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Neodymium-catalyzed intramolecular alkyne-hydroarylation with arenes

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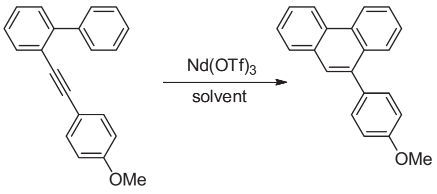
ABSTRACT

A $Nd(OTf)_3$-catalyzed alkyne-hydroarylation with arenes is reported. This reaction shows a wide range of functional group tolerance. Such a catalytic methodology enriches lanthanide element chemistry and provides a new route for synthesizing phenanthrene derivatives.

Phenanthrene and its derivatives are a class of important compounds in organic chemistry. A large portion of phenanthrenes have been found as natural products in plants belonging to the Orchidaceae, Betulaceae, and Combretaceae families.[1] Such biologically active natural products have been used to prepare antiviral,[2] anticancer,[3] antianxietic,[4] anti-HIV,[5] and Anti-inflammatory[6] agents. Apart from medical usage, they have also been widely applied in photoconducting, photochemical, electroluminescent, and fluorescent materials.[7] Numerous strategies have been developed for the synthesis of phenanthrenes.[8,9] However, most of these protocols are faced with low compatibility of functional groups or harsh reaction conditions. Lewis acid catalysis in this field has attracted much attention from organic chemists for its 100% atom economy and relatively mild reaction condition. Numerous achievements[10,11] have been reported, among which In,[11a] Hf,[11b] Pd,[11c] Fe,[11e] Rh,[11f] Au,[11g,k] Ag,[11h] and Ru[11i] showed nice catalytic activity in the hydroarylation of alkynes. Lanthanide elements have wide applications in organic chemistry owing to their relative abundance in nature and nontoxicity to environment. Those elements have predominarily one stable oxidation state (3 +) which is quite different from transition metals and main group metals. The trivalent lanthanide salts, like lanthanide triflates, generally show strong Lewis acidity and are insensitive to air and moisture, which is superior to main group metal and transition metal salts. To date, a series of transformations can be catalyzed by lanthanide Lewis acid,[12] such as hydroamination[13]

Table 1
Optimization of reaction conditions[a]



1a **2a**

Entry	Solvent	Temperature (°C)	$Nd(OTf)_3$ (mol %)	Time (h)	Yield (%)[b]
1	Ethyl acetate	rt	100	30	0 (99)[c]
2	Acetone	rt	100	30	0 (99)[c]
3	EtOH	rt	100	27	0 (99)[c]
4	CH_3CN	rt	100	30	8 (92)[c]
5	CH_2Cl_2	rt	100	12	92
6	CH_3NO_2	rt	100	9	95
7	CH_3NO_2	rt	20	24	3 (97)[c]
8	CH_3NO_2	115	20	3	99
9	CH_3NO_2	115	5	9	98
10[d]	CH_3NO_2	115	5	10	99 (99)[e]
11[d]	CH_3NO_2	115	0	10	0 (99)[c]

[a] The reaction of **1a** (0.2 mmol) and $Nd(OTf)_3$ in anhydrous solvent (5 mL) in a sealed tube was carried out at tested temperature under argon atmosphere.
[b] Yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as internal standard.
[c] Recovered yield of **1a**.
[d] **1a** (0.5 mmol) in anhydrous CH_3NO_2 (12.5 mL) was applied.
[e] Isolated yield of **2a**.

