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Expedient Synthesis of Phenanthrenes via In(III)-Catalyzed 6-*Exo*-*Dig* Cycloisomerization

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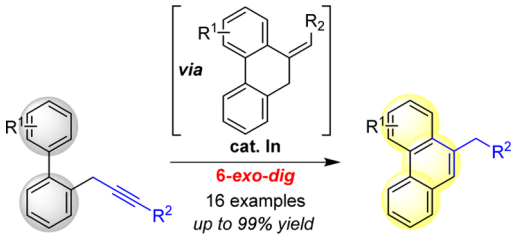
ABSTRACT



This paper documents the first example of In(III)-catalyzed selective 6-*exo-dig* hydroarylation of *o*-propargylbiaryls and their subsequent double-bond migration to obtain functionalized phenanthrenes. Electron-rich biaryl substrates undergo hydroarylation more effectively, and the substrates with various types of substituents on the alkyne can also be smoothly and selectively converted to phenanthrenes.

Phenanthrenes are of widespread interest because of their versatile physicochemical properties, such as photoconduction and electroluminescence.[1] In addition to their potential applications in materials science, they are present within a large number of natural products and synthetic compounds that exhibit diverse biological activities.[2] Consequently, many synthetic routes have been developed for their preparation.[3,4]

Among the various synthetic approaches to phenanthrenes, the intramolecular hydroarylation of *o*-alkynylbiaryls has captured attention because of its ability to create a large variety of polysubstituted phenanthrenes. Examples of either base- or metal cation-mediated carbocyclization of *o*-alkynylbiaryls are known in the literature (Scheme 1). In the base-catalyzed cyclization, the base induces the isomerization of alkynylbiaryls to the allene intermediate, which then undergoes a 6π cycloaddition and subsequent aromatization at very high temperatures (Scheme 1, eq 1).[5] In the metal-catalyzed process, metal ion coordination to the triple bond renders it susceptible to nucleophilic attack by the aromatic ring under relatively mild conditions. Although the metal-catalyzed cyclization of *o*-alkynylbiaryls potentially allows for substantial structure variations, and it can be applied in the related heterocyclic series, it inherently possesses a regioselectivity problem: the competition between 6-*endo*-*dig* and 5-*exo*-*dig* cyclization pathways. The selectivity between these two cyclization modes varies depending on the metal catalysts employed as well as the substrate type. For example, the 6-*endo* cyclization of *o*-alkynylbiaryls is preferred when transition-metal catalysts, such as $Fe(OTf)_3$, $PtCl_2$, $AuCl_3$, or $GaCl_3$ (Scheme 1, eq 2), are employed.[6] Substrates with an electron-withdrawing

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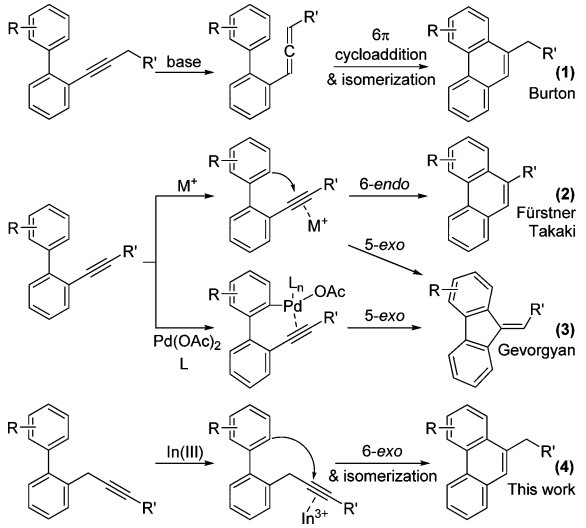
group on the alkyne show a pronounced preference for 5-*exo* cyclization to give the fluorene framework.[6a,b] The electron-neutral and electron-deficient *o*-alkynylbiaryls undergo palladium-catalyzed 5-*exo*-*dig* cyclization, presumably via a mechanism involving C−H activation (Scheme 1, eq 3).[7]

