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Rhodium(III)-Catalyzed Oxidative Annulation of 4-Aminoquinolines and Acrylate through Two Consecutive C(sp^2)−H Activations

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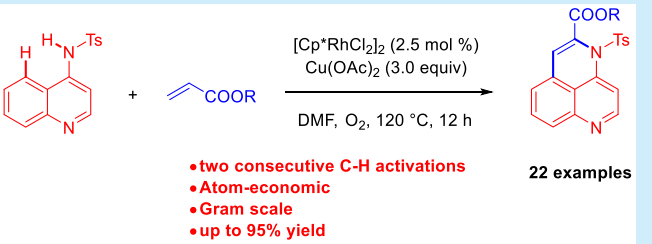
ABSTRACT: The C−H annulation of the five-position of quinolines and acrylates to afford heterocycles is an active field of research in organic synthesis. Herein the annulation of 4-aminoquinolines with acrylates through two consecutive C−H activations catalyzed by Rh(III) is described. The reaction proceeds with high atom efficiency under mild reaction conditions, and this protocol will provide appealing strategies for the synthesis of fused quinoline heterocycles.



Quinoline scaffolds are widely found in many pharmacologically molecules, natural products, catalysts, and functional materials.[1,2] Indeed, 4-aminoquinoline fragments exist in a tremendous number of approved drugs and active natural products such as neratinib, bosutinib, and so on (Figure 1a).[3] At the C2, C3, C4, and C8 positions of the quinoline substrates, quinoline as a building block has a broad prospect for structural functionalization.[4−6] The C5-modified quinolines have been one of the essential heterocycles in organic synthesis and medicinal chemistry owing to their diverse biological activities and unique properties (Figure 1b).[7] However, it should be noted that there are few examples of quinoline functionalization at the C5 position. Furthermore, most of the reactions in the C5 position of quinoline often need severe conditions owing to its less favorable electronic factors.[8] Therefore, the development of efficient, general, and reliable methods for chemical modification, especially annulation on the five-position of quinoline, has been considered to be a great challenge in the organic chemistry community.[9]

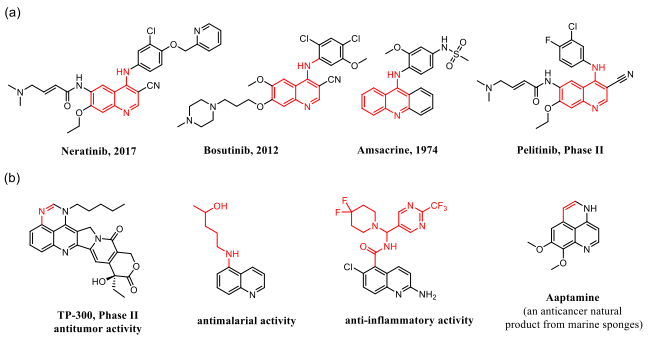


Figure 1. (a) Representative drugs containing 4-aminoquinoline moieties. (b) Representative compounds modified on the five-position of quinoline ring.

Scheme 1. Transition-Metal-Catalyzed C−H Functionalization

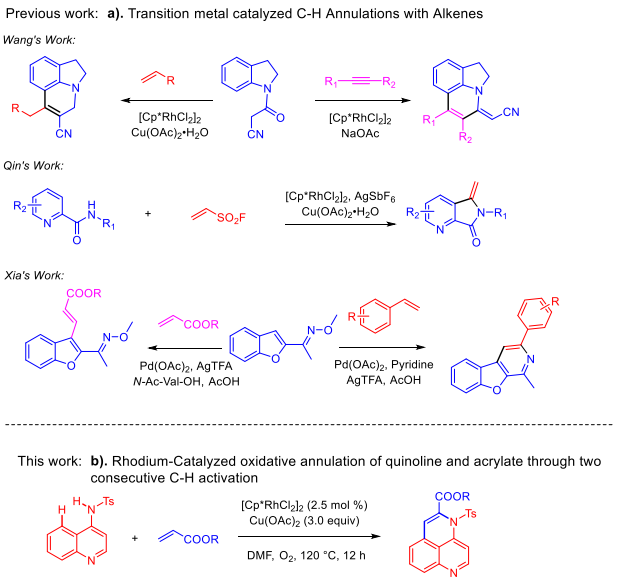


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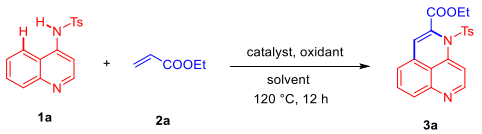
Table 1. Screening the Reaction Conditions[a]



