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Rh(III)-Catalyzed C–C Coupling of Diverse Arenes and 4-Acyl-1-sulfonyltriazoles via C–H Activation

Miaomiao Tian,[†] Bingxian Liu,[†] Jiaqiong Sun,[‡] and Xingwei Li*[,†,‡,§]

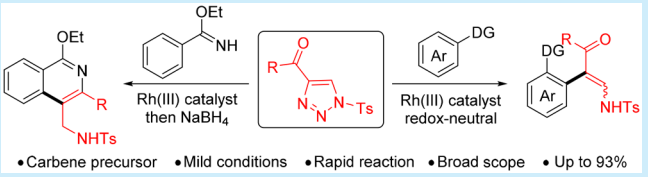
[†]Henan Key Laboratory of Organic Functional Molecule and Drug Innovation, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China

[‡]School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xian 710119, China

[§]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

Supporting Information

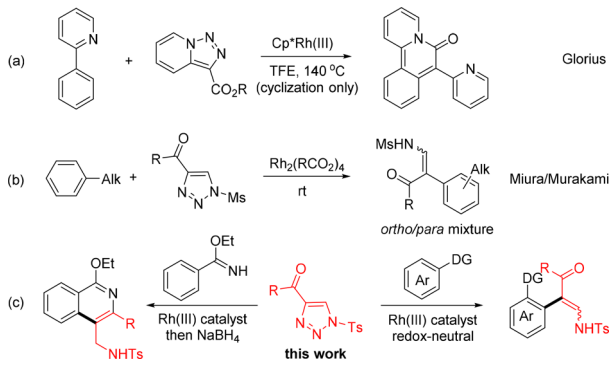
ABSTRACT: 4-Acyl-1-sulfonyltriazoles act as versatile carbene reagents in Cp*Rh(III)-catalyzed ortho-selective coupling with arenes via C–H activation. The coupling led to olefination with possible cyclization, depending on the nature of the arene.



Metal-catalyzed C–H activation has been established as an increasingly important strategy for direct functionalization of arenes.[1] The ready availability of arenes and high atom/step economy render this strategy highly attractive. C–H bond activation generates a reactive metal–carbon species that is nucleophilic in nature and is compatible with various electrophilic coupling partners for subsequent functionalization.[2] Carbenes,[3] especially those bearing EWGs, are unsaturated electrophilic reagents that are widely applicable in coupling with arenes, especially when catalyzed by high valent transition metals such as Rh(III),[3g] Ir(III),[3j] and Co(III).[3k] In these systems, the polarized M(III)–C(aryl) bond generated from C–H activation interacts more favorably with the ligated carbene/nitrene species via migratory insertion, leading to C–C/C–N bond formations.[4] Significantly, this inner-sphere pathway stays in contrast to the outer-sphere C–H functionalization mechanism of carbenes/nitrenes, where no preformation of M–C(aryl) species is involved.[3a−c,5]

In recent years, Rh(III)-catalyzed coupling of arenes and carbene reagents has allowed efficient and selective C–H bond alkylation. Furthermore, various annulative couplings have been realized for arenes bearing a nucleophilic directing group via C–H alkylation–cyclization.[6] Ideally, C–H activation of arenes introduces more than one functional group, leading to molecular diversity under operationally simple conditions. This boils down to establishment of a bifunctional coupling reagent. We reasoned that bifunctionalzation is fulfilled using a cyclic coupling reagent.[1e] The ring scission gives two-atom synthons (functional groups), and the coupling gives rise to a new bond tethered to a pendant functional group. In this context, *N*-sulfonyltriazoles are powerful carbene reagents that integrate ready availability, high reactivity, stability, and bifunctionality,[7] but their applications in arene functionalization via C–H activation through a metal–carbon species have been rather limited.[8] Only pyridotriazoles have been identified as triazole variants in Rh(III)-catalyzed C–H activation reported by Glorius[9] (Scheme 1a) and Lee,[10] likely due to generation of a pendant pyridyl activating group, although simple *N*-sulfonyltriazoles are known to function as arene substrates in the coupling with alkynes under Rh(III) catalysis.[11] Very recently, the Miura and Murakami groups realized Rh(II)-catalyzed elegant coupling of arenes and *N*-sulfonyltriazoles[12] via a Friedel–Crafts type insertion of arenes into the electrophilic Rh(II) carbene intermediate (Scheme 1b).[12e] Consequently, the para/ortho regioselectivity was only moderate for alkylbenzenes, anisoles, and dialkylaminobenzenes. Therefore, there is a large room for improvement in the reactivity and selectivity of the coupling of arenes and triazoles. We now report the efficient and regioselective coupling of arenes with 4-acyl-1-sulfonyltriazoles for C–H olefination with possible subsequent annulation (Scheme 1c).

