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Hydrohalogenative aromatization of multiynes promoted by ruthenium alkylidene complexes†

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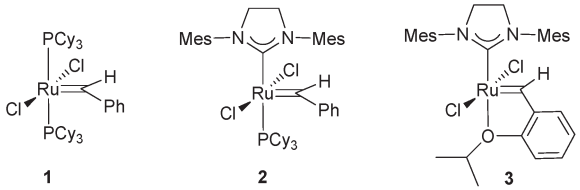
A new functionalization method of arynes promoted by a novel catalytic role of the Grubbs-type ruthenium alkylidene complex is described. Through a sequence of aryne formation followed by their halo-functionalization, various bis-1,3-diynes were directly converted to functionalized aryl chlorides, bromides and iodides in good yields in the presence of a catalytic amount of a ruthenium alkylidene complex and halogenated hydrocarbons such as CH_2Cl_2, $CHCl_3$, CH_2Br_2, and CH_2I_2. The utility of this novel transformation is demonstrated by a formal synthesis of herbindole B.

Introduction

Since the discovery of the well-defined ruthenium based alkylidene complex in 1992,[1] Grubbs alkylidene complexes have continued to evolve with improved stability, reactivity and selectivity in the metathesis of various formats over the past twenty years.[2,3] The greatest impact of Grubbs catalysts (**1–3**) lies in olefin metathesis whereby the synthesis of countless organic molecules of interest was achieved ranging from natural products and pharmaceuticals to advanced materials including polymers with special characteristics.[4] Over the years, various synthetically useful nonmetathetic reactions catalyzed by Grubbs-type complexes have been documented.[5] Therefore, the discovery of a new catalytic reactivity of these complexes will further broaden their synthetic utility.



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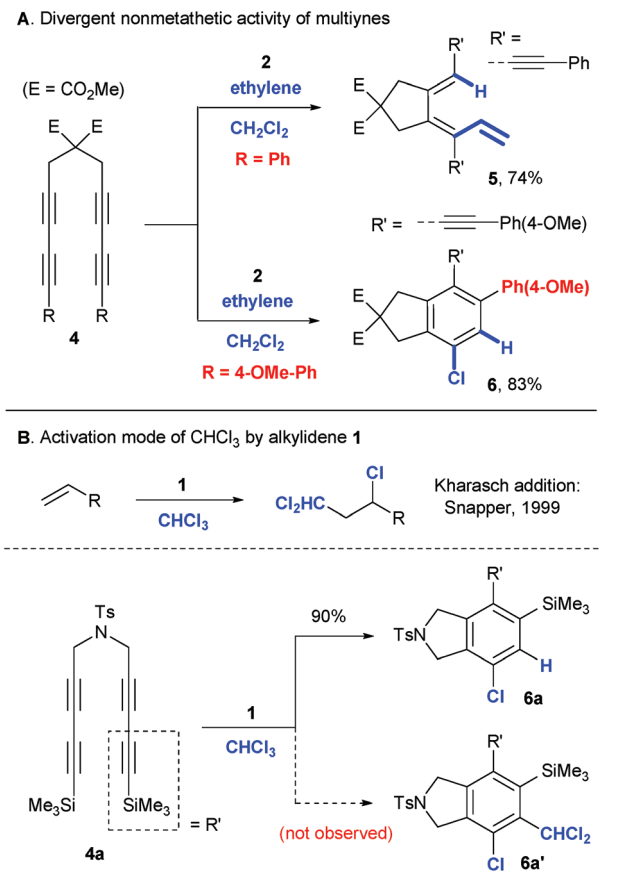
Recently we reported an unusual nonmetathetic catalytic activity of ruthenium alkylidenes by which an efficient 1,4-hydrovinylative cyclization of multiynes with concomitant incorporation of an ethylene molecule was achieved, forming multiple conjugated products **5** (Scheme 1A).[6,7] During the exploration of this unusual transformation, we observed yet another unexpected reaction when variation of the electronic nature of the alkyne substituent was introduced to the multiyne substrates. It was remarkable to find that a simple change



Scheme 1 Distinctive nonmetathetic activity of ruthenium alkylidenes.

in the phenyl group with a 4-methoxy group in substrate **4**, under otherwise identical reaction conditions, completely changed the reaction course, producing the aryl chloride **6**.

