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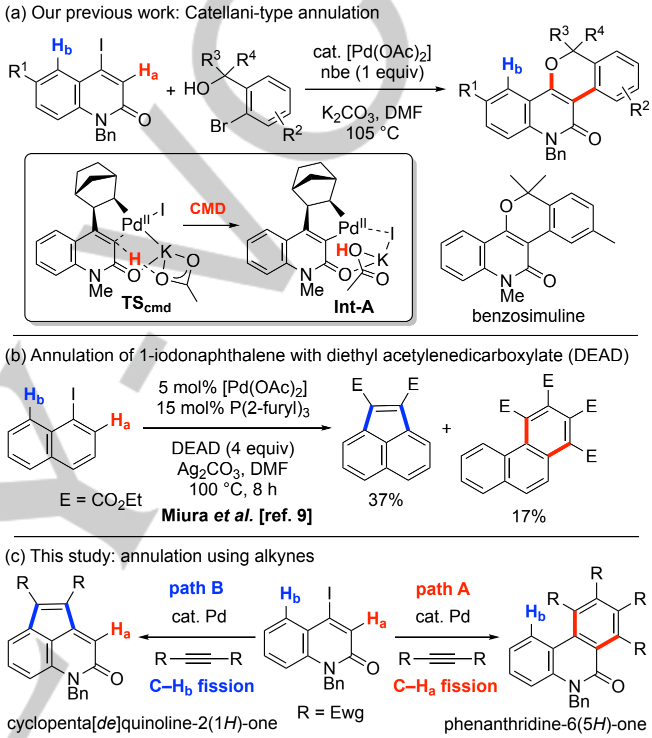
Palladium-Catalyzed [3+2] and [2+2+2] Annulations of 4-Iodo-2-quinolones with Activated Alkynes *via* Selective C–H Activation

Yoshihiko Yamamoto,*[a] Jiyue Jiang,[a] and Takeshi Yasui[a]

Abstract: The palladium-catalyzed reaction of 4-iodo-2-quinolones with activated alkynes was investigated. Cyclopenta[*de*]quinoline-2(1*H*)-ones and/or phenanthridine-6(5*H*)-ones were obtained *via* [3+2] annulation involving aromatic C–H activation or [2+2+2] annulation involving vinylic C–H activation, respectively. Reasonable mechanisms for the formation of these annulation products have been proposed based on density functional theory calculations.

Introduction

2(1*H*)-Quinolone (2-quinolone) is a privileged nitrogen-containing heterocyclic motif, which is found in natural products and pharmaceutical agents.[1] Therefore, various synthetic methods have been reported for the synthesis of 2-quinolone derivatives.[2] However, the discovery of an unprecedented synthetic route is still important toward the identification of novel bioactive 2-quinolones. In this regard, we have reported the modular assembly of 3,4-fused 2-quinolones and 4-aryl-2-quinolones using suitably protected (*ortho*-aminophenyl)propiolates as building blocks.[3] Moreover, we have investigated the Catellani-type annulation of 4-iodo-2-quinolones, which are prepared *via* hydroiodination/lactamization of (*ortho*-aminophenyl)propiolates.[4] We found that the Pd(0)/norbornene-mediated reaction occurred preferentially at the vinylic C–H_a bond over the aromatic C–H_b bond, affording analogs of the natural product, benzosimuline (Scheme 1a). Based on the mechanism reported for the Catellani reaction[5] and our own density functional theory (DFT) calculations, we proposed that a concerted metalation-deprotonation (CMD) step occurred *via* **TS$_{cmd}$** to produce five-membered palladacycle intermediate **Int-A**.[6] Therefore, we further envisaged that the palladium-catalyzed reaction of 4-iodo-2-quinolones with alkynes would afford the [2+2+2] annulation products, phenanthridine-6(5*H*)-ones, *via* activation of the vinylic C–H_a bond (path A, Scheme 1c). Alternatively, previously unknown cyclopenta[*de*]quinoline-2(1*H*)-ones can be obtained upon activation of the aromatic C–H_b bond (path B, Scheme 1c).



Scheme 1. (a) Pd/norbornene-mediated Catellani-type annulation of 4-iodo-2-quinolones, (b) Pd-catalyzed annulation of 1-iodonaphthalene with DEAD, and (c) Pd-catalyzed annulation of 4-iodo-2-quinolone with alkynes.

Prototypical annulations of iodoarenes with diphenylacetylene were pioneered by Heck and Grigg. The Heck group performed the reaction of iodobenzene using $[Pd(OAc)_2]$/$2PPh_3$ and Et_3N as a catalyst and a base, respectively, to obtain tetraphenylnaphthalene in 47% yield through a [2+2+2] annulation *via* activation of the *ortho* C–H bond.[7] In contrast, Grigg and coworkers disclosed that the reaction of 1-iodonaphthalene with diphenylacetylene using TlOAc as a base afforded the acenaphthylene derivative in 45% yield through a [3+2] annulation *via* C–H activation at the 8-position.[8] Later, Miura and coworkers reported the palladium-catalyzed reaction of 1-iodonaphthalene with diethyl acetylenedicarboxylate (DEAD) in the presence of Ag_2CO_3 as a base (Scheme 1b).[9] In this case, both the [3+2] and [2+2+2] annulation products were obtained with the former as the major product. Moreover, Dyker and the Larock group separately discovered unusual annulations of iodobenzene with diphenylacetylene, which produced phenanthrene or benzylidenefluorene derivatives *via* multiple C–H activation steps.[10,11] Thus, these precedents exemplify the divergent C–H activation reactivity of iodoarenes, which is

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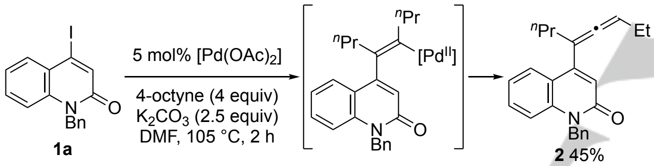
dependent on the reaction conditions and/or substrate used. Nevertheless, carboannulation of iodinated heterocycles involving C–H activation has been underdeveloped, despite the importance of heteropolycycles as drug lead compounds.[12,13] Herein, we report our study on the palladium-catalyzed annulation of 4-iodo-2-quinolones with alkynes *via* C–H activation.

