OL Organic Letters

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Iodonium Ylides as Carbene Precursors in Rh(III)-Catalyzed C−H Activation

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02618 Read Online

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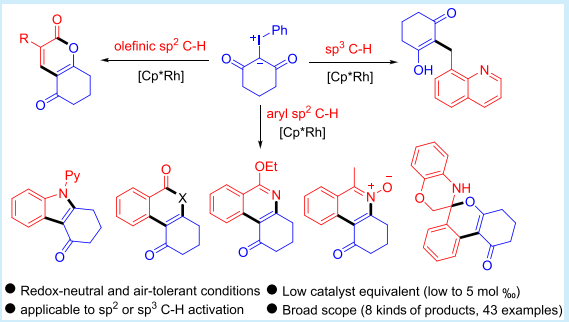
ABSTRACT: The rhodium(III)-catalyzed coupling of C−H substrates with iodonium ylides has been realized for the efficient synthesis of diverse cyclic skeletons, where the iodonium ylides have been identified as efficient and outstanding carbene precursors. The reaction systems are applicable to both sp^2 and sp^3 C−H substrates under mild and redox-neutral conditions. The catalyst loading can be as low as 0.5 mol % in a gram-scale reaction. Representative products exhibit cytotoxicity toward human cancer cells at nanomolar levels.

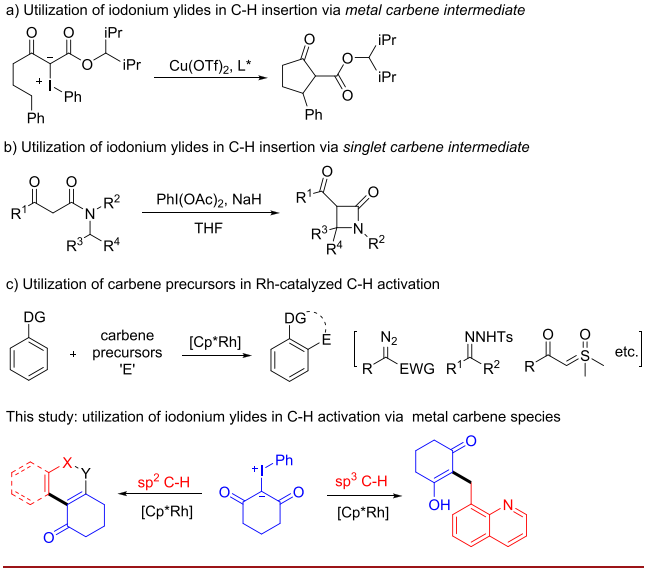


Hypervalent iodine compounds, which are versatile and environmental friendly, are known as important reagents in organic synthesis.[1] Among them, iodonium ylides are known to show good stability as singlet carbene reagents or metal carbene species for synthetic purposes.[2] Furthermore, iodonium ylides can be applied as both nucleophiles and electrophiles,[1b,2d,3] and their applications in single-electron-transfer (SET) processes have also be reported.[4] On the contrary, the abundance and ready availability of C−H bonds has inspired tremendous endeavors in C−H activation studies. Despite important advances in iodonium ylide chemistry, only limited examples of C−H insertion into iodonium-ylide-derived carbenoid species have been reported (Scheme 1a,b).[2,5,6] Thus the synthetic potential of iodonium ylides is far from being fully exploited. In contrast, other carbene precursors such as diazo compounds,[7] hydrazones,[8] and sulfoxonium ylides,[9] among others,[10] have been extensively used as efficient coupling partners in rhodium-catalyzed C−H activation for constructions of various complex skeletons (Scheme 1c).[11] Given the ready availability, stability, and relatively high reactivity of iodonium ylides, it is necessary to fully explore the fundamental carbene properties of iodonium ylides in transition-metal-catalyzed C−H activation.

We now report the application of hypervalent iodonium ylides in the Rh(III)-catalyzed C−H activation of arenes. A diverse scope of sp^2 C−H and sp^3 C−H bonds in arenes has been defined. Meanwhile, the catalyst loading can be decreased to 0.5 mol % in gram-scale synthesis, which showcases the high reactivity of iodonium ylides as carbene precursors in C−H functionalization.

