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Selective Synthesis of Isoquinolines by Rhodium(III)-Catalyzed C−H/N−H Functionalization with α-Substituted Ketones

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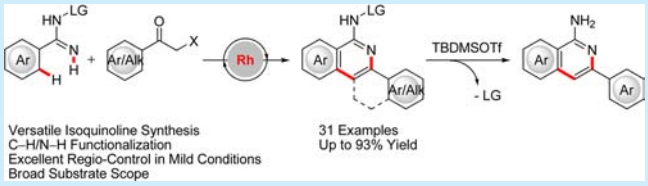
Supporting Information

ABSTRACT: A rhodium(III)-catalyzed C−H/N−H bond functionalization for the synthesis of 1-aminoisoquinolines from aryl amidines and α-MsO/TsO/Cl ketones was achieved under mild reaction conditions. Thus, this approach provides a practical method for the site-selective synthesis of various synthetically valuable isoquinolines with wide functional group tolerance.



In recent years, transition-metal catalyzed C−H bond activation/cyclization has been recognized as an increasingly viable tool for the preparation of pharmacologically useful heterocycles,[1] which provides an attractive strategy to streamline chemical synthesis.[2] Thus far, due to its high catalytic efficacy, rhodium complexes have specifically attracted considerable attention as versatile catalysts for C−H activation.[3] Obviously, alkyne annulation is one of the most commonly applied approaches to prepare heterocycles through rhodium(III)-catalyzed C−H functionalization, along with the use of external or internal oxidants.[4] However, except the sporadic reports,[5] terminal alkynes proved to be restricted as nucleophiles, although they worked successfully for cobalt catalysis.[6] Since π bonds have encountered bottlenecks in this reaction pattern, practical advances were achieved by Glorius[7] and co-workers using easily accessible α-MsO/TsO/Cl ketones[8] as oxidized alkyne equivalents in rhodium(III)-catalyzed redox-neutral annulations to synthesize C3-monosubstituted *N*-heterocycles, such as isoquinolones, benzothiazines, and indole (Figure 1a). Despite these major advances, rhodium-catalyzed C−H functionalizations on aryl amidines to the synthetically useful family of C4-unsubstituted aminoisoquinolines[9] have thus far proven elusive.

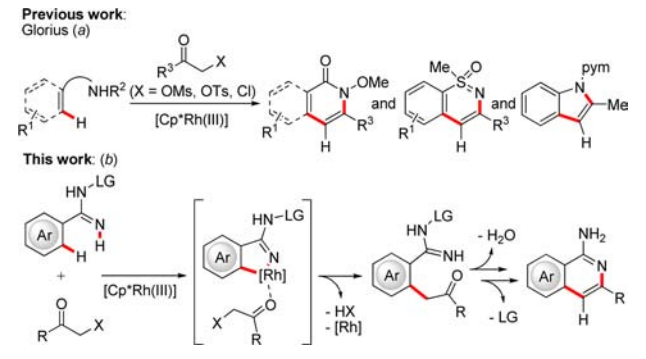


Figure 1. Rh(III)-catalyzed synthesis of decorated *N*-heterocycles with α-MsO/TsO/Cl ketones. LG = leaving group.

Ubiquitous amidines[10] have, to the best of our knowledge, been exploited in rhodium(III)-,[10b] ruthenium(II)-[10a] and cobalt(III)-catalyzed[11] annulations of alkynes or diazo compounds[9] through C−H activation. In addition, selectively substituted aminoisoquinolines are key structural motifs of various compounds with activities of relevance to medicinal chemistry.[12] Therefore, we became intrigued by exploring novel amidine-assisted rhodium(III)-catalyzed intermolecular annulation with α-pseudohalo and halo ketones. Very recently, Wu developed a catalyst-free approach to generate 1-aminoisoquinolines, which was only promoted by stoichiometric *t*BuOK under heating.[13] However, functional groups, such as ketone, ester, and aldehyde, cannot be tolerated under these harsh reaction conditions. Moreover, the strong base could induce some other undesired byproducts. Herein, we report a two-step sequence consisting of rhodium(III)-catalyzed C−H functionalization and further condensation, delivering C3-monosubstituted aminoisoquinolines under mild reaction conditions (Figure 1b).

