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Catalysis

A Combined Experimental and Computational Study on the Cycloisomerization of 2-Ethynylbiaryls Catalyzed by Dicationic Arene Ruthenium Complexes

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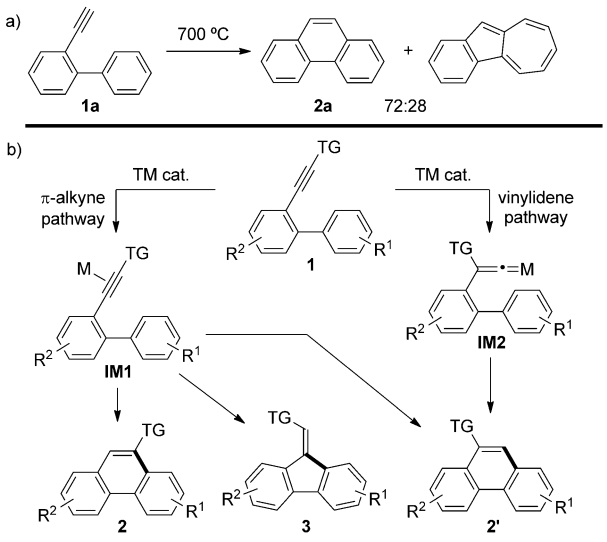
Abstract: Ruthenium-catalyzed cycloisomerization of 2-ethynylbiaryls was investigated to identify an optimal ruthenium catalyst system. A combination of [η^6-(*p*-cymene)$RuCl_2(PR_3)$] and two equivalents of $AgPF_6$ effectively converted 2-ethynylbiphenyls into phenanthrenes in chlorobenzene at 120 °C over 20 h. Moreover, 2-ethynylheterobiaryls were found to be favorable substrates for this ruthenium catalysis, thus achieving the cycloisomerization of previously unused heterocyclic substrates. Moreover, several control experiments and DFT calculations of model complexes were performed to propose a plausible reaction mechanism.

Introduction

The cycloisomerization of 2-ethynylbiphenyl (**1a**) provides a straightforward access to phenanthrene (**2a**) because this reaction proceeds by the intramolecular hydroarylation between the ethynyl and phenyl moieties connected by a phenylene tether (Scheme 1a).[1] Thus, this cycloisomerization is essentially an atom-economical process[2] as one of the *ortho* C–H bonds is directly converted into a C–C bond with concomitant intramolecular H-transfer. However, the thermal cycloisomerization of **1a** to **2a** requires a very high reaction temperature (700 °C) that would be incompatible with labile substrates. Moreover, benzazulene is formed as a side product. Therefore, transition-metal catalysts have been sought to promote this reaction under much milder conditions. In their seminal studies, Fürstner and co-workers identified metal salts with carbophilic π-acid character, such as $PtCl_2$, $AuCl_n$ ($n=1$ and 3), $GaCl_3$, and $InCl_3$, that catalyzed the cycloisomerization of various 2-alkynylbiaryls **1**, affording phenanthrenes **2** even at 80 °C (Scheme 1b).[3] Notably, internal alkynes including 1-haloalkynes (**1**, terminal group (TG) = Br and I) participated in the cycloisomerization reaction in the presence of an appropriate catalyst. Moreover, π-acid catalysts also enabled the use of heterobiaryl substrates for cycloisomerization as thiophene, pyrrole, and indole participated in the C–C bond formation with pendant alkynes under mild reaction conditions. Since the pioneering report from Fürstner's group, this method has been extensively applied to the synthesis of polyaromatic molecules with intriguing structural and optoelectronic properties, such as (hetero)pyrenes,[4] (hetero)helicenes,[5] and larger polyaromatic hydrocarbons.[6] The use of π-acid catalysts with a wide functional-group compatibility also makes the 2-alkynylbiaryl cycloisomerization applicable to the syntheses of natural products and bioactive molecules such as aporphine alkaloids,[3b,c] tylophora alkaloids and analogues,[7] (+)-kibdelone A,[8] and HIV-1 integrase inhibitors.[9]



Scheme 1. Thermal and transition-metal-catalyzed cycloisomerizations of 2-alkynylbiphenyls **1**.

Despite the significant progress in this field, some limitations still remain to be solved. The electrophilic activation of alkynes using π-acid catalysts prefers electron-rich aryl rings (R^1 = electron-donating groups) as the coupling partners; therefore, aryl groups substituted with electron-withdrawing groups are essentially incompatible because of their insufficient nucleophilicity. The cycloisomerization of unsymmetrically substituted

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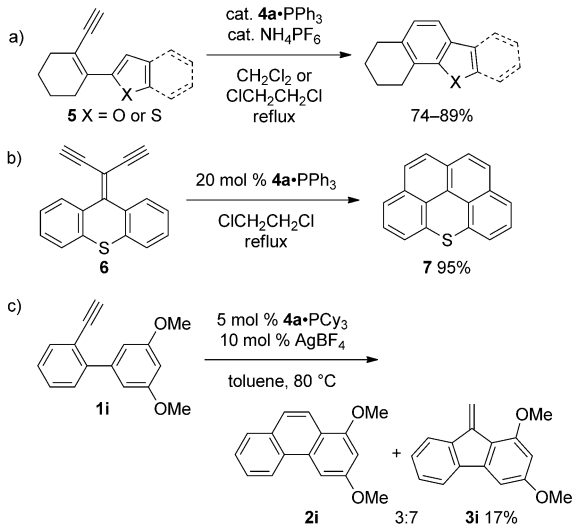
substrates suffers from poor regioselectivity. Moreover, the cycloisomerizations involving *meta*-substituted aryl rings often lead to a mixture of the expected 6-*endo* cyclization product **2** and the undesired 5-*exo* cyclization product **3** (Scheme 1b).[3c] To solve these problems, new methods have been developed by investigating under-used metal elements and/or ligands. For example, the cycloisomerization of electron-deficient biarylalkynes to the corresponding phenanthrenes has been achieved using $Fe(OTf)_3$ as the catalyst, even though the alkyne moiety is limited to those possessing a phenyl terminal (**1**, TG = Ph).[10] In the presence of $In(OTf)_3$ or a cationic gold(I) catalyst with an N-heterocyclic carbene ligand, biarylalkynes possessing a phenylselenyl terminal (**1**, TG = SePh) underwent selective 6-*endo* cycloisomerization irrespective of the substitution pattern on the aryl rings involved in the C–C bond formation, albeit with the concomitant 1,2-migration of the phenylselenyl group via vinylidene intermediates (vide infra) for the gold-catalyzed reactions.[11] Furthermore, Alcarazo and co-workers reported that platinum(II) and gold(I) complexes selectively catalyzed the 6-*endo* cycloisomerization of diverse challenging ethynylbiaryl substrates under mild reaction conditions. In particular, the cationic gold catalyst enabled the cycloisomerization of 2′,6-disubstituted 2-ethynylbiphenyls, affording highly strained 4,5-disubstituted phenanthrenes even at room temperature.[12b] In these examples, strong π-acid ligands, 2,3-dialkylaminocyclopropenium-substituted phosphines, play important roles in the electrophilic activation of the ethynyl moiety, thus facilitating the desired 6-*endo* cycloisomerization. In striking contrast, Gevorgyan and Chernyak reported that the neutral palladium(II) catalyst with 1,1′-bis(phoshino)ferrocene ligands generally catalyzed the 5-*exo* cycloisomerization of biarylalkynes possessing (hetero)aryl or ethoxycarbonyl terminal groups on the alkyne moiety (**1**, TG = aryl or CO_2Et), resulting in the stereoselective formation of alkylidenefluorene derivatives **3**.[13] Notably, the palladium-catalyzed 5-*exo* cycloisomerization preferred electron-deficient substrates (R^1 = electron-withdrawing substituents) rather than electron-rich substrates, and an aromatic C–H activation pathway is proposed based on kinetic isotope effects observed in deuterium-labeling experiments. Therefore, the reaction efficiency, substrate scope, and product selectivity should be controlled by the judicious choice of neutral/cationic metal–ligand combinations.

