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Palladium-Catalyzed Aerobic Oxidative Cyclization of Aliphatic Alkenyl Amides for the Construction of Pyrrolizidine and Indolizidine Derivatives

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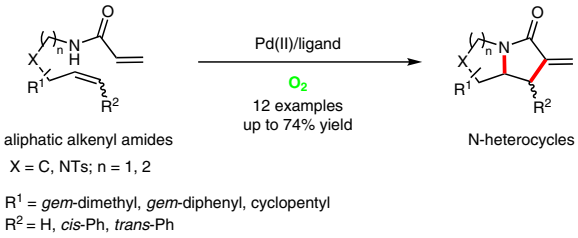

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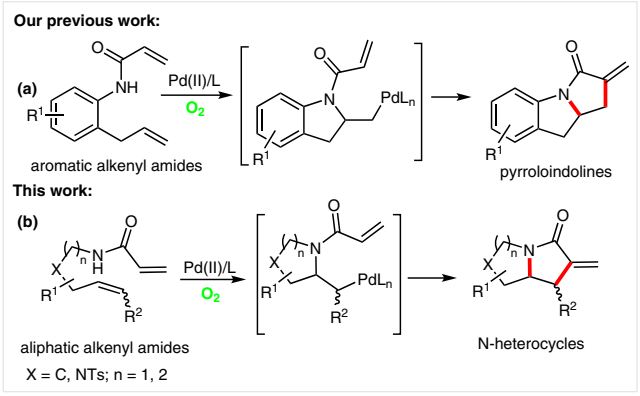
Abstract An efficient palladium-catalyzed aerobic oxidative cyclization has been developed to synthesize a variety of pyrrolizidine and indolizidine derivatives from simple aliphatic alkenyl amides in moderate to good yields. The reaction features the capability of accessing various N-heterocycles and the use of molecular oxygen (1 atm) as the green oxidant.

Key words palladium catalysis, aerobic oxidation, cascade cyclization, aminopalladation, N-heterocycles

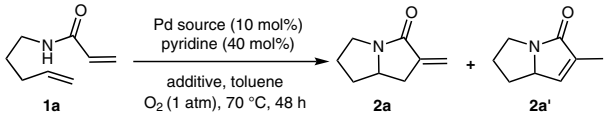
Molecular oxygen (O_2), as an abundant, inexpensive, and environmentally friendly oxidant, has been widely employed as the ideal oxidant in many transition-metal-catalyzed transformations.[1] Among them, palladium-catalyzed aerobic oxidation reactions have evolved as a powerful tool in organic transformations,[2] such as alcohol oxidation, Wacker oxidation, and oxidative Heck reaction. Although significant advances in palladium-catalyzed aerobic oxidation reactions have been achieved, the palladium-catalyzed aerobic oxidative tandem reactions have been less extensively investigated.[3] In the past few years, our group has made many efforts toward the development of palladium-catalyzed aerobic oxidative cascade cyclizations,[4] which provide synthetically useful approaches for accessing diversely functionalized N-heterocycles. For example, an efficient palladium-catalyzed aerobic oxidative cyclization of unactivated alkenes bearing pendant unsaturated amide nucleophiles has been developed for constructing pyrroloindoline derivatives (Scheme 1, a).[4a–d] However, substrate scope in previous transformations were mostly restricted to aromatic alkenyl amides, which undoubtedly limited its wide application in heterocycle synthesis. Compared to aromatic ones with fused phenyl ring backbones, aliphatic alkenyl amides are less favorable for the intramolecular cyclization due to their more flexible backbones[5] and lower acidity of aliphatic amide.[6] There are only two successful reports of enantioselective cascade cyclizations of alkene-tethered aliphatic acrylamides with limited substrate scope.[7a,b] On the basis of our continued interest in palladium-catalyzed aerobic oxidative cascade cyclizations, we herein report a palladium-catalyzed aerobic cyclization of aliphatic alkenyl amides, allowing for the rapid construction of various N-heterocycles, including pyrrolizidines, indolizidines, and azatricyclic heterocycles, in moderate to good yields.