Results and Discussion

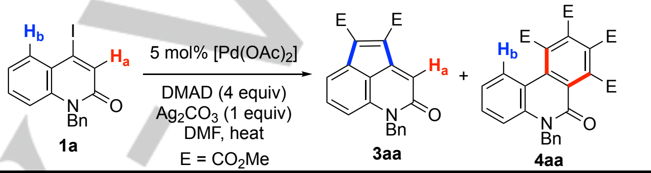
Reaction of 4-iodo-2-quinolone with non-activated internal alkynes. At the outset of this study, the reaction of 4-iodo-2-quinolone **1a** with 4-octyne (4 equiv) as an internal alkyne under conditions similar to the previously reported Catellani-type annulation was investigated (Scheme 2). As a result, 4-allenylated product **2** was obtained in 45% yield, instead of the expected annulation product. As previously suggested for similar allenylation reactions of iodobenzenes,[14] allene **2** was formed *via* β-hydride elimination of an alkenylpalladium(II) intermediate, indicating that the desired alkyne insertion took place. Accordingly, internal alkynes bearing no propargylic hydrogens should be used to realize the desired annulation.



Scheme 2. Formation of 4-allenyl-2-quinolone **2** from **1a** and 4-octyne.

Reaction of 4-iodo-2-quinolones with activated internal alkynes. Subsequently, the reactivity of dimethyl acetylenedicarboxylate (DMAD) as an activated internal alkyne was investigated because Miura and coworkers have previously reported that acetylenedicarboxylates are efficient alkyne components for the palladium-catalyzed annulation of iodoarenes (Table 1).[9] The reaction of **1a** with DMAD (4 equiv) was performed under the same reaction conditions to those outlined in Scheme 2, which resulted in no reaction. Thus, the reaction was conducted at a higher temperature (120 °C), but only an intractable mixture was obtained (entry 1). Ag_2CO_3 was used as the base instead of K_2CO_3 according to the report of Miura and coworkers.[9] 4-Iodo-2-quinolone **1a** was consumed within 4 h and two new products were formed along with hexamethyl mellitate (HMM), which was formed *via* the cyclotrimerization of DMAD (entry 2). Purification by silica gel chromatography afforded cyclopenta[*de*]quinoline-2(1*H*)-one **3aa** as the major product in 42% yield. The expected product, phenanthridinone **4aa**, was also obtained in 15% yield as an inseparable mixture with small amounts of HMM (6% yield). This result shows that the aromatic hydrogen (H_b) was preferably activated over the vinylic hydrogen (H_a). The reaction also proceeded at a lower temperature (80 °C), although a longer reaction time (20 h) was required (entry 3). The selectivity toward product **3aa** over **4aa** slightly increased at a lower temperature. The use of toluene as the solvent instead of DMF at 80 °C resulted in the recovery of **1a** (70% yield) and the annulation products were not detected. The use of P(2-furyl)$_3$ as the ligand (3 mol%) did not improve the outcome of the reaction (entry 4). Using AgOAc (2 equiv) as the base instead of Ag_2CO_3 resulted in an incomplete reaction (75% conversion of **1a**) even upon heating at 100 °C for 4 h and lower product selectivity (entry 5). The observed annulation of 4-iodo-2-quinolone **1a** with DMAD is remarkable because 4-iodoquinoline (Figure 1) failed to afford the corresponding annulation products, and produced an intractable product mixture under the same reaction conditions.

Table 1. Reaction of **1a** with DMAD.



Entry	Temp. [°C]	Time [h]	**3aa**, **4aa**, HMM [%]	**3aa**/**4aa** ratio
1[a]	120	24	ND	ND
2	100	4	42, 15, 6	2.8
3	80	20	53, 13, 12	4.1
4[b]	80	20	32, 13, 8	2.5
5[c]	100	4	41, 30, 8	1.4

[a] K_2CO_3 was used as the base. [b] P(2-furyl)$_3$ (3 mol%) was added. [c] AgOAc (2 equiv) was used instead of Ag_2CO_3.

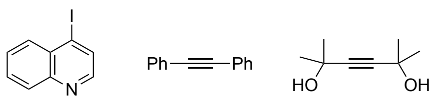
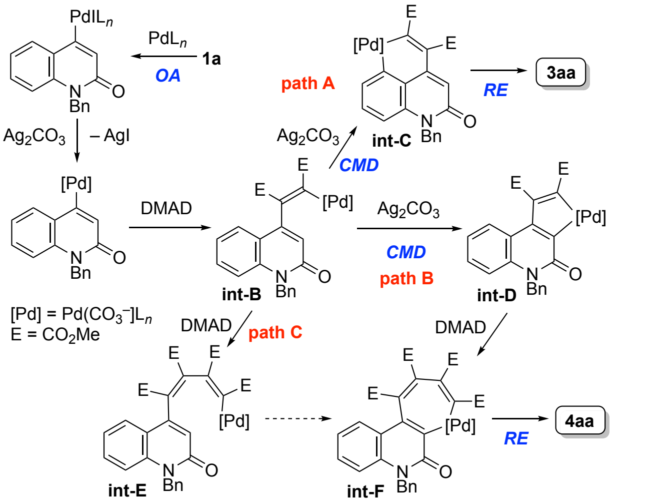


Figure 1. Unsuccessful reactants.

