

## RESEARCH ARTICLE

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## Pd(IV)-induced nucleophile delivery in a cascade double Heck reaction†

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A new cascade reaction has been described. Unsaturated 1,2-diiodides participate in a double Heck coupling with an unprecedented nucleophile inclusion into the core of the first alkene fragment. Thus, the complex carcass of the target molecule is coherently constructed from four independent components in one domino procedure. The assumed mechanism of the transformation sequence is presented. As a key step, the Pd(IV) complex is formed by a previously unreported intramolecular oxidative addition of the transitional  $\sigma$ -alkyl Pd(II) species obtained after the first carbopalladation. This Pd(IV) intermediate is capable of successful reductive elimination, which is unfavorable earlier, therefore connecting the attached  $sp^3$ -carbon and heteroatom of the nucleophile. As a result, three new important bonds – C( $sp^2$ )–C( $sp^2$ ), C( $sp^2$ )–C( $sp^3$ ), and C( $sp^3$ )–O/N – are built in the process. Water, phenols, secondary amines, and anilines were employed as a nucleophile source in basic aqueous media. General synthetic protocols have been devised for styrenes as the employed alkene, although one example of methyl acrylate usage is also revealed. 1,2-Diiodocyclopentene serves as an example of a non-activated olefinic substrate, while multiple examples of 1,2-diiodoarene and 2,3-diiodo-1,4-naphthoquinone usage are reported. The prospects of further development of the discovered reaction include different fields in organic chemistry and catalysis.

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## Introduction

For 50 years, palladium-catalyzed Mizoroki–Heck reaction has been serving as an endless source of new applications, synthetic procedures, studies of mechanism, ligand development, media variations, and many other aspects of organic and physical organic chemistry.<sup>1</sup> In organic synthesis, an ability of the intermediate organopalladium species to retain their reactivity during the overall catalytic conversion has dramatically extended the boundaries of the application of the conventional Heck reaction by arranging extra crucial steps in connection to the coupling process.<sup>2</sup> Thus, in a tandem sequence, Heck addition could either precede another transformation,<sup>3</sup> intra- or intermolecularly, or come behind one.<sup>4</sup> If the former scenario is employed, control over the undesired terminative palladium  $\beta$ -hydride elimination becomes critical to the final outcome. This goal is generally achieved by implementing a bifunctional substrate for intramolecular cyclization to produce a stable organopalladium intermediate, which is then captured by a variety of means, affording arylation,<sup>5</sup> alkylation,<sup>6</sup> allylation,<sup>7</sup> alkynylation,<sup>8</sup> hydrogenation,<sup>9</sup> or borylation,<sup>10</sup> at the second stage of the

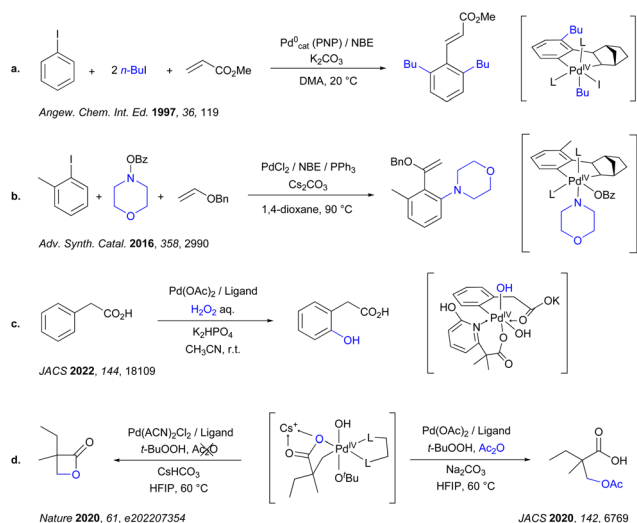
tandem succession. On the other hand, examples of intermolecular Heck domino conversions are rare<sup>11</sup> and usually require a neighbouring coordinative group in order to suppress otherwise dominating undesired  $\beta$ -hydride elimination. Considering the rising interest in tandem transformations, due to the time-, resources-, atom-, and step-economy they provide, a general intermolecular Heck cascade reaction as a reliable method remains highly sought after.

The Catellani reaction was one of the first examples of a combination of both intra- and intermolecular reactivity of Heck-type intermediates (Scheme 1b).<sup>12</sup> In fact, norbornene plays a crucial role as it produces an active Pd–norbornene species that protects against H-elimination. As a result, being in direct intramolecular reach of hydrogen in the *ortho*-position, this species proceeds with a C–H activation. The following oxidative capture of *n*-butyl iodide, and subsequently, reductive elimination from the formed Pd(IV) complex, furnish a new C( $sp^2$ )–C( $sp^3$ ) bond. Thus, astoundingly, the Catellani reaction has also turned out to be a pioneer in the area of Pd(IV) catalysis.

Pd(IV) intermediates in organic catalytic transformations have been intensively studied in recent years.<sup>13</sup> Two main beneficial features of Pd(IV) species include resistance to  $\beta$ -hydride cleavage, common for Pd(II), and facilitated reductive elimination. The latter phenomenon was described for the C–O and C–N bond formation process for both palladium oxidation states.<sup>14</sup> Indeed, the corresponding reductive elimination from

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**Scheme 1** Literature examples of Pd(IV)-induced reductive elimination.

Pd(II) usually requires sophisticated and profound ligands to proceed,<sup>15</sup> while Pd(IV) just ‘delivers’ an otherwise sluggish nucleophile to the associated carbon. For example, a C(sp<sup>2</sup>)-N bond was built in a Catellani-type manner when Pd(II)-norbornene species were oxidized to Pd(IV) by addition of morpholine benzoate (Scheme 1b) with just triphenylphosphine as a ligand.<sup>16</sup> At the same time, the Yu group developed a practical approach to Pd(II)-Pd(IV) oxidation, after either C(sp<sup>2</sup>)-H or  $\beta$ -C(sp<sup>3</sup>)-H bond activation, with common and trivial oxidants, like aqueous hydrogen peroxide and *t*-BuOOH. As a result, the formed Pd(IV) species tended to undergo reductive elimination, producing hydroxylated (Scheme 1c),<sup>17</sup> acetoxyated (Scheme 1d),<sup>18</sup> lactonized (Scheme 1d),<sup>19</sup> and lactamized<sup>20</sup> target materials with constructed C-O or C-N bonds.

These examples demonstrate the potency of Pd(IV) intermediates in connecting nucleophilic fragments, either as another part of the molecule or exogenous, and the attached palladium carbon atom. So, summarizing all the above, one final question rises, “Is it possible to conduct a tandem sequence of intermolecular Heck coupling–nucleophile addition *via* a Pd(IV) transition complex?”

In this article, a cascade nonsymmetric double Heck reaction of unsaturated 1,2-diiodides is presented. The input symmetry of the starting diiodide is lost as a result of the nucleophile insertion at the first Heck attachment. In fact, after the initial migratory addition of the styrene the formed  $\sigma$ -alkylpalladium intermediate is intercepted by the intramolecular oxidative addition of Pd(II) to the neighbouring second Ar-I bond. This apparently leads to the appearance of the key Pd(IV) intermediate that is capable of delivering the adjoining nucleophile (that originally came from the media to the palladium shell) to the attached sp<sup>3</sup>-carbon. Thus, after the second Heck coupling, a total of four separate framework pieces are united in one target molecule in one process. Various styrenes, diiodides and nucleophiles participate in this general reaction sequence with the construction of two C(sp<sup>2</sup>)-C(sp<sup>2</sup>/sp<sup>3</sup>) bonds and one

C(sp<sup>3</sup>)-nucleophile (C-O or C-N) bond. The developed procedures afford an efficient synthetic route to various substituted benzylic alcohols, ethers, amines, and anilines.

