

# Palladium-Catalyzed Regio- and Stereoselective $\gamma$ -Arylation of Tertiary Allylic Amines: Identification of Potent Adenylyl Cyclase Inhibitors

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## Supporting Information

**ABSTRACT:** Substituted allylic amines and their derivatives are key structural motifs of many drug molecules and natural products. A general, mild, and practical palladium-catalyzed  $\gamma$ -arylation of tertiary allylic amines, one of the most challenging Heck arylation substrates, has been developed. The  $\gamma$ -arylation products were obtained in excellent regio- and stereoselectivity. Moreover, novel and potent adenylyl cyclase inhibitors with the potential for treating neuropathic and inflammatory pain have been identified from the  $\gamma$ -arylation products.



$\gamma$ -Arylated *N,N*-dialkylallylamines are ubiquitous structural motifs and have been widely found in biologically active natural products, life-saving drugs, and other molecules of important functions.<sup>1</sup> For example, naftifine (1, Figure 1A) is an allylamine antifungal drug and selectively blocks sterol biosynthesis via inhibition of the squalene 2,3-epoxidase enzyme.<sup>2</sup> Cinnarizine (2) and flunarizine (3) are effective calcium channel blockers and are characterized as antihistamines. They have been widely used for various conditions such as nausea, vertigo, migraine, and vascular diseases.<sup>3</sup> Abamine SG (4) is an abscisic acid biosynthesis inhibitor to target 9-*cis*-epoxycarotenoid dioxygenase.<sup>4</sup> Various strategies have been developed for the construction of  $\gamma$ -arylated *N,N*-dialkylallylamine derivatives.<sup>5</sup> One of the most desirable and straightforward ways would be a Heck arylation of *N,N*-dialkylallylamines at the terminal olefinic carbon ( $\gamma$ -position). In general, Heck arylations work well with activated and biased olefins such as acrylates and styrenes.<sup>6</sup> Recently, significant progress in the Heck arylation of electronically nonbiased olefins have been made by the groups of Sigman (cf. eq 1, Figure 1B), Zhou, Jamison, Stahl, and others.<sup>7</sup> Because of these elegant studies, regio- and stereoselective arylations of simple terminal olefins such as allylic alcohols, homoallylic alcohols, and other unactivated olefins have become important and powerful synthetic tools in preparing complex and functional molecules.

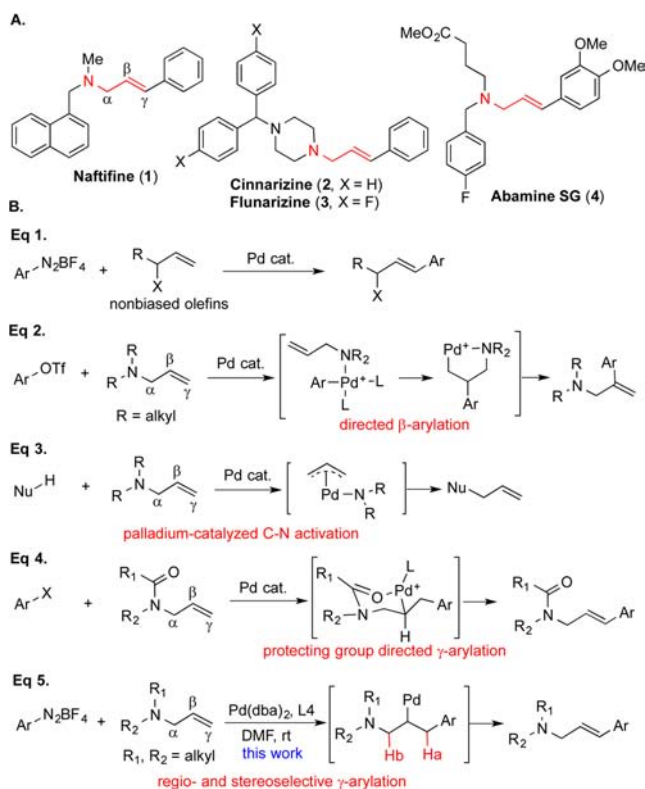
Despite these significant advancements, stereoselective  $\gamma$ -arylation of *N,N*-dialkylallylamines persists as a great synthetic challenge due to the following difficulties presented by *N,N*-dialkylallylamine substrates. (I) The strong basicity and coordinating capability of these tertiary amines make most of the Heck arylation conditions invalid for  $\gamma$ -arylation. For example, Hallberg and Wu have independently reported palladium-catalyzed Heck arylation of *N,N*-dialkylallylamines, and in both cases,  $\beta$ -arylated products were obtained

