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PALLADIUM-CATALYZED OXIDATIVE CARBOACETOXYLATION OF ACTIVATED ALKYNES WITH AMINO ACIDS

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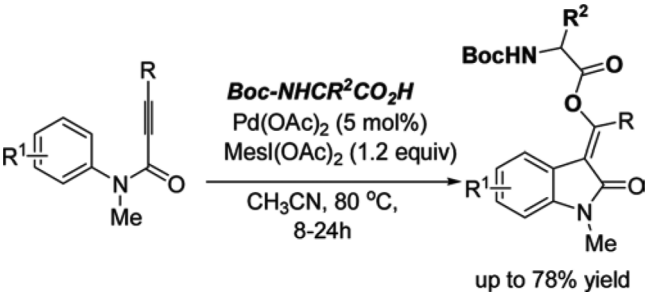
GRAPHICAL ABSTRACT



Abstract *A palladium-catalyzed intramolecular oxidative carboacetoxylation reaction of alkynes with various amino acids has been demonstrated for the first time, forming pharmaceutically important 3-methyleneindolin-2-one. In the presence of* $Pd(OAc)_2$ *and* $ArI(OAc)_2$, N-*arylpropiolamides underwent tandem acetoxypalladation/C-H functionalization reactions with various Boc-amino acids to form corresponding methyleneindolin-2-ones bearing amino acid motifs in moderate to excellent yields.*

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Keywords Acetoxypalladation; amino acids; C-H activation; methyleneindolin-2-one; tandem reaction

INTRODUCTION

3-Methyleneindolin-2-ones, especially the ones bearing hetero atoms on the side chain, are pharmaceutically interesting compounds that display great potential utilizations in many major therapeutic areas, such as oncology, inflammation, the

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central nervous system, immunology, and endocrinology.[1] For example, sunitinib, BIBF1120, and tenidip were recently commercialized by Plifzer to treat gastrointestinal stromal tumor and inflammation (Fig. 1).

The traditional synthetic method for these compounds is via the intermolecular condensation of an oxindole with a diaryl ketone.[1,2] However, the methodology is limited to some extent because of its low selectivity and tedious steps. Considerable efforts have been devoted to develop the metal-catalyzed domino reactions for the synthesis of 3-methyleneindolin-2-ones to solve these drawbacks.[3] We recently developed several oxidative Pd-catalyzed tandem heteropalladation/C-H activation reactions to prepare a wide variety of 3-heteromethyleneindolin-2-ones.[4] Note that a wide variety of carboxylic acids including aliphalic and aryl acids could, among those tandem acetoxypalladation/C-H activation reactions, involved the smooth acetoxypalladation of actived alkynes (Scheme 1). However, little progess has been achieved toward acetoxypalladation invoving amino acids. Given the biological and medicinal importance of amino acid motifs, the by introducing amino acid

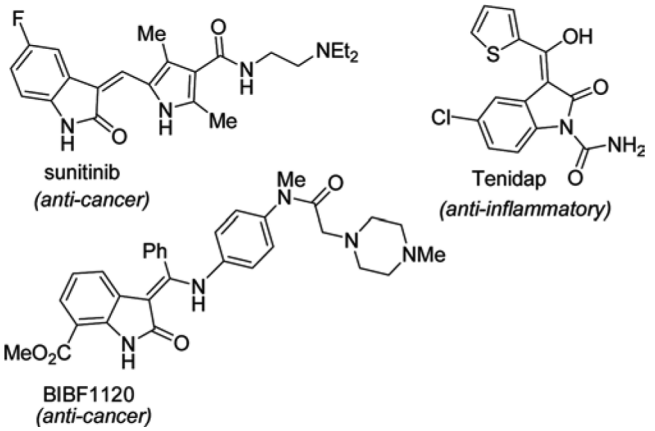
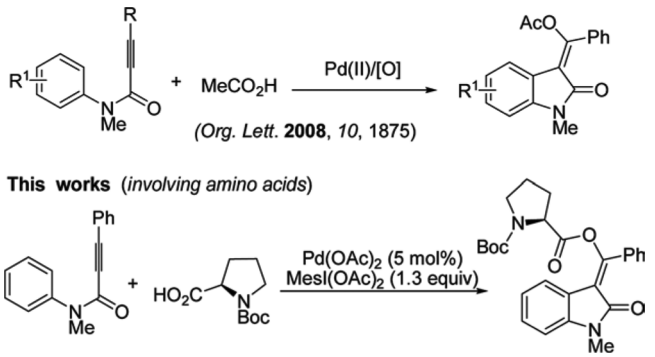


Figure 1. Three commercial medicines.