With this background, we focused on the ruthenium-catalyzed cycloisomerizations of biarylalkynes. In a seminal study by Merlic and Pauly, a monocationic catalyst with an arene ligand, which was derived in situ from [(*p*-cymene)$RuCl_2(PPh_3)$] (**4a**·PPh_3) and NH_4PF_6, was reported to be an efficient catalyst for the cycloisomerization of heteroarylenynes **5** (Scheme 2a).[14] However, the ruthenium-catalyzed cycloisomerizations of 2-ethynylbiaryls have not been investigated. Subsequently, Donovan and Scott reported the cycloisomerization of enediyne **6** to pentacycle **7** in an excellent yield using **4a** without any additive, even though a similar reaction of an oxa analogue of **6** afforded the corresponding product in < 10% yield (Scheme 2b).[6a] This substrate-dependent variation of the catalyst efficiency is a severe drawback for the ruthenium catalyst system. Moreover, Fürstner and co-workers screened several



Scheme 2. Catalytic cycloisomerizations using [(*p*-cymene)$RuCl_2(PR_3)$] as precatalysts.

ruthenium catalysts for the cycloisomerization of 2-ethynyl-3′,5′-dimethoxybiphenyl (**1i**) with a 5 mol% catalyst loading in toluene at 80 °C (Scheme 2c).[3c] A complete consumption of **1i** was observed by using a dicationic catalyst, which was derived in situ from [(*p*-cymene)$RuCl_2(PCy_3)$] (**4a**·PCy_3) and two equivalents of $AgBF_4$, even though the 6-*endo*/5-*exo* selectivity was as low as 3:7 and the isolated yield of the major 5-*exo* product **3i** was only 17%. Independently, Liu and co-workers reported that a different cationic ruthenium catalyst, [TpRu$(PPh_3)(CH_3CN)_2PF_6$] (Tp = tris(pyrazolyl)borate), efficiently catalyzed the 6-*endo* cycloisomerization of 2-ethynylbiphenyl (**1a**), affording phenanthrene (**2a**) in a high yield.[6b] This indicates that an appropriate combination of ancillary ligands, positive ionic charges, and counterions possibly improves the efficiency and substrate scope of the cycloisomerization of 2-alkynylbiaryls.

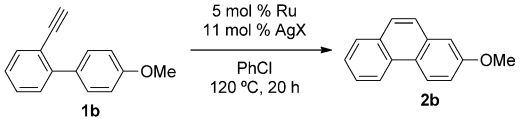
Therefore, we decided to reinvestigate the ruthenium catalyst system based on [(η^6-arene)$RuCl_2(PR_3)$] (**4**·PR_3) because they are readily prepared,[15] and the catalytic efficiency can be readily modulated by altering the η^6-arene and phosphine ligands as well as silver additives. In this paper, we report the development of ruthenium catalysts for the catalytic cycloisomerization of diverse 2-ethynylbiaryls.

Results and Discussion

Screening of ruthenium catalysts

At the outset of this study, a ligand set and a silver additive were optimized for the ruthenium-catalyzed cycloisomerization of ethynylbiphenyl **1b** as a representative substrate (Table 1). In the absence of a silver salt, a solution of **1b** and 5 mol% **4a**·PPh_3 in chlorobenzene was heated at 120 °C (Table 1, entry 1). However, no reaction occurred within 20 h. Then, the reaction was repeated by adding 11 mol% $AgBF_4$, resulting in the complete consumption of **1b** (entry 2). Purification using

Table 1. Optimization of ruthenium catalyst **4**·PR_3/*n*AgX.



1b **2b**

Entry	Ru complex[a]	AgX	**2b** Isolated yield [%]
1	**4a**·PPh_3	–	no reaction
2	**4a**·PPh_3	$AgBF_4$	74
3	**4a**·PPh_3	$AgPF_6$	77
4	**4a**·PPh_3	$AgPF_6$[b]	44
5	**4a**·PPh_3	AgOTf	59
6	**4a**·PPh_3	$AgNTf_2$	complex mixture
7	**4a**·P(*p*-$MeOC_6H_4$)$_3$	$AgPF_6$	74
8	**4a**·P(*p*-FC_6H_4)$_3$	$AgPF_6$	79
9	**4a**·P(*p*-$F_3CC_6H_4$)$_3$	$AgPF_6$	73
10	**4a**·PCy_3	$AgPF_6$	53
11	**4a**·$P(OMe)_3$	$AgPF_6$	72
12	**4a**	$AgPF_6$	21
13	**4b**·PPh_3	$AgPF_6$	68
14	**4c**·PPh_3	$AgPF_6$	73
15	$[RuCl_2(PPh_3)_3]$	$AgPF_6$	30

[a] Arene ligands are *p*-cymene, benzene, and hexamethylbenzene for **4a**, **4b**, and **4c**, respectively. [b] 7.5 mol%.

silica gel chromatography afforded phenanthrene **2b** in 74% yield. The use of $AgPF_6$ instead of $AgBF_4$ resulted in a slightly better yield (entry 3), whereas the loading of $AgPF_6$ was decreased to half, leading to an incomplete reaction (entry 4). These results clearly indicate that the dicationic ruthenium species of the type $[(\eta^6\text{-arene})Ru(PR_3)]^{2+}$ are competent catalysts. The use of AgOTf or $AgNTf_2$ as the additives caused inferior results, which indicated that less coordinating counterions are essential (entries 5 and 6). Next, the effect of phosphine ligands was investigated. When P(*p*-$MeOC_6H_4$)$_3$ and P(*p*-FC_6H_4)$_3$, with similar cone angles but electron-donating and -withdrawing, respectively, compared to PPh_3, were used, comparable yields were obtained (entries 7 and 8). Because the latter gave a slightly higher yield, more electron-withdrawing P(*p*-$CF_3C_6H_4$)$_3$ was investigated to improve the yield (entry 9). However, the yield was slightly lowered. Moreover, the yield was considerably decreased, when bulky and strongly electron-donating PCy_3 was the phosphine ligand, which was previously used by Fürstner and co-workers (entry 10).[3c] Small and electron-withdrawing $P(OMe)_3$ was a better ligand than PCy_3 (entry 11). The importance of phosphine ligands was unambiguously shown by the reaction conducted using **4a** without PPh_3, affording **2b** in only 21% yield (entry 12). In addition to *p*-cymene complex **4a**·PPh_3, similar complexes **4b**·PPh_3 and **4c**·PPh_3, with more electron-donating hexamethylbenzene and less electron-donating benzene as the η^6-arene ligands, respectively, were used as the precatalysts, resulting in slightly lower yields of **2b** (entries 13 and 14). Thus, *p*-cymene was the optimal η^6-arene ligand. The necessity of the η^6-arene ligand was also confirmed by the reaction using $[RuCl_2(PPh_3)_3]$ as the precatalyst (entry 15). In this case, **2b** was obtained in only 30% yield. Finally, $AgPF_6$ exhibited no catalytic activity.

