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Microwave-Assisted Palladium-Catalyzed Reductive Cyclization/Ring-Opening/Aromatization Cascade of Oxazolidines to Isoquinolines

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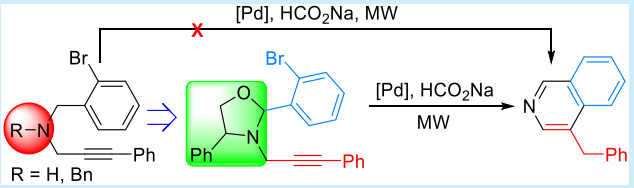
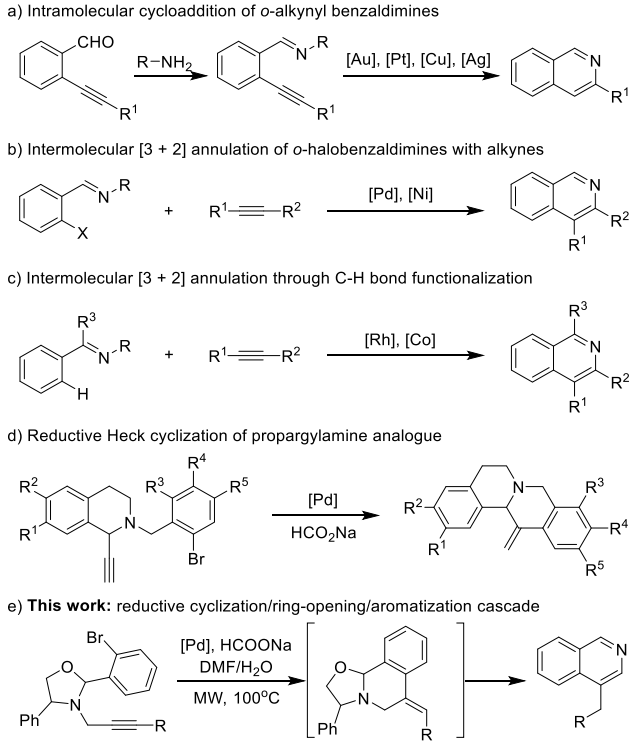
ABSTRACT: An efficient palladium-catalyzed reaction of *N*-propargyl oxazolidines for the construction of 4-substituted isoquinolines under microwave irradiation is developed. This transformation proceeds through a sequential palladium-catalyzed reductive cyclization/ring-opening/aromatization cascade via C−O and C−N bond cleavages of the oxazolidine ring. The practical value of this method has also been explored by conducting a millimole-scale reaction, as well as by transforming the isoquinoline into a key intermediate for the synthesis of a lamellarin analogue.



Isoquinolines, an important class of nitrogen-containing heterocycles, are frequently found in numerous natural products and medicinally active compounds,[1] such as inhibitors of 11β-HSD1[2] and anti-HIV compounds,[3] and as precursors of dopamine agonists and antagonists.[4] They are also widely employed as chiral ligands in asymmetric catalysis[5] and serve as phosphorescent OLED emitters.[6] In the past few decades, a huge number of synthetic methods have been developed for the construction of the isoquinoline framework.[7] Among them, transition-metal-catalyzed annulation of alkynes has emerged as one of the most efficient tools for the synthesis of the isoquinoline motif.[8] For example, *o*-alkynyl benzaldimines,[9] which can be formed from an *o*-alkynyl benzaldehyde and an amine,[10] have been explored to produce 3-substituted isoquinolines in the presence of metal-based catalysts such as gold, platinum, copper, and silver (Scheme 1a). Strategies for isoquinoline construction via the intermolecular [3 + 2] annulation of 2-halobenzaldimines with alkynes have been well developed (Scheme 1b).[11] In addition, transition-metal-catalyzed C−H functionalization has been demonstrated as an atom- and step-economical process to construct 3,4-disubstituted or 3-substituted isoquinolines (Scheme 1c).[12] However, a general protocol for the introduction of a 4-substituent on the isoquinoline is lacking.[13] Although 4-substituted isoquinolines can be produced by the cross-coupling of 4-bromoisoquinolines with organometallic reagents[14] or dehydrogenation of N-heterocycles,[15] both strategies suffer from a rather limited substrate scope. Therefore, the development of practical and flexible approaches for the synthesis of 4-substituted isoquinolines is still highly desirable.

