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Intramolecular Cascade Hydroarylation/Cycloisomerization Strategy for the Synthesis of Polycyclic Aromatic and Heteroaromatic Systems

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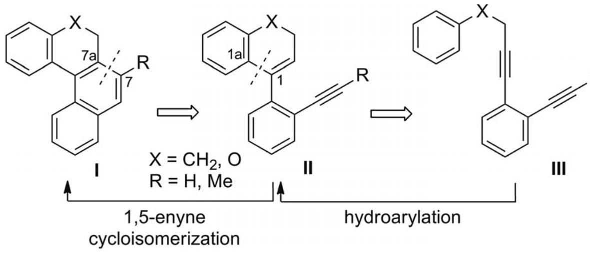
A new $PtCl_2$/$PtCl_4$-catalyzed hydroarylation/cycloisomerization cascade reaction leading to the formation of two aromatic or heteroaromatic rings in one step is reported. The strategy developed is exemplified by the synthesis of the 5,6-dihydrobenzo[*c*]phenanthrene and 6*H*-naphtho[2,1-*c*]chromene skeletons. Attempts to prepare [8]helicene-like molecules are also discussed.

Introduction

Over the past few years, significant research has been directed toward the development of new methodologies for synthetic efficiency and atom economic processes. Transition-metal-catalyzed enyne cycloisomerization is one of the most important strategies used to form functionalized cyclic structures.[1] Among several transition metals, the use of platinum(II,IV)-based catalysts has many advantages. The reactions tend to be operationally safe, simple, and practical to perform, and they also do not generally require rigorously inert conditions. $Pt^{II,IV}$ chlorides are able to catalyze a broad range of C–C bond-forming reactions that allow enynes and related substrates to be converted into significantly increased, structurally complex carbo- and heterocyclic products.[2] Recently, we have shown that the double $PtCl_2$-catalyzed intramolecular hydroarylation of biphenylyl naphthalenes bearing an alkyne unit in the *ortho* position leads to the formation of carbo- and hetero[6]helicene backbones.[3] As part of our ongoing interest in the synthesis of helicenes and helicene-like molecules, we now report the way to 6*H*-naphtho[2,1-*c*]chromene and 5,6-dihydrobenzo[*c*]phenanthrene derivatives and attempts to prepare [8]helicene-like molecules through intramolecular $PtCl_2$/$PtCl_4$-catalyzed hydroarylation/cycloisomerization cascade reactions.

Results and Discussion

The development of cascade reactions for the efficient construction of complex molecules is an important goal in organic synthesis from the viewpoint of operational simplicity and assembly efficiency. This work is focused on synthetic investigations of proposed cascade reactions and their viability to build helical backbones. Our retrosynthetic strategy outlined in Scheme 1 is based on simple disconnection of the C7–C7a bond in **I** to form 1,5-enyne **II**. A second disconnection is made at the C1–C1a bond to give corresponding diyne **III**. In the direction of synthesis, the first transformation step would be a hydroarylation reaction to yield 2*H*-chromene and 1,2-dihydronaphthalene derivatives. Further transformation in the cascade sequence would involve cycloisomerization to afford the target molecules.



Scheme 1. Retrosynthesis.

To probe the viability and outcome of the envisaged cycloisomerization process, suitable model compounds were prepared (Scheme 2). (4-Iodo-1-butynyl)trimethylsilane[4] was converted into the zinc reagent[5] and treated with iodobenzene under copper(I) iodide mediated Negishi coupling conditions to afford **1b** after deprotection with tetrabutylammonium fluoride (TBAF). Sonogashira coupling with [(2-iodophenyl)ethynyl]trimethylsilane[6] and 1-iodo-2-(propynyl)benzene prepared from 1-bromo-2-(propynyl)benzene[3b] afforded diynes **2a** and **2c**. Subsequent deprotection of the trimethylsilyl (TMS) group gave diyne **2b**. To achieve the desired intramolecular hydroarylation/cycloisomerization cascade and, accordingly, to build the benzo[*c*]phenanthrene skeleton, diyne **2b** was exposed to a catalytic mixture of $PtCl_2$/$PtCl_4$ in toluene at 90 °C overnight. Product

