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Palladium(II)-Catalyzed Oxidative Cascade Cyclization Reactions of Anilides and Anilines: Scope and Mechanistic Investigations

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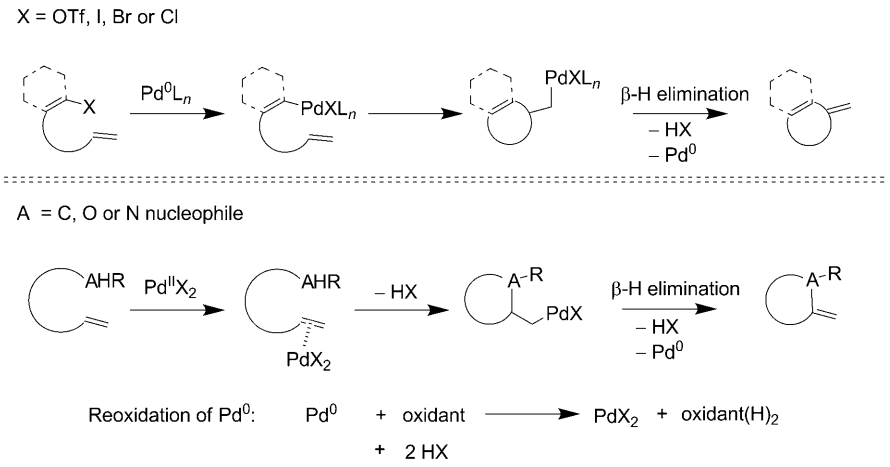
Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Abstract: With $Pd(OAc)_2$/pyridine as the catalyst system and molecular oxygen as a green oxidant, acrylanilides and *N*-allylanilines undergo oxidative cascade cyclization to form heterocyclic rings in high yields. This methodology is applicable to acrylanilides of different substitution patterns on olefinic units. Mechanistic studies revealed that cyclization of acrylanilides proceeded through an intramolecular *syn*-amidopalladation pathway. The reversible nature of amidopalladation serves as a "scavenging process" to prevent β-hydride elimination from occurring halfway through the catalytic cycle, thus favoring the formation of cascade cyclization products. In addition, internal coordination between an σ-alkylpalladium species and a tethered olefinic C=C double bond also appears to disfavor β-hydride elimination.

Keywords: cyclizations · domino reactions · homogeneous catalysis · palladium · reaction mechanism

Introduction

Palladium-catalyzed cascade cyclization reactions are direct, versatile, and fundamental synthetic strategies for building polycyclic ring structures and establishing multiple stereocenters in a single step.[1] Over the last few decades, numerous examples of natural product syntheses have been reported by utilizing palladium(0)-catalyzed cascade cyclization reactions, many of which are intramolecular Heck cyclizations (Scheme 1).[2] However, drawbacks of these reactions include 1) the inevitable involvement of prefunctionalized precursors, such as aryl (or vinyl) triflates and halides, 2) palladium complexes as catalysts that usually feature air-sensitive phosphine ligands, and 3) the scope is mostly restricted to carbon–carbon bond formation, rather than the more-versatile carbon–heteroatom bond formation.[3] Therefore, further development of cascade cyclization reactions to make it more atom-economical[4] and allow carbon–heteroatom bonds to form remains an important goal in the synthesis of complex polycyclic molecules.



Scheme 1. Top route: Heck-type cyclization involves oxidative addition to preactivated carbon nucleophiles, thus requiring Pd^0 catalysis. Bottom route: Oxidative cyclization is initiated through nucleophilic attacks on Pd^{II}–olefin complexes and external oxidants are required to regenerate Pd^{II} from Pd^0 species.

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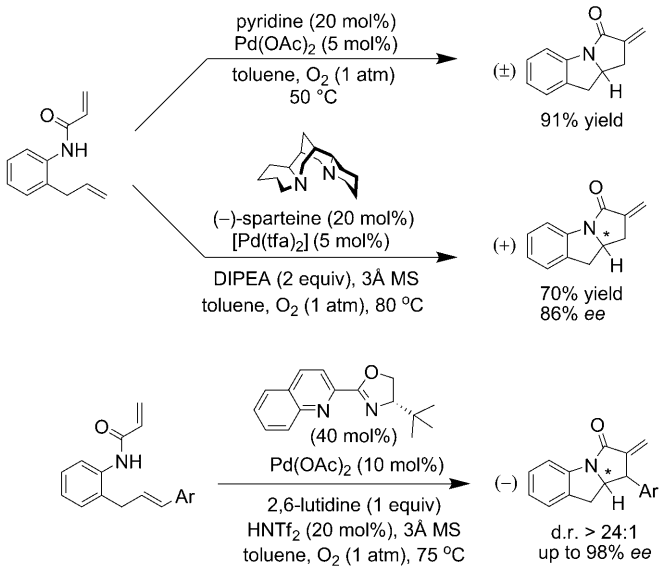
In recent years, a variety of oxidative C–C, C–O, and C–N bond-forming reactions have been reported when using palladium catalysts in the presence of external oxidants, in particular, molecular oxygen.[5] In particular, carbocycles and heterocycles have been constructed through intramolecular formation of C–C,[6] C–O,[7] and C–N[8] bonds (Scheme 2). Such oxidative palladium catalysis can be applied to cascade reactions, provided that the organopalladium intermediates generated in situ, upon the formation of the new bond, can be further manipulated in various ways, including carbonylation,[9] heteroatom incorporation,[10] olefin insertion,[11] and arene insertion.[12] However, the development of palladium-catalyzed oxidative cascade cyclization is challenging because of the possibility of undesired β-hydride elimination occurring halfway through the catalytic cycle. Recently, we reported that oxidative cascade cyclizations employing amides as nitrogen-centered nucleophiles could afford a variety of racemic and enantioenriched indoline derivatives, when using Pd^{II}/pyridine, Pd^{II}/(−)-sparteine, and Pd^{II}/quinoline–oxazoline as the catalytic system, respectively (Scheme 2).[13] Importantly, our oxidative cascade cyclization reactions did not produce any undesired monocyclization products, even in the absence of tandem relays, which are usually required in cascade reactions.[1a] Understanding the selectivity of such cyclizations would allow us to extend the scope toward complex polycyclic ring structures.[14]



Scheme 2. Palladium-catalyzed oxidative cascade cyclization reactions. DIPEA = *N*,*N*-diisopropylethylamine.