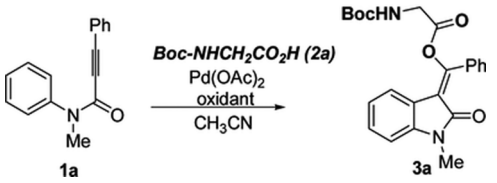
Scheme 1. Oxidative carboacetoxylation of alkynes.

motifs into the 3-methyleneindolin-2-one skeleton is possible to find some pharmeceutically important 3-methyleneindolin-2-ones.[5] With our continuing interest in tandem reactions combining heteropalladation and C-H activation, we herein demonstrate a tandem acetoxypalladation/C-H activation of activated alkynes and amino acids to introduce amino acid motifs into 3-methyleneindolin-2-ones.

RESULTS AND DISCUSSION

In the course of our research project aiming at Pd-catalyzed carboacetoxylation of *N*-arylpropiolamide and amino acids, *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) was employed as the starting substrate to explore the optimal conditions (Table 1). Initially, glycine ($NH_2CH_2CO_2H$) was used as the nucleophile, and none

Table 1. Screening of conditions[a]



Entry	Oxidant	Solvent	Yield of **3a** (%)[b]
1[c]	$PhI(OAc)_2$	CH_3CN	0
2[d]	$PhI(OAc)_2$	CH_3CN	35
3	$PhI(OAc)_2$	CH_3CN	55
4[e]	$PhI(OAc)_2$	CH_3CN	52
5	***MesI(OAc)₂***	***CH₃CN***	***71***
6	$PhI(OCOCF_3)_2$	CH_3CN	43
7	$PhI(OCO^tBu)_2$	CH_3CN	56
6	$Cu(OAc)_2$	CH_3CN	11
7	$Cu(OAc)_2/O_2$	CH_3CN	13
8	$Cu(OAc)_2$/AgOAc	CH_3CN	17
9	$K_2S_2O_8$	CH_3CN	<10
10	O_2	CH_3CN	<10
11	$MesI(OAc)_2$	Dioxane	21
12	$MesI(OAc)_2$	THF	15
13	$MesI(OAc)_2$	DMF	<10
14	$MesI(OAc)_2$	Toluene	23
15[f]	$MesI(OAc)_2$	CH_3CN	63
16[g]	$MesI(OAc)_2$	CH_3CN	12
17[h]	$MesI(OAc)_2$	CH_3CN	56

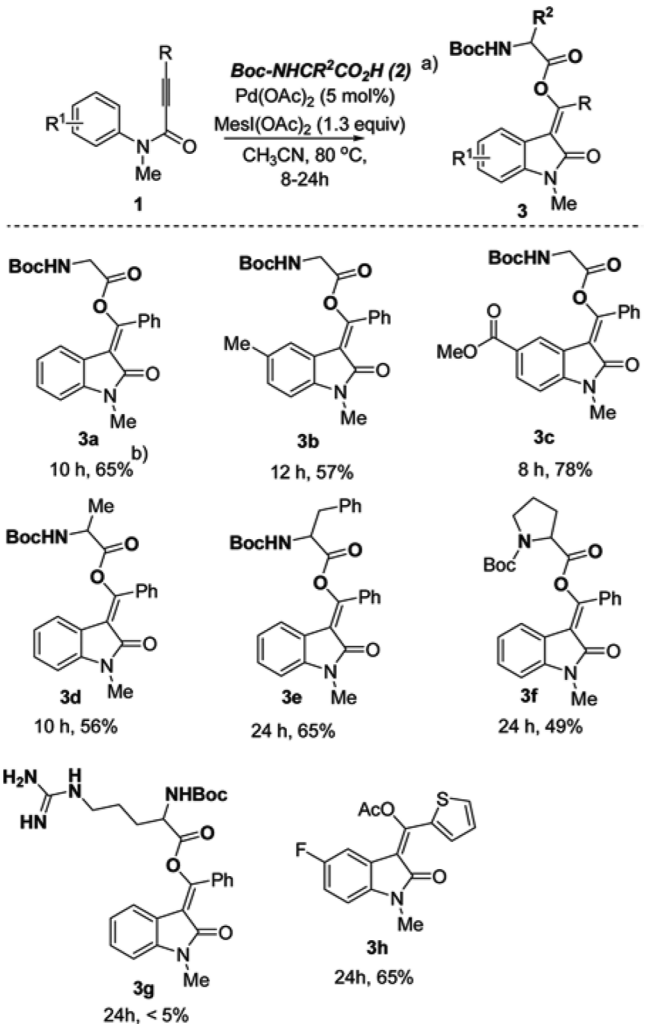
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), oxidant (1.3 eq) in CH_3CN (2 mL) at 80 °C for 10 h.
[b]Determined by GC with a dodecane as internal standard.
[c]Glycine (5 equiv) instead of **2a**.
[d]3 equiv of **2a**.
[e]8 equiv of **2a**.
[f]3 mol% of $Pd(OAc)_2$ for 24 h.
[g]At rt.
[h]At 100 °C.

