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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides at room temperature: a practical and efficient route to 4-aminoisoquinolone derivatives†

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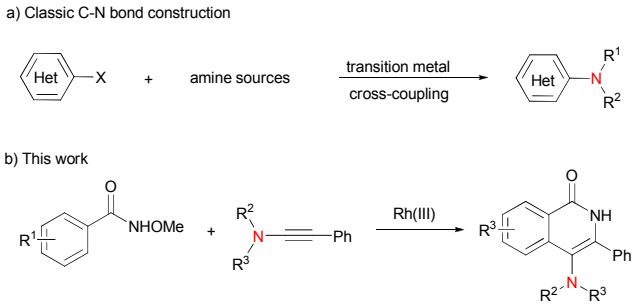
Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A practical and efficient Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides for the synthesis of 4-aminoisoquinolone derivatives has been developed under external-oxidant-free conditions at room temperature. This protocol features good functional group tolerance and excellent selectivity.

Amination of heteroaromatic compounds is an area of intense research in the synthetic organic chemistry community.[1] 4-Aminoisoquinolone derivatives are key precursors and structural motifs of many pharmaceuticals and biologically active molecules, and their synthesis has attracted considerable attention.[2] Conventional methods for the synthesis of 4-aminoisoquinolone derivatives usually require harsh reaction conditions and multiple-step sequences.[2,3] During the past decades, remarkable achievements have been made in the field of transition metal-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions.[4] Though the transition metal-catalyzed amination of heteroarenes has emerged as an ideal and powerful tool (Scheme 1a),[5] direct installation of amino or amido groups on C4 position of isoquinolones still remains unsolved. Therefore, it is highly desirable to develop a mild and practical alternative to the preparation of 4-aminoisoquinolone derivatives.

To date, transition metal-catalyzed C–H activation/annulation has become an attractive synthetic method to produce isoquinolones.[6-12] In 2010, Fagnou et al. reported the rhodium-catalyzed annulation of *N*-methoxybenzamides with alkynes using the N−O bond as an internal oxidant.[8a] Rovis et al. independently disclosed the rhodium-catalyzed oxidative C–H activation/annulation of benzamides with alkynes.[8c] In a recent elegant report, the divergent synthesis of heterocyclic boronic acid derivatives has been developed by Glorius via rhodium-catalyzed C−H activation and cycloaddition with alkyne MIDA boronates.[7] Typically, rhodium-catalyzed annulation reactions feature high efficiency, good functional group tolerance and excellent chemo- and site-selectivity.

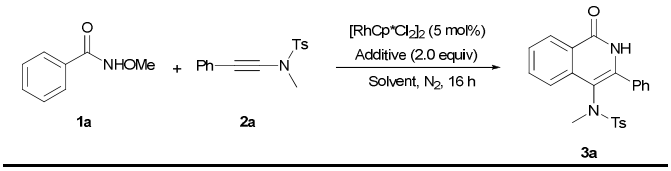
Ynamides represent an important, unique and versatile building block in synthetic chemistry. They have been considered as a modern functional group and widely used in transition metal-catalyzed transformations.[13,14] Thus, we envisioned that ynamides could be compatible in rhodium-catalyzed C−H activation and subsequent annulation reaction. Herein, we would like to disclose a mild Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides under external-oxidant-free conditions, which offers a practical and efficient route to 4-aminoisoquinolone compounds (Scheme 1b).



Scheme 1 Transition metal-catalyzed synthesis of aminated heteroaromatics.

Our study commenced with the annulation of *N*-methoxybenzamide **1a** with *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide **2a** as the model reaction. Initially, the desired product **3a** could be obtained in 83% yield by using 5 mol% of $[Cp^*RhCl_2]_2$ as the catalyst and 2.0 equiv of NaOAc as the additive in methanol at 80 °C for 16 h (Table 1, entry 1). This reaction afforded a decreased yield when the additive was changed to either CsOAc or CsOPiv (Table 1, entries 2 and 3). In the presence of $AgSbF_6$, **3a** was obtained in 30% yield (Table 1, entry 4). A further solvent screening revealed MeOH to be superior to toluene, DCE, 1,4-dioxane and *tert*-AmylOH (Table 1, entries 1 and 5-8). We were pleased to find that the reaction could proceed smoothly at room temperature, delivering **3a** in 86% yield (Table 1, entries 9-11). Furthermore, the yield of **3a** was dramatically decreased to 18% when the reaction was performed under an air atmosphere (Table 1, entry12).

