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Metal-free cycloisomerizations of *o*-alkynylbiaryls†

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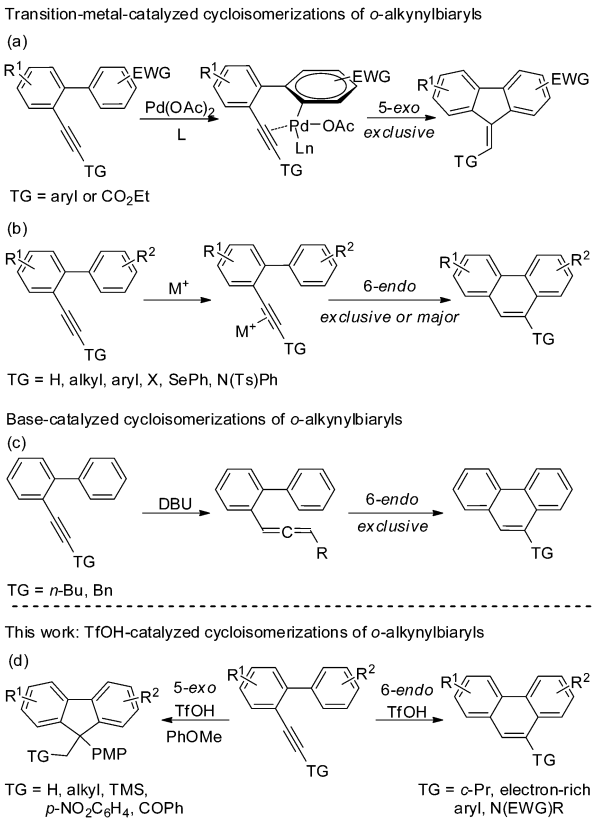
We describe a novel and highly efficient metal-free strategy to construct 9,9-disubstituted fluorenes and phenanthrenes *via* the TfOH-catalyzed cycloisomerizations of *o*-alkynylbiaryls. Notably, the significant effects of the electronic properties and steric hindrance of the alkyne terminus on the reaction selectivity have been observed.

The cycloisomerization of *o*-alkynylbiaryls is a powerful tool for the construction of fused five- and six-membered ring systems. Although the thermal cycloisomerization of *o*-ethynylbiphenyl provides a straightforward access to phenanthrene, this method suffers from high reaction temperature (700 °C) and a tedious isolation procedure caused by the benzazulene byproduct.[1] Therefore, transition-metal catalysts have been sought to promote the cycloisomerization of *o*-alkynylbiaryls under mild conditions. Palladium-catalyzed exclusive 5-*exo*-*dig* cyclization of *o*-alkynylbiaryls possessing aryl or ethoxycarbonyl terminal groups on the alkyne moiety (TG = aryl or CO_2Et) was first reported by Gevorgyan and co-workers (Scheme 1a),[2] but this cyclization preferred electron-deficient substrates and no other new methods about 5-*exo*-*dig* cyclization of *o*-alkynylbiaryls have been developed.

In striking contrast, the transition-metal-catalyzed exclusive or predominant 6-*endo*-*dig* cycloisomerization of *o*-alkynylbiaryls possessing electron-rich aryl rings (R^2 = electron-donating groups) was first demonstrated by Fürstner *et al.* (Scheme 1b).[3] Since the pioneering report from Fürstner's group, this method has been extensively applied to the syntheses of polyaromatic molecules,[4–6] natural products, and bioactive molecules.[7] Meanwhile, since the electron-deficient *o*-alkynylbiaryls are essentially incompatible with the reaction conditions, and the cyclization of unsymmetrically substituted substrates suffers from poor regioselectivity, new methods have been developed to solve these limitations (Scheme 1b). For instance, $Fe(OTf)_3$-catalyzed 6-*endo*-*dig* cyclization of electron-deficient biarylalkynes has been achieved, even though the alkyne moiety is limited to those possessing a



Scheme 1 Cycloisomerizations of *o*-alkynylbiphenyls.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, crystallographic data in CIF and NMR spectra. CCDC 1847362 (**7ee**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc05484c