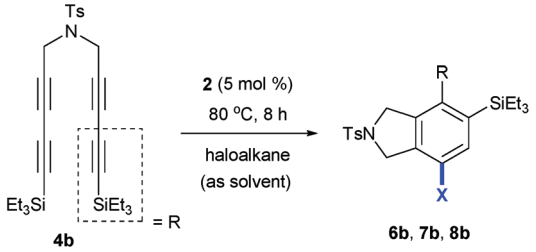
Because the only source of chlorine atom incorporated into the aryl moiety of **6** is CH_2Cl_2 (except the ligands in the ruthenium complex), the chlorine atom must come from dichloromethane used as the solvent. The same reaction with deuterated dichloromethane or chloroform provided the same product **6** with a high level of deuterium incorporation, thus it is evident that the hydrogen incorporated into the product is also from dichloromethane. Although not identical, this ruthenium-catalyzed activation of chlorinated hydrocarbon seems to be closely related to the Kharasch addition of $CHCl_3$ with alkenes catalyzed by ruthenium alkylidene **1** in Snapper's seminal study (Scheme 1B).[8] Thus, we carefully examined whether the reaction of tetrayne **4a** with $CHCl_3$ produced the Kharasch-type addition product **6a′** when catalyzed by ruthenium alkylidene **1**. From this reaction, however, the Kharasch-type $CHCl_3$ adduct **6a′** or its regioisomer was not observed, and the aryl chloride **6a** was isolated in 90% yield. Based on this initial observation, we further investigated the generality of the reaction and herein we report the unprecedented non-metathetic activity of Grubbs-type ruthenium complexes to activate halogenated hydrocarbons for the formation of a range of functionalized aryl halides from various bis-1,3-diyne substrates.[9]

Results and discussion

First we investigated the reactivity of various conventional haloalkanes as the source of HX in the cycloaromatization of symmetrical bis-1,3-diyne **4b** catalyzed by Grubbs second-generation complex **2**.[10] When halogenated hydrocarbons (CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, CH_2Br_2, $BrCH_2CH_2Br$, and CH_2I_2) were used as either a solvent or a reagent the corresponding chloro-, bromo-, and iodo-substituted arenes **6b**, **7b**, and **8b** were generated except for CCl_4 probably due to the lack of a hydrogen atom source (Table 1). While the hydrochlorinated product **6b** was produced in a range of 85–92% yields (entries 1–3), the corresponding hydrobrominated product **7b** was obtained in slightly lower yields when CH_2Br_2 and $BrCH_2CH_2Br$ were used as the source of HBr (entries 5 and 6), and in the presence of CH_2I_2, aryl iodide **8b** was obtained in a significantly lower yield (entry 7). In all cases, HX addition turned out to be highly regioselective, thus the other isomer was not observed within the detectable limit. Interestingly, the reaction of substrate **4a** with methyl iodide (CH_3I) produced a mixture of the hydrogen iodide-incorporated product **8b** and the methyl iodide-incorporated product **8b′** in 68% yield with a 1 : 3.5 ratio (Scheme 2).

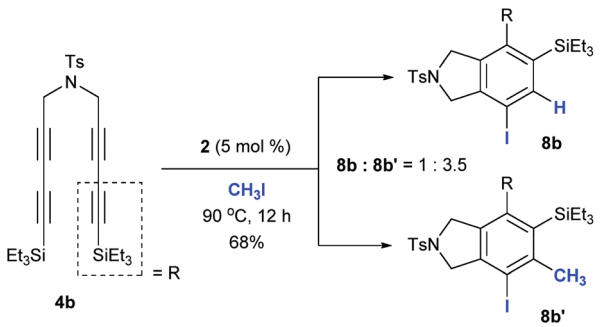
Based on these promising preliminary results, the scope of this catalytic hydrohalogenative cycloaromatization reaction was further explored with variously substituted symmetrical bis-1,3-diyne substrates mainly employing CH_2Cl_2, CH_2Br_2 and CH_2I_2 as the HX source (Table 2). In general, the substrates