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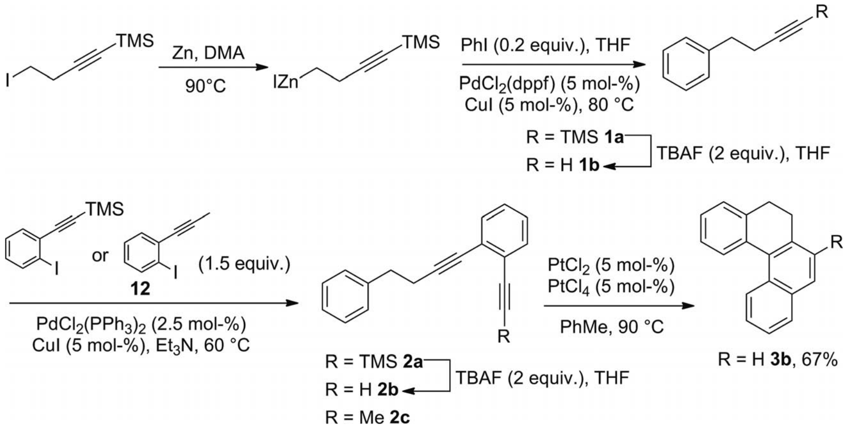
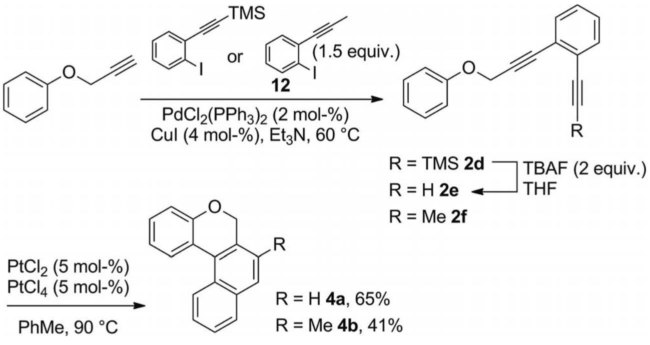


Scheme 2. Model synthesis of 5,6-dihydrobenzo[*c*]phenanthrene.

3 was isolated in 67% yield. Unfortunately, propyne derivative **2c** did not afford the desired product under similar conditions. Changing the solvent from nonpolar toluene to polar acetonitrile also failed; the reaction at 80 °C provided a complex mixture with trace amounts of the desired product (analyzed by GC–MS). The use of harsher conditions (180 °C, toluene or acetonitrile, MW) also did not work.

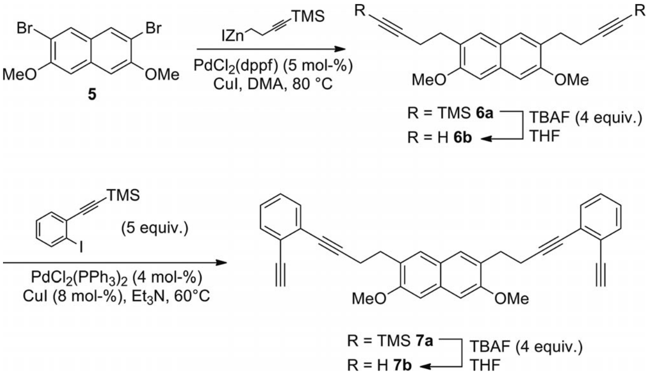
To explore the scope of this approach, we decided to synthesize heteroanalogues **2e** and **2f**. Propargyl phenyl ether[7] was transformed into the diynes by simple steps in good yields (Scheme 3).



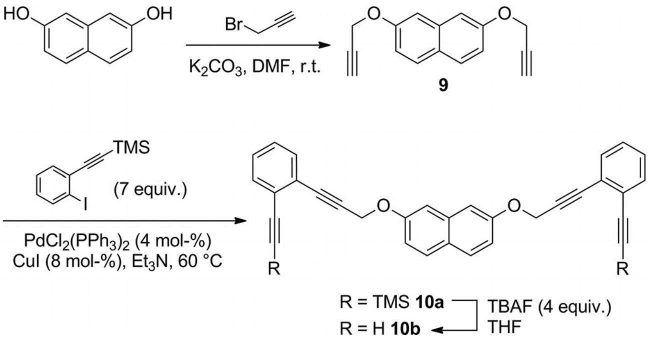
Scheme 3. Model synthesis of 6*H*-naphtho[2,1-*c*]chromene.

Intramolecular hydroarylation/cycloisomerization induced by PtCl$_2$/PtCl$_4$ proved to be effective, and 6*H*-naphtho[2,1-*c*]chromene **4a** was obtained in 65% yield. In the case of **2f**, toluene as a reaction medium did not prove to be the solvent of choice. The use of acetonitrile as a commonly used polar solvent for enyne cycloisomerizations was ineffective at 80 °C, and only at higher temperatures (180 °C, 30 min, MW) was **4b** repeatedly obtained in 40% yield.

After screening the cascade reaction we set out to attempt a similar process for the preparation of [8]helicene-like molecules. Among π-conjugated molecules, helicenes, which consist of *ortho*-annulated aromatic rings,[8] have attracted much attention because of their inherent chirality, and this has recently led to promising applications in asymmetric catalysis, enantioselective molecular recognition, and chiroptical and electro-optical functional materials.[9] Our attempts to prepare these products required tetraynes **7b** (Scheme 4) and **10b** (Scheme 5) as precursors.



Scheme 4. Synthesis of tetrayne **7b**.

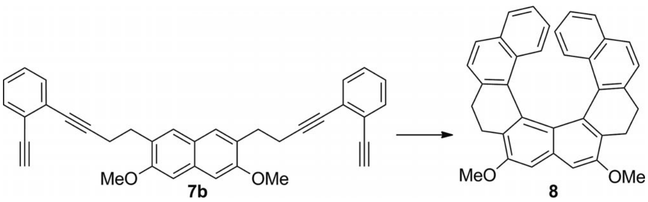


Scheme 5. Synthesis of tetrayne **10b**.