Substrate scope and limitations

The general applicability of the ruthenium-catalyzed cycloisomerization was investigated using 5 mol% **4a**·PPh_3 and 11 mol% $AgPF_6$ in PhCl at 120 °C for 20 h as the standard reaction conditions (Table 2). 2-Ethynylbiphenyl **1a** and 4′-chloro analogue **1c** underwent cycloisomerization to afford phenan-

Table 2. Cycloisomerizations of 2-ethynylbiphenyls using **4a**·PAr_3/$AgPF_6$.[a]

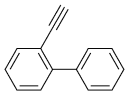
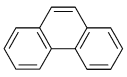
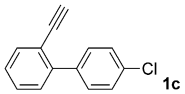
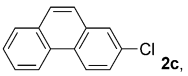
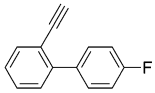
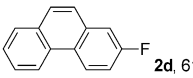
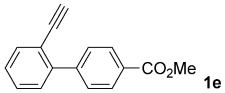
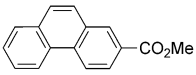
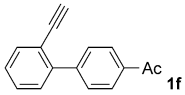
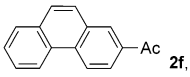
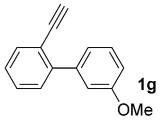
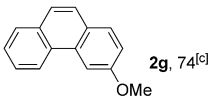
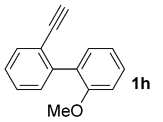
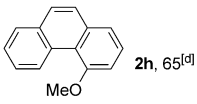
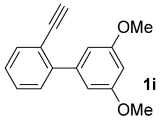
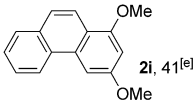
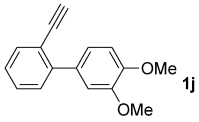
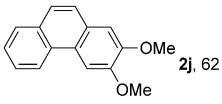
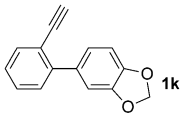
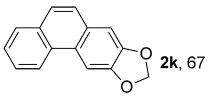
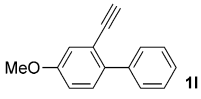
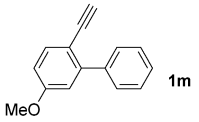
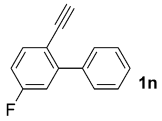
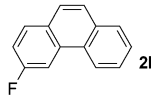
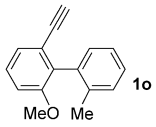
Entry	Substrate	Product, yield [%][b]
1	 **1a**	 **2a**, 72
2	 **1c**	 **2c**, 74
3	 **1d**	 **2d**, 61 (67)
4	 **1e**	 **2e**, 56
5	 **1f**	 **2f**, 47
6	 **1g**	 **2g**, 74[c]
7	 **1h**	 **2h**, 65[d]
8	 **1i**	 **2i**, 41[e]
9	 **1j**	 **2j**, 62
10	 **1k**	 **2k**, 67
11	 **1l**	**2b**, 50
12	 **1m**	**2g**, 18

Table 2. (Continued)

Entry	Substrate	Product, yield [%][b]
13	 **1n**	 **2l**, 57 (63)
14	 **1o**	complex mixture

[a] Standard conditions: 5 mol% **4a**·PPh_3, 11 mol% $AgPF_6$, PhCl, 120 °C, 20 h. [b] Isolated yields. Yields obtained using P(*p*-$MeOC_6H_4$)$_3$ as the ligand are shown in parentheses. [c] An inseparable mixture of **2g** and its 1-methoxy isomer **2g′** with 13:1 ratio. [d] **1h** was recovered in 13% yield. [e] An inseparable mixture with the **2i**/**3i** ratio of 4:1.

threnes **2a** and **2c** in 72 and 74% yields, respectively (Table 2, entries 1 and 2). On the other hand, the reaction of more electron-deficient 4′-fluoro substrate **1d** afforded **2d**, albeit in a moderate yield of 61% (entry 3). These results indicate that the substituents on the phenyl ring that undergo intramolecular C–H alkenylation have a significant electronic impact on the reaction efficiency, and an electron-withdrawing group lowers the product yield. This electronic effect was more pronounced in the cycloisomerizations of substrates possessing methoxycarbonyl and acetyl substituents at the 4′ positions, affording **2e** and **2f** in 56 and 47% yields, respectively (entries 4 and 5).

The effect of the substitution pattern was then investigated by using 2-ethynylbiphenyls **1g** and **1h** possessing a methoxy group at the 3′ or 2′-positions, respectively, as the substrates (Table 2, entries 6 and 7). The reaction of **1g** afforded an inseparable mixture of 3-methoxyphenanthrene (**2g**) and 1-methoxyphenanthrene in 74% combined yield with a 3-MeO/1-MeO ratio of 13:1, whereas the reaction of **1h** afforded 4-methoxyphenanthrene **2h** in a moderate yield (65%). The lower yield of **2h** was caused by the unfavorable steric repulsion between the methoxy group and hydrogen atom at the 4- and 5-positions, respectively.[12b] The reactivity of problematic 3′,5′-dimethoxy-substituted substrate **1i** was reinvestigated (entry 8), because Fürstner and co-workers previously used **4a**·PCy_3/$AgBF_4$ as the catalyst in toluene at 80 °C to obtain 5-*exo* cycloisomerization product **3i** in 17% yield as the major isomer (Scheme 2c).[3c] The new catalyst system in this study produced **2i** and **3i** as an inseparable mixture in 41% combined yield with a **2i**/**3i** ratio of 4:1. Thus, the different phosphine ligands, counterions, and reaction conditions not only improved the catalytic efficiency, but also inversed the 6-*endo*/5-*exo* selectivity. In contrast to **1i**, 3′,4′-dimethoxy analogue **1j** and benzo[1,3]dioxole derivative **1k** underwent selective 6-*endo* cycloisomerization to afford the corresponding phenanthrenes **2j** and **2k** in 62 and 67% yields, respectively (entries 9 and 10).

Furthermore, the cycloisomerization of 2-ethynyl-4-methoxybiphenyl **1l** was carried out under the standard reaction conditions, affording phenanthrene **2b** in 50% yield (Table 2, entry 11). Moreover, the reaction of 5-methoxy analogue **1m** afforded a complex mixture of products, and **2g** was isolated in a low yield (entry 12). These results are in striking contrast to the fact that the same products **2b** and **2g** were obtained in much better yields from substrates **1b** and **1g**, respectively. Thus, the electron-donating substituents on the ethynyl-substituted phenyl ring negatively affected the cyclization efficiency. On the other hand, the reaction of 5-fluoro derivative **1n** afforded the corresponding phenanthrene **2l** in a higher yield of 57% (entry 13). However, substrate **1o** possessing substituents on both phenyl rings resulted in a complex product mixture (entry 14).

Subsequently, the cycloisomerizations by intramolecular heteroarene C–H alkenylation were investigated as summarized in Table 3. Under the standard reaction conditions, benzofuran derivative **8a** efficiently underwent cycloisomerization to

Table 3. Cycloisomerizations of 2-ethynylheterobiaryls using **4a**·PPh_3/$AgPF_6$.[a]

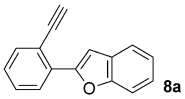
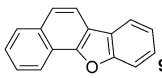
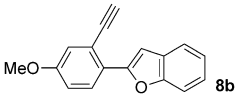
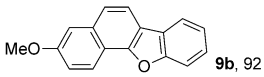
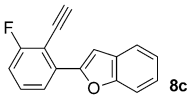
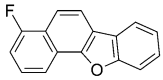
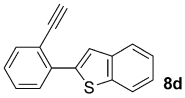
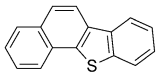
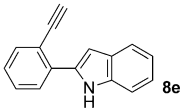
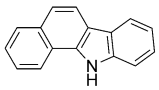
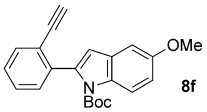
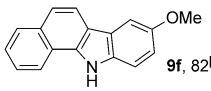
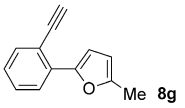
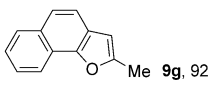
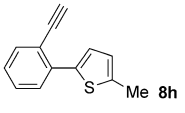
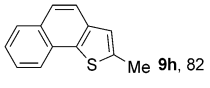
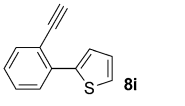
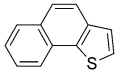
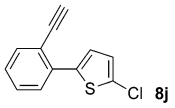
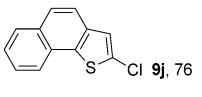
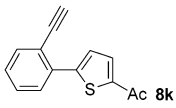
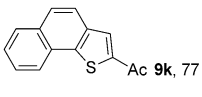
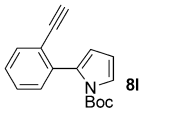
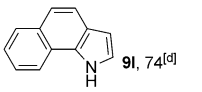
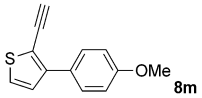
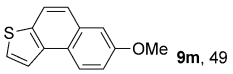
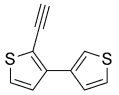
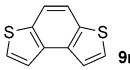
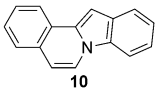
Entry	Substrate	Product, yield [%][b]
1	 **8a**	 **9a**, 85
2	 **8b**	 **9b**, 92
3	 **8c**	 **9c**, 82
4	 **8d**	 **9d**, 90
5	 **8e**	 **9e**, 67[c]
6	 **8f**	 **9f**, 82[d]
7	 **8g**	 **9g**, 92
8	 **8h**	 **9h**, 82
9	 **8i**	 **9i**, 72

