

# Palladium-Catalyzed $\alpha$ -Arylation of Cyclic Vinylogous Esters for the Synthesis of $\gamma$ -Arylcyclohexenones and Total Synthesis of Aromatic **Podocarpane Diterpenoids**

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**Supporting Information** 

**ABSTRACT:** Described is a method for the formal  $\gamma$ -arylation of cyclohexenones allowing synthesis of a remote all-carbon quaternary center. The process involves the palladium-catalyzed  $\alpha$ -arylation of a  $\alpha$ -substituted cyclic vinylogous ester followed by the Stork-Danheiser transposition. The synthetic utility of this protocol is featured in the total syntheses of  $(\pm)$ -12hydroxy-13-methylpodocarpa-8,11,13-trien-3-one,  $(\pm)$ -3 $\beta$ ,12-



n all-carbon quaternary stereocenter bearing an aryl unit is Aa prevailing structural motif in natural products and molecules of pharmaceutical significance.<sup>1</sup> A useful tactic for rapid access to this substitution pattern is the direct  $\alpha$ -arylation of  $\alpha$ -tertiary carbonyl compounds empowered by transition metal catalysis.<sup>2</sup> While the use of catalytic  $\alpha$ -arylation of carbonyl derivatives to form a quaternary carbon center constitutes an extensively investigated field, analogous means for installing an aromatic grouping at the  $\gamma$ -position of  $\gamma$ branched enone precursors have not yet reached the same level of refinement.<sup>3</sup> In particular, the construction of a  $\gamma$ -quaternary aryl stereocenter through distal arylation of cyclic dienolate species still represents a formidable challenge. Difficulties in developing the  $\gamma$ -arylation protocol are posed by a few factors including the liability of self-condensation through Michael addition and issues of controlling regioselectivity. Despite these obstacles, Hyde and Buchwald have demonstrated a few examples of palladium-catalyzed direct  $\gamma$ -arylation of unconjugated cyclohexenones to generate a remote all-carbon quaternary center.<sup>4</sup> Nevertheless, a general approach for the synthesis of  $\gamma$ -aryl- $\gamma$ -alkyl cycloalkenones from readily accessible starting materials remains eminently desirable.<sup>5</sup>

In our quest for a united route to aromatic cyclic terpenoids, we sought to develop a sequence for the formal  $\gamma$ -arylation of 2cyclohexenones that involves palladium-catalyzed  $\alpha$ -arylation of  $\alpha$ -substituted cyclic vinylogous esters in tandem with the Stork–Danheiser transposition<sup>6,7</sup> (Scheme 1). Central to our design plan is the exploitation of the regioselective enolate formation of 3-alkoxy-2-cyclohexenones<sup>7</sup> followed by parlaying it into the catalytic arylation step. It is noteworthy that Zhang and co-workers have reported a  $\alpha$ -arylative, tertiary centerforming reaction of 3-ethoxy-2-cyclohexenone under catalysis of Pd(OAc)<sub>2</sub> and BINAP; however, yields of the coupling reaction fluctuated dramatically according to the electronic properties of the aryl donors.8 At the outset of this project, intermolecular anylative substitution of  $\alpha$ -methine hydrogen of

Scheme 1. Catalytic  $\alpha$ -Arylation Approach for the Synthesis of  $\gamma$ -Arylcyclohexenones



generic structure 1 ( $R^2$  = alkyl) had not been delineated for producing the strategic benzylic quaternary carbon.<sup>9</sup> Until very recently, such transformation was realized by Lautens and coworkers,<sup>10</sup> and it prompted us to disclose our effort in this field. Herein, we present our studies in the Pd-catalyzed crosscoupling reaction of 1 with various bromoarenes and synthetic studies toward podocarpane-type diterpenoids.