Table 1 Screening of halogen sources[a]



Entry	Haloalkane	Product	X	Yield[b] (%)
1	CH_2Cl_2	**6b**	Cl	92
2	$CHCl_3$	**6b**	Cl	90
3	$ClCH_2CH_2Cl$	**6b**	Cl	85
4	CCl_4	**6b**	Cl	<5
5	CH_2Br_2	**7b**	Br	76
6	$BrCH_2CH_2Br$	**7b**	Br	76
7	CH_2I_2	**8b**	I	45

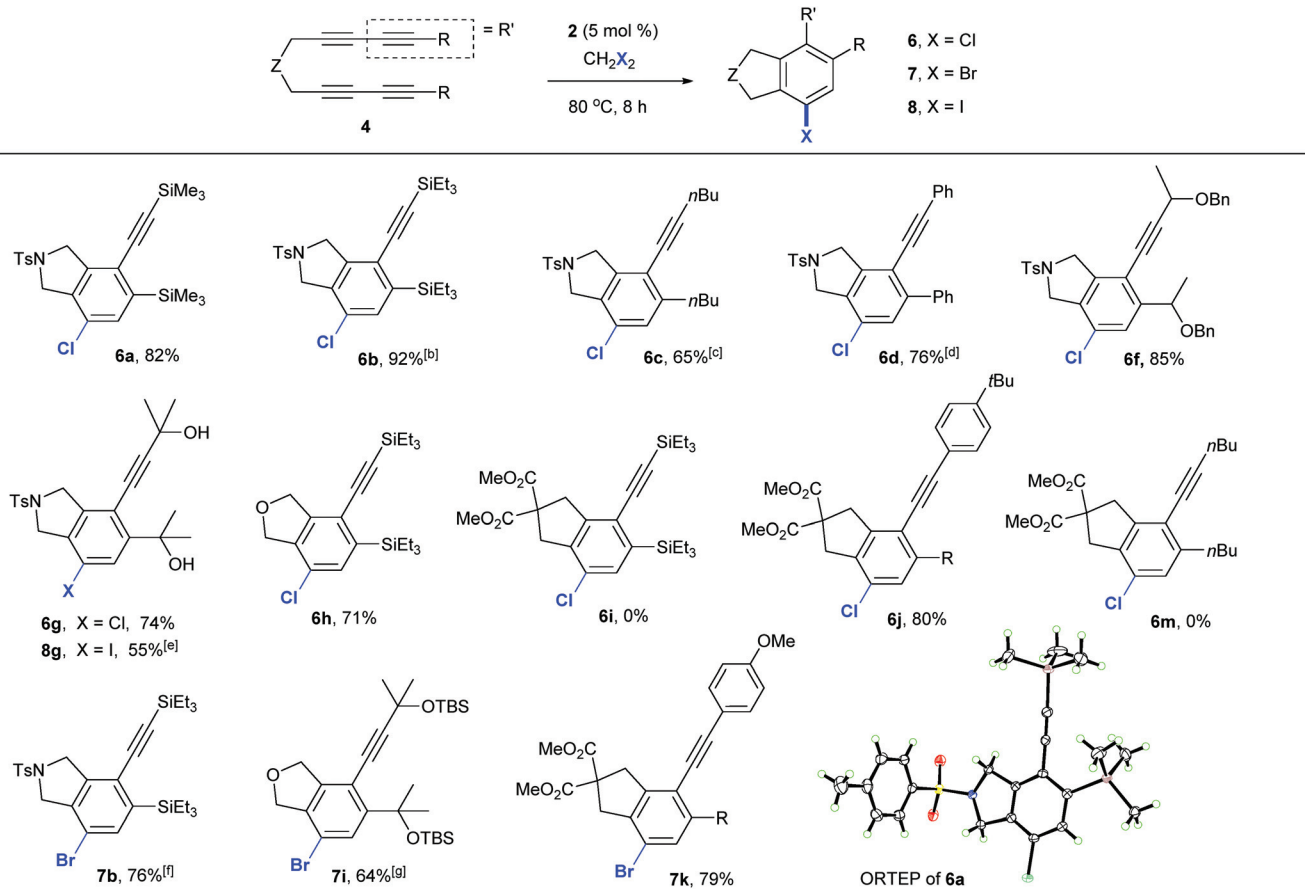
[a] Reaction conditions: 0.1 mmol of **4b**, 5 mol% **2**, 2 mL of haloalkanes as the solvent. [b] Isolated yield.



