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Palladium-Catalyzed Isoquinoline Synthesis by Tandem C−H Allylation and Oxidative Cyclization of Benzylamines with Allyl Acetate

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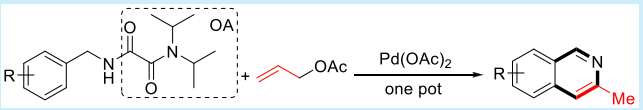
ABSTRACT: A novel approach to synthesize 3-methylisoquinolines via a one-pot, two-step, palladium(II)-catalyzed tandem C−H allylation/intermolecular amination and aromatization is reported. A wide series of 3-methylisoquinoline derivatives were obtained directly using this method in moderate to good yields, and we highlight the synthetic importance of this new transformation.



Isoquinoline, as an important structural framework, is encountered frequently in biologically active natural products, organic materials, drugs, and some important ligands and possesses unique activities and functionalities.[1] Over the past few decades, various approaches to construct isoquinoline skeletons have been extensively explored. Traditionally, the Bischler−Napieralski, Pomeranz−Fritsch, and Pictet−Gams reactions[2] have provided practical methods for the synthesis of isoquinolines. However, these methods usually suffer from harsh reaction conditions or limited substrate scope. Transition-metal-catalyzed C−H functionalizations have received significant attention[3] and have become an effective pathway to realize important synthetic skeleton construction.[4] Several groups such as the Miura,[5] Hua,[6] Li,[7] Yang,[8] Wang,[9] Zhu,[10] and Ackermann groups[11] have successfully demonstrated the isoquinolines can be easily prepared by C−H functionalizations and developed transition-metal (Rh, Pd, Co, Ru, Mn)-catalyzed formation of isoquinolines with assistance from directing groups such as aromatic imines, oxime, hydrazones, azide, etc. (Figure 1).[12] For example, Miura's group disclosed a highly efficient rhodium-catalyzed C−H bond cleavage and oxidative coupling reaction of aromatic imines with alkynes to produce isoquinoline derivatives.[5]

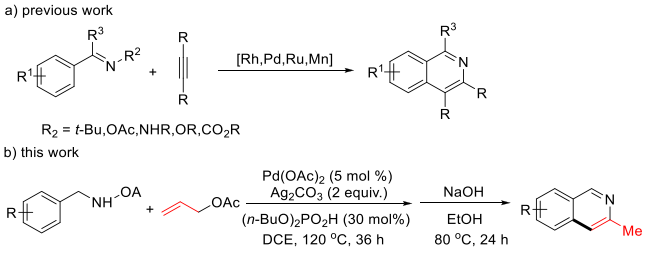


Figure 1. Transition-metal-catalyzed C−H activation to synthesize isoquinoline derivatives

Subsequently, Hua's group developed a convenient one-pot synthesis of isoquinolines using a three-component reaction mixture of aryl ketones, hydroxylamine, and alkynes.[6] In 2015, Ackermann's group also developed a synthesis of isoquinoline skeletons via a Co catalyst.[11b] Although these C−H activation strategies have provided effective methodologies for the preparation of isoquinolines, the skeleton of isoquinolines is usually limited to 1,3,4-substituted products as another coupling partner is the 1,2-disubstituted alkynes. The construction of unsubstituted or monosubstituted isoquinolines is still difficult. What is more, the magic methyl effect is well acknowledged in medicinal chemistry. This seemingly simple exchange of a C−H for a C−CH_3 can affect important drug properties. Therefore, the construction of methyl-substituted isoquinolines has potential application value. We herein report a palladium-catalyzed oxalylamide-assisted, one-pot approach for the synthesis of isoquinolines from readily available benzylamines and allyl acetate, which can be transformed further into isoquinolines by direct treatment with sodium hydroxide. A wide variety of 3-methylisoquinoline derivatives were obtained directly from this one-pot, two-step synthetic method. A preliminary mechanistic study showed the reaction proceeded via a palladium(II) acetate catalyzed, tandem C−H allylation, and intermolecular amination reaction to afford these isoquinolines.

Our group has reported the oxalylamide directing group is an effective N,O-bidentate directing group for assisted remote C−H activation of aromatic alkylamines.[13] In addition, allyl acetate is an effective agent in the synthesis of heterocyclic

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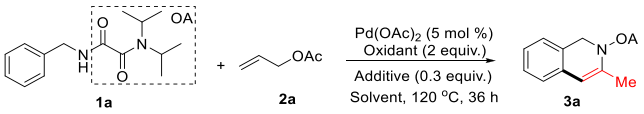
compounds via tandem reactions.[14] On the basis of these results, we speculated that isoquinolines may be directly obtained by treating the oxalylamide-protected benzylamine with allyl acetate via a C−H allylation followed by an intermolecular amination reaction.