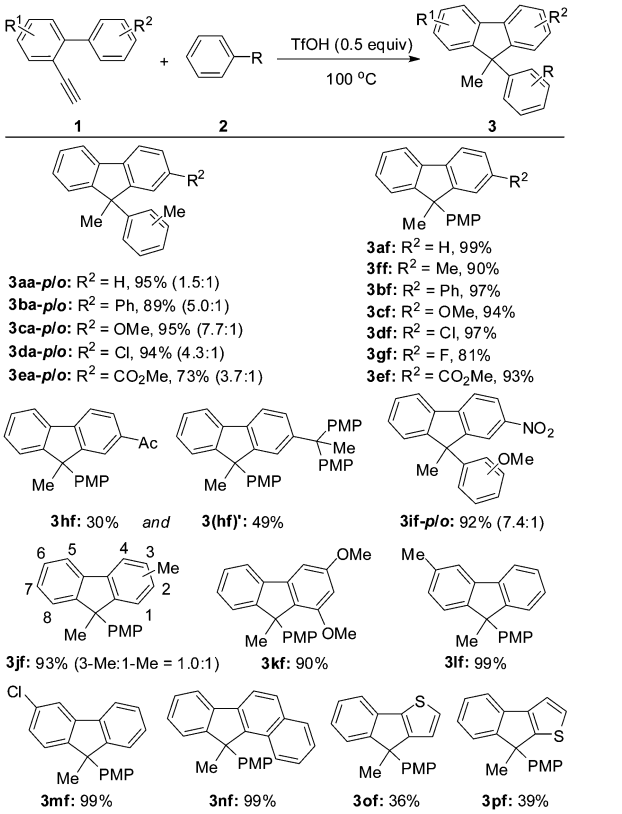
phenyl terminal (TG = Ph).[8] $In(OTf)_3$ or AuCl(IPr)/$AgSbF_6$-catalyzed 6-*endo-dig* cyclization of biarylalkynes possessing a phenylselenyl terminal (TG = SePh) was successfully performed irrespective of the substitution pattern on the aryl rings involved in the C–C bond formation.[9] Furthermore, Pt(II), Au(I), or Ru(II)-catalyzed 6-*endo-dig* cyclizations of diverse *o*-ethynylbiaryls were described.[10] And it was mentioned that the selectivity and efficiency for the cycloisomerization of *o*-alkynylbiaryls should be controlled by the judicious choice of neutral/cationic metal–ligand combinations.[10c]

In regard to the metal-free cycloisomerization of *o*-alkynylbiphenyls,[11,12] to the best of our knowledge, only one strategy has been realized *via* the DBU-catalyzed 6-*endo-dig* cyclization of *o*-alkynylbiphenyls possessing *n*-butyl or benzyl terminal (TG = *n*-Bu or Bn). However, this protocol is limited to the alkyl terminal groups on the alkyne moiety since the cyclization proceeds *via* an allene intermediate (Scheme 1c).[12] Herein, a metal-free exclusive 5-*exo-dig* cycloisomerization of *o*-ethynylbiaryls for efficient synthesis of 9,9-disubstituted fluorenes is described. Further study on the cyclization of the terminally substituted *o*-alkynylalkynes was achieved, and we found that the reaction selectivity is controlled by the properties of the terminal groups on the alkyne moiety. Furthermore, the metal-free intramolecular cyclization in a 6-*endo* mode enables highly selective and orthogonal access to phenanthrenes as well (Scheme 1d).

We initiated our investigation by the reaction of *o*-ethynylbiphenyl **1a** in various solvents under the catalyst TfOH. After condition optimization (see ESI† for details), the scope and generality of this cyclization have been assessed (Table 1). It was found that a variety of *o*-ethynylbiaryls **1** bearing electron-neutral, electron-deficient, and even more surprisingly electron-rich aryl rings, underwent highly effective 5-*exo-dig* cyclization to give 9,9-disubstituted fluorenes **3aa–nf** in good to excellent yields. Various groups, such as OMe, Cl, F, CO_2Me, Ac, and NO_2, were perfectly tolerated under the reaction conditions. Although the cyclizations of *o*-ethynylbiaryls **1** with toluene **2a** exhibited not high regioselectivity (**3aa–ea**), significant effects of the nature of R^2 on *o*-ethynylbiaryl **1** have been observed. The regioselectivity could be improved by increasing steric or electron-donating effect of R^2. Remarkably, cyclization of all *o*-ethynylbiaryls **1a–n** with anisole **2f** proceeded with high *para*-selectivity, merely providing PMP-substituted fluorenes, except that the nitro-substituted *o*-ethynylbiaryl **1i** (R^2 = NO_2) delivered small amount of *o*-methoxyphenyl-substituted fluorene **3if–*o***. It should be noted that, besides the fluorene **3hf**, the reaction of acetyl-substituted *o*-ethynylbiaryl **1h** (R^2 = Ac) afforded the product **3(hf)′** due to the carbonyl group further taking part in the Friedel–Crafts alkylation reaction. It was noteworthy that *o*-ethynylbiaryls having 2-thienyl and 3-thienyl groups were compatible with the reaction conditions, leading to the desired geometrically pure fluorenes **3of** and **3pf**.

