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Palladium(II)-Catalyzed Intramolecular Tandem Aminoalkylation via Divergent C(sp^3)−H Functionalization

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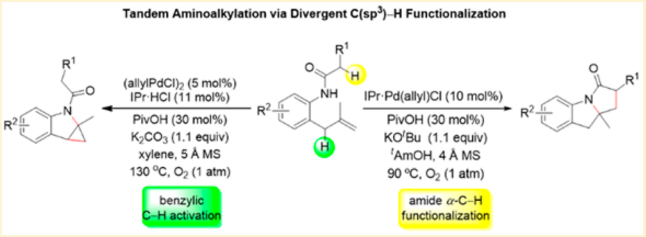
Supporting Information

ABSTRACT: We have developed a Pd(II)-catalyzed oxidative tandem aminoalkylation via divergent C(sp^3)−H functionalization, affording three- and five-membered-ring fused indolines in good yields under two optimized conditions, respectively. The mechanism studies have indicated that the benzylic C−H cleavage involved in the former transformation is the rate-determining step, while the cleavage of amide α-C−H in the latter is not. This is the first example of a Pd-catalyzed tandem reaction involving C(sp^3)−H activation without the employment of prefunctionalized reagents (e.g., halogenated and boron reagents) and directing groups, representing a green and economic protocol for the construction of *N*-containing heterocycles.



INTRODUCTION

Transition-metal catalyzed direct C−H functionalization represents a highly efficient, straightforward, and powerful method for the construction of organic frameworks.[1] Compared to the well-established C(sp^2)−H functionalization,[2] decorating less reactive C(sp^3)−H bonds is more challenging, as they lack π electrons that can readily interact with transition metals.[3−6] In particular, C(sp^3)−C(sp^3) bond formation through C(sp^3)−H functionalization via a σ-alkylmetal intermediate is much less developed, and current methods for this strategy inevitably require the employment of prefunctionalized substrates (directing groups, boron or halogenated reagents) or stoichiometric organic oxidants.[7] Thus, more atom-economical processes are highly desirable. With continuing effort toward our previous interest in the construction of *N*-heterocycles through tandem reactions involving C−N/C-(sp^2)−C(sp^3) formation (Scheme 1, eqs 1 and 2),[8] here we describe a novel aminoalkylation [C−N/C(sp^3)−C(sp^3) formation] via C(sp^3)−H functionalization of simple unsaturated anilides with molecular oxygen as the sole oxidant (Scheme 1, eq 3). The σ-alkylPd(II) intermediates formed in the aminopalladation step could activate benzylic C−H or amide α-C−H divergently under different conditions and deliver the corresponding cyclopropane-fused-indolines or pyrolizidines respectively, which are structural units in many natural products and pharmaceutics.[9,10]

RESULTS AND DISCUSSION

Initially, the readily accessible unsaturated anilide **1a** was subjected to the conditions employed by Fagnou et al. for intramolecular C(sp^3)−H activation,[11] with oxygen as an environmentally benign oxidant. Surprisingly, both **2a** and **3a** were obtained in 19% and 13% yields, respectively (Scheme 2). We reasoned that, after the first aminopalladation step, the σ-alkylPd(II) intermediate underwent benzylic C−H and amide α-C−H activation, thereby affording corresponding product **2a** or **3a**, respectively.

With this encouraging result, further optimization for aminoalkylation through benzylic C−H activation was then carried out by employing isobutyranilide **1c** as a substrate (Table 1), as we expected that the other pathway, i.e., the amide α-C−H functionalization, might be inhibited due to the steric hindrance of the isopropyl group. To our delight, the desired product **2c** was obtained in 45% yield without the formation of **3c** (entry 1). However, the phosphine ligand was not compatible with the oxygen atmosphere.[12,13] Therefore, nitrogen and *N*-heterocyclic carbene (NHC) ligands were evaluated (entries 2−4). IPr·HCl [1,3-bis(2,6-diisopropylphenyl)imidazolium chloride] as an NHC precursor proved to be the best, affording **2c** in a moderate yield (41%; entry 4). Subsequent screening of reaction conditions revealed that the yield of **2c** could be improved to 87% under the following reaction conditions: $(allylPdCl)_2$ (5 mol %), IPr·HCl (11 mol %), pivalic acid (30 mol %), K_2CO_3 (1.1 equiv), and 5 Å molecular sieves in xylene under an oxygen atmosphere at 130 °C (entries 5−9).[14]