We initiated our investigation by testing the feasibility of rhodium(III)-catalyzed C−H/N−H annulations of α-TsO acetophenone (**2aa**) with aryl amidine **1a** (Table 1). Thus, far, the only reported rhodium-catalyzed direct C−H activation with α-MsO/TsO/Cl ketones by Glorius was accomplished with $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ as the catalyst.[7] However, the catalyst delivered no desired product with the assistance of benzamidine under the same reaction conditions (Table 1, entry 1). Similar observations were obtained when employing various representative solvents (see SI, Table 1). A significant breakthrough was made when TFE was used as the reaction medium, delivering the C3-monoarylated product **3aa** in a unsatisfactorily low yield (entry 2). The yield was slightly increased when $Cu(OAc)_2$ was used as an additive (entry 3). However, there was no significant improvement with other carboxylate salts as the base (see SI, Table 1). Among a set of

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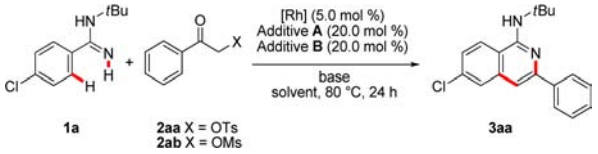
Table 1. Optimization of Rh(III)-Catalyzed C−H/N−H Functionalization with Benzamidine 1a[a]



1a; 2aa X = OTs, 2ab X = OMs; 3aa

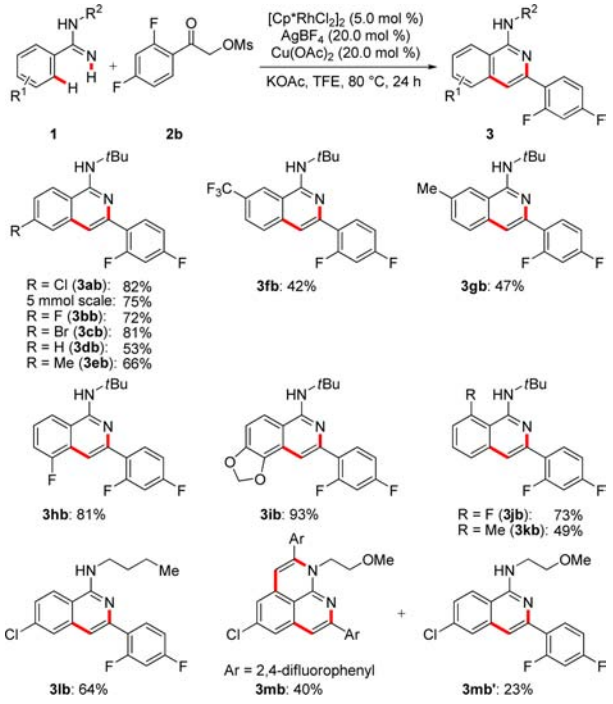
entry	[Rh]/additive **A**	additive **B**	base	solvent	yield (%)[b]
1	$Cp^*RhL_3(SbF_6)_2$	–	NaOAc	MeOH	<1[c]
2	$Cp^*RhL_3(SbF_6)_2$	–	NaOAc	TFE	24[c]
3	$Cp^*RhL_3(SbF_6)_2$	$Cu(OAc)_2$	NaOAc	TFE	28[c]
4	$Cp^*RhL_3(SbF_6)_2$	$Cu(OAc)_2$	KOAc	TFE	40[d]
5	$[Cp^*RhCl_2]_2$/$AgSbF_6$	$Cu(OAc)_2$	KOAc	TFE	41[d]
6	$[Cp^*RhCl_2]_2$/$AgNTf_2$	$Cu(OAc)_2$	KOAc	TFE	36[d]
7	$[Cp^*RhCl_2]_2$/$AgPF_6$	$Cu(OAc)_2$	KOAc	TFE	34[d]
8	$[Cp^*RhCl_2]_2$/$AgBF_4$	$Cu(OAc)_2$	KOAc	TFE	57[d]
9	$Cp^*RhL_3(SbF_6)_2$	$Cu(OAc)_2$	KOAc	TFE	50[d]
10	$[Cp^*RhCl_2]_2$/$AgBF_4$	$Cu(OAc)_2$	KOAc	TFE	76
11	**$[Cp^*RhCl_2]_2$/$AgBF_4$**	**$Cu(OAc)_2$**	**KOAc**	**TFE**	**80**[e]
12	$Cp^*RhL_3(BF_4)_2$	$Cu(OAc)_2$	KOAc	TFE	71[e]
13	$[Cp^*IrCl_2]_2/AgBF_4$	$Cu(OAc)_2$	KOAc	TFE	0[e]
14	$Cp^*CoI_2(CO)$/$AgBF_4$	$Cu(OAc)_2$	KOAc	TFE	0[e]

