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Selective Synthesis of Phenanthrenes and Dihydrophenanthrenes via Gold-Catalyzed Cycloisomerization of Biphenyl Embedded Trienynes

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Supporting Information Placeholder
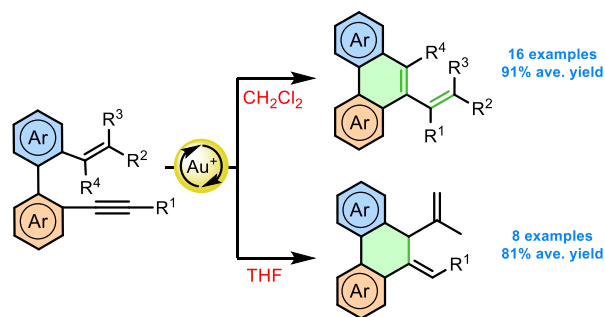
ABSTRACT: Readily available *o´*-alkenyl-*o*-alkynylbiaryls, a particular type of 1,7-enynes, undergo a selective cycloisomerization reaction in the presence of a gold(I) catalyst to give interesting phenanthrene and dihydrophenanthrene derivatives in high yields. The solvent used provokes a switch in the evolution of the gold intermediate and plays a key role in the reaction outcome.

Phenanthrenes and their dihydro derivatives have attracted considerable attention due to their widespread occurrence in natural products and pharmaceuticals with biological activities, which have led to their application in the treatment of microbial or viral infections, allergies, cancer or malaria.[1] Moreover, phenanthrenes, which are small polycyclic aromatic hydrocarbons (PAHs),[2] also exhibit outstanding electrochemical and photophysical properties with wide-ranging applications in organic optical and electronic materials.[3] As a consequence, intensive efforts to construct phenanthrene skeletons with different substitution patterns have been made. The methods described include: oxidative alkene-arene or arene-arene couplings in vinyl biaryls and stilbenes;[4] intramolecular McMurry coupling of suitable 2,2'-disubstituted biaryls or related carbonyl or olefin metathesis and carbene dimerizations;[5] aryne annulations;[6] metal- or visible light-induced intermolecular cyclizations of *ortho*-functionalized biaryl derivatives with acetylenes;[7] metal-catalyzed sequential Csp^2-Csp^2 bond-forming reactions;[8] and electrophilic cycloisomerizations of *ortho*-alkynylbiaryls.[9] However, these methods require harsh reaction conditions, densely functionalized starting materials, multistep routes and/or display limited substrate scope and tolerance to functionalities. In addition, procedures to access non-symmetric and/or selectively substituted phenanthrenes are scarce. As such, the development of efficient methodologies to synthesize phenanthrenes, or their derivatives, with selective substitution is highly desirable.

Scheme 1. Regioselective synthesis of phenanthrenes by cycloisomerization of *o*-alkynylbiaryls

a) Cycloisomerization of *o*-alkynylbiaryls
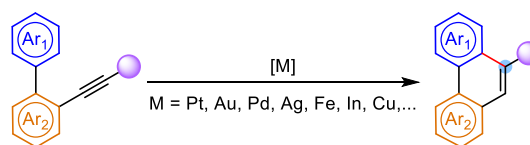
b) This work: cycloisomerization of *o'*-alkenyl-*o*-alkynylbiaryls
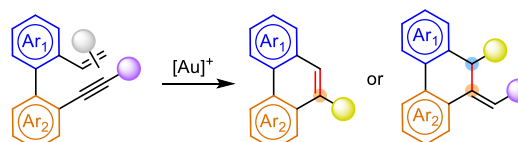
In these regard, metal-catalyzed 6-*endo* carbocyclizations of biaryls bearing an internal alkyne, which is a general and straightforward route to furnish the phenanthrene core, regioselectively afford

phenanthrenes substituted at the carbon next to the arene that acts as a nucleophile (Ar$_1$) in the catalytic process (Scheme 1a).[9] Herein, we describe that, in the presence of cationic gold(I) catalysts,[10] related o'-alkenyl-o-alkynylbiaryls, a particular type of 1,7-enynes,[11] selectively react to produce phenanthrenes substituted at the carbon bonded to the arene (Ar$_2$) originally linked to the triple bond (Scheme 1b). Thus, the catalytic method developed provides a complementary synthetic strategy to the most common one depicted in Scheme 1a that differs in the substitution pattern at the internal cycle of the phenanthrene skeleton constructed. Moreover, upon careful selection of the appropriate reaction conditions, mainly the solvent, unsymmetrically (9,10)-disubstitued dihydrophenanthrenes can also be prepared from the same starting 1,3,5-trien-7-ynes (Scheme 1b).