We initially examined the reactivity of iodonium ylide in olefinic C−H activation.[12] Although olefinic C−H functionalization has been widely investigated, the couplings of olefins with carbene precursors via a C−H activation pathway are rare, likely due to the high tendency of olefins to undergo cyclopropanation.[1,2] By treating 2-benzylacrylic acid (**1a**)

Scheme 1. Reaction Modes of Iodonium Ylides with C−H Substrates



Received: August 5, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02618
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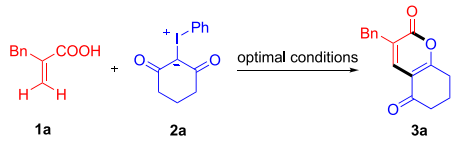
with iodonium ylide cyclohexane-1,3-dione (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (2 mol %) and NaOAc (25 mol %) in HFIP, a lactone product, 3-benzyl-7,8-dihydro-2*H*-chromene-2,5(6*H*)-dione, was obtained in almost quantitative yield (Table 1, entry 1). $Cp^*Rh(OAc)_2$ was also a workable

Table 1. Optimizations of the Model Reaction



1a 2a 3a

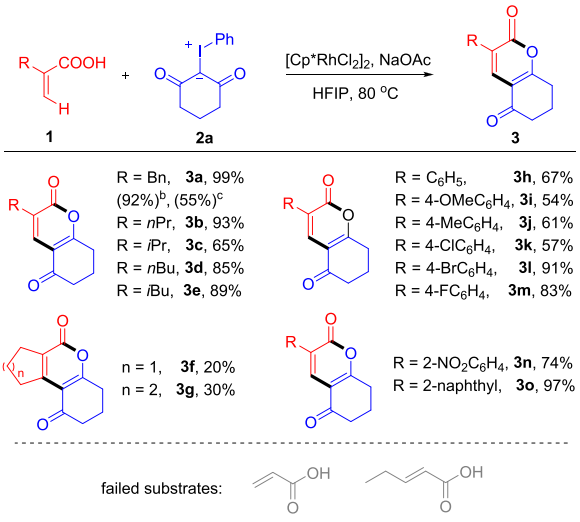
entry	changes from optimal conditions	yield (%)
1	no changes	99
2	$Cp^*Rh(OAc)_2$ (4 mol %) instead of $[Cp^*RhCl_2]_2$/NaOAc	69
3	H_2O instead of HFIP	65
4	EtOH instead of HFIP	22
5	cyclohexanedione (0.24 mmol) and $PhI(OAc)_2$ (0.24 mmol) instead of **2a**	63
6	2-diazocyclohexane-1,3-dione instead of **2a**	14
7	60 °C	90
8	40 °C	28
9	without $[Cp^*RhCl_2]_2$	n.d.
10	without NaOAc	64

catalyst for this coupling reaction, with a slightly dropped yield (entry 2, 69%). A moderate yield of 65% was achieved by using H_2O as the solvent (entry 3), whereas a poor yield was obtained when EtOH was used as a solvent (entry 4, 22%). In situ generation of **2a** in this catalytic system was found to be possible but with decreased yield (entry 5, 63%). For comparisons, 2-diazocyclohexane-1,3-dione was also tested but with quite a low yield of the same product (entry 6). The reaction system seemed to be sensitive to the reaction temperature (entries 7 and 8). Control experiments were conducted; no corresponding product was detected without the Cp*Rh catalyst, and only a moderate yield was achieved in the absence of NaOAc (entries 9 and 10).

The scope of acrylic acids in the coupling with **2a** for the construction of 7,8-dihydro-2*H*-chromene-2,5(6*H*)-diones was explored (Scheme 2). As shown in Scheme 2, alkyl-group-substituted acrylic acids at the α-position all reacted with **2a** to deliver the corresponding products in good to excellent yields (**3a**–**3e**, 65–99%). Cyclic acrylic acids such as 1-cyclopentenecarboxylic acid (**1f**) and 1-cyclohexenecarboxylic acid (**1g**) also reacted to give the corresponding products (**3f** and **3g**, 20 and 30%, respectively). Slightly decreased yields of the products were detected when aryl-substituted acrylic acids bearing an electron-donating group were used (**3h**–**3j**, 54–67%). The introduction of halogens is tolerated in the system, and good to excellent yields were isolated (**3k**–**3m**, 57–91%). Substrates with an electron-withdrawing group (NO_2) and 2-naphthyl group substituted acrylicacid were also tolerated (**3n** and **3o**). However, no product was detected when simple acrylic acid and β-ethyl acrylic acid were used.