Subsequently, we assessed how terminally substituted biarylalkynes **5** behave under the reaction conditions (Table 2). Alkyl-terminated biarylalkynes **5a–e** proceeded smoothly to give the 5-*exo-dig* cyclization products **6a–e** in excellent yields even for the bulkier *n*-hexyl- and benzyl-substituted biarylalkynes.

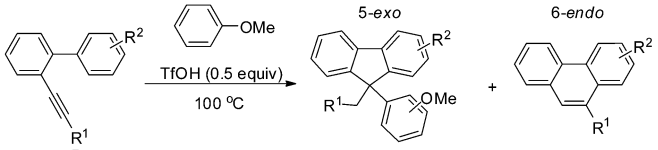
Table 1 Cycloisomerization of *o*-ethynylbiaryls[a,b]



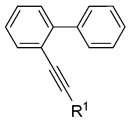
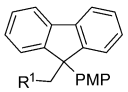
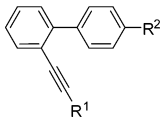
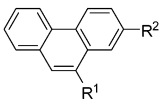
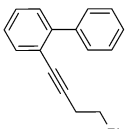
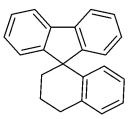
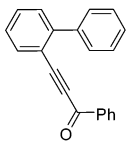
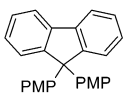
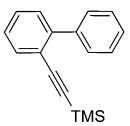
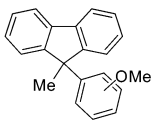
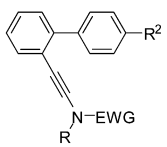
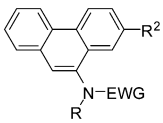
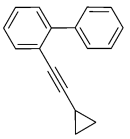
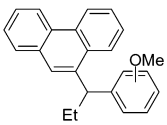
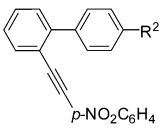
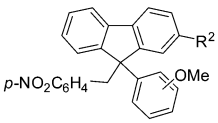
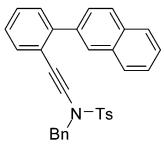
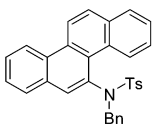
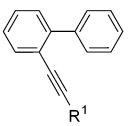
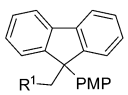
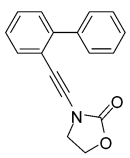
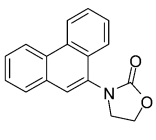
[a] Reactions were carried out using **1** (0.20 mmol) and **2** (0.50 mL) with TfOH (0.10 mmol) at 100 °C. [b] Isolated yields.

And even more surprisingly, the phenethyl-terminated biarylalkyne **5f** efficiently provided a spirocyclic product **6f′**, which may be formed *via* a Friedel–Crafts cyclization of **5f** followed by an intramolecular Friedel–Crafts alkylation reaction. Biarylalkyne **5g** possessing a trimethylsilyl terminal worked well, affording the desilication product fluorene **6g** in high yield, albeit with poor diastereoselectivity. And we were especially excited by the discovery that the biarylalkyne **5h** bearing a cyclopropyl terminal underwent selective 6-*endo-dig* cycloisomerization followed by an intermolecular Friedel–Crafts alkylation reaction, leading to phenanthrene **7h** in excellent yield with moderate diastereoselectivity. Subsequently, various aryl-terminated biarylalkynes **5i–s** were tested and reacted smoothly with almost quantitative conversion. Meanwhile significant effects on the reaction selectivity were observed. The transformation of the reaction selectivity from 5-*exo-dig* to 6-*endo-dig* cyclization is most likely due to the increasing electron-donating property (**5p–s** *vs.* **5i–n**) and steric hindrance (**5o** *vs.* **5m**) of the terminal groups on the alkyne moiety. Once again the interesting phenomenon has occurred, just as the nitro-substituted *o*-ethynylbiaryl **1i**, the nitro-substituted biarylalkynes **5i** and **5j** (R^1 = *p*-$NO_2C_6H_4$) resulted small amount of *o*-methoxyphenyl-substituted fluorenes **6i–*o*** and **6j–*o***, and the 5-*exo-dig* cyclization of the other biarylalkynes with anisole proceeded with high *para*-selectivity, merely providing PMP-substituted fluorenes. In order to better verify the effect of the

