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Synthesis of [5,6]-Bicyclic Heterocycles with a Ring-Junction Nitrogen via Rh(III)-Catalyzed C-H Functionalization of Alkenyl Azoles

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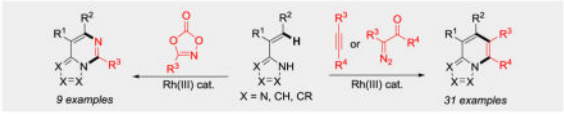
Abstract

The first syntheses of privileged [5,6]-bicyclic heterocycles with ring-junction nitrogens by transition-metal-catalyzed C-H functionalization of *C*-alkenyl azoles is disclosed. Several reactions are applied to alkenyl imidazoles, pyrazoles and triazoles to provide products with nitrogen incorporated at different sites. Alkyne and diazoketone coupling partners give azolopyridines with various substitution patterns. In addition, 1,4,2-dioxazolone coupling partners yield azolopyrimidines. Furthermore, the mechanisms for the reactions are discussed and the utility of the developed approach is demonstrated by iterative application of C-H functionalization for the rapid synthesis of a patented drug candidate.

Ride that bicycle

A wide range of [5,6]-bicyclic heterocycles with a ring-junction nitrogen could be accessed via a Rh(III)-catalyzed C-H functionalization strategy. Alkenyl imidazoles, pyrazoles and triazoles as C-H activation substrates in combination with alkynes, diazoketones or 1,4,2-dioxazolones as reaction partners allows for formation of this privileged class of heterocycles with rich diversity in substitution pattern and nitrogen incorporation.



Keywords

C-H activation; nitrogen heterocycles; homogeneous catalysis; azolopyridine; azolopyrimidine

Perhaps due to their electronic and shape complementarity to the adenine and guanine nucleobases, [5,6]-bicyclic heterocycles with a ring-junction nitrogen have become increasingly prominent in medicinal chemistry, as exemplified by clinical candidates such as filgotinib, volitinib and dinaciclib, as well as the FDA-approved drugs zolpidem, trazodone, ibudilast, ponatinib and zaleplon.[1] Transition-metal-catalyzed chelation-assisted aromatic

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and, to a lesser extent, alkenyl C(sp^2)-H activation and annulation has enabled the convergent synthesis of diverse heterocyclic compounds.[2] However, despite their pharmaceutical importance, only a narrow subset of [5,6]-bicyclic heterocycles with a ring-junction nitrogen have been assembled by this approach, specifically with the Rh(III)-catalyzed annulation of *N*-vinyl imidazoles and alkynes (Figure 1a).[3,4]

Herein we describe general methods for the Rh(III)-catalyzed alkenyl C(sp^2)-H functionalization of *C*-alkenyl azoles for the synthesis of fused [5,6]-bicyclic heterocycles that incorporate from two to four nitrogens (Figure 1b,c). While previous reports have demonstrated C-H-functionalization of *C*-aryl azoles for the synthesis of tricyclic and higher order heterocycles,[5] to the best of our knowledge, this study represents the first investigation of *C*-alkenyl azole substrates.[6] These transformations are effective for alkenyl imidazoles, pyrazoles and triazoles incorporating a variety of substitution patterns on both the alkene and the azole. With alkyne or diazoketone coupling partners, azolopyridines are obtained (Figure 1b), while dioxazolones give azolopyrimidines (Figure 1c).

Upon identifying optimal conditions for the annulation of C-alkenyl azoles and alkynes (see Table S1), the reactivity of a variety of alkenyl azole and alkyne substrates was evaluated (Table 1). Both alkyl- and aryl-substituted alkynes coupled with a *C*-2 trisubstituted alkenyl imidazole in good yields to give imidazopyridines **3a** and **3b**, respectively. In addition, reaction of non-symmetric 1-phenyl-1-propyne gave product **3c** with high regioselectivity. Imidazole substrates lacking a β-substituent on the alkene (**3d** and **3e**) and with a β-methyl group (**3f**) were all effective coupling partners, while a *C*-vinyl imidazole coupled in a more modest yield (**3g**). As illustrated with **3h**, substitution on the imidazole ring was also tolerated.

The reaction of alternative alkenyl diazoles was also investigated. Methyl urocanate, with an alkene at the 4-position of the imidazole, reacted with 3-hexyne to give **3i**, and reaction with 1-phenyl-1-propyne yielded **3j** with high regioselectivity. Moreover, an alkenyl pyrazole was a competent substrate in the reaction, giving pyrazolopyridine **3k** upon reaction with 3-hexyne.

Notably, coupling an α-chloroalkenyl pyrazole provided the chloro-substituted pyrazolopyridine **3l** in good yield. To our knowledge, this represents the first example of group IX metal-catalyzed C(sp^2)-H haloalkene annulation,[7] and is of utility because chloro-substituents on fused [5,6]-bicyclic nitrogen heterocycle frameworks are present in clinical candidates[8] and serve as versatile handles for further elaboration. Finally, alkenyl 1,2,4-triazoles gave triazolopyridines **3m–3r** with a >90:10 cyclization regioselectivity to provide the depicted triazolo[4,3-*a*]pyridines as confirmed by X-ray crystallography of **3m**.[9]

We next investigated the reaction of alkenyl azoles with diazoketones **4** (Table 2). These compounds have emerged in the past several years as competent coupling partners for heterocycle synthesis via Rh(III)-catalyzed C-H functionalization.[10] Unlike for alkyne coupling, the reaction of alkenyl azoles with diazoketones is redox-neutral and requires no stoichiometric oxidant. For C-alkenyl imidazoles, simple heating at 40 °C in THF was

effective (see Table S2 for optimization). The reaction of ethyl diazoacetoacetate (**4a**) with alkenyl imidazoles gave imidazopyridines **3s–3v** with ester substituents. A substrate with a methyl substituent on the imidazole ring underwent annulation with high selectivity to give the methyl substituted imidazopyridine **3w**. It was also possible to vary the identity of the diazoketone substrate. A phenyl ketone coupled efficiently to afford **3x**, and imidazopyridine products containing ketone (**3y**), sulfone (**3z**), and phosphonate (**3aa**) substituents were also synthesized in good to excellent yields.