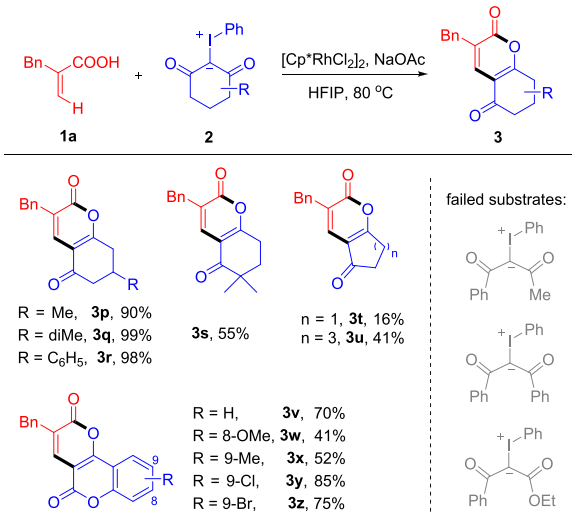
The scope of iodonium ylides was next investigated (Scheme 3). As shown in Scheme 3, different substituted cyclohexane-1,3-diones generally provided the desired products in good to excellent yields. Functional groups such as methyl and phenyl in the cyclohexa-2,5-dienone ring were tolerated, affording the desired products **3p**–**3r** (90–99%). The structure of **3s** was confirmed by NOESY spectroscopy of the corresponding

Scheme 2. Scope of Acrylic Acids[a]



[a]Reaction conditions: acrylic acids (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), NaOAc (25 mol %), HFIP (2 mL), 80 °C, 12 h, under air, isolated yield. [b]$[Cp^*RhCl_2]_2$ (5 mol ‰). [c]$[Cp^*RhCl_2]_2$ (3 mol ‰).

Scheme 3. Scope of Iodonium Ylides[a]



[a]Reaction conditions: 2-benzylacrylic acid (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), NaOAc (25 mol %), HFIP (2 mL), 80 °C, 12 h, under air, isolated yield.

derivative by treatment with $MeNH_2$–HCl. (See the SI). We also applied this protocol to iodonium ylides such as cyclopentane-1,3-dione and cycloheptane-1,3-dione, and the desired products (**3t** and **3u**) were isolated in diminished yields (16 and 41% yield). These results indicate that the reaction system is sensitive to the size of the dione rings. To further investigate the scope of the protocol, coumarin-derived fused iodonium ylides (**2v**–**2z**) were also explored, affording the desired tricyclic compounds in moderate to good yields (**3v**–**3z**, 41–85%). In contrast with the above success, several prepared or in-situ-generated acyclic iodonium ylides all failed to undergo the desired coupling under the standard conditions.

As reported, compounds containing a 2*H*-pyran-2-one motif, such as isocoumarins, are known to possess anticancer bioactivity.[6b,13] Thus the bioactivities of selected products

https://dx.doi.org/10.1021/acs.orglett.0c02618
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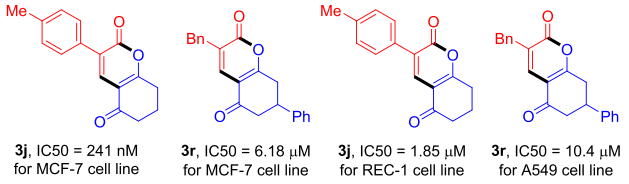
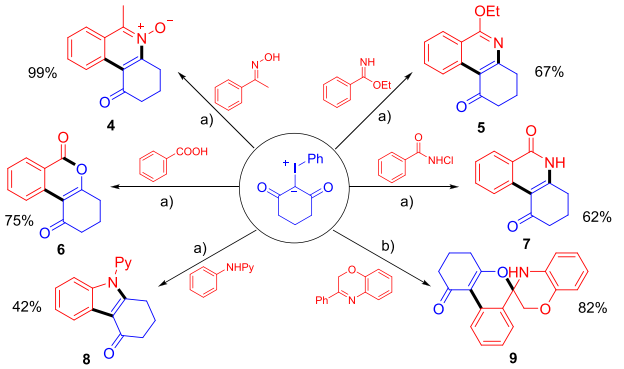
were evaluated toward MCF-7 cells, REC-1 cells, and A549 cells. Impressive results have been achieved in that the 50% inhibitory concentration (IC50) of the selected compounds is calculated to be at the nanomolar level toward the MCF-7 cell line and at the micromolar level toward the A549 cell line and REC-1 cell line (Scheme 4), which indicates that our products may exhibit the potential to be a kind of anticancer agent precursor.

