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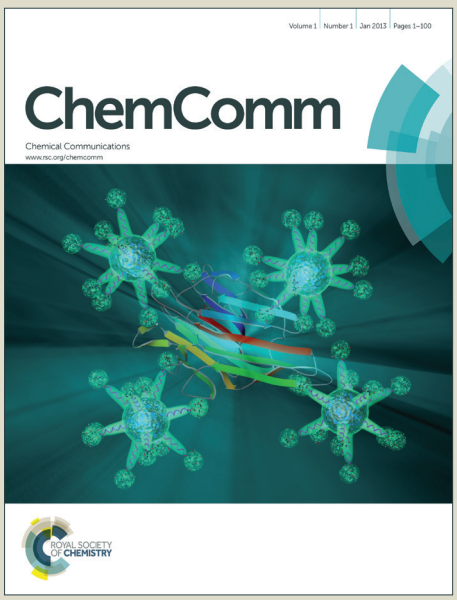

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Rhodium(III)-Catalyzed Oxidative Bicyclization of 4-Arylbut-3-yn-1-amines with Internal Alkynes Through C-H Functionalization

Received 00th January 20xx,
Accepted 00th January 20xx

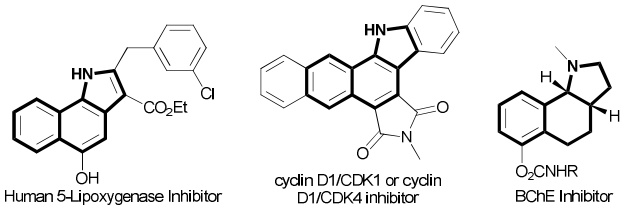
DOI: 10.1039/x0xx00000x

www.rsc.org/

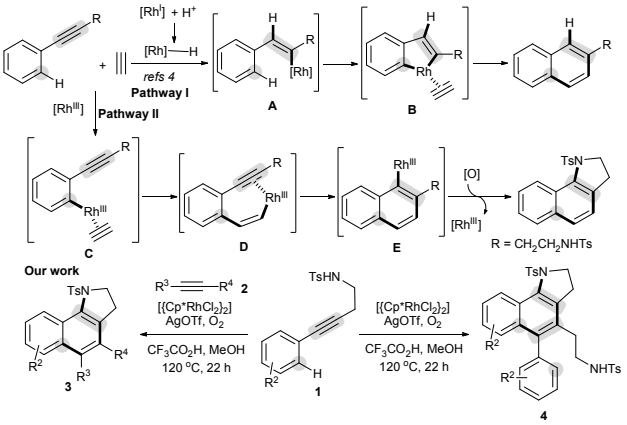
Rui Pi, [a] Ming-Bo Zhou, [a] Yuan Yang, [a] Cai Gao, [a] Ren-Jie Song [a] and Jin-Heng Li*[ab]

A new Rh(III)-catalyzed oxidative bicyclization through C-H functionalization is presented. This reaction allows the selective assembly of diverse benzo[*g*]indoles from 4-arylbut-3-yn-1-amines and internal alkynes *via* a sequence of aromatic C(sp^2)-H functionalization, cyclodimerization and nucleophilic cyclization.

Ring-fused naphthalenes,[1] including benzo[*g*]indoles (Scheme 1),[2] are an important class of polycyclic hydrocarbons in organic synthesis, chemical biology, pharmaceutical discovery, and materials science. As a result, much attention has been attracted to the development of new efficient methods to build ring-fused naphthalenes.[1-6] Traditional approaches for such compound synthesis are derived from the preexisting naphthalene skeletons via several steps.[1-3] In recent years, transition-metal-catalyzed tandem annulation reactions and especially tandem annulation strategy between aromatic compounds and alkynes through aryl C(sp^2)-H functionalization have emerged as an efficient, convergent method to assemble naphthalenes[4-7] and ring-fused naphthalenes.[8] However, the majority of these transformations are limited by the use of alkynes only as the 2-carbon synthons,[5,6,8] and approaches to ring-fused naphthalenes are quite rare.[8] In 1998, Kisch and co-workers developed a novel HCl-facilitated rhodium-catalyzed aryl C(sp^2)-H functionalization and [4+2] cyclodimerization of arylalkynes for building naphthalene skeletons, in which one arylalkyne molecule was used as the 4-carbon synthon and the other arylalkyne molecule as the 2-carbon synthon.[7a] Miura and co-workers have reported a new rhodium/phosphine/amine·HBr catalyst system for the highly chemoselective synthesis of multisubstituted naphthalenes by aryl C(sp^2)-H functionalization and [4+2] cyclodimerization of two different internal alkynes; the catalytic conditions tolerated various internal alkynes and made the cross-dimerization to predominate over the conceivable homo-dimerization.[7b] During the cyclodimerization process (Pathway I, Scheme 2),[7] the rhodium hydride species first formed from the Rh(I) species and a hydrogen cation (H^+) would subsequently undergo the insertion of a C-C triple bond in an arylalkyne to the Rh-H bond and geometrical isomerization *via* a zwitterion to give intermediate **A**. *ortho*-Metalation of intermediate **A** with the liberation of HX produces rhodacycle **B**, followed by selective insertion of another alkyne molecule to the rhodium-aryl or -alkenyl bond and reductive elimination afford naphthalenes.



