Site-Selective Palladium-Catalyzed 1,1-Arylamination of Terminal Alkenes

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Many of the commonly used pharmaceuticals and biologically active natural products are nitrogen-containing compounds. Recently, the transition-metal-catalyzed or the radical-mediated 1,2-carboamination of alkenes has been well explored to access amine scaffolds. However, synthetic strategies toward the 1,1-carboamination of alkenes are severely limited. Herein, we describe a method to achieve the 1,1-arylamination using readily available building blocks enabled by palladium catalysis. This sequential three step-Heck arylation, metal migration, followed by aza-1,6-Michael addition process exhibits excellent chemo- and regioselectivity. To showcase the potential as a method for diversity-oriented drug discovery, the modification of numerous structurally complex bioactive molecules was also successfully performed.

Keywords: alkene, 1,1-arylamination, palladium-catalyzed, site-selective, nitrogen-containing molecules

Introduction

Nitrogen-containing molecules play a vital role in drug exploitation, sensor design, and agrochemical development. In the preceding decades, transition-metal catalysis,5-9 photocatalysis,10-13 and electrocatalysis14-17 have shown their unique merits in the synthesis of amine scaffolds. The development of these novel C–N bond-forming reactions has proven to be a valuable supplement to traditional methods, such as Hofmann alkylation,18 amide reduction,19 imine alkylation20-22 and carbonyl reductive amination.23,24 However, the demand for practical methods for amine functionalization in drug discovery and industrial productions has not yet been fulfilled.

Alkenes are deemed one of the most available feedstocks, which engage in diverse organic transformations involving all facets of chemistry. Catalytic difunctionalization of alkenes is an elegant route that permits the simultaneous generation of two new bonds in an operation to provide structurally diverse molecules.25-28 Consequently, the transition-metal-catalyzed or the radical-mediated 1,2-/2,1-carboamination of alkenes is particularly popular and provides efficient approaches to generate the versatile nitrogen-containing architectures (Scheme 1a).29-41 For instance, Piou and Rovis39 achieved a rhodium-catalyzed diastereoselective syn-carboamination of alkenes with enoxyphthalimide in 2015. In 2018, Stephenson and co-workers40 disclosed a photocatalytic 1,2-aminoarylation of alkenes with arylsulfonylacetamides as the bifunctional reagents. Engle and co-workers41 also reported the 1,2-carboamination of unactivated alkenes with amines and aryl electrophiles via a directed aminopalladation strategy. Aside from these remarkable achievements in alkene 1,2-carboamination, however, advances in the site-selective 1,1-carboamination of alkenes have rarely been reported. In addition, the transition-metal-catalyzed 1,1-aryloxygenation, 1,1-arylhalogenation, 1,1-diarylation, 1,1-arylboronation, 1,1-diboration, 1,1-alkynylboration, and 1,1-dialkynylation of alkenes have been successively...
disclosed by Sanford et al., Toste et al., Hong et al., Sigman et al., and Fu et al., and more recently, Ellman and co-workers described a rhodium-catalyzed 1,1-arylamination of alkenes to generate α-branched secondary amines with electrophilic aminating agents (Scheme 1b). The heteroatom-based directing group figured as a crucial factor in the control of regioselectivity, which promotes the Rh catalyst migration to the benzyl site for the nitrene insertion. Herein, we describe an innovative tactic to show the alkene 1,1-arylamination with 4-iodophenols and N-nucleophiles (Scheme 1c). The regioselectivity is derived through an intriguing palladium-catalyzed Heck arylation/metal migration/isomerization process. This process affords a thermodynamically stable para-quinone methide intermediate, which can be used for further amination decoration. The remarkable substrate scope and generality of this method is demonstrated in more than 70 examples, including over 20 cases of structurally complex alkene-containing biologically active molecules, offering a workable platform for diversity-oriented drug discovery.

**Experimental Methods**

A sealed tube was assembled with alkenes (0.2 mmol, 1.0 equiv), 4-iodophenols (0.4 mmol, 2.0 equiv), amines (0.4 mmol, 2.0 equiv), Pd$_2$(dba)$_3$ (0.01 mmol, 9.2 mg, 5.0 mol %), K$_3$PO$_4$ (0.2 mmol, 42.4 mg, 1.0 equiv), tetrabutyl ammonium chloride (TBAC, 0.2 mmol, 55.6 mg, 1.0 equiv), and in dry 1,4-dioxane (1.0 mL). The reaction mixture was stirred at 80 °C under argon for 24 h. Then the reaction was diluted with ethyl acetate (5.0 mL) and filtered through a plug of Celite. The solvent was removed under vacuum conditions, and the crude product was purified by flash chromatography on silica gel to afford the corresponding products.