Scheme 4. Antitumor Bioactivities of Selected Compounds



Encouraged by the above results, we next explored the generality of iodonium ylides in arene C−H activation−annulation reactions. More than six types of arenes bearing a nucleophilic directing group (NH, oxime, or OH) or an electrophilic directing group (imine) have been examined. In all cases, the reaction proceeded via C−H activation, carbene insertion, and nucleophilic cyclization, leading to the efficient synthesis of a diverse heterocyclic scaffold as well as spiro-heterocycles in moderate to excellent yields (Scheme 5, products **4**−**9**, 42−99% yield).

Scheme 5. Scope of the Arenes[a]

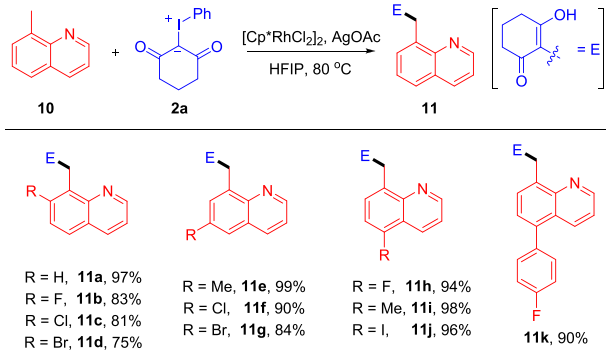


[a]Reaction conditions: (a) standard conditions with AgOAc instead of NaOAc. (b) Arenes (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), NaOAc (50 mol %), DCE (2 mL), 80 °C, 12 h, under air, isolated yield.

In addition to sp^2 C−H activation, the utilization of iodonium ylides in 8-methylquinoline benzylic C(sp^3)−H functionalization was also investigated.[14] After simple optimization, an efficient reaction system was realized using 8-methylquinolines as the substrates (Scheme 6). The scope is quite decent with mostly excellent yields (**11a**−**11k**, 75−99%). Different substituents at the five-, six-, and seven-positions all exhibit marginal influence on the reaction efficiency.

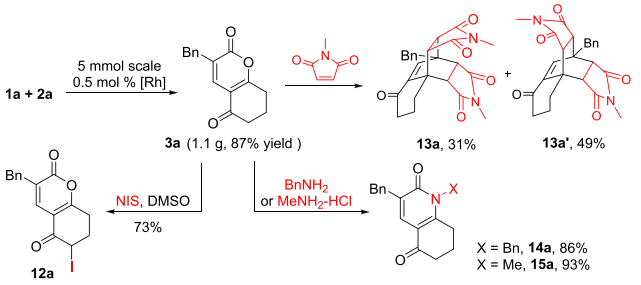
To showcase the synthetic utility, the gram-scale synthesis of **3a** was conducted (Scheme 7), which proceeded smoothly even with a catalyst loading as low as 0.5 mol % (87% yield). Furthermore, several derivatization reactions were conducted. The selective iodization of **3a** with NIS gave product **12a** (73%). The treatment of **3a** with an excess of *N*-

Scheme 6. Scope of the sp^3 C−H Substrates[a]



[a]Reaction conditions: **10** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (20 mol %), HFIP (2 mL), 80 °C, 12 h, under air, isolated yield.

