5**) as ligand in CH₂Cl₂/THF provided the desired product **3a** with the highest yield [86%; Eq. (1)]. The



[*] Dr. C. X. Wang, Dr. D. P. Wang, H. Yan, Dr. H. L. Wang, Dr. B. Pan, Dr. X. Y. Xin, Dr. X. C. Li, F. Wu, Prof. Dr. B. S. Wan
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (China)
E-mail: bswan@dicp.ac.cn

[**] This work was supported by NSFC (21372219). We also thank Prof. Yonggui Zhou (DICP), Dr. Guoyong Song (RIKEN), and one reviewer for helpful suggestions on revising the manuscript.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201407394>.

structure of **3a** was unambiguously confirmed by X-ray crystal diffraction.^[14] It is noteworthy that under rhodium catalysis a di- or trimerization of diynes is commonly detected.^[15] This phenomenon was also observed in this reaction, thus slightly lowering the yield of **3a**.

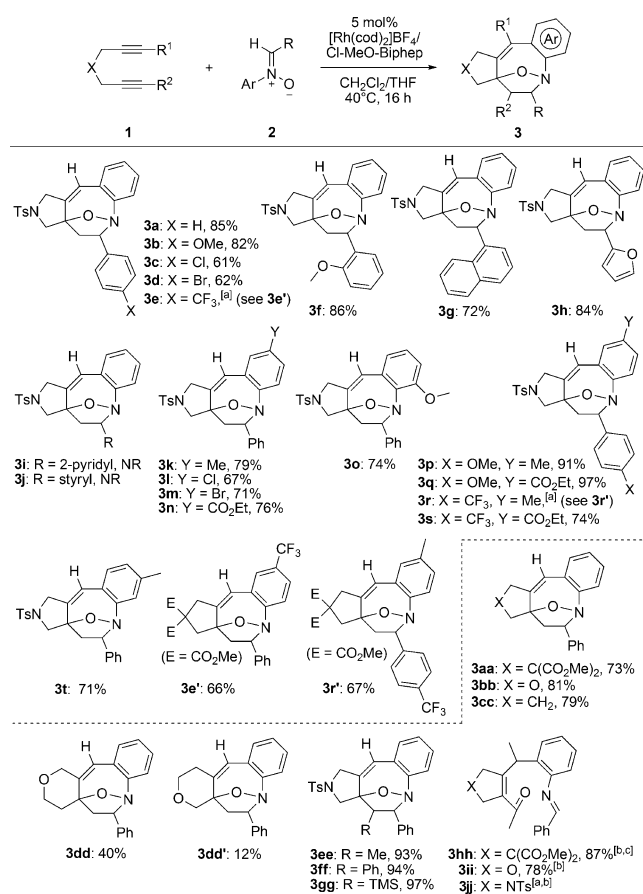
The scope of nitrones was then tested under the above-optimized reaction conditions (Scheme 2). Different substituents of the C-aryl ring (**2a–2g**) resulted in the corresponding cycloadducts **3a–3g** in moderate to good yields, regardless of their electronic and steric effects. For nitron **2h**, which bears a 2-furyl group, the desired product **3h** was obtained in 84 % yield. Unfortunately, nitrones **2i** and **2j** bearing a 2-pyridyl and a styryl group, respectively, were completely unreactive. This result may be ascribed to the ability of the pyridine and alkene moieties to coordinate to the rhodium center. The cycloaddition reactions can be further extended to nitrones bearing various N-aryl substituents (**2k–2t**). Moreover, different combinations of electron-withdrawing and electron-donating groups on the C- and N-aryl rings (**2p–2s**) also provided the products (**3p–3s**) in good to excellent yields. It is

worth noting that the reaction with 3-methyl-substituted nitron **2t** afforded the product **3t** as a single regioisomer,^[14] in which the sterically less-hindered position of the phenyl ring was linked to the alkene moiety.