## Results and discussion

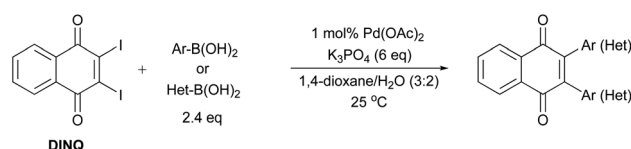
### Discovery

There are many known examples in chemistry when a discovery comes as an unexpected result. In my search for symmetric photochromic molecules,<sup>21</sup> exploration of the Suzuki–Miyaura reaction of promising 2,3-diiodo-1,4-naphthoquinone (DINQ) has granted access to symmetric aryl and hetaryl bisubstituted 1,4-naphthoquinones (Scheme 2).<sup>22</sup> Reasonably, I continued the search in this area by attempting the Heck coupling of DINQ with styrene under analogous slightly modified conditions (using K<sub>2</sub>HPO<sub>4</sub> as a base and increasing the reaction temperature). Much to my surprise, instead of the expected symmetric double Heck adduct, the main product **1** had a hydroxy group attached to the one of the styrene fragments!

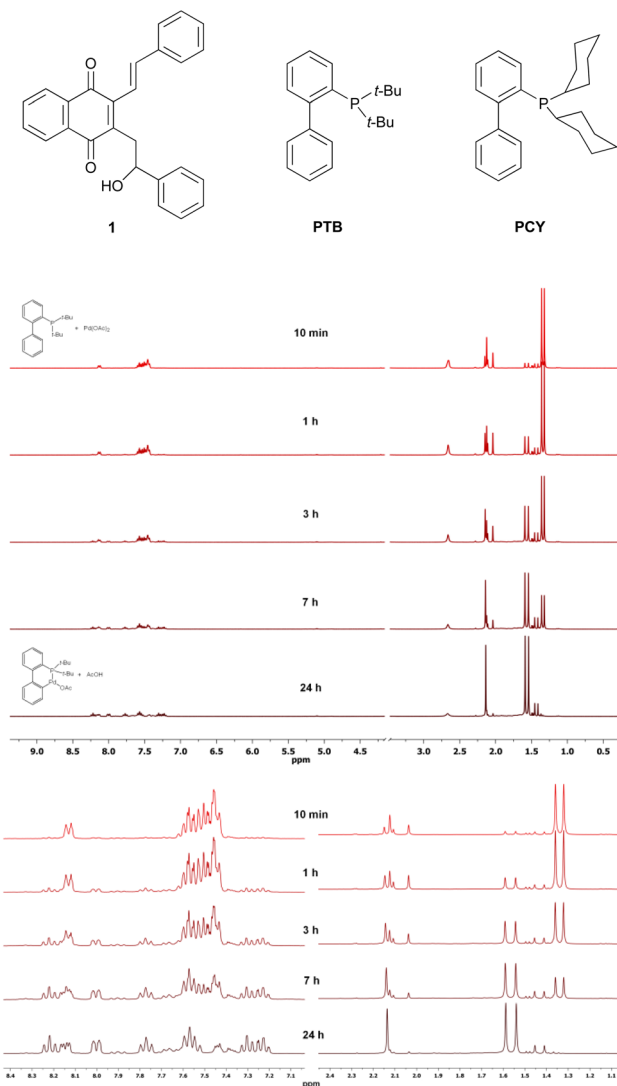
This startling outcome, of what seemed to be a trivial procedure, compelled me to optimize the applied conditions in order to force the reaction to completion. This task did not appear to be straightforward owing to the inclination of DINQ toward hydrolysis in basic media at elevated temperatures.<sup>22</sup> Ultimately, it was established that with the addition of commercially available Buchwald’s phosphine ligand<sup>23</sup> PTB to Pd(OAc)<sub>2</sub>, the reaction proceeds at 70 °C with full consumption of the starting material. At the same time, similarly structured PCY showed inferior results under identical conditions. Importantly, construction of the corresponding palladacycle (either Pd-PTB or Pd-PCY) should be done separately in advance, since it takes up to 24 h for it to form in 1,4-dioxane solution at room temperature (Fig. 1). In general, application of the solution of the catalyst has proved to be much more convenient and expedient than its solid use,<sup>24</sup> especially at the micromolar test run scale.

As a result, two similar operative protocols were devised with either 5 or 10 mol% Pd being employed in a mixture of 1,4-dioxane and water. 5 equivalents of K<sub>2</sub>HPO<sub>4</sub> as a base were sufficient, while 2.1 equivalents of styrene were found to be optimal for the effective conversion. Surprisingly, methyl acrylate turned out to be the only non-styrene alkene to participate in this reaction under the tested conditions (Scheme 3).

Products **1–6** were isolated and fully characterized. In addition, the crystal structures of **4** and **6** confirmed the earlier assignment of the hydroxy group. Therefore, this series of nonsymmetric bisubstituted naphthoquinones has become



**Scheme 2** Synthesis of symmetric bisubstituted naphthoquinones.

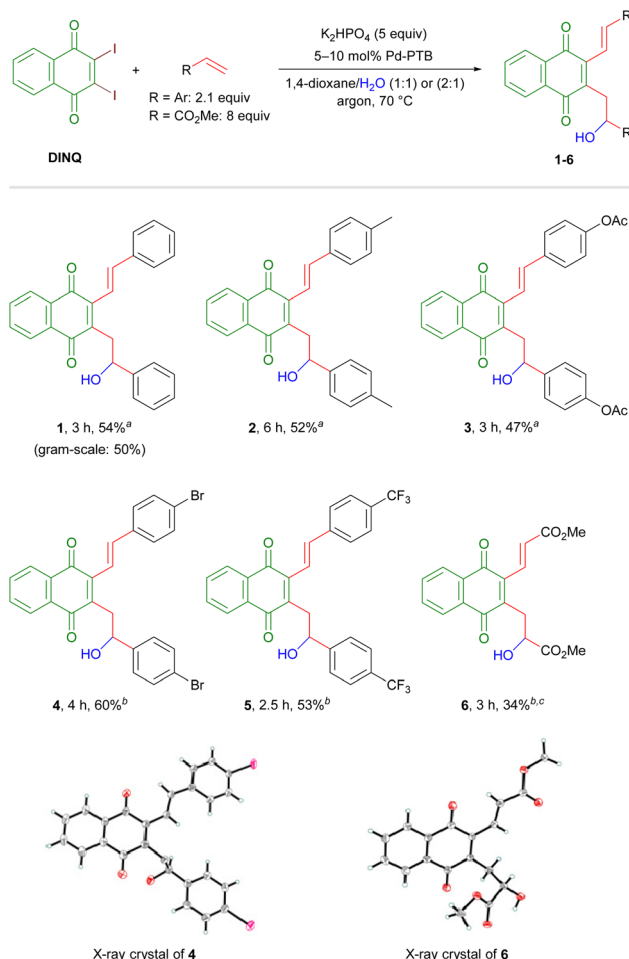


**Fig. 1**  $^1\text{H}$  NMR spectra monitoring of the formation of palladacycle Pd-PTB in 1,4-dioxane.

the first example of a successful cascade construction, affording a benzyl alcohol fragment instead of the expected substituted alkene unit.

