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# Palladium-catalyzed stereoselective domino arylation–acylation: an entry to chiral tetrahydrofluorenone scaffolds†

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**A palladium-catalyzed domino arylation-cyclization of biocatalytically derived cyclic 1,3-dienes is demonstrated. The reaction introduces a high degree of structural complexity in a single step, giving access to tricyclic tetrahydrofluorenones with full regio- and stereoselectivity. The transformation proceeds through a novel acylation-terminated Heck-type sequence, and quantum chemical calculations indicate that C–H activation is involved in the terminating acylation step.**

Palladium-catalyzed domino reactions provide an efficient means of rapidly constructing bi-, tri- and tetracyclic molecules,<sup>1</sup> and have been applied in the formation of various natural products<sup>2</sup> and heterocycles.<sup>1b,3</sup> The tricyclic hydrofluorenone motif is well suited to benefit from such a synthesis and is present in a number of known bioactive compounds, such as taiwaniaquinol,<sup>4</sup> asterogynin B,<sup>5</sup> and kinamycin F<sup>6</sup> (Fig. 1).

While palladium catalysis has been applied in this context,<sup>7</sup> the use of domino reactions is as yet limited.<sup>8</sup> Wu and Walsh have employed domino Heck/Tsuji–Trost reactions in the synthesis of chiral tetrahydrofluorenones,<sup>9</sup> and asterogynin derivatives,<sup>10</sup> but other reports are scarce.<sup>11</sup> If the central ring of the tetrahydrofluorenone could be formed by a Pd-catalyzed intramolecular acylation, this could open up for new synthetic routes to such polycyclic structures. Acylation of an arylpalladium species has been described with aldehydes by Martin in the synthesis of benzocyclobutenones (Scheme 1a),<sup>12</sup> while Solé,<sup>13</sup> and Burke,<sup>14</sup> cyclized heteroatom-tethered aryl halides

with aldehydes. An sp<sup>3</sup>-palladium acylation, in the form of a domino nucleopalladation – acylation, has been reported by Liu and Lei (Scheme 1b).<sup>15</sup> Heck-type arylation of alkynes and arynes with 2-halobenzaldehydes has been shown to trigger intramolecular acylation of the resultant alkenylpalladium species, as demonstrated by Heck, Larock and others (Scheme 1c).<sup>16</sup> A few examples of nickel-catalyzed cyclizations between 2-halobenzaldehydes and alkenes or alkynes have also been reported.<sup>17</sup> We here show that homochiral tetrahydrofluorenones can be formed in a single step using a Pd-catalyzed domino Heck-type carbopalladation–acylation reaction, starting from a (2-iodoaryl)-aldehyde and a chiral cyclohexadiene (Scheme 1d). The reaction presented herein is to our knowledge the only example of a cyclative Pd-catalyzed Heck-type domino alkene insertion-acylation.

Our investigation was triggered by the discovery that the Pd-catalyzed arylation of diene **1** with 2-iodobenzaldehyde resulted in the formation of tricyclic tetrahydrofluorenone **2** (Scheme 2). Attempted use of other palladium or silver sources was not successful, while the amount of aryl halide could be lowered to 1.5 equiv with only a minor lowering of the yield (see ESI†).

Diene **1** derives from a biocatalytic arene oxidation (BAO) product, readily obtainable in multigram quantities *via* a dearomatizing oxidation of benzoic acid by *R. eutropha* B9 (Scheme 3).<sup>18</sup> A range of other diene substrates were also prepared from the same BAO oxidation product by acetal