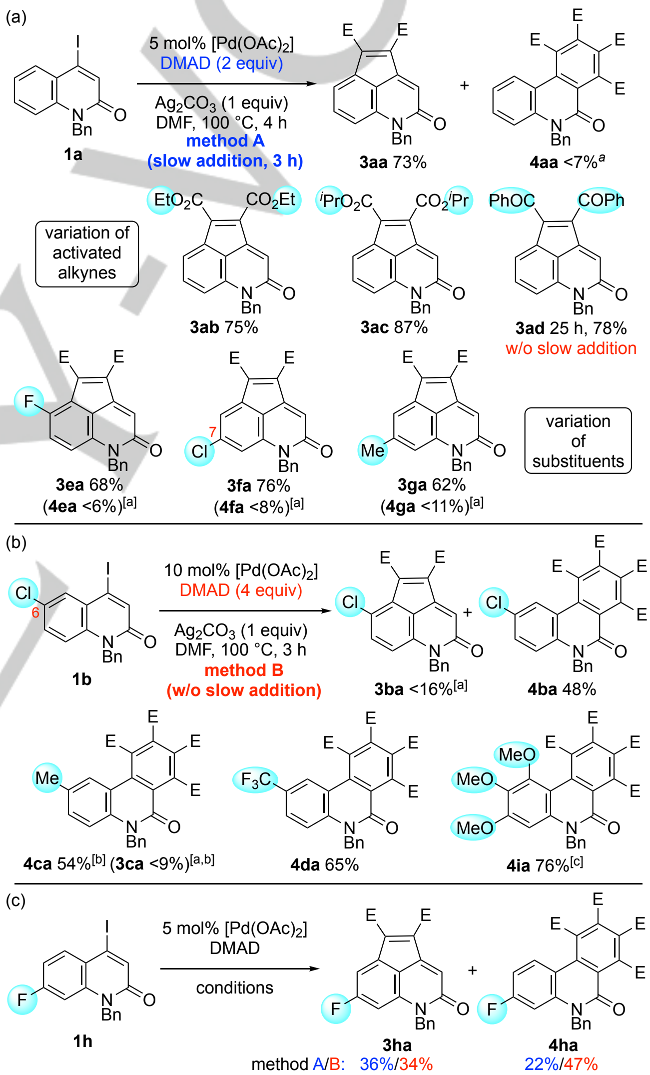
Plausible pathways for the formation of **3aa** and **4aa** are outlined in Scheme 3. Initially, oxidative addition (OA) of **1a** is followed by the insertion of DMAD to generate alkenylpalladium intermediate **int-B**, which is the bifurcation point to **3aa** and **4aa**. The major product **3aa** is produced *via* six-membered palladacycle intermediate **int-C**, which is generated from **int-B** *via* CMD of the aromatic hydrogen (path A). On the other hand, CMD of the vinylic hydrogen converts **int-B** into five-membered palladacycle intermediate **int-D** (path B), which undergoes insertion of a second DMAD molecule. Finally, reductive elimination occurs from the resulting seven-membered palladacycle intermediate **int-F** to afford minor product **4aa**. Alternatively, the insertion of DMAD occurs from **int-B** to generate dienylpalladium intermediate **int-E** (path C), which can be converted into **4aa**.



Scheme 3. Plausible pathways for the formation of **3aa** and **4aa**.

Accordingly, minor product **4aa** can be produced *via* two pathways (path B and path C). The selectivity toward path A vs. path B can be determined by the relative rate of the intramolecular C–H activation step, while the rate of path C should be influenced by the concentration of DMAD. Thus, to improve the selectivity of **3aa** over **4aa**, we next conducted the reaction of **1a** with the slow addition of DMAD (2 equiv) in DMF for 3 h using a syringe pump (method A, Scheme 4a). As a result, the formation of **4aa** was effectively suppressed (<7%) and **3aa** was obtained in 73% yield. Similarly, the use of bulkier diethyl and diisopropyl esters instead of DMAD predominantly afforded **3ab** and **3ac** in 75% and 87% yields, respectively. In addition to acetylenedicarboxylates, dibenzoylacetylene can be used as the activated alkyne component. Notably, the reaction of **1a** with dibenzoylacetylene resulted in the predominant formation of [3+2] annulation product **3ad** in 78% yield without recourse to the slow-addition technique. In striking contrast, the use of diphenylacetylene and 2,5-dimethylhex-3-yne-2,5-diol (Figure 1) instead of DMAD resulted in no reaction. Thus, the activating groups play a dispensable role in the reaction.

Next, 4-iodo-2-quinolones **1b**–**d**, bearing a substituent at the 6-position, were examined as substrates (Scheme 4b). The reaction of 6-chloro derivative **1b** was conducted without the slow addition of DMAD (method B) to preferably afford phenanthridinone **4ba** (48% yield) over [3+2] annulation product **3ba** (<16% yield). Similar selectivity was observed for the reaction of 6-methyl analog **1c**; ^{1}H NMR analysis of the crude product showed that **3ca** and **4ca** were formed in 17% and 65% yields, respectively. However, the purification of these products was rather difficult due to the formation of inseparable byproducts. Thus, the reaction of **1c** was again conducted at a lower temperature (80 °C) and **4ca** was isolated in 54% yield. Notably, CF_3-analog **1d** exclusively afforded the corresponding product **4da** in 65% yield.[15] These results suggest that the substituent at the 6-position hinders the aromatic C–H activation step. In striking contrast, 6-fluoro-substituted substrate **1e** selectively afforded [3+2] annulation product **3ea** in 68% yield using the slow addition method, showing that a small fluorine atom at the 6-position was well tolerated (Scheme 4a). When 4-iodo-2-quinolone **1i** bearing no proton at the 5-position was used as the substrate, the desired phenanthridinone **4ia** was exclusively obtained in 76% yield (Scheme 4b).



Scheme 4. Substrate scope of the palladium-catalyzed annulation of 4-iodo-2-quinolones (E = CO_2Me). [a] These minor products include non-negligible impurities. [b] 80°C, 20 h. [c] 2 h.