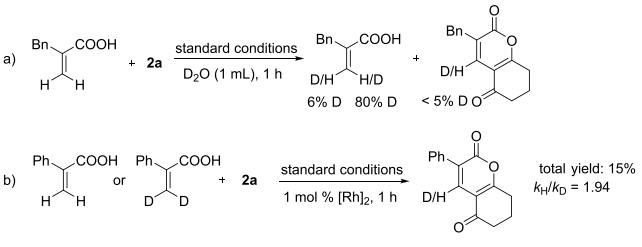
Scheme 7. Gram-Scale Synthesis and Derivatization of the Products



methylmaleimide led to a diastereomeric mixture of products **13a** and **13a′** (31 and 49% yield, respectively). The products were delivered via a Diels−Alder reaction of **3a** with 1 equiv of *N*-methylmaleimide, a retro-Diels−Alder reaction with the concomitant extrusion of carbon dioxide, and a second Diels−Alder reaction.[15] The 2*H*-pyran-2-one skeletons can also be transformed to be pyridin-2(1*H*)-ones in good yields when treated with a primary amine (**14a** and **15a**).

To gain some insight into the mechanism, deuterium labeling experiments were performed. By using D_2O as the reaction solvent, H/D exchange was observed at the vinyl reactive site of **1a** in the presence of iodonium ylide **2a**, indicating the reversibility of the olefinic C−H activation (Scheme 8a). An intermolecular kinetic isotope effect (KIE)

Scheme 8. Mechanistic Studies



value of 1.9 was determined using **1h** and **1h-*d*$_2$** by parallel reactions (Scheme 8b). This result indicates that the cleavage of the C−H bond might not be involved in the turnover-limiting step.

A catalytic cycle is proposed in Scheme 9 on the basis of the above reaction results and reported reports on related carbene

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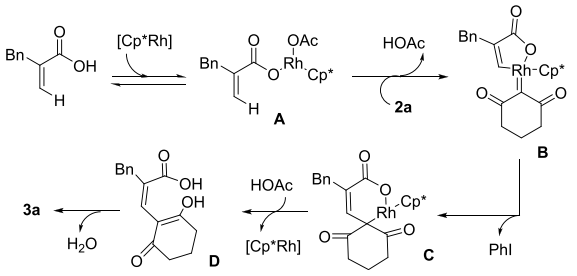
Scheme 9. Proposed Reaction Pathway



migration insertions.[11,16] Intermediate **A** is achieved by ligand exchange between acetate and acrylate, which follows the vinyl C−H activation and subsequent coordination of the ylide via the elimination of PhI to give a carbene species **B**. Migratory insertion of the carbene unit is proposed to give the intermediate **C**, which undergoes protonation to give the C−C-coupled intermediate **D** together with regeneration of the active Rh(III) catalyst. Intermediate **D** eventually undergoes nucleophilic cyclization−dehydration to yield the final product.

In summary, a diverse scope of cyclic skeletons has been readily assembled via Rh(III)-catalyzed C−H activation of arenes using iodonium ylides as a coupling reagent. The reaction system exhibits relatively high efficiency with wide substrate compatibility. Besides olefinic C−H substrates, arenes and sp^3 C−H substrates are also applicable. The utilization of iodonium ylides provides an alternative carbene procedure in Rh-catalyzed C−H activation. Meanwhile, the reaction products showed cytotoxicity toward some human cancer cell lines at the nanomolar or micromolar level, which may constitute a potential skeleton for the further development of anticancer agents. Subsequent research to extend the application and overcome the limitation of iodonium ylides in this field may make the versatile and environmentally benign reagent more useful in the synthesis of organic intermediates and drug-related compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02618.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NSFC (nos. 21801066, 21525208, U1804283, and 21801067), research fund from Henan Educational Committee (19A150028 and 20B350001), the Central Plains Scholars and Scientists Studio Fund (2018002), fund from Henan Normal University (2019QK04), and Natural Science Foundation of Henan Province (182300410131) are acknowledged.

■ REFERENCES

(1) For selected reviews on hypervalent iodine chemistry, see: (a) Yang, R.-Y.; Dai, L.-X. *Chin. J. Org. Chem.* **1994**, *14* (2), 113. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (c) Duan, Y.; Jiang, S.; Han, Y.; Sun, B.; Zhang, C. *Youji Huaxue* **2016**, *36*, 1973. (d) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.