entry	catalyst (mol %)	oxidant (equiv)	solvent	yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	DMF	54
2	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (4)	DMF	trace
3	$[Cp^*RhCl_2]_2$ (5)	CuI (4)	DMF	ND[c]
4	$[Cp^*RhCl_2]_2$ (5)	AgOAc (4)	DMF	trace
5	$[Cp^*RhCl_2]_2$ (5)	AgOTf (4)	DMF	ND[c]
6	$[Cp^*RhCl_2]_2$ (5)	Ag_3PO_4 (4)	DMF	trace
7	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	MeOH	5
8	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	DCE	7
9	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	DMA	32
10	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	toluene	14
11	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	NMP	19
12	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	DMSO	11
13	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	*i*-PrOH	ND[c]
14	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (4)	H_2O	ND[c]
15	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (3)	DMF	70
16[d]	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2$ (3)	DMF	81
17[d]	$[Cp^*RhCl_2]_2$ (2.5)	$Cu(OAc)_2$ (3)	DMF	85
18[d]	$[RuCl_2(p\text{-cymene})]_2$ (2.5)	$Cu(OAc)_2$ (3)	DMF	ND[c]
19[d]	$Pd(OAc)_2$ (2.5)	$Cu(OAc)_2$ (3)	DMF	ND[c]
20[d]	$Ni(COD)_2$ (2.5)	$Cu(OAc)_2$ (3)	DMF	ND[c]
21[d]	$[Cp^*RhCl_2]_2$ (2.5)		DMF	ND[c]
22[d]		$Cu(OAc)_2$ (3)	DMF	ND[c]

[a]Reaction conditions: 4-aminoquinolines **1a** (0.34 mmol), ethyl acrylate **2a** (0.50 mmol), catalyst, oxidant, and solvent (5 mL); reactions run in a sealed tube at 120 °C under a nitrogen atmosphere for 12 h. [b]Isolated yields. [c]Desired product was not detected. [d]Reaction was carried out under an O_2 atmosphere.

Over the past two decades, the transition-metal-catalyzed carbon−hydrogen (C−H) functionalization via the directing group has gained much attention, and these methods are still being widely applied for the construction of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds in medicinal chemistry, organic synthesis, and materials science.[10,11] In particular, the rhodium(III)-catalyzed C−H functionalization of alkynes or alkenes has been proven to be one of the more effective strategies for the synthesis of complex molecules other than other transition metals.[12] Among these studies, the participation of alkynes is often required in the one-step annulation reaction, and acrylates are utilized for alkenylation modification. Nevertheless, there is limited literature about intermolecular C−H annulation reactions with acrylates. This is because if this cyclization takes place, then two consecutive C−H activations occur, which requires higher activation energy and makes the reaction more difficult. In 2016, Wang's group demonstrated Rh(III)-catalyzed carbocyclization reactions with alkynes and alkenes with a broad range of substrates and high yields.[13a] Then, in 2019, Qin and coworkers reported the Rh(III)-catalyzed coupling reactions of olefins and picolinamides and completed the application of this method in the structural modification of sorafenib.[13b] Additionally, Xia's group developed a reaction for the C−H alkenylation and annulation of *O*-methylketoxime with styrenes via palladium catalysis to synthesize benzothienopyridines and benzofuropyridines (Scheme 1a).[13c] In these studies, the directing group can also be transformed into value-added molecules with olefins, which would be of great significance.

In recent years, the research on the C−H functionalization of quinoline substrates has focused mainly on the C2, C3, C4, and C8 positions rather than C5.[4c,5e] Considering the five-position functionalization of quinoline, the C5 annulation-modified compounds may possess particularly good biological activity, and thus it is necessary to develop an effective method for the C−H annulation of the five-position of quinoline to construct a heterocycle. As far as we know, reactions of the five-position of quinolines and acrylates to synthesize annulated products via Rh(III)-catalyzed C−H activation reaction have not been reported. Herein we first report the synthesis of the annulated five-position of 4-aminoquinolines and acrylates through two consecutive C−H activations catalyzed by Rh(III) (Scheme 1b). Furthermore, in this transformation, four hydrogen atoms are efficiently removed, and this also demonstrates good atom efficiency.