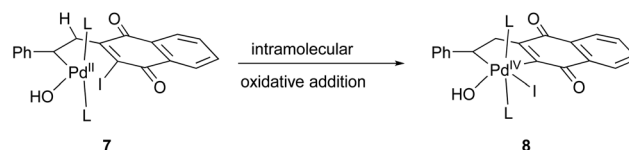
Several key points are worth mentioning for the uncovered tandem transformation: the devised procedure turned out to be fully reproducible and upgradable to the gram scale; the results were consistent regardless of supplier of the  $\text{Pd}(\text{OAc})_2$  (as a palladacycle precursor); various sensitive groups (e.g. bromides and esters) remained intact throughout the reaction under these conditions, while increased temperatures resulted in higher dehydration rates of the products (leading to the corresponding traditional double Heck adduct as the dominating side product).

As for speculations as to the reaction mechanism, reasonably enough, the key palladium intermediate must include both a  $\sigma$ -alkylpalladium component and a hydroxy group simultaneously attached to the same Pd atom. While the former is



**Scheme 3** Cascade double Heck-hydroxide addition reaction of 2,3-diiodo-1,4-naphthoquinone. <sup>a</sup>Reaction conditions for 5 mol% Pd-PTB: DINQ (0.27 mmol), styrene (2.1 equiv.),  $\text{K}_2\text{HPO}_4$  (5 equiv.), Pd-PTB (5 mol%), 1,4-dioxane (3 mL),  $\text{H}_2\text{O}$  (3 mL), argon, 70 °C, 3–6 h. <sup>b</sup>Reaction conditions for 10 mol% Pd-PTB: DINQ (0.27 mmol), styrene (2.1 equiv.),  $\text{K}_2\text{HPO}_4$  (5 equiv.), Pd-PTB (10 mol%), 1,4-dioxane (4 mL),  $\text{H}_2\text{O}$  (2 mL), argon, 70 °C, 2.5–4 h. <sup>c</sup>Reaction was conducted at 60 °C with 8 equiv. (1.16 mmol) of methyl acrylate.

acquired after a routine migratory insertion, the Pd-OH bond is persistent in the presence of water,<sup>25</sup> especially under basic conditions. In addition, the intermediate palladium complex **7** might be transformed to **8** by the second oxidative addition:



Indeed, after such an assumption the picture of this cascade reaction becomes much clearer! The undesired H-elimination from Pd(II) in **7** can proceed until the rotation around the Pd-C bond is possible. However, the second available Ar-I group, being essentially in intramolecular proximity,

captures the palladium atom, thus building Pd(IV) species **8**. Since the reductive elimination from Pd(IV) is significantly easier than that from Pd(II), hydroxide migration has become the main outcome of the first styrene addition. Yet the full mechanistic picture should also provide an explanation for the observed side paths throughout the process and, therefore, will be presented after the study of 1,2-diiodobenzene, as a more durable substrate.

### Reaction optimization

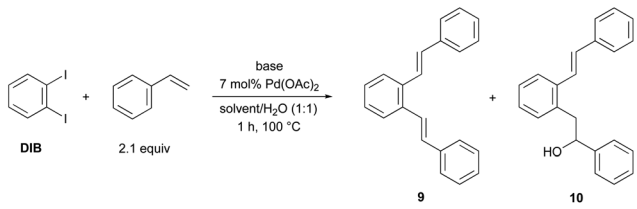
Having developed a general working protocol for the naphthoquinone scaffold, I decided to investigate the applicability of the newfound reaction to the aromatic core. Thus, 1,2-diiodobenzene (DIB) was chosen as a basic model for this research. At the same time, Pd(OAc)<sub>2</sub> was used for experiments as a widely available precatalytic source of palladium without the addition of phosphine ligands. Indeed, organic solvents and, especially, water are known to stabilize the active Pd catalytic species, thus promoting the coupling reactions.<sup>1a,i,26</sup> The test runs were carried out in screw-cap-sealed tubes at 100 °C under an argon atmosphere and at maximum stirring speed.

Two main products, **9** and **10**, were generally detected. Their full isolation together with the unreacted starting material was performed after each run. The resulting yields are presented in Table 1.

Unfortunately, the original conditions (with K<sub>2</sub>HPO<sub>4</sub> as a base, entry 2) led to an incomplete reaction, nonetheless affording benzylic alcohol **10** as a major product. Contrary to expectations, a rational increase in the amount of K<sub>2</sub>HPO<sub>4</sub> (from 5 to 9 equivalents) did not benefit the conversion (entry 3). Quite the opposite, the reaction rate decreased, leaving most of the DIB intact. Apparently, the formation of a biphasic 1,4-dioxane/water mixture with 9 equivalents of K<sub>2</sub>HPO<sub>4</sub> effectively partitioned the organic material from the water-soluble Pd species. Conversely, by replacing 1,4-dioxane with DMF, full consumption of the diiodide was observed with a moderate yield of the desired product (entry 4).

The application of strong bases, such as K<sub>3</sub>PO<sub>4</sub> and KOH, in the 1,4-dioxane/water system predominantly led to the appearance of palladium black and, consequently, reaction stoppage (entries 5 and 6). At the same time, undesirable precipitation of the catalyst was also observed with KOAc (as a weak base), as the produced acetic acid remained not expelled from the reaction mixture (entry 7). Alternatively, the use of bases of moderate strength, like K<sub>2</sub>CO<sub>3</sub> and Et<sub>3</sub>N, provided comparable yields of **9** and **10** (entries 8 and 9). Hence, a weak base with the potential to completely remove H<sup>+</sup> should have been the optimal candidate for further research. Indeed, bicarbonates have shown the most promising results when applied as the potassium or sodium salts (entries 10 and 16). Additional tests demonstrated the need for a significant excess of KHCO<sub>3</sub> (up to 9 equivalents, entry 11) in a 1:1 mixture of 1,4-dioxane/water (entries 12 and 13), while a decrease in the proportion of water in the system inevitably led to a substantial drop in the reaction rate (entry 14). Finally, Pd-PTB displayed similar efficiency and can be used as a practical substitute for this

**Table 1** Optimization of reaction conditions<sup>a</sup>



Entry	Base (equiv.)	Solvent	Yield <sup>b</sup> (%) DIB	Yield <sup>b</sup> (%) <b>9</b>	Yield <sup>b</sup> (%) <b>10</b> <sup>c</sup>
1	No base	Dioxane <sup>d</sup>	89	2	5
2	K <sub>2</sub> HPO <sub>4</sub> (5)	Dioxane	45	8	35
3	K <sub>2</sub> HPO <sub>4</sub> (9)	Dioxane	77	3	13
4	K <sub>2</sub> HPO <sub>4</sub> (5)	DMF	—	13	46
5	K <sub>3</sub> PO <sub>4</sub> (5)	Dioxane	77	6	3
6	KOH (5)	Dioxane	64	12	—
7	KOAc (9)	Dioxane	20	16	31
8	K <sub>2</sub> CO <sub>3</sub> (5)	Dioxane	—	32	36
9	Et <sub>3</sub> N (9)	Dioxane	19	32	23
10	KHCO <sub>3</sub> (9)	Dioxane	—	24	51
11	KHCO <sub>3</sub> (5)	Dioxane	5	13	46
12	KHCO <sub>3</sub> (9)	DMF	—	11	39
13 <sup>e</sup>	KHCO <sub>3</sub> (9)	CH <sub>3</sub> CN	25	13	36
14 <sup>f</sup>	KHCO <sub>3</sub> (9)	Dioxane	51	16	25
15 <sup>g</sup>	KHCO <sub>3</sub> (9)	Dioxane	—	24	53
16	NaHCO <sub>3</sub> (9)	Dioxane	—	25	54
17 <sup>h</sup>	KHCO <sub>3</sub> (9)	Dioxane	—	22	55
18 <sup>i</sup>	K <sub>2</sub> HPO <sub>4</sub> (5)	DMF	—	14	51