Scheme 1. Triazole Derivatives as Carbene Precursors in C–H Activation/Functionalization



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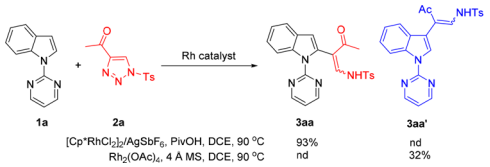
We initially selected 4-phenyl-1-sulfonyltrizole as a coupling reagent for functionalization of *N*-pyrimidylindoles via C−H activation. However, no desired coupling occurred after extensive exploration using Rh(III) or Ir(III) catalysts. Inspired by the report by Miura and Murakami,[12e] we reasoned that the low reactivity may be ascribed to lack of an electron-withdrawing activation group. Thus, we switched to 4-acyl-1-sulfonyltriazole, and the Rh(III)-catalyzed coupling of *N*-pyrimidinylindole (**1a**) and 4-acetyl-1-sulfonyltriazole (**2a**) was optimized in the presence of $[RhCp^*Cl_2]_2/AgSbF_6$ catalyst and PivOH additive (eq 1). A desired coupling

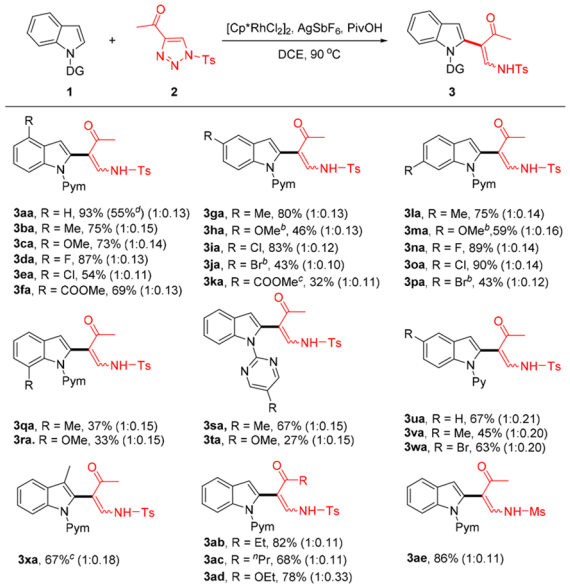


(1)

occurred to give the C(2)-olefination product **3aa** in 86% yield and 1:0.15 *Z*/*E* selectivity (Supporting Information, Table S1, entry 1). Switching to TFE, PhCl, and 1,4-dioxane solvents all essentially shut down the reaction. The yield of **3aa** was lowered to 75% when PivOH was omitted (Table S1, entry 6). The yield was improved to 90% when the reaction temperature was slightly increased (Table S1, entry 7). Moreover, the reaction time could be shortened to 1 h (Table S1, entry 8). In stark contrast, the regioisomeric product **3aa′** was isolated (32%) in 1:0.23 *Z*/*E* selectivity when $Rh_2(OAc)_4$ was used as a catalyst (Table S1, entry 9), and the similar result had been reported by Anbarasan.[13]

With the establishment of the optimal reaction conditions, we next investigated the scope of this coupling system (Scheme 2). A broad scope of *N*-pyrimidylindoles underwent smooth coupling with **2a**, regardless of electron-donating and -withdrawing substituents at the C4-, C5-, and C6- positions