We next investigated the coupling of alternative alkenyl azoles with diazoketones. Pyrazole and triazole substrates were competent C-H partners, giving products **3ab** and **3ac**, respectively (Table 2). Compound **3ac** was isolated as a single isomer that was characterized by X-ray crystallography to be distinct from that previously obtained for alkyne coupling (**3m**–**3r**, Table 1).[11]

In addition to the diazoketones substituted with an electron-withdrawing group, when CsOAc was employed as a stoichiometric additive, phenyl-substituted diazoketone **4f** also coupled to give products **3ad** and **3ae** (Figure 2a). It can be challenging to develop reactions in which both “acceptor/acceptor” and “donor/acceptor” diazo compounds react;[12] to the best of our knowledge, this report represents the first example of Rh(III)-catalyzed C-H addition into both classes of diazo compounds. Moreover, it is significant that the phenyl diazoketone exclusively provided compound **3ae**, while regioisomeric **3c** preferentially formed in the alkyne coupling, demonstrating the complementary nature of these approaches (Figure 2b).

It is noteworthy that divergent isomer formation with alkyne and diazoketone coupling partners was also observed for the alkenyl triazole substrates; reaction with alkynes gave triazolo[4,3-*a*]pyridines **3m**–**3r** (Table 1), while the reaction with a diazoketone yielded triazolo[1,5-*a*]pyridine **3ac** (Table 2). The different product outcome can be understood by the disparate mechanisms for product formation (Scheme 1). Alkyne coupling begins with the concerted metalation/deprotonation of alkenyl triazole to form rhodacycle **A** (Scheme 1a).[13] Migratory insertion of 3-hexyne gives intermediate **B**, and reductive elimination yields product **3m**. Oxidation of Rh(I) then regenerates the Rh(III) catalyst. The isomer formed is determined by selective rhodium coordination at N4 of the 1,2,4-triazole substrate, presumably because the electron density is greatest at this site. Reductive elimination then gives the triazolo[4,3-*a*]pyridine.

In contrast, reaction of a diazoketone with rhodacycle **A** results in loss of nitrogen to give intermediate **C** (Scheme 1b). Protonolysis releases intermediate **D** and regenerates the catalyst. Cyclodehydration of **D** then provides triazolopyridine **3ac**. The high regioselectivity for cyclization of **D** likely occurs to avoid unfavorable steric interactions between the triazole methyl group and the methyl ketone.

In addition to azolopyridines, we sought to develop a method for the synthesis of azolopyrimidines, which contain an additional nitrogen atom within the six-membered ring. We investigated the reaction of alkenyl azoles with dioxazolones **5**, which have previously been employed in Rh(III)-catalyzed C-H amidation,[14] and found that heating at 80 °C in

1,4-dioxane for five hours was optimal for the synthesis of enamides **6**. Treatment with acetic acid facilitated cyclization of the enamides to the desired azolopyrimidines **7** (Table 3). Reaction of alkenyl imidazoles with a methyl-substituted dioxazolone gave imidazopyrimidines **7a–7d** in moderate to high yields. Annulation of a substrate with a methyl group on the imidazole ring afforded imidazopyrimidine **7e** with complete selectivity for the methyl group at the 2-position. Reactions with a phenyl-substituted dioxazolone provided products **7f** and **7g**. For these entries, a higher temperature was necessary in the second step, as the intermediate enamide cyclizes less efficiently. Finally, the alkenyl 1,2,4-triazole substrate coupled to afford triazolopyrimidine **7h**, but required that both the C-H bond addition and cyclization be performed in acetic acid. This one-step protocol was successful for other substrate pairings, but was lower yielding for the imidazopyrimidines. Selective formation of the triazolopyrimidine isomer **7h** occurs during the cyclization step, likely due to minimization of unfavorable steric interactions in analogy to the synthesis of triazolopyridines from diazoketones (see Scheme 1b).

The utility of the developed methodology was demonstrated by the modular and iterative application of C-H functionalization methods for the rapid synthesis of **12**, a potential drug candidate for CNS disorders (Scheme 2).[15] An initial C-H alkylation of quinoline by Rh(I) catalysis[16] provided **8**, which upon reaction with hydrazine gave hydrazide **9** in high yield. Condensation of **9** with imidate **10** afforded alkenyl-substituted triazole **11**. Final Rh(III)-catalyzed annulation with dioxazolone **5a** provided the target compound **12** in 78% yield. By the application of two Rh-catalyzed C-H functionalization steps, this target could be synthesized in only 4 steps and in a good overall yield.