We initiated our study by exploring reaction conditions for the envisioned two consecutive C−H activations of 4-aminoquinolines **1a** with ethyl acrylate **2a**. (See the Supporting Information for details.) Quinoline (**1a**, 0.34 mmol) was treated with ethyl acrylate (**2a**, 0.50 mmol) in the presence of a catalytic amount of $[Cp^*RhCl_2]_2$ (5 mol %) and $Cu(OAc)_2$ (4.0 equiv) as an oxidant and DMF (5 mL) as a solvent at 120 °C under a nitrogen atmosphere for 12 h. To our delight, the reaction furnished the desired annulated product **3a** in a 54% isolated yield (Table 1, entry 1). Later, to improve the reactivity, other oxidants such as $AgSbF_6$, CuI, AgOAc, AgOTf,

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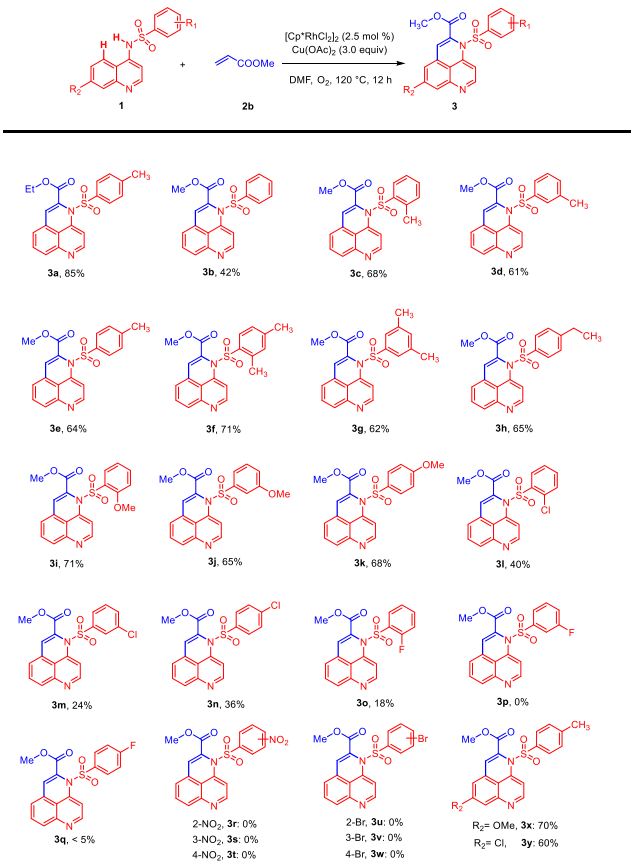
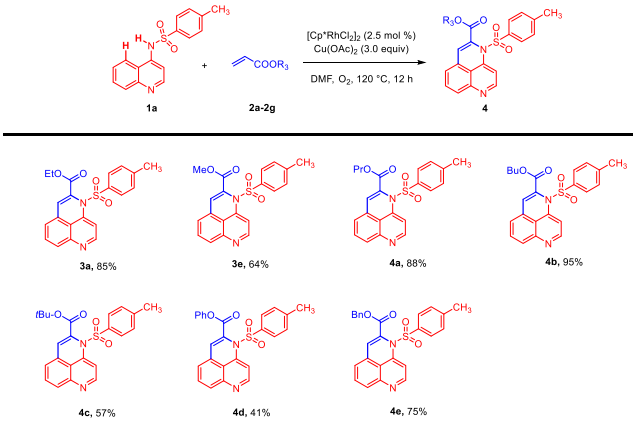
Scheme 2. Substrate Scope of Quinoline[a,b]



[a]Reaction conditions: 4-aminoquinoline (0.34 mmol), acrylate (0.50 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (1.02 mmol), and solvent (5 mL); reaction run in a sealed tube at 120 °C under an oxygen atmosphere for 12 h. [b]Isolated yields.

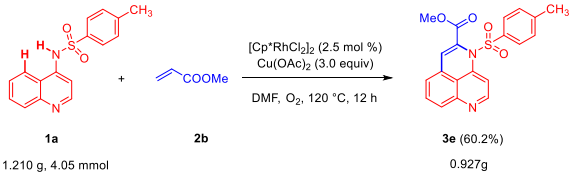
Scheme 3. Substrate Scope of Acrylate[a,b]



[a]Reaction conditions: 4-aminoquinolines (0.34 mmol), acrylate (0.50 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (1.02 mmol), and solvent (5 mL); reactions run in a sealed tube at 120 °C under an oxygen atmosphere for 12 h. [b]Isolated yields.