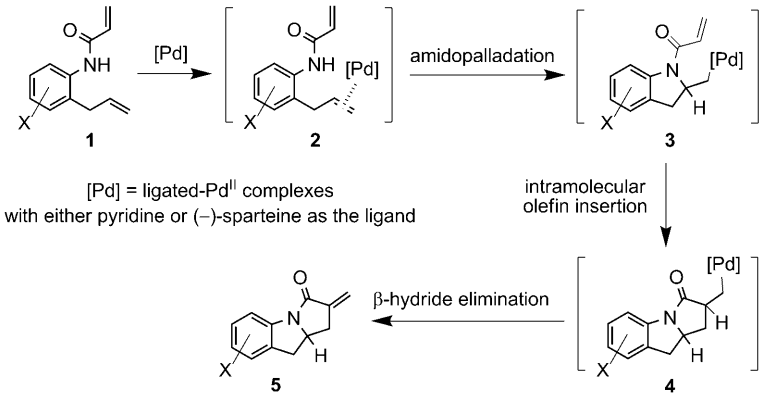
Scheme 3 illustrates the steps involved in these palladium-catalyzed oxidative cascade cyclizations. Cyclization of anilide **1** is catalyzed by Pd^{II} complexes, which could be either achiral or chiral, depending on the choice of ligands. The electron-deficient Pd^{II} complex coordinates to the *ortho*-allyl group of anilide **1** to generate intermediate **2**, which undergoes amidopalladation to give σ-alkylpalladium intermediate **3**. Following intramolecular olefin insertion, the σ-alkylpalladium intermediate **4** is formed, which is transformed into product **5** upon subsequent β-hydride elimination.

In this study, we investigated the mechanism of the palladium-catalyzed oxidative cascade cyclization reaction with respect to: 1) the electronic effects of the oxidative cascade cyclization, 2) the stereochemistry of amidopalladation, and 3) the reasons why the monocyclization product was not formed in the reaction.

Results and Discussion

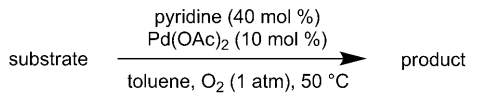
Electronic Effects

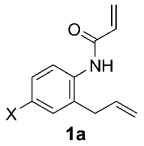
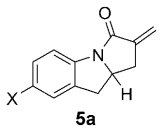
A reactivity trend of palladium-catalyzed oxidative cascade cyclizations was observed when employing a series of *para*-substituted anilides **1a–f** (Table 1). Electron-deficient anilides cyclized faster than their electron-rich counterparts. For example, shorter reaction times were required to achieve complete conversion of anilides **1b** (X = Cl, Table 1, entry 2), **1c** (X = F, entry 3), and **1d** (X = COOMe, entry 4) than those of **1e** (X = Me, entry 5) and **1f** (X = OMe, entry 6). Notably, the cyclizations of electron-rich anilides **1e** and **1f** were particularly slow (less than 50% conversion after 48 h) as a result of extensive aggregation of palladium catalyst when pyridine was used as the ligand. Replacing pyridine with triphenylphosphine resulted in a more efficient cyclization of **1e** (entry 5) and **1f** (entry 6).



Scheme 3. Oxidative cascade cyclization through sequential amidopalladation/olefin insertion.

Table 1. Oxidative cascade cyclization of *para*-substituted anilides.[a]



Entry	Substrate	Product	*t* [h]	Yield [%][b]
1	 **1a**	 **5a**	19	95
2	**1b** (X = Cl)	**5b**	19	83
3	**1c** (X = F)	**5c**	12	89
4	**1d** (X = COOMe)	**5d**	7	88
5[c]	**1e** (X = Me)	**5e**	22	85
6[c]	**1f** (X = OMe)	**5f**	48	74

[a] Unless otherwise indicated, all reactions were performed at 50 °C by using the substrate (0.3 mmol), pyridine (40 mol %), and $Pd(OAc)_2$ (10 mol %) in toluene (3 mL) under O_2 (1 atm.). [b] Isolated yields. [c] PPh_3 (40 mol %) was used instead of pyridine.

Kinetic studies of the oxidative cascade cyclization reactions were performed by monitoring the relative initial rates of reactions of anilides **1a–f** under identical reaction conditions (i.e., 40 mol % pyridine and 10 mol % $Pd(OAc)_2$). The investigation provided a quantitative measure of the relative reactivities of **1a–f**. A linear Hammett plot with a positive slope, $\rho = +1.23$, was obtained (Figure 1).[15] The trend reveals the presence of a significant electronic effect in palladium-catalyzed oxidative cascade cyclizations.

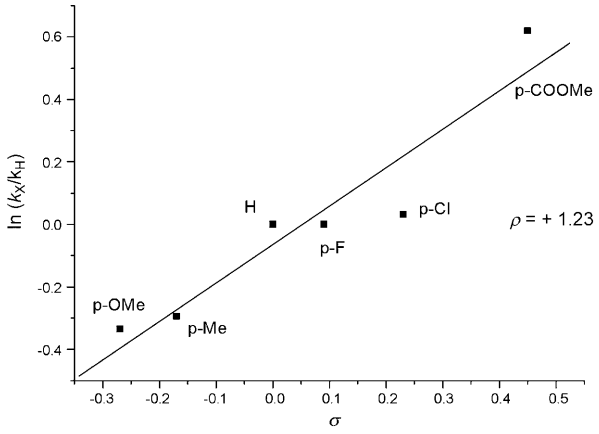
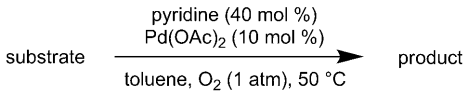


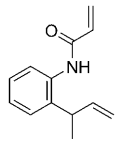
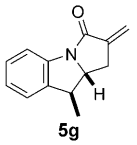
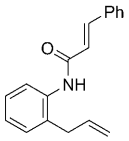
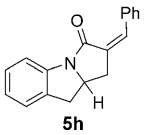
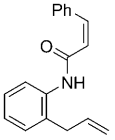
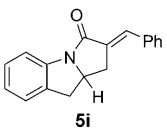
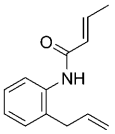
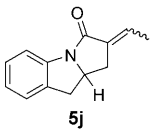
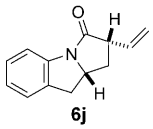
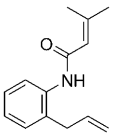
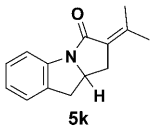
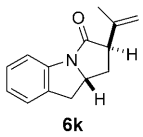
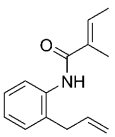
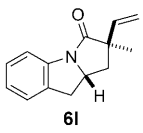
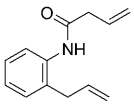
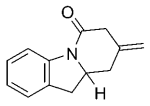
Figure 1. Hammett plot for Pd^{II}-catalyzed oxidative cascade cyclizations.