Notably, pivalic acid, which is considered to be helpful for C(sp^3)−H activation via a concerted metalation−deprotonation (CMD) pathway, did improve the yield significantly (entry 5 vs 6).[15] It is interesting that a strong base, ^{t}BuOK, resulted in the formation of **3c** in 35% yield without the formation of **2c** (entry 8). It was probably because a strong base would prefer to deprotonate the α-C−H of the amide rather than activate the benzylic C−H. This provided very useful information for us to

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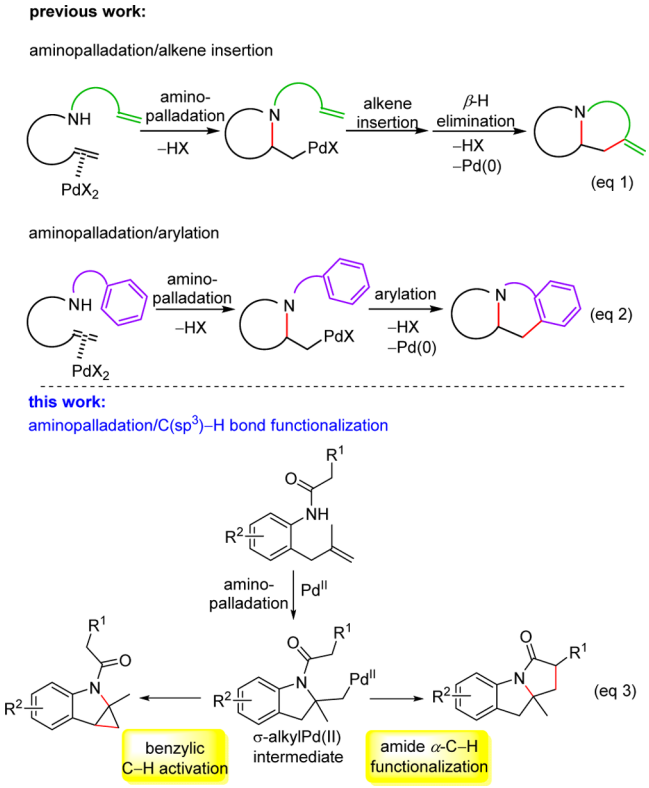
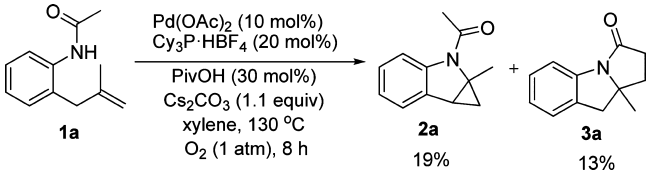
Scheme 1. Tandem Cyclization involving C−N/C−C Formation for Synthesis of *N*-Heterocycles



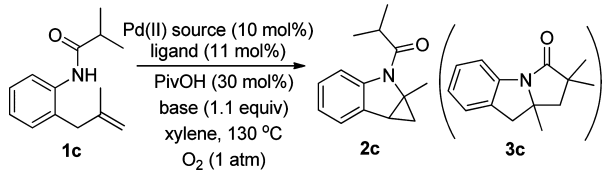
Scheme 2. Preliminary Result of Pd(II)-Catalyzed Aminoalkylation



optimize the tandem reaction for functionalization of the α-C−H of amides (vide infra).