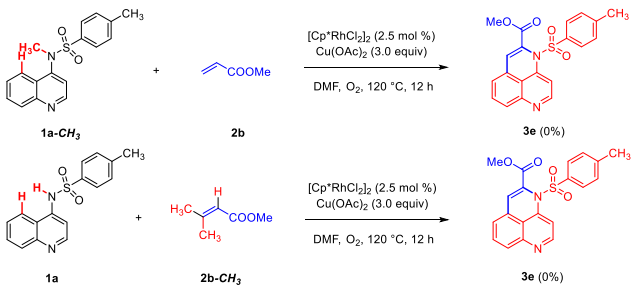
and Ag_3PO_4 were investigated separately (entries 2−6). Finally, only when we used $Cu(OAc)_2$ as an oxidant was the desired product afforded. Thus the choice of $Cu(OAc)_2$ as the oxidant was essential for the cyclization process, owing to the fact that $Cu(OAc)_2$ furnished the acetate source for the rhodium deprotonation metalation pathway.[14] The solvent has

Scheme 4. Gram-Scale Synthesis of 3e

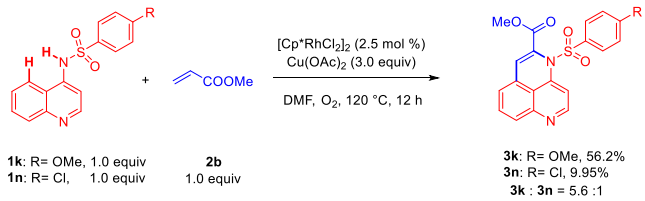


Scheme 5. Control Experiments

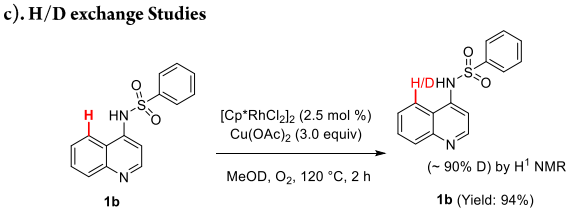
a). Control Experiment



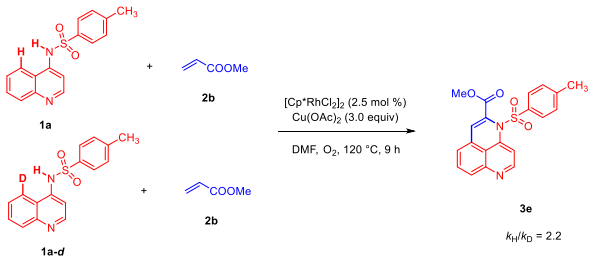
b). Intermolecular Competition Experiment



c). H/D exchange Studies



d). KIE analysis



an obvious effect on the yield of the reaction, and the effect of different solvents was examined (entries 7−14). In general, when switching to the other solvents, the C−H activation reaction did not improve, and in some case it provided no product. DMF was still the best solvent. Gratifyingly, after screening the ratio of oxidant and catalyst, the reaction proceeded smoothly, and the desired product yield was promoted. The optimized ratios of $Cu(OAc)_2$ and Rh(III) were 3.0 and 2.5 mol % (entry 15 vs 1, 16 vs 17). Subsequently, it was noteworthy that an 85% yield was attained for **3a** when the reaction was carried out under an

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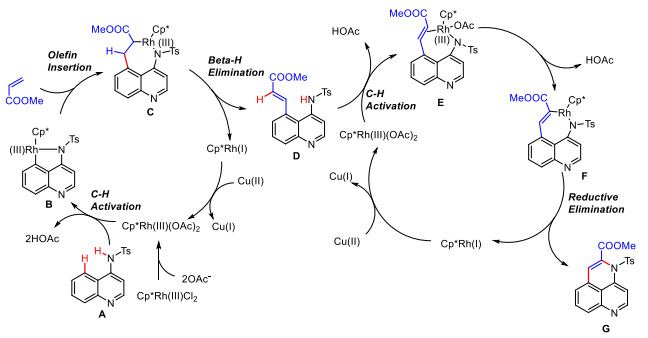
Scheme 6. Plausible Mechanism