Table 3. (Continued)

Entry	Substrate	Product, yield [%][b]
10	 **8j**	 **9j**, 76
11	 **8k**	 **9k**, 77
12	 **8l**	 **9l**, 74[d]
13	 **8m**	 **9m**, 49
14	 **8n**	 **9n**, 44

[a] Standard conditions: 5 mol% **4a**·PPh_3, 11 mol% $AgPF_6$, PhCl, 120 °C, 20 h. [b] Isolated yields. [c] Compound **10** was also formed in 7% yield. [d] Two-step yields after removal of the Boc group.



10

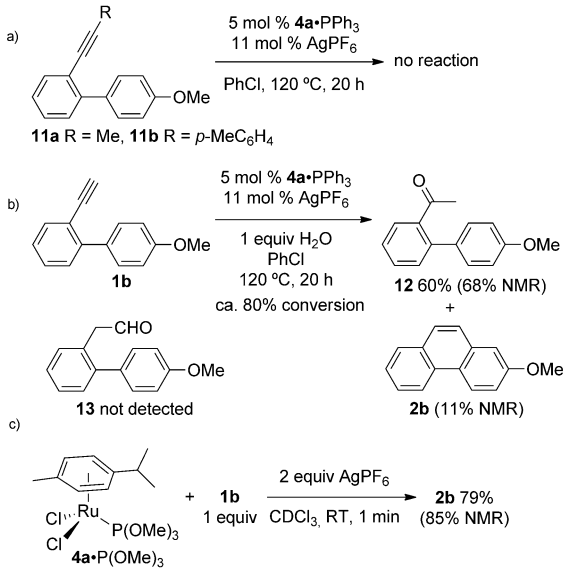
afford the desired benzo[*d*]naphtho[1,2-*b*]furan (**9a**) in 85% yield (entry 1). The cycloisomerizations of similar substrates **8b** and **8c** possessing electron-donating methoxy and electron-withdrawing fluoro substituents, respectively, on the ethynyl-substituted phenyl ring were conducted without difficulty, affording the corresponding products **9b** and **9c** in high yields of over 80% (entries 2 and 3). These results are in striking contrast to the fact that the reactions of biaryls **1l**–**n** resulted in lower yields compared to other biaryl substrates (Table 2, entries 11–13). Although the reaction of benzothiophene derivative **8d** also afforded benzo[*d*]naphtho[1,2-*b*]thiophene (**9d**) in 90% yield (Table 3, entry 4), 11*H*-benzo[*a*]carbazole (**9e**) was obtained in 67% yield along with small amounts of intramolecular hydroamination byproduct **10** from indole-derived substrate **8e** (entry 5). This result is consistent with that of the previous report: the platinum(II)-catalyzed cycloisomerization of **8e** also afforded **9e** and **10**.[3c] Thus, a similar substrate **8f** with *N*-Boc protection was subjected to the present cycloisomerization conditions to avoid the undesired side reaction (entry 6). Because a partial deprotection occurred, the crude products were directly treated with trifluoroacetic acid (TFA) at 60 °C for 3 h. This one-pot procedure successfully afforded the desired benzocarbazole derivative **9f** in 82% yield. Similarly, 2-methylfuran derivative **8g** and 2-methylthiophene derivative **8h** were efficiently converted into 2-methylnaphtho[1,2-*b*]furan (**9g**) and 2-methylnaphtho[1,2-*b*]thiophene (**9h**) in 92 and 82% yields, respectively (entries 7 and 8). The reactions of parent thiophene analogue **8i** and 2-chloro and 2-acetyl analogues **8j** and **8k** also afforded the desired products in good yields (72–77%, entries 9–11). Moreover, 1*H*-benzo[*g*]indole **9l** was successfully obtained in 74% yield by the one-pot cycloisomerization/deprotection of *N*-Boc pyrrole derivative **8l** (entry 12). In contrast to the above examples, the cycloisomerizations of 2-ethynyl-3-(4-aryl)thiophenes **8m** and **8n** were problematic. The reactions of these substrates afforded 7-methoxynaphtho[2,1-*b*]thiophene (**9m**) and benzo[1,2-*b*:4,3-*b'*]dithiophene (**9n**), albeit in 49 and 44% yields, respectively (entries 13 and 14). As a whole, the ruthenium-catalyzed cycloisomerization was highly efficient for 2-ethynylheterobiaryl substrates except for the 2-ethynylthiophene derivatives.

Mechanistic considerations

As shown in Scheme 1b, several reaction pathways were proposed for the transition-metal-catalyzed cycloisomerizations of 2-alkynylbiphenyls **1**, affording phenanthrenes **2** and alkylidenefluorenes **3**. Based on the recent theoretical studies, the electrophilic activation of the alkyne moiety by the formation of π-alkyne complexes **IM1** has been postulated as the initial step of cycloisomerizations using π-acid platinum, gold, and indium catalysts.[12,16] A subsequent intramolecular Friedel–Crafts-type cyclization followed by sequential hydrogen shifts afford phenanthrenes **2** or alkylidenefluorenes **3**. Alternatively, the involvement of the intramolecular cyclopropanation of **IM1** was also proposed for the platinum-catalyzed cycloisomerization, affording phenanthrenes **2**.[12,16] When the cycloisomerizations of 2-(2-haloalkynyl)biphenyls **1** (TG = I or Br) were performed using AuCl as the catalyst, the corresponding phenanthrenes **2'** were obtained rather than isomeric **2**.[3] Although a pathway involving the formation of vinylidene complexes **IM2** by 1,2-halide migration was initially proposed to explain this phenomenon, an alternative mechanism comprising the Friedel–Crafts-type cyclization of π-alkyne complexes **IM1** and a subsequent 1,2-halide migration was later proposed based on theoretical studies.[16] Therefore, the π-alkyne pathway has been accepted as the general mechanism for the cycloisomerizations using π-acid catalysts.