[a]General reaction conditions: **1a** (0.25 mmol), **2aa** (0.50 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgBF_4$ (20.0 mol %), $Cu(OAc)_2$ (20.0 mol %), KOAc (2.0 equiv), TFE (2.0 mL), under Ar, 80 °C, 24 h. [b]Isolated yield. [c][Rh] (5.0 mol %), **2aa** (1.2 equiv), KOAc (1.2 equiv), 60 °C. [d][Rh] (5.0 mol %). [e]**2ab** (2.0 equiv). **L** = MeCN, TFE = trifluoroethanol.

rhodium sources and representative silver(I) salts, a combination of Cp^*RhCl_2 and $AgBF_4$ was identified to be the efficient metal catalyst of choice, along with $Cu(OAc)_2$ as the cocatalytic additive and stoichiometric KOAc as the base (entries 4−10). Notably, mesylate **2ab** was further tested and furnished **3aa** in 80% yield (entry 11), as was also observed when employing $[Cp^*Rh(MeCN)_3(BF_4)_2]$ as the catalyst, albeit in a slightly reduced yield (entry 12). However, omission of either of the catalyst's components or decreasing the amounts of KOAc resulted in a significantly reduced yield or completely stopped the reaction (see SI, Table 1). Thus, the presence of additives and carboxylates could contribute to the *in situ* formation of a versatile cationic rhodium(III) catalyst. Notably, other transition-metal catalysts were found to be noneffective in this transformation (entries 13−14).

With the optimized reaction conditions in hand, we further extended the substrate scope of amidines **1** with α-mesyloxyketone **2b** (Scheme 1). Notably, the chelation-assisted C−H/N−H bond functionalization proved to be broadly applicable. Both electron-rich and electron-deficient aryl amidines were transformed into desired isoquinolines **3ab**−**3eb** in good to excellent yields. Moreover, this transformation can be easily scaled up to gram scale with high efficiency. Intramolecular competition experiments with substrates bearing *meta*-trifluoromethyl or *meta*-methyl substituents were largely governed by steric interactions to generate the products **3fb** and **3gb** at the less sterically hindered position, albeit with

Scheme 1. Rh(III)-Catalyzed Synthesis of Aminoisoquinolines with 2b



lower yields. Importantly, C−H functionalization of the substrates **1h** and **1i** with a *meta*-fluoro or 3,4-dioxymethylene substituent featured a considerable secondary directing group effect,[14] thereby leading to the site selectivity that afforded the more sterically hindered compounds **3hb** and **3ib** as the sole products in excellent yields. As expected, substrate **1j** bearing an *ortho*-fluoro gave the desired product **3jb** in high yield. However, **3kb** was obtained in a significantly reduced yield when using a more sterically hindered *ortho*-methyl substituted amidine **1k**. It is worth noting that a less bulky *N*-substituted benzamidine **1l** was successfully employed as well. Interestingly, a cascade twofold C−H/N−H bond functionalization was obtained as the major product, when the 2-methoxyethyl substituted benzamidine **1m** was utilized as the starting material.