oxygen atmosphere instead of nitrogen (entry 17). In addition, whereas we explored using different transition-metal catalysts, such as palladium, ruthenium, and nickel, together with the same oxidant, surprisingly, the oxidative annulation reaction did not occur (entries 18−20). Finally, several control experiments were conducted to prove that each component of the scheme was critical to the reaction efficiency (entries 21 and 22). After the extensive screening of different parameters, optimized conditions for these two consecutive C−H reaction were established: quinoline (1.0 equiv), ethyl acrylate (1.5 equiv), rhodium (2.5 mol %), and $Cu(OAc)_2$ (3.0 equiv) in DMF at 120 °C under an oxygen atmosphere for 12 h.

With the optimized conditions in hand, we then tested the versatility and scope of two consecutive rhodium(III)-catalyzed C−H activations with the structural diversity of various 4-aminoquinolines by assessing the substitution effect on the quinoline framework. As shown in Scheme 2, electron-donating substituents generally have excellent tolerance, providing the desired products **3c**−**k** bearing *mono*-methyl (**3c**−**e**), dimethyl (**3f**,**g**), ethyl (**3h**), and methoxy (**3i**−**k**) in moderate to good yield of 61−71%. Interestingly, the significant influence of the same substituents at different positions on this transformation was observed. For example, *ortho*-methyl (**3c**: 68%), *ortho*-methoxy (**3i**: 71%) gave better yields than the corresponding *meta*-methyl (**3d**: 61%), *meta*-methoxy (**3j**: 65%) and *para*-methyl (**3e**: 64%), *para*-methoxy (**3k**: 68%). As for the dimethyl-substituted compounds, the 2,4-dimethyl substrate was likewise converted with higher efficiency, and the desired product **3f** was obtained in a higher 71% yield compared with the 62% yield of the 3,5-dimethyl-substituted compound **3g**. Meanwhile, as for the electron-withdrawing groups, a relatively lower yield was observed in the reaction of the substrate bearing chlorine and fluorine at different positions (**3l**: 40%, **3m**: 24%, **3n**: 36%; **3o**: 18%, **3p**: 0%, **3q**: <5%). In particular, a strong electron-withdrawing nitro group resulted in oxidative annulation reaction difficulty, and no desired products **3r**−**t** were found. The bromine substituents (**3u**−**w**) were also not tolerated for this reaction. They mainly contributed to the removal of bromine atoms during the reaction process. Similarly, when the seven-position of the quinoline scaffold was replaced by an electron-rich methoxy group (**3x**: 70%), a better yield was obtained compared with that of the corresponding electron-deficient chlorine groups (**3y**: 60%). Therefore, whether this C−H activation reaction could take place depended on the electronic effects of the aromatic rings.

Subsequently, the impact of different substituted acrylate substrates on this Rh-catalyzed oxidative annulation reaction was also investigated (Scheme 3). In general, the cyclization of various acrylates **2a**−**g** and the same 4-aminoquinoline **1a** proceeded smoothly to provide the annulated product **3a**, **3e**, and **4a**−**e** with yields ranging from 41 to 95%. Interestingly, with the rise of the electron-donating ability of the ester group, the yield of this reaction was also enhanced. Consequently, the highest yield of the desired product **4b** could reach 95% through two consecutive activation reactions of *n*-butyl acrylate and 4-aminoquinoline **1a**. However, the large *t*-butyl-substituted substrate provided the desired product **4c** in only 57% yield, which also revealed that the steric effects of the acrylate substrates had a great influence on the annulation reaction.

To further verify the synthetic utility of this reaction, a gram-scale synthesis of **3e** was carried out under the standard reaction conditions (Scheme 4). Interestingly, 0.927 g of desired product **3e** was obtained in 60.2% yield when the reaction was performed on a 4.05 mmol scale. The yield was comparable to that obtained in the small-scale experiment.