With these conditions in mind, we examined the reaction of oxalylamide-protected benzylamine **1a** (0.1 mmol) and allyl acetate **2a** (0.2 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) as the catalyst and AgOAc (2 equiv) as the oxidant in *tert*-amyl−OH at 120 °C for 36 h. To our delight, the desired product **3a** was obtained in 17% yield, along with a recovery of **1a** (Table 1, entry 1). Next, we investigated additives such as

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

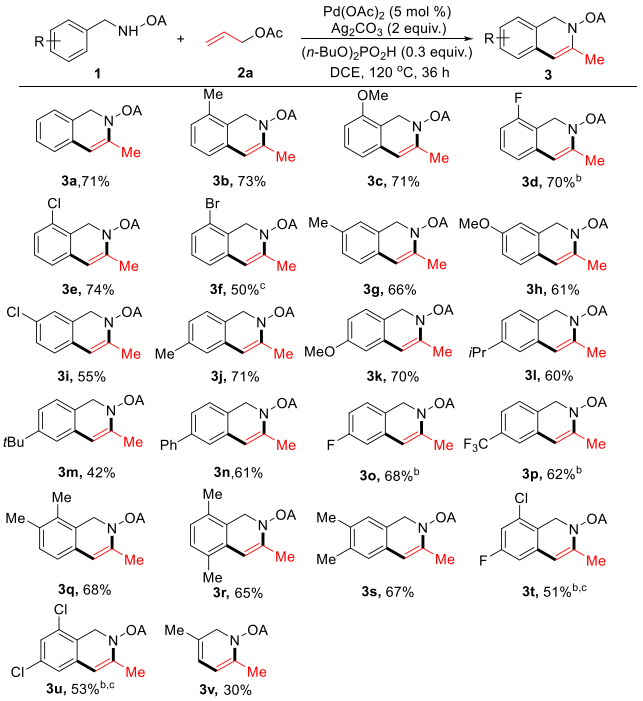
entry	oxidants	additive	yield[b] (%)
1	AgOAc		17
2	AgOAc	AcOH	23
3	AgOAc	PivOH	56
4	AgOAc	1-AdOH	36
5	AgOAc	Ac-Gly-OH	51
6	AgOAc	$(BnO)_2PO_2H$	67
7	AgOAc	$(EtO)_2PO_2H$	70
8	AgOAc	$(n\text{-}BuO)_2PO_2H$	73
9	AgOAc	$(PhO)_2PO_2H$	65
10	AgOAc	BNDHP	55
11	Ag_2CO_3	$(n\text{-}BuO)_2PO_2H$	81
12	Ag_2O	$(n\text{-}BuO)_2PO_2H$	trace
13	$Cu(OAc)_2$	$(n\text{-}BuO)_2PO_2H$	trace
14	$PhI(OAc)_2$	$(n\text{-}BuO)_2PO_2H$	trace
15[c]	Ag_2CO_3	$(n\text{-}BuO)_2PO_2H$	none

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (2 equiv), and additive (0.3 equiv) in the solvent at 120 °C in an oil bath for 36 h under air in a sealed tube. [b]Yields were based on GC analysis using tridecane as an internal standard. [c]No $Pd(OAc)_2$.

AcOH, PivOH, 1-AdOH, Ac-Gly-OH, and $(BnO)_2PO_2H$ (Table 1, entries 2−6), well-known for promoting C−H activation, to improve the efficiency of this transformation. Those results showed that additives PivOH, Ac-Gly-OH, and $(BnO)_2PO_2H$ all showed a good promoting effect; **3a** was obtained in yields up to 67% when $(BnO)_2PO_2H$ was used as the additive (Table 1, entry 6). We explored several other phosphates including $(EtO)_2PO_2H$, $(n\text{-}BuO)_2PO_2H$, $(PhO)_2PO_2H$, and (BNDHP) to improve the yield of **3a** (Table 1, entries 7−10). Encouragingly, **3a** was obtained when $(n\text{-}BuO)_2PO_2H$ was used as the additive (Table 1, entry 8).[15] Although the role of $(n\text{-}BuO)_2PO_2H$ remained unclear, it probably took part in proton transfer and in stabilization of Pd(0) during the catalytic cycle. What is more, organic phosphoric acids might work as a solid-to-solution phase-transfer catalyst (PTC), slowly bringing Ag^+ ions into the solution phase.[16] A series of oxidants were also screened; after adding commonly used oxidants such as Ag_2CO_3, Ag_2O, $Cu(OAc)_2$, and $PhI(OAc)_2$ (Table 1, entries 11−14), Ag_2CO_3 provided the target product in 81% yield (Table 1, entry 11). A control experiment showed the $Pd(OAc)_2$ catalyst was essential for this tandem reaction (Table 1, entry 15).