<sup>a</sup> Reaction conditions: DIB (0.135 mmol), styrene (2.1 equiv.), base (5 or 9 equiv.), Pd(OAc)<sub>2</sub> (7 mol%), solvent (1.5 mL), water (1.5 mL), argon, 100 °C, 1 h. <sup>b</sup> Yield of isolated product. <sup>c</sup> Mixture of isomers. <sup>d</sup> 1,4-Dioxane. <sup>e</sup> 90 °C, 1 h. <sup>f</sup> 2:1 mixture of 1,4-dioxane (2 mL) and water (1 mL). <sup>g</sup> Pd-PTB instead of Pd(OAc)<sub>2</sub>. <sup>h</sup> DIB (0.35 mmol), styrene (2 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), 90 °C, 5 h. <sup>i</sup> DIB (0.35 mmol), styrene (3 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), 100 °C, 1.5 h.

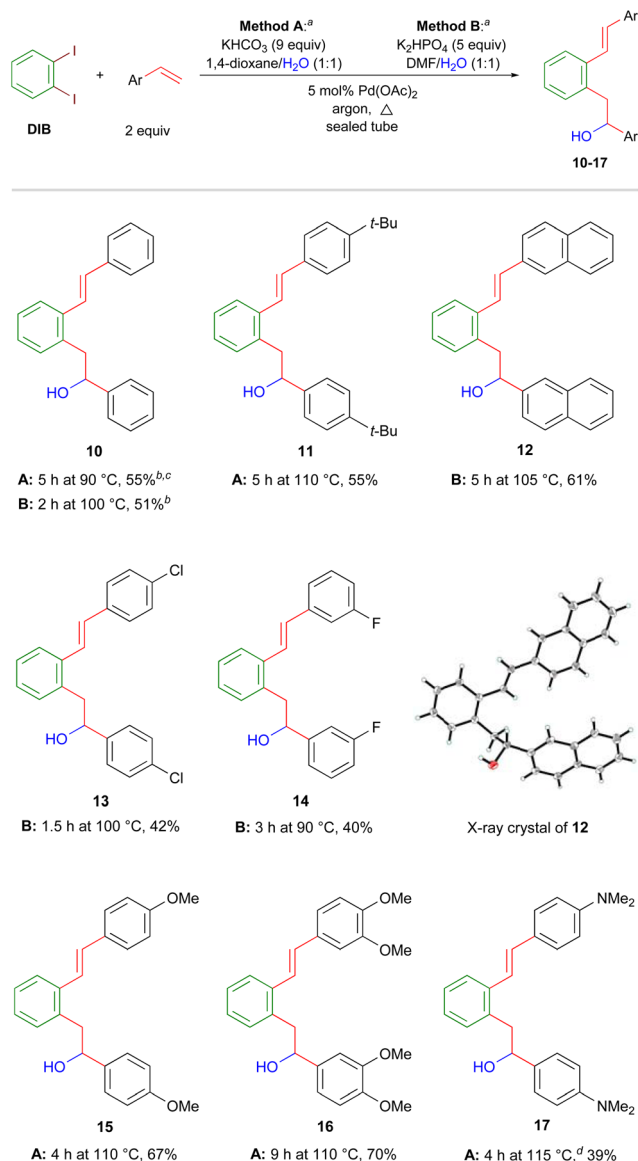
transformation (entry 15). It should be noted that Pd-PCY, having a similar structure, was considerably less successful, mainly producing palladium black when heated under the tested conditions. Apparently, the protection of palladium from the media by the *t*-Bu group is sufficiently effective to create only low-concentration active Pd colloids, which successfully catalyze the process, while faster degradation of Pd-PCY results in rapid agglomeration of soluble catalytic species to insoluble palladium black.<sup>27</sup>

### Water as a nucleophile

As a result, two alternative procedures have been developed (entries 17 and 18). In Method A, 9 equivalents of KHCO<sub>3</sub> were employed as a base in 1,4-dioxane/water mixture (1:1), while 5 equivalents of K<sub>2</sub>HPO<sub>4</sub> were applied in DMF/water (1:1) in Method B. The correct choice of method made it possible to couple 1,2-diiodobenzene with most styrenes tested (Scheme 4).

An excess of styrene was found to significantly reduce the reaction rate under the conditions of Method A, while no influence was observed in DMF/water. Also, the reaction rate was dependent on the mixing efficiency, so the maximum rpm available (1250) was set for the reported times.





**Scheme 4** Cascade double Heck-hydroxide addition reaction of 1,2-diiodobenzene. <sup>a</sup>Reaction conditions. Method A: DIB (0.35 mmol), styrene (2 equiv.), KHCO<sub>3</sub> (9 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), 1,4-dioxane (3.9 mL), H<sub>2</sub>O (3.9 mL), argon, heating. Method B: DIB (0.35 mmol), styrene (3 equiv.), K<sub>2</sub>HPO<sub>4</sub> (5 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), DMF (3.9 mL), H<sub>2</sub>O (3.9 mL), argon, heating. <sup>b</sup>Mixture of isomers. <sup>c</sup>0.81 mmol of DIB was used. <sup>d</sup>TBAB (1 equiv.) was added.

In general, styrenes, either unfunctionalized or with electron-donating groups, participate in the reaction with just 5 mol% Pd, affording the corresponding nonsymmetric double Heck adducts in fair yields, although *para*-dimethylamino-styrene required harsher reaction conditions and the addition of TBAB as a stabilizer for palladium species.<sup>28</sup> On the other hand, the presence of a chloro- or fluoro-substituent on the styrene ring reduced the yield to moderate, supposedly due to facilitation of the double bond formation pathway to the corresponding symmetric double Heck molecule.

Contrary to the naphthoquinone series, a minor isomer accompanied the target molecule when DIB was used as a substrate. However, the yields of this impurity were generally below 5% and in most cases it was easily removed by chromatography. Thus, compounds **11**–**17** were isolated as pure materials, while **10** remained contaminated with the inseparable isomer. X-ray crystallography of the dinaphthyl product **12** confirmed the assigned structure. Thus, 1,2-diiodobenzene became the second established substrate to undergo the discovered domino sequence with various styrenes according to the developed synthetic procedures.

Finally, a more thorough study of the reported cascade double Heck-nucleophile addition reaction was performed on a model coupling DIB (0.81 mmol) and styrene according to Method A (Scheme 5).