Based on our experience in the electrophilic cycloisomerization of ortho-alkynylstyrenes,[12] we selected 2-(2-methylprop-1-en-1-yl)-2'-(phenylethynyl)-1,1'-biphenyl (**1a**) as model for assessing the reactivity in the presence of gold catalysts. This substrate possesses two nucleophilic entities—an arene and the olefin—in suitable locations to react with the alkyne that would render different cycloadducts. However, we envisioned that the high substitution of the alkene would facilitate its selective 6-exo nucleophilic addition to the metal-activated acetylene, thus furnishing the desired phenanthrene skeleton. At the outset, several gold-derived complexes as catalysts, and different solvents, were studied, and the most significant results are summarized in Table 1.

Table 1. Optimization of reaction conditions[a]
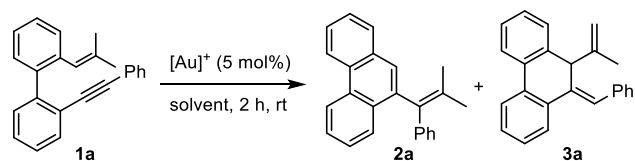
entry	[Au]$^+$	solvent	product	conv. (%)[b]
1	PPh$_3$AuNTf$_2$	CH$_2$Cl$_2$	**2a**	100 (94)
2	PPh$_3$AuNTf$_2$	toluene	**2a**	70[c]
3[d]	PPh$_3$AuNTf$_2$	THF	**3a**	100 (79)
4	ArO$_3$PAuCl/AgNTf$_2$[e]	CH$_2$Cl$_2$	**2a**	100[c]
5	tBu$_3$PAuNTf$_2$	CH$_2$Cl$_2$	**2a**	80
6	XPhosAuNTf$_2$	CH$_2$Cl$_2$	**2a**	100 (98)
7	JohnPhosAu(MeCN)SbF$_6$	CH$_2$Cl$_2$	**2a**	100 (99)
8	IPrAuCl/AgNTf$_2$	CH$_2$Cl$_2$	**2a**	100 (97)
9	AuCl$_3$	CH$_2$Cl$_2$	**2a**	100 (98)
10[f]	JohnPhosAu(MeCN)SbF$_6$	CH$_2$Cl$_2$	**2a**	100 (99)[g]

[a] Reactions conducted using 0.05 mmol of **1a** in 1 mL of solvent at 25 °C for 2 h. [b] Conversion estimated by ^{1}H NMR spectroscopy (300 Hz); isolated yield in brackets for an experiment conducted with 0.2 mmol of **1a**. <5% of **3a** was detected. [c] Significant amounts of **3a** and other unidentified products were observed. [d] Conducted for 72 h. [e] Ar = 2,4-(tBu)$_2$C$_6$H$_3$. [f] Conducted with 1.0 mol% of catalyst. [g] Same isolated yield was obtained in an experiment conducted with 1.0 mmol of **1a**.

The reaction of **1a** in the presence of 5 mol% AuPPh$_3$NTf$_2$ as catalyst in dichloromethane at room temperature selectively afforded the 9-substituted phenanthrene **2a** in less than 2 h (entry 1). Remarkably, the competitive pathway resulting from addition of the arene to the alkyne, which would produce the corresponding regioisomeric phenanthrene, described in Scheme 1a, was not detected. Encouraged by this initial result, the influence of the solvent on the

cycloisomerization of **1a** was explored. Thus, the reaction conducted in toluene also gave **2a** as the major product, albeit with lower conversion and selectivity (entry 2). From that crude mixture, the formation of a disubstituted 9,10-dihydrophenanthrene **3a** was determined. Interestingly, a complete switch in the regioselectivity occurred when THF was employed as solvent and the reaction was conducted for an extended reaction time (72 h). Thus, under these conditions, dihydrophenanthrene **3a** could be selectively obtained in good yield (entry 3). Analogous experiments in THF varying the gold catalyst gave varying mixtures of **2a**, **3a** and other unidentified products, whereas no evolution was observed in other solvents such as acetonitrile or DMF.[13]