predominantly due to the intrinsic directing ability of the nitrogen atom (eq 2, Figure 1B).<sup>8</sup> (II) Oxidative addition of palladium(0) catalyst with allylamines to form  $\pi$ -allyl palladium species competes with the Heck arylation, which renders allylamines as allyl group donors (eq 3, Figure 1B) or amine sources.<sup>8a</sup> Zhang and Tan have independently reported elegant examples of using allylamines as allyl donors.<sup>9</sup> (III) Selective  $\beta$ -hydride elimination ( $H_a$  vs  $H_b$ , eq 5, Figure 1B) to form the desired product remains as an issue as well. In order to get around these intrinsic competing factors and obtain desired  $\gamma$ -arylated products, protecting and directing group strategies have been employed (eq 4, Figure 1B).<sup>10</sup> The basic nitrogen atoms are masked as amides, carbamates, etc. The protecting groups also serve as directing groups to ensure the arylation takes place at the  $\gamma$ -position. Still, in some of these cases poor regioselectivity or  $\beta$ -arylation were obtained.<sup>11</sup> In addition to the installation of the required protecting and directing groups, extra steps are required to remove them or convert them to the desired alkyl groups. Our recent need of diverse  $\gamma$ -arylated *N,N*-dialkylallylamines with potential CNS activity<sup>12</sup> (cf. 7aa, Table 1) prompted us to develop a straightforward synthesis of them (eq 5, Figure 1B). Herein, we report a mild palladium-catalyzed regio- and stereoselective  $\gamma$ -arylation of *N,N*-dialkylallylamines and the identification of potent adenylyl cyclase inhibitors with therapeutic potential for treating neuropathic and inflammatory pain from the arylation products.

Since aryl diazonium salts have been used frequently in Heck arylation of nonactivated olefins,<sup>7d</sup> our investigation started with phenyl diazonium tetrafluoroborate (6a) and a relatively complex and challenging allylic amine substrate, 5a. In order to override the intrinsic coordination of the tertiary nitrogen with palladium center to control the regioselectivity, 2,2'-bipyridine

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**Figure 1.** Selected allylic amine drugs, Heck arylation of nonbiased olefins, current status of arylation of allylic amine derivatives, and our method.

ligand **L1** was selected. When **5a** (1 equiv) and **6a** (1.5 equiv) were subjected to the conditions of Pd(dba)<sub>2</sub> with **L1** (Pd:L = 1:1.2) at room temperature in DMF, the desired product **7aa** was obtained in 54% yield. Other solvents such as THF, CH<sub>3</sub>CN, DMSO, and DMA are inferior to DMF or completely inhibit the reaction (see the Supporting Information). Slightly reduced yield was obtained when the reaction was conducted at an elevated temperature (entry 3). Bases such as triethylamine and K<sub>2</sub>CO<sub>3</sub> shut down the reaction (entries 4 and 5). A further increase in the amount of **6a** or the catalyst–ligand loading has beneficial effects. We also found that among the four nitrogen-containing bidentate ligands tested, **L4** gave the best result (entry 12). The reaction yield dropped significantly when several bidentate phosphine ligands were used (see the Supporting Information). Other palladium catalysts including PdCl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd(OAc)<sub>2</sub> were less effective than Pd(dba)<sub>2</sub>. Overall, under the optimized conditions (entry 12), the desired product could be produced in 90% yield with excellent regio- and stereoselectivity.

We then evaluated the substrate scope. As summarized in Figure 2, this reaction is very general and compatible with many functional groups including halogens (I, Br, Cl, and F), ester groups, amides, nitro groups, and indoles. Diazonium salts with both electron-withdrawing and electron-donating groups are effective coupling partners. A variety of  $\gamma$ -arylated *N,N*-dialkylallylamines were produced in good to excellent yield, including those derived from azepanes, diazepanes, and piperazines. Notably, we were able to produce naftifine (**1**) in 90% yield. When the reaction was conducted on a gram scale, naftifine (**1**) was obtained in 72% yield. Cinnarizine (**2**) and flunarizine (**3**) were synthesized smoothly as well, while the corresponding substrates present several challenging factors