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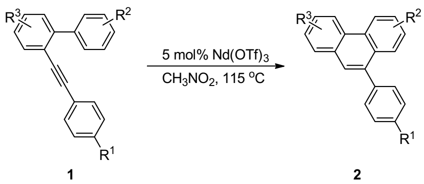
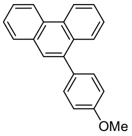
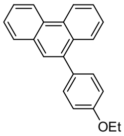
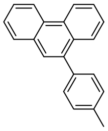
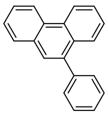
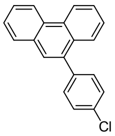
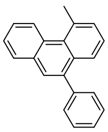
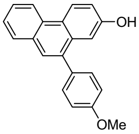
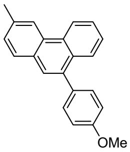
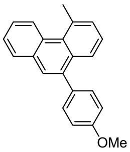
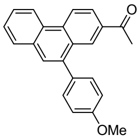
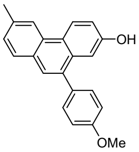
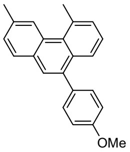
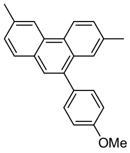
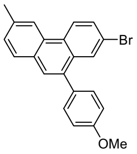
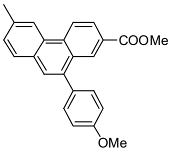
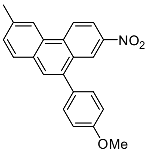
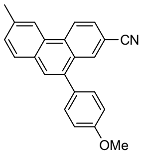
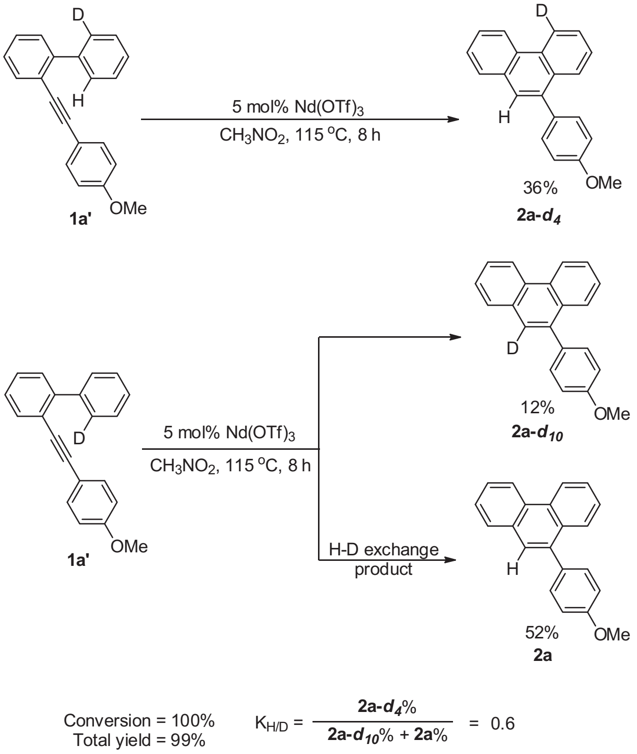
Table 2
Scope of this hydroarylation[a]



 **2a** 10 h, 99%	 **2b** 14 h, 75%	 **2c** 68 h, 45%
 **2d** 72 h, 57%	 **2e** 72 h, 22% (78%)[b]	 **2f** 47.5 h, 74%
 **2g** 26.5 h, 92%	 **2h** 13.3 h, 97%	 **2i** 14.5 h, 89%
 **2j** 37 h, 97%	 **2k** 27 h, 93%	 **2l** 16.5 h, 96%
 **2m** 17 h, 99%	 **2n** 16.5 h, 92%	 **2o** 37 h, 94%
 **2p** 35 h, 81%	 **2q** 44 h, 79%	

[a] All reactions were carried out using **1** (0.5 mmol) and $Nd(OTf)_3$ (0.025 mmol) in anhydrous CH_3NO_2 (12.5 mL) in a sealed tube at 115 °C under argon atmosphere. Isolated yield was reported.