Under the optimized conditions for aminopalladation/benzylic C−H activation, the substrate scope was examined (Table 2). Acetamide **1a** gave rise to three-membered-ring product **2a** and five-membered-ring product **3a** in 84% and 12% yield, respectively, after 20 h. The amide α-C(sp^3)−H functionalization was prevented when substrates **1b** and **1c** with α-substituents were employed, and the desired products **2b** and **2c** were obtained, respectively, in very good yield. However, the cyclopropyl substituted substrate **1d** led to the formation of five-membered-ring product **3d** in 28% yield in addition to desired product **2d** in 66% yield, probably because of the higher acidity of the α-C−H on the cyclopropane ring. As expected, substrates **1e** and **1g** without α-C−H cyclized smoothly. Remarkably, the reaction was compatible with the carboxybenzyl (Cbz) group, which could be easily deprotected by hydrogenation. Substrate **1f** that bears a phenylacetamide unit generated both **2f** and **3f** in 19% and 44% yield, respectively, with **3f** as the major product, probably because the α-C−H of **1f** is more acidic than that of other substrates. When diphenyl amine substrate **1h** was subjected to the standard conditions, **4h** rather than **2h** was obtained, indicating that the C(sp^2)−H

Table 1. Condition Optimization for Pd(II)-Catalyzed Tandem Cyclization via Aminopalladation/Benzylic C−H Activation[a]



entry	Pd(II)	ligand	base	time (h)	yield (%)[b]
1[c]	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	Cs_2CO_3	8	45
2[c]	$Pd(OAc)_2$	pyridine	Cs_2CO_3	20	8
3[c]	$Pd(OAc)_2$	1,10-phen	Cs_2CO_3	20	N.R.
4	$Pd(OAc)_2$	IPr·HCl	Cs_2CO_3	40	41
5[d]	$(allylPdCl)_2$	IPr·HCl	Cs_2CO_3	40	60
6[d,e]	$(allylPdCl)_2$	IPr·HCl	Cs_2CO_3	40	42
7[d]	$(allylPdCl)_2$	IPr·HCl	K_2CO_3	40	60
8[d]	$(allylPdCl)_2$	IPr·HCl	KO^{t}Bu	40	0 (35)[g]
9[d,f]	$(allylPdCl)_2$	IPr·HCl	K_2CO_3	20	87

[a]Reaction conditions: substrate **1c** (0.2 mmol), Pd(II) source (10 mol %), ligand (11 mol %), PivOH (30 mol %), and base (1.1 equiv) in xylene (2.0 mL) at 130 °C under an O_2 atmosphere. [b]NMR yield of **2c** with nitrobenzene as an internal standard. [c]20 mol % ligand was used. [d]5 mol % $(allylPdCl)_2$ was used. [e]Without PivOH. [f]5 Å molecular sieves (1 g/mmol substrate) were added. [g]Yield of **3c** determined by ^{1}H NMR analysis with nitrobenzene as an internal standard in the parentheses.

activation is more facile than the C(sp^3)−H activation. Then the electronic effect on the aryl ring was examined with a series of propionanilides. Substrates **1i−n** with an electron-donating or -withdrawing group on the *para*- or *meta*-position all afforded products **2i−n** in very good yields, and notably, those electron-deficient anilides **1k** and **1n** cyclized faster than their electron-rich counterparts (**1i**, **1j**, and **1m**). An ethyl and even a phenyl angular substituent were well tolerated, and the desired products **2o** and **2p** were obtained in good yield, respectively. Interestingly, usually difficult six-*exo* cyclization was realized by employing aliphatic amide substrate **1q** albeit with a low yield (20%). However, anilide **1r** failed to undergo cyclization in a similar manner, because the C−H bond to be functionalized is not at the benzylic position.