Thereafter, a broad range of ketones **2** were also investigated under this catalytic system (Scheme 2). Valuable electrophilic functional groups, such as fluoro, chloro, bromo, and iodo substituents **2c**−**f**, were found to be well tolerated by a robust rhodium(III) catalyst, as was also observed when employing substrates **2a** or **2g**−**h** with an electron-donating group pattern. Furthermore, even substrate **2i** bearing a sensitive ketone functionality could also work with high efficacy. Remarkably, this reaction was not restricted to α-mesyloxy- and α-tosyloxyketones, but proved also feasible to α-chloroketone **2jc**. To our surprise, 2-chloro-1-(4-cyanophenyl)ethanone displayed the best reactivity, while mesylate **2jb** was inherently less reactive. Moreover, a more sterically hindered substrate **2k** bearing a 2,4-dichloro substituent was found to be viable as well, thereby delivering the desired product **3ak**.

Beyond that, we further extended its versatility to other heteroaryl amidines, including thiophene and indole derivatives, while only **1n**, along with **2b** or **2k**, delivered the annulated azabenzothiophenes **3nb**, **3nk** in good yields. Besides the heterocyclic amidines, we were also pleased to find that

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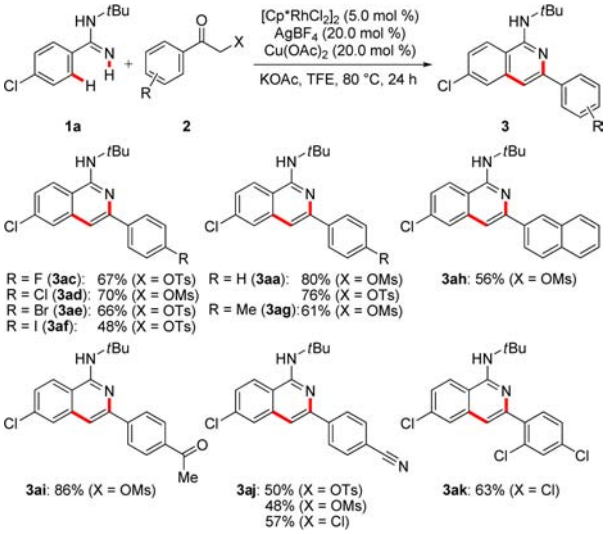
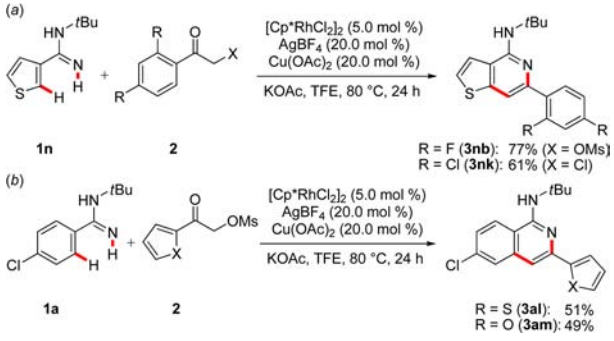
Scheme 2. Substrate Scope of Rh(III)-Catalyzed C−H/N−H Functionalization



heteroaromatic ketone derivatives **2l−m** could also be employed in the reactions, furnishing the corresponding products **3al−am** in moderate yields (Scheme 3).