To provide insight into the mechanism of these two rhodium-catalyzed consecutive C−H activations, a series of control experiments were designed and performed. Once the N atom on sulfonamide was methylated and thus could not act as a directing group, the transformation did not work. When the hydrogen atom on acrylate alkenyl was substituted by methyl, the reaction also did not occur. It was proved that the oxidative annulation reaction was a C−H activation process (Scheme 5a). In addition, the influence of substituents on the intermolecular competition revealed that the electron-donating group reacts more readily than the electron-withdrawing group (Scheme 5b). Then, the mechanistic study was further explored. When the starting material reacted in deuterium solvent for 2 h, 90% deuterium product was obtained (Scheme 5c). It was thereby proved that the C−H activation reaction was reversible. Furthermore, the kinetic isotope effect of deuterium was investigated by the intermolecular competitive reaction between **1a** and **1a**-*d*. As a result, the kinetic isotope effect (k_H/k_D) was 2.2, indicating that the cleavage of the aromatic C−H bond in **1a** was the rate-determining step (Scheme 5d).[15]

On the basis of the results of these experiments and the reported transition-metal-catalyzed C−H bond functionalization reactions,[16] a plausible mechanism was proposed for the present C−H activation reaction (Scheme 6). First, the cationic rhodium catalyst $[Cp^*Rh(OAc)_2]$ was formed by the reaction of the catalyst $[Cp^*RhCl_2]_2$ and the oxidant $Cu(OAc)_2$. The second step is likely to generate a five-membered intermediate **B** through a $C(sp^2)$−H activation process, which would subsequently involve the coordination and insertion of acrylate. As a result, a seven-membered metallacycle intermediate **C** was generated. After *β*-H elimination, the intermediate **D** was obtained in the absence of $Cu(OAc)_2$, while the first C−H activation was finished. Meanwhile, Cp*Rh(I) was oxidized to $Cp^*Rh(OAc)_2$ and participated in the next catalytic cycle. Similarly, the coordination amino of intermediate **D** to $Cp^*Rh(OAc)_2$ followed by metalation afforded an intermediate **E**. Coordinative insertion into the double bond of intermediate **E** afforded a seven-membered metallacycle **F**. This intermediate **F** might undergo a reductive elimination to afford the desired product **G**. Finally, the second C−H activation was completed, and the remaining active $Cu(OAc)_2$ was regenerated under an oxygen atmosphere.

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In summary, we have reported here an unprecedented synthesis of the annulated five-position of 4-aminoquinolines and acrylate that furnishes heterocycles through two consecutive C−H activations catalyzed by rhodium(III). A wide variety of functional groups can be successfully incorporated into these heterocycles. The reaction proceeds with high atom efficiency, mild reaction conditions, and experimental simplicity, rendering the methodology highly useful for the synthesis of five-position-fused quinoline heterocycles. A plausible mechanism has been proposed, and more details of the mechanism are being explored. In our laboratory, further optimization of reaction conditions to achieve a broader scope is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00630.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Romero, E. A.; Chen, G.; Gembicky, M.; Jazzar, R.; Yu, J.-Q.; Bertrand, G. *J. Am. Chem. Soc.* **2019**, *141*, 16726. (b) Yang, Y. F.; Chen, G.; Hong, X.; Yu, J. Q.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 8514. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (d) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (e) Hughes, G.; Bryce, M. R. *J. Mater. Chem.* **2005**, *15*, 94.

(2) (a) Wang, H. W.; Lu, Y.; Zhang, B.; He, J.; Xu, H. J.; Kang, Y. S.; Sun, W. Y.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 7449. (b) Ashok, P.; Ganguly, S.; Murugesan, S. *Drug Discovery Today* **2014**, *19*, 1781. (c) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2000**, *19*, 1851.

(3) (a) Singh, H.; Walker, A. J.; Amiri-Kordestani, L.; Cheng, J.; Tang, S.; Balcazar, P.; Barnett-Ringgold, K.; Palmby, T. R.; Cao, X.; Zheng, N.; Liu, Q.; Yu, J.; Pierce, W. F.; Daniels, S. R.; Sridhara, R.; Ibrahim, A.; Kluetz, P. G.; Blumenthal, G. M.; Beaver, J. A.; Pazdur, R. *Clin. Cancer Res.* **2018**, *24*, 3486. (b) Rossari, F.; Minutolo, F.; Orciuolo, E. *J. Hematol. Oncol.* **2018**, *11*, 84. (c) Martin, M.; Holmes, F. A.; Ejlertsen, B.; Delaloge, S.; Moy, B.; Iwata, H.; von Minckwitz; Chia, S.; Mansi, J.; Barrios, C. H.; et al. *Lancet Oncol.* **2017**, *18*, 1688. (d) Vitaku, E.; Smith, D. T.; Njardarson, J.T. J. *J. Med. Chem.* **2014**, *57*, 10257.