**Results and Discussion**

We initiated this work with commercially available 1-phenylpent-4-en-1-one 1a, 4-iodophenol 2a, and indoline 3a. In 1,4-dioxane, the branched tertiary amine 4a could be achieved in 78% yield employing 5.0 mol % catalyst loading of Pd$_2$(dba)$_3$, K$_3$PO$_4$, and TBAC (Table 1, entry 1). Other Pd-catalysts, such as Pd(dba)$_2$ and Pd(PPh$_3$)$_4$, resulted in low yield of 4a (Table 1, entries 2 and 3). Replacing the Pd$_2$(dba)$_3$ with Pd(OAc)$_2$ delivered 4a in a trace amount (Table 1, entry 4). Product 4a could be observed in Ni-catalyzed conditions, albeit in a low yield (Table 1, entry 5). With the reduction of the amount of catalyst, the transformation efficiency of the reaction...
Table 1 | Effect of Reaction Parameters

| Entry | Deviation from Standard Conditions | Yield (%) |
|-------|-----------------------------------|-----------|
| 1     | None                             | 78        |
| 2     | Pd(dba)$_2$ instead of Pd$_2$(dba)$_3$ | 67        |
| 3     | Pd(PPPh$_3$)$_2$ instead of Pd$_2$(dba)$_3$ | 31        |
| 4     | Pd(OAc)$_2$/PPPh$_3$ instead of Pd$_2$(dba)$_3$ | Trace     |
| 5     | Nil$_2$ instead of Pd$_2$(dba)$_3$ | 46        |
| 6     | 2.5 mol % Pd$_2$(dba)$_3$         | 63        |
| 7     | tBuOK instead of K$_3$PO$_4$      | 28        |
| 8     | Na$_2$CO$_3$ instead of K$_3$PO$_4$ | 71        |
| 9     | Et$_3$N instead of K$_3$PO$_4$    | Trace     |
| 10    | Without K$_3$PO$_4$              | n.d.      |
| 11    | THF instead of 1,4-dioxane        | 55        |
| 12    | DCM instead of 1,4-dioxane       | 37        |
| 13    | DMF instead of 1,4-dioxane       | 65        |

Note: DCM, dichloromethane; DMF, dimethylformamide; THF, tetrahydrofuran. n.d. = the 1,1-arylamination product was not detected.

$^a$ Reaction condition: 1a (0.2 mmol), 2a (0.4 mmol), 3a (0.4 mmol), Pd$_2$(dba)$_3$ (5.0 mol %), K$_3$PO$_4$ (0.2 mmol), TBAC (0.2 mmol), in dry 1,4-dioxane (1.0 mL) at 80 °C under argon for 24 h. Isolated yields.

$^b$ 11% yield of Heck byproduct was isolated.

$^c$ 10.0 mol % catalyst was used.

$^d$ 1.0 equiv Zn was used.

The transformation capable of functionalizing bioactive molecules into related analogues without resorting to de novo synthesis offers a potential to diversity-oriented drug discovery, and has aroused widespread interest in academia and the pharmaceutical industry. To illustrate the generality and practicality of this method, we turned our attention to modifying structurally complex alkene-containing biologically active molecules (4y–4as), which were all achieved in moderate to good yields (Table 2b).

Subsequently, aryl iodides and amines were checked to expand the substrate scope (Table 3). The electrical properties and steric hindrance of 4-iodophenols have no obvious influence on the conversion efficiency of the reaction, offering the products 5b–5m in moderate to good yields. It is worth noting that 2-iodophenol and malonate diesters-substituted aryl iodide were also suitable for this reaction, and 5n and 5o could be isolated in 62% and 41% yields. Indolines (3b–3e) and tetrahydroquinolines (3f–3h) delivered the products 6b–6h in good yields. Benzomorpholine (3i), N-acetyl-substituted tetrahydroquinoline (3j) offered 6i and 6j in 67% and 51% yields. Acyclic N-methylaniline (3k) and simple aniline (3l) successfully took part in this transformation. Aside from aryl amines, sulfonamides (3m and 3n) and morpholin-4-amine (3o) were also compatible with the reaction system. In addition, subject of 2-(allyloxy)aniline (7) with 4-iodophenol could deliver the medium ring compound 8 in 51% yield. At present, the alkylamines are still challenging substrates for this reaction.