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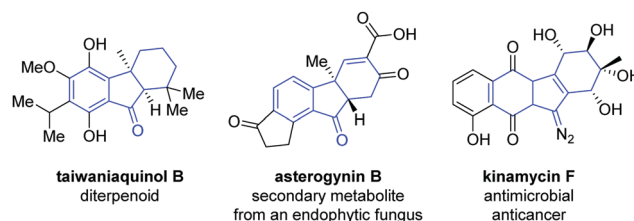
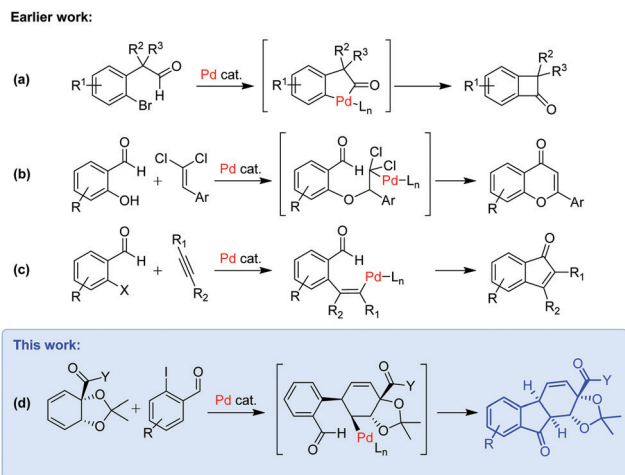


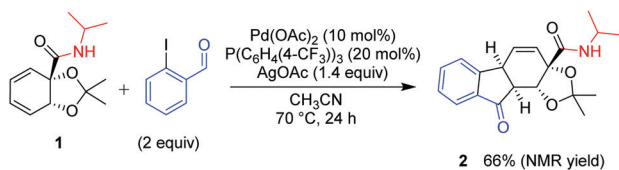
Fig. 1 Hydrofluorenone-based natural products.



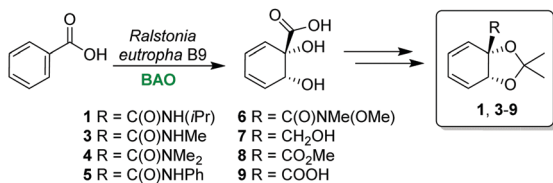
## Communication



Scheme 1 Pd-catalyzed intramolecular acylation to form fused cyclic compounds.



Scheme 2 Formation of tricyclic tetrahydrofluorenone **2**.

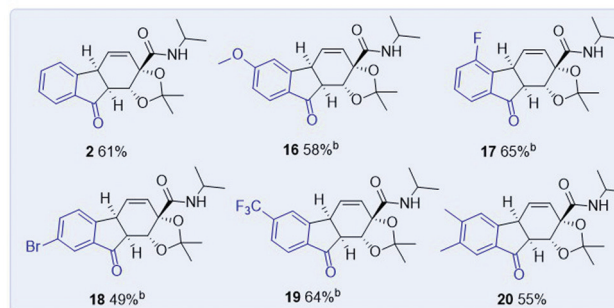
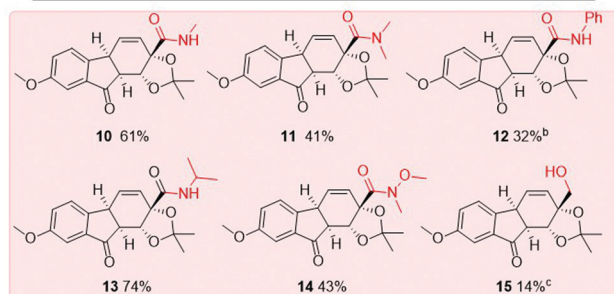
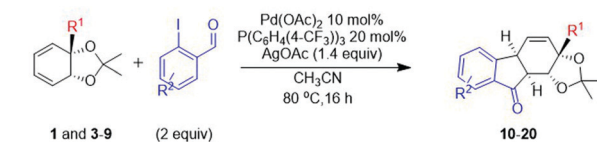


Scheme 3 Biocatalytic arene oxidation (BAO) to access chiral dienes **1** and **3–9**.

protection of the diol followed by functional group conversion of the carboxylic acid.