In summary, we have developed novel methods for the synthesis of fused [5,6]-bicyclic heterocycles with a ring-junction nitrogen via Rh(III)-catalyzed C-H functionalization of *C*-alkenyl azoles. The three different classes of coupling partners that were employed allow for the construction of diverse heterocycles of biological relevance. Moreover, the applicability to drug discovery was illustrated by modular and iterative application of C-H functionalization methods for the preparation of a patented compound with CNS activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Typing the names of these drugs and drug candidates into PubChem provides the compound structure, bioactivity, full list of literature, and access to ongoing clinical trials, applications, and usage.
2. For relevant reviews, see: Satoh T, Miura M. Chem Eur J. 2010; 16:11212. [PubMed: 20740508] Song G, Wang F, Li X. Chem Soc Rev. 2012; 41:3651. [PubMed: 22377832] Yamaguchi J, Yamaguchi AD, Itami K. Angew Chem Int Ed. 2012; 51:8960.Angew Chem. 2012;

124:9092.Mesganaw T, Ellman JA. Org Process Res Dev. 2014; 18:1097. [PubMed: 25288871] Gulías M, Mascareñas JL. Angew Chem Int Ed. 2016; 55:11000.Angew Chem. 2016; 128:11164.

3. Huang JR, Zhang QR, Qu CH, Sun XH, Dong L, Chen YC. Org Lett. 2013; 15:1878. [PubMed: 23537406] Dong L, Huang JR, Qu CH, Zhang QR, Zhang W, Han B, Peng C. Org Biomol Chem. 2013; 11:6142. [PubMed: 23925493] For imidazo[1,2-a]pyridinium salts, see: Thenarukandiyil R, Thrikkykkal H, Choudhury J. Organometallics. 2016; 35:3007.
4. Methods have been developed for the direct C-H arylation of pre-assembled azolopyridines and azopyrimidines. For reviews that provide leading references, see: Seregin IV, Gevorgyan V. Chem Soc Rev. 2007; 36:1173. [PubMed: 17576484] Rossi R, Lessi M, Manzini C, Marianetti G, Bellina F. Synthesis. 2016; 48:3821.
5. a) Umeda N, Tsurugi H, Satoh T, Miura M. Angew Chem Int Ed. 2008; 47:4019.Angew Chem. 2008; 120:4083;.b) Morimoto K, Hirano K, Satoh T, Miura M. Org Lett. 2010; 12:2068. [PubMed: 20377234] c) Li X, Zhao M. J Org Chem. 2011; 76:8530. [PubMed: 21913640] d) Ma WB, Graczyk K, Ackermann L. Org Lett. 2012; 14:6318. [PubMed: 23234384] e) Kavitha N, Sukumar G, Kumar VP, Mainkar PS, Chandrasekhar S. Tetrahedron Lett. 2013; 54:4198.r) Wang R, Falck JR. J Organomet Chem. 2014; 759:33.g) Zheng L, Hua R. J Org Chem. 2014; 79:3930. [PubMed: 24712329] h) Algarra AG, Cross WB, Davies DL, Khamker Q, Macgregor SA, McMullin CL, Singh K. J Org Chem. 2014; 79:1954. [PubMed: 24564771]
6. For the synthesis of pyridinylamines by C-H functionalization and ring fragmentation of alkenyl oxadiazolones, see: Yu X, Chen K, Wang Q, Guo S, Zha S, Zhu J. Angew Chem Int Ed. 2017; 56:5222;.Angew Chem. 2017; 129:5306.
7. For C-H halogenation of an alkenyl bromide, see: Kuhl N, Schröder N, Glorius F. Org Lett. 2013; 15:3860. [PubMed: 23906080]
8. See PubChem Compound Identifier numbers 54897 (alpidem) and 68234908.
9. CCDC 1509748 (3m) contain the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See SI for additional details.
10. Selected examples: Chan WW, Lo SF, Zhou Z, Yu WY. J Am Chem Soc. 2012; 13:13565.Shi Z, Koester DC, Boultadakis-Arapnis M, Glorius F. J Am Chem Soc. 2013; 135:12204. [PubMed: 23889167] Shi L, Yu K, Wang B. Chem Commun. 2015; 51:17277.Wu Y, Sun P, Zhang K, Yang T, Yao H, Lin A. J Org Chem. 2016; 81:2166. [PubMed: 26821090] Li XG, Sun M, Jin Q, Liu K, Liu PN. J Org Chem. 2016; 81:3901. [PubMed: 27042947] Chen X, Hu X, Bai S, Deng Y, Jiang H, Zeng W. Org Lett. 2016; 18:192. [PubMed: 26710082]
11. CCDC 1509749 (3ac) contain the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See SI for additional details.
12. Hyster TK, Ruhl KE, Rovis T. J Am Chem Soc. 2013; 135:5364. [PubMed: 23548055]
13. a) Li L, Brennessel WW, Jones WD. J Am Chem Soc. 2008; 130:12414. [PubMed: 18714995] b) Walsh AP, Jones WD. Organometallics. 2015; 34:3400.
14. For a review, see: Park Y, Kim Y, Chang S. Chem Rev. 2017; :117.doi: 10.1021/acs.chemrev.6b00644For selected examples: Park Y, Park KT, Kim JG, Chang S. J Am Chem Soc. 2015; 137:4534. [PubMed: 25789561] Wang H, Tang GD, Li XW. Angew Chem Int Ed. 2015; 54:13049.Angew Chem. 2015; 127:13241.Wang J, Zha S, Chen K, Zhang F, Song C, Zhu J. Org Lett. 2016; 18:2062. [PubMed: 27058735] Wang Q, Wang F, Yang X, Zhou X, Li X. Org Lett. 2016; 18:6144. [PubMed: 27934348]
15. Campbell JE, Hewitt MC, Jones P, Xie L. PCT Int Appl. 2011:150156.
16. Tran G, Hesp KD, Mascitti V, Ellman JE. Angew Chem Int Ed. 2017; 56:5899.Angew Chem. 2017; 129:5993.