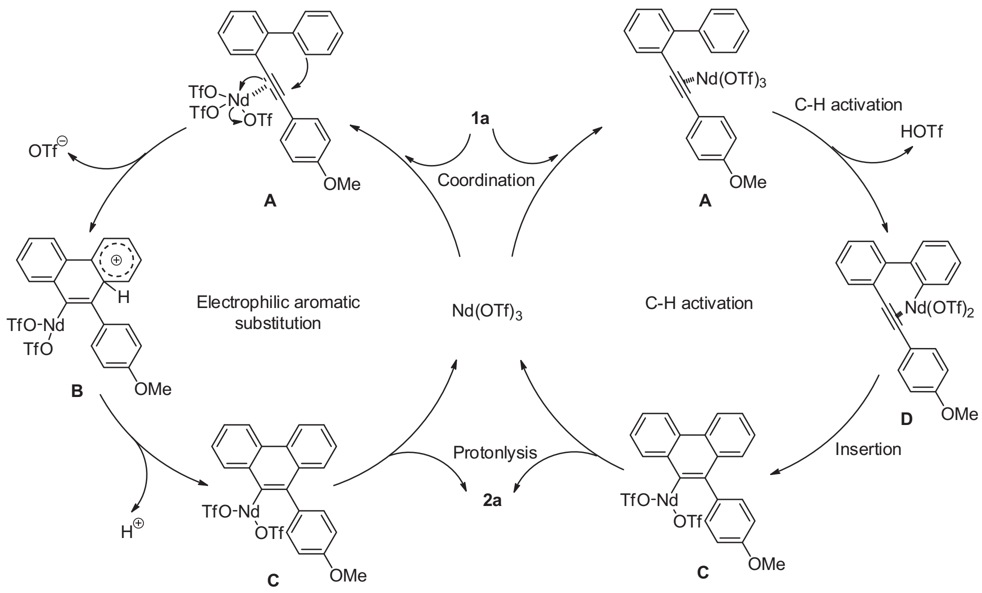
[b] Recovered yield of **2e**.



Scheme 1. Isotope experiment of deuterated 1a′ under standard condition.

and hydroalkoxylation.[14] However, lanthanide Lewis acid-catalyzed hydroarylation of alkynes remains unexplored. With regard to enriching the methodology, a deep investigation of the catalytic activity of lanthanide elements in this reaction is highly desired. Herein, we wish to report the $Nd(OTf)_3$-catalyzed intramolecular alkyne-hydroarylation with arenes. The reaction proceeded efficiently with catalytic amount of $Nd(OTf)_3$ and exhibited good functional group tolerance, providing a novel method for the synthesis of phenanthrenes.

The initial reaction was carried out at room temperature using 2-((4-methoxyphenyl)-ethynyl)-1,1′-biphenyl **1a** as the model substrate and 1 equiv of $Nd(OTf)_3$ as the catalyst. Disappointingly, reactions in ethyl acetate, acetone, or EtOH did not proceed at all (Table 1, entries 1–3). Fortunately, when the reaction was conducted in CH_3CN, an 8% NMR yield of the desired hydroarylation product **2a** was formed, although the conversion rate was very low (Table 1, entry 4). When CH_2Cl_2 or CH_3NO_2 was used as the solvent, we were delighted to see that the yield increased significantly (Table 1, entries 5 and 6). Considering that the highest yield and reaction speed were observed in CH_3NO_2 (Table 1, entry 6), CH_3NO_2 was chosen as the optimized solvent for this reaction. Next, we tried to decrease the catalyst loading. Unfortunately, the reaction with 20 mol% of $Nd(OTf)_3$ yielded only 3% of **2a** (Table 1, entry 7). Therefore, an elevated temperature was applied, which gave a 99% NMR yield of **2a** in the presence of 20 mol % of $Nd(OTf)_3$ at 115 °C (Table 1, entry 8). Further study indicated that 5 mol % of $Nd(OTf)_3$ was enough to catalyze this transformation, affording **2a** in nearly quantitative yield (Table 1, entry 9). Subsequently, we conducted the reaction at a larger scale, the reaction efficiency remained the same (Table 1, entry 10). Finally, the reaction at 115 °C without catalyst was tested. The fact that no reaction occurred demonstrated that $Nd(OTf)_3$ was indeed the catalyst for this reaction (Table 1, entry 11).



Scheme 2. Plausible mechanism for this reaction.