Scheme 1 Selected examples of important benzo[*g*]indole compounds.



Scheme 2 Rhodium-catalyzed annulation of arylalkynes.

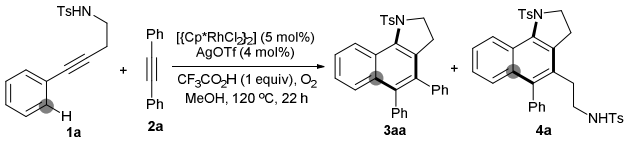
[a] *State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. Fax: 0086731 8871 3642; Tel: 0086731 8882 2286; E-mail: jhli@hnu.edu.cn Prof. Dr. J.-H. Li*

[b] *State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou 730000, China*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI:10.1039/x0xx00000x

In contrast, Rh(III)-catalyzed oxidative aromatic C(sp^2)-H functionalization and annulation reactions with alkynes are initiated via the direct insertion of Rh(III) species to the aromatic C(sp^2)-H bond leading to intermediate **C** (Pathway II, Scheme 2).[5,6,8] On this basis, we speculated that a Rh^{III} oxidative catalysis might trigger novel C-H functionalization and cyclodimerization reactions of arylalkynes through different quenching from the Rh^{I} catalysis to provide intermediate **E**, which would react with a nucleophile to afford ring-fused naphthalene skeletons. Herein, we report the first Rh(III)-catalyzed oxidative bicyclization of 4-arylbut-3-yn-1-amines with internal alkynes through C-H functionalization; this reaction proceeds by a sequence of aromatic C(sp^2)-H functionalization, cyclodimerization and nucleophilic cyclization and represents an practical method to access benzo[*g*]indoles (Scheme 2).

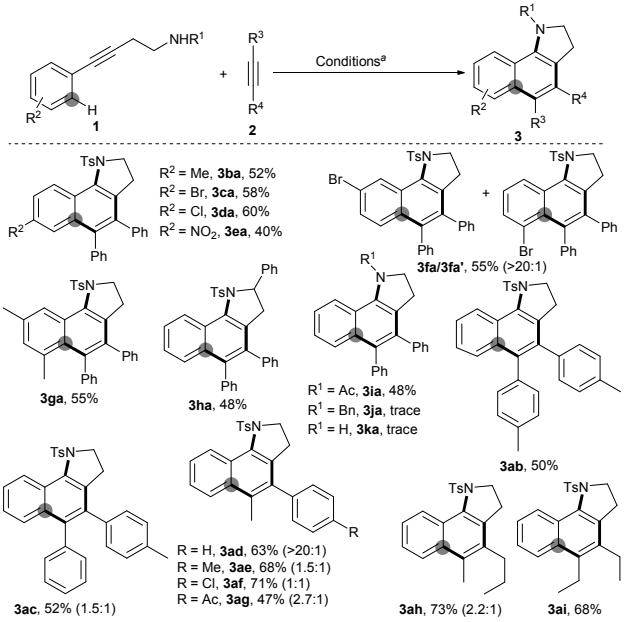
Table 1 Screening of the optimal reaction conditions[a]



Entry	Variation from the standard conditions	Isolated yield [%]	
		3aa	**4a**
1[b]	none	66	8
2	at 130 °C	65	10
3	at 100 °C	28	trace
4[c]	[{Cp*RhCl$_2$}$_2$] (10 mol%)	21	15
5	Without [{Cp*RhCl$_2$}$_2$]	0	0
6	without AgOTf	0	0
7	$AgSbF_6$ instead of AgOTf	35	5
8	AgOAc instead of AgOTf	19	trace
9	$AgCO_2CF_3$ instead of AgOTf	18	trace
10	$Cu(OTf)_2$ instead of AgOTf	40	10
11	$Sc(OTf)_3$ instead of AgOTf	trace	trace
12	without CF_3CO_2H	46	9
13	TfOH instead of CF_3CO_2H	10	trace
14	N_2 (1 atm) instead of O_2	27	trace
15	$Cu(OAc)_2$ (1 equiv) instead of O_2	21	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), [{Cp*RhCl$_2$}$_2$] (5 mol%), AgOTf (4 mol%), CF_3CO_2H (1 equiv), O_2 (1 atm), MeOH (anhydrous, 2 mL), 120 °C, 22 h. [b] Other side-products, including 4-methyl-*N*-(4-oxo-4-phenylbutyl)benzenesulfonamide (**5a**; 15%) from hydration of alkyne **1a,** were observed. [c] Side-product **5a** in 36% yield.