Compounds **1** and **3–9** were then evaluated with 2-iodo-5-methoxybenzaldehyde as the aryl halide (Scheme 4). Methyl amide **3** performs well, affording **10** in 61% yield. Secondary amide **4** and aryl amide **5** are also compatible, producing **11** and **12** in somewhat lower yields. A better result (74%) is obtained with isopropylamide **1**. Weinreb amide **14** provides a useful functionality for further transformations. Alcohol **15** could be formed by switching to DMF as the solvent, albeit in a low yield. For diene **8**, with a pendant carboxylic acid, degradation of the diene starting material took place under the reaction conditions. For methyl ester **9**, no conversion to product was seen, indicating that the amide hydrogen might have an activating effect in the reaction.

The scope of aryl halides was then evaluated with diene **1** under the same reaction conditions. With 2-iodobenzaldehyde,

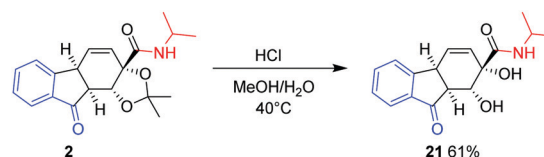


Scheme 4 <sup>a</sup>Scope and limitations of diene and aryl halide. <sup>b</sup>Isolated yields. <sup>b</sup>100 °C in 1,4-dioxane. <sup>c</sup>100 °C in DMF.

cyclization product **2** can be isolated in 61% yield. 2-Iodo-5-methoxybenzaldehyde affords **13** in 74% yield and the isomeric 2-iodo-4-methoxybenzaldehyde product **16** can be isolated in 58% yield using a higher reaction temperature. A higher temperature is also needed if the aryl iodide is substituted by a second halide or by a CF<sub>3</sub>-group (**17–19**), while dimethylated product **20** can be formed using the standard reaction conditions. Heteroaromatic aryl halides, containing a thiophene or indole moiety, proved unsuccessful. Likewise, the reaction seems limited to aryl iodides, with only trace amounts of **2** formed when 2-bromobenzaldehyde is used.

Acetonide deprotection to form **21** was also demonstrated, (Scheme 5). Diol **21** crystallizes readily, permitting structural elucidation by X-ray diffraction (Fig. 2).

We here propose a mechanism in which, after the initial arylation of the diene through migratory insertion, the formed organopalladium intermediate undergoes an acylation by the adjacent aldehyde. As no non-cyclized Heck-product is detected, this acylation must be favoured over the β-hydride elimination forming **22** (Scheme 6, path C). In earlier work



Scheme 5 Acetonide deprotection of cyclization product **2**.



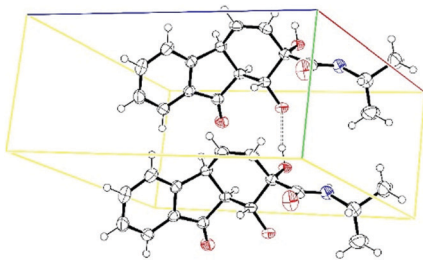


Fig. 2 Solid state structure of **21** (CCDC 2043870†).

from our group, we have seen that  $\beta$ -hydride elimination is indeed favoured if no formyl group is present on the aryl halide.<sup>19</sup> To form product **2**, two pathways are possible: the cyclization could either result from an aldehyde C–H activation, followed by C–C bond formation *via* reductive elimination (path A). Alternatively, it might result from an aldehyde insertion into the Pd–C bond, followed by oxidation of the formed benzylic alkoxide by  $\beta$ -hydride elimination (path B).