Recently, elegant examples of Pd-catalyzed reductive Heck cyclization of propargylamines for the formation of hydroisoquinolines have emerged (Scheme 1d).[16] On the basis of

Scheme 1. Transition-Metal-Catalyzed Strategies to Access Isoquinolines



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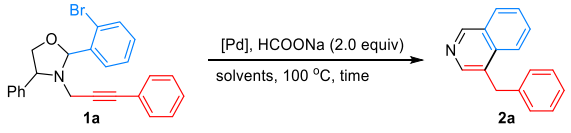
our interest in the conversion of oxazolidines,[17] we hypothesized that the *N*-propargyl oxazolidine, readily generated via A^3 coupling,[18] might be transformed into a 4-substituted isoquinoline through a Pd-catalyzed intramolecular reductive cyclization/ring-opening/aromatization process of an oxazolidine under microwave irradiation (Scheme 1e). If successful, the reaction would not only develop a new type of aromatization strategy but also open a complementary protocol for isoquinoline synthesis.

Our studies commenced by investigating the Pd-catalyzed reaction of the 1,3-oxazolidine **1a** in the presence of HCOONa. Screening of various solvents showed that the combination of DMF and H_2O as the solvent is the best choice for this reaction, giving the desired product **2a** in 83% yield (Table 1, entries 1−6). When H_2O was replaced by methanol, the yield of **2a** decreased to 55% (entry 7). It should be noted that the desired product could not be observed without H_2O addition (entry 8). These results revealed that H_2O plays a vital role in the formation of **2a**. However, changing the amount of DMF and H_2O did not improve the yield of **2a** (entries 9 and 10). Other Pd sources, such as $Pd(dba)_2$ and $Pd_2(dba)_3$, provided the desired product **2a** in only 29% and 17% yields, respectively (entries 11 and 12). In addition, we tried to change the catalytic loading of $Pd(PPh_3)_4$, but no increased yield was observed (entries 13 and 14). Importantly, when the reaction temperature was reduced to 80 °C, the desired product was not formed (entry 15). Increasing the reaction temperature to 120 °C resulted in a decreased yield of **2a** (entry 16). To our delight, when the reaction time was shortened to 12 h, the yield of **2a** was improved to 93% (87% isolated yield, entry 17). Shortening the reaction time to 10 h afforded a slightly decreased yield of the desired product (entry 18). Satisfactorily, when this reaction was conducted under microwave irradiation for 30 min, the desired product was delivered in an 85% isolated yield (entry 19).

Table 1. Optimization of the Reaction Conditions for 1a[a]



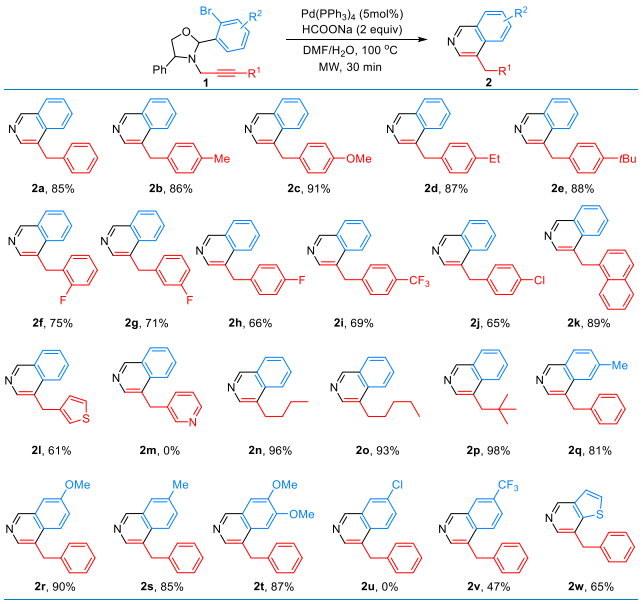
1a 2a

entry	[Pd] (mol %)	solvent (mL)	time (h)	yield (%)
1	$Pd(PPh_3)_4$	DMA/H_2O (1.5/0.5)	18	55
2	$Pd(PPh_3)_4$	THF/H_2O (1.5/0.5)	18	0
3	$Pd(PPh_3)_4$	CH_3CN/H_2O (1.5/0.5)	18	24
4	$Pd(PPh_3)_4$	DMSO/H_2O (1.5/0.5)	18	21
5	$Pd(PPh_3)_4$	NMP/H_2O (1.5/0.5)	18	36
6	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	18	83
7	$Pd(PPh_3)_4$	DMF/MeOH (1.5/0.5)	18	55
8	$Pd(PPh_3)_4$	DMF	18	0
9	$Pd(PPh_3)_4$	DMF/H_2O (0.75/0.25)	18	61
10	$Pd(PPh_3)_4$	DMF/H_2O (3/1)	18	75
11	$Pd(dba)_2$	DMF/H_2O (1.5/0.5)	18	29
12	$Pd_2(dba)_3$	DMF/H_2O (1.5/0.5)	18	17
13[c]	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	18	77
14[d]	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	18	80
15[e]	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	18	0
16[f]	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	18	71
17	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	12	93 (87[b])
18	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	10	81
19[g]	$Pd(PPh_3)_4$	DMF/H_2O (1.5/0.5)	0.5	85[b]

[a]Reaction conditions unless specified otherwise: **1a** (0.15 mmol), HCOONa (2.0 equiv), $Pd(PPh_3)_4$ (5 mol %), solvent, 100 °C, 12−18 h. Yields were determined by ^{1}H NMR using 2,4,6-trimethoxybenzaldehyde as an internal standard. [b]Isolated yield. [c]$Pd(PPh_3)_4$ (3 mol %) was used. [d]$Pd(PPh_3)_4$ (10 mol %) was used. [e]The reaction was performed at 80 °C. [f]The reaction was performed at 120 °C. [g]The reaction was performed under microwave irradiation with 150 W maximum power.