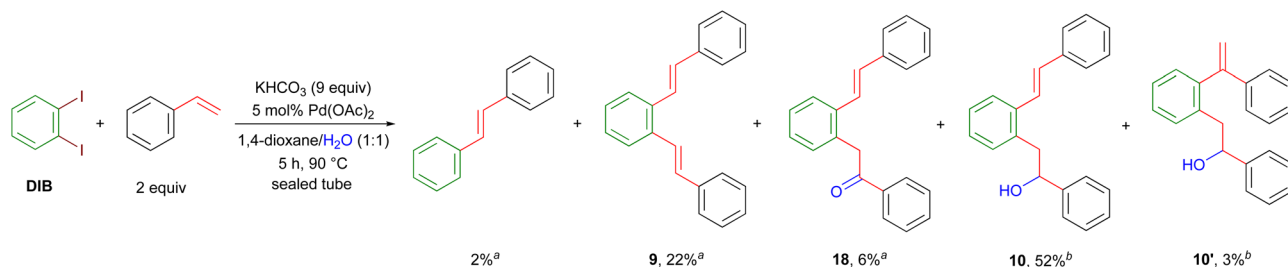
Five different products were thus detected and isolated either in pure form (stilbene, **9**, and **18**) or as a mixture of two isomers (**10** and **10'**). The yield of each isomer was determined using NMR with the ratio being 18 to 1, respectively. Moreover, individually pure crystalline **10** was obtained from the mixture by slow evaporation of the Et<sub>2</sub>O/hexane solution at 5 °C.

### Proposed mechanism

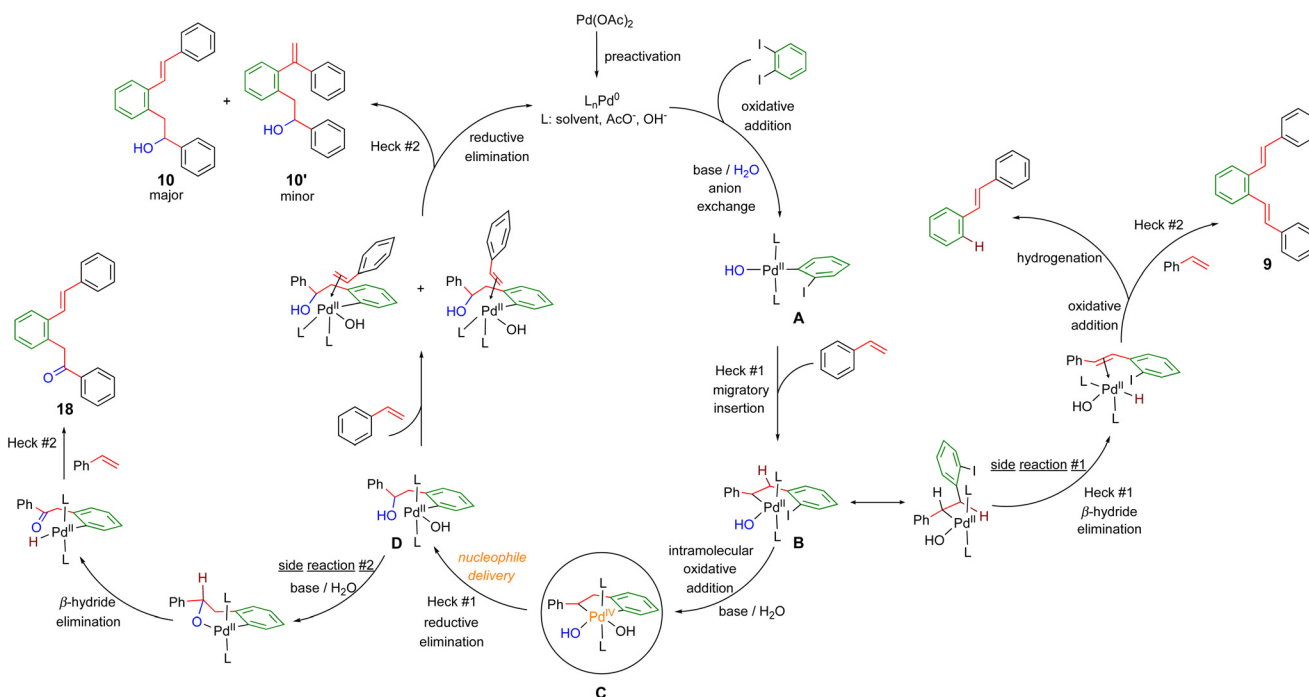
Having determined the structures of the reaction products and by-products, I therefore advanced to propose a plausible mechanistic pathway for the discovered cascade transformation (Scheme 6).

Obviously, the catalytic cycle initiates by preactivation of Pd (OAc)<sub>2</sub> with a formation of Pd(0) nanoparticles stabilized by the surrounding solvent molecules and available anions.<sup>29</sup> With so much research being done on this subject lately,<sup>1f,30</sup> my purpose is not to review the presumed process, but to highlight the role of the admittedly anionic nature of active palladium species.<sup>1b,31</sup> So, after the first, conventional, oxidative addition, the counterion exchange at Pd(II) is apparently fast,<sup>1a,10,32</sup> resulting in the appearance of the intermediate complex **A**. The subsequent transformation to **B** is also ordinary and is the result of the migratory insertion of the styrene molecule. At this stage, the reaction can advance by two possible pathways. During the first one, marked as side reaction #1, common *syn* β-hydride elimination occurs, producing a monosubstituted intermediate. This product continues the sequence by ensuing oxidative addition followed by either hydrogenation or Heck #2 to afford stilbene (as a minor impurity) and the symmetric double Heck adduct **9**, respectively.

The second pathway is a key process for the researched reaction. It was postulated in the literature that the anionic nature of the Pd(II) complexes promotes further oxidation to Pd(IV).<sup>13b,33</sup> In addition, intramolecular oxidative addition, as a rate-determining step, should proceed more willingly than the theoretically possible intermolecular one.<sup>34</sup> Thus, by analogy with the 7 to 8 conversion, the second Ar-I bond readily captures palladium in **B**, and after another anion exchange in basic aqueous media the Pd(IV) intermediate complex **C** is presumably formed. However, now Pd(IV) promotes the otherwise reluctant reductive elimination, therefore interconnecting the



**Scheme 5** Model cascade reaction of 1,2-diiodobenzene with styrene and water. Reaction procedure: DIB (267 mg, 0.81 mmol) and styrene (168 mg, 1.62 mmol, 2 equiv.) were dissolved in 1,4-dioxane (7.18 mL). 0.8 M aqueous solution of  $\text{KHCO}_3$  (9 mL, 9 equiv.) was added to the formed homogeneous solution in one portion followed by addition of 22.3 mM  $\text{Pd}(\text{OAc})_2$  1,4-dioxane solution (1.82 mL, 5 mol%) under an argon atmosphere. The mixture was vigorously stirred at room temperature for 15 min and then placed in a preheated to 90 °C oil bath for 5 h. <sup>a</sup>Yield of isolated product. <sup>b</sup>Yield determined by NMR from the isolated mixture of isomers.



**Scheme 6** Suggested mechanism for cascade double Heck–hydroxide addition reaction.

hydroxide and  $\sigma$ -alkyl fragment, completing the nucleophile delivery in **D**.

Side reaction #2 is possible at this stage. Indeed, the coordination of a newly formed benzylic alcohol to palladium *via* Pd–O bond and then continuing with H-elimination<sup>15b</sup> provides **18** as a by-product. However, alternative oxidation routes should also be considered, either *via* a Wacker-type process<sup>35</sup> or in the presence of molecular oxygen.<sup>36</sup> For this, several additional experiments were carried out. At first, a standard test run was conducted under an oxygen atmosphere to show no influence on the final product ratio. Subsequent attempts made to react pure **9** or **10** under general conditions in the presence of oxygen were also futile, leaving the starting material intact. Hence, the genesis of **18** is limited to the formation of **D** and most likely proceeds *via* the suggested Pd–H elimination.