The reactions of various diynes with nitron **2a** were also investigated. Malonate- and O-tethered terminal diynes (**1aa**, **1bb**) could undergo this cyclization and were transformed into the corresponding cycloadducts in good yields. Notably, methylene-linked diyne **1cc** reacted smoothly with **2a** to afford **3cc** in 79 % yield, thus indicating that the Thorpe–Ingold effect^[17] had less influence in this case. However, the reaction of **2a** with unsymmetrical 1,7-diyne **1dd** furnished **3dd** as the main product accompanied by the minor regioisomer **3dd'** in 40 % and 12 % yield, respectively. In contrast, high regioselectivity was observed in the reaction of unsymmetrical 1,6-diynes **1ee–1gg**, which possess a hydrogen atom and an aliphatic/aryl group (Me, TMS, or Ph) at each alkyne terminus. Single regioisomers were obtained in excellent yields (93–97 %). X-ray crystal diffraction of **3gg** showed that the adjacent R substituent is on the *cis* position of the phenyl group.^[14] Unexpectedly, when internal diynes **1hh–1jj** were subjected to the reaction, acyclic compounds **3hh** and **3ii**, which possess enone and imine moieties, were obtained in good yields.^[14,17] Although the reason is still unknown, the existing results suggest that the additional methyl group at the alkyne terminus (e.g. **3ee** versus **3jj**), rather than the tethers, plays a crucial role. Importantly, these products allowed access to other molecules. For example, product **3a** was readily converted into cyclic amino alcohols by N–O bond cleavage, and multicyclic amine by further dehydration (see the Supporting Information).

As suggested by the structure of the product, a C–H bond cleavage was observed on the N-phenyl ring of nitrones. To probe the reaction mechanism, the reaction of **1a** with deuterated nitron $[D_5]$ -**2a** was first investigated. To our delight, the desired product $[D_5]$ -**3a** was obtained with more than 99 % deuterium incorporation (Scheme S1-1, see the Supporting Information). Besides, the reaction of **1a** and **2a** in the presence of CD_3OD or CH_3COOD did not provide any deuterated product (Scheme S1-2). Furthermore, when an equimolar mixture of **2b** and $[D_5]$ -**2b** was stirred under standard reaction conditions, no H–D exchange occurred at the *ortho* position of the N-phenyl ring (Scheme S1-3). Taken together, these results indicated that the C–H functionalization on the N-phenyl ring is irreversible.

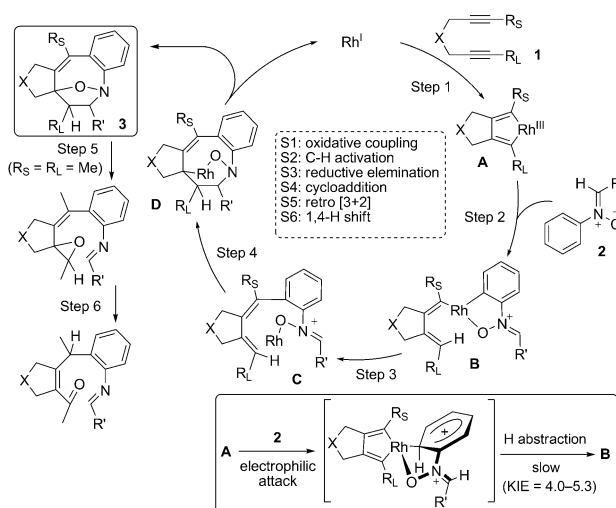
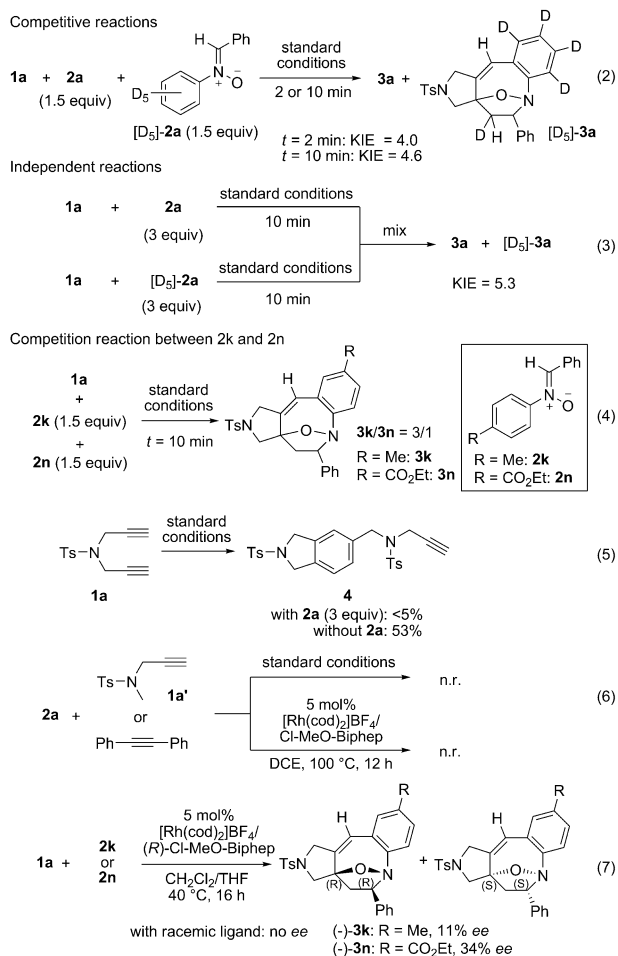
Under this premise, kinetic isotope effect (KIE) studies were performed. The intermolecular competitive reactions between **2a** and $[D_5]$ -**2a** with **1a** gave a KIE value of 4.0 at 2 min [or 4.6 at 10 min, Eq. (2)] on the basis of 1H NMR analysis. Furthermore, the KIE values of independent reactions of **1a** with **2a** or $[D_5]$ -**2a** were measured to provide a KIE value of 5.3 [Eq. (3)]. These data suggest that a C–H activation is likely to be involved in the rate-determining step.^[18] Additionally, the competition between **2k** and **2n** in the reaction with **1a** was examined [Eq. (4)], affording the corresponding products **3k** and **3n** in a 3:1 molar ratio. This result demonstrates that nitrones with electron-rich substituents on the N-aryl moiety preferentially reacted with diynes, supporting the possibility of an electrophilic aromatic sub-