With the optimal conditions in hand (Table 1, entry 19), we started to explore the substrate scope of this reaction by investigating the series of *N*-propargyl oxazolidines **1** (Scheme 2). We first examined the effect of the R^1 substituent of the *N*-propargyl oxazolidine **1**. A phenyl group with various electron-donating groups, such as methyl, methoxy, ethyl, and *tert*-butyl, on the *para* position afforded the corresponding products **2b−e** in good yields. However, relatively low yields were obtained when electron-withdrawing groups such as fluoro, trifluoromethyl, and chloro were introduced at different positions of the phenyl ring, providing the desired products **2f−j** in 65−75% yield. In addition, the target product **2k** was obtained in 89% yield when the phenyl group was switched to a naphthyl group. A substrate bearing a thiophenyl group also afforded the desired product **2l** in moderate yield. However, no desired product **2m** was detected using the pyridyl-substituted starting material. Subsequently, a series of substrates bearing an alkyl group such as propyl, butyl, and *tert*-butyl were investigated under the standard conditions. To our delight, they all delivered the corresponding products **2n−p** in excellent yields. We then investigated the influence of the R^2 substituent of the *o*-bromophenyl moiety tethered on the oxazolidine ring. Substrates bearing electron-donating groups (methyl and methoxy) gave the targeted products **2q−t** in good to excellent yields. However, when a chloro-containing substrate was used,

Scheme 2. Scope of the Palladium-Catalyzed Reductive Cyclization/Ring-Opening/Aromatization Cascade[a]



[a]Standard conditions: all reactions were performed on a 0.15 mmol scale, $Pd(PPh_3)_4$ (5 mol %), HCOONa (2 equiv), DMF/H_2O (3/1, 2 mL), 100 °C, microwave irradiation with 150 W maximum power for 30 min.

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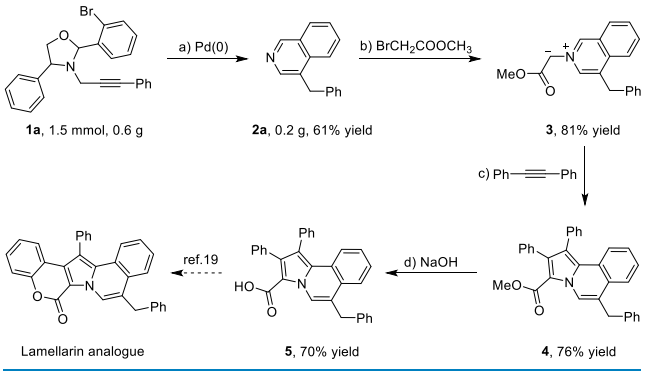
compound **2a** was formed in 63% yield due to dechlorination. Satisfactorily, when the substrates **1v,w** were employed, the desired products **2v,w** were obtained in 47% and 65% yields, respectively.

To demonstrate the practical applicability of this strategy, we performed a millimole-scale reaction of **1a** (Scheme 3). The

Scheme 3. Transformations of Product 2a[a]

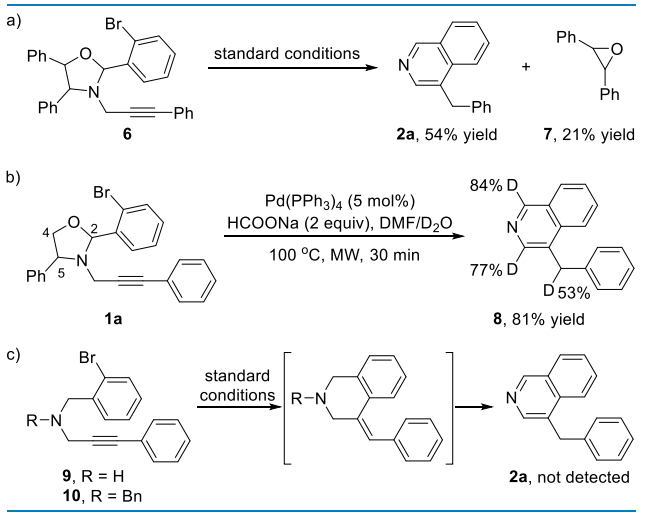


[a]Standard conditions: (a) $Pd(PPh_3)_4$ (5 mol %), HCOONa (2 equiv), DMF/H_2O (3/1, 4 mL), 100 °C, microwave irradiation with 150 W maximum power for 2 h; (b) $BrCH_2COOCH_3$ (1.1 equiv), THF (2 mL), 70 °C, 4 h; (c) 1,2-diphenylethyne (1.0 equiv), $(Cp^*RhCl_2)_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv), KOAc (2 equiv), DCE (1.5 mL), 120 °C, 12 h; (d) 1 M NaOH in H_2O, EtOH (2 mL), 85 °C, overnight.