The minimal influence of the nature of the cationic gold(I) complex was determined from the outcome of the reactions conducted in DCM. Thus, phenanthrene **2a** was obtained exclusively from model substrate **1a** in quantitative yields with most of the catalysts tested, including less active gold(III) salts such as AuCl$_3$ (entries 4−9). Of these gold complexes, JohnPhosAu(MeCN)SbF$_6$ exhibited a slightly improved selectivity and no traces of the regioisomeric cycloadduct **3a** could be detected. Moreover, different temperatures or concentrations resulted in a higher percentage of by-products, whereas a limited screening with silver salts showed no beneficial effect or improvement in this process.[13] Finally, lowering the catalyst loading to 1 mol% or scaling the reaction to 1 mmol had no impact on either the yield or the reaction time (entry 10). In summary, an appropriate choice of catalyst and solvent allows the selective formation of phenanthrene **2a** (entry 10) and dihydrophenanthrene **3a** (entry 3).

With these results in hand, and based on previous studies in the cycloisomerization of 1,n-enynes,[10,11c,12,14] we propose the following mechanism that accounts for the formation of both phenanthrene derivatives **2a** and **3a** (Scheme 2).

Scheme 2. Proposed mechanism
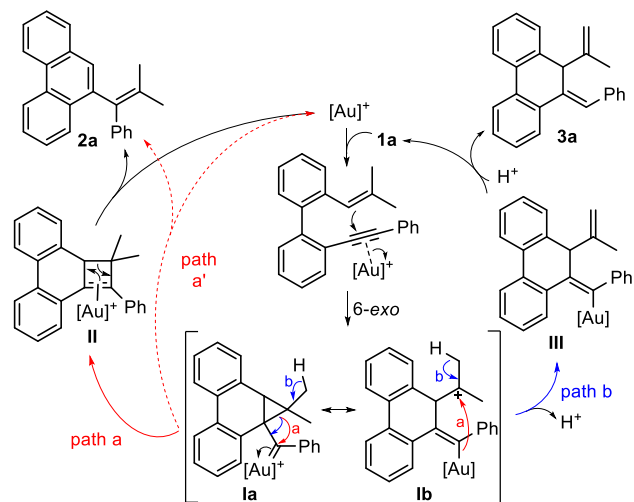
The reaction is initiated upon activation of the acetylene of the starting enyne **1a** upon coordination to the gold complex, followed by an intramolecular 6-exo-dig nucleophilic addition of the alkene moiety to give cationic intermediate **I**. This intermediate can be described as the resonance hybrid of two structures, namely the cyclopropylgold(I) carbene **Ia** and the gold-stabilized homoallylic carbocation intermediate **Ib**, which delocalizes the positive charge over the molecule. Cyclopropyl ring expansion of **Ia** then furnishes the (η^2-cyclobutene)gold(I) complex **II**,[15] which, after ring opening of the cyclobutene and subsequent demetalation, would lead to phenanthrene **2a** and release the gold catalyst for a new cycle (path a). An alternative pathway (a') involving the direct transformation of

intermediate **I** into the final phenanthrene, thus avoiding the formation of cyclobutene species **II**, can also be envisioned.[16] Both proposed pathways (a/a') are consistent with the well-documented gold-catalyzed, single-cleavage type rearrangements of 1,n-enynes, which formally imply 1,3-migration of the external carbon of the olefin to the acetylene terminal position of the trienyne **1a**.[11c,14] On the other hand, intermediate **I** could also undergo a proton elimination, thus giving rise to a vinyl-gold species **III** (path b).[12] This pathway is preferred if THF is used as solvent, probably due to the stabilization of the homoallyl cationic resonance structure **Ib**, which favours the elimination event leading to 9,10-dihydrophenathrenes Subsequent protodemetalation would lead to dihydrophenanthrene **3a** and regenerate the catalyst.