Subsequently, the effect of the substituents at the 7-position on the chemoselectivity was investigated using 7-chloro-, 7-methyl-, and 7-fluoro-substituted substrates **1f**–**h** under slow-addition conditions (method A). While the reactions of **1f** and **1g**

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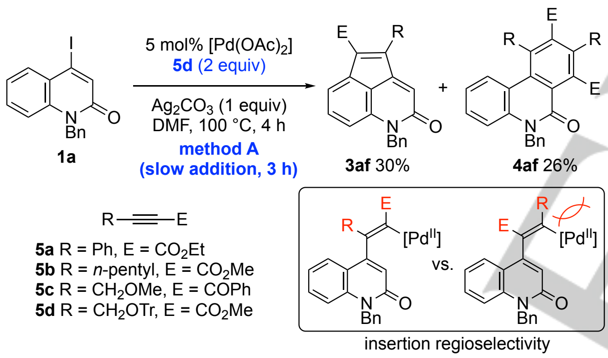
selectively afforded the expected [3+2] annulation products **3fa** and **3ga** in 76% and 62% yields, respectively (Scheme 4a), the chemoselectivity almost disappeared for fluoro-analog **1h**, affording **3ha** and **4ha** in 36% and 22% yields, respectively (Scheme 4c). Furthermore, the [2+2+2] annulation was favored over [3+2] annulation when the reaction was repeated using method B and the yield of **4ha** was significantly increased (47% yield). Although the details are unclear at this stage, the fluorine substituent at the 7-position has a significant electronic impact on the selectivity of the C–H activation step.

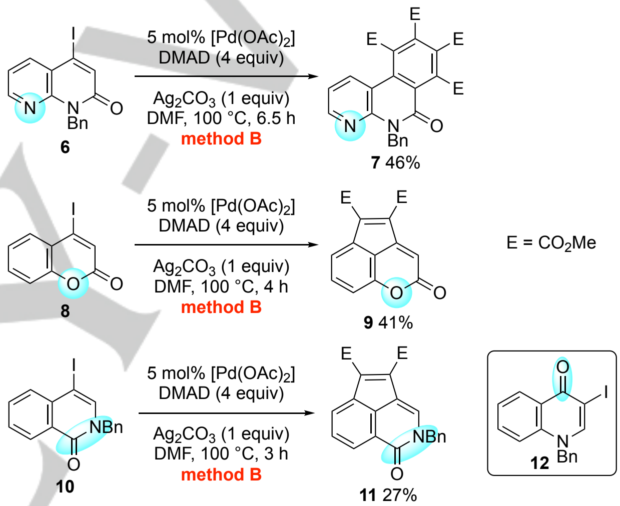
The reaction of **1a** with an unsymmetrical alkyne is rather formidable probably due to the lack of regioselectivity in the alkyne insertion step (Scheme 5). The use of alkynyl esters **5a** and **5b**, or ketone **5c** without slow addition at 80–100 °C afforded a complex mixture of products. Nevertheless, the reaction of **1a** with alkynyl ester **5d** bearing a bulky trityl ether moiety under slow-addition conditions (method A) produced the expected annulation products **3af** and **4af** in 30% and 26% yields, respectively. Notably, these products were obtained as single regioisomers. Although the regioselectivities are unknown at this stage, we considered that insertion occurred in such a way that the Pd center is placed on the less congested carbon α to the ester group.



Scheme 5. Reaction of **1a** with unsymmetrical alkynes.

Reactivity of related iodinated heterocycles. As described above, the palladium-catalyzed reaction of 4-iodo-2-quinolones with DMAD afforded cyclopenta[*de*]quinolone and/or phenanthridinone derivatives depending on the substrate structure and reaction conditions used. In contrast, 4-iodoquinoline failed to afford the corresponding annulation products. These results demonstrate the distinct reactivity of 4-iodo-2-quinolones toward the palladium-catalyzed annulations with activated alkynes. Thus, we investigated the reactions of related iodinated heterocycles, such as 4-iodo-1,8-naphthyridin-2(1*H*)-one (**6**), 4-iodocoumarin (**8**), 4-iodo-1-isoquinolone (**10**), and 3-iodo-4-quinolone (**12**) to compare their reactivity with that of 4-iodo-2-quinolone (**1a**) (Scheme 6).

The reaction of 4-iodo-1,8-naphthyridin-2(1*H*)-one (**6**) with DMAD was conducted for 6.5 h using method B to selectively afford [2+2+2] annulation product **7** in 46% yield. The corresponding [3+2] annulation product was not detected, although small amounts of unidentifiable byproducts were obtained. In a similar manner, 4-iodocoumarin (**8**) predominantly afforded [3+2] annulation product **9** in 41% yield without recourse to the slow addition technique. The reaction of 4-iodo-1-isoquinolone (**10**) resulted in a complex mixture of products. Nevertheless, cyclopenta[*de*]isoquinolin-1(2*H*)-one **11** was isolated, albeit in a low yield (27%). The corresponding [2+2+2] annulation product was not detected. In striking contrast, 3-iodo-4-quinolone (**12**) failed to afford the expected [2+2+2] annulation product along with **12** recovered in 60% yield, as indicated by ^{1}H NMR analysis of a crude reaction mixture. These results demonstrate that 4-iodo-2-quinolones **1** are much superior as the substrates to iodinated heterocycles **6**, **8**, **10**, and **12**, and the product selectivity varies depending on the heterocyclic framework.



Scheme 6. Palladium-catalyzed reactions of 4-iodinated heterocycles with DMAD.