Table 1 Optimization of reaction conditions[a]

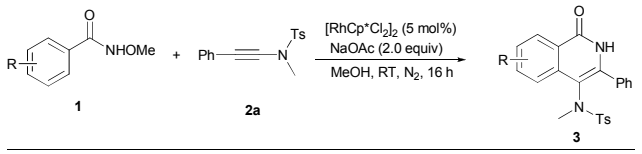


1a 2a 3a

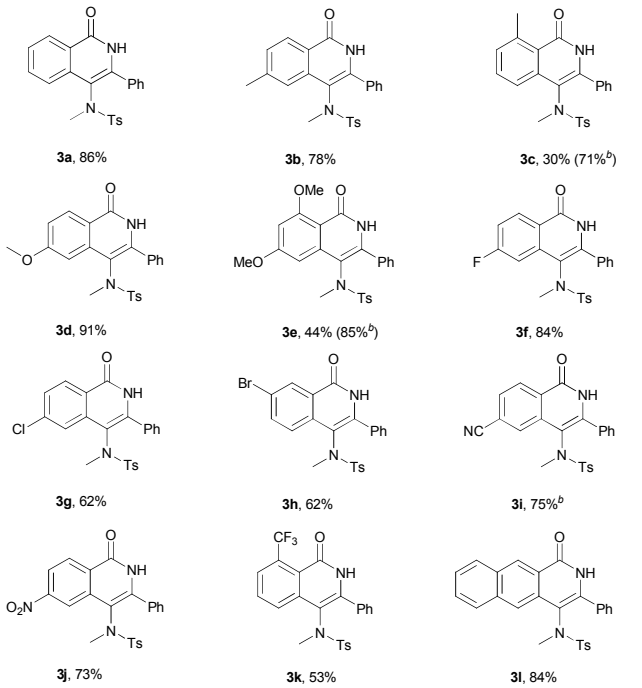
Entry	Additive	Solvent	*T*(°C)	Yield(%)[b]
1	NaOAc	MeOH	80	83
2	CsOAc	MeOH	80	80
3	CsOPiv	MeOH	80	68
4[c]	NaOAc	MeOH	80	30
5	NaOAc	toluene	80	75
6	NaOAc	DCE	80	76
7	NaOAc	*t*-AmylOH	80	71
8	NaOAc	dioxane	80	69
9	NaOAc	MeOH	100	82
10	NaOAc	MeOH	60	84
11	**NaOAc**	**MeOH**	**RT**	**86**
12[d]	NaOAc	MeOH	80	18

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (5.0 mol%) and additive (2.0 equiv) in solvent (1.0 mL) for 16 h under an N_2 atmosphere. [b] Isolated yields. [c] 20 mol% of $AgSbF_6$ was used. [d] Air atmosphere.

Table 2 Scope of substituted *N*-methoxybenzamides[a]



1 2a 3

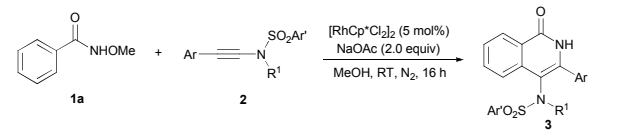


[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.30 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (5.0 mol%) and NaOAc (2.0 equiv) in MeOH (1.0 mL) at room temperature for 16 h. Isolated yields. [b] At 80 ºC.

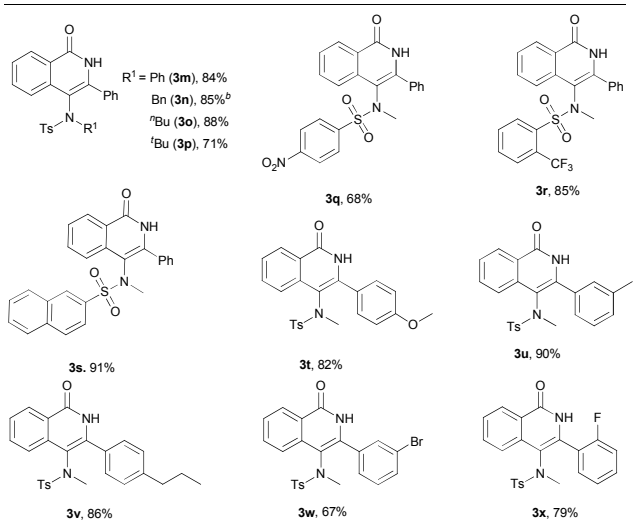
Under the optimized conditions, our attention focused on an investigation of the scope of *N*-methoxybenzamides with ynesulfonamide **2a**. As shown in Table 2, benzhydroxamic acid substituents possessing electron-donating groups on the aryl moiety could react with **2a** to afford the desired products in good to excellent yields (**3b** and **3d**). *ortho*-Substituted *N*-methoxybenzamides exhibited an obvious steric effect, and an elevated temperature (80 °C) was required to obtain satisfactory yields (**3c**, **3e** and **3k**). Electron-withdrawing groups such as halide (F, Cl and Br), CN, NO_2 and CF_3 could be tolerated in this annulation reaction, and the corresponding products were obtained in moderate to excellent yields (**3f-3k**). In particular, when *meta*-substituted substrate was used, C−H activation occurred at the less-hindered position and exhibited complete regioselectivity (**3h**). Moreover, *N*-methoxy-2-naphthamide smoothly underwent this transformation in 84% yield (**3l**).