(4) (a) Iwai, T.; Sawamura, M. *ACS Catal.* **2015**, *5*, 5031. (b) Du, B. N.; Qian, P.; Wang, Y.; Mei, H. B.; Han, J. L.; Pan, Y. *Org. Lett.* **2016**, *18*, 4144. (c) Bering, L.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 3134.

(5) (a) Zhu, L. Z.; Sheng, X. H.; Li, Y.; Lu, D.; Qiu, R. H.; Kambe, N. *Org. Lett.* **2019**, *21*, 6785. (b) Degorce, S. L.; Barlaam, B.; Cadogan, E.; Dishington, A.; Ducray, R.; Glossop, S. C.; Hassall, L. A.; Lach, F.; Lau, A.; McGuire, T. M.; Nowak, T.; Ouvry, G.; Pike, K. G.; Thomason, A. G. *J. Med. Chem.* **2016**, *59*, 6281. (c) Sun, K.; Lv, Y. H.; Wang, L. J.; Sun, J. J.; Liu, L. L.; Jia, M. Y.; Liu, X.; Li, Z. D.; Wang, X. *Org. Lett.* **2015**, *17*, 4408. (d) Ribelles, P.; Ramos, M. T.; Menendez, J. C. *Org. Lett.* **2012**, *14*, 1402. (e) Kumar, S.; Pradhan, S.; Roy, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2019**, *84*, 10481.

(6) (a) Chen, X. P.; Cui, X. L.; Wu, Y. J. *Org. Lett.* **2016**, *18*, 3722. (b) Kim, J.; Kim, S.; Kim, D.; Chang, S. *J. Org. Chem.* **2019**, *84*, 13150. (c) Sharma, R.; Kumar, R.; Sharma, U. *J. Org. Chem.* **2019**, *84*, 2786. (d) Sharma, U.; Park, Y.; Chang, S. *J. Org. Chem.* **2014**, *79*, 9899.

(7) (a) Chekerov, R.; Hilpert, F.; Mahner, S.; El-Balat, A.; Harter, P.; De Gregorio, N.; Fridrich, C.; Markmann, S.; Potenberg, J.; Lorenz, R.; et al. *Lancet Oncol.* **2018**, *19*, 1247. (b) Centelles, M. N.; Wright, M.; So, P. W.; Amrahli, M.; Xu, X. Y.; Stebbing, J.; Miller, A. D.; Gedroyc, W.; Thanou, M. *J. Controlled Release* **2018**, *280*, 87. (c) Hawkins, D. S.; Chi, Y.-Y.; Anderson, J. R.; Tian, J.; Arndt, C. A.S.; Bomgaars, L.; Donaldson, S. S.; Hayes-Jordan, A.; Mascarenhas, L.; McCarville, M. B.; et al. *J. Clin. Oncol.* **2018**, *36*, 2770. (d) Naro, Y.; Ankenbruck, N.; Thomas, M.; Tivon, Y.; Connelly, C. M.; Gardner, L.; Deiters, A. *J. Med. Chem.* **2018**, *61*, 5900. (e) Vandekerckhove, S.; Van Herreweghe, S.; Willems, J.; Danneels, B.; Desmet, T.; de Kock, C.; Smith, P. J.; Chibale, K.; D'hooghe, M. *Eur. J. Med. Chem.* **2015**, *92*, 91. (f) Rech, J. C.; Bhattacharya, A.; Branstetter, B. J.; Love, C. J.; Leenaerts, J. E.; Cooymans, L. P.; Eckert, W. A.; Ao, H.; Wang, Q.; Chaplan, S. R.; Wickenden, A. D.; Lebsack, A. D.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4781. (g) Yu, H. B.; Yang, F.; Sun, F.; Li, J.; Jiao, W. H.; Gan, J. H.; Hu, W. Z.; Lin, H. W. *Mar. Drugs* **2014**, *12*, 6003.

(8) (a) Zhang, Z. P.; Tanaka, K.; Yu, J. Q. *Nature* **2017**, *543*, 538. (b) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (c) Zhu, L.; Qiu, R.; Cao, X.; Xiao, S.; Xu, X.; Au, C. T.; Yin, S. F. *Org. Lett.* **2015**, *17*, 5528. (d) Cong, X.; Zeng, X. *Org. Lett.* **2014**, *16*, 3716. (e) Stephens, D. E.; Larionov, O. V. *Tetrahedron* **2015**, *71*, 8683.