**Table 1. Condition Optimization<sup>a</sup>**

entry	Pd cat.	x	y	solvent	ligand	base	yield <sup>b</sup> (%)
1	Pd(dba) <sub>2</sub>	1.5	5	DMF	L1		54
2	Pd(dba) <sub>2</sub>	1.5	5	DMA	L1		33
3	Pd(dba) <sub>2</sub>	1.5	5	DMF	L1		49 <sup>c</sup>
4	Pd(dba) <sub>2</sub>	1.5	5	DMF	L1	Et <sub>3</sub> N	0
5	Pd(dba) <sub>2</sub>	1.5	5	DMF	L1	K <sub>2</sub> CO <sub>3</sub>	0
6	Pd(dba) <sub>2</sub>	2.0	5	DMF	L1		73
7	Pd(dba) <sub>2</sub>	2.5	5	DMF	L1		71
8	Pd(dba) <sub>2</sub>	2.0	8	DMF	L1		80
9	Pd(dba) <sub>2</sub>	2.0	10	DMF	L1		85
10	Pd(dba) <sub>2</sub>	2.0	10	DMF	L2		81
11	Pd(dba) <sub>2</sub>	2.0	10	DMF	L3		54
12	Pd(dba) <sub>2</sub>	2.0	10	DMF	L4		90
13	Pd(dba) <sub>2</sub>	2.0	10	DMF			54
14	Pd(OAc) <sub>2</sub>	2.0	10	DMF	L4		55
15	PdCl <sub>2</sub>	2.0	10	DMF	L4		trace
16	Pd(PPh <sub>3</sub> ) <sub>4</sub>	2.0	10	DMF	L4		trace

<sup>a</sup>General reaction conditions unless otherwise noted: A mixture of palladium catalyst and ligand in DMF was stirred at rt for 20 min under argon before **5a** and **6a** were added. The reaction mixture was stirred at rt and monitored by thin-layer chromatography. <sup>b</sup>Isolated reaction yield. <sup>c</sup>60 °C.

including two basic nitrogen atoms, potential debenzoylation, and deallylation reactions.

Additionally, these  $\gamma$ -arylated products could be converted to other useful products as well (Scheme 1). For example, amine oxidation followed by [2,3]-sigmatropic rearrangement converted **1** to **11**.<sup>13</sup> Dihydroxylation or hydrogenation converted **1** to **12** or **13**, respectively, in good yields. A one-pot, double-bond isomerization followed by Pictet–Spengler reaction converted **7aa** to tetrahydro- $\beta$ -carboline **14**.<sup>14</sup> The latter represents the core structure of many bioactive natural products and pharmaceutical molecules.<sup>15</sup>

We then evaluated these  $\gamma$ -arylated *N,N*-dialkylallylamine products for their ability to inhibit adenylyl cyclase activity. Adenylyl cyclases are enzymes that catalyze the production of cAMP from ATP. These enzymes are very important mediators of signaling through G protein-coupled receptors.<sup>16</sup> There are nine different isoforms of membrane-bound adenylyl cyclases, each of which displays unique regulatory properties and expression patterns. Adenylyl cyclase type I (AC1) belongs to a family of adenylyl cyclases that are stimulated by calcium in a calmodulin-dependent manner.<sup>17</sup> Notably, AC1 has been associated with chronic pain responses in several regions of the central nervous system.<sup>18</sup> It has been previously shown that administration of NB001, a small molecule inhibitor of AC1 (IC<sub>50</sub> = 10  $\mu$ M in cell models) leads to analgesic effects in both inflammatory and neuropathic pain rodent models.<sup>19</sup>

To determine whether these  $\gamma$ -arylated products have an inhibitory effect on AC1 activity, HEK (human embryonic kidney) cells stably expressing AC1 (HEK-AC1) were