With the optimized reaction conditions in hand, we started to investigate the substrate scope (Table 2). In general, strong electron-donating groups were favored on R^1 position. Substrates bearing methoxy or ethoxy group gave their corresponding cyclized products in 99% or 75% isolated yields, respectively (**2a** and **2b**). The structure of **2** was determined by **2a** which is a known compound.[15] Substrates bearing a weak electron-donating group or H atom afforded the desired products in moderate yields (**2c** and **2d**). While for substrates with electron-withdrawing groups, the reaction speed was very low, affording phenanthrene derivative **2e** in only a 22% isolated yield after 72 h. The above data clearly indicated that electron-withdrawing R^1 group would reduce the reaction speed, which might be due to the lower coordination ability of electron deficient alkyne moiety. When R^2 was 2-methyl, the reaction proceeded smoothly to produce **2f** in a 74% yield. Then a series of disubstituted substrates were applied in this reaction (**2g**–**2j**). Strong electron-donating groups, like hydroxyl, could be well tolerated, affording the corresponding product **2g** in a 92% yield. Weak electron-donating substrates could also be efficiently converted to their corresponding products (**2h** and **2i**). Notably, the reaction of reactants with strong electron-withdrawing groups, like acetyl, could proceed smoothly, generating the phenanthrene derivative **2j** in an excellent yield. Subsequently, several trisubstituted substrates were also applied in this reaction (**2k**–**2q**). It was worthy to note that many functional groups, such as hydroxyl, bromo, methoxycarbonyl, nitro, and cyano, could be well tolerated, yielding trisubstituted phenanthrenes in good to excellent yields (**2k**, **2n**, **2o**, **2p**, and **2q**). Furthermore, the fact that electron-donating R^2 groups could accelerate the reaction speed might suggest a Friedel–Craft mechanism (vide infra).

To gain an insight into the reaction mechanism, a deuterated model substrate **1a**′ was synthesized and applied under the standard condition. After full conversion, a quantitative total yield of the desired products was obtained. Careful exploration of ^1H NMR spectra (see Page S44 in Supplementary data) of the product mixtures demonstrated that **2a** was formed in a 52% yield, which meant that 52% of deuterium was missing during the whole transformation. The fact that the *ortho*-hydrogen was scrambled usually indicates significant C–H activation by a metal species, which has been observed in other types of rare earth metal-catalyzed C–H addition reactions.[16] Considered that the solvent CH_3NO_2 was the only hydrogen source, we assumed that there might be some H-D exchange with CH_3NO_2. As shown in Scheme 1, the kinetic constant $K_{H/D}$ was found to be 0.6. This value clearly indicated a secondary, inverse kinetic isotope effect, which meant that C–H activation was not involved in the rate-determining step.[17]

Based on the above experimental evidence, two reaction pathways, electrophilic aromatic substitution (EAS)[18] and C–H activation,[19] are depicted as shown in Scheme 2. For the EAS reaction pathway, the electrophilic $Nd(OTf)_3$ initiates the reaction by coordination with the alkyne, where the coordination of $Nd(OTf)_3$ with alkyne renders the increased electrophilicity of alkyne. The following intramolecular 6-endo-dig electrophilic addition results in the Wheland intermediate **B** which will generate the vinylneodymium intermediate **C** via deprotonation. Finally, protonlysis of **C** yields the phenanthrene product and regenerates the catalyst. For the C–H activation reaction pathway, four key steps are involved. (i) coordination of $Nd(OTf)_3$ with alkyne to afford (Nd-alkyne) complex **A**, (ii) C–H activation to form arylneodymium intermediate **D**, (iii) insertion of C–C triple bond into C–Nd bond to yield the vinylneodymium intermediate **C**, and (iv) protonlysis of **C** to give the product and regenerate the catalyst.

In conclusion, we have investigated lanthanide element Lewis acid $Nd(OTf)_3$-catalyzed intramolecular alkyne-hydroarylation with arenes. The reaction yielded a series of phenanthrene derivatives in good to excellent yields. A lot of functional groups were tolerated in this reaction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.053.

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