Substrate Scope

Oxidative cascade cyclization of anilides bearing *ortho*-monosubstituted olefins (**1g–m**) took place efficiently when using a Pd^{II}/pyridine catalyst system (Table 2). Diastereoselective cascade cyclization (diastereomeric ratio (d.r.) 5.9:1) of **1g** furnished **5g** and its minor diastereomer in 92 % yield (Table 2, entry 1). Anilides **1h** and **1i**, which have *E* and *Z* configurations, respectively, afforded products **5h** and **5i**, respectively (entries 2 and 3), thereby demonstrating that the

Table 2. Scope of the Pd^{II}-catalyzed oxidative cascade cyclization of anilides.[a]



Entry	Substrate	Product	*t* [h]	Yield [%][b]
1[c]	 **1g**	 **5g**	14	92 (d.r. 5.9:1)[d]
2	 **1h**	 **5h**	23	84
3	 **1i**	 **5i**	19	82
4	 **1j**	 **5j**  **6j**	20	10 (**5j**)[e] 70 (**6j**) (d.r. 1.8:1)[d]
5	 **1k**	 **5k**  **6k**	36	17 (**5k**) 63 (**6k**) (dr 7:1)[d]
6[f]	 **1l**	 **6l**	36	50 (**6l**) (d.r. 24:1)[d]
7	 **1m**	 **5m**	19	72

[a] Unless otherwise indicated, all reactions were performed at 50 °C by using the substrate (0.3 mmol), pyridine (40 mol %), and $Pd(OAc)_2$ (10 mol %) in toluene (3 mL) under O_2 (1 atm.). [b] Isolated yields. [c] 5 mol % $Pd(OAc)_2$ and 20 mol % pyridine were used. [d] Ratio determined by ^1H NMR spectroscopy; major diastereomer is depicted. [e] Mixture of stereoisomers. [f] Quinoline (40 mol %) was used instead of pyridine.

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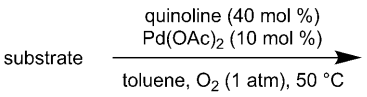
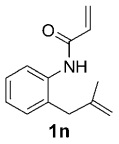
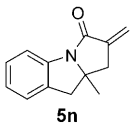
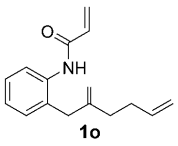
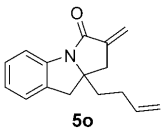
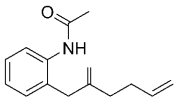
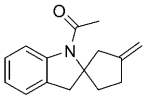
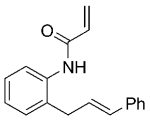
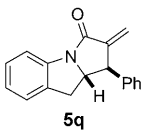
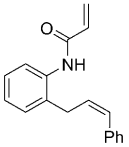
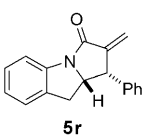
olefin geometry of the product is determined by that of the starting material. When **1j** and **1k** were used as substrates, olefin-insertion products **5** and **6** were obtained. In the cyclization of **1j**, **5j** was formed in 10% yield as a mixture of stereoisomers, whereas olefin-migration products (**6j** and its diastereomer) were obtained in 70% yield (d.r. 1.8:1, entry 4). On the other hand, cyclization of **1k** led to **5k** in 17% yield and olefin-migration products in 63% yield (**6k** as major diastereomer; d.r. 7:1, entry 5). By replacing the pyridine ligand with quinoline, **6l** was obtained in excellent diastereoselectivity from **1l** (d.r. 24:1, entry 6). Notably, **1m** with two unactivated olefinic groups could also be cyclized, leading to **5m** in 72% yield (entry 7).

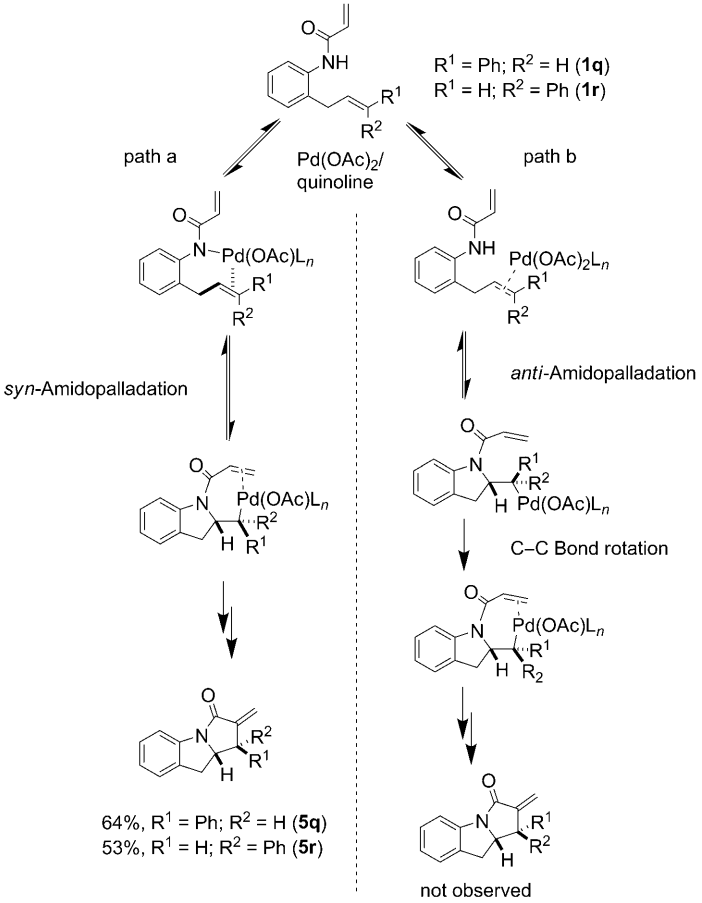
With the Pd^{II}/quinoline system, anilides **1n–r** containing an *ortho*-olefinic unit of other substitution patterns (1,1- and 1,2-disubstitution) are useful to establish quaternary or contiguous stereogenic centers (Table 3). For instance, **1n** cyclized to furnish **5n** in 91% yield (Table 3, entry 1). The exocyclic olefin moiety of **5n** is stable under optimized reaction conditions and no olefin isomerization product was formed.[16a] Interestingly, cascade cyclization of **1o** preferentially proceeded with a *N*-acrylic olefin instead of a tethered olefin, resulting in fused-indoline **5o** in 59% yield (entry 2). Alternatively, spiro-indoline **5p** was formed from **1p**, albeit less efficiently (entry 3). Cyclization of **1q** was stereospecific and afforded **5q** as the only product (64% yield, entry 4). Its relative configuration (i.e., the β-phenyl group is *syn* to the angular hydrogen) was determined by 2D NOESY experiments. On the contrary, cyclization of **1r** yielded product **5r** exclusively (53% yield, entry 5). These results support the proposal that *syn*-amidopalladation is the only mode of cyclization (path a, Scheme 4). Hence, the *anti*-amidopalladation pathway (path b) should be ruled out as it is not concordant to the observed outcomes.[17]