Copper(I) iodide assisted coupling of **5**, prepared from 3,6-dibromonaphthalene-2,7-diol,[10] with a zinc reagent gave diyne **6**. Sonogashira coupling of **6b** with [(2-iodophenyl)ethynyl]trimethylsilane provided desired tetrayne **7b**. Synthesis of the dioxa analogue started from commercially available naphthalene-2,7-diol, which was treated with propargyl bromide to give bis-ether **9**. Its conversion into **10b** was achieved under the same conditions as those used to prepare the carbo analogue.

Having prepared the suitable building block, we could approach the hydroarylation/cycloisomerization experiments. Cycloisomerization of **7b** with the mixed $PtCl_2/PtCl_4$ catalyst proved to be the proper choice. The best results were obtained with a catalyst loading of 20 mol-% each, but the yield did not exceed 20%. Other catalysts that were tested (Table 1) provided only starting material or complex reaction mixtures, and in no case was there any detectable formation of the desired product.

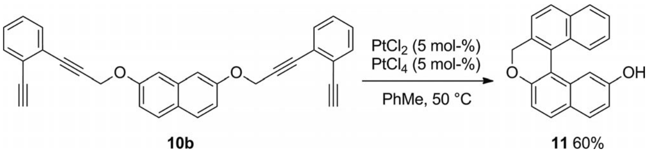
Table 1. Catalytic experiments for **7b**.



Entry	Catalyst[a]	Solvent	T [°C]	Yield [%]
1	$PtCl_2$	toluene	90	0
2	$PtCl_4$	toluene	90	0
3	$PtCl_2/PtCl_4$[b]	acetonitrile	80	0
4	$PtCl_2/PtCl_4$[b]	toluene	90	20
5	$InCl_3$	toluene	90	0
6	$AuCl_3$	toluene	90	0
7	$AuCl(PPh_3)$	DCM	r.t.	0
8	$AuCl(PPh_3)$, $AgBF_4$	DCM	r.t.	0
9	$AuCl_3$, PPh_3	DCM	r.t.	0
10	$Hg(OTf)_2$	acetonitrile	60	0
11	$Hg(OTf)_2 \cdot 3TMU$[c]	acetonitrile	60	0

[a] Catalyst loading 10 mol-%. [b] $PtCl_2$ (20 mol-%), $PtCl_4$ (20 mol-%). [c] TMU = tetramethylurea.

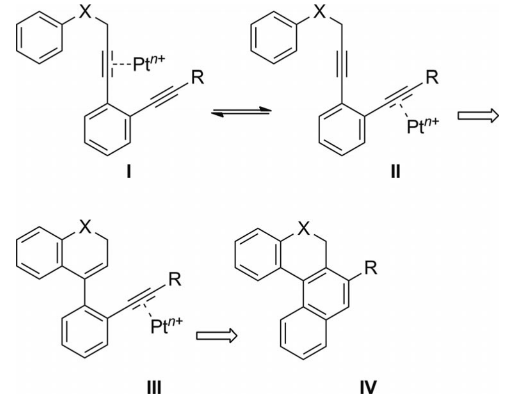
Further effort was directed at converting dioxa analogue **10b** into dihydrodioxa[8]helicene under the same catalytic conditions as those used for **7b**. We found that a catalyst loading of 20 mol-% for each species at 90 °C caused complete ether cleavage and afforded only naphthalene-2,7-diol. A decrease in the catalyst loading to 5 mol-% for each species and a decrease in the temperature to 50 °C afforded oxa[5]helicenol **11** in 60% yield (Scheme 6), but no detectable amount of the desired product. Further screening did not improve the result. The low yield of **8** in comparison to that of **3** is most likely caused by steric effects, which is in accordance with the cycloisomerization of **10b**.



Scheme 6. Cyclization of **10b**.

Conclusions

In summary, we have described a platinum(II,IV)-catalyzed hydroarylation/cycloisomerization cascade reaction that can be used to form two aromatic or heteroaromatic rings in one step. Fused aromatic systems can be prepared readily in moderate yields from simple diyne precursors. To the best of our knowledge, this is the first example of a one-pot cascade reaction comprising two diverse cycloisomerization transformations. The need for a Pt^{2+}/Pt^{4+} system arises from the presence of two different alkyne bonds. For the reaction to be successful there has to be a coordination step of a Pt^{n+} species to the alkyne bond to give **I** and **II** (Scheme 7). Considering the fact that both triple bonds are very similar in nature, we can assume that the Pt salts might coordinate equally well to both alkynes, and thus, **I** and **II** will be in equilibrium throughout the reaction, although only **I** enables the hydroarylation step. Enyne **III** then undergoes a second Pt^{n+} coordination to give **IV**. If there are electronic influences (alkyne substitution) that would result in the formation of the more stable form **II**, the reaction provides complex mixtures or no conversion. Our ongoing studies are in progress and are focused on mechanistic considerations.



Scheme 7. Mechanism.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all products.

Acknowledgments

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