of the desired product was observed, owing to possible unproductive binding of the basic amino group (-NH_2) to the Pd catalyst. The next screening discovered less nucleophlic Boc-glycine afforded the desired 3-methyleneindolin-2-one in 35% yield. Encouraged by this improvement, we then examined the impact of the amount of *Boc*-glycine, and the results showed that the amount of *Boc*-glycine has considerable influence on the reaction in view of yield and rate (Table 1, entries 2–4). In the presence of 5 equiv of *Boc*-$NHCH_2CO_2H$ (**2a**), the reaction of amide **1a** with $Pd(OAc)_2$ and $PhI(OAc)_2$ in MeCN proceeded smoothly and afforded the product **3a** in a yield of 55% (entry 2). It is worth mentioning that side-product 3-(diphenyl-methylene)-1-methylindolin-2-one originating from carbopalladation of $PhI(OAc)_2$ was detected along with the desired product **3a**. [3d]. Further screening of oxidants discovered that bulk $MesI(OAc)_2$ could suppress the mentioned side reaction to enhance the yield to 71% and other typical oxidants regenenated Pd(II) and/or Pd(IV) specices, such as $PhI(OCOCF_3)_2$ (PIFA), $PhI(OCO^tBu)$, $Cu(OAc)_2$, and $Cu(OAc)_2/O_2$. $Cu(OAc)_2$/AgOAc and $K_2S_2O_8$ afforded **3a** in unparallel yield (enties 6–10). Solvent screening revealed CH_3CN as the best choice. The reaction can be conducted in good yields even at a loading of 3 mol% Pd after prolonging the reaction time (entry 15). However, no reaction was observed without $Pd(OAc)_2$ (entry 8). Finally, the temperature effect was investigated, and greater temperature favored the reaction (entries 16 and 17).

With optimal carboacetoxylation conditions of *N*-arylpropiolamide in hand, we then investigated substrate scope of the reaction shown in Scheme 2. Expectedly, *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) with various *Boc*-amino acids could undergo tandem aetoxypalladation/C-H activation to form corresponding 3-methyleneindolin-2-ones in moderate to good yield. Note that various *Boc*-amino acids can involve the carboacetoxylation smoothly with *N*-arylpropiolamide irrespective of steric and electronic character of the substituent groups. Noteworthy is that ester and methyl groups on the aromatic ring of amide were successfully tolerated and afforded the target product **3b** and **3c** in 57% and 78% yield respectively. *Boc*-alanine and *Boc*-phenylanine could also involve the carboacetoxylation to give the desired oxindoles. Unexpectedly, treatment of the steric *Boc*-proline with *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) underwent the tandem acetoxlpalladation/C-H activation to yield the desired 3-methyleneindolin-2-ones in a moderate yield (49%). Unfortunately, the *N-a-Boc*-arginine proved to be inefficient for this transformation owing to the existance of a basic guanidyl group in *N-a-Boc*-arginine with which to bind the Pd catalyst unproductively. Expectedly, the optimization conditions aslo allowed the amide **1d** bearing other heterocyclic motif (thienyl ring) and HOAc to undergo the carboacetoxylation to give the corresponding product **3h**.

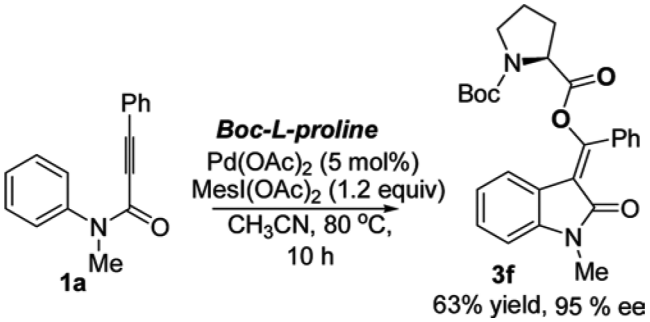
Subsequently, we treated optical pure *Boc*-L-proline with *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) under standard conditions [$Pd(OAc)_2$ (5 mol%) and $MesI(OAc)_2$(1.3 eq eq) in MeCN] to investigate the racemization of chiral amino acid in this transformation. We were happy to find that *Boc*-L-proline underwent the tandem acetoxylation/C-H activation process with good chirality retention and gave the desired 3-methyleneindolin-2-one **3f** in 95% *ee* (Scheme 3).