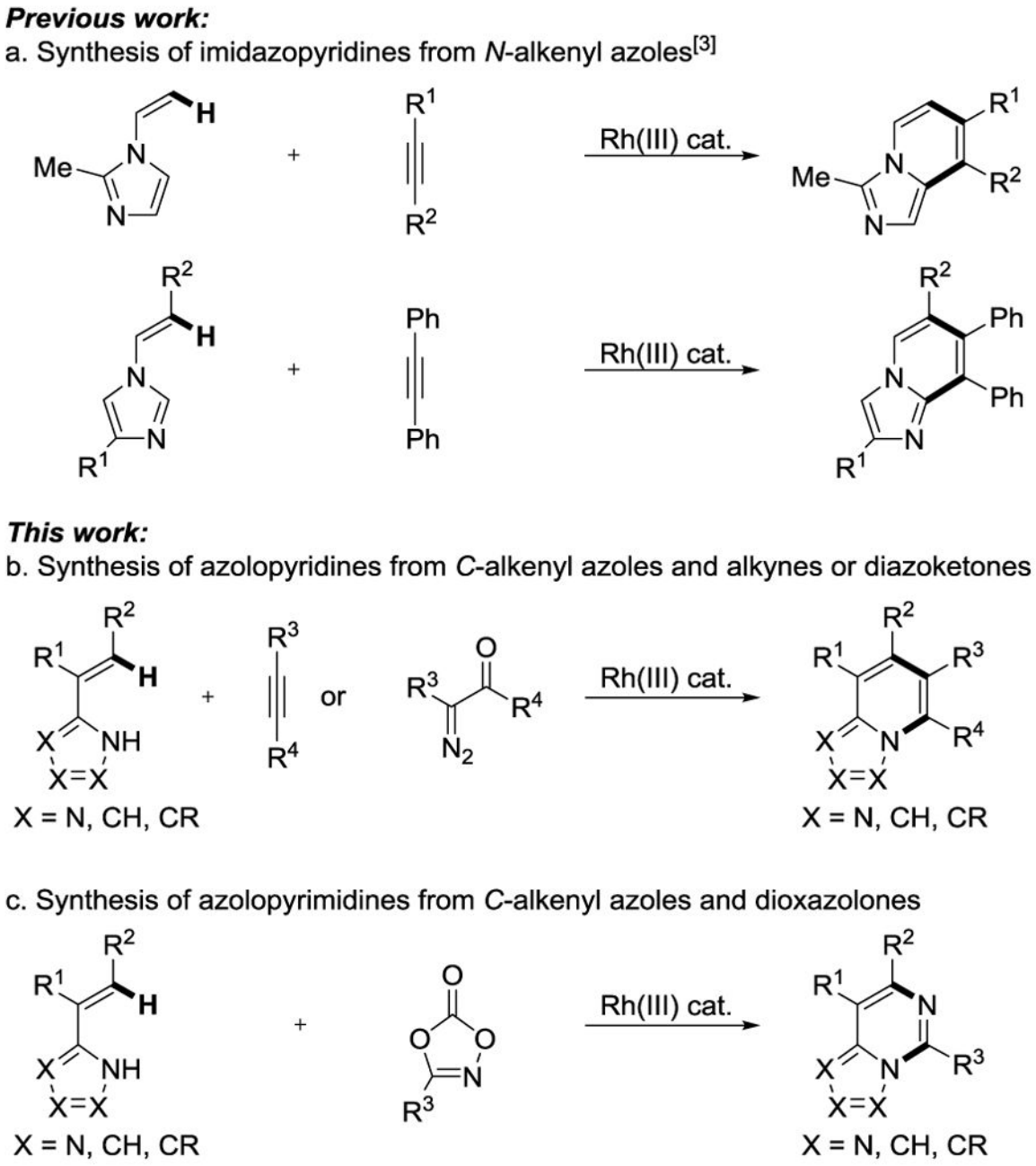


Figure 1.
Synthesis of fused [5,6]-bicyclic nitrogen heterocycles via Rh(III)-catalyzed C-H functionalization.