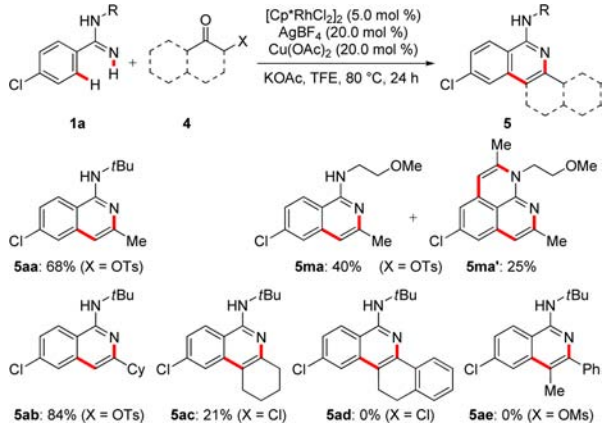
Scheme 3. Rh(III)-Catalyzed C−H Activation of the Heteroarenes 1 and 2



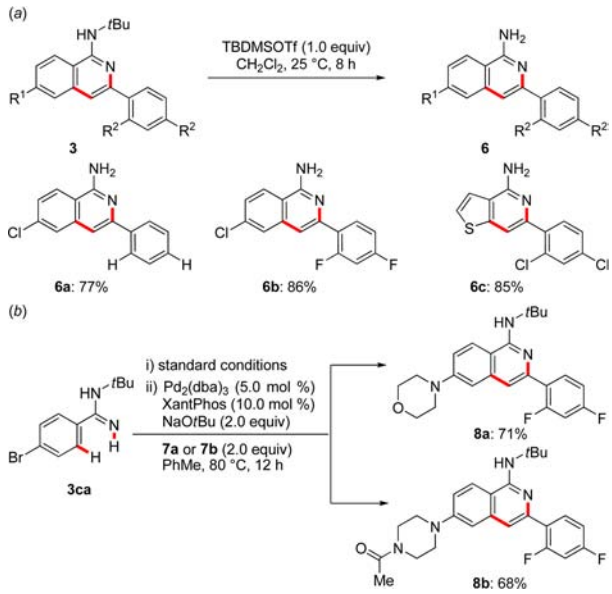
It is worth noting that the rhodium(III)-catalyzed redox-neutral annulation can be easily extended on dialkyl ketones; 2-oxopropyl tosylate (**4a**) and 2-cyclohexyl-2-oxoethyl tosylate (**4b**) reacted with **1a** to yield the corresponding isoquinolines with remarkably high efficacy, while the 2-methoxyethyl substituted amidine **1m** led to a low yield of the 3-methyl-1-aminoisoquinoline **5ma**, because 25% of twofold C−H/N−H annulated product **5ma′** were formed as well. Intriguingly, the 2-chlorocyclohexanone **4c** also delivered the product **5ac**, which was not expected, albeit in a quite low yield, as was not observed when employing another internal chloride (**4d**) or mesylate (**4e**) as the preoxidized alkynes (Scheme 4).

Subsequently, we illustrated the synthetic potency of the protocol by developing a facile removal of the tertiary butyl group[15] under exceedingly mild reaction conditions, generating the corresponding heteroaromatic anilines **6a−c** (Scheme 5a). Finally, in order to exploit the synthesis of the decorated 1-aminoisoquinolines **8a−b** we subsequently devised a two-step reaction sequence consisting of an initial rhodium-catalyzed C−H/N−H bond functionalization followed by palladium-catalyzed amination.[16] The multicatalytic approach sets the

Scheme 4. Reactions of α-Chloro and α-Tosyloxyketones 4 with Benzamidine 1a



Scheme 5. (a) Removal of Protecting Group; (b) Multicatalytic Synthesis of Decorated Isoquinolines 8



stage for the synthesis of isoquinolines **8**, which could not be easily obtained (Scheme 5b).

In conclusion, we have reported on a novel rhodium(III)-catalyzed 1-aminoisoquinolines synthesis by C−H bond functionalization on aryl amidines with α-MsO/TsO/Cl ketones. Thus, aryl amidines were directly functionalized with a broad substrate scope, as well as excellent functional group tolerance and regioselectivity. This efficient protocol sets the stage for the preparation of C4-unsubstituted aminoisoquinolines, which are difficult to access by other metal-catalyzed C−H functionalizations with alkynes.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compound (PDF)

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Notes

The authors declare no competing financial interest.

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