Mechanistic considerations. To obtain insights into the reaction mechanism, DFT calculations [SMD (DMF) B3LYP(GD3BJ)/SDD–6-31++G(d,p)//B3LYP(GD3BJ)/LanL2DZ–6-31G(d)] were carried out with a particular focus on each individual step. For computational efficiency, *N*-methyl 2-quinolones were analyzed instead of the *N*-benzyl derivatives used in this study (for details, see Supporting Information). The present reaction requires Ag_2CO_3 as the base, in striking contrast to our previous Catellani-type annulation; the use of K_2CO_3 instead of Ag_2CO_3 led to an intractable mixture of products (Table 1, entry 1). These observations suggest that the Ag^+ ion plays a significant role. Thus, Ag^+ was included in the model complexes. Because there are many examples of the related palladium-catalyzed annulations of iodoarenes,[7-11] it is reasonable to propose that the present palladium-catalyzed annulation starts with the oxidative addition of 4-iodo-2-quinolone to an active Pd(0) species (Scheme 3).[16] After oxidative addition, the resultant vinyl palladium iodide is assumed to undergo facile ligand exchange in the presence of

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Ag_2CO_3 and DMAD to produce vinyl palladium carbonate complexes **s0** and **sI** with a η^2-alkyne ligand (Figure S2 in Supporting Information). Alkyne complex **sI** bearing a κ^1-OCO_2Ag ligand associated with additional Ag_2CO_3 was located 12.8 kcal/mol lower in energy than **s0** bearing only κ^2-OCO_2Ag. Subsequent insertion of the coordinated DMAD was found to be facile as it proceeds from **sI** *via* $\mathbf{TS_{sI\text{-}sII}}$ with a small activation barrier of $\Delta G^{\ddagger}$ = +10.8 kcal/mol, resulting in the highly exergonic (–38.1 kcal/mol) formation of dienyl palladium intermediate **sII**. In contrast, the second insertion step was found to be less efficient as its activation barrier was estimated to be 9.4 kcal/mol higher ($\Delta G^{\ddagger}$ = +20.2 kcal/mol) than that for the first insertion step and the formation of trienyl palladium **sIV** is less exergonic (–29.1 kcal/mol) when compared to the first insertion step (Figure S3 in Supporting Information).

Next, the C–H activation step was investigated. Previously, on the basis of their DFT study, Schaefer and coworkers suggested that a Pd–Ag heterobimetallic complex intermediate with bridging acetate ligands plays a critical role in the CMD step of the directed ortho C–H functionalization of benzamides.[17] In contrast, we couldn't locate any heterobimetallic intermediate bearing a carbonate bridge. Instead, we found vinyl Pd(κ^2-CO_3)Ag•Ag_2CO_3 complexes **Ia** and **Ib** as precursors to the CMD step (Figure 2a). The latter is slightly more stable than the former. From these intermediates, the CMD step proceeds *via* $\mathbf{TS_{Ia\text{-}II}}$ and $\mathbf{TS_{Ib\text{-}III}}$ with activation barriers of $\Delta G^{\ddagger}$ = +9.8 and +12.8 kcal/mol, respectively. The formation of six-membered palladacycle **II** from **Ia** was found to be more exergonic (–21.8 kcal/mol) than that of five-membered palladacycle **III** from **Ib** (–12.9 kcal/mol).

Figure 3a outlines the energy profile for the transformation from **sI** to **II** and **III** *via* DMAD insertion/CMD or from **sI** to **V** *via* a double DMAD insertion/CMD. The first DMAD insertion (**sI** → **sII**) is facile, characterized by a small activation barrier and high exergonicity. The subsequent CMD of the aromatic proton proceeds from intermediate **Ia**, which is slightly less stable than initially formed isomer **sII**. The energetic span[18] between **sII** and $\mathbf{TS_{Ia\text{-}II}}$ for this process is +10.5 kcal/mol. On the other hand, intermediate **Ib**, which undergoes the competitive CMD of the vinylic proton, is slightly more stable than **sII** and thus, the energetic span for this process is identical with its activation barrier (+12.8 kcal/mol). Accordingly, the aromatic CMD is kinetically favored over the vinylic CMD, as the energetic span is smaller. In addition, the resultant six-membered palladacycle **II** is more stable than five-membered palladacycle **III**. Thus, it is reasonable to assume that the aromatic CMD leading to thermodynamically more stable palladacycle **II** is favored over the vinylic CMD leading to less stable palladacycle **III**. In fact, $\mathbf{TS_{Ia\text{-}II}}$ is less strained and earlier than $\mathbf{TS_{Ib\text{-}III}}$ as indicated by the C–H_b and O–H_b distances in $\mathbf{TS_{Ia\text{-}II}}$ are shorter and longer than those of C–H_a and O–H_a in $\mathbf{TS_{Ib\text{-}III}}$, respectively (Figure 3b).

The association of one DMAD molecule with **sII** produces η^2-alkyne complex **sIII**, which is more stable than **sII**, **Ia**, and **Ib**. The activation barrier for the second DMAD insertion is higher than those of the CMDs. Therefore, the second insertion is less feasible than the CMDs. However, it is assumed that the second insertion is non-negligible because the activation barrier is small enough to be overcome under the experimental conditions and an excess amount of DMAD hampers the CMD step by capturing intermediates **Ia** and **Ib** (Figure 3c). In fact, the slow addition of DMAD (method A) decreased the formation of the [2+2+2] annulation products. Accordingly, paths A and B are favored over path C with the lower DMAD concentration, while path C becomes competitive with the higher DMAD concentration (Scheme 3).