We then optimized the reaction conditions for amide α-C−H functionalization by employing acetylanilide **1a** as the substrate owing to it being the least bulky at the α-position (Table 3). KO^{t}Bu was used as the base since it seemed to favor the amide α-C−H functionalization (vide supra). Good regioselectivity was achieved (entry 1) although a stoichiometric amount of KO^{t}Bu was necessary for the transformation (entry 1 vs 2). Addition of PivOH was found to give better results.[16] Polar solvents, especially *tert*-amyl alcohol (^{t}AmOH), were superior to the nonpolar one (xylene), affording **3a** in good yield without the formation of **2a** (entries 3−4 vs entry 1). This was probably because the solubility of KO^{t}Bu in polar solvents was better, and thus the deprotonation of α-C−H was easier. Interestingly, IPr·Pd(allyl)Cl provided a higher yield than that of the combination of $(allylPdCl)_2$ and IPr·HCl (entry 5 vs 3). Lowering the temperature to 90 °C led to a slightly increased yield (entry 6).

With the optimized conditions in hand, more anilides were investigated for the tandem cyclization involving amide α-C−H functionalization (Table 4). To our delight, most reactions

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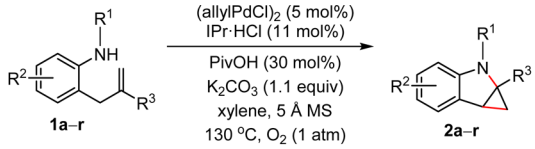
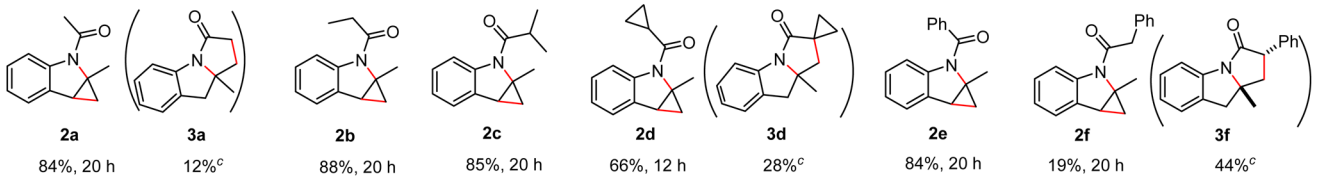
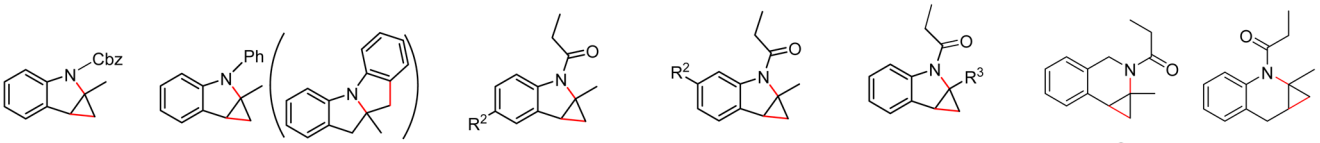
Table 2. Substrate Scope of Pd(II)-Catalyzed Tandem Cyclization via Aminopalladation/Benzylic C−H Activation[a,b]





2a	3a	2b	2c	2d	3d	2e	2f	3f
84%, 20 h	12%[c]	88%, 20 h	85%, 20 h	66%, 12 h	28%[c]	84%, 20 h	19%, 20 h	44%[c]



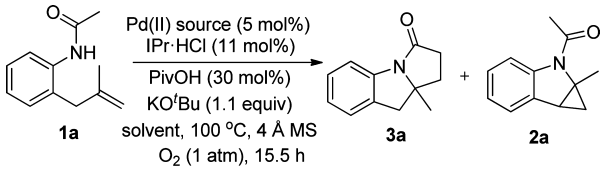
2g	2h	4h
80%, 24 h	0, 24 h	94%[c]