The efficient carboacetoxylation of *N*-arylpropiolamide with *Boc*-amino acid is understood in terms of the catalytic cycles shown in Scheme 4.[4–8] First, Pd^{II} with

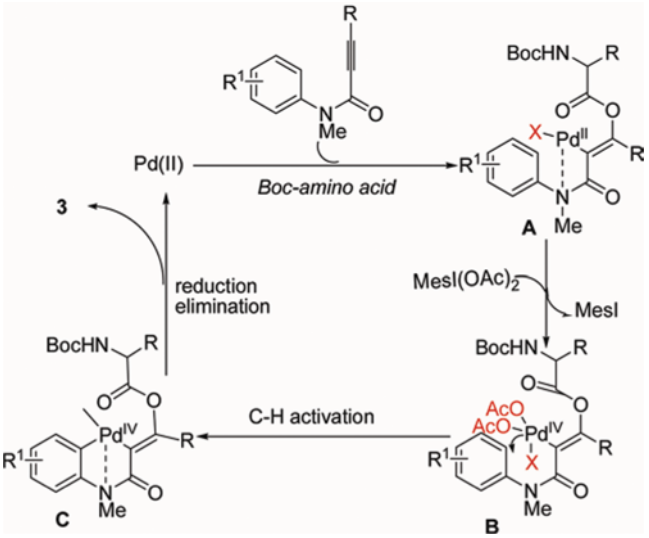


Scheme 2. Carboacetoxylation of **1** with *Boc*-amino acids: (a) reaction conditions: **1** (0.3 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), $MesI(OAc)_2$ (1.3 eq) in CH_3CN (2 mL) at 80 °C for 10–24 h: (b) Isolated yield.

alkyne and *Boc*-amino acid readily occurred to afford intermediate **A** via a acetoxypalladation process. The Pd^{II} intermediate **B** is then oxidized by $MesI(OAc)_2$ to give a Pd^{IV} intermediate **C**. The Pd^{IV} intermediate **C** is formed by activation of *ortho*-C-H bond of intermediate **B**. The reductive elimination of intermediate **C** occurs readily to yield the desired 3-methyleneindolin-2-ones and the active Pd^{II} species. However, we cannot rule out the possibility of a Pd^{II}/Pd^0 mechanism because the target product could be obtained in the presence of $Cu(OAc)_2$, a traditional Pd^{II}/Pd^0 oxidant.[9]



Scheme 3. Carboacetoxylation of **1a** with *Boc*-L-proline.



Scheme 4. Proposed reaction mechanism process. (Figure is provided in color online.)

CONCLUSIONS

In summary, we have developed an efficient carboacetoxylation reaction of activated alkynes with amino acid through an oxidative tandem acetoxypalladation/C-H activation process for the first time. It opens a door for constructing pharmeceuticallly important 3-methyleneindolin-2-ones bearing amino acid motifs. The detailed mechanism and application of the novel reaction to more complex targets are currently under study in our laboratory.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with

argon prior to use. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. Column chromatographical purifications were performed using SiO_2(0.040−0.063 mm, 230−400 mesh ASTM) from Merck. Unless otherwise noted, commercial available starting materials and solvents were purchased from commercial sources and used without further purification. *N*-Arylpropiolamides were prepared according to literature procedures.[3d,6] $Pd(OAc)_2$ was purchased from Strem and used without further purification.

A mixture of *N*-methyl-N,3-diphenylpropiolamide **1a** (0.3 mmol), *Boc*-$NHCH_2CO_2H$ **2a** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), and $MesI(OAc)_2$ (0.39 mmol) in CH_3CN (2 mL) was stirred at 80 °C for the indicated time until complete consumption of starting material as monitored by thin-layer chromatography (TLC). After the reaction was finished, the mixture was poured into ethyl acetate, which was washed with brine. The aqueous layer was further extracted with ethyl acetate. The combined organic layers was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane / ethyl acetate 5:1) to afford the desired product **3a** (a yellowish oil, 80 mg, 65%), Rf = 0.31. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J =$ 7.6 Hz, 1H), 7.46–7.41 (m, 3H), 7.32–7.27 (m, 1H), 7.10–7.05 (m. 1H), 6.81 (d, $J =$ 6.8 Hz, 1H), 5.10 (br, 1H), 4.24 (s, 2H), 3.19 (S, 3H), 1.45 (S, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.6, 166.6, 155.9, 142.5, 133.2, 130.7, 129.9, 127.9, 126.3, 117.4, 123.6, 122.2, 121.5, 108.0, 80.4, 42.9, 28.2, 25.9. IR (KBr, cm^{-1}) ν 1753.4, 1705.8, 1696.4, 1605.4. MS (EI, 70 eV): m/z (%) = 251 [$M^+ + 1$-$COCH_2NHBoc$] (100), 173 (65). HRMS (EI): calcd. for $C_{23}H_{24}N_2O_5$: 408.1685. Found: 408.1683.

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