Scheme 1 Palladium-catalyzed aerobic oxidative cyclization reactions

The linear aliphatic alkenyl amide **1a** was selected as a model substrate to test the feasibility of this cascade cyclization. Due to the lack of Thorpe–Ingold effect[8] in linear substrate **1a**, its cyclization is commonly unfavorable. To our delight, the azabicyclic product **2a** could be obtained in moderate yield when 10 mol% $Pd(OAc)_2$ was used as the catalyst, 40 mol% pyridine as the ligand, and O_2 as the oxi-

Table 1 Optimization of Reaction Conditions[a]

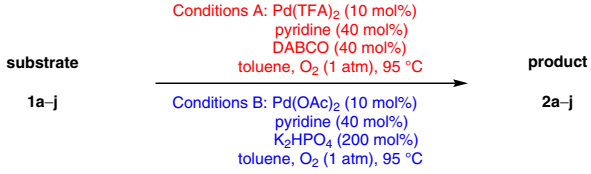


Entry	Pd source	Additive (mol%)	Conv. (%)[b]	Yield (%)[b]
1	$Pd(OAc)_2$	–	66	52 (4)
2	$Pd(OAc)_2$	DABCO (40)	86	56
3	$Pd(OAc)_2$	DABCO (100)	90	45
4	$Pd(TFA)_2$	DABCO (40)	84	60
5[c]	$Pd(TFA)_2$	DABCO (40)	91	64
6[d]	$Pd(TFA)_2$	DABCO (40)	100	70 (8)
7[d]	$Pd(OAc)_2$	K_2HPO_4 (200)	100	71 (9)
8[d]	$Pd(OAc)_2$	K_2HPO_4 (40)	100	54(5)

[a] All reactions were carried out with **1a** (0.3 mmol), palladium source (0.03 mmol), and pyridine (0.12 mmol) in 3 mL of toluene under oxygen atmosphere at 70 °C for 48 h.
[b] The conversions and yields were determined by isolation and the values in parentheses are yields of olefin isomerization products.
[c] The reaction temperature was 80 °C.
[d] The reaction temperature was 95 °C. DABCO = 1,4-Diazabicyclo[2.2.2]octane.

dant (Table 1, entry 1). The addition of 40 mol% DABCO was found to accelerate the reaction and give a slightly higher yield, while the use of stoichiometric amount of DABCO resulted in a decreased yield. It seems that DABCO acts as a ligand to compete with pyridine and a base to deprotonate the amido proton (Table 1, entries 2 and 3). Among the investigated palladium catalysts, $Pd(TFA)_2$ exhibited the best reactivity (Table 1, entry 4). The reaction temperature also had impact on the reaction efficiency and the best yield was obtained at 95 °C (Table 1, entries 4–6). Interestingly, 2.0 equivalents of K_2HPO_4 in place of DABCO as an additive could give a comparable yield of **2a** when the less expensive $Pd(OAc)_2$ was employed as the catalyst (Table 1, entry 7). However, reducing its amount to 40 mol% gave a diminished yield (Table 1, entry 8). Notably, the olefin isomerization product **2a′** was detected under several conditions. Hence, two optimal conditions were selected. Conditions A: substrate **1**, 10 mol% $Pd(TFA)_2$, 40 mol% pyridine and 40 mol% DABCO in toluene under 1 atm oxygen at 95 °C; Conditions B: substrate **1**, 10 mol% $Pd(OAc)_2$, 40 mol% pyridine and 200 mol% K_2HPO_4 in toluene under 1 atm oxygen at 95 °C.