(2) (a) Muller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *J. Phys. Org. Chem.* **1998**, *11*, 321. (b) Muller, P. *Acc. Chem. Res.* **2004**, *37*, 243. (c) Muller, P.; Allenbach, Y. F.; Chappellet, S.; Ghanem, A. *Synthesis* **2006**, *2006*, 1689. (d) Malamidou-Xenikaki, E.; Spyroudis, S. *Synlett* **2008**, *2008*, 2725. (e) Jia, M.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134.

(3) (a) Antos, A.; Elemes, Y.; Michaelides, A.; Nyxas, J. A.; Skoulika, S.; Hadjiarapoglou, L. P. *J. Org. Chem.* **2012**, *77*, 10949. (b) Huang, H.; Yang, Y.; Zhang, X.; Zeng, W.; Liang, Y. *Tetrahedron Lett.* **2013**, *54*, 6049. (c) Chelli, S.; Troshin, K.; Mayer, P.; Lakhdar, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2016**, *138*, 10304.

(4) (a) Zhao, Z.; Luo, Y.; Liu, S.; Zhang, L.; Feng, L.; Wang, Y. *Angew. Chem., Int. Ed.* **2018**, *57*, 3792. (b) Zhao, Z.; Kong, X.; Wang, W.; Hao, J.; Wang, Y. *Org. Lett.* **2020**, *22*, 230.

(5) Gomes, L. F. R.; Veiros, L. F.; Maulide, N.; Afonso, C. A. M. *Chem. - Eur. J.* **2015**, *21*, 1449.

(6) (a) Müller, P.; Boléa, C. *Molecules* **2001**, *6*, 258. (b) Batsila, C.; Gogonas, E. P.; Kostakis, G.; Hadjiarapoglou, L. P. *Org. Lett.* **2003**, *5*, 1511.

(7) For selected papers, see: (a) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (b) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (c) Tang, G.-D.; Pan, C.-L.; Li, X. *Org. Chem. Front.* **2016**, *3*, 87. (d) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508. (e) Chen, R.; Cui, S. *Org. Lett.* **2017**, *19*, 4002.

(8) For selected papers, see: Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364.

(9) For selected papers, see: (a) Barday, M.; Janot, C.; Halcovitch, N. R.; Muir, J.; Aissa, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 13117. (b) Xu, Y.-W.; Zhou, X.-K.; Zheng, G.-F.; Li, X.-W. *Org. Lett.* **2017**, *19*, 5256.
(10) For other carbene precursors, see: (a) Zhang, H.; Wang, K.; Wang, B.; Yi, H.; Hu, F.; Li, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13234. (b) Hong, S. Y.; Jeong, J.; Chang, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 2408. (c) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975.
(11) For selected reviews of carbene precursors on C−H activation, see: (a) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810. (b) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986−7995.
(12) For selected reviews of alkene C−H activation, see: (a) Maraswami, M.; Loh, T.-P. *Synthesis* **2019**, *51*, 1049. (b) Wang, K.; Hu, F.; Zhang, Y.; Wang, J. *Sci. China: Chem.* **2015**, *58*, 1252. (c) Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253.
(13) (a) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. (b) Tutov, A.; Bakulina, O.; Dar'in, D.; Krasavin, M. *Tetrahedron Lett.* **2018**, *59*, 1511. (c) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 2689. (d) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1996**, *59*, 765.
(14) For selected papers of Rh-catalyzed sp^3 C−H activation, see: (a) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141. (b) Liu, B.; Zhou, T.; Li, B.; Xu, S.; Song, H.; Wang, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 4191. (c) Huang, X.; Wang, Y.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 9404. (d) Wang, X.; Yu, D.-G.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10280. (e) Hou, W.; Yang, Y.; Wu, Y.; Feng, H.; Li, Y.; Zhou, B. *Chem. Commun.* **2016**, *52*, 9672.
(15) Fernandez, D. F.; Casanova, N.; Mascarenas, J.; Gulías, M. *ACS Omega* **2019**, *4*, 6257.
(16) Li, Y.; Wang, Q.; Yang, X.; Xie, F.; Li, X. *Org. Lett.* **2017**, *19*, 3410.

https://dx.doi.org/10.1021/acs.orglett.0c02618
Org. Lett. XXXX, XXX, XXX−XXX