Having established biphenyl embedded trienyne **1a** as a suitable precursor for the intended selective synthesis of phenanthrene **2a**, we explored the scope of this catalytic transformation by varying the substitution at the main points of diversity of the molecule (Scheme 3).
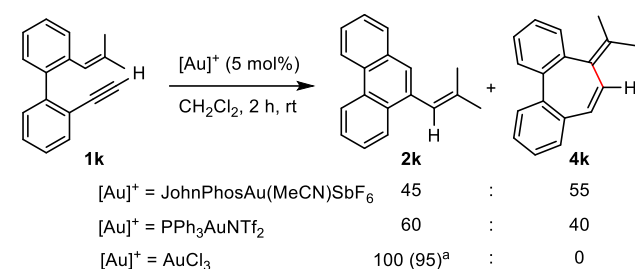
Scheme 3. Synthesis of phenanthrene derivatives 2

2a (99%)   **2b** (99%)

R[1]
4-ClC$_6$H$_4$ **2c** (99%)
o-Tolyl   **2d** (−)
2-Thienyl   **2e** (83%)
E-CH=CHPh   **2g** (70%)
n-Bu   **2h** (81%)
TIPS   **2j** (−)

iso-3f (72%)[a]

R[2] = Me **2l** (88%, dr 2:1)[b]
R[2] = Ph **2m** (98%, dr >15:1)[b]   **2n** (96%) (dr = 4:1)[b]   **2o** (83%) (dr >10:1)[b]

2p (97%)   **2q** (74%)   **2r** (99%)   **2s** (95%)
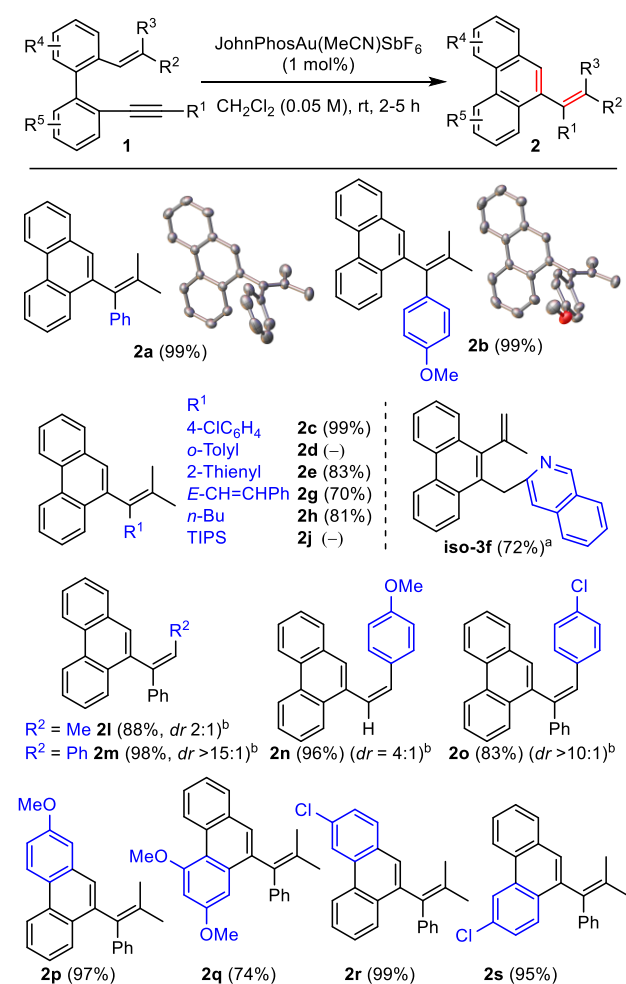
*Isolated yields from reactions performed using 0.4 mmol of **1**. [a] Conducted in the presence of PTSA (1 equiv.) for 24 h. [b] Same dr of the starting material, with the exception of **2n** (**1n** dr > 10:1).