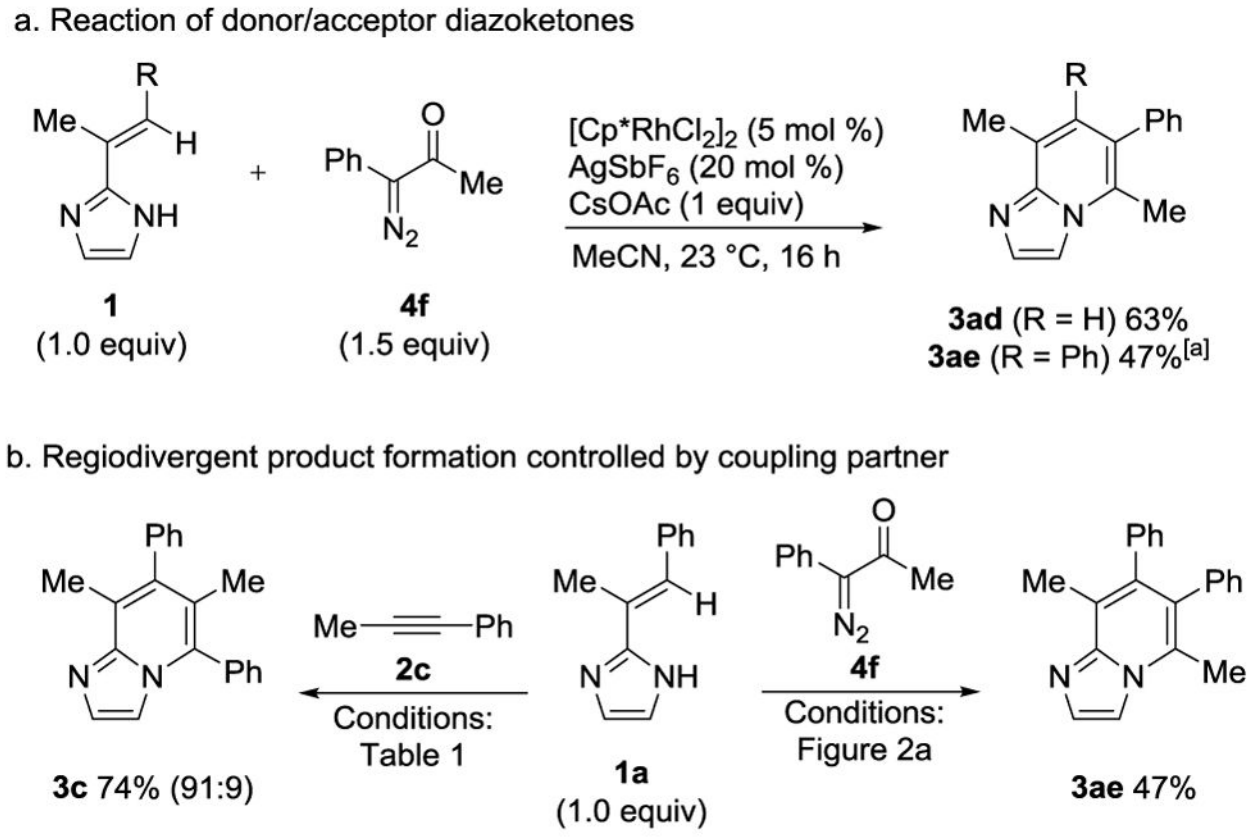
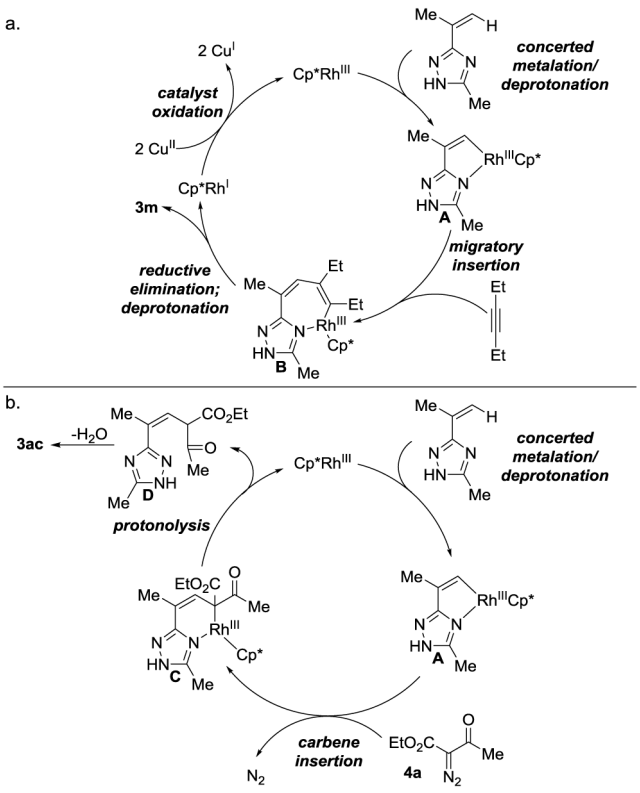