Our investigations commenced employing dimethyl-substituted cyclic vinylogous ester 1a<sup>11</sup> and bromoarene 4a as coupling partners, wherein the use of 1a is pivotal to our research endeavor toward the diterpenoid synthesis (vide infra). Of numerous reaction parameters examined,12 the conditions similar to those proven efficacious for the  $\alpha$ arylation of  $\alpha$ -branched esters by Hartwig and co-workers afforded the cleanest reaction profile.<sup>13</sup> In our case, the optimal catalyst scheme called for the combination of  $Pd(dba)_2$  (1 mol %) and  $P(t-Bu)_3$  (1 mol %) with lithium dicyclohexylamide functioning as a base (Table 1, entry 4). On the other hand, the reactions employing either LDA or LiTMP gave a significant amount of intractable materials (entries 2 and 3). We showed that the arylation of  ${\bf 1a}$  by treating the air stable  $HBF_4$  salt of  $P(t-Bu)_3^{14}$  worked reasonably well to produce **2a** (entry 5).

The optimized conditions described above were utilized to carry out the  $\alpha$ -arylation of 1a with a range of aromatic

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Table 1. Effects of Base and Ligand on the  $\alpha$ -Arylation of  $1a^{\alpha}$ 



<sup>*a*</sup>Reactions were conducted with 1 equiv of **4a** (2.0 mmol) and 1.1 equiv of **1a**. For detailed procedures, see the Supporting Information. <sup>*b*</sup>Yield of isolated product based on **4a**. dba = *trans,trans*dibenzylideneacetone. LiHMDS: lithium hexamethyldisilazide. LDA: lithium diisopropylamide. LiTMP: lithium 2,2,6,6-tetramethylpiperidide. LiNCy<sub>2</sub>: lithium dicyclohexylamide.

substrates 4b-k (Table 2). The reactions of electron-rich aryl bromides produced desired aryl carbonyl products in good yields (entries 1-4). Notably, the arylation is compatible with a sterically demanding ortho-substituted substrate (4e), albeit at a slower rate. Even electron-deficient bromoarenes 4f and 4g were effectively cross-coupled with 1a (entries 5 and 6). The scope of substituted bromobenzene appears broad in terms of electronic and steric considerations, so we next examined the compatibility of heterocyclic bromides in this transformation. The reaction of thiophene 4h proceeded smoothly to install a 3-thienyl substituent at the  $\alpha$  carbon of 1a (entry 7). This method can accommodate N-silyl-indole 4i and N-Boccarbazole 4j to deliver the corresponding  $\alpha$ -heteroarylated compounds, but the reactions were relatively sluggish and required either a longer reaction time (entry 8) or a higher catalyst loading (entry 9). Although we found 4k failed to react with 1a under the standard conditions,<sup>15</sup> a modest yield of the coupling product 2k could be obtained in the presence of  $Pd(OAc)_2$  (entry 10). In this particular example, we observed a noticeable competing pathway to give 2,6-dimethyl-3-ethoxyphenol through oxidative aromatization of 1a.

In their comprehensive study,<sup>10</sup> Lautens and colleagues showed that the coupling of **1b** with 4-bromoveratrole (**4**) catalyzed by commercially available palladacycle  $(Pd-P(t-Bu)_3-G2)$  was accompanied by alkene isomerization, thus generating compound **5** in moderate yield (Scheme 2a). With our catalytic system, the reaction of **1b** and **41** furnished **21** as the sole product, and a quaternary allyl aryl stereocenter was conveniently synthesized (Scheme 2b). From a synthetic standpoint, these examples are complementary tools for assembling highly functionalized building blocks.