Scheme 1. Cycloisomerizations of *o*-Alkynylbiaryls and *o*-Propargylbiaryls



We envisioned that the intramolecular hydroarylation of *o*-propargylbiaryls would offer an alternative opportunity for the synthesis of phenanthrenes (Scheme 1, eq 4). Both possible competing cyclization modes of *o*-propargylbiaryls, 6-*exo*-*dig* and 7-*endo*-*dig*, are favored by Baldwin's rules.[8] The selectivity between these two cyclization modes is influenced by many factors including the stereoelectronic properties and the enthalpy of the transition state.[8,9] On the basis of entropic considerations, which play an important role in the kinetics of ring closure,[10] the formation of a six-membered ring is predicted to be faster than the formation of seven-membered ring. Thus, we anticipated that the carbocyclization of *o*-propargylbiaryls would preferentially afford a phenanthrene framework. Herein, we report the first example of an In(III)-catalyzed selective 6-*exo*-*dig* hydroarylation of *o*-propargylbiaryls and a subsequent double-bond migration that forms phenanthrenes.

The electron-rich propargylbiaryl **1a** (Table 1) was initially chosen as the model substrate to test the viability of the envisioned cycloisomerization process. A simple primary alkyl group was attached to the alkyne terminus to curtail the influence of substituents on the reactivity of the alkyne group. The *o*-propargylbiaryl **1a** was prepared via the addition of lithium acetylide to the readily available *o*-bromomethylbiaryl.[11] Various alkynophilic transition metal catalysts (10 mol %) were screened in toluene (0.05 M) at 80 °C (oil bath) to test the viability of the cycloisomerization. The representative results are summarized in Table 1. $AuCl_3$, AuCl, AgOTf, $Pd(OAc)_2$, and $[Ru(CO)_3Cl_2]_2$ failed to give the desired product, resulting in the recovery of unreacted starting material or decomposition products. When $PtCl_2$ or $PtCl_4$ was employed, the desired product **2a** was formed in low conversion and yield (entries 1 and 2). Substantial amounts of the starting material remained even after 40 h. The 7-*endo*-*dig* product, dibenzo[*a*,*c*]cycloheptene **3a**, was also formed as a minor component in a 3−4:1 ratio.[12] The reaction using $GaCl_3$ as the catalyst resulted in good conversions and gave appreciable yield. However, the regioselectivity was poor, resulting in a mixture of **2a** and **3a** in a ca. 4:1 ratio (entry 3).

Among the tested metal species, In(III) salts most efficiently induced the desired 6-*exo*-*dig* hydroarylation and subsequent double-bond migration. The reactions with $InCl_3$ and $InBr_3$ resulted in rapid, efficient (1 h at 80 °C), and extremely regioselective conversions that resulted in phenanthrene **2a** in 91% and 89% yields, respectively (entries 4 and 5). Upon changing the solvent to 1,2-dichloroethane (1,2-DCE), the yield improved to 94% with little effect on the reaction rate (entry 6). Remarkably, we found that the In(III)-promoted reaction was not air and moisture sensitive. The reaction also proceeded in the presence of water and air to give the product in 91% yield (entry 7). When the reaction was conducted in the presence of D_2O, two deuterium atoms were incorporated at the benzylic position (66%, *d*-incorporation) in the phenanthrene product **2a**.

When the $InCl_3$ loading was reduced to 5 mol % (entry 8) or the temperature was lowered to 50 °C (entry 9), the reaction time increased but the yield remained almost the same. Under these milder conditions, we could identify the intermediate that was gradually converted to phenanthrene **2a**. The identity of this intermediate was revealed to be a nonaromatized intermediate **4a**.[12] Heating of the isolated **4a** in 1,2-DCE at 80 °C for 1 h in the presence of $InCl_3$ resulted in the aromatized product **2a**, while performing the same reaction without the $InCl_3$ did not yield **2a**. The identification of intermediate **4a** strengthened our mechanistic hypothesis that the phenanthrene framework was formed from *o*-propargylbiaryl substrates via 6-*exo*-*dig* intramolecular hydroarylation and subsequent *exo*-*endo* double bond migration as shown in Scheme 2.