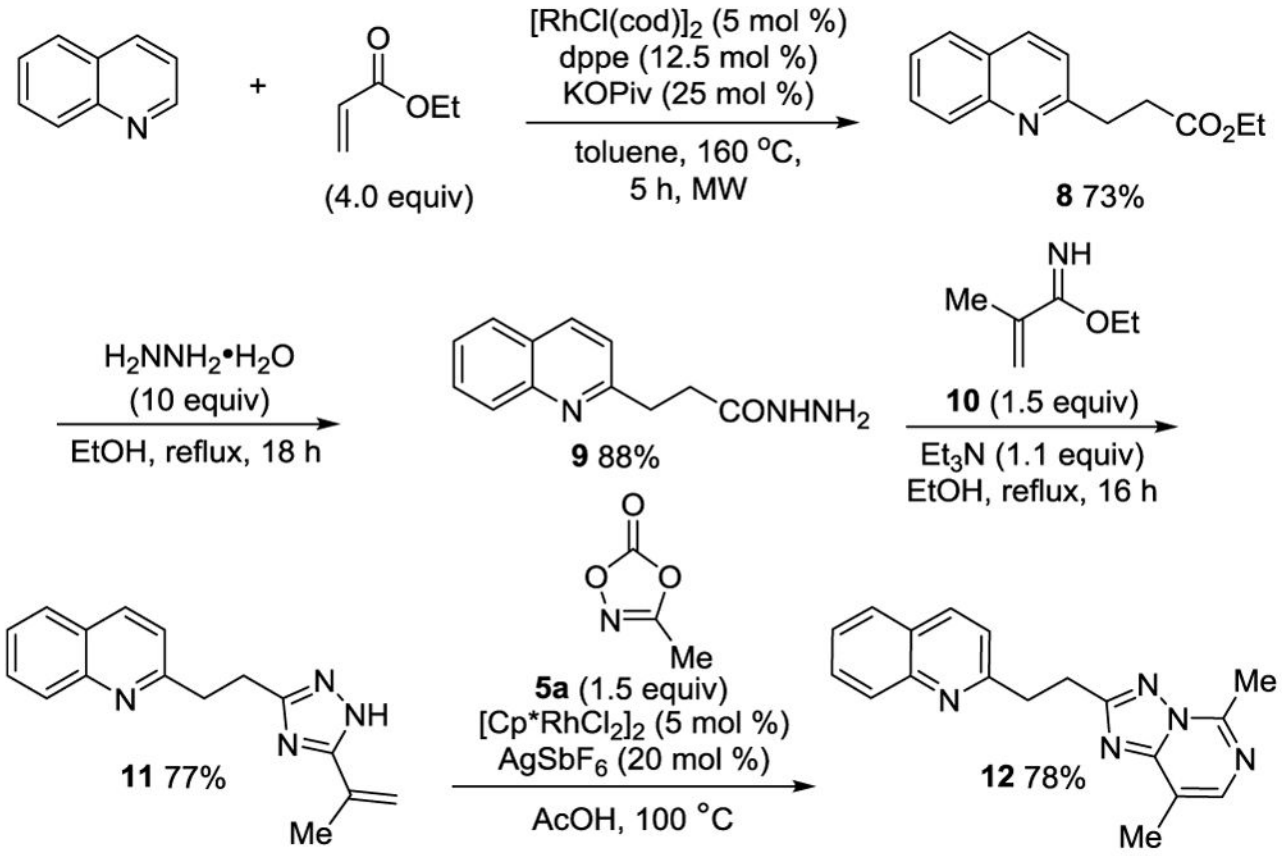
Figure 2.

Reaction of donor/acceptor diazoketone allowing for divergent product formation. [a]After 16 h, added AcOH (5 mL) and stirred at 100 °C for 24 h.



Scheme 1.

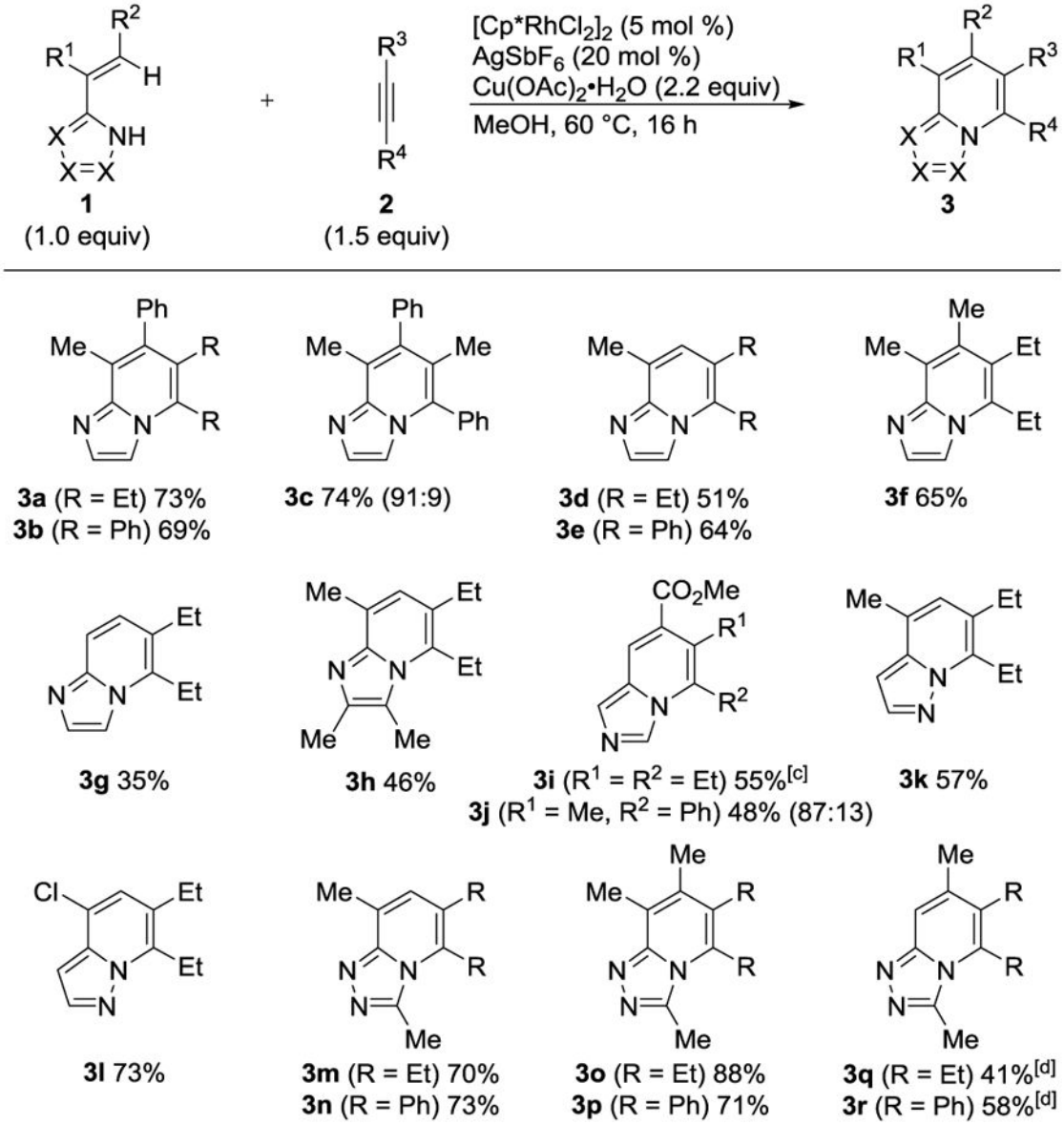
a) Mechanism of Rh(III)-catalyzed coupling of alkenyl azoles with alkynes. b) Mechanism of Rh(III)-catalyzed coupling of alkenyl azoles with diazoketones.