With the optimal conditions in hand, the functional group tolerance of this transformation was investigated as shown in Scheme 1. Generally, the ortho-substituted oxalylamide-

Scheme 1. Scope of OA-Protected Benzylamines[a]



[a]Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.4 mmol), and $(n\text{-}BuO)_2PO_2H$ (0.3 equiv) in DCE (0.3 mL) at 120 °C in an oil bath for 36 h; isolated yields. [b]$Pd(OAc)_2$ (10 mol %). [c]140 °C.

protected benzylamines performed well. Functional groups such as methyl, methoxy, fluoride, chloride, and bromide were all well-tolerated, leading to the corresponding products in moderate to good yields. The *meta*- or *para*-substituted benzylamines were all compatible with this transformation, yielding the corresponding products in moderate to good yields as well. It is worth noting that when benzylamines with strong electron-withdrawing groups such as F and CF_3 were examined, the reaction achieves good results by increasing the catalyst amount (**3o**−**3p**). Meanwhile, *para*-substituted benzylamines with isopropyl, *tert*-butyl, and phenyl substituents also could proceed, but yields were lower (**3l**−**3n**). Disubstituted substrates have also been converted successfully, including methyl- and halogen-substituted benzylamines, to obtain the target product in moderate to good yields (**3q**−**3u**). Interestingly, when 2-methylallylamine was used, the reaction yielded pyridine derivative in 30% yield (**3v**) and suggested a potentially powerful tool for the synthesis of pyridine.

To demonstrate the practicality of this method, we tried to remove the directing group under basic conditions. Gratifyingly, oxalylamide was readily removed when **3a** dissolved in ethanol and heated at 80 °C for 24 h. It was surprising that the product underwent aromatization while removing the directing group without adding any other oxidant, directly generating isoquinoline **4** in excellent yield (see the Supporting Information). We then attempted to synthesize isoquinoline derivatives by direct addition of NaOH and ethanol to the reaction and heating at 80 °C for 24 h. The isoquinolines were

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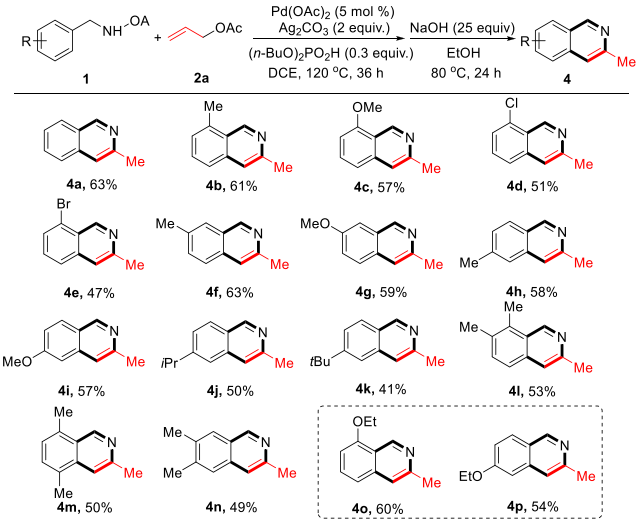
obtained in 68% yield with oxalylamide-protected benzylamine as the product (**4a**). We evaluated a large group of substrates for this one-pot, two-step method (Scheme 2). As before, a

Scheme 2. One-Pot Approach to Isoquinoline Synthesis[a]

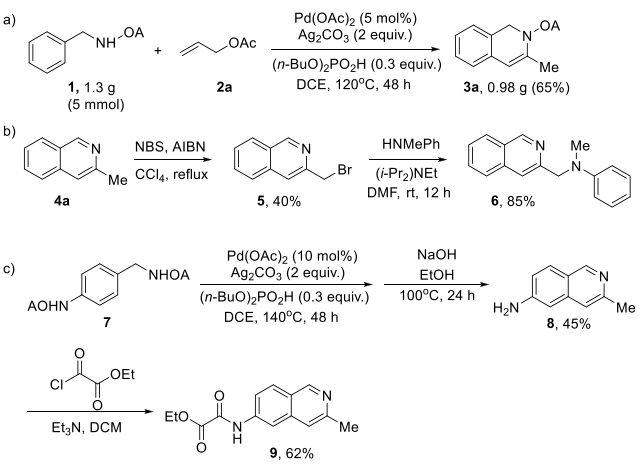


[a]Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (0.4 mmol), and additive (0.3 equiv) in DCE (0.3 mL) at 120 °C in an oil bath for 36 h. Followed by NaOH (25 equiv) and EtOH (1.5 mL); isolated yields.

series of 3-methylisoquinoline derivatives were successfully synthesized in moderate to good yields. Various substituted benzylamines, such as methyl, methoxy, *tert*-butyl, isopropyl, fluorine, chlorine, and bromine all resulted in good yields. Substitutions at any position were all compatible. Interestingly, when we used the fluorine-substituted benzylamine substrate, the resulting fluorine-containing isoquinoline products reacted with the ethanol solvent to yield ethoxy-substituted isoquinoline products (**4o**, **4p**).