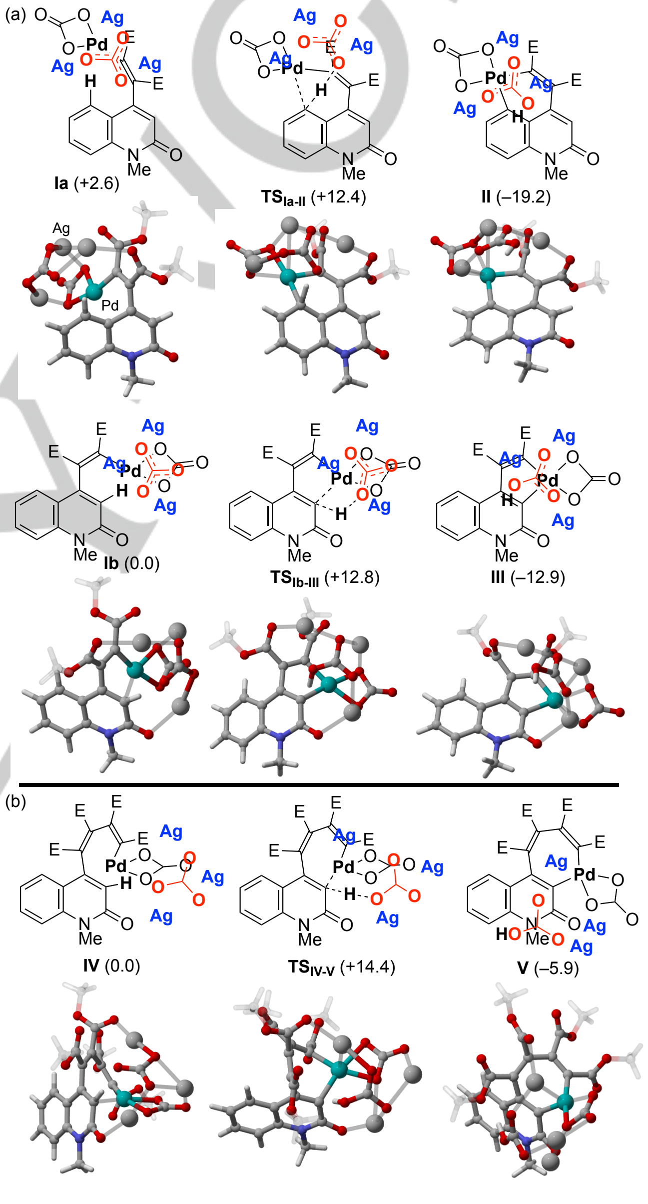

Figure 2. Calculated model quinolones (E = CO_2Me) related to the CMD step. The relative Gibbs free energies (298 K, 1 atm) are given in the parentheses (kcal/mol).

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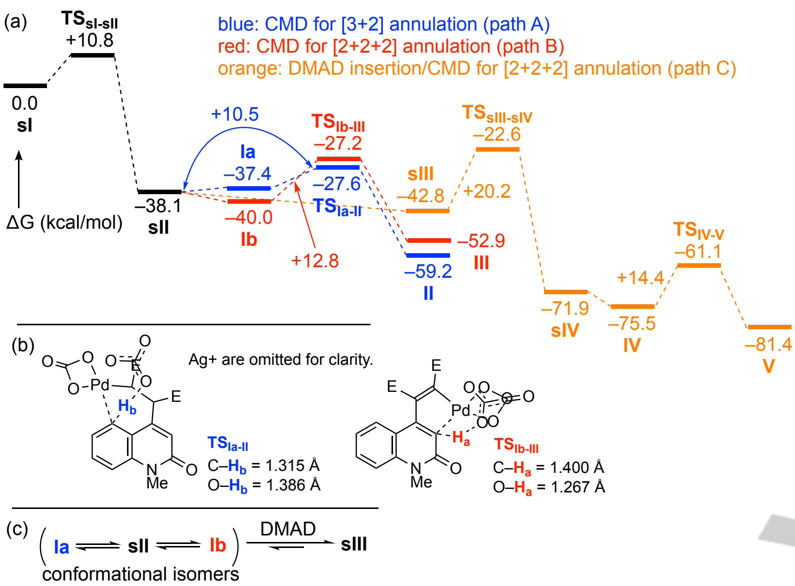


Figure 3. Energy profile for the transformation from model quinolone complex **sI** to intermediates **II**, **III**, and **V**. The relative Gibbs free energies (298 K, 1 atm) are given in the parentheses (kcal/mol).

Double insertion product **sIV** is considered to be an intermediate for the [2+2+2] annulation *via* the seven-membered palladacycle. Thus, we next analyzed the CMD step from **sIV**. DFT calculations identified **IV**, which is the isomer of **sIV**, as the precursor for the CMD step (Figure 2b). The former was located slightly lower in energy than the latter. CMD occurs *via* **TS**$_{\mathbf{IV\text{-}V}}$ with an activation barrier of $\Delta G^{\ddagger}$ = +14.4 kcal/mol. This value is reasonably low enough for the CMD step to occur at ambient temperature, but higher than the activation barriers of the CMD steps from **Ia** and **Ib**. The formation of seven-membered palladacycle **V** from **IV** is only slightly exergonic (–5.9 kcal/mol). Accordingly, the CMD of **IV** is less favorable than those of **Ia** and **Ib** (Figure 3a).

The reductive elimination step from the model six-membered palladacycles was next investigated using DFT calculations (Figure 4 and Figure S4 in Supporting Information). Because the anion $AgCO_3^-$ ligand on the palladium center was replaced by the aryl ligand after the CMD step, reductive elimination of palladacycle **VI** bearing the Pd(II) center with one neutral ligand was analyzed. It was found that when the neutral ligand is DMF, the reductive elimination proceeds *via* **TS**$_{\mathbf{VIa\text{-}VIIa}}$ with a reasonable activation barrier of $\Delta G^{\ddagger}$ = +21.6 kcal/mol and the formation of [3+2] annulation product **VIIa** containing a [Pd(0)(dmf)] fragment is exergonic by –15.7 kcal/mol. Thus, this process is both kinetically and thermodynamically favorable under the experimental conditions. The replacement of DMF with electron-withdrawing DMAD reduces the activation barrier to $\Delta G^{\ddagger}$ = +13.4 kcal/mol and increases the exergonicity to –25.0 kcal/mol. These results imply that electron-withdrawing alkynes facilitate the reductive elimination step by reducing the electron density of the Pd(II) center in palladacycle **VIb**.