To elucidate the mechanism of the cycloisomerization catalyzed by the dicationic ruthenium complex, several control experiments were performed (Scheme 3). First, the substrates possessing an internal alkyne moiety were subjected to the standard cycloisomerization conditions. In the presence of 5 mol% **4a**·PPh_3 and 11 mol% $AgPF_6$, **11a** and **11b** with methyl and *p*-tolyl terminal groups, respectively, were separately heated in chlorobenzene at 120 °C for 20 h, resulting in the 91 and 93% recovery of intact **11a** and **11b**, respectively (Scheme 3a). These results indicate that this cycloisomerization of 2-ethynylbiaryls proceeds by the electrocyclization of vinylidene intermediates such as **IM2**. Moreover, the vinylidene mechanism was also proposed for the previous ruthenium-catalyzed cycloisomerizations.[6a,b,14,17]

However, evidence that contradicts the vinylidene mechanism was also obtained. This ruthenium(II)-catalyzed cycloisomerization of 2-ethynylbiaryls should be performed under rig-



Scheme 3. Control experiments.

orously anhydrous conditions because of the hydration of the alkyne moiety when the reaction was carried out in the presence of adventitious water. In fact, the reaction of representative substrate **1b** was performed under the standard cycloisomerization conditions except for adding one equivalent of H_2O, affording the known ketone **12**[18] as the major product (68% NMR) along with phenanthrene **2b** (11% NMR) and intact **1b** (20% NMR) as shown in Scheme 3b. The formation of **12** can be attributed to the Markovnikov hydration via a π-alkyne intermediate, and the anti-Markovnikov hydration product **13** was not detected. These observations are in contrast to those reported by Wakatsuki and co-workers, who showed that the ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes proceeded via vinylidene intermediates to afford aldehydes.[19]

Furthermore, a stoichiometric reaction of representative substrate **1b** with *p*-cymene ruthenium complex **4a** was carried out (Scheme 3c). $P(OMe)_3$ was selected as the supporting ligand for a clear ^1H NMR spectroscopic analysis. When a 1:1 mixture of **4a**·$P(OMe)_3$ and **1b** in $CDCl_3$ was treated with two equivalents of $AgPF_6$ at room temperature, a spontaneous change in the color of the solution from red to brown and concomitant precipitation were observed. The ^1H NMR spectroscopic analysis of the resulting crude reaction mixture showed the clean formation of phenanthrene **2b** in 85% NMR spectroscopic yield without any noticeable side product other than the decomposed complex. Therefore, an elevated reaction temperature of 120 °C is probably required for the catalytic reactions to restore the catalytically active species from the resting states stabilized by the coordination of the product (i.e. product inhibition). In contrast, the cycloisomerization of substrate **11a** with an internal alkyne failed under the same stoichiometric reaction conditions.

Then, the DFT calculations of model complexes were performed, using η^6-benzene and PH_3 as the simplified ligands for computational efficiency because the electronic effects of the η^6-arene and phosphine ligands are less important for the cyclization efficiency (for details of computation, see the Supporting Information). Three starting complexes relevant to the present reaction were located (Figures 1–3). Among these intermediates, π-alkyne complex **A1** and η^1-allenylruthenium complex **B1** have similar energy, and vinylidene complex **C1** was located approximately 3 kcal mol^{-1} higher than **A1** and **B1**. Subsequent calculations indicate that the 6-*endo* cyclization to afford a phenanthrene complex occurs from complexes **A1** and **C1** (Figures 1 and 2), while complex **B1** ultimately evolves to a methylenefluorene complex by 5-*exo* cyclization (Figure 3).

Figure 1 shows the free energy surface for the conversion of π-alkyne complex **A1** to η^2-phenanthrene complex **A5**. In **A1**, the ethyne moiety was significantly bent by the coordination of the ruthenium center as shown by the bond angles of C2-Cα-Cβ = 148.3 and Cα-Cβ-H = 139.3° and the Cα–Cβ bond length of 1.317 Å is similar to that of a typical Csp^2=Csp^2 double bond. The 6-*endo* cyclization of **A1** proceeded by transition-state $\mathbf{TS_{A1A2}}$ with an activation energy of $\Delta G^{\ddagger} = +10.1$ kcal mol^{-1}. On transferring from **A1** to $\mathbf{TS_{A1A2}}$, the Cβ–C2′ distance decreased from 3.002 to 2.212 Å. The cyclization product **A2**, which is a distorted η^1-alkenyl complex with a Ru–C single-bond length of 2.108 Å and bond angles of Ru-Cα-Cβ = 99.7 and Ru-Cα-C2 = 135.1° had a slightly higher energy than **A1** (+0.003 kcal mol^{-1}); thus, **A1** and **A2** are in equilibrium. A subsequent 1,2-shift of the C2′ proton occurred by transition-state $\mathbf{TS_{A2A3}}$ with a smaller activation energy of $\Delta G^{\ddagger} = +7.9$ kcal mol^{-1} than that of $\mathbf{TS_{A1A2}}$. The formation of carbene complex **A3** with a short Ru=Cα bond length of 1.958 Å is highly exergonic (−24.3 kcal mol^{-1}). The newly formed Cβ–H2 bond is oriented perpendicular to the Ru=Cα bond (Ru-Cα-Cβ-H2 = 94.0°), while the original Cβ–H1 bond makes a very weak agostic interaction with the ruthenium center (Ru–H1 = 2.358 Å). Complex **A3** and its conformational isomer **A4** are in equilibrium with a very small activation barrier of approximately 2 kcal mol^{-1}. In **A4**, the Cβ–H2 bond makes a very weak agostic interaction with the ruthenium center (Ru–H2 = 2.320 Å). Finally, **A4** evolved to η^2-phenanthrene complex **A5** by the 1,2-shift of the original Cα proton H1 by transition-state $\mathbf{TS_{A4A5}}$. The activation energy of this step is $\Delta G^{\ddagger} = +16.7$ kcal mol^{-1}, and the formation of **A5** is exergonic (−16.2 kcal mol^{-1}). Overall, the initial 6-*endo* cyclization followed by the first 1,2-H shift occurs with relatively small activation barriers. Although the activation barrier of the second 1,2-H shift is the largest, this is small enough to override under the experimental conditions. The formation of **A3** can be considered as irreversible because this step is highly exergonic, and transition state $\mathbf{TS_{A1A2}}$ has the highest energy. Thus, the 6-*endo* cyclization step is the product- and rate-determining step. Because the activation barriers are <20 kcal mol^{-1}, the ruthenium-mediated transformation of 2-ethynylbiphenyl to phenanthrene should proceed even at room temperature. This was indeed confirmed by the stoichiometric reaction of **4a**·$P(OMe)_3$ with **1b** as shown in Scheme 3c.