Table 2 Substrate Scope of Palladium-Catalyzed Oxidative Cascade Cyclization[a]



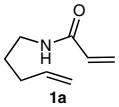
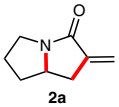
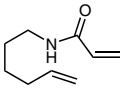
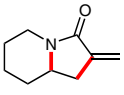
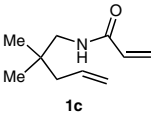
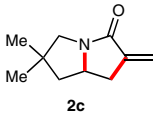
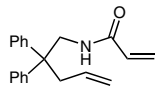
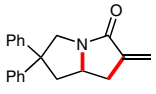
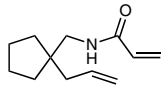
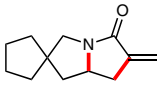
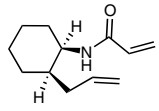
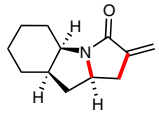
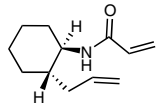
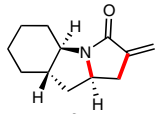
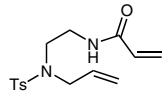
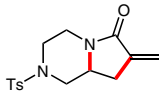
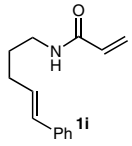
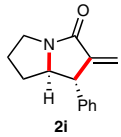
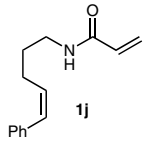
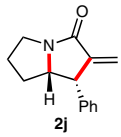
Entry	Substrate	Product	Conditions	Time (h)	Conv. (%)[b]	Yield (%)[b,c]
1	 **1a**	 **2a**	A	21	100	74 (9)
2			B	36	100	74 (4)
3	 **1b**	 **2b**	A	24	91	58 (9)
4			B	28	100	73
5	 **1c**	 **2c**	A	20	98	63 (9)

Table 2 (continued)

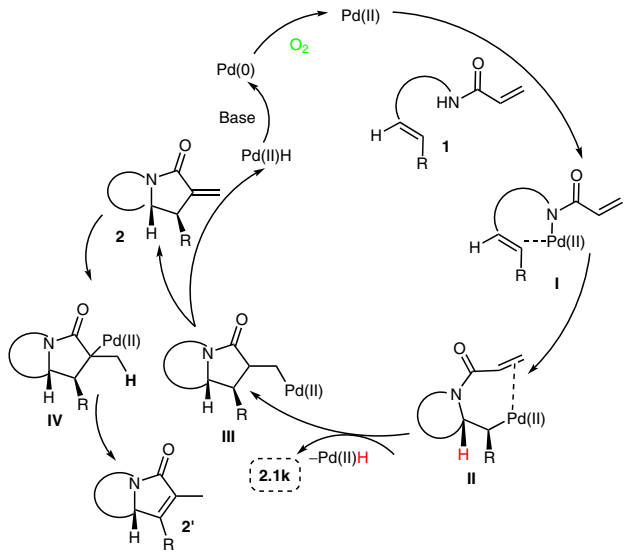
Entry	Substrate	Product	Conditions	Time (h)	Conv. (%)[b]	Yield (%)[b,c]
6	 **1d**	 **2d**	A	20	98	63 (9)
7	 **1e**	 **2e**	A	17	100	64 (16)
8	 **1f**	 **2f**	A	70	83	50 (3)[d]dr = 2:1
9			B	66	68	27 (3)[d]dr = 4:1
10	 **1g**	 **2g**	A	23	100	37 (4)[d]dr = 4:1
11			B	66	95	42 (8)[d]dr = 11:1
12	 **1h**	 **2h**	A	43	94	58
13	 **1i**	 **2i**	A	69	87	38
14	 **1j**	 **2j**	A	53	95	60

[a] Conditions A: substrate **1** (1 mmol), palladium(II) trifluoroacetate (0.1 mmol), pyridine (0.4 mmol) and DABCO (0.4 mmol) in 10 mL of toluene under 1 atm oxygen at 95 °C; Conditions B: substrate **1** (1 mmol), palladium(II) acetate (0.1 mmol), pyridine (0.4 mmol) and K_2HPO_4 (2 mmol) in 10 mL of toluene under 1 atm oxygen at 95 °C.
[b] The yields and conversions were determined by isolation.
[c] The values in parentheses are yields of olefin isomerization products.
[d] Products indicated are the major products.