Previously, Glorius and coworkers proposed that AgOAc oxidizes the Pd(II) center in the key palladacycle intermediate and thereby, the resultant Pd(IV) palladacycle undergoes facile reductive elimination.[19,20] Thus, reductive elimination from palladacycle **VIc** containing a Pd(IV) center coordinated by a κ^2-CO_3^{2-} ligand was also investigated. In accordance with Glorius' suggestion, the activation barrier was significantly reduced ($\Delta G^{\ddagger}$ = +5.6 kcal/mol) and the formation of **VIIc** with a Pd(II) fragment was found to be highly exergonic (–40.2 kcal/mol). Accordingly, oxidation of the palladacycle intermediate dramatically enhances the reductive elimination step. However, the involvement of a highly unstable Pd(IV) oxidation state is less likely since Ag_2CO_3 is a weak oxidant.

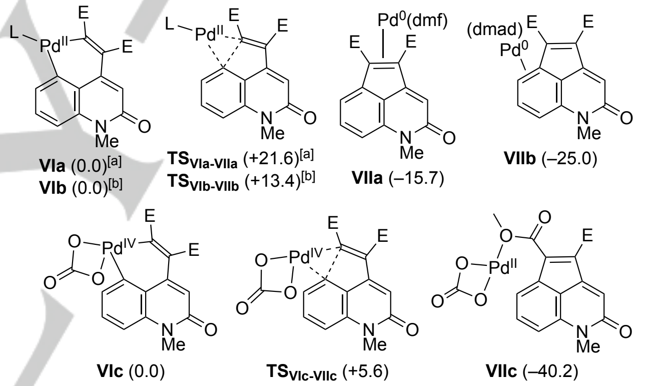
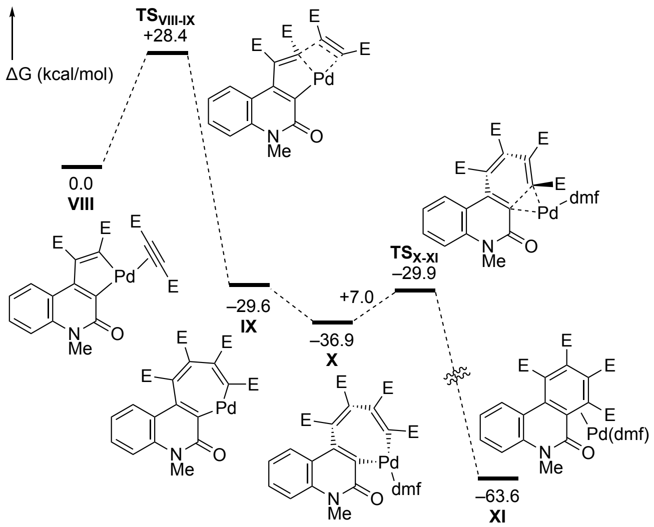


Figure 4. Calculated model quinolones (E = CO_2Me) related to the reductive elimination step. The relative Gibbs free energies (298 K, 1 atm) are given in the parentheses (kcal/mol; [a] L = DMF and [b] L = DMAD).

Formation of the [2+2+2] annulation product was analyzed (Scheme 7 and Figure S5 in Supporting Information). Alkyne insertion into the C(vinyl)–Pd bond of five-membered palladacycle **VIII** occurs *via* **TS**$_{\mathbf{VIII\text{-}IX}}$ with a relatively higher activation barrier of $\Delta G^{\ddagger}$ = +28.4 kcal/mol, resulting in the highly exergonic (–29.6 kcal/mol) formation of seven-membered palladacycle **IX** with an open coordination site. Subsequently, coordination of DMF on the Pd(II) center results in the formation of tub-shaped palladacycle **X**, in which the α carbons are placed in close proximity to each other. From **X**, facile reductive elimination proceeds *via* **TS**$_{\mathbf{X\text{-}XI}}$ with a small activation barrier of $\Delta G^{\ddagger}$ = +7.0 kcal/mol, resulting in the highly exergonic (–63.6 kcal/mol) formation of arene complex **XI**. Accordingly, the DMAD insertion step from five-membered palladacycle **VIII** is the most difficult step in the [2+2+2] annulation pathway.



Scheme 7. The energy surface for the transformation of model quinolone complex **VIII** to arene complex **XI** (E = CO_2Me). The relative Gibbs free energies (298 K, 1 atm) are given in the parentheses (kcal/mol).

Finally, the reaction of diphenylacetylene (DPA) was analyzed for comparison with that of DMAD. The initial DPA insertion from η^2-alkyne complex **sV** and subsequent aromatic CMD were investigated (Figures S6, Supporting Information). It was found that the DPA insertion occurs *via* $\mathbf{TS_{sV\text{-}sVI}}$ with an activation barrier of $\Delta G^‡$ = +18.3 kcal/mol, which is larger than that for the DMAD insertion from **sI** ($\Delta G^‡$ = +10.8 kcal/mol). This inefficiency can be ascribed to the larger geometrical change from **sV** to $\mathbf{TS_{sV\text{-}sVI}}$ than that for the corresponding DMAD complexes (**sI** → $\mathbf{TS_{sI\text{-}sII}}$) as evidenced by the significant decrease in the C_1–C_2 distance for the DPA complexes (Figure S7). The aromatic CMD of **sVIIa** proceeds *via* $\mathbf{TS_{sVIIa\text{-}sVIII}}$ with an activation barrier of $\Delta G^‡$ = +14.6 kcal/mol, which is ca. 5 kcal/mol larger than that for DMAD-derived intermediate **Ia** ($\Delta G^‡$ = +9.8 kcal/mol). Due to the coordination of the ester carbonyl group to the Ag^+ counter ion, the carbonate base is placed in closer proximity to the abstracted H atom in the DMAD-derived vinyl Pd complex **Ia** (the H–O distance = 2.239 Å) than in **sVIIa** (the H–O distance = 2.475 Å, Figure S8). NBO analyses also indicate that the electron donation from the carbonate oxygen lone pairs to the C_{sp^2}–H antibonding orbital is stronger in **Ia** than in **sVIIa**. Therefore, proton abstraction is more facile for **Ia**.