Table 3. Scope of the Pd^{II}-catalyzed oxidative cascade cyclization of anilides.[a]



Entry	Substrate	Product	*t* [h]	Yield [%][b]
1	 **1n**	 **5n**	48	91
2	 **1o**	 **5o**	48	59
3	 **1p**	 **5p**	48	58[c]
4[d]	 **1q**	 **5q**	48	64[e]
5[d]	 **1r**	 **5r**	48	53[e]

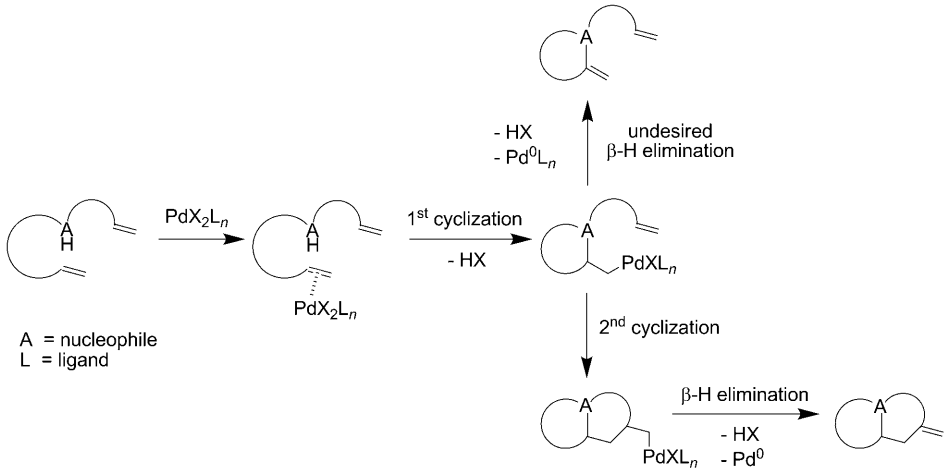
[a] Unless otherwise indicated, all reactions were performed at 50 °C by using the substrate (0.3 mmol), quinoline (40 mol %), and $Pd(OAc)_2$ (10 mol %) in toluene (3 mL) under O_2 (1 atm.). [b] Isolated yields. [c] Yield based on 52% conversion. [d] At 70 °C. [e] Single diastereomer was formed.



Scheme 4. Stereospecific Pd-catalyzed oxidative cascade cyclization.

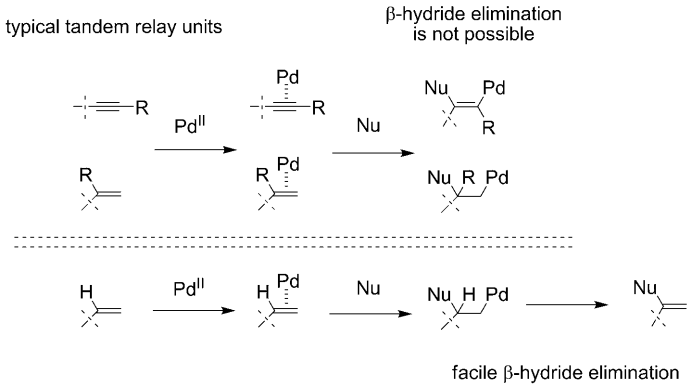
Structure–Reactivity Relationship: Origin of Selectivity in Oxidative Cascade Cyclization Reactions

Applying a Pd-catalyzed cyclization strategy to the construction of multiple-ring systems is challenging because midway β-hydride elimination[18] is usually a competing pathway, resulting in mixtures of monocyclization and cascade cyclization products (Scheme 5).[19] In both Pd^0- and Pd^{II}-catalyzed cascade cyclization reactions, undesired β-hydride elimina-

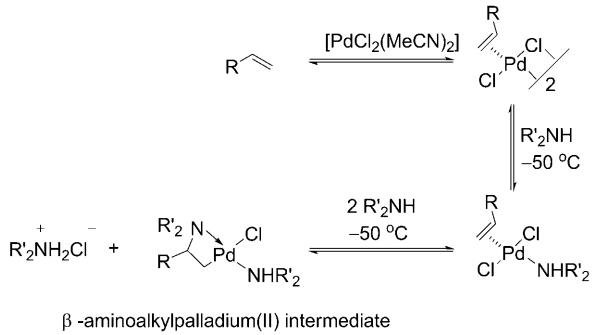


Scheme 5. Midway β-hydride elimination disrupting oxidative cascade cyclization.

In the seminal works reported by Hegedus and co-workers,[16] palladium-assisted amination of olefins was initiated with an excess amount (2 equiv or more) of aliphatic amines. An aliphatic amine would attack the palladium(II)–olefin complex reversibly to give the β-aminoalkylpalladium intermediate, which is rather stable towards further transformations (Scheme 7). Owing to the stronger coordinating ability of aliphatic amines than olefins towards Pd^{II}, addition reactions to olefins can proceed only in



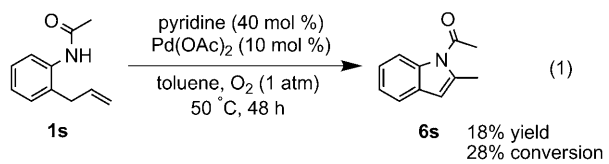
Scheme 6. Common tandem relays to avoid β-hydride elimination.



Scheme 7. Hegedus's model on palladium-mediated amination of olefin.

tion occurring halfway through the catalytic cycle can be avoided by designing substrates possessing tandem relays, such as substituted alkynes or 1,1-disubstituted alkenes (Scheme 6), rendering β-hydride elimination either energetically unfavorable or impossible (no β-hydrogen atom available).