Scheme 2. Scope of Olefination of *N*-Pyrimidylindoles[a]

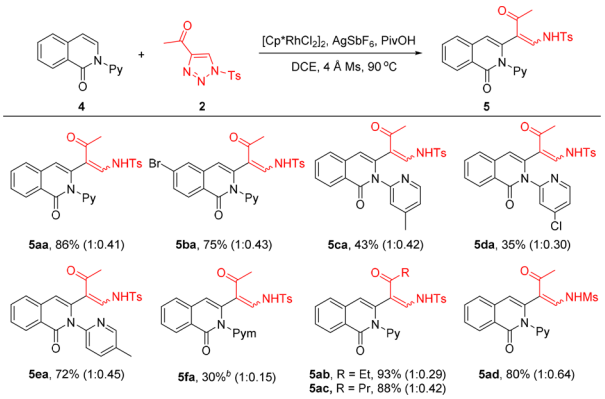


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), PivOH (100 mol %), DCE (2 mL), 90 °C, 1 h, isolated yield (*Z*/*E* ratio in parentheses). [b]8 h. [c]$[Cp^*IrCl_2]_2$ (4 mol %) was used. [d]3.0 mmol scale.

(**3ba**−**3pa**). The yield was attenuated with the introduction of a C7- group (**3qa**, **3ra**). The directing group was successfully extended to substituted pyrimidyl and pyridyl (**3sa**−**3wa**). While essentially no reaction occurred for a 3-methylindole under the Rh(III)-catalyzed conditions, the $[IrCp^*Cl_2]_2$-catalyzed coupling afforded **3xa** in 67% yield. Other 4-acyl-1-sulfonyltriazoles also participated in this reaction in good to high yields (**3ab**−**3ac** and **3ae**). When the acyl was switched to an ester group, **3ad** was isolated in 78% yield with reduced *Z*/*E* selectivity (1:0.33).

The arene substrate was smoothly extended to *N*-pyridylisoquinolones (**4**, Scheme 3). While the coupling of

Scheme 3. Scope of Olefination of *N*-Pyridylisoquinolones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), PivOH (100 mol %), 4 Å MS (200 mg), DCE (2 mL), 90 °C, 18 h, isolated yield (*Z*/*E* ratio in parentheses). [b]$[Cp^*IrCl_2]_2$ (4 mol %) was used.

4a and **2a** only afforded **5aa** in only 31% yield under the above reaction conditions, the yield was improved to 86% yield (*Z*/*E* = 1:0.41) when 4 Å MS was introduced. With the presence of a bromo group at the C6-positions of the isoquinolone, the coupling afforded **5ba** in 75% yield. An excellent yield was obtained when the acyl or sulfonyl group of the triazole substrate was varied (**5ab**−**5ad**), indicating the generality of the coupling system. In contrast, no desired reaction occurred when *N*-pyridyl-2-pyridone was subjected to the reaction conditions.

Ethyl benzimidate with a nucleophilic NH directing group (**6**) was then examined as an arene (Scheme 4). The Rh(III)-catalyzed coupling of **6a** with triazole **2a** in the presence of $Zn(OAc)_2$ yielded an *N*-Ts imine-functionalized isoquinoline (**7aa**, 98%) as a *Z*/*E* mixture of the imine. $NaBH_4$ reduction of the imine afforded the corresponding amine **8aa** in 82% yield (Scheme 4). A wide variety of ethyl benzimidates with an electron-donating and -withdrawing group at different positions of the benzene ring were tolerated (**8ba**−**8oa**). The reaction occurred at the less hindered ortho site for meta Me or bromo-substituted benzimidates. In contrast, in the reaction of meta Cl-, OMe-, and F-substituted benzimidates, the minor or the sole product corresponds to C−H action at the more hindered ortho position. Methyl benzimidate also coupled in essentially the same yield (**8pa**). Triazoles with different acyl and sulfonyl substituents reacted to deliver the corresponding products in moderate to good yields (**8ab**−**8ad**).