Scheme 2. Substrate scope. Reaction conditions: **1** (0.25 mmol), **2** (0.75 mmol), $[Rh(cod)_2]BF_4$ (5 mol %), Cl-MeO-Biphep (5 mol %), CH_2Cl_2 (1 mL), THF (1 mL), 40 °C, 16 h; yields of isolated products are reported. [a] The conversion to products **3e**, **3r**, and **3jj** was good, however, they were not isolated because their polarity was similar to that of the corresponding nitron. [b] Reaction conditions: $[Rh(cod)_2]BF_4$ (5 mol %), Segphos (5 mol %), CH_2Cl_2 (2 mL), 40 °C, 16 h. [c] Yield determined by HPLC.

stitution pathway (S_EAr)^[19] in the reaction. The high KIE values (4.0–5.3) observed in this reaction suggest that slow hydrogen abstraction might be involved after the electrophilic attack of Rh on the N-phenyl ring in the C–H activation process.^[20]

It is noteworthy that the dimerization product of diyne **1a** was observed as by-product when the reaction conditions were screened. Moreover, in the absence of nitrones, dimer **4** was isolated in 53% yield along with some trimerization product [Eq. (5)], indicating the existence of a competition between the dimerization of diynes and the coupling of nitrones with diynes in this reaction. Next, monoyne **1a'** or diphenylacetylene were reacted with nitrone **2a**, but no new product was observed under Rh^I catalysis, even at a higher temperature [Eq. (6)]. According to these observations, we hypothesize that the C–H activation step is less likely in the presence of a Rh^I catalyst, but is probably initiated after the formation of the rhodacyclopentadiene intermediate. Unfortunately, attempts to isolate the rhodacyclopentadiene intermediate from the stoichiometric reaction between **1a** and $[Rh(cod)_2]BF_4/L5$ did not succeed,^[21] possibly because of the fast dimerization of diynes. The enantioselectivity of this reaction was also investigated [Eq. (7)]. Interestingly, in the presence of (*R*)-Cl-MeO-Biphep, chiral (–)-**3k** and (–)-**3n** were obtained in 11 and 34% *ee*, respectively, suggesting that products of high enantiopurity can be obtained if the reaction is optimized with chiral catalysts.



Scheme 3. Proposed mechanism.

On the basis of the above results, a plausible mechanism was proposed in Scheme 3. The reaction starts with the coordination of the diyne to rhodium, generating rhodacyclopentadiene intermediate **A**. This then reacts with the nitrone through C–H activation to afford intermediate **B**, in which the N-aryl group is close to the sterically less-hindered position (R_S) of the metallacycle. The C–H activation process might follow the S_EAr mechanism through electrophilic attack and slow hydrogen abstraction.^[20] Subsequently, reductive elimination provides dienylation intermediate **C**.^[22] Finally, the rhodium-mediated [3+2] cycloaddition and further reductive elimination provides product **3**, and regenerates the catalyst. In the cases of internal diynes, retro-[3+2] cycloaddition followed by 1,4-H shift furnishes the ring-opening product. The driving force for the ring cleavage might be attributed to the release of ring tension caused by the methyl group.