As monosubstituted alkenes are not conventionally regarded as tandem relays, we were particularly interested in identifying the origin of the selectivity of our oxidative cascade cyclization reactions. Applying the $Pd(OAc)_2$/pyridine catalyst system, cyclization of anilide **1a** yielded the cascade cyclization product **5a** exclusively without producing monocyclization product (Table 1, entry 1). In contrast, anilide **1s** cyclized to afford **6s** in modest yield[20] after 48 hours [Eq. (1)] even though the acidity of the N–H bond is similar in **1a** and **1s**.



the preformed Pd^{II}–olefin complexes.[21] In this context, palladium-catalyzed oxidative amination of olefins becomes efficient only when electron-deficient nitrogen-centered nucleophiles are used (i.e., anilides in our case). In the cyclization of **1a**, it is likely that β-heteroatom elimination (the reversal of amidopalladation) serves as a "scavenging process" to convert **3a-1** and **3a-2** back to **2a** instead of undergoing midway β-hydride elimination (Scheme 8). As an efficient leaving group, electron-deficient nitrogen nucleophiles favor β-heteroatom elimination in **3a-1** over β-hydride elimination.[22]

With an acryl olefinic unit, efficient and relatively rapid olefin insertion/β-hydride elimination sequence takes place in **3a-1** and **3a-2**, driving the cascade cyclization to completion. The carbonyl moiety might coordinate to the alkyl–Pd^{II} species[12b,16d,17a,23] in **3a-2** in an intramolecular fashion, maintaining a staggered conformation. As a result, midway β-hydride elimination in **3a-2**, which requires the Pd–C_α and C_β–H bonds to be aligned in a *syn*-orientation,[24] would be suppressed.

Owing to the similar acidities of the N–H bond of **1a** and **1s**, the formation of intermediates **2s** and **3s** should be quite similar to that of **2a** and **3a**, that is, a rapid N–H deprotonation and a slow *syn*-amidopalladation process (Scheme 9).

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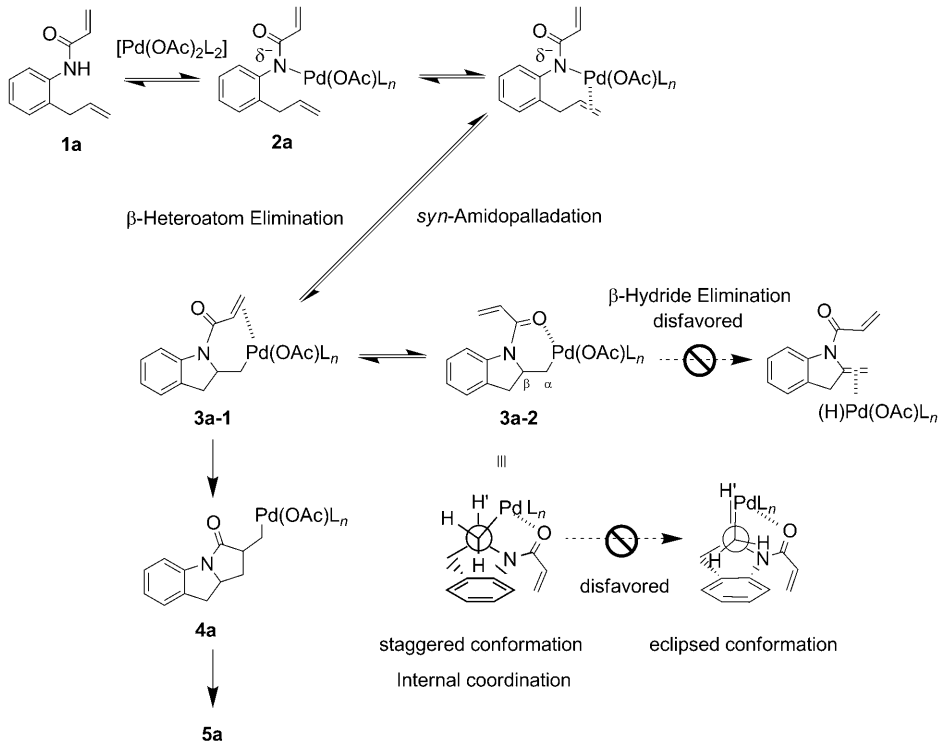
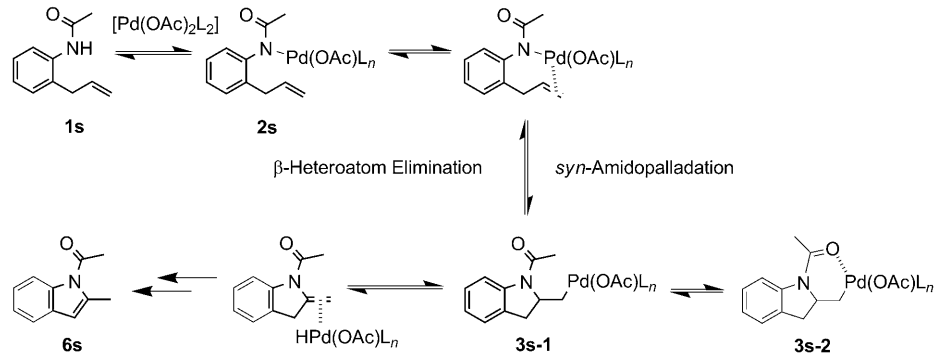


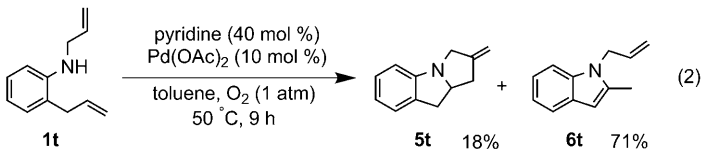
Scheme 8. Mechanistic pathways of the cascade cyclization of **1a**.



Scheme 9. Mechanistic pathways of the cascade cyclization of **1s**.

As **3s** does not possess an acryl olefinic unit for subsequent insertion, it readily reverts back to **2s** through β-heteroatom elimination. Indeed, the conversion of **1s** to **6s** was inefficient at 50 °C but it could be improved at elevated temperatures,[20] which implies that β-hydride elimination of **3s** could not compete efficiently with β-heteroatom elimination at lower temperature.