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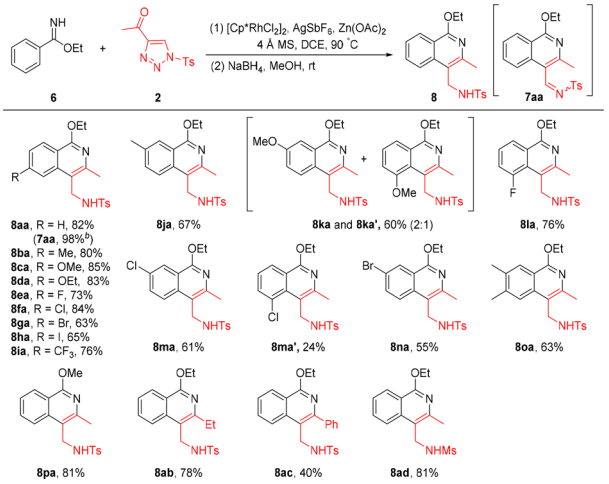
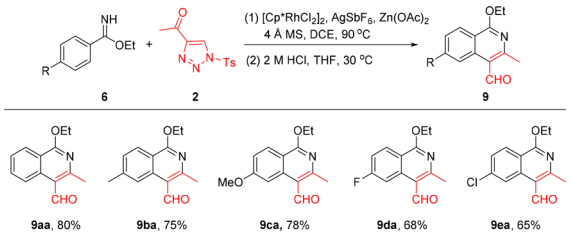
Scheme 4. Annulative Coupling between Benzimidates and 4-Acyl-1-Sulfonyltriazoles[a]



[a]Reaction conditions: (1) **6** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Zn(OAc)_2$ (30 mol %), 4 Å MS (200 mg), DCE (2 mL), 90 °C, 1 h; (2) $NaBH_4$ (0.4 mmol), MeOH (2 mL), rt, 15 min, isolated yield. [b]**7aa** was obtained after step 1, isolated yield.

Following the formation of imine product **7aa**, further hydrolysis in hydrochloric acid gave the corresponding aldehyde (**9aa**) in 80% total yield (Scheme 5). The scope of this one-pot annulation−hydrolysis reaction was briefly investigated, and aldehydes **9ba**−**9ea** were isolated in 65−78% yields (the overall yield of two steps).

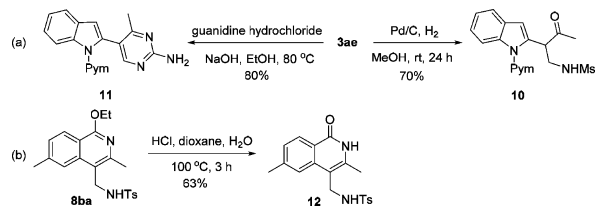
Scheme 5. Annulative Coupling and Subsequent Hydrolysis for Synthesis of Aldehydes[a]



[a]Reaction conditions: (1) **6** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Zn(OAc)_2$ (30 mol %), 4 Å MS (200 mg), DCE (2 mL), 90 °C, 1 h. (2) HCl (2 M, 1 mL), THF (1 mL), 30 °C, 2 h.

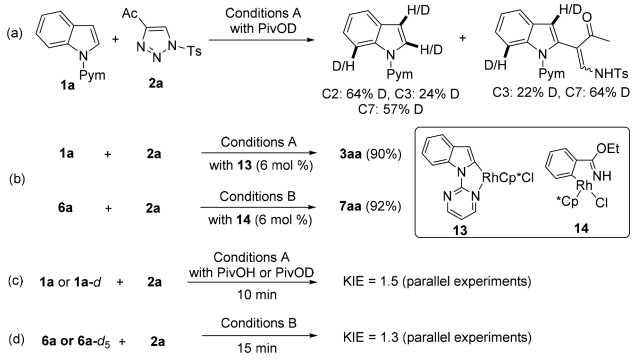
Synthetic applications have been demonstrated in several derivatization reactions (Scheme 6). Hydrogenation of enamide **3ae** gave *β*-amino ketone **10** in 70% yield. Treatment of **3ae** with guanidine afforded the aminopyrimidine product **11** in 80% yield. Hydrolysis of isoquinoline **8ba** in HCl/dioxane generated NH isoquinolone **12** in 63% yield.