The coordination of the second styrene molecule to **D** determines the ratio of isomers in the final product. Steric factors govern the carbopalladation step in the closing Heck #2, thus forming **10** as the major outcome and **10'** as the minor, with an approximate distribution of 18 to 1. These numbers are in full agreement with the known selectivity for styrenes under ligand-free Heck conditions.<sup>37</sup> Lastly, the concluding reductive elimination brings the palladium species to the beginning of the catalytic cycle.

### Phenols and allomaltol as nucleophiles

After completing the research on hydroxide addition in the studied cascade sequence, I decided to investigate other suitable nucleophiles. Indeed, if the claimed mechanism is correct, then any ligand attached to Pd(IV) can serve as an

actual reductive elimination partner. Although the question is, how do we now suppress the competing formation of benzyl alcohol described above, which is an inevitable product under basic aqueous conditions?

Phenols came into the study as the first choice.<sup>38</sup> Certainly, being widely available, they form a stable anion that could compete with the water/hydroxide pair for a vacancy in the palladium shell. Fortunately, only minor modifications to the previously developed conditions were needed to achieve satisfactory results. Finally it turned out that 2.2 equivalents of styrene, 5 equivalents of ArOH, 8 equivalents of KHCO<sub>3</sub> as a base, 0.5 equivalents of TBAB, and 5 mol% of Pd(OAc)<sub>2</sub> (as 1,4-dioxane solution) were used for 1 equivalent of DIB in 1,4-dioxane/water (1 : 1) (Scheme 7).

The developed procedure has enabled the synthesis of various aryl ethers **19–25** in fair yields. As expected, the alternative pathway to benzyl alcohol **10** was effectively con-

strained by the presence of at least 5 equivalents of the corresponding phenol in basic media, while lesser amounts made the two processes more competitive. Various functional groups (*i.e.* bromide, aldehyde, nitro, *etc.*) persist under the reaction conditions presented, making their further use possible. Moreover, the application of allomaltol as a carrier of the heterocyclic hydroxy group reveals the potential of this transformation for other acidic OH-containing molecules beyond the traditional pool of phenols.

The presence of an electron-acceptor group in the aryloxy fragments most likely stabilizes the intermediate Pd(IV) complex, building the desired framework *via* reductive elimination. At the same time, electron-donating groups, such as MeO<sup>−</sup>, might contribute either to a decrease in the stability of the corresponding aryloxy ion, impeding migration, or to the side oxidation of the aryloxy core with potent Pd(IV), thereby reducing the final yield of the target product.

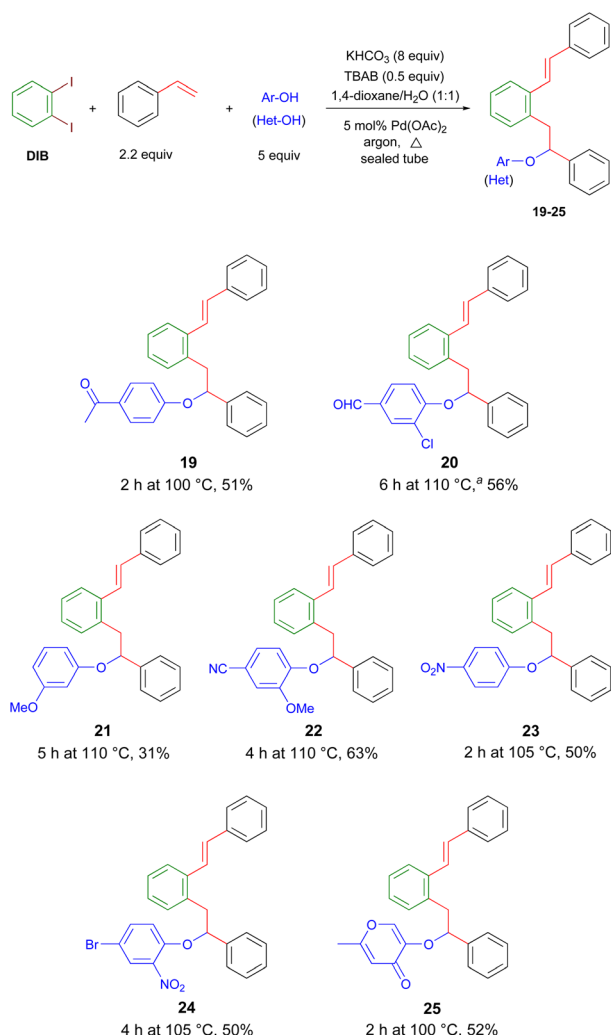
### Secondary amines and anilines as nucleophiles

Having successfully delivered phenols as nucleophiles during the first Heck addition in this cascade sequence, I decided to explore the possibility of C–N bond formation. Obviously, amines were the most promising nucleophiles for this purpose, so an aqueous solution of dimethylamine was chosen for the test experiments. To my delight, the long search for optimal conditions again proved unnecessary, as only a slight modification of the protocol reported earlier was required. It was found that the use of a 10-equivalent excess of amine together with 2 equivalents of K<sub>2</sub>HPO<sub>4</sub> in 1,4-dioxane/water (1:1) furnished the target material **26** in 74% yield (Scheme 8). At the same time, the larger and less mobile piperidine turned out to be less effective, while the employment of morpholine made it possible to obtain fair yields of an inseparable mixture of isomers (**28**) (formed after Heck #2, as in Scheme 6). X-ray crystallography of both dimethylamine- (**26**) and piperidine- (**27**) adducts confirmed these structures.

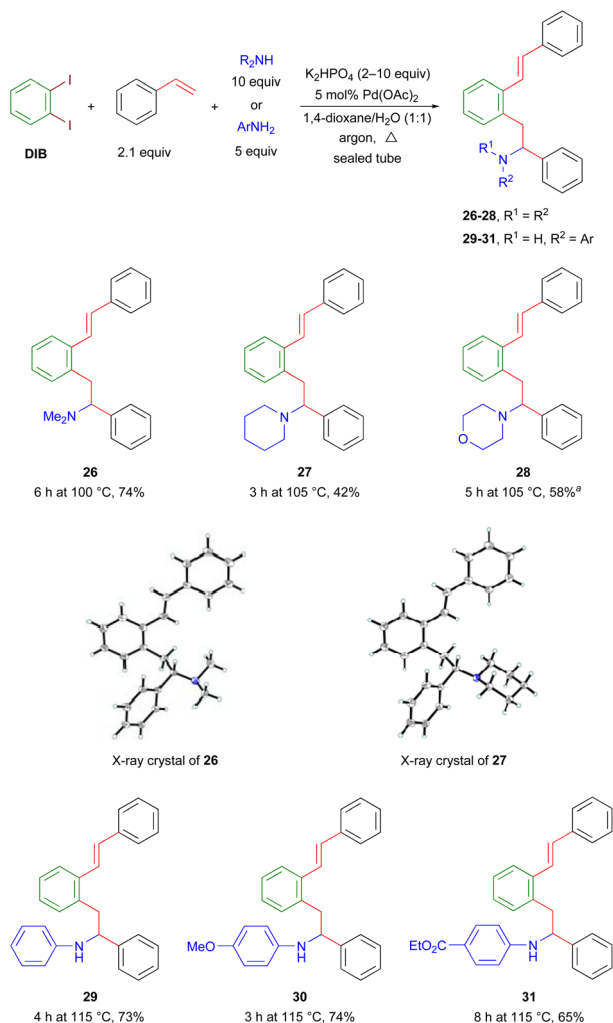
Unfortunately, primary amines did not provide satisfactory results in this reaction, either retarding the process even at higher temperatures (*n*-amylamine) or producing **9** and **10** as the main outcome (benzylamine).