R^2 = OMe	**2i**	87%, 15 h	R^2 = OMe	**2m**	82%, 17 h	R^3 = Et,	**2o** 84%, 20 h
Me	**2j**	83%, 17 h	F	**2n**	84%, 8 h	= Ph,	**2p** 66%, 7 h
NO_2	**2k**	74%, 10 h					
F	**2l**	88%, 20 h					

2q	2r
20%, 48 h	0, 48 h

[a]Reaction conditions: substrate (0.3 mmol), $(allylPdCl)_2$ (5 mol %), IPr·HCl (11 mol %), PivOH (30 mol %), K_2CO_3 (1.1 equiv), and 5 Å molecular sieves (1 g/mmol substrate) in xylene (3.0 mL) at 130 °C under an O_2 atmosphere. [b]Isolated yield. [c]Isolated yield of side product.

Table 3. Condition Optimization for Pd(II)-Catalyzed Tandem Cyclization via Aminopalladation/Amide α-C−H Functionalization[a]



entry	Pd(II)	solvent	yield (%)[b]
1	$(allylPdCl)_2$	xylene	66 (11)[c]
2[d]	$(allylPdCl)_2$	xylene	20
3[e]	$(allylPdCl)_2$	^{t}AmOH	71
4	$(allylPdCl)_2$	dioxane	60
5[e,f]	IPr·Pd(allyl)Cl	^{t}AmOH	80
6[e,f,g]	IPr·Pd(allyl)Cl	^{t}AmOH	88

[a]Reaction conditions: substrate **1a** (0.2 mmol), Pd(II) source (5 mol %), IPr·HCl (11 mol %), PivOH (30 mol %), KO^{t}Bu (1.1 equiv), and 4 Å molecular sieve (1 g/mmol substrate) in xylene (2.0 mL) at 100 °C under an O_2 atmosphere for 15.5 h. [b]Yield of **3a** determined by ^{1}H NMR analysis with nitrobenzene as an internal standard. [c]Yield of **2a** shown in parentheses determined by ^{1}H NMR analysis with nitrobenzene as an internal standard. [d]11 mol % KO^{t}Bu was added. [e]Reaction time 4 h. [f]10 mol % IPr·Pd(allyl)Cl was used, without IPr·HCl. [g]90 °C.

were completed in 4 h. Acetamide **1a** afforded **3a** in 80% yield. The substrates **1c** and **1d** with two α-substituents afforded low yields of desired products due to steric congestion, and three-membered-ring products **2c** and **2d** from benzylic C−H activation were formed, whereas substrate **1b** with only one α-substituent gave rise to **3b** in a good yield with a dr ratio of 6:1. The electronic effect on the aryl ring was also studied. Substrates **1s−u** with either an electron-donating or -withdrawing group on the *para*-position all gave satisfactory yields of desired products **3s−u**, respectively, while **1w** bearing a *meta*-F substituent afforded a lower yield than that of the *meta*-OMe substituted **1v**. The substituent on the benzylic position of **1x** seemed not to affect the desired cyclization, and products **3x** and **3x′** were isolated in 64% combined yield with a dr ratio of 1.3:1. While **3y** with an angular ethyl group could be obtained in good yield, **3z** with a Ph group was not formed unexpectedly. Remarkably, substrate **1ab** with one more carbon in the side chain afforded the indolizidine derivative **3ab** in 61% yield; in contrast, aliphatic amide **1aa** failed to provide the desired product, probably because of the less acidic NH compared to other anilide substrates.

To discern the rate-determining step of the tandem aminopalladation/benzylic C−H activation reaction, we applied Singleton's NMR technique to determine the product $^{12}C/^{13}C$ kinetic isotope effect (KIE) from cyclization of **1e** under the optimized conditions.[17] The most pronounced carbon isotope effect on the benzylic position (C1) of **2e** was observed, by comparing the ^{13}C composition of the product **2e** at a low conversion (ca. 20%) to that of **2e** at 100% conversion (Figure 1).[18] This result indicated that the activation of the benzylic C−H is likely the rate-determining step.