In summary, we have developed a formal [2+2+5] approach to access bridged eight-membered heterocycles through the rhodium-catalyzed cyclization of diynes with nitrones under mild conditions, in which the nitrone group serves as both a directing group for catalytic C–H activation on the N-phenyl ring of the nitrone and a five-atom coupling partner. Until now, nitrones were commonly used as three-atom building units in cycloadditions, and no catalytic C–H activation on the N-phenyl ring of nitrones has been reported. The findings of this study may provide new insight into the chemistry of nitrones and find applications in the synthesis of other heterocycles. Further exploration on enantioselective versions and other reactions involving nitrones are currently underway.

Experimental Section

Representative procedure: $[Rh(cod)_2]BF_4$ (5 mol%) and Cl-MeO-Biphep (5 mol%) were weighed in the glove box and placed in a dried Schlenk tube. Subsequently, 2 mL of solvent ($\text{THF}/\text{CH}_2\text{Cl}_2 = 1/1$, v/v) was added. The resulting mixture was stirred at room temperature for 30 min to afford a light-yellow clear solution. Nitrone **2** (0.75 mmol,

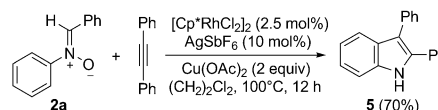
3 equiv) was added followed by diyne **1** (0.25 mmol, 1 equiv). The reaction mixture was stirred at 40°C for 16 h. The solvent was evaporated and the crude product was directly purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to give product **3**.