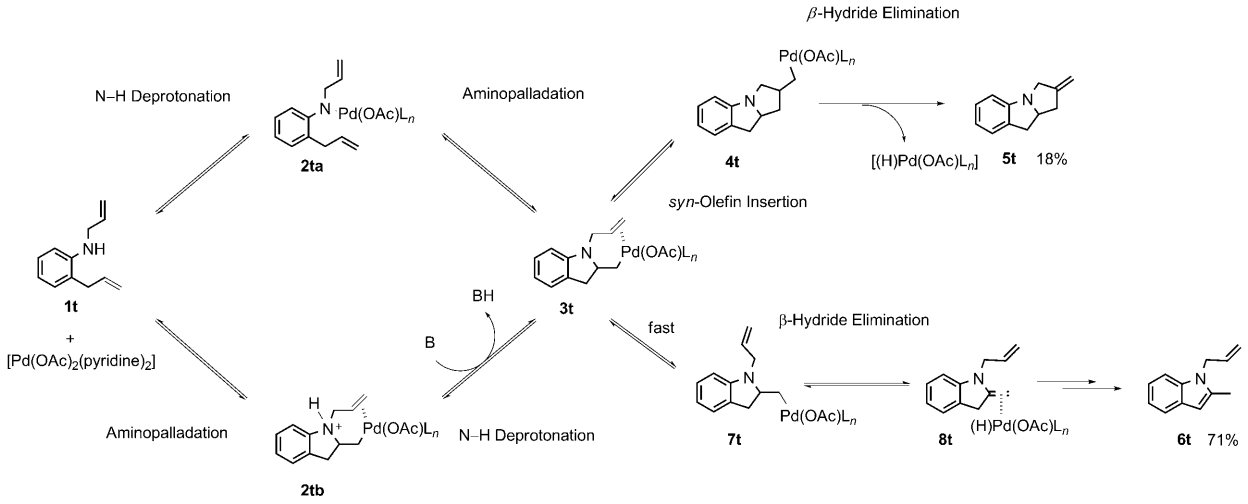
In contrast to the cyclization of **1a**, *N*-allylaniline **1t** was cyclized [Eq. (2)] to afford a mixture of cascade cyclization product (**5t**, 18%) and monocyclization product (**6t**, 71%). In addition, the cyclization of **1t** proceeded faster (9 h) than that of anilide **1a** (19 h; Table 1, entry 1) under identical reaction conditions. It was postulated that monocyclization product **6t** and cascade cyclization product **5t** were formed through β-hydride elimination and intramolecular olefin insertion, respectively, from σ-alkylpalladium intermediate **3t**, which was generated from the first 5-*exo*-trig cyclization of aniline **1t** (Scheme 10). Owing to its greater basicity, N–H deprotonation of **1t** to furnish **2ta** would be more difficult than that of **1a**. In addition, anilines are more nucleophilic than anilides, thereby making aminopalladation of **1t** to afford **2tb** more efficient than that of **1a**. Therefore, the possibility of **1t** converting into **3t** through an aminopalladation/N–H deprotonation pathway could not be excluded.



(2)

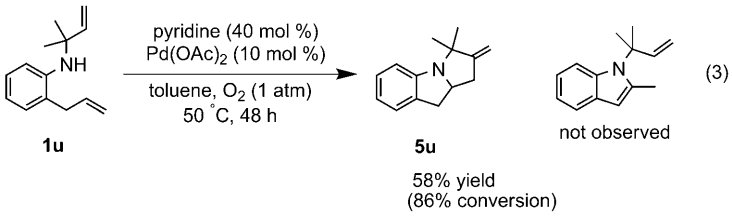
The fate of **3t** may not be restricted to β-heteroatom elimination (the reverse of aminopalladation) and intramolecular olefin insertion, which eventually yields the cascade cyclization product **5t** upon β-hydride elimination from **4t**. Instead, β-hydride elimination of **3t** could be an alternative competing process for two reasons. Firstly, the π-coordination between the *N*-allyl unit and the palladium center in **3t** could be readily disrupted through the rapid and unrestricted N–C single-bond rotation to give intermediate **7t**, from which β-hydride elimination took place readily to give **6t**.[25] Secondly, because aniline **1t** possesses a more basic nitrogen-centered nucleophile than anilide **1a** does, β-heteroatom elimination of **3t** would proceed significantly slower than both intramolecular olefin insertion and, in particular, the β-hydride elimination processes; in other words, β-heteroatom elimination of **3t** would be inefficient to serve as a "scavenging process" as is the case for **3a**. Therefore, cyclization reaction of **1t** yielded a mixture of cascade cyclization product **5t** and monocyclization product **6t**.

To improve the cyclization selectivity on aniline-type substrates, one solution is to avoid midway β-hydride elimina-



Scheme 10. Mechanistic pathways of the cascade cyclization of **1t**.

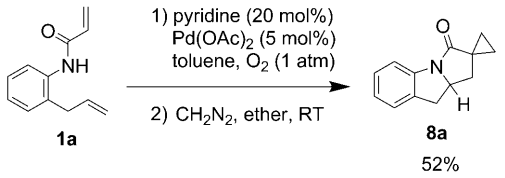
tion of intermediate **3**. To this end, increasing the rotational barrier about the N–C_α bond might serve this purpose. To test this hypothesis, *N*-allylaniline **1u** possessing a *gem*-dimethyl moiety at the *N*-allylic position was prepared. Interestingly, cyclization of aniline **1u** gave **5u** as the exclusive cyclization product (58% yield; 86% conversion), whereas the corresponding monocyclization product was not formed [Eq. (3)]. The result is different from the cyclization of **1t**.



(3)

As both **1t** and **1u** are *N*-alkyl anilines, β-heteroatom eliminations of the corresponding intermediates **3t** and **3u** are expected to be inefficient (Scheme 11). The presence of a *gem*-dimethyl group[26] in aniline **1u** should increase the rotational barrier of the N–C bond and, thus, enhance the internal coordination between the olefinic group and the palladium center in intermediates **3ua** and **3ub**, leading to the formation of the cascade cyclization product **5u**. In contrast, the intermediate **3uc** is disfavored because of severe steric repulsion between the *gem*-dimethyl substituents and the σ-alkylpalladium moiety.

Indoline **5a** is capable of undergoing further transformations. Under hydrogenation conditions, diastereoselective reduction took place to establish two stereogenic centers in **7a** (Scheme 12). On the other hand, $Pd(OAc)_2$-cyclopropanation of electron-deficient olefins with diazomethane furnished **8a** in 81% yield. Notably, oxidative cascade cyclization of **5a** and cyclopropanation gave **8a** in 52% yield under one-pot conditions [Eq. (4)].