microwave irradiation time was extended to 2 h, resulting in the formation of **2a** in 61% yield. This was followed by a reaction with methyl 2-bromoacetate to afford product **3** in 81% yield. Subsequently, the rhodium-catalyzed cyclization of **3** with 1,2-diphenylethyne was performed to give the pyrrole derivative **4** in 76% yield. Compound **4** underwent ha ydrolysis reaction to deliver the corresponding acid **5**, which is an intermediate for the synthesis of a lamellarin analogue.[19]

To get more insight into the mechanism, we performed the reaction of substrate **6** under the standard conditions; the desired product **2a** was isolated in 54% yield together with ethylene oxide **7** in 21% yield (Scheme 4a). We performed a

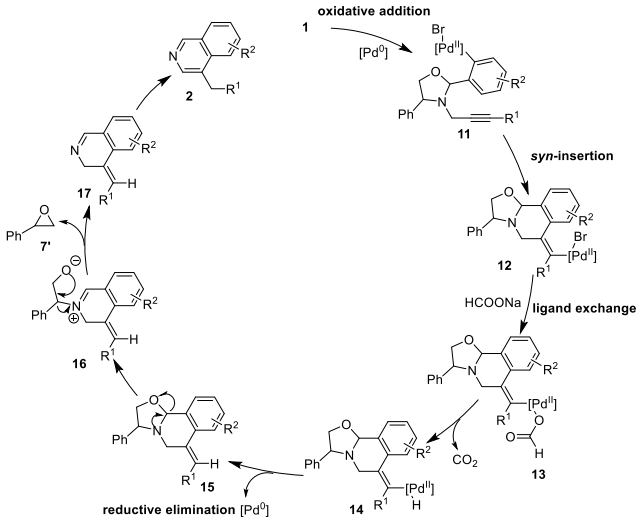
Scheme 4. Control Experiments



deuteration experiment with substrate **1a**. This was reacted under the standard conditions in the presence of deuterated water, providing product **8** with deuterium atoms incorporated at three positions as indicated (Scheme 4b). This result suggests the existence of intermediate **15** in the mechanism, and it can easily undergo a proton exchange with H_2O during the process of the ring-opening/aromatization cascade to deliver product **2** (*vide infra*). Finally, the use of compound **9** or **10** as substrate did not result in the formation of **2a** (Scheme 4c), implying that our strategy has a new reaction mechanism in comparison to the well-known process of intramolecular reductive cyclization and oxidative aromatization.[20]

On the basis of the above results and previous reports,[16] we propose the following mechanism (Scheme 5). Initially, the

Scheme 5. Plausible Mechanism



oxidative addition of Pd(0) to the aryl bromide of **1** gives the Pd species **11**. This is followed by a syn insertion into the carbon−carbon triple bond, affording the cyclized intermediate **12**. This undergoes ligand exchange with HCOONa, leading to intermediate **13**, which loses carbon dioxide to generate intermediate **14**. Next, the reductive elimination of intermediate **14** gives intermediate **15** with regeneration of the Pd^0 catalyst. C−O bond cleavage of the oxazole ring of the intermediate **15** results in the formation of the intermediate **16**, which undergoes C−N bond cleavage to form intermediate **17** and epoxide **7′**. Finally, spontaneous aromatization delivered the desired product **2**.

In summary, we have successfully developed a microwave-assisted palladium-catalyzed domino reaction of *N*-propargyl oxazolidines for the construction of a series of 4-substituted isoquinolines bearing different substituents. This reaction is performed through a palladium-catalyzed reductive cyclization/ring-opening/aromatization process of oxazolidines. The results reveal that the key for its success is the introduction of an oxazolidine unit to the substrates, which promotes the process of hydroisoquinoline aromatization. In addition, we have demonstrated the utility of this process by the synthesis of a lamellarin analogue.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02416.

Experimental procedures and spectral data (PDF)
FAIR data, including the primary NMR FID files, for compounds **1a−w**, **2a−l,n−t,v,w**, **3−7**, **9**, and **10** (ZIP)

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Notes

The authors declare no competing financial interest.

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