Received: July 19, 2014

Published online: September 12, 2014

Keywords: alkenylation · C–H activation · cyclization · nitrones · rhodium

- [1] a) F. Cardona, A. Goti, *Angew. Chem. Int. Ed.* **2005**, *44*, 7832–7835; *Angew. Chem.* **2005**, *117*, 8042–8045; b) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Eur. J.* **2009**, *15*, 7808–7821.
- [2] a) C. Qin, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 14516–14519; For selected reviews on [3+2] cycloadditions of nitrones, see: b) G. Song, D. Chen, Y. Su, K. Han, C. L. Pan, A. Jia, X. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 7791–7796; *Angew. Chem.* **2011**, *123*, 7937–7942; c) R. C. F. Jones in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, Hoboken, **2003**, pp. 1–81; d) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887–2902.
- [3] a) I. S. Young, M. A. Kerr, *Angew. Chem. Int. Ed.* **2003**, *42*, 3023–3026; *Angew. Chem.* **2003**, *115*, 3131–3134; b) M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765; c) Y. B. Kang, X. L. Sun, Y. Tang, *Angew. Chem. Int. Ed.* **2007**, *46*, 3918–3921; *Angew. Chem.* **2007**, *119*, 3992–3995.
- [4] a) F. Liu, Y. Yu, J. Zhang, *Angew. Chem. Int. Ed.* **2009**, *48*, 5505–5508; *Angew. Chem.* **2009**, *121*, 5613–5616; b) F. Liu, D. Qian, L. Li, X. Zhao, J. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 6669–6672; *Angew. Chem.* **2010**, *122*, 6819–6822; c) Z. M. Zhang, P. Chen, W. Li, Y. Niu, X. L. Zhao, J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4350–4354; *Angew. Chem.* **2014**, *126*, 4439–4443.
- [5] a) X. Wang, X. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2011**, *133*, 16402–16405; b) Y. Qian, X. Xu, X. Wang, P. J. Zavalij, W. Hu, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 5900–5903; *Angew. Chem.* **2012**, *124*, 6002–6005; c) X. Wang, Q. M. Abrahams, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2012**, *51*, 5907–5910; *Angew. Chem.* **2012**, *124*, 6009–6012; d) X. Xu, P. J. Zavalij, M. P. Doyle, *Chem. Commun.* **2013**, *49*, 10287–10289.
- [6] W. Yang, T. Wang, Y. Yu, S. Shi, T. Zhang, A. S. K. Hashimi, *Adv. Synth. Catal.* **2013**, *355*, 1523–1528.
- [7] R. Shintani, S. Park, W. L. Duan, T. Hayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 5901–5903; *Angew. Chem.* **2007**, *119*, 6005–6007.
- [8] a) R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356–12357; b) A. C. Stevens, C. Palmer, B. L. Pagenkopf, *Org. Lett.* **2011**, *13*, 1528–1531.
- [9] a) Y. Bai, J. Fang, J. Ren, Z. Wang, *Chem. Eur. J.* **2009**, *15*, 8975–8978; b) Y. Zhang, F. Liu, L. Zhang, *Chem. Eur. J.* **2010**, *16*, 6146–6150; c) T. Wang, J. Zhang, *Chem. Eur. J.* **2011**, *17*, 86–90.
- [10] S. A. Gawade, S. Bhunia, R. S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 7835–7838; *Angew. Chem.* **2012**, *124*, 7955–7958.
- [11] M. I. Alexandrovna, B. I. Ionin, J. C. Tebbby in *Alkynes in Cycloadditions* (Ed.: J. Tebbby), Wiley, New Delhi, **2014**.
- [12] a) C. X. Wang, X. C. Li, F. Wu, B. S. Wan, *Angew. Chem. Int. Ed.* **2011**, *50*, 7162–7166; *Angew. Chem.* **2011**, *123*, 7300–7304; b) F. Xu, C. X. Wang, X. C. Li, B. S. Wan, *ChemSusChem* **2012**, *5*, 854–857; c) F. Xu, C. X. Wang, D. P. Wang, X. C. Li, B. S. Wan, *Chem. Eur. J.* **2013**, *19*, 2252–2255; d) C. X. Wang, D. P. Wang, F. Xu, B. Pan, B. S. Wan, *J. Org. Chem.* **2013**, *78*, 3065–3072; e) B. Pan, C. X. Wang, D. P. Wang, F. Wu, B. S. Wan, *Chem. Commun.* **2013**, *49*, 5073–5075; f) B. Pan, X. D. Lu, C. X. Wang, Y. C. Hu, F. Wu, B. S. Wan, *Org. Lett.* **2014**, *16*, 2244–2247.
- [13] A C–H activation step is observed on the C-phenyl ring of the nitrones, see: a) Q. Yao, M. Zabawa, J. Woo, C. Zheng, *J. Am. Chem. Soc.* **2007**, *129*, 3088–3089; b) Y. Zhang, G. Song, G. Ma, J. Zhao, C. L. Pan, X. Li, *Organometallics* **2009**, *28*, 3233–3238; c) Z. Qi, M. Wang, X. Li, *Org. Lett.* **2013**, *15*, 5440–5443.
- [14] CCDC 977775 (**3a**), CCDC 1002035 (**3t**), CCDC 1008187 (**3dd**), CCDC 1019777 (**3gg**), and CCDC 978897 (**3hh**) contain 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.
- [15] M. Amatore, D. Leboeuf, M. Malacria, V. Gandon, C. Aubert, *J. Am. Chem. Soc.* **2013**, *135*, 4576–4579.
- [16] M. E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735–1766.
- [17] The reactions performed under standard conditions also afforded product **3hh** and **3ii**, but in a slightly lower yield. In addition, product **3hh** is easily hydrolyzed on silica gel (on the column), even on neutralized silica gel or Al₂O₃. Therefore, the yield was determined by HPLC.
- [18] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072; *Angew. Chem.* **2012**, *124*, 3120–3126.
- [19] For a mechanistic discussion on classical S_EAr, see: F. A. Carey, R. J. Sundberg in *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, Sedth edSpringer, New York, **2007**, pp. 771–816.
- [20] High KIE values (3.1–3.9) were observed in palladium-catalyzed *ortho*-arylation reactions, for which an S_EAr mechanism was proposed. See: X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837–5844, and references therein.
- [21] Despite the failure to isolate a Rh^{III} intermediate, in a related study, the reaction of **2a** and diphenylacetylene under Rh^{III} catalyst provided 2,3-diphenylindole **5** in 70% yield. This result indicated that the C–H bond cleavage of nitron might occur under Rh^{III} catalysis. Detailed information of this reaction will be reported in due course.



- [22] a) K. Tanaka, Y. Otake, A. Wada, K. Noguchi, M. Hirano, *Org. Lett.* **2007**, *9*, 2203–2206; b) K. Tsuchikama, Y. Kuwata, Y. K. Tahara, Y. Yoshinami, T. Shibata, *Org. Lett.* **2007**, *9*, 3097–3099; c) Y. Shibata, Y. Otake, M. Hirano, K. Tanaka, *Org. Lett.* **2009**, *11*, 689–692.