For tandem aminopalladation/amide α-C−H functionalization, on the other hand, an intermolecular $^1H/^2H$ KIE experiment was carried out to test whether the amide α-C−H bond cleavage is the rate-determining step. Both **1a** and deuterated substrate *d*-**1a** were subjected to the standard conditions (Scheme 3). After 2 h, **3a** was obtained in 56% yield but without any deuterium atom at the amide α-position, and 28% of **1a** was recovered without any observation of *d*-**1a**. As protic solvent ^{t}AmOH and acidic additive pivalic acid were employed in the reaction, the amide α-C−H might be deprotonated in the presence of strong base KO^{t}Bu. The fact that the D/H exchange readily occurred in the tandem cyclization reaction implies that the amide α-C−H bond cleavage is unlikely to be the rate-determining step.

Based on the above experimental results, we proposed a possible mechanism for the divergent cyclizations at the benzylic and amide α-positions (Scheme 4). **1a** proceeds

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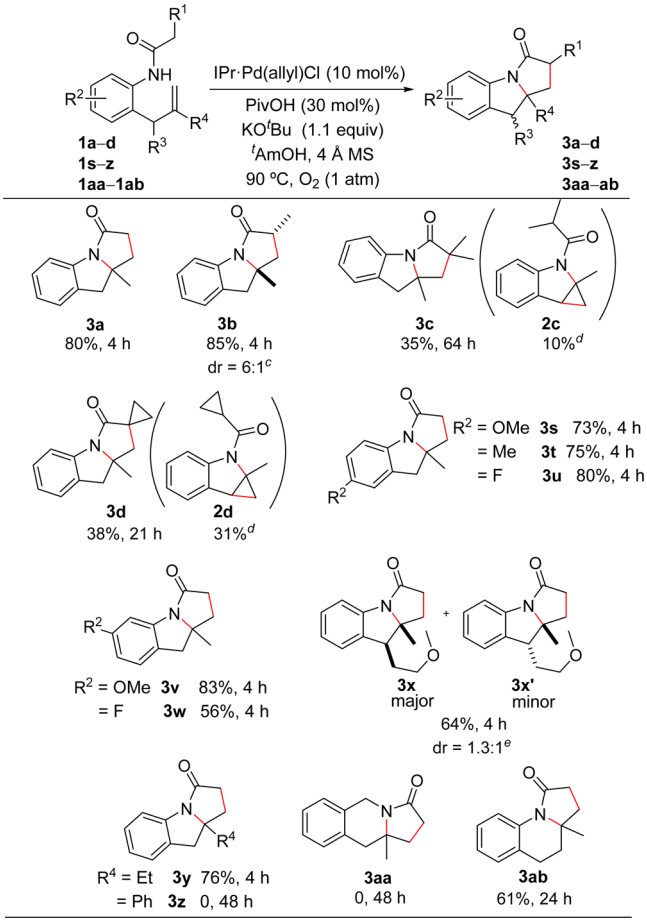
Table 4. Substrate Scope of Pd(II)-Catalyzed Tandem Cyclization via Aminopalladation/Amide α-C−H Functionalization[a,b]



[a]Reaction conditions: substrate (0.3 mmol), IPr·Pd(allyl)Cl (10 mol %), PivOH (30 mol %), KO^{t}Bu (1.1 equiv), and 4 Å molecular sieve (1 g/mmol substrate) in ^{t}AmOH (3.0 mL) at 90 °C under O$_2$. [b]Isolated yield. [c]The dr ratio was calculated based on the isolated yields of the two isomers. [d]Isolated yield of side product (in parentheses). [e]The dr ratio was determined by ^{1}H NMR spectroscopy.