Another possible mechanistic path via an allene intermediate **5a** (Scheme 2) was considered.[13] However, this

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(9) For selected examples of 6-*exo*-*dig*/7-*endo*-*dig* cyclization, see: (a) Girard, A.-L.; Enomoto, T.; Yokouchi, S.; Tsukano, C.; Takemoto, Y. *Chem. Asian J.* **2011**, *6*, 1321. (b) Ramana, C. V.; Induvadana, B.; Srinivas, B.; Yadagiri, K.; Deshmukh, M. N.; Gonnade, R. G. *Tetrahedron* **2009**, *65*, 9819. (c) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907.

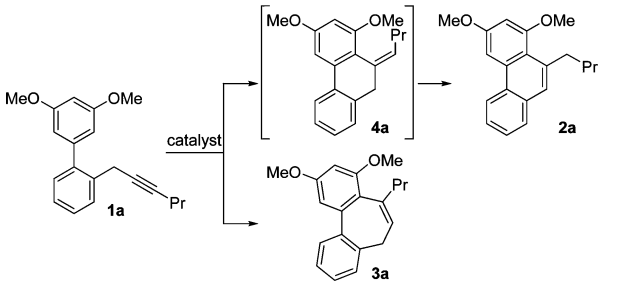
(10) Iluminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(11) See the Supporting Information for synthesis details.

(12) The mixture was virtually inseparable by thin-layer chromatography. The separation was achieved by HPLC.

(13) For recent examples of allene-mediated construction of phenanthrenes from the propargylic substrates, see: (a) Saifuddin, M.; Agarwal, P. K.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10122. (b) Spencer, W. T.; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 7730.

Table 1. Screening of the Transition-Metal Catalysts for the Cycloisomerization of Substrate **1a**



entry	catalyst (10 mol %)	solvent	temp (°C)	time (h)	**2a**:**3a**[a]	yield[b] (%)
1	$PtCl_2$	toluene	80	40	74:26	23 (38)
2	$PtCl_4$	toluene	80	40	80:20	32 (60)
3	$GaCl_3$	toluene	80	6	82:18	86
4	$InCl_3$	toluene	80	1	>99:1	91
5	$InBr_3$	toluene	80	1	>99:1	89
6	$InCl_3$	1,2-DCE	80	1	>99:1	94
7	$InCl_3$	1,2-DCE/H_2O[c]	80	3	>99:1	91
8	$InCl_3$[d]	toluene	80	6	>99:1	89
9	$InCl_3$	1,2-DCE	50	4	>99:1	91

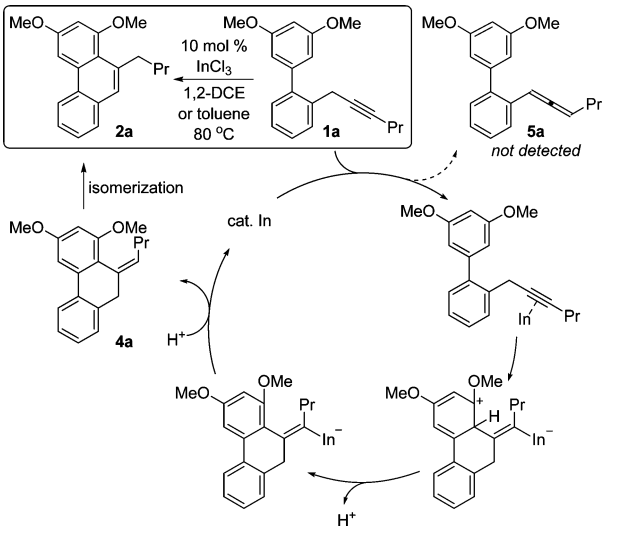
[a] Determined by ^1H NMR analysis. [b] Isolated yield of the mixture of **2a** and **3a**. The values in parentheses indicate the yield of recovered starting material. [c] Ratio of 1,2-DCE/H_2O = 10:1. [d] Using 5 mol % of catalyst.