(4)

Conclusions

In summary, we demonstrated herein the palladium(II)-catalyzed oxidative cascade cyclization of unsaturated anilides as an efficient synthetic method to construct nitrogen heterocycles. The methodology involves the sequential formation of C–N and C–C bonds by using $Pd(OAc)_2$/pyridine as the catalyst system and molecular oxygen (1 atm.) as a green oxidant. Studies of electronic effects, rate-determining step of cascade cyclization, stereochemical modes of amidopalladation, and selectivities of cascade cyclization products gave useful insights into the reaction mechanism. On the basis of kinetic studies (Hammett relationship), we propose a mechanistic pathway that consists of a rapid N–H deprotonation followed by slow amidopalladation to form an *N*-palladium–anilide intermediate. In addition, the oxidative cascade cyclizations of specific prochiral substrates proceed in a stereoselective manner with the establishment of two defined stereogenic centers. The stereochemical outcomes suggest a *syn*-amidopalladation pathway.

Furthermore, we propose that the exclusive formation of cascade cyclization products from acrylanilides is due to the reversible nature of the amidopalladation process. The β-heteroatom elimination (the reverse process of amidopalla-

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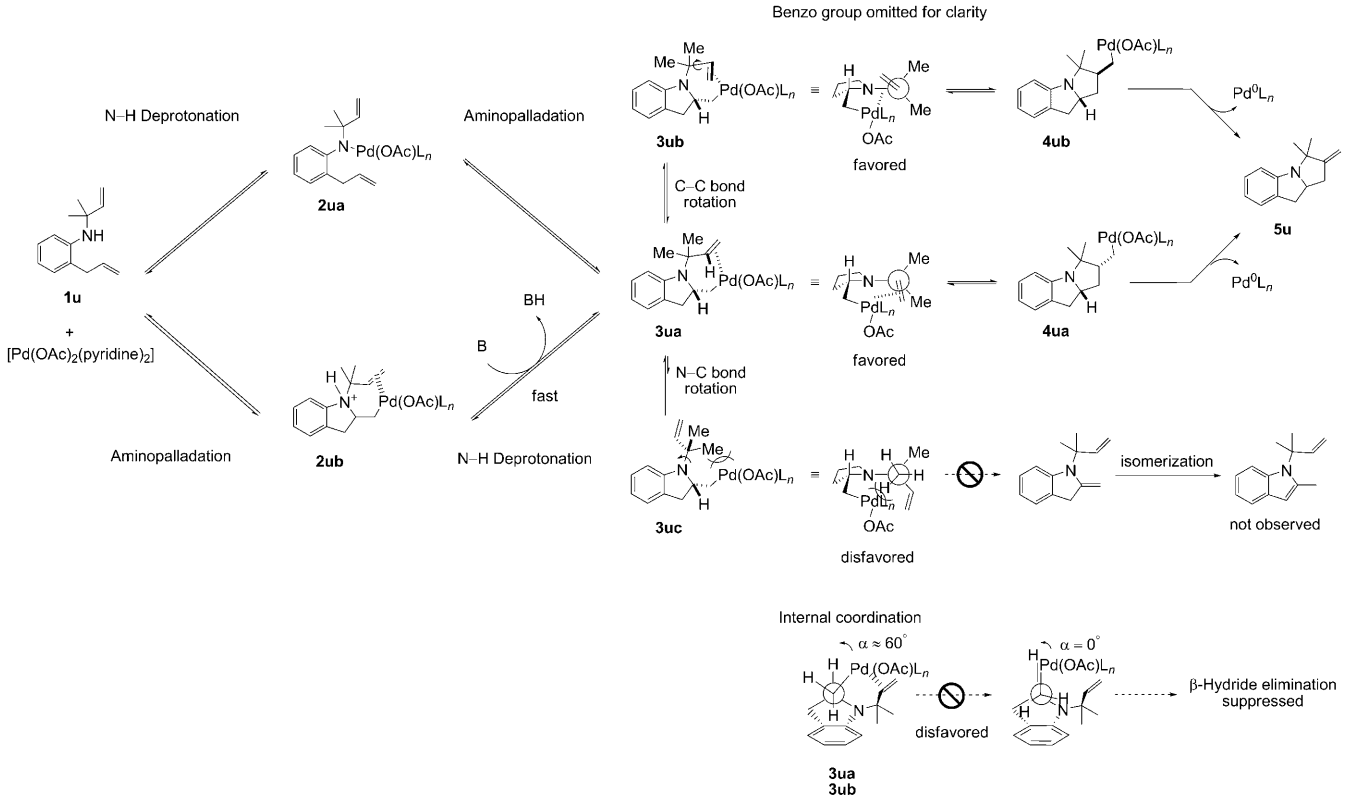
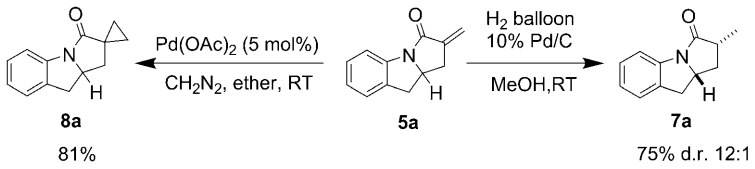


Scheme 11. Mechanistic pathways of the cascade cyclization of **1u**.



Scheme 12. Synthetic transformation of cascade cyclization product **5a**.

dation) of β-amidopalladium intermediate **3** serves as a "scavenging process" to prevent the undesired β-hydride elimination. This finding exemplifies the potential synthetic importance (serving as tandem relay in our case) of β-heteroatom elimination from β-amidopalladium intermediates. Meanwhile, we have extended the substrate scope of the oxidative cascade cyclization to *N*-allylaniline. These studies have prompted us to develop new C–N bond-forming cyclization strategies to synthesize structurally versatile and biologically important N-heterocycles.

Experimental Section

General Methods

All reactions were performed in oven-dried flasks. Palladium(II) acetate was purchased from Aldrich and was used as received. All other commercially available chemicals were used as received. Toluene was distilled over calcium hydride and stored over activated 4 Å molecular sieves (beads). Reactions were monitored by TLC using E. Merck silica gel 60 precoated glass plates with 0.25 mm thickness. Components were visualized by illumination with a short-wavelength ultraviolet light and/or staining in phosphomolybdic acid (PMA) solution followed by heating. Flash column chromatography was performed on E. Merck silica gel 60 (230–400 mesh ASTM) by using ethyl acetate/n-hexane as eluting solvents.

^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard at ambient temperature, unless otherwise indicated, on a Bruker Avance DPX 300 Fourier Transform Spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C NMR, or a Bruker Avance DPX 400 Fourier Transform Spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR. IR absorption spectra were recorded as a solution in CH_2Cl_2 with a Bio-Rad FTS 165 Fourier Transform spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low and high resolution mass spectra. Melting points were determined by Axiolab ZEISS microscope apparatus and were uncorrected.