Subsequently, the scope of ynesulfonamides was examined. Ynesulfonamides with various sulfonamido substituents (Ar' = PhMe-*p*; R^1 = Ph, Bn, ^{n}Bu, ^{t}Bu) were compatible with the current Rh(III)-catalyzed annulation in good to excellent yields (Table 3, **3m-3p**).[15] Ynesulfonamides with different sulfonyl groups gave the desired products **3q-3s** in 68%-91% yields. Additionally, arenynes containing both electron-donating and electron-withdrawing groups on the aromatic moiety could undergo the annulation (Table 3, **3t-3x**).

Table 3 Scope of substituted ynesulfonamides[a]

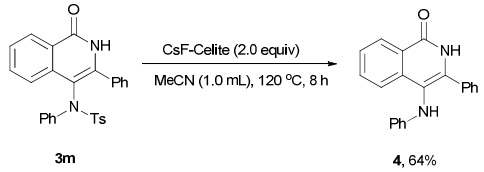


1a 2 3



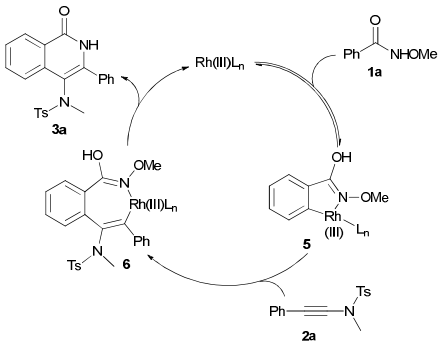
[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.30 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (5.0 mol%), and NaOAc (2.0 equiv) in MeOH (1.0 mL) at room temperature for 16 h. Isolated yields. [b] At 80 ºC.

The deprotection of **3m** was next conducted (Scheme 2). Using 2.0 equiv of supported CsF on Celite as the catalyst and MeCN as the solvent, 3-phenyl-4-(phenylamino)isoquinolin-1(2*H*)-one **4** was obtained in 64% yield.[16]



Scheme 2 Deprotection of **3m**. Conditions: **3m** (0.10 mmol) and CsF-Celite (0.20 mmol, 2.0 equiv) in MeCN (1.0 mL) at 120 ºC for 8 h. Isolated yields.

Finally, a plausible mechanism for the annulation reaction was proposed (Scheme 3).[8,17] First, the cyclorhodium intermediate **5** was afforded through a C–H activation process. Coordination of the ynesulfonamide **2a** to the resulting **5** and a subsequent insertion into the C–Rh bond gave the intermediate **6**. After C–N bond formation and N–O bond cleavage, the product **3a** was formed, and the active Rh(III) species was regenerated for the next cycle.



Scheme 3 Plausible mechanistic pathway.

In conclusion, we have demonstrated a Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides under external-oxidant-free conditions at room temperature. A series of advantages in this protocol include mild condition, wide substrate scope, excellent selectivity and outstanding functional group tolerance. Undoubtedly, this strategy has demonstrated a novel, practical and efficient approach to 4-aminoisoquinolone derivatives.

We thank the financial support from the National Basic Research Program of China (973 Program, 2011CB808601) and the National NSF of China (Nos 21025205, 21272160, 21321061 and J1103315/J0104).

Notes and references

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c000000x

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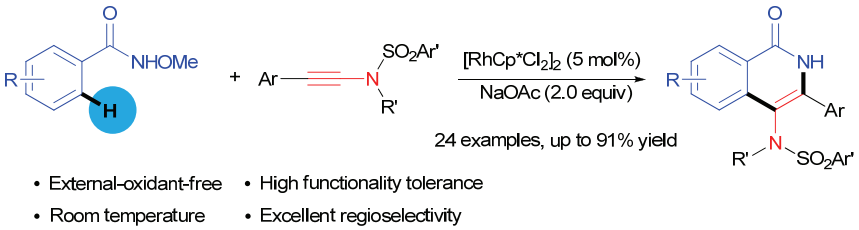
Graphic Abstract

Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides at room temperature: a practical and efficient route to 4-aminoisoquinolone derivatives

Guangying Tan, Xiaolei Huang, Qian Wu, Luo-Qiang Zhang and Jingsong You*



A mild Rh(III)-catalyzed annulation of *N*-methoxybenzamides with ynesulfonamides has been developed for the synthesis of 4-aminoisoquinolone derivatives under external-oxidant-free conditions.