With two optimized reaction conditions in hand, we then explored the generality of this cascade cyclization. Notably, reaction rate under conditions A is generally faster than that under conditions B (Table 2, entries 1, 2 and 10, 11); however, high diastereoselectivity can be obtained under conditions B. A variety of pyrrolizidine and indolizidine derivatives can be obtained in moderate to good yields (Table 2, entries 1–7, 13, and 14). For the challenging linear substrates **1a** and **1b**, cyclizations proceeded smoothly to afford the pyrrolizidine **2a** and indolizidine **2b** in good yields, along with a small amount of olefin isomerization product (Table 2, entries 1–4). When germinal disubstituted substrates **1c–e** were subjected to the optimal conditions A, the azabicyclic products were obtained in good yields, with higher reaction rate than linear counterparts (Table 2, entries 3–5), which might be explained by the

Thorpe–Ingold effect.[8] It is interesting that substrates **1f** and **1g** cyclized to afford two diastereomers in moderate yields, respectively, and the cyclization of *trans*-configuration substrate **1g** gave higher diastereoselectivity (up to 11:1) than *cis* isomer **1f** (up to 4:1). It is noteworthy that substrate **1h** with a tosyl-protected nitrogen group on the carbon chain can be cyclized in 58% yield to afford **2h** (Table 2, entry 12), which contains a pyrazine core widely found in pharmaceutical molecules.[9] The more challenging 1,2-disubstiuted alkenes **1i** and **1j** were also applicable in this transformation. Notably, **2i** and **2j** were obtained from **1i** and **1j** in 38% and 60% yield as single diastereomer, respectively, after oxidative cascade cyclization, indicating that the aminopalladation of aliphatic unsaturated amides proceeds via a highly *syn*-selective pathway.[10]

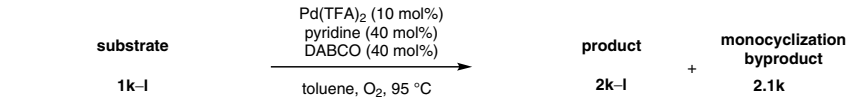
The investigation of the applicability of this methodology was then focused on the synthesis of more challenging azatricyclic systems (Table 3). Ring-containing unsaturated amides **1k**,**l** were tested under conditions A. However, they are more difficult to undergo cyclization reaction than amides **1a**–**j**. In contrast, the competing β-H elimination as a major side reaction occurred to deliver bicyclic byproducts with two diastereomers **2.1k** and **2.1k′**. For substrate **1k**, the densely fused aza-tricyclic product was only obtained in 22% yield, whereas spiro aza-tricyclic product **2l** was isolated in 24% yield from **1l**, accompanied by lots of unidentified byproducts.

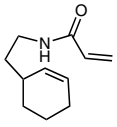
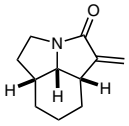
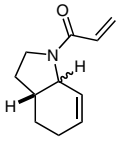
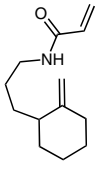
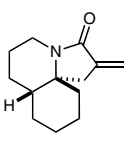


Scheme 2 A proposed mechanism for the palladium-catalyzed aerobic oxidative cascade cyclization and competing pathways

On the basis of previous reports[4,10] and above results, a proposed reaction mechanism is shown in Scheme 2. The initial coordination of amide and olefin to palladium(II) center forms complex **I**, followed by intramolecular aminopalladation to afford alkylpalladium(II) complex **II**. This C–N bond-formation step is proposed to proceed in a highly *syn*-selective fashion,[10] of which the R group is on the same face

Table 3 Substrate Scope of Azatricyclic Products[a]



Entry	Substrate	Product	Monocyclization product	Time (h)	Conv. (%)[b]	Yield (%)[b,c]
1	 **1k**	 **2k**	 **2.1k & 2.1k'**	24	100	22 (29, 23)
2	 **1l**	 **2l**	–	86	80	24