We started our optimization investigation with the bicyclization reaction between 4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (**1a**) and 1,2-diphenylethyne (**2a**) (Table 1). When a combination of [{Cp*RhCl$_2$}$_2$] (5 mol%) with AgOTf (4 mol%), CF_3CO_2H (1 equiv) and O_2 (1 atm) in the medium MeOH at 120 °C for 22 h was employed, the cross-bicyclization product **3aa**[9] was furnished in the highest yield (66%) with two side-products, the homo-bicyclization product **4a** and hydration product **5a**, from substrate **1a** in 8% and 15% yields, respectively (entry 1). While a higher reaction temperature gave the same results with those at 120 °C (entry 2), a lower reaction temperature had a negative effect (entry 3). However, the yield of **3aa** decreased sharply when using 10 mol% of [{Cp*RhCl$_2$}$_2$] because the side-reactions were promoted (entry 4). Notably, the Rh^{III} catalyst and AgOTf play a crucial role in the reaction, as omittance of any one of these species leads to no detectable products **3aa** (entries 5 and 6). Other Ag salts, namely $AgSbF_6$, AgOAc and $AgCO_2CF_3$, were less efficient than AgOTf (entries 7-9). Use of $Cu(OTf)_2$ instead of AgOTf showed activity for the reaction, albeit giving a lower yield (entry 10). However, $Sc(OTf)_3$ was ineffective (entry 11). These results support that Ag salts and Cu salts act as a promoter to activate the Rh^{III} species, not as a Lewis acid. Screening on the effect of acids confirmed that the role of CF_3CO_2H is to improve the reaction (entries 1, 12 and 13 and Table S1 in the Supporting Information). The yield of **3aa** decreased dramatically when N_2 or $Cu(OAc)_2$ was used to replace O_2 (entries 14 and 15).



Scheme 3 Bicyclization of 4-arylbut-3-yn-1-amines (**1**) with internal alkynes (**2**). [a] Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), [{Cp*RhCl$_2$}$_2$] (5 mol%), AgOTf (4 mol%), CF_3CO_2H (1 equiv), O_2 (1 atm), MeOH (anhydrous, 2 mL), 120 °C, 22 h. The regioselective ratio based on unsymmetrical alkynes **2** as the 2-carbon synthons is given in parenthesis. Two main side-products **4** and **5** were observed.

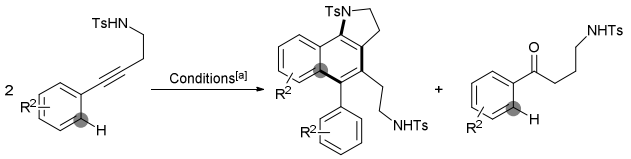
The scope of this cross-bicyclization reaction with regard to 4-arylbut-3-yn-1-amines reacting with different internal alkynes was first investigated by using the optimal reaction conditions (Scheme 3). The substituents, namely Me, Br, Cl and NO_2 groups, on the aryl ring in 4-arylbut-3-yn-1-amines **1b-h** were well-tolerated. For example, treatment of 4-Br- or 4-Cl-susbtitutted substrates **1c** or **1d** with 1,2-diphenylethyne (**2a**), [{Cp*RhCl$_2$}$_2$], AgOTf, CF_3CO_2H and O_2 afforded the desired benzo[*g*]indoles **3ca-da** in moderate yields, which may provide opportunities for further additional modifications of the product. Notably, 3-Br-susbtituted substrate **1f** led to a mixture of regioselective bicyclization products **3af/3af'**. Gratifyingly, substrate **1h** with a phenyl group on the 1 position was also compatible with the optimal conditions and gave **3ha** in 48% yield. Substrate **1i** with a Ac group instead of the Ts group also

afforded the expected product **3ia** in moderate yield. However, substrates **1j** and **1k** with a Bn group or two free hydrogen atoms on the nitrogen atom were not viable for the bicyclization reaction and lea to no formation of **3ja** and **3ka**.

The optimal conditions were found to be applicable to various internal alkynes **2b-i** (**3ab-ai**). Using symmetrical internal alkynes, 1,2-di-*p*-tolylethyne (**2b**) and hex-3-yne (**2i**), to react with substrate **1a**, [{Cp*$RhCl_2$}$_2$], AgOTf, CF_3CO_2H and O_2 successfully furnish **3ab** and **3ai** in high yields. For unsymmetrical internal alkynes **2c-h**, a mixture of regioselective products were observed. For example, (4-methylphenyl)phenylethyne (**2c**) was converted into **3ac** with >20:1 regioselectivity.[9] Aryl-substituted prop-1-ynes **2d-g** were suitable substrates and the substitution effect of the aryl group had a fundamental influence on the regioselectivity (**3ad-ag**). Gratifyingly, hex-2-yne (**2h**), an aliphatic internal alkyne, also led to **3ah** with 73% yield and 2.2:1 regioselectivity.