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Table 2 | Substrate Scope

(a) Substrate scope of alkenes

(b) Substrate scope of structurally complex alkene-containing bioactive molecules

* Reaction condition (unless otherwise specified): 1 (0.2 mmol), 2 (0.4 mmol), 3a (0.4 mmol), Pd2(dba)3 (5.0 mol %), K3PO4 (0.2 mmol), TBAC (0.2 mmol), dry 1,4-dioxane (1.0 mL) at 80 °C under argon for 24 h. Isolated yields.

b X = Br.

c Yield of the corresponding product after the tert-butylchlorodimethylsilane protection (TBSCI) protection.
Further application values of this protocol were next demonstrated (Scheme 2). Initially, a gram-scale synthesis of 4q (1.21 g) was obtained in 77% yield on the 3.8 mmol scale under the standard conditions (Scheme 2a). Further transformations of product 4q were showcased by the conversion of indoline and phenol hydroxy moieties into a portfolio of useful functional groups (Supporting Information Figure S2). Compound 9 containing the indole framework was afforded in good yield under the oxidation condition. Trifluoromethansulfonylation of 4q provided compound 10 in 87% yield, which could be easily reduced to compound 11 in 80% yield. Additionally, subjecting 10 to the Pd-catalyzed Heck or Suzuki coupling reaction could lead to the compounds 12 and 13 in good yields (Scheme 2b).

To better clarify the reaction pathway, we designed and carried out some verification experiments. The reaction occurred smoothly to give product 4a in good yield in the presence of 2,2,6,6-tetramethyl-1-piperinedinyloxy (TEMPO) or butylated hydroxytoluene (BHT), which excluded the possibility of a radical pathway (Scheme 3a). In addition, when iodobenzene 14 or 4-methoxybenzenediazonium tetrafluoroborate 16 was tested, only Heck byproduct 15 and C–N cross-coupling byproduct 17 were formed (Scheme 3b, 1 and 2). Afterward, a potential intermediate 18 was synthesized and examined, delivering the compound 19 in 88% and 91% yields with or without Pd2(dba)3 (Scheme 3b, 3), which illustrated that the para-quinone methide was likely the key intermediate, and could exclude palladium’s role in C–N bond formation. To further explore this process, (but-3-en-1-yl-4,4-d2)benzene 1l-D was added to the reaction and yielded the product 4l-D in 61% yield with approximately 44% deuterium atom transferred to the β-position of phenol framework. This result demonstrated a process involving β-H elimination and reinsertion steps (Scheme 3c). Next, we carried out a crossover reaction with 1a and 1l-D as the substrates, and only the

| Substrate Scope* |
|------------------|
| ![Substrate Scope](image) |

* Reaction condition (unless otherwise specified): 1a (0.2 mmol), 2 (0.4 mmol), 3 (0.4 mmol), Pd2(dba)3 (5.0 mol %), K3PO4 (0.2 mmol), TBAC (0.2 mmol), dry 1,4-dioxane (1.0 mL) at 80 °C under argon for 24 h. Isolated yields.

b 25 °C.

c Yield of the corresponding product after the TBSCl protection.
corresponding products 4a and 4l-D were observed, indicating that the coordination between the catalysts and the alkenes was not dissociated before the reinsertion process or the formation of the final products (Scheme 3d). Finally, the observed kinetic isotopic effect value is 1.13, which confirmed that the process of β-H elimination/migratory insertion might not be participated in the rate-determining step (Scheme 3e).

Scheme 2 | (a and b) Further studies. (a) PhI(OAc)$_2$, 1,4-dioxane, r.t. (b) Tf$_2$O, Et$_3$N, DCM, r.t. (c) Pd/C, Et$_2$NH, H$_2$, MeOH, r.t. (d) Phenylboronic acid, trimethylamine, Pd(OAc)$_2$, PPh$_3$, H$_2$O, 1,4-dioxane under argon. (e) Methyl acrylate, Pd (OAc)$_2$, PPh$_3$, K$_2$CO$_3$, toluene, 110 °C under argon.

Scheme 3 | (a–e) Mechanistic studies.
Based on the literature reports and the mechanistic study experiments, a proposed pathway to this 1,1-arylamination reaction is shown in Scheme 4. Initially, the active palladium species reacts with 4-iodophenol through oxidative addition to produce arylpalladium species I. Subsequently, migratory insertion of alkene into the Pd–Ar bond generates intermediate II, which undergoes selective β-Ha elimination to deliver intermediate III. PdHa reinserts into the species III to give benzylpalladium intermediate IV. A base-assisted electron transfer process affords a thermodynamically stable para-quinone methide intermediate V, which is followed by an aza-1,6-Michael addition with amine to form the desired branched tertiary amine 4a.

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**Conclusion**

We have realized a site-selective palladium-catalyzed 1,1-arylamination of terminal alkenes with phenol-derived aryl iodides and N-nucleophiles. Diverse synthetically flexible branched tertiary amines were synthesized in moderate to good yields. This reaction adopted a broad-spectrum of functional groups and showcased an extensive substrate scope. A reasonable mechanism was proposed based on multiple control experiments.

**Supporting Information**

Supporting Information is available, including the experiment procedures, NMR spectra, and X-ray crystallographic data for 4d (CCDC no. 1962677).

**Conflict of Interest**

There is no conflict of interest to report.

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**Scheme 4** | Proposed mechanism.

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