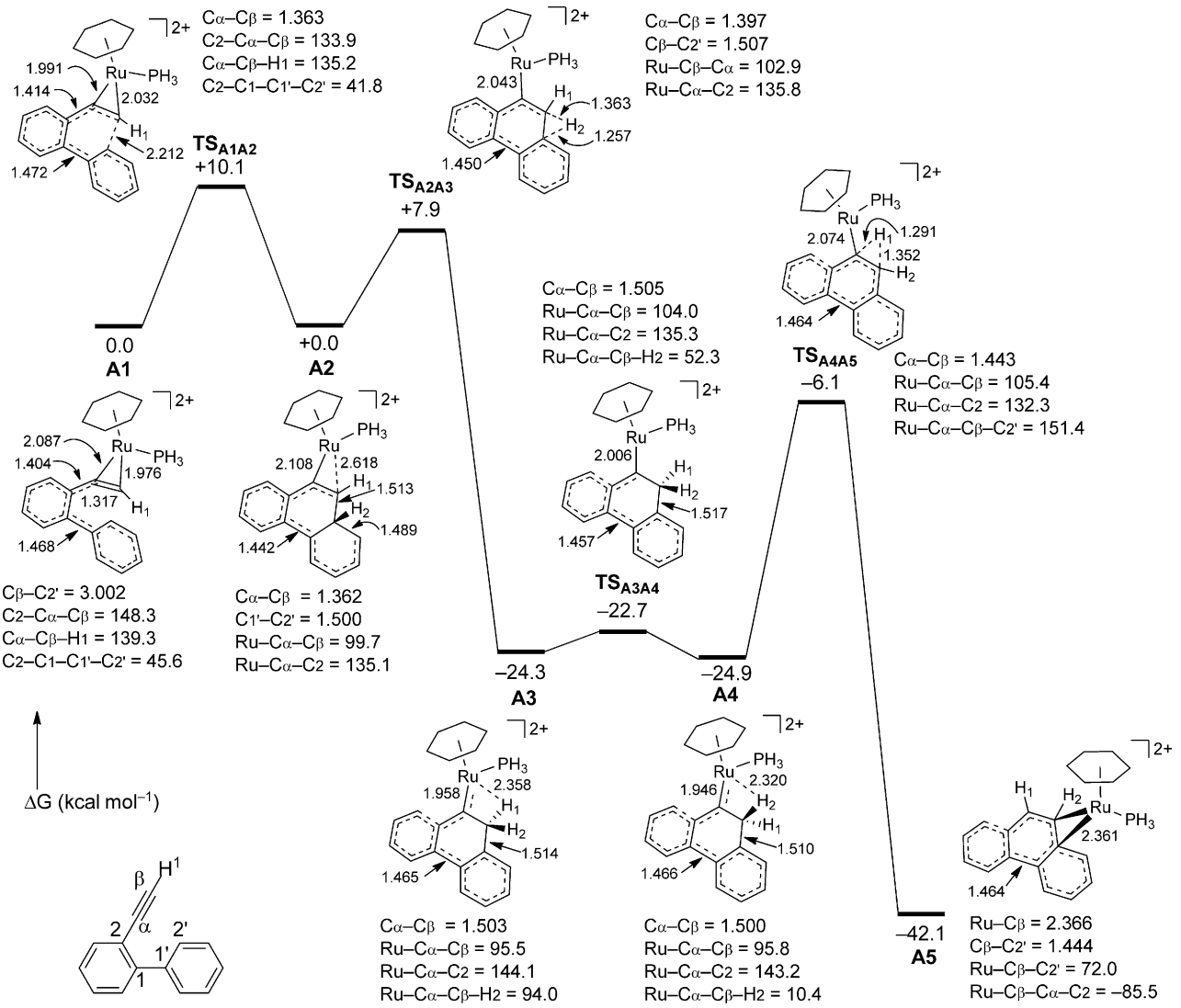


Figure 1. Energy surface for conversion of **A1** to **A5** with relative Gibbs free energies in chlorobenzene at 298 K.

Next, the energy surface for the conversion of π-alkyne complex **A1** to η^2-methylenefluorene complex **B4** was calculated as shown in Figure 2. Because the attempt to locate a transition state for the direct 5-*exo* cyclization from **A1** failed, an alternative route from η^1-allenyl complex **B1** was investigated. The rotation around the C1–C1′ bond of **A1** induced the isomerization to **B1**, which may be a delocalized η^1-alkyne complex located -0.1 kcal mol^{-1} below **A1**. Complexes **A1** and **B1** are in equilibrium with very small activation barriers of less than $+2$ kcal mol^{-1}. The 5-*exo* cyclization of **B1** proceeded via transition-state $\mathbf{TS_{B1B2}}$ with an activation energy of $\Delta G^{\ddagger} = +14.8$ kcal mol^{-1}, and the formation of η^1-alkenyl complex **B2** was 2.7 kcal mol^{-1} endergonic. A subsequent 1,2-H shift from **B2** occurred via transition-state $\mathbf{TS_{B2B3}}$ with an activation energy of $\Delta G^{\ddagger} = +14.7$ kcal mol^{-1}, which is larger than that of the retrocyclization from **B2** to **B1** ($\Delta G^{\ddagger} = +12.1$ kcal mol^{-1}). The formation of carbene complex **B3** with a Ru=Cβ bond length of 1.898 Å is 11.8 kcal mol^{-1} exergonic. The second 1,2-H shift from **B3** afforded the final η^2-methylenefluorene complex **B4** with a large exergonicity of 24.0 kcal mol^{-1}. This step proceeded via transition-state $\mathbf{TS_{B3B4}}$ with an activation energy of $+13.7$ kcal mol^{-1}, which is comparable to that of the first 1,2-H shift. According to these analyses, the 5-*exo* cyclization route from η^1-allenyl complex **B1** to η^2-methylenefluorene complex **B4** is less efficient than the above 6-*endo* cyclization from π-alkyne complex **A1**, because the activation barrier of the rate-determining 5-*exo* cyclization step is much larger than that of the 6-*endo* cyclization from **A1** ($\Delta G^{\ddagger} = +14.8$ vs. $+10.1$ kcal mol^{-1}) and the subsequent 1,2-H shift is also less facile than that in the 6-*endo* route ($\Delta G^{\ddagger} = +14.7$ vs. 7.9 kcal mol^{-1}). Therefore, it is concluded that the 6-*endo* cyclization mode is more favorable than the 5-*exo* cyclization mode for the ruthenium-catalyzed cycloisomerization of 2-ethynylbiaryls.

The involvement of a vinylidene intermediate was also investigated (Figure 3). Because a transition state for the direct conversion of π-alkyne complex **A1** to a vinylidene complex could not be located, the 1,2-H shift from η^1-allenyl complex **B1** was investigated, resulting in the identification of transition-state

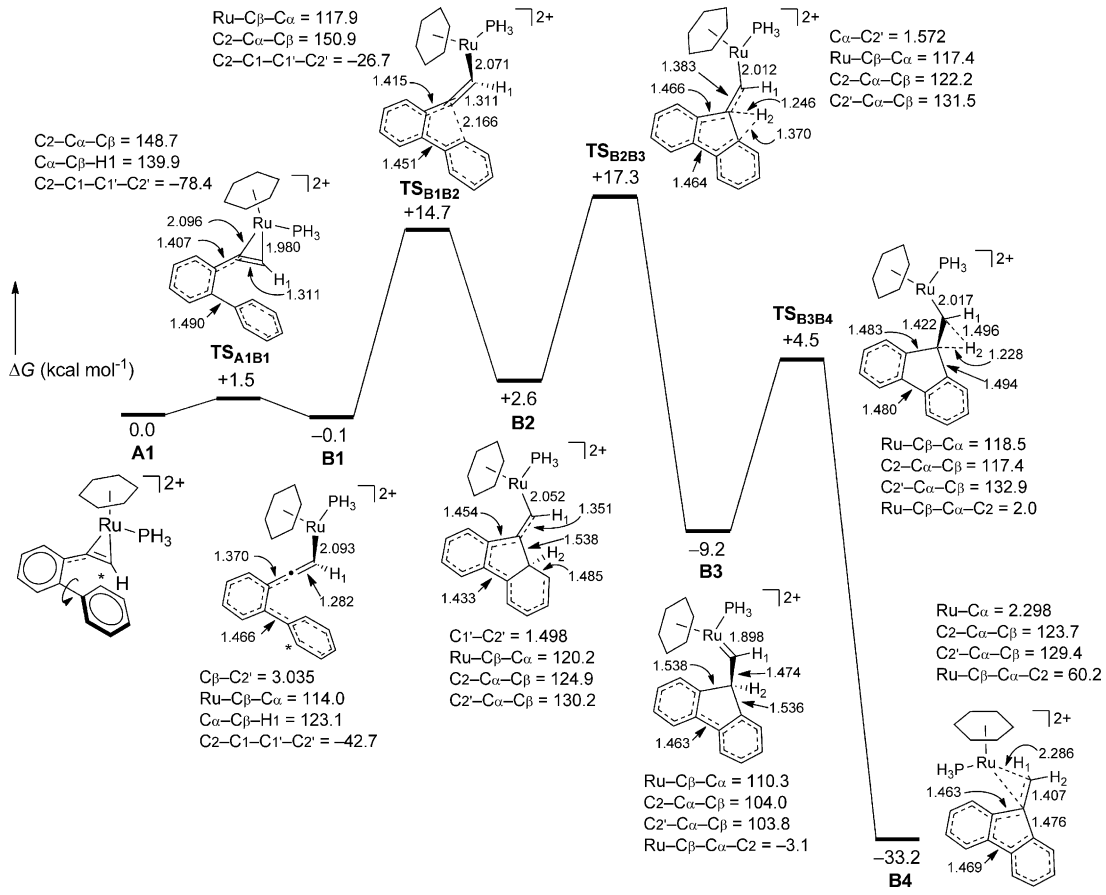


Figure 2. Energy surface for conversion of **A1** to **B4** with relative Gibbs free energies in chlorobenzene at 298 K.