Scheme 2.
Synthesis of potential drug candidate **12** utilizing developed methodology.

Table 1

Rh(III)-catalyzed C-H functionalization of alkenyl azoles with alkynes.[a,b]



[a]Conditions: **1** (0.50 mmol), **2** (1.5 equiv), 0.1 M, 16 h.

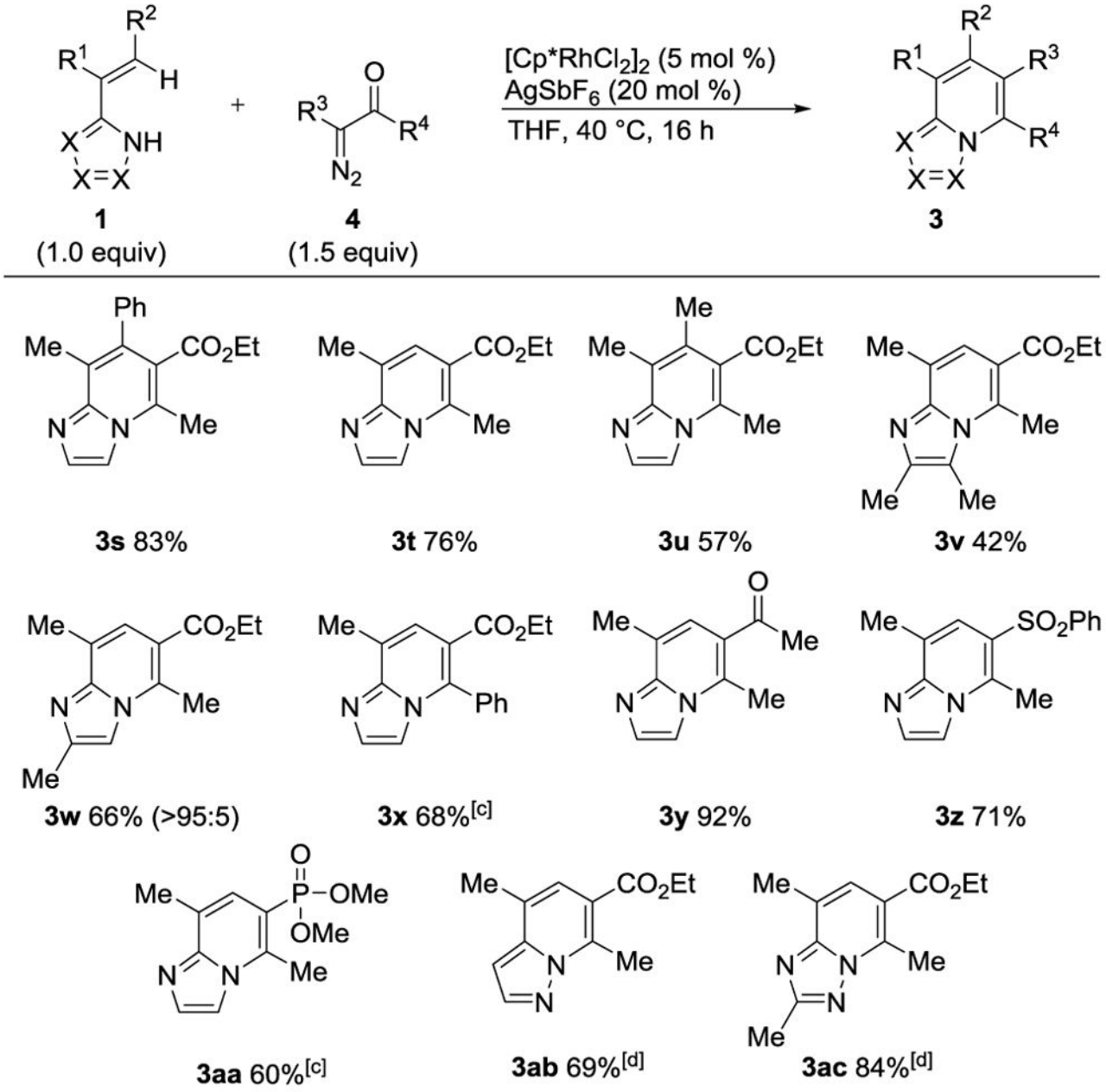
[b]Yield of isolated products after chromatography on silica.