pathway is less likely because such an intermediate was not detected when the reaction of **1a** was analyzed. In addition, the In(III) catalyzed reaction of *o*-propargylbiaryl substrate **6e** (vide infra), which is less reactive in hydroarylation than **1a**, resulted in nearly quantitative recovery of the starting material under the reaction conditions described in entry 6 of Table 1. This result again implies that the alkyne−allene isomerization is not feasible under the above conditions and that an allene intermediate is not involved in the mechanism.[14] Furthermore, our experiments with allene **5a**[11] gave rise to different reaction outcomes when compared to those with **1a**. For example, the *exo*-double bond intermediate **4a** was not observed when **5a** was subjected to the mild conditions used in entry 8. Phenanthrene product **2a** was formed from allene **5a** under the conditions stated in entry 6. However, the yield (71%) and conversion rate (4 h) were lower compared with those from the propargylic substrate **1a**. These results also support our mechanistic rationale that an allene intermediate is not involved.

Encouraged by the remarkable results of In(III)-mediated cycloisomerization of **1a**, we next investigated analogous propargylbiaryls having a functionalized alkyne group. The results are summarized in Scheme 3. Remarkably, all compounds investigated showed an exclusive preference for the 6-*exo*-*dig* hydroarylation over the conceivable 7-*endo* mode. Under the conditions described in entry 6 (Table 1) (10 mol % of $InCl_3$, 1,2-DCE, 80 °C),

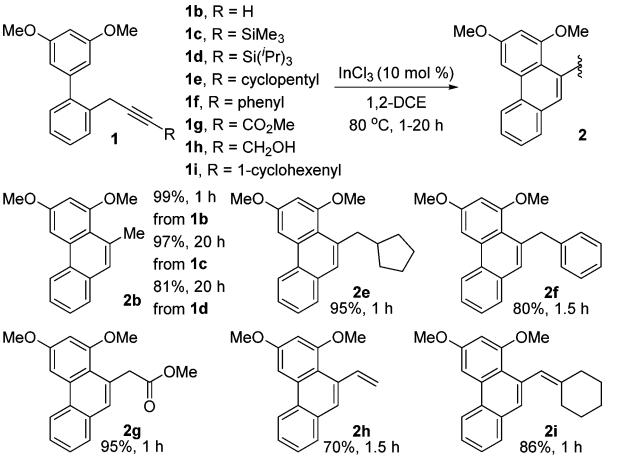
(14) The alkyne−allene isomerization occurs generally under the catalysis of base. The acid-catalyzed isomerization is rare.

Scheme 2. Plausible Mechanism for the Cycloisomerization of *o*-Propargylbiaryl



terminal alkyne **1b** underwent smooth cycloisomerization to afford the desired phenanthrene **2b** in nearly quantitative yield. The silyl-substituted alkynes, **1c** and **1d**, afforded the same product **2b** also in excellent yield. This product was presumably formed via a protodesilylation of the initially generated vinylsilane intermediate.[15] The reaction of alkyne **1e** bearing a secondary alkyl group produced the corresponding product in high yield. The aryl-substituted alkyne **1f** readily produced **2f** in 80% yield. Substrate **1g** containing an electron-withdrawing ester group afforded the cyclization product **2g** in nearly quantitative yield. Interestingly, the reaction of propargyl alcohol **1h** did not afford the expected alcoholic product, but instead resulted in the formation of the dehydrated olefinic product **2h** in 70% yield. The cycloisomerization of olefin-substituted alkyne **1i** resulted in the double-bond migration product **2i** in 86% yield, presumably via a [1,5] hydride shift.