Both C–H activation<sup>12,20</sup> and aldehyde insertion<sup>13,21</sup> have been suggested in related aryl Pd-acylations. Rodrigo reported an aldehyde C–H activation by an alkylpalladium species leading to a decarbonylation,<sup>22</sup> however, only one example of an acylation between a C(sp<sup>3</sup>)–Pd species and an aldehyde has been disclosed.<sup>15</sup> An aldehyde insertion pathway was suggested in this case, but no mechanistic investigation was conducted to distinguish between these two pathways. As no distinction between the two mechanisms can be made based on our experiments, we have conducted a quantum chemical investigation using Density Functional Theory calculations. Calculations were performed at the SMD-B3LYP-D3/def2-TZVPD//def2-SVPD level of theory using Gaussian 16.<sup>23</sup> Computational details, energies and optimized geometries of all structures can be found in the ESI.†

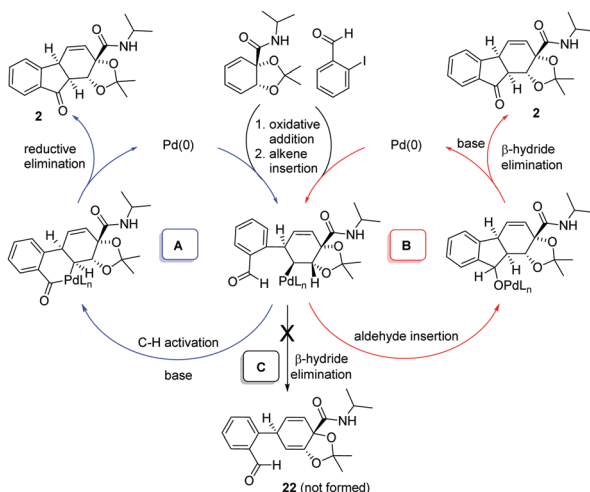
The formation of product **2** without added ligand was chosen as a model reaction to limit the cost of the calculations. Fig. 3 shows computed reaction profiles for the two possible

acylations to form **2** (paths A and B) and  $\beta$ -hydride elimination to form **22** (path C). The three reaction profiles all start from the intermediate **IN1**, which is formed after initial oxidative addition of 2-iodobenzaldehyde, displacement of iodide by acetate and subsequent migratory insertion of **1**.

Our calculations predict path A, involving C–H activation, to be dominant, and clearly favoured over aldehyde insertion. The initial C–H activation step (**TS3**) has a barrier of 12.8 kcal mol<sup>−1</sup> and is predicted to be the highest energy point along this reaction path. The second step of path A proceeds through deprotonation of the formed palladium(IV) complex (**IN3**) and loss of acetic acid through **TS4**, producing the palladium(II) species **IN4**. The **IN4** intermediate is then predicted to undergo a reductive elimination through **TS5** to form product **2**. A possible alternative mechanism to pathway A is C–H activation through a concerted metalation-deprotonation,<sup>24</sup> which has been suggested in related aryl acylations.<sup>13b,20a</sup> However, despite exhaustive efforts, no transition state for this type of mechanism could be located.

The aldehyde insertion (**TS1**) in pathway B computes as having a relatively high barrier of 28.6 kcal mol<sup>−1</sup>. A possible explanation for the high relative energy of **TS1** is that the highly directional C(sp<sup>3</sup>)–Pd bond is almost completely broken in this transition state. Our modelling of this reaction shows that if aldehyde insertion would occur, then subsequent oxidation of the formed palladium alkoxide **IN2** has a relatively low barrier. In other words, if **IN2** is formed it could proceed to form product **2**. Our calculations suggest that the rate determining step for path C is deprotonation of the palladium-hydride complex formed after the  $\beta$ -hydride elimination. This deprotonation (**TS7**) has a barrier of 13.7 kcal mol<sup>−1</sup>, which is  $\sim 1$  kcal mol<sup>−1</sup> higher than the barrier for C–H activation. A predicted lower reaction rate for  $\beta$ -hydride elimination (path C) agrees with our experiments, where no arylation product **22** was observed. The backwards barrier for the alkene insertion forming **IN1** was calculated to 19.1 kcal mol<sup>−1</sup>, making the formation of **IN1** irreversible (ESI† Part 2). The migratory insertion transition state contains a hydrogen bond between the amide and the aldehyde, indicating that the amide can help facilitate the reaction with *ortho* aryl halides.