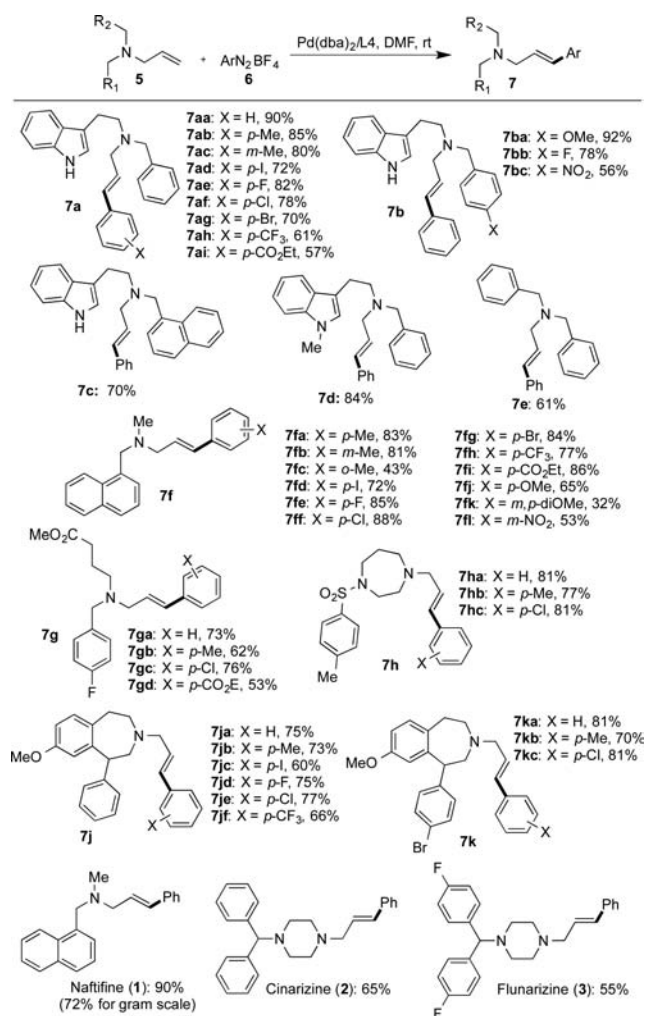
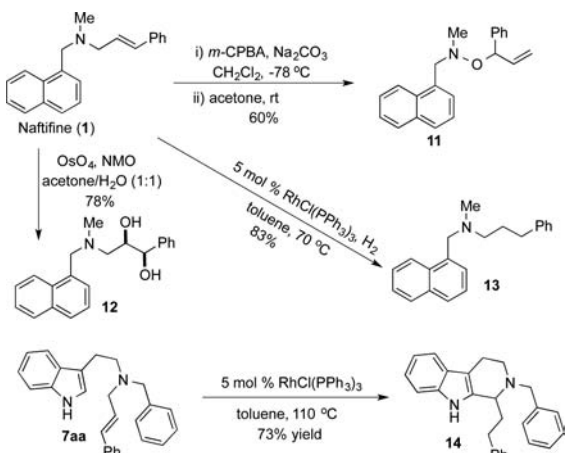


Figure 2. Substrate scope.

Scheme 1. Diversification of the  $\gamma$ -Arylation Products

employed, and inhibition of Ca<sup>2+</sup>-stimulated cAMP accumulation was determined. A23187 is a Ca<sup>2+</sup> ionophore that promotes Ca<sup>2+</sup> binding to calmodulin in the cells and subsequent stimulation of AC1. As expected, treatment of HEK-AC1 cells with A23187 led to a robust increase in cAMP accumulation consistent with Ca<sup>2+</sup>/calmodulin activation of AC1 (data not shown). Several of the  $\gamma$ -arylated *N,N*-dialkylallylamine products from the 7a–c and 7j series dose-

dependently inhibited this cAMP response (Table 2). These compounds displayed IC<sub>50</sub> values in the low micromolar range, with the most potent being 7ag, with an IC<sub>50</sub> value of 6.91 ( $\pm 0.50$ )  $\mu\text{M}$ .

Table 2. AC1 Inhibition

compd	7ag	7aa	7c	7je
IC <sub>50</sub> ( $\mu\text{M}$ )	6.91 ( $\pm 0.50$ )	9.92 ( $\pm 2.28$ )	8.95 ( $\pm 1.55$ )	9.10 ( $\pm 0.82$ )

In summary, we have developed a general and practical palladium-catalyzed  $\gamma$ -arylation of tertiary allylic amines. The arylated products were obtained in high regio- and stereo-selectivity. We have applied it to prepare several drug molecules including naftifine, cinarizine, flunarizine, and their analogues. Moreover, we have identified potent adenylyl cyclase type I inhibitors from the  $\gamma$ -arylation products. These novel AC1 inhibitors are of great potential for treating neuropathic and inflammatory pain. The new synthetic capability developed here will also facilitate the optimization of these lead compounds in terms of potency, isoform selectivity, and pharmacological properties.

## ■ ASSOCIATED CONTENT

## S Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## Notes

The authors declare no competing financial interest.

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