Scheme 2 Competing reactions between hydroiodination and methyliodination.

possessing a tosyl amide linker or an oxygen tether provided aryl halide products in good yields regardless of the substituent on the diyne. Thus, substrates containing silyl groups on the 1,3-dienes provided the corresponding chlorinated and brominated arenes **6a**, **6b**, **7b** in 82, 92 and 76% yields, respectively, as a single regioisomer. The structural confirmation of these products was established by nOe experiments and further by single crystal X-ray crystallographic analysis of **6a**.[11] While a *t*-butyl group-containing substrate produced a 10 : 1 mixture of isomers of **6c** in 65% yield, the corresponding substrate possessing a phenyl group afforded a 20 : 1 mixture of isomers **6d**. Hydrochlorinated and hydroiodinated arenes **6f**, **6g** and **8g** carrying secondary and tertiary carbon-containing substituents were generated as single isomers in good yields. A tertiary hydroxyl group at the propargylic carbon in the substrate did not interfere with the formation of hydrohalogenated products. Silyl- and alkyl group-substituted bis-1,3-diynes containing an oxygen linkage also afforded the corresponding aryl chlorides and bromides in good yields under

Table 2 Scope of hydrohalogenative aromatization of symmetrical bis-1,3-diyne substrates[a]



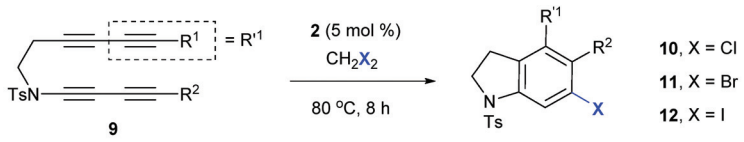
[a] Reaction conditions: 0.1 mmol of **4**, 5 mol% ruthenium alkylidene **2**, 2 mL of CH_2X_2 (as the solvent). [b] 87% yield was obtained when catalyst **3** was employed. [c] 10 : 1 mixture of regioisomers formed. [d] 20 : 1 mixture of regioisomers formed. [e] 13 : 1 mixture of iodinated and chlorinated products formed. [f] 10 : 1 mixture of brominated and chlorinated products formed. [g] 12 : 1 mixture of brominated and chlorinated products formed.

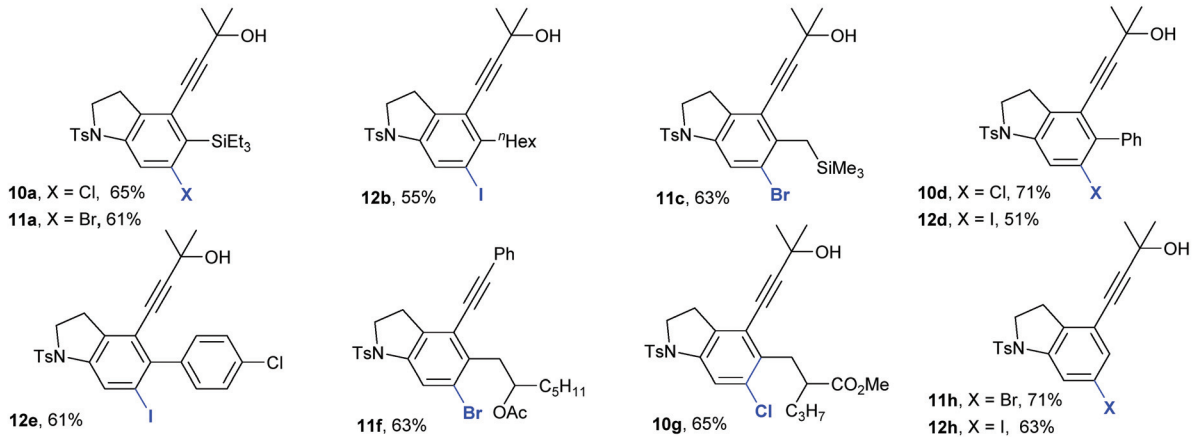
standard reaction conditions. In contrast, the substituent on the 1,3-diyne of dimethylmalonate-containing substrates significantly affected the reaction efficiency. For example, aryl chloride **6j** and bromide **7k** were isolated in 80 and 79% yields, respectively, whereas **6i** and **6m** could not be obtained even after prolonged heating at 150 °C; instead, the corresponding bis-1,3-diynes were recovered intact with minor decomposition.