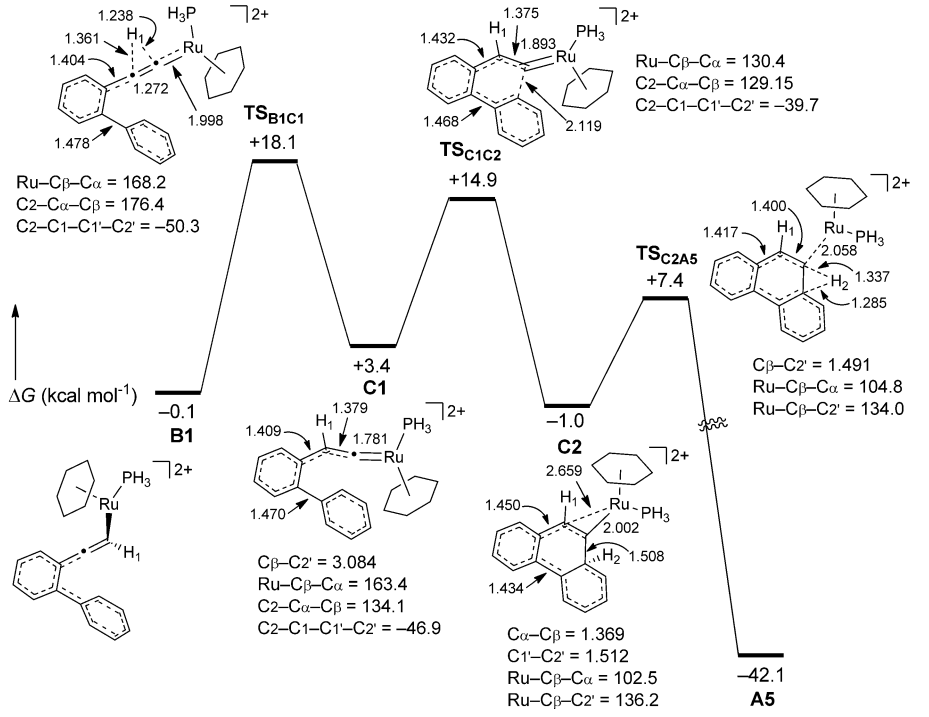
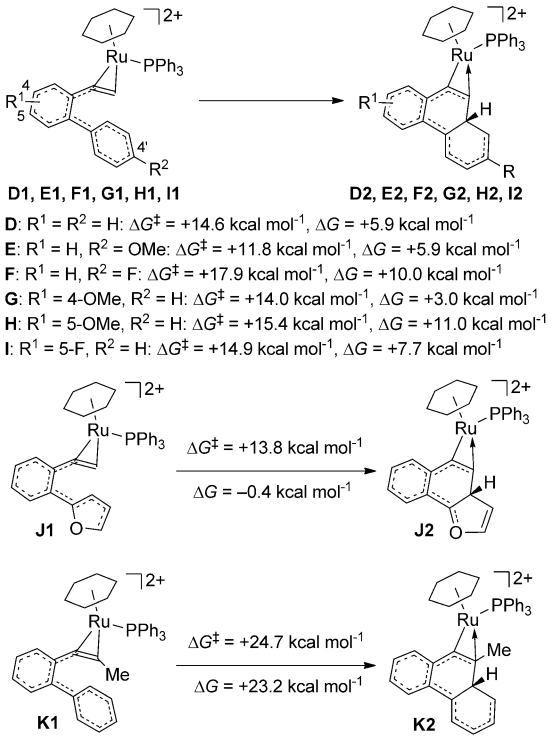


Figure 3. Energy surface for conversion of **A1** to **A5** via **C1** with relative Gibbs free energies in chlorobenzene at 298 K.

TS_{B1C1}. The activation energy for this step was estimated as $\Delta G^{\ddagger} = +18.2$ kcal mol^{-1}, and the formation of **C1** is endergonic by 3.5 kcal mol^{-1}. Therefore, the formation of vinylidene complex **C1** is less favorable, although the subsequent cyclization from **C1** proceeded via transition-state **TS_{C1C2}** with an activation energy ($\Delta G^{\ddagger} = +11.5$ kcal mol^{-1}) that is comparable to that of the 6-*endo* cyclization from **A1**. The final 1,2-H shift from **C2** to η^2-phenanthrene complex **A5** via **TS_{C2A5}** was facile ($\Delta G^{\ddagger} = +8.4$ kcal mol^{-1}) and highly exergonic (41.1 kcal mol^{-1}). Consequently, the vinylidene route can be excluded because of the unfavorable formation of vinylidene intermediate **C1**.

The key 6-*endo* cyclization step was further evaluated by performing the calculations for model complex **D1** with the



Scheme 4. 6-*Endo* cyclizations of model complexes **E1**–**K1**.

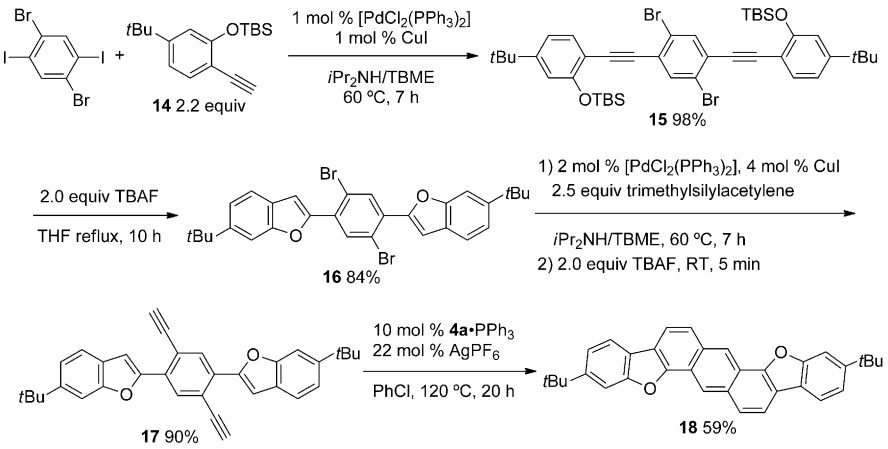
PPh_3 ligand (Scheme 4). The cyclization of 2-ethynylbiphenyl complex **D1** proceeded with an activation energy of $\Delta G^{\ddagger} = +14.6$ kcal mol^{-1}. This value is 4.5 kcal mol^{-1} larger than that of **A1** with the PH_3 ligand, but is still small enough for the cyclization to proceed at ambient temperature. Moreover, the formation of **D2** was endergonic (+5.9 kcal mol^{-1}). The effect of the structural variation was further evaluated by computing various models. The activation energy for the cyclization of **E1** with an electron-donating methoxy substituent on the 4′ position was estimated as $\Delta G^{\ddagger} = +11.8$ kcal mol^{-1}, which is 2.8 kcal mol^{-1} lower than that of **D1**. Conversely, a significantly larger activation energy of $\Delta G^{\ddagger} = +17.9$ kcal mol^{-1} was obtained for the cyclization of **F1** with an electron-withdrawing fluoro substituent at the 4′-position. Moreover, the latter case was approximately 4 kcal mol^{-1} more endergonic. These results indicate that the electrophilic character of the cyclization mediated by the dicationic ruthenium complex. On the other hand, introduction of substituents on the ethynyl-substituted phenyl ring has an insignificant effect on the activation barrier of the cyclizations: The calculated activation energies for models **G1**, **H1**, and **I1** were ~15 kcal mol^{-1}, which are comparable to that of **D1**. However, the formations of **H2** and **I2** with a substituent at the 5-position were more endergonic than that of **D2**. In particular, the formation of 5-methoxy analogue **H2** was highly endergonic as the activation energy of the reverse process, $\Delta G^{\ddagger} = +4.4$ kcal mol^{-1}, was much smaller than that of the forward process, $\Delta G^{\ddagger} = +15.4$ kcal mol^{-1}. The low-yield formation of **2 g** from **1 m** (Table 2, entry 12) is consistent with this theoretical prediction.