A gram-scale reaction was carried out to demonstrate the synthetic value of this new strategy (Scheme 3a); the target product was obtained in 65% yield. Next we explored the transformation of **4a** to further demonstrate the synthetic value of this process in the synthesis of 3-methylisoquinolines (Scheme 3b). When **4a** was subjected to NBS/AIBN in carbon

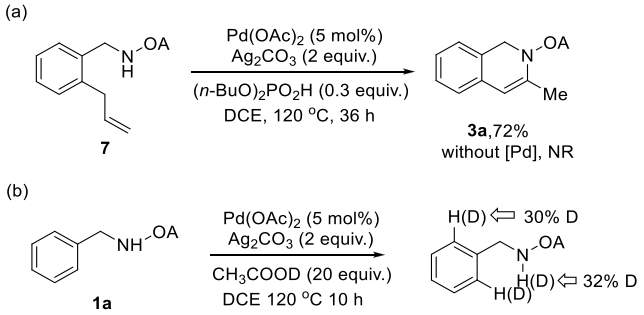
Scheme 3. Synthetic Approach



tetrachloride, the bromomethylisoquinoline **5** was achieved in 60% yield,[17] which was converted to **6** in short order.[18] 2-((4-(Aminomethyl)phenyl)amino)-2-oxoacetic acid is considered to be a bioactive molecule.[19] Its derivative **9**, which contained an isoquinoline backbone, could also be easily synthesized from *p*-aminobenzylamine (Scheme 3c).

Some control experiments were performed to understand the reaction pathway (Scheme 4). We used the allylation

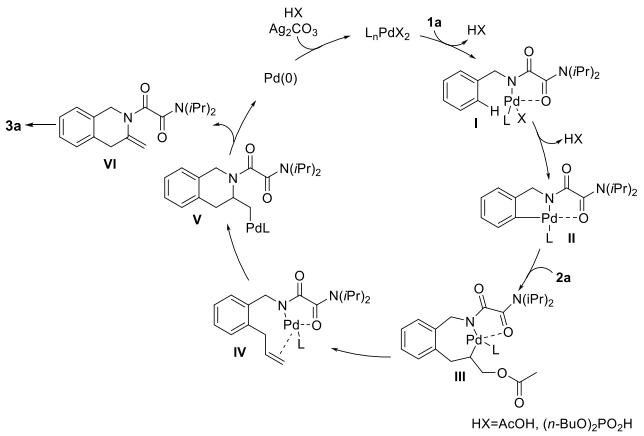
Scheme 4. Preliminary Mechanistic Studies



product of oxalylamide-protected benzylamine as the starting material; under standard reaction conditions, a 72% yield was obtained for the target compound, this indicated the reaction went through an allylation and might show *β*-OAc elimination as reported in previous literature (Scheme 4a).[20] In the absence of $Pd(OAc)_2$, no target product was formed, indicating the palladium catalyst was crucial for the formation of C−C and C−N bonds. Subsequently, we conducted deuterium labeling experiments by adding acetic acid-d_4 under standard conditions; those results indicated that ortho C−H bond might undergo reversible activation.

Based on these results and previous literature,[13,21] a possible mechanism is proposed (Scheme 5): A palladacycle

Scheme 5. Plausible Catalytic Cycle



intermediate **II** was initially formed by oxalylamide-directing *ortho*-C−H bond activation; intermediate **II** then underwent migratory alkene insertion to form a new seven-membered cyclic intermediate **III**, which then underwent *β*-OAc elimination to generate a new olefin-containing Pd complex **IV**.[20] The next step involved palladium-catalyzed aminopalladation of **IV** via an intramolecular cyclization to generate intermediate **V**.[22] Finally, the target product **3a** was formed by *β*-hydride elimination and double bond isomerization.

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In conclusion, we have developed an efficient synthesis of dihydroisoquinoline derivatives by a $Pd(OAc)_2$ catalyzed tandem of C−H allylation and intermolecular amination reactions, which are further transformed into isoquinolines by direct treatment with sodium hydroxide. A series of 3-methylisoquinoline derivatives were obtained from this one-pot, two-step method in moderate to good yields, highlighting the synthetic importance of this new transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01153.

Experimental procedures, new compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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