In summary, we have presented a palladium-catalyzed stereoselective domino arylation-cyclization reaction of enzymatically derived dienes with 2-iodobenzaldehydes. The combination of enzyme- and transition metal catalysis allows for introduction of a high degree of molecular complexity in just a few steps, from two simple aromatic precursors, *i.e.* benzoic acid and a 2-iodobenzaldehyde. The reaction proceeds in good yields and tolerates a range of aryl iodides, as well as some variation in terms of the diene substrate. In total, 12 homo-chiral products are reported with yields ranging from 14–74%. Quantum chemical calculations suggest that the cyclization is a result of a C–H activation that follows the initial Heck-type carbopalladation. The C–H activation is competitive despite the presence of a pendent  $\beta$ -hydrogen. This cyclization is, to our knowledge, the first example of a cyclative Heck-type alkene carbopalladation-acylation domino reaction.



Scheme 6 Potential mechanistic pathways.



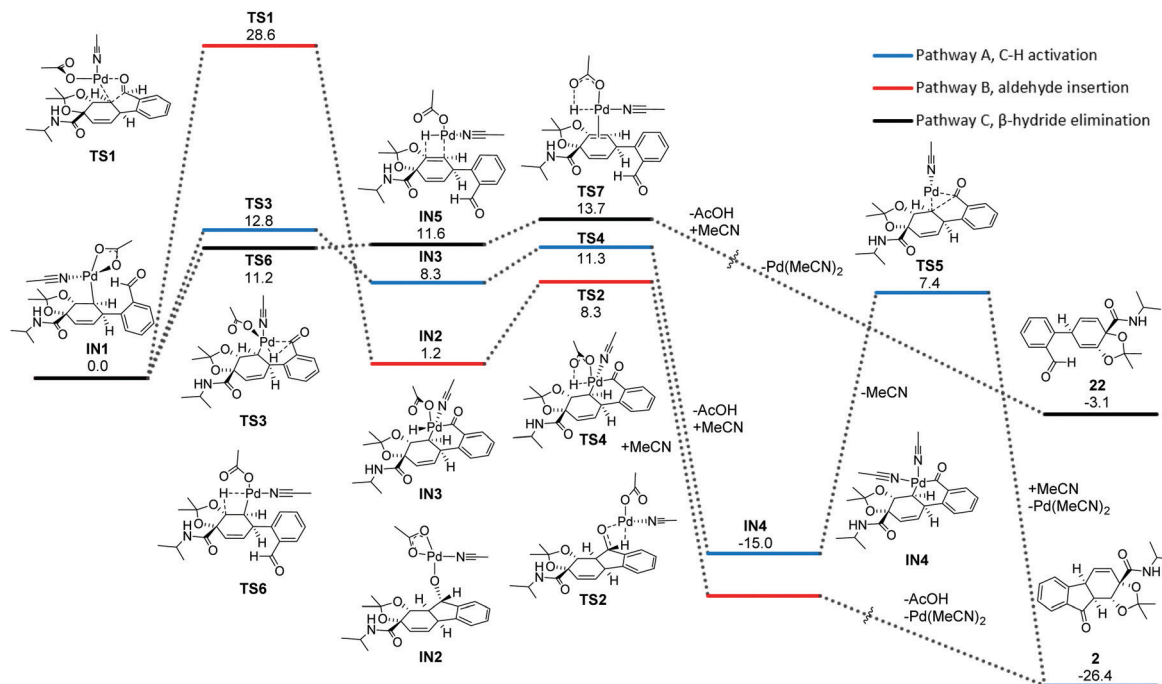


Fig. 3 Gibbs free energy (1 M, 298.15 K, in kcal mol<sup>-1</sup>) reaction profile for the two proposed reaction paths and the competing  $\beta$ -hydride elimination. Geometry optimizations and frequency calculations were performed at the SMD-B3LYP-D3/def2-TZVPD//def2-SVPD level of theory. Energies are shown relative to **IN1**. Extended energy profiles for the aldehyde insertion and  $\beta$ -hydride elimination can be found in the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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