Table 2 Cycloisomerization of terminally substituted *o*-alkynylbiaryls

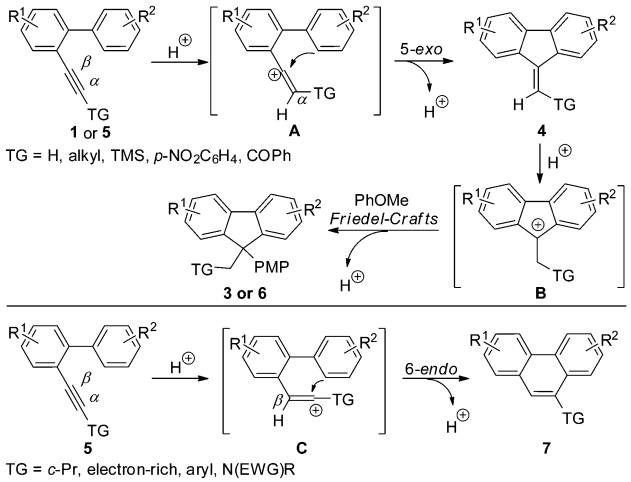


5 **6** **7**

Entry[a]	Alkyne	Product[b]	Entry[a]	Alkyne	Product[b]
1	 **5a** (R^1 = Me) **5b** (R^1 = *n*-Pr) **5c** (R^1 = *n*-hex) **5d** (R^1 = Bn) **5e** (R^1 = $(CH_2)_3Ph$)	 **6a:** 99% **6b:** 99% **6c:** 94% **6d:** 99% **6e:** 96%	7	 **5o** (R^1 = *o*-PhC_6H_4, R^2 = H) **5p** (R^1 = *p*-MeC_6H_4, R^2 = H) **5q** (R^1 = *p*-$MeOC_6H_4$, R^2 = H) **5r** (R^1 = 2-thienyl, R^2 = H) **5s** (R^1 = *p*-$MeOC_6H_4$, R^2 = OMe)	 **7o:** 99% **7p:** 99% **7q:** 99% **7r:** 98% **7s:** 95%
2	 **5f**	 **6f′:** 95%	8	 **5t**	 **6t′:** 81%
3	 **5g**	 **6g-*p*/*o*:** 90% (2.1:1)	9[c]	 **5u** (EWG = Ts, R = Bn, R^2 = H) **5v** (EWG = Mbs, R = Bn, R^2 = H) **5w** (EWG = Cs, R = Bn, R^2 = H) **5x** (EWG = Ns, R = Bn, R^2 = H) **5y** (EWG = Ts, R = Me, R^2 = H) **5z** (EWG = Ts, R = Ph, R^2 = H) **5aa** (EWG = Ts, R = , R^2 = H) **5bb** (EWG = Ts, R = Bn, R^2 = Me) **5cc** (EWG = Ts, R = Bn, R^2 = CO_2Me) **5dd** (EWG = Ts, R = Bn, R^2 = Ac)	 **7u:** 98% **7v:** 82% **7w:** 97% **7x:** 96% **7y:** 96% **7z:** 91% **7aa:** 94% **7bb:** 97% **7cc:** 92% **7dd:** 91%
4	 **5h**	 **7h-*p*/*o*:** 95% (4.9:1)			
5	 **5i** (R^2 = H) **5j** (R^2 = OMe)	 **6i-*p*/*o*:** 99% (6:1) **6j-*p*/*o*:** 93% (5:1)	10[c]	 **5ee**	 **7ee:** 95%
6	 **5k** (R^1 = *p*-FC_6H_4) **5l** (R^1 = *p*-ClC_6H_4) **5m** (R^1 = *p*-PhC_6H_4) **5n** (R^1 = Ph)	 **6k:** 22% **6l:** 37% **6m:** 23% **6n:** 33%	11[c]	 **5ff**	 **7ff:** 99%