In contrast, the lactam carbonyl moiety plays a role of the directing group for Ag_2CO_3, facilitating the vinylic CMD. Accordingly, the CMD of DPA-derived complex **sVIIb** proceeds *via* $\mathbf{TS_{sVIIb\text{-}sIX}}$ with an activation barrier of $\Delta G^‡$ = +13.1 kcal/mol (Figure S6), which is comparable with that of DMAD-derived complex **Ib** ($\Delta G^‡$ = +12.8 kcal/mol, Figure 2). Moreover, **sVIIb** was located ca. 5 kcal/mol lower than **sVIIa**. Thus, the five-membered palladacycle **sIX** is expected to be produced predominantly (Figure S9). However, the subsequent insertion of DPA into the Pd–C bond of palladacycle **sX** was found to be difficult as the activation barrier is too high to overcome under the experimental conditions ($\Delta G^‡$ = +33.8 kcal/mol, Figure s10). Therefore, the formation of palladacycle **sIX** is assumed to be a dead end of the reaction of DPA.

Conclusions

In summary, we have successfully developed the palladium-catalyzed annulation of 4-iodo-2-quinolones with activated internal alkynes involving C–H activation. 4-Iodoquinolones were treated with activated alkynes such as DMAD in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in DMF at 100 °C to produce the [3+2] annulation products (cyclopenta[*de*]quinoline-2(1*H*)-ones) *via* aromatic C–H activation along with the [2+2+2] annulation products (phenanthridine-6(5*H*)-ones) *via* vinylic C–H activation. The product selectivity ([3+2] vs. [2+2+2]) varied depending on the substituents on the benzene ring of the quinolone substrate, activated alkyne, and reaction conditions. It was found that 4-iodo-2-quinolone is an exceptional substrate for the present palladium-catalyzed annulation; 4-iodoquinoline and 3-iodo-4-quinolone all failed to undergo the annulation, and 4-iodo-1,8-naphthyridin-2(1*H*)-one, 4-iodocoumarin, and 4-iodo-1-isoquinolone exhibited diminished reactivity. We also investigated the individual steps in the catalytic cycle using DFT calculations on model 4-iodo-2-quinolones. Notably, it was suggested that the Ag^+ ions and ester moieties of DMAD play significant roles in the CMD steps; the coordination network, consisting of the Ag^+ ion, ester moieties, and carbonate ligand on the Pd center, effectively places the carbonate base in close proximity to the proton abstracted.

Experimental Section

Reaction of iodinated heterocycles with activated alkynes

Representative procedure A: A solution of 4-iodo-2-quinolone **1a** (71.7 mg, 0.199 mmol), $[Pd(OAc)_2]$ (2.4 mg, 0.0107 mmol), and Ag_2CO_3 (56.8 mg, 0.206 mmol) in dry DMF (2.0 mL) was degassed at –90 °C. To this solution was added a solution of DMAD (49 μL, 0.400 mmol) in dry degassed DMF (2.0 mL) via syringe pump (0.01 mL/min) under an argon atmosphere at 100 °C. The reaction mixture was stirred at 100 °C for an additional 1 h. After cooling to room temperature, insoluble materials were removed by filtration. To the filtrate was added H_2O (20 mL) and the obtained mixture was extracted with EtOAc/hexane (1:1, 3 × 20 mL). The combined organic layer was washed with H_2O (2 × 40 mL) and brine (40 mL), and dried over Na_2SO_4. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1~1:1) to afford **3aa** (54.4 mg, 73%) as an orange solid (mp. 151.9–153.7 °C) and then **4aa** (6.7 mg, 7%) as a yellow solid (mp 191.2–193.5 °C).

Representative procedure B: A solution of 4-iodo-2-quinolone **1b** (78.5 mg, 0.198 mmol), $[Pd(OAc)_2]$ (4.7 mg, 0.0209 mmol), Ag_2CO_3 (56.0 mg, 0.203 mmol), and DMAD (100 μL, 0.816 mmol) in dry DMF (4.0 mL) was degassed at –90 °C. The reaction mixture was stirred under an argon atmosphere at 100 °C for 3 h. After cooling to room temperature, insoluble materials were removed by filtration. To the filtrate was added H_2O (20 mL) and the obtained mixture was extracted with EtOAc/hexane (1:1, 3 × 20 mL). The combined organic layer was washed with H_2O (2 × 40 mL) and brine (40 mL), and dried over Na_2SO_4. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1~1:1) to afford **3ba** (12.8 mg, 16%; including minor impurity) as a yellow solid (mp 163.1–169.1 °C) and then **4ba** (52.9 mg, 48%) as a yellow solid (mp 102.2–106.3 °C).

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Keywords: palladium • quinolone • alkyne • C-H activation • DFT calculation

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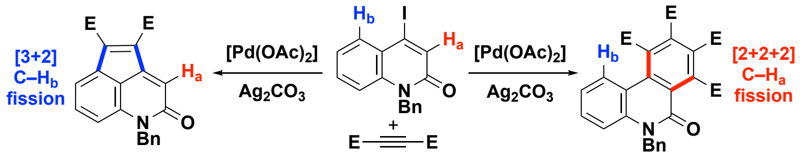

The palladium-catalyzed reaction of 4-iodo-2-quinolones with activated alkynesaforded cyclopenta[*de*]quinoline-2(1*H*)-ones and/or phenanthridine-6(5*H*)-ones *via* [3+2] annulation involving aromatic C–H activation or [2+2+2] annulation involving vinylic C–H activation, respectively. Reasonable mechanisms for the formation of these annulation products have been proposed based on density functional theory calculations.

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Palladium-Catalyzed [3+2] and [2+2+2] Annulations of 4-Iodo-2-quinolones with Activated Alkynes via Selective C–H Activation