Since anilines are much weaker nucleophiles than amines, the formation of **10** *via* competing hydroxide addition, as mentioned above, is a likely problem. However, the initial search for reaction operating conditions, shown in Table 1 (entry 3), already suggested a probable solution. Indeed, a 9 equivalent excess of K<sub>2</sub>HPO<sub>4</sub> in the 1,4-dioxane mixture led to a two-phase system, which significantly reduced the conversion rate, apparently due to the retention of water (as a nucleophile source) from the organic components. Therefore, in organic surroundings, anilines might procure an available place at the palladium as a nucleophile under these conditions.

Indeed, this assumption was justified, as the combination of 5 equivalents of ArNH<sub>2</sub> and 10 equivalents of K<sub>2</sub>HPO<sub>4</sub> has worked out well at 115 °C for the tested anilines. Moreover, the presence of either an electron-donating group or an acceptor had no noticeable effect on the consistently good yields of



**Scheme 7** Cascade double Heck–aryloxy addition reaction of 1,2-diiodobenzene. Reaction conditions: DIB (0.215 mmol), styrene (2.2 equiv.), phenol (5 equiv.), KHCO<sub>3</sub> (8 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), TBAB (0.5 equiv.), 1,4-dioxane (2.4 mL), H<sub>2</sub>O (2.4 mL), argon, heating. <sup>a</sup>0.8 equiv. of TBAB was used.



**Scheme 8** Cascade double Heck–secondary amine or aniline addition reaction to 1,2-diiodobenzene. Reaction conditions: DIB (0.35 mmol), styrene (2.1 equiv.), secondary amine (10 equiv.) +  $K_2HPO_4$  (2 equiv.) or aniline (5 equiv.) +  $K_2HPO_4$  (10 equiv.),  $Pd(OAc)_2$  (5 mol%), 1,4-dioxane (3.9 mL),  $H_2O$  (3.9 mL), argon, heating. <sup>a</sup>Mixture of isomers.

target products 29–31. The structure of 30 was further verified by 2D NMR spectroscopy (see the ESI†).

Thereby, formation of the C–N bond through nucleophile addition (of either secondary amines or anilines) in the tandem double Heck coupling also takes place, indicating the versatility of the discovered reaction. Indeed, only the nucleophile itself, lodged at the palladium, designates the reductive elimination process from the acquired  $Pd(IV)$ . The devised general protocols for water, phenols, secondary amines, and anilines as a nucleophile source provide straightforward access to a library of new compounds, also by varying the styrene component and the 1,2-diiodo-containing substrate.

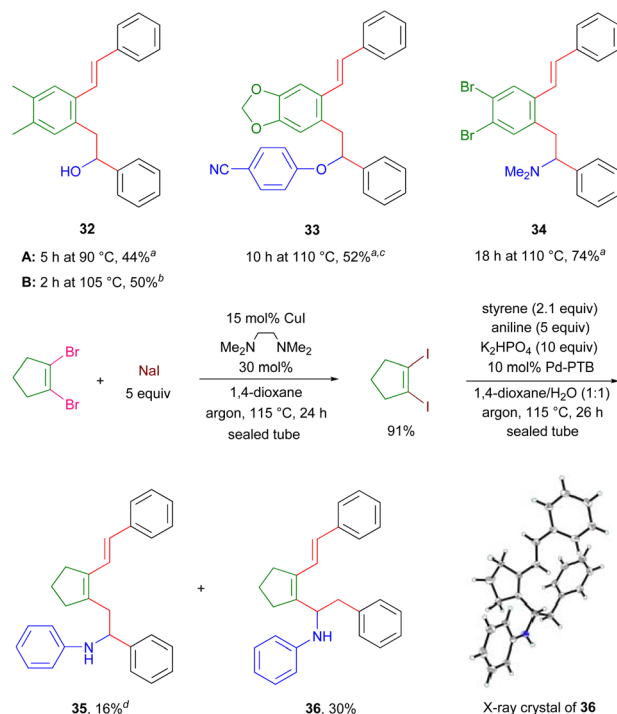
### Various unsaturated 1,2-diiodides

Several accessible symmetric 1,2-diiodoarenes were selected to demonstrate the applicability of the latter. The reactions were conducted according to the respective procedures described

above to give the expected pure target materials 32–34 in fair yields (Scheme 9). Again, an accompanying minor isomer was observed for most second Heck additions, as it was detected in the reactions of DIB with water, phenols, or amines/anilines as nucleophiles (Schemes 4, 7, and 8).

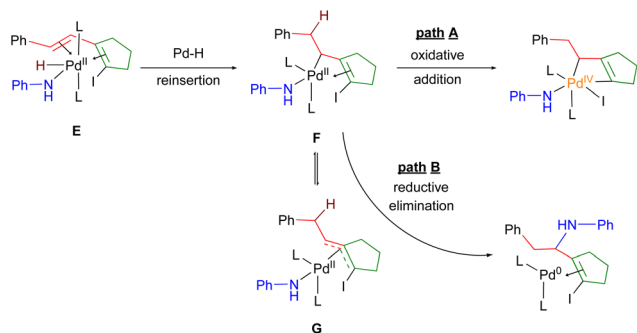
Eventually, the employment of 1,2-diiodocyclopentene as a substrate came as a surprise. Indeed, initially its reactivity was under question due to the olefinic nature of the double bond. Nevertheless, despite the prolonged reaction time, this substrate was completely consumed in the process with the formation of two major products (aside from the conventional symmetric double Heck adduct). To my astonishment, the expected product 35 came only as a minor share, while the unexpected 36 yielded twice as much. The structure of the molecule was later confirmed by X-ray studies, thus requiring a mechanistic explanation.

Apparently, the formation of 35 occurs in accordance with the sequence proposed earlier (Scheme 6) through  $Pd(IV)$ -induced nucleophile delivery. However, in this case, the course of the main side reaction (#1) is different. Indeed, the butadienic structure produced after  $\beta$ -hydride elimination readily coordinates to the palladium atom, therefore retaining complex **E** (Scheme 10). Most likely,  $Pd-H$  reinsertion<sup>11,39</sup> takes place at this stage with the formation of the  $\sigma$ -allyl  $Pd$ -intermediate **F**, additionally stabilized by the  $\pi$ -allyl isomerization to **G**.<sup>40</sup> Two controversial reaction pathways could be suggested at this point. Path A involves an intramolecular oxi-



**Scheme 9** Selected cascade reaction products of various unsaturated 1,2-diiodides. <sup>a</sup>Standard reaction conditions; 7 mol%  $Pd(OAc)_2$  was used. <sup>b</sup>Standard reaction conditions; 5 mol%  $Pd(OAc)_2$  was used. <sup>c</sup>0.8 equiv. of TBAB was used. <sup>d</sup>Unstable in pure state.