Typical procedure for Pd^{II}-catalyzed oxidative cascade cyclizations (Table 1, entry 1)

In a 5 mL round-bottomed flask equipped with a magnetic stirrer bar, $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) was dissolved in dry toluene (2 mL) and the solution was stirred at room temperature. After 5 min (or until all the $Pd(OAc)_2$ was dissolved), pyridine (9.7 μL, 0.12 mmol) was added to the mixture by microsyringe. After 15 min, substrate **1a** (0.3 mmol) in toluene (1 mL) was transferred to the solution mixture containing palla-

dium complexes. The reaction flask was assembled with an air condenser, sealed with a rubber septum, connected to an oxygen atmosphere, and heated to 50 °C. After 19 h, the reaction mixture was cooled, filtered through a short pad of silica gel (EtOAc as eluent), and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc and n-hexane as eluents) to give **5a** in 95% yield.

*Product **5a***

White solid; m.p. 83–84 °C; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.30$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 7.7$ Hz, 1H), 7.25–7.17 (m, 2H), 7.04 (dt, $J = 7.5$, 0.9 Hz, 1H), 6.04 (dd, $J = 3.3$, 1.6 Hz, 1H), 5.40 (dd, $J = 2.8$, 1.3 Hz, 1H), 4.61–4.50 (m, 1H), 3.23–3.10 (m, 2H), 2.87 (dd, $J = 15.4$, 10.7 Hz, 1H), 2.75–2.65 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.5$, 143.9, 139.8, 134.2, 127.9, 125.5, 124.9, 117.4, 115.2, 60.2, 36.3, 34.2 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3055$, 2987, 2915, 1693, 1658, 1606, 1484, 1442 cm^{-1}; LRMS (EI, 20 eV): m/z: 185 (100) $[M]^+$; HRMS (EI): m/z: calcd for $C_{12}H_{11}NO$: 185.0841 $[M]^+$; found: 185.0844.

*Hydrogenation of **5a*** (Scheme 12)

A methanol solution (8 mL) of **5a** (149 mg, 0.8 mmol) was degassed with argon for 30 min. The reaction flask was evacuated and refilled with argon three times. After the addition of 10% Pd/C (149 mg), the flask was evacuated and refilled with a H_2 balloon three times. The reaction mixture was stirred at room temperature for 14 h. The solution was filtered through a short pad of Celite (Et_2O as eluent) and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc and *n*-hexane as eluents) to afford **7a** and its minor diastereomer in 75% total yield.

*Product **7a***

White solid; m.p. 77–78 °C; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.46$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 7.8$ Hz, 1H), 7.23–7.17 (m, 2H), 7.02 (dt, $J = 7.5$, 0.8 Hz, 1H), 4.54–4.47 (m, 1H), 3.18 (dd, $J = 15.7$, 8.5 Hz, 1H), 2.95–2.83 (m, 2H), 2.68–2.63 (m, 1H), 1.65–1.58 (m, 1H), 1.25 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.2$, 139.4, 134.0, 127.7, 125.3, 124.0, 114.8, 60.2, 41.9, 38.8, 35.8, 15.1 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3055$, 2986, 2932, 1694, 1605, 1486, 1405 cm^{-1}; LRMS (EI, 20 eV): m/z: 187 (59) $[M]^+$, 118 (100); HRMS (EI): m/z: calcd for $C_{12}H_{13}NO$: 187.0997 $[M]^+$; found: 187.0993.

Minor diastereomer

White solid; m.p. 125–126 °C; analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.31$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.8$ Hz, 1H), 7.23–7.17 (m, 2H), 7.03 (dt, $J = 7.5$, 1.0 Hz, 1H), 4.78–4.71 (m, 1H), 3.17 (dd, $J = 15.5$, 8.4 Hz, 1H), 2.90–2.80 (m, 2H), 2.22–2.13 (m, 2H), 1.39 ppm (d, $J = 7.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 175.0, 139.3, 134.4, 127.7, 125.2, 124.2, 115.0, 61.0, 43.0, 36.4, 36.0, 16.5 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3055$, 2987, 1691, 1604, 1486, 1407 cm^{-1}; LRMS (EI, 20 eV): m/z: 187 (59) $[M]^+$, 118 (100); HRMS (EI): m/z: calcd for $C_{12}H_{13}NO$: 187.0997 $[M]^+$; found: 187.1000.

*Cyclization/cyclopropanation of **1a** under one-pot conditions [Eq. (4)]*

In a 10 mL round-bottomed flask equipped with a magnetic stirrer bar, a mixture of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and pyridine (4.8 μL, 0.06 mmol) in dry toluene (3 mL) was stirred at room temperature. After 30 min (or until all $Pd(OAc)_2$ was dissolved), substrate **1a** (56.0 mg, 0.3 mmol) was added. The reaction flask was assembled with an air condenser, sealed with a rubber septum, connected to an oxygen atmosphere, and heated to 50 °C. After reaction completion was shown by TLC analysis, the reaction mixture was cooled to room temperature and bubbled with argon for 10 min.

An ethereal solution (~3 mL) of diazomethane was slowly added by a glass dropper to the resulting solution. After 14 h, the diethyl ether was evaporated with a flow of compressed air (inside a well-ventilated fumehood). The toluene solution was filtered through a short pad of silica gel (EtOAc as eluent) and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc and n-hexane as eluents) to give **8a** in 52% yield (from **1a**).

*Product **8a***

Pink solid; m.p. 96–97 °C; analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.44$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.7$ Hz, 1H), 7.24–7.19 (m, 2H), 7.02 (dt, $J = 7.5$, 0.9 Hz, 1H), 4.75–4.69 (m, 1H), 3.21 (dd, $J = 15.5$, 8.4 Hz, 1H), 2.90 (dd, $J = 15.5$, 10.5 Hz, 1H), 2.35 (dd, $J = 12.4$, 9.4 Hz, 1H), 2.20 (dd, $J = 12.4$, 7.0 Hz, 1H), 1.39–1.32 (m, 1H), 1.14–1.07 (m, 1H), 1.00–0.93 (m, 1H), 0.74–0.68 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.7$, 140.1, 134.2, 128.0, 125.5, 124.2, 114.8, 60.3, 37.1, 36.5, 27.5, 15.8, 11.1 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3055$, 2988, 1693, 1486, 1422 cm^{-1}; LRMS (EI, 20 eV): m/z: 199 (100) $[M]^+$; HRMS (EI): m/z: calcd for $C_{13}H_{13}NO$: 199.0997 $[M]^+$; found: 199.0996.

Acknowledgements

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