[a] Unless otherwise noted, reactions were carried out using **5** (0.20 mmol) with TfOH (0.10 mmol) in anisole (0.50 mL) at 100 °C. [b] Isolated yields. [c] Reactions were carried out using **5** (0.20 mmol) with TfOH (0.10 mmol) in CH_2Cl_2 (0.50 mL) at rt except for the synthesis of **7u** using anisole as solvent. TMS = trimethylsilyl.

electronic properties of the terminal groups (**5**, R^1) on the reaction selectivity, we turned our attention to the cycloisomerization of benzoyl-terminated biarylalkyne and biarylynamides. As our proposed, due to the electron-withdrawing effect of the benzoyl group, biarylalkyne **5t** (R^1 = Bz) gave the cyclization product fluorene **6t′** with high yield, which was probably formed *via* a 5-*exo-dig* cyclization of **5t** followed by an inverse aldol reaction and intermolecular Friedel–Crafts alkylation reaction with anisole. On the contrary, due to the electron-donating effect of the nitrogen lone pair, all of the biarylynamides underwent highly effective 6-*endo-dig* cyclization to give 9-aminophenanthrenes with good to excellent yields. Various biarylynamides bearing electron-withdrawing, and electron-donating sulfonyl systems, were compatible with the



Scheme 2 Proposed mechanisms for the cycloisomerizations.

reaction conditions giving high yields of the desired aminophenanthrenes (**7u–x**). Other *N*-alkyl, aryl-, and alkenyl-substituted biarylynamides also afforded the cyclization products (**7y–aa**) with excellent yields even for the bulkier phenyl-substituted biarylynamide **5z**. It is worth mentioning that diverse biarylynamides **5bb–5ee** underwent the 6-*endo-dig* cycloisomerization smoothly irrespective of the substitution pattern on the aryl rings. Notably, the cycloisomerization of unsymmetrically substituted biarylynamide **5ee** shows high regioselectivity, merely providing aminophenanthrene **7ee** with 95% yield. And we were also pleased to find that the oxazinanone-substituted biarylynamide **5ff** underwent highly effective cyclization to give aminophenanthrene **7ff** in almost quantitative yield.

Calculations on this cycloisomerizations (see the ESI†) mapped out the mechanisms in Scheme 2. The cycloisomerizations are initiated by the formation of acetylene-cation **A** or **C**. For the *o*-ethynylbiaryl **1** or *o*-alkynylbiaryl **5** possessing electron-withdrawing terminal groups, the preferred electrophilic attack of α carbon by the proton from catalyst TfOH gives **A**, which is intercepted by the adjacent aromatic ring, a C–C bond formation with concomitant release of the catalyst ensues to form **4**. A subsequent Friedel–Crafts reaction of **4** *via* the carbocation **B** furnishes the final product **3** or **6**; on the contrary, for the *o*-alkynylbiaryl **5** possessing electron-donating or bulky terminal groups, the preferred electrophilic attack of β carbon by the proton gives **C**, which is intercepted by the adjacent aromatic ring with concomitant release of the catalyst affording phenanthrene **7**.

In conclusion, we have demonstrated the first example of metal-free exclusive 5-*exo-dig* cycloisomerization of *o*-ethynylbiaryls, and this method allows for efficient cyclization of a variety *o*-ethynylbiaryls possessing electron-neutral, electron-rich, and electron-deficient aryl rings into the corresponding fluorenes. Further study on this metal-free cycloisomerization of the terminally substituted biarylalkynes was achieved, and the significant effects of the alkyne terminus on the reaction selectivity have been observed for the first time. Furthermore, the metal-free intramolecular cyclization in a 6-*endo* mode enables highly selective and orthogonal access to phenanthrenes as well. We believe that these simple yet powerful cycloisomerizations will be eagerly adopted into the repertoire of synthetic chemistry.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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