Scheme 6. Derivatization Reactions



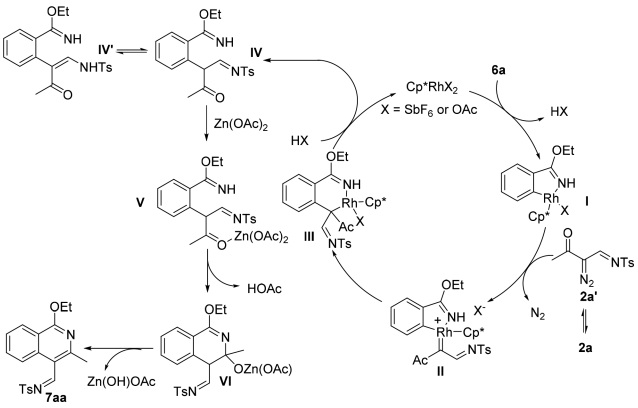
Several experiments have been performed to explore the mechanism (Scheme 7). The coupling of **1a** and **2a** in the presence of PivOD afforded the product with deuterium scrambling at the 3- and 7-positions (Scheme 7a). In addition, the recovered indole was also partially deuterated at the 2-, 3-, and 7-positions, indicating reversibility of the C−H activation process. To probe this C−H activation process, the coupling of **1a** or **6a** with **2a** was performed using the corresponding rhodacyclic complex **13**[14] or **14**,[15] respectively, which was a catalyst precursor (Scheme 7b). High efficiency was realized in each case, further indicating the relevance of C−H activation. Kinetic isotope effect (KIE) experiments were then performed for each coupling system. The KIE value of the coupling of **1a** and **2a** was measured to be 1.5 at a low conversion, and a similar magnitude was obtained for the reaction of **6a** and **2a** (Scheme 7c, d), which indicates that cleavage of the C−H bond is likely not involved in the turnover-limiting step.

Scheme 7. Mechanistic Studies



On the basis of these results and previous reports,[9,10,16] a plausible mechanism for the formation of imine **7aa** is proposed (Scheme 8). An active rhodium(III) catalyst $RhCp^*X_2$ is generated from the anion exchange between $[RhCp^*Cl_2]_2$ and $AgSbF_6$ or $Zn(OAc)_2$. Cyclometalation of iminate ester **6a** delivers a rhodacyclic intermediate **I**. Meanwhile, reversible ring scission of **2a** gives the diazo tautomer **2a′**. Coordination and denitrogenation of **2a′** affords a rhodium carbene intermediate **II**. Subsequent migratory insertion of the Rh-aryl bond into the carbene generates a Rh(III) alkyl intermediate **III**. Protonolysis of **III** produces the

Scheme 8. Proposed Catalytic Cycle



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alkylated intermediate **IV** that stays in equilibrium with its enamide tautomer **IV′**. Zn(II)-catalyzed[16,17] cyclization−condensation (via **V** and **VI**) eventually furnishes the coupled product **7aa**.

In summary, we have developed 4-acyl-1-sulfonyl triazoles as highly efficient carbene reagents for coupling with arenes via Rh(III)-catalyzed C−H bond activation. The installation of the 4-EWG activates this coupling reagent. The C−C coupling leads to olefination with possible cyclization, depending on the nature of the arene substrate. In both coupling systems, the reaction proceeded via a chelation-assisted C−H activation pathway with ortho selectivity. This selectivity stands in contrast to that in Rh(II) catalyzed coupling of triazoles with arenes bearing no directing group. The utilization of this triazole reagent expended the arsenal of carbene reagents and may find applications in the construction of complex structures via efficient and concise C−C bond formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02078.

Experimental procedures, characterization of new compounds, NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xwli@dicp.ac.cn.