Next, we examined the reaction scope of hydrohalogenative aromatization with unsymmetrical substrates of type **9** (Table 3). Regardless of the substituent on the alkyne, complete regioselectivity was observed for the formation of halogenated arenes from unsymmetrical substrates containing an ynamide tether.[12] It is worthy of note that the regiochemistry of HX incorporation into the product is opposite to that of the symmetrical bis-1,3-diynes shown in Table 2. Thus halogenated arenes **10a**, **10d**, **11a**, **11c**, **12b**, **12d**, **12f** were generated in moderate to good yields, where X (Cl, Br, I) was incorporated at the *ortho* (*meta* to *N*Ts) position of the silyl, alkyl, and aryl substituents.[13] Substrates with various forms of oxygen-based functional groups such as an ester or a tertiary hydroxyl group did not interfere with the formation of halides **10g**, **11f**, **11h**, and **12h**. Also less substituted bromo- and iodoarenes **11h** and **12h** were obtained with slightly improved yields from the corresponding substrate containing a terminal alkyne moiety.

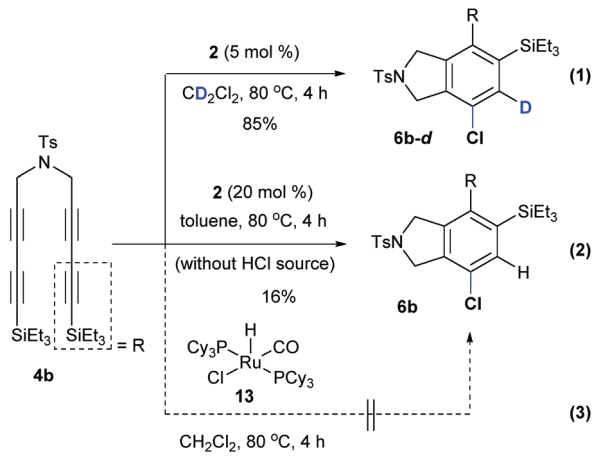
To gain mechanistic insight into this novel hydrohalogenative aromatization process, we carried out the reaction of substrate **4b** with CD_2Cl_2 (eqn (1) in Scheme 3). The obtained product **6b–d** from this reaction shows 90% deuterium incorporation at the carbon *ortho* to the silyl group. This clearly indicates that CD_2Cl_2 is the source of both Cl and D, which allows us to conclude that the halogenated hydrocarbons are the source of not only X but also H in all of the reactions above. The reaction of **4b** with 20 mol% ruthenium alkylidene complex **2** in a nonhalogenated solvent such as toluene provided 16% of the aryl chloride **6b** (eqn (2) in Scheme 3). This result suggests that the chloride ligands on **2** could be transferred to form the chlorinated product. To examine the role of an alternative catalytic species such as ruthenium hydride, one of the typical decomposition products of Grubbs-type

Table 3 Scope of hydrohalogenation for unsymmetrical substrates[a]