[c]3.0 equiv **2**.

[d]100 °C.

Table 2

Rh(III)-catalyzed C-H functionalization of alkenyl azoles with diazoketones.[a,b]



[a]Conditions: **1** (0.50 mmol), **4** (1.5 equiv), 0.1 M, 16 h.

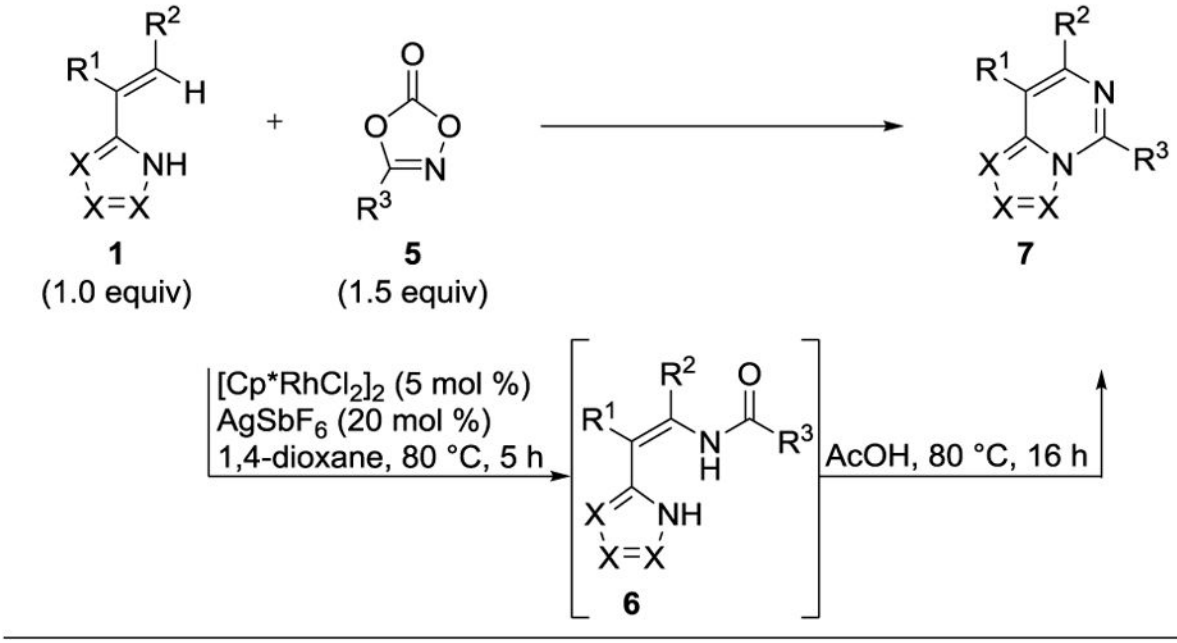
[b]Yield of isolated products after chromatography on silica.

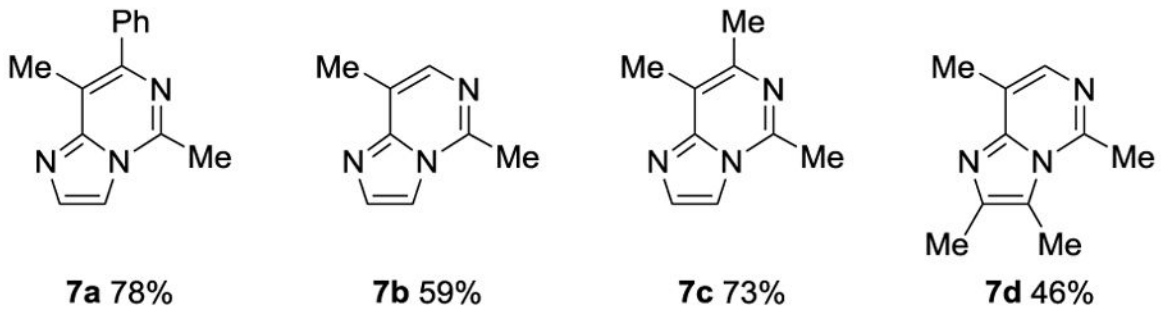
[c]60 °C

[d] 80 °C, MeOH as solvent.

Table 3

Rh(III)-catalyzed C-H functionalization of alkenyl azoles with dioxazolones.[a,b]



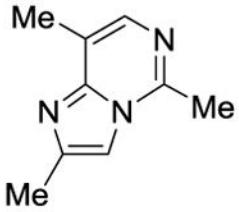


7a 78%

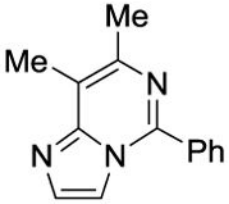
7b 59%

7c 73%

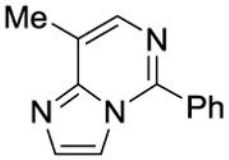
7d 46%



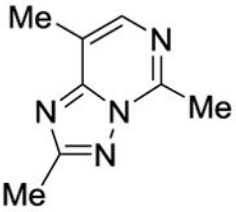
7e 67%



7f 66%[c]



7g 43%[c]



7h 67%[d]

[a] Conditions: **1** (0.50 mmol), **5** (1.5 equiv), 0.1 M, 16 h.

[b] Yield of isolated products after chromatography on silica.

[c] Second step at 100 °C.

[d] Addition and cyclization performed at 80 °C with AcOH as solvent.