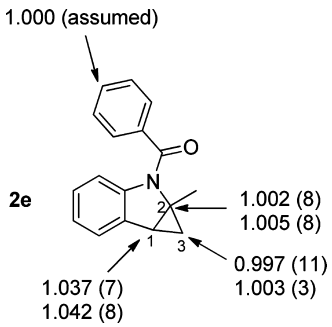
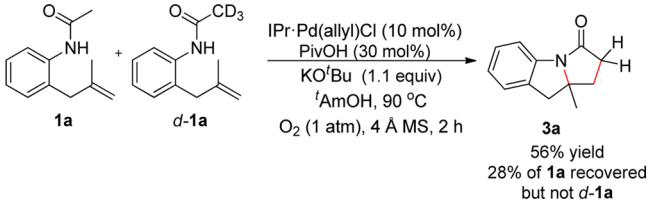


Figure 1. Experimental ^{13}C KIEs (k^{12}C/k^{13}C) for the tandem aminopalladation/benzylic C−H activation reaction of **1e** under the optimized conditions from two independent experiments. The numbers in parentheses represent the standard deviation on the last digit.

through the aminopalladation first to generate intermediate **I**, which could not undergo β-hydride elimination due to the existence of the angular methyl group.[19] For the activation of the benzylic C−H pathway, a three-center agostic intermediate

Scheme 3. Intermolecular ^{1}H/^{2}H KIE Study for the Tandem Aminopalladation/α-C−H of Amides Functionalization Reaction of 1a and d-1a under the Optimized Conditions



III might be involved (left side).[20] Recently, an inner-sphere pivalate assisted CMD mechanism had been proposed for Pd-catalyzed C(sp^3)−H activation reactions.[11a,15] In our case, pivalate did improve the yield of **2a**; in addition, bidentate ligands poisoned the reaction while electron-rich monodentate ligand (IPr) provided the best result. All these observations are consistent with the CMD mechanism. The rate-determining step, benzylic C−H abstraction assisted by pivalate, generates a four-membered palladacycle intermediate **IV**, which gives **2a** via reductive elimination. On the other hand, the α-C−H of the amide is deprotonated to form an enolate **V** in the presence of a strong base (KO^{t}Bu) (right side). The enolate formation pathway had been reported in Pd-catalyzed α-arylation reactions.[4b,c,e] Besides, the requirement of a stoichiometric amount of a strong base and the KIE study are both consistent with this proposed pathway. Addition of the enolate amide would afford a six-membered palladacycle intermediate **VI**, and **3a** is then formed through reductive elimination.

CONCLUSION

In summary, we have developed a Pd(II)-catalyzed oxidative cascade aminoalkylation via C(sp^3)−H functionalization for divergent synthesis of three-membered-ring or five-membered-ring fused indolines. The benzylic C−H and amide α-C−H can be selectively activated under different reaction conditions. This is the first example of a palladium-catalyzed tandem reaction involving C(sp^3)−H activation without employment of prefunctionalized reagents (halogenated or boron reagents) and/or directing groups, representing a green and economic protocol for the construction of *N*-containing heterocycles.

EXPERIMENTAL PROCEDURES

General Procedure for Oxidative Cascade Cyclization via Aminopalladation/Benzylic C−H Activation. In a 5 mL round-bottom flask equipped with a magnetic stir bar, dry xylene (3 mL) was added to a mixture of (allylPdCl)$_2$ (5.5 mg, 0.015 mmol), IPr·HCl(14.0 mg, 0.033 mmol), pivalic acid (9.2 mg, 0.09 mmol), **1** (0.3 mmol), K$_2$CO$_3$ (45.6 mg, 0.33 mmol), and activated 5 Å molecular sieves (300 mg). The reaction flask was then connected to an oxygen atmosphere and heated to 130 °C until TLC monitoring indicated the complete conversion of the starting material. The reaction mixture was cooled, filtered through a short pad of silica gel (EtOAc as eluent), and concentrated *in vacuo*. The residue was purified by flash column chromatography to give cyclopropane-fused-indoline **2**.