**Scheme 10** Proposed palladium intermediates responsible for the formation of compound **36**.

dative addition leading to a Pd(IV) complex, as shown above. Indeed, despite being rarely encountered, a four-membered Pd(IV) palladacycle intermediate was recently reported by the Hartwig group.<sup>41</sup> Subsequently, further reductive elimination provides the aniline-containing fragment. Another possibility, path B, involves a cyclopentene-assisted C–N forming reductive elimination from Pd(II). Such a conversion, however, is also a highly unusual process requiring either a specific substrate and/or finely tuned ligands.<sup>15c,42</sup> Unfortunately, the available data are insufficient for a more accurate description of potential intermediates, while thorough mechanistic studies of cascade addition to 1,2-diiodocyclopentene, specifically, are beyond the purpose of this article. Yet, regardless of the palladium transition complex, **36** eventually forms after the second Heck coupling. Thus, 1,2-diiodocyclopentene becomes a distinctive example of a successful olefinic substrate, thereby expanding the scope of unsaturated 1,2-diiodides suitable for this cascade sequence.

### Limitations

After presenting practical synthetic applications, it is justified to mention the limitations found (mainly for Pd(OAc)<sub>2</sub> and Pd–PTB usage as a catalyst). As for the investigated substrate, various 1,2-disubstituted arenes were tried under the reported conditions. The study included bromides, triflates, and tosylates as functionalities, along with their combination with *ortho*-iodides. As expected, iodides were the first to undergo traditional Heck attachment, while bromides required higher temperatures for the same conversion. Regrettably, the neighbouring position in the arene ring did not affect the conventional Heck route, occurring with no inclusion of a nucleophile. Overall, the tosylate group remained intact during test runs, while hydrolysis of the triflate became a major side process under the indispensable basic aqueous conditions, rivaling the traditional Heck coupling.

Furthermore, the attempts undertaken to attest the desired cascade sequence by employing open-chained olefinic 1,2-diiodides (e.g. 4,5-diiodooct-4-ene, 1,2-diiodo-1,2-diphenylethene, (1,2-diiodovinyl)benzene, *etc.*) were also unsuccessful, mostly yielding the corresponding alkyne.

With regard to the alkene component, styrenes were found to be the most practical choice for this reaction, succeeding

with all substrates and nucleophiles tried. However, substituents on the aromatic ring of styrene can affect the dehydration rate of the hydroxylated products. Thus, with *para*-nitrostyrene, poor results were observed, since the symmetrical Heck double product dominated at the required temperatures. Similarly, acrylates, vinyl ketones, and their derivatives did not produce the corresponding nonsymmetric products. In fact, the use of DINQ and methyl acrylate appeared to be the only example of such a conversion (which was carried out at 60 °C). Application of non-functional alkenes was also futile, displaying a slow transformation rate even at elevated temperatures, while yielding a complex mixture of several products.

### Prospects

Finally, a brief general overview of the prospects for further development of the discovered reaction is important at this point. Firstly, the search for active catalysts (including plethora of ligands, palladacycles, pincer complexes, *etc.*), if successful, should lead to a significant decrease in the temperatures required for the process, thus expanding the scope of participating alkenes and substrates. For instance, the use of a triflate (or even a tosylate), be it an appropriate group for this cascade sequence, would greatly increase the availability of substrates due to the abundance of the catechol moiety in chemistry along with the direct synthetic accessibility of *ortho*-iodophenols.

Secondly, the application of chiral ligands should provide specific stereochemical routes for the reaction, as reductive elimination from Pd(IV) is most likely to proceed under the regulating control of such ligands.

Thirdly, the use of nonsymmetric 1,2-diiodides, especially those with an influential functionality, might lead to electronic (or neighboring) governance of the oxidative addition of the first Ar–I bond, thereby directing the alkene–nucleophile pair to this location exclusively.

Fourthly, a wide variety of aqueous stable nucleophiles are available to be tested for potential incorporation into the alkene core of the first Heck adduct as described here for the hydroxy-, aryloxy-, amino-, and arylamino-fragment inclusion. The possibility of a domino construction of two adjacent Heck fragments, simultaneously forming the third C–C or C–heteroatom bond by introducing a chosen functionality, is a highly desirable goal in modern chemistry.

Lastly, a mechanistic review is an essential part of modern publications on transition metal catalysis. The presented reaction provides simple and effortless access to the cascade transformation with different palladium oxidation states, which can serve as a model for studying the most questionable and most sought-after areas of palladium catalysis.

## Conclusions

In summary, a new palladium-catalyzed cascade reaction has been discovered that includes the crucial nucleophile addition during a nonsymmetric intermolecular double Heck coupling.

As a result, complex target compounds were constructed in a single domino process from four individual components: a substrate, two styrene molecules, and a nucleophile. Presumably, the key step in this transformation is the intramolecular oxidative addition of the transient  $\sigma$ -alkylpalladium species, which is obtained after carbopalladation of the first styrene molecule. This generates an intermediate Pd(IV) complex that subsequently proceeds with the facilitated reductive elimination. Therefore, a new C(sp<sup>3</sup>)-O (or C(sp<sup>3</sup>)-N) bond is created by delivering the associated nucleophile to the connected sp<sup>3</sup>-carbon. Water, phenols, secondary amines, and anilines serve as a media nucleophile source under basic aqueous conditions and give consistent reproducible yields according to the devised general protocols. All the procedures are straightforward and easily manageable, requiring just a screw-cap tube, a magnetic bar, and a hotplate stirrer. Gram-scale synthesis was also performed, emphasizing the synthetic potential of this cascade assembly. One example of the methyl acrylate used as an alkene and one case of the participation of cyclic olefinic 1,2-diiodide used as a substrate are also established and described. Moreover, the coupling of 1,2-diiodocyclopentene with styrene and aniline advances through two apparently different mechanistic pathways with the formation of two structural isomers. Finally, the prospects for the further development of the findings reported here suggest a rising ubiquitous interest in the uncovered reaction in many areas of organic synthesis and catalysis.

## Experimental

**Gram-scale procedure for 1.** 2,3-Diiodo-1,4-naphthoquinone (1.11 g, 2.7 mmol) and styrene (0.59 g, 5.7 mmol, 2.1 equiv.) were dissolved in 24 mL of 1,4-dioxane. To the formed homogeneous orange solution 0.45 M K<sub>2</sub>HPO<sub>4</sub> water solution (30 mL, 13.5 mmol, 5 equiv.) was added followed by the addition of 22.3 mM 1,4-dioxane solution of Pd-PTB (6 mL, 0.134 mmol, 5 mol%) under an argon atmosphere. The suspension was vigorously stirred in an aqueous bath at 70 °C for 3 h until full consumption of the starting diiodide. Solid NaCl was then added to the reaction mixture (until saturation of the aqueous layer) followed by extractions with MTBE (3 × 30 mL). The combined organic layer was evaporated to dryness; the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and evaporated with 6 g of silica gel. The powder residue was subjected to silica gel column chromatography to afford 0.5 g (50%) of pure target material as an orange solid. Full experimental details and characterization of new compounds can be found in the ESI.†

## Data availability

The experimental details, <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds and X-ray crystal data are available in the ESI.† The crystallographic data for compounds 4, 6, 12, 26, 27 and 36 have been deposited in the Cambridge Crystallographic Data Centre under accession numbers CCDC 2222212–2222217, respectively.†

## Author contributions

The manuscript was written through a contribution of one author.

## Conflicts of interest

There are no conflicts to declare.

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