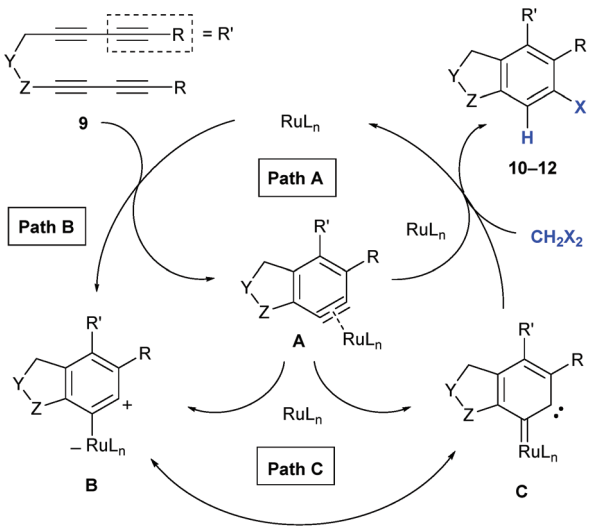




[a] Reaction conditions: 0.1 mmol of **9**, 5 mol% ruthenium alkylidene **2**, 2 mL of CH_2X_2 (as the solvent).

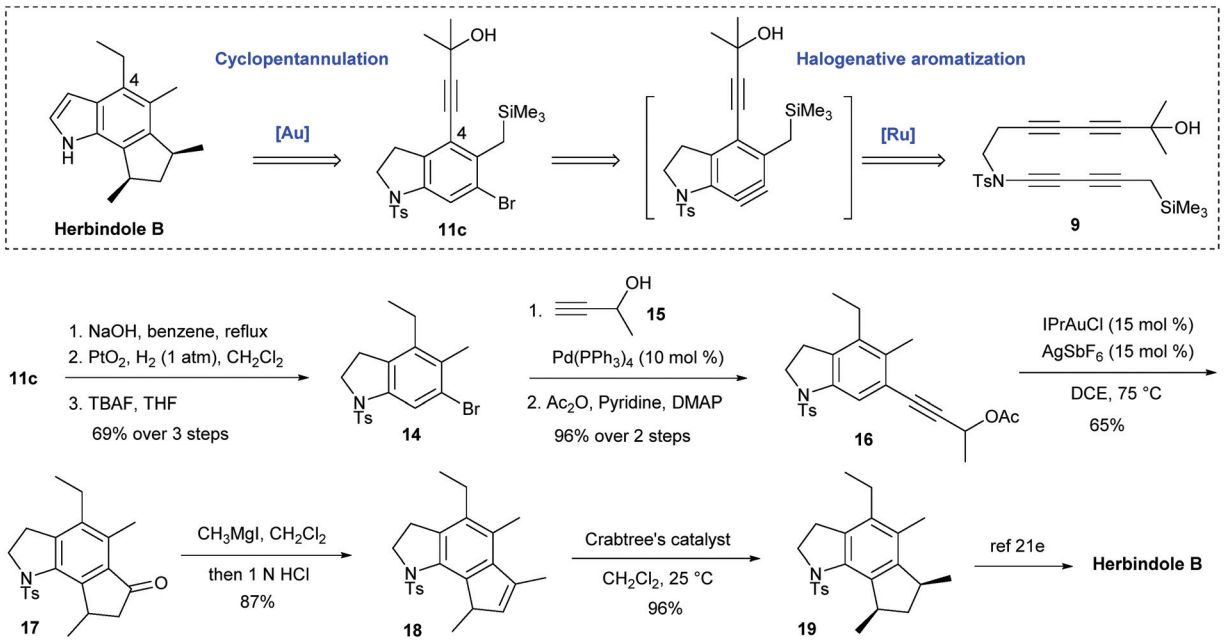


Scheme 3 Experiments for mechanistic insight.