General Procedure for Oxidative Cascade Cyclization via Aminopalladation/Amide α-C−H Functionalization. In a 5 mL round-bottom flask equipped with a magnetic stir bar, distilled ^{t}AmOH (3 mL) was added to a mixture of IPrPd(allyl)Cl (17.2 mg, 0.03 mmol), pivalic acid (9.2 mg, 0.09 mmol), **1** (0.3 mmol), KO^{t}Bu (37.0 mg, 0.33 mmol), and activated 4 Å molecular sieves (300 mg). The reaction flask was then connected to an oxygen atmosphere and heated to 90 °C until TLC monitoring indicated the complete conversion of the starting material. The reaction mixture was cooled, filtered through

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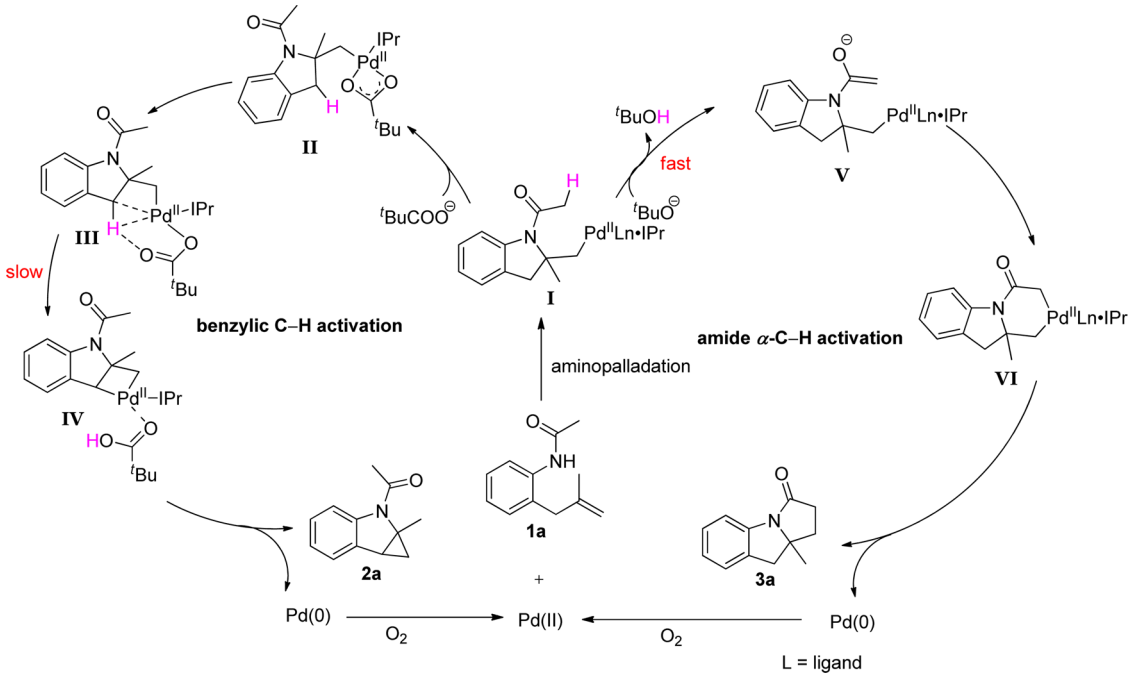
Scheme 4. Proposed Mechanism for the Palladium(II)-Catalyzed Intramolecular Tandem Aminoalkylation via Divergent C(sp^3)−H Functionalization



a short pad of silica gel (EtOAc as eluent), and concentrated in vacuo. The residue was purified by flash column chromatography to give pyrrolizidine **3**.

■ ASSOCIATED CONTENT

Supporting Information

Information regarding materials and methods, and all characterization data of compounds from this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) The involvement of a radical intermediate can be excluded, as addition of a stoichiometic amount of TEMPO had little effect on the cyclization.

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