[a] Reaction conditions: substrate **1** (1 mmol), palladium(II) trifluoroacetate (0.1 mmol), pyridine (0.4 mmol), and DABCO (0.4 mmol) in 10 mL of toluene under 1 atm oxygen at 95 °C.
[b] Isolated yield unless otherwise indicated.
[c] The values in parenthesis are yields of two inseparable monocyclized diastereomers, which were determined by ^{1}HNMR spectrum using 4-nitrobenzene as the internal standard.

as the angular hydrogen, as evidenced by the observed stereochemistry of **2i** and **2j**. This is different from our precedent work[7b] where a high *anti* selectivity was observed,[11] which might be resulted from different ligands employed in the two reaction systems. Olefin insertion of complex **II** delivers σ-organopalladium(II) complex **III** and subsequent β-hydride elimination gives the final product **2** and palladium(II) hydride species. The active palladium(II) species is recycled through the reoxidation of palladium(II) hydride by molecular oxygen.[12] For ring-containing amide **1k**, the conversion of alkylpalladium(II) complex **II** into complex **III** is unfavorable due to large ring strain. Therefore, the competing β-hydride elimination predominantly occurred to produce bicyclic side products and their corresponding diastereomers. On the other hand, re-insertion of Pd-H species to product **2** is likely to proceed to deliver complex **IV**, which was transformed into isomeric product **2′** via β-hydride elimination.

In conclusion, we have developed an aerobic oxidative cascade cyclization of aliphatic alkenyl amides for rapid assembly of various N-heterocycles, including pyrrolizidine and indolizidine derivatives as well as azatricyclic heterocycles in moderate to good yields, using molecular oxygen as the green oxidant.[13] The observed stereochemistry indicates the aminopalladation step proceeds via a *syn* manner. This cascade cyclization may be applied in the synthesis of related natural products.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588502.

References and Notes

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(13) **General Procedure**

To a well-stirred solution of $Pd(TFA)_2$(33.2 mg, 0.1 mmol) in toluene (5 mL) were added pyridine (32.3 μL, 0.4 mmol) and DABCO (44.9 mg, 0.4 mmol). The mixture was stirred continuously until the solid dissolved. The reaction solution was oxygenated for 15 min, then amide **1a** (139.2 mg, 1.0 mmol) and toluene (5 mL) were added. The resulting solution was stirred under an O_2 atmosphere for 15 min, then heated at 95 °C with an air condenser under an O_2 atmosphere for 21 h. The reaction mixture was filtered through a short pad of Celite, then concen-

trated in vacuo. The residue was purified by flash column chromatography to afford **2a** (101.5 mg, 0.74 mmol, 74% yield) as a yellow oil.

2-Methylenehexahydro-3*H*-pyrrolizin-3-one (2a)

Yellow liquid; analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, R_f = 0.18. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (t, *J* = 2.7 Hz, 1 H), 5.28 (t, *J* = 2.2 Hz, 1 H), 3.77 (tt, *J* = 7.2, 4.9 Hz, 1 H), 3.67 (dt, *J* = 12.0 Hz, 8.1 Hz, 1 H), 3.21 (ddd, *J* = 12.3, 9.6, 3.0 Hz, 1 H), 3.00 (ddt , *J* = 17.0 Hz, 7.4 Hz, 2.1 Hz, 1 H), 2.50 (ddd, *J* = 17.0 Hz, 7.4 Hz, 3.1 Hz, 1 H), 2.26–1.93 (m, 3 H), 1.30–1.21 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 (C), 143.0 (C), 115.2 (CH_2), 58.5 (CH), 41.4 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 25.9 (CH_2); IR (CH_2Cl_2) 3048, 2981, 2888, 1692, 1659, 1445, 1244, 1208, 1156 cm^{-1}. LRMS (EI, 20 eV): *m*/*z* = 137 (100) [M$^+$]. HRMS (EI): *m*/*z* calcd for $C_8H_{11}NO$ [M$^+$]: 137.0841; found: 137.0843.