ORCID

Bingxian Liu: 0000-0001-9872-9876

Xingwei Li: 0000-0002-1153-1558

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (c) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (d) Arnold, P. L.; McMullon, M. W.; Rieb, J.; Kühn, F. E. *Angew. Chem., Int. Ed.* **2015**, *54*, 82. (e) Wang, F.; Yu, S.; Li, X. *Chem. Soc. Rev.* **2016**, *45*, 6462.

(2) (a) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (b) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. (c) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163. (d) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333.

(3) Selected reviews on carbene insertion: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (d) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (e) Jia, M.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134. (f) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810. For representative reports, see: (g) Tsoi, Y.-T.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2011**, *13*, 5370. (h) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364. (i) Ye, b.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896. (j) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. - Eur. J.* **2014**, *20*, 17653. (k) Planas, O.; Roldán-Gómez, S.; Martin-Diaconescu, V.; Parella, T.; Luis, J. M.; Company, A.; Ribas, X. *J. Am. Chem. Soc.* **2017**, *139*, 14649.

(4) Vásquez-Céspedes, S.; Wang, X.; Glorius, F. *ACS Catal.* **2018**, *8*, 242.

(5) Selected reviews on outer-sphere C−H functionalization of carbenes/nitrenes: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (c) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (d) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (e) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (f) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S. *Chem. Soc. Rev.* **2017**, *46*, 4299. For a representative report, see: (g) Xie, H.; Ye, Z.; Ke, Z.; Lan, J.; Jiang, H.; Zeng, W. *Chem. Sci.* **2018**, *9*, 985.

(6) For selected examples of Rh(III)-catalyzed C−H alkylation with carbene reagents: (a) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (b) Yu, X.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444. (c) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598. (d) Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem. Commun.* **2014**, *50*, 6483. (e) Barday, M.; Janot, C.; Halcovitch, N. R.; Muir, J.; Älssa, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 13117. (f) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. *Org. Lett.* **2017**, *19*, 5256.

(7) For reviews of using *N*-sulfonyltriazoles as carbene reagents: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (b) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. *Synthesis* **2014**, *46*, 3004. (c) Jiang, Y.; Sun, R.; Tang, X.-Y.; Shi, M. *Chem. - Eur. J.* **2016**, *22*, 17910.

(8) (a) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470. (b) Selander, N.; Worrell, B. T.; Chuprakov, S.; Velaparthi, S.; Fokin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 14670. (c) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (d) Xing, Y.; Sheng, G.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 1244. (e) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151. (f) Shi, Y.; Gevorgyan, V. *Chem. Commun.* **2015**, *51*, 17166.

(9) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975.

(10) Jeon, W. H.; Son, J.-H.; Kim, J.; Lee, P. *Org. Lett.* **2016**, *18*, 3498.

(11) Yang, Y.; Zhou, M.-B.; Ouyang, X.-H.; Pi, R.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2015**, *54*, 6595.

(12) (a) Yadagiri, D.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 2510. (b) Park, S.; Yong, W.-S.; Kim, S.; Lee, P. H. *Org. Lett.* **2014**, *16*, 4468. (c) Shin, S.; Park, Y.; Kim, C.-E.; Son, J.-Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 5859. (d) Samala, S.; Shin, J.; Shim, J. Y.; Yoo, E. J. *Asian J. Org. Chem.* **2017**, *6*, 998. (e) Miura, T.; Zhao, Q.; Murakami, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 16645.

(13) Rajasekar, S.; Yadagiri, D.; Anbarasan, P. *Chem. - Eur. J.* **2015**, *21*, 17079.

(14) Qi, Z.; Kong, L.; Li, X. *Org. Lett.* **2016**, *18*, 4392.

(15) Wang, H.; Li, L.; Yu, S.; Li, Y.; Li, X. *Org. Lett.* **2016**, *18*, 2914.

(16) Tian, M.; Zheng, G.; Fan, X.; Li, X. *J. Org. Chem.* **2018**, *83*, 6477.

(17) Wang, Q.; Wang, F.; Yang, X.; Zhou, X.; Li, X. *Org. Lett.* **2016**, *18*, 6144.

DOI: 10.1021/acs.orglett.8b02078
Org. Lett. 2018, 20, 4946−4949