As shown in Table 2, the homo- bicyclization of 4-methyl-*N*-(4-arylbut-3-yn-1-yl)benzenesulfonamides **1a-g** were examined. 4-Phenylalkyne **1a** was treated with [{Cp*$RhCl_2$}$_2$], AgOTf, CF_3CO_2H and O_2 smoothly, providing the desired homo-bicyclization product **4a** in 65% yield with 25% yield of the hydration product **5a** (entry 1). Alkynes **1b-d** and **1f-g** bearing a 4-MeC_6H_4, a 4-BrC_6H_4, a 4-ClC_6H_4, a 3-BrC_6H_4 or a 3,5-diMeC_6H_4 group at the 4 position, successfully delivered **4b-d** and **4f-g** in moderate yields (entries 2-6).[9] Notably, 4-arylalkyne **1f** with a Br group at the meta position gave a mixture of regioselective isomers **4f/4f'** based on alkyne **1f** (entry 5).

Table 2 Homo-bicyclization of 4-arylalkynes(**1**)[a]

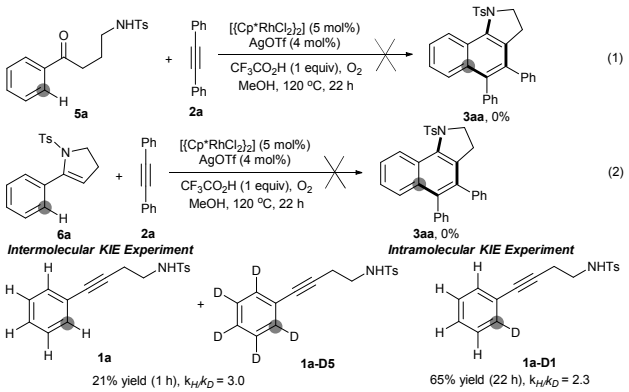


1 **4** **5**

Entry	R^2(**1**)	Isolated Yield [%]	
		4	**5**
1	H, **1a**	**4a**, 65 (>20:1)	**5a**, 25
2	4-Me, **1b**	**4b**, 67 (>20:1)	**5b**, 26
3	4-Br, **1c**	**4c**, 57 (>20:1)	**5c**, 38
4	4-Cl, **1d**	**4d**, 59 (>20:1)	**5d**, 32
5[b]	3-Br, **1f**	**4f** (8-Br)/**4f'** (6-Br), 62	**5f**, 26
6	3,5-diMe, **1g**	**4g**, 60 (>20:1)	**5g**, 33

[a] For reaction conditions, see Table 1 and Scheme 3. The regioselective ratio based on unsymmetrical alkynes as the 2-carbon synthons is given in parenthesis. [b] The regioselectivity ratio of **4f**/**4f'** is 2.5:1 based on alkyne **1f** as the 4-carbon synthon.

To understand the mechanism for this bicyclization reaction (Pathway II, Scheme 2), some control experiments were performed (Scheme 4). Substrates **5a** and **6a** could not be converted into the expected product **3aa**, suggesting that they were not intermediates for this bicyclization reaction [Eq (1) and Eq (2)].[10] The intermolecular (k_H/k_D = 3.0) and intramolecular (k_H/k_D = 2.3) kinetic isotope effect experiments support that the C(sp^2)-H functionalization is the rate-limiting step.[5]



Scheme 4 Control experiments.

In conclusion, we have developed a Rh(III)-catalyzed oxidative bicyclization reaction of 4-arylbut-3-yn-1-amines with internal alkynes via C(sp^2)-H functionalization, cyclodimerization and nucleophilic cyclization cascades, which enables a variety of ring-fused naphthalenes with excellent functional-group tolerance. In contrast to the catalytic cycle of the Rh^I catalysis, this Rh^{III} catalysis is initiated by C-H functionalization and quenched through nucleophilic cyclization, which may be useful for the construction of diverse polycyclic structures in organic synthesis and medicinal chemistry. Further studies on the mechanism and applications of this bicyclization strategy are currently under way in our laboratory.

Notes and references

‡ We thank the Natural Science Foundation of China (Nos. 21472039 and 21172060), Hunan Provincial Natural Science Foundation of China (No. 13JJ2018) and Specialized Research Fund for the Doctoral Program of Higher Education (No. 20120161110041) for financial support.

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9 CCDC 1063383 (**3aa**), CCDC 1063384 (**3ad**) and CCDC 1063386 (**4c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10 Another possible mechanism initiated by the first nucleophilic cyclization was proposed in Scheme S1 of the Supplementary Information.