As shown, the process developed is tolerant to the presence of a broad range of substituents at the alkyne terminus of the polyunsaturated substrate **1**, including aromatic (irrespective of their electronic nature) (**1a-c**), heteroaromatic (**1e**), alkenyl (**1g**), and alkyl groups (**1h**). However, complex mixtures were observed with **1d** bearing an o-tolyl substituent, and no evolution was detected with

trienyne **1j**, which contain a bulkier TIPS group, or quinoline-derived enyne **1f**, under the optimized reaction conditions or even after heating at reflux in DCE for 24 h. The outcome for the latter starting material can be rationalized in terms of consumption of the gold catalyst by the nitrogenated heterocycle, thus preventing it from participating in the catalytic cycle. The addition of one equivalent of PTSA to the reaction media avoided this catalytic inhibition, but also triggered the formation of 9,10-disubstituted phenanthrene **iso-3f** instead of the expected **3f**. Interestingly, reaction of ethynyl-substituted biphenyl **1k** occurred to give nearly equimolecular mixtures of the corresponding phenanthrene **2k** and dibenzocycloheptatriene **4k** as a result of a formal 7-*endo* cyclization (Scheme 4). After some experimentation, phenanthrene **2k** could be obtained exclusively in excellent yield using AuCl$_3$ as catalyst, whereas no improvement in the selectivity for **4k** could be achieved.[13] Reaction of substrate **1i**, which bears a trimethylsilyl group, gave a mixture of the same compounds **2k** and **4k** in a similar ratio, thus indicating that desilylation took place prior to the cycloisomerization event.

Scheme 4. Cycloisomerization of terminal substrate 1k

| [Au]$^+$		2k		4k
[Au]$^+$ = JohnPhosAu(MeCN)SbF$_6$		45	:	55
[Au]$^+$ = PPh$_3$AuNTf$_2$		60	:	40
[Au]$^+$ = AuCl$_3$		100 (95)[a]	:	0

[a]Isolated yield of reaction performed using 0.4 mmol of **1k**.

Next, trienynes **1** with different substitution patterns and electronic properties at the olefin, as well as at the biphenyl core, were evaluated. Thus, we found that reactions of substrates **1l-m**, alkyl or aryl monosubstituted at the β carbon of the styrene moiety, selectively produce the corresponding phenanthrenes **2l-m** in good to excellent yields with no 7-*endo* adducts being detected, even with terminal trienyne **1n**. Moreover, phenanthrenes **2p-s**, which bear electron-donating or -withdrawing substituents at any of the external arenes of the tricyclic skeleton, also proved to be accessible in high yields using the developed methodology starting from appropriately substituted conjugated enynes **1p-s**. No competitive addition of the arene that would give phenanthrenes with different substitution patterns (see Scheme 1a), or dihydrophenanthrene **3** formation, was observed for any of the substrates tested, with the sole exception of substrate **1f** (see above). Furthermore, the structural assignment for phenanthrenes **2**, initially determined on the basis of NMR studies, was confirmed by single-crystal X-ray diffraction analysis of **2a** and **2b** (Scheme 3).[17]
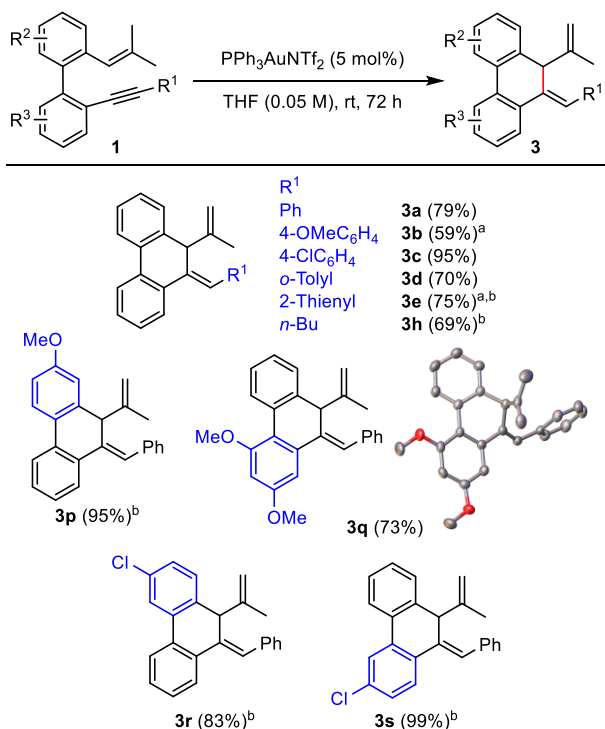
We also analyzed the applicability of this catalytic procedure for the construction of unsymmetrically 9,10-disubstituted phenanthrenes, which are not easily accessible using other methods. To this end, less reactive α-disubstituted-β,β-unsubstituted styrene substrate **1t** was synthesized and submitted to the optimized reaction conditions to afford cyclobutene compound **5t** after 24 h (Scheme 5).[18] This tetracyclic compound **5t**, the structure of which was confirmed by single-crystal X-ray diffraction analysis,[17] could be transformed into the corresponding desired phenanthrene **2t** simply by heating at 90 °C. Moreover, **2t** could be directly obtained from **1t** by performing the catalytic reaction under the heating conditions. These experiments both expand the scope of the developed methodology to the preparation of unsymmetrically 9,10-disubstituted phenanthrenes and support the participation of cyclobutene species **II** in the catalytic cycle (see Scheme 2).