Scheme 4 Possible mechanisms for hydrohalogenation.

ruthenium alkylidene complexes,[14] independently prepared ruthenium hydride complex **13** was tested as the catalyst for the reaction of **4b** (eqn (3) in Scheme 3). But not even a trace amount of **6b** was observed. Moreover, a linear correlation was evidently established between the amounts of an intact ruthenium alkylidene species in the reaction (measured by the characteristic ^{1}H NMR signal at 19.1 ppm in CD_2Cl_2) and the observed speed of the conversion of substrates to the products. From these observations, we propose a mechanistic hypothesis (Scheme 4), albeit a more accurate picture of the mechanism is yet to be established. In this mechanistic scenario, the role of the ruthenium alkylidene complex can be envisioned in three distinctive manners. First, in Path A, a thermal hexadehydro Diels–Alder reaction[15,16] of the substrate **9** to form an aryne intermediate **A** followed by hydrohalogenation where the role of the ruthenium alkylidene is to activate halogenated hydrocarbons similar to the Kharasch-type addition observed by Snapper.[8] In Path B, the interaction between substrate **9** and the catalyst promotes the formation of a ruthenium–aryne complex **B** or an alternative form **C**. The electron-deficient intermediate **B** or **C** may interact with halohydrocarbons analogous to that of the metal–carbenoid reported by Lovely and Moriarty,[17] or the vinyl cations reported by Johnson, Curran, and Kozmin.[18] Alternatively, in Path C, thermally generated



Scheme 5 Formal synthesis of herbindole B.

aryne **A** intercepts intermediate **B** or **C** upon interacting with the ruthenium species.[19,20] Furthermore, the efficiency of forming aryne **A** and its trapping with weak nucleophiles (MeOH, AcOH) was not affected by the catalyst,[21] which is however indispensible for hydrohalogenated products **10–12**. Thus, we conclude that Path A is the most plausible mechanism where CH_2X_2 is activated by the ruthenium catalyst for HX transfer to the aryne intermediate **A**.

The utility of this hydrohalogenative cyclization is showcased with the synthesis of a cyclopent[*g*]indole natural product herbindole B, which was isolated from the Western Australian sponge *Axinella* sp., and exhibits cytotoxicity against KB cells and a general fish antifeedant activity (Scheme 5).[22,23]

From a retrosynthetic perspective, the structural feature of herbindole can take advantage of the existing alkyne moiety at the C4 position of the aryl halide **11** that is generated by the hydrohalogenative cyclization of a suitably substituted unsymmetrical bis-1,3-diyne **9**. In turn, the installation of the benzo-fused dimethyl cyclopentane moiety would be achieved by the gold-catalyzed Nazarov cyclization of an acetoxyalkynyl arene derived from the aryl halide **11**.[24] The synthesis of herbindole B commenced with conversion of the alkyne moiety of **11c** to **14** *via* a three-step sequence involving removal of the tertiary alcohol moiety, hydrogenation, and desilylation of the benzylic trimethylsilyl group. The Sonogashira coupling between **14** and alkyne **15** followed by subsequent acetylation furnished **16**. Gold-catalyzed tandem [3,3]-rearrangement of the propargylic acetate moiety in **16** followed by a Nazarov cyclization effectively created the benzo-fused methylcyclopentanone moiety in **17**. The missing methyl group was installed *via* the addition of MeMgI to the ketone and subsequent dehydration of the resultant tertiary alcohol, generating the indene derivative **18**. Stereoselective hydrogenation of **18** using the Crabtree catalyst provided the known compound **19** with the *cis*-relationship of the methyl groups, from which Sato and coworkers achieved a total synthesis of herbindole B in two steps.[23e]

Conclusions

In conclusion, we have discovered a new functionalization method of arynes promoted by a novel catalytic activity of the Grubbs-type ruthenium alkylidene complex whereby variously tethered bis-1,3-diynes were directly converted into structurally novel halo-functionalized arenes. In these transformations, halogenated hydrocarbons were used as the reagent or as a solvent, which effectively serve as the source of HX. This new benzannulation process showed a broad substrate scope and excellent regioselectivity in hydrohalogen incorporation, and thus allows for efficient preparation of a range of halofunctionalized indolines, isoindolines and related structures. The utility of this transformation was illustrated by a formal synthesis of herbindole B. Further investigation on this unique catalytic activity of Grubbs-type ruthenium alkylidene complexes is in progress.

Acknowledgements

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