Scheme 3. In(III)-Catalyzed Cycloisomerization

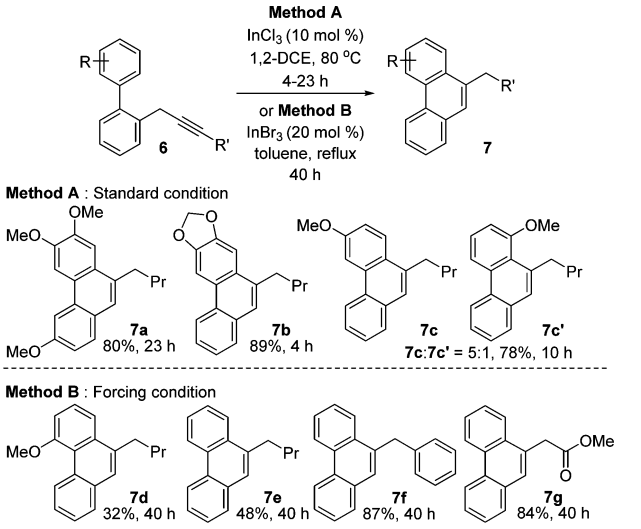


To further explore the reaction scope, the cycloisomerization chemistry has been extended to other biaryl systems (Scheme 4). In general, substrates bearing electron-donating groups on the upper ring of the biaryl backbone underwent effective 6-*exo*-*dig* carbocyclization to give phenanthrenes after isomerization. Under the standard conditions (10 mol % of $InCl_3$, 1,2-DCE, 80 °C, method A), the 3,4-dimethoxy- or 3,4-methylenedioxy-substituted substrates **6a** and **6b** smoothly afforded the corresponding phenanthrene products **7a** and **7b** in high yield. However, the reaction required longer time compared with that of the 3,5-dimethoxy substrate **1a**. The cycloisomerization of the 3-methoxy functionalized **6c** afforded a 5:1 regiochemical mixture of 6-*exo*-*dig* products **7c** and **7c′**, with more favorable cyclization to the less hindered position. Substrate **6d** with 2-methoxy group and substrate **6e** with unfunctionalized biaryl backbone failed to produce the desired phenanthrene products, under the standard reaction conditions. We hypothesize this result is because of the lower nucleophilicity of their aryl ring moieties. Most of the starting material was recovered unchanged. However, under the more forcing reaction conditions (20 mol % of $InBr_3$, toluene, reflux, method B), these substrates produced the corresponding products **7d** and **7e**, albeit in low yield. Interestingly, changing the propyl group of **6e** to an alkyne-activating group such as phenyl or ester group dramatically increased the yield (**7f** and **7g** vs **7e**).

In summary, the electrophile-promoted nucleophilic cyclization of *o*-propargylbiaryls was investigated as an alternative and selective path for synthesizing phenanthrenes. Environmentally benign In(III) efficiently induced the desired hydroarylation and subsequent double-bond migration. In the In(III)-catalyzed reactions, the complete regioselectivity of intramolecular hydroarylation for six- over seven-membered rings is noteworthy. Similar to the other electrophile-promoted hydroarylation reactions, the electron-rich biaryl substrates undergo hydroarylation more effectively. Unlike hydroarylation of *o*-alkynylbiaryl systems, diverse substituent groups are tolerated on the alkynyl carbon of *o*-propargylbiaryl system without affecting the regioselectivity. This efficient synthetic protocol for securing functionalized phenanthrenes might be applied to the synthesis of related heterocyclic series.

(15) The 1-(trialkylsilyl)acetylene systems were found to be stable under the conditions employed.

Scheme 4. Scope of Cycloisomerization of *o*-Propargylbiaryls



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Supporting Information Available. ^1H and ^{13}C NMR spectra of all new compounds and preparation of starting materials. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.