Scheme 5. Cycloisomerization of α-disubstituted-β,β-unsubstituted styrene substrate 1t
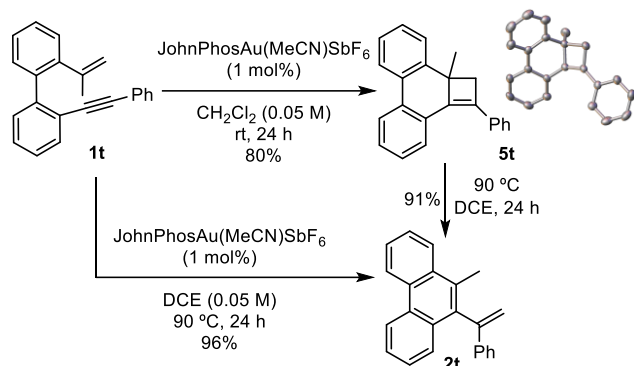
Finally, using the optimized conditions for the preparation of **3a**, a family of 9,10-dihydrophenanthrenes **3** that proved the scope and usefulness of this catalytic procedure was synthesized (Scheme 6). Thus, reactions of selected substrates with different substitution at both the alkyne terminus and the biphenyl moiety occurred to form the anticipated disubstituted tricyclic compounds **3**. The yield and selectivity were, in general, very high when using the optimized conditions or heating at 50 °C for some examples. Only enynes **1b,e**, which possess an electron-rich (hetero)arene at the acetylene, led to moderate yields and mixtures with their phenanthrene isomers **2**. Moreover, in this case, substrate **1d**, which bears an *o*-tolyl group, efficiently evolved to the corresponding dihydrophenanthrene **3d** in good yield. Additionally, the structure of **3q** was confirmed by single-crystal X-ray diffraction analysis (Scheme 6).[17]

Scheme 6. Synthesis of dihydrophenanthrenes 3

R[1]		
Ph	**3a**	(79%)
4-OMeC₆H₄	**3b**	(59%)[a]
4-ClC₆H₄	**3c**	(95%)
o-Tolyl	**3d**	(70%)
2-Thienyl	**3e**	(75%)[a,b]
n-Bu	**3h**	(69%)[b]

3p (95%)[b]   **3q** (73%)

3r (83%)[b]   **3s** (99%)[b]

*Isolated yields of reactions performed using 0.4 mmol of **1**. [a] A mixture with **2b,e** was obtained. [b] Conducted at 50 °C

In conclusion, we have developed an efficient and solvent-controlled gold-catalyzed synthesis of phenanthrenes and dihydrophenanthrenes from easily available biphenyl embedded trienynes **1**. These processes occur with good to excellent yields, broad scope and complete selectivity. Consequently, the phenanthrene synthesis described here is complementary to the well-developed strategy that produces regioisomeric phenanthrenes resulting from the competitive nucleophilic addition of biphenyl to the activated alkyne. Further studies on the reactivity of biphenyl embedded trienynes that provide straightforward access to other relevant polycyclic scaffolds via new and selective reaction pathways are currently underway in our laboratories and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, NMR spectra for all new compounds and X-ray crystallographic data for **2a,b**; **3q** and **5t** (PDF).

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Author Contributions

The manuscript was written with contributions from all authors

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(17) CCDC-2011662 (**2a**), 2011663 (**2b**), 2011664 (**3q**), and 2011665 (**5t**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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