The 6-*endo* cyclization of furyl analogue **J1** proceeded with an activation energy of $\Delta G^{\ddagger} = +13.8$ kcal mol^{-1}, which is comparable to that for **D1**. In contrast to the cyclizations of the above biphenyl models, the formation of **J2** is slightly exergonic. These results indicate that a heterocyclic analogue with lesser aromaticity is a better substrate for the present cyclization. This is consistent with the experimental results that heteroaryl substrates are superior to biphenyl substrates. In striking contrast, the activation energy for the 6-*endo* cyclization of **K1** with an internal alkyne ($\Delta G^{\ddagger} = +24.7$ kcal mol^{-1}) is considerably larger than those of terminal alkyne complexes. Moreover, the formation of **K2** is significantly endergonic (+23.2 kcal mol^{-1}). Thus, the inverse process is more feasible as the corresponding activation barrier is much smaller ($\Delta G^{\ddagger} = +1.5$ kcal mol^{-1}). Therefore, it can be concluded that the cyclization of internal biphenylalkynes is not facile both kinetically and thermodynamically. This conclusion is consistent with the experimental results for internal alkyne substrates **11 a** and **11 b** (Scheme 3a).

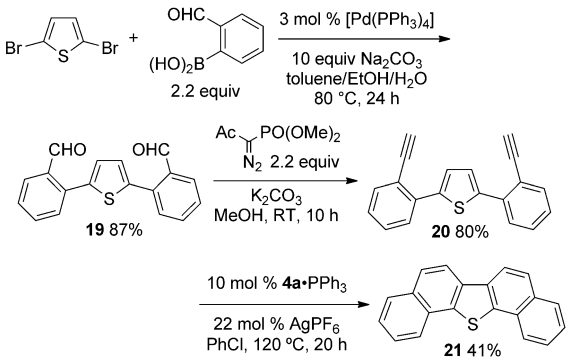
Synthetic application: Synthesis of polyheteroaromatic molecules by tandem cycloisomerizations

Polyaromatic compounds containing dibenzofuran and dibenzothiophene moieties are attractive synthetic targets because of their optoelectronic properties.[21,22] Thus, the tandem cycloisomerizations of 2-ethynylheterobiaryls to polyheteroarenes were investigated to demonstrate the synthetic potential of the present ruthenium-catalyzed cycloisomerization (Schemes 5 and 6).

The Sonogashira coupling of 1,4-dibromo-2,5-diiodobenzene with 2.2 equivalents of *o*-siloxyphenylacetylene **14**, which was prepared from commercially available 5-*tert*-butyl-2-iodophe-



Scheme 5. Synthesis of anthra[1,2-*b*:5,6-*b*′]bisbenzofuran **18** via Ru-catalyzed tandem cycloisomerization.



Scheme 6. Synthesis of dinaphtho[1,2-*b*:2′,1′-*d*]thiophene (**21**) via Ru-catalyzed tandem cycloisomerization.

nol in three steps, afforded diyne **15** in 98% yield (Scheme 5). Subsequent removal of the TBS groups with tetrabutylammonium fluoride (TBAF) in refluxing THF converted **15** to bisbenzofuran **16** in 84% yield. Finally, the Sonogashira coupling with trimethylsilylacetylene followed by desilylation afforded the desired substrate **17** in 90% yield. The final tandem cycloisomerization of **17** was carried out under the standard reaction conditions, affording the expected product **18**, with the hitherto unknown anthra[1,2-*b*:5,6-*b*′]bisbenzofuran framework, in 59% yield.

Furthermore, dinaphtho[1,2-*b*:2′,1′-*d*]thiophene (**21**) was obtained in 41% yield via the tandem cycloisomerization of diyne **20**, which was straightforwardly prepared by the tandem Suzuki–Miyaura coupling of commercially available 2,5-dibromothiophene with *o*-formylphenylboronic acid followed by Ohira–Bestmann alkynylation of **19** (Scheme 6).

Conclusion

We successfully identified the optimal ruthenium catalyst system for the cycloisomerization of 2-ethynylbiaryls as [η^6-(*p*-cymene)$RuCl_2(PR_3)$] (**4a**•PR_3) with two equivalents of $AgPF_6$. As the phosphine ligand, PPh_3, and its analogues and $P(OMe)_3$ were comparably efficient. Under the optimized reaction conditions (5 mol% catalyst, chlorobenzene, 120 °C, 20 h), *o*-ethynylbiphenyls were converted to the corresponding phenanthrenes in various yields. Moreover, this ruthenium catalyst was more efficient for the cycloisomerization of heteroaryl analogues, affording the corresponding polyheterocycles in higher yields. Based on several control experiments and the DFT calculations of model complexes, the electrophilic 6-*endo* cyclization involving a π-alkyne complex and subsequent consecutive 1,2-H shifts are proposed as the most probable mechanism for this ruthenium-catalyzed cycloisomerization of 2-ethynylbiaryls. As the demonstration of the synthetic potential of thus developed ruthenium-catalyzed cycloisomerization, a concise synthesis of the anthra[1,2-*b*:5,6-*b*′]bisbenzofuran framework was accomplished for the first time, and a three-step route to dinaphtho[1,2-*b*:2′,1′-*d*]thiophene from commercially available starting materials was also established using tandem cycloisomerizations.

Experimental Section

General procedure for ruthenium-catalyzed cycloisomerization—Synthesis of 2b

$AgPF_6$ (6.7 mg, 0.027 mmol) was added to a solution of [η^6-(*p*-cymene)$RuCl_2(PPh_3)$] (**4a**•PPh_3) (6.8 mg, 0.012 mmol) in dry degassed chlorobenzene (2 mL) and the mixture was stirred under an argon atmosphere at room temperature for 5 min. To this catalyst solution was added a solution of 2-ethynylbiphenyl **1b** (50.0 mg, 0.24 mmol) in dry chlorobenzene (1 mL) at room temperature, and the reaction mixture was degassed three times at −78 °C. The reaction mixture was then heated at 120 °C under argon for 20 h. After having been cooled to room temperature, the reaction mixture was concentrated in vacuo, and the crude material was purified with silica gel column chromatography (hexane/AcOEt = 50:1) to give **2b**[23] (38.3 mg, 77% yield) as a colorless solid (m.p. 93.0–94.0 °C, lit. m.p. 93.5–94.5 °C[23]). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.97 (s, 3H), 7.26–7.32 (m, 2H), 7.51–7.56 (m, 1H), 7.60–7.66 (m, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 8.59 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 55.3, 108.5, 117.0, 122.1, 124.2, 124.6, 125.5, 126.4, 126.6, 127.5, 128.5, 130.4, 131.0, 133.4, 158.2 ppm.

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Keywords: ethynylbiaryls · cycloisomerization · heterocycles · phenantherenes · ruthenium catalyst

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FULL PAPER

Catalysis

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A Combined Experimental and Computational Study on the Cycloisomerization of 2-Ethynylbiaryls Catalyzed by Dicationic Arene Ruthenium Complexes

Polyaromatics: A combination of [η^6-(*p*-cymene)$RuCl_2(PPh_3)$] and two equivalents of $AgPF_6$ effectively converted diverse 2-ethynylbiaryls into polyaromatics in chlorobenzene at 120 °C for 20 h (see scheme). Several control experiments and DFT calculations of model complexes were performed to propose a plausible reaction mechanism.