To further demonstrate the significance of our arylative methodology, we embarked on total syntheses of  $(\pm)$ -12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (9),<sup>16</sup>  $(\pm)$ -3 $\beta$ ,12-dihydroxy-13-methylpodocarpane-8,11,13-triene (10),<sup>17</sup> and  $(\pm)$ -O-methyl nimbinone (11).<sup>18</sup> Compounds 9 and 10 belong to a family of podocarpane diterpenoids that have been isolated from several terrestrial plant sources,<sup>19</sup> and compound 11 is known as a synthetic derivative of naturally occurring nimbinone.<sup>20</sup> These structurally unique bisnorditerpenoids possess a  $\gamma$ -quaternary- $\gamma$ -aryl cyclohexanone scaffold,





Table 2. Catalytic Cross-Coupling of 1a with Different

"Scope was evaluated using 2.0 mmol of bromoarenes. <sup>b</sup>Yield of isolated product based on 4. <sup>c</sup>Reaction time = 18 h. <sup>d</sup>Reaction time = 4.5 h. <sup>e</sup>With 7.5 mol % Pd(dba)<sub>2</sub> and 8 mol % P(t-Bu)<sub>3</sub>·HBF<sub>4</sub>·<sup>f</sup>With 5 mol % Pd(OAc)<sub>2</sub> and 10 mol % P(t-Bu)<sub>3</sub>; Reaction time = 18 h.

and are therefore well suited for our methodology.<sup>21</sup> Compound 9 exhibited notable biological profiles including antifungal activity<sup>22</sup> and in vitro cytotoxic activity against selected human tumor cell lines with  $IC_{50}$  values ranging from

Scheme 2. Reaction Courses of an Allyl Substrate

a) Lautens and co-workers:



3.0 to 6.3  $\mu$ M.<sup>23</sup> Compound **10** displays anti-HCV activity<sup>24</sup> as well as inhibitory effects on lipopolysaccharide-induced NO production.<sup>25</sup> Despite promising biomedicinal potentials of these targets, there has been only one total synthesis of 9, described by Zhang and co-workers,<sup>26</sup> and total synthesis of 10 is hitherto unknown.

Integrating our own protocol with a cyclialkylation-based strategy developed by Majetich and co-workers allowed us to streamline the synthesis of functionalized hydrophenanthrene skeletons (Scheme 3).<sup>27</sup> The coupling reaction of 1a with  $4m^{28}$ 

## Scheme 3. Total Synthesis of Aromatic Podocarpane Diterpenoids



trien-3-one (9), 74% yield

took place uneventfully to give the desired arylated product 2m. Conjugated dienone 6 was prepared via a Stork-Danheiser transposition comprising 1,2-addition of vinylmagnesium bromide followed by acidic hydrolysis. In this case, it was necessary to apply cerium(III) chloride to facilitate the organometallic addition to the sterically congested carbonyl carbon.<sup>29</sup> Intramolecular Friedel–Crafts reaction of 6 mediated by a Lewis acid led to the formation of tricyclic compound 7. Reductive alkylation of 7 under dissolving-metal conditions gave 8 by establishment of the trans-decalin system and introduction of the gem-dimethyl moiety.<sup>30</sup> The facile removal of the O-methyl group with boron tribromide delivered 9 in 74% yield. Accordingly, the total synthesis of racemic 12hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (9) was achieved in five steps and 18% overall yield from known vinylogous ester 1a.<sup>11</sup> When subjected to Luche conditions,<sup>3</sup> ketone 9 was reduced in excellent diastereoselectivity, thus accomplishing the first total synthesis of racemic  $3\beta$ ,12dihydroxy-13-methylpodocarpane-8,11,13-triene (10). Additionally, we showed that  $(\pm)$ -O-methyl nimbinone (11) could be prepared through regioselective benzylic oxidation of a common intermediate 8.<sup>3</sup>

In summary, we have developed a method for the Pdcatalyzed  $\alpha$ -arylation of cyclic vinylogous esters. This process enables the synthesis of an all-carbon quaternary aryl stereocenter and is effective with a range of aryl or heteroaryl bromides. We have demonstrated the utility of the  $\alpha$ -arylated products in a Stork-Danheiser transposition that provides ready access to densely substituted  $\gamma$ -arylcyclohexenones. The combined arylation/Stork-Danheiser transposition sequence is highlighted in a united route to aromatic podocarpane-type diterpenoids. Further applications of this protocol in natural product synthesis are underway and will be described in due course.

## ASSOCIATED CONTENT

#### **Supporting Information**

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Experimental procedures and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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