(9) (a) Ge, S. Z.; Chaładaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149. (b) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 7242. (c) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323. (d) Rousseaux, S.; Liegault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. (e) Kulkarni, A.; Torok, B. *Green Chem.* **2010**, *12*, 875. (f) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707. (g) Gao, Y.; Yang, F.; Sun, F.; Liu, L.; Liu, B.; Wang, S.-P.; Cheng, C.-W.; Liao, H.; Lin, H.-W. *Org. Lett.* **2019**, *21*, 1430. (h) Heredia, D. A.; Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2016**, *2016*, 1397. (i) Liao, G.; Song, H.; Yin, X. S.; Shi, B. F. *Chem. Commun.* **2017**, *53*, 7824.

(10) (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q. *Chem. Rev.* **2017**, *117*, 8754. (b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247. (c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (d) Chen, Z.; Wang, B.; Zhang, j.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (e) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Zhang, Q.; Shi, B. F. *Chin. J. Chem.* **2019**, *37*, 647. (i) Rao, W. H.; Shi, B. F. *Org. Chem. Front.* **2016**, *3*, 1028.

(11) (a) Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev.* **2017**, *117*, 9086. (b) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (f) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Rev.* **2011**, *111*, 1293. (g) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem.* **2009**, *121*, 5196. (h) Zhou, J.; Li, X.; Liao, G.; Shi, B. F. *Chin. J. Chem.* **2018**, *36*, 1143. (i) Qian, Z. C.; Zhou, J.; Li, B.; Hu, F.; Shi, B. F. *Org. Biomol. Chem.* **2014**, *12*, 3594. (j) Zhou, J.; Li, B.; Hu, F.; Shi, B. F. *Org. Lett.* **2013**, *15*, 3460. (k) Wei, X. H.; Wang, F.; Song, G. Y.; Du, Z. Y.; Li, X. W. *Org. Biomol. Chem.* **2012**, *10*, 5521.

(12) (a) Martinez, A. M.; Rodriguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 6105. (b) Cai, S.; Chen, C.; Shao, P.; Xi, C. *Org. Lett.* **2014**, *16*, 3142. (c) Zhou, J.; Li, B.; Qian, Z.-C.; Shi, B.-F. *Adv. Synth. Catal.* **2014**, *356*, 1038. (d) Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *Org. Lett.* **2013**, *15*, 1528. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (f) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (g) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (h) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.

(13) (a) Zhou, T.; Wang, Y. W.; Li, B.; Wang, B. Q. *Org. Lett.* **2016**, *18*, 5066. (b) Li, C.; Qin, H. L. *Org. Lett.* **2019**, *21*, 4495. (c) Fu, X. P.; Yang, J. Y.; Deng, K. Z.; Shao, L. Y.; Xia, C. C.; Ji, Y. F. *Org. Lett.* **2019**, *21*, 3505.

(14) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Cai, S. J.; Chen, C.; Shao, P.; Xi, C. J. *Org. Lett.* **2014**, *16*, 3142. (c) Wang, X. Y.; Qiu, X.; Wei, J. L.; Liu, J. Z.; Song, S.; Wang, W.; Jiao, N. *Org. Lett.* **2018**, *20*, 2632.

(15) (a) Li, M. B.; Grape, E. S.; Backvall, J. E. *ACS Catal.* **2019**, *9*, 5184. (b) Wu, X. Y.; Fan, J. J.; Fu, C. L.; Ma, S. M. *Chem. Sci.* **2019**, *10*, 6316. (c) Li, H.; Zhang, S.; Feng, X. J.; Yu, X. Q.; Yamamoto, Y.; Bao, M. *Org. Lett.* **2019**, *21*, 8563.

(16) (a) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (b) Wang, X. G.; Zhang, J.; Chen, D.; Wang, B.; Yang, X. F.; Ma, Y. M.; Szostak, M. *Org. Lett.* **2019**, *21* (17), 7038. (c) Dutta, U.; Maiti, S.; Pimparkar, S.; Maiti, S.; Gahan, L. R.; Krenske, E. H.; Lupton, D. W.; Maiti, D. *Chem. Sci.* **2019**, *10*, 7426.

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