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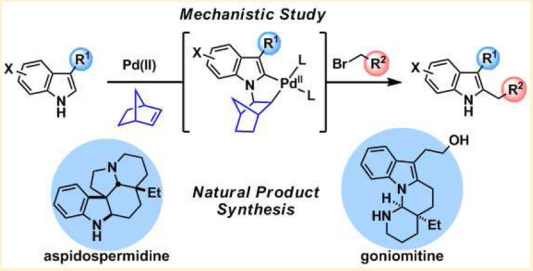
Pd(II)-Catalyzed Regioselective 2-Alkylation of Indoles via a Norbornene-Mediated C−H Activation: Mechanism and Applications

Lei Jiao, Eberhardt Herdtweck, and Thorsten Bach*

Lehrstuhl für Organische Chemie I and Catalysis Research Center (CRC), Technische Universität München, Lichtenbergstrasse 4, 85747 Garching, Germany

Supporting Information

ABSTRACT: A palladium-catalyzed direct 2-alkylation reaction of free *N*-H indoles was developed based on a norbornene-mediated regioselective cascade C−H activation. The detailed reaction mechanism was investigated by NMR spectroscopic analyses, characterization of the key intermediate, deuterium labeling experiments, and kinetic studies. The results indicate that a catalytic cycle operates, in which an *N*-norbornene type palladacycle is formed as the key intermediate. Oxidative addition of alkyl bromide to the Pd(II) center in this intermediate is the rate-determining step of the reaction. The synthetic utility of this indole 2-alkylation method was demonstrated by its application in natural product total synthesis. A new and general strategy to synthesize *Aspidosperma* alkaloids was established employing the indole 2-alkylation reaction as the key step, and two structurally different *Aspidosperma* alkaloids, aspidospermidine and goniomitine, were synthesized in concise routes.

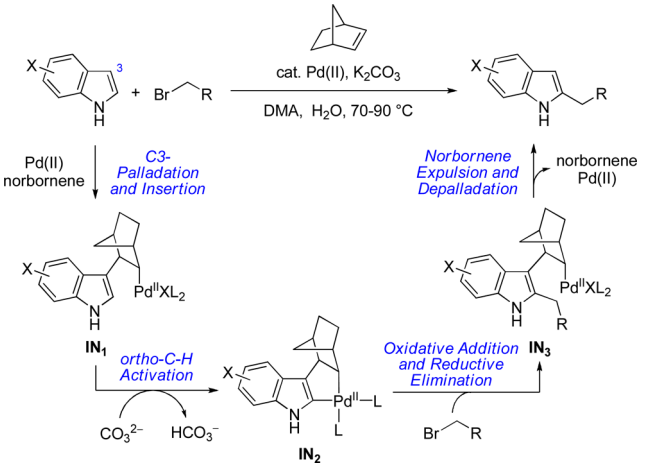


INTRODUCTION

The direct C−H functionalization of heterocycles has attracted increasing research interest due to the structural prevalence of substituted heterocycles in natural products, drugs, and other biologically active molecules.[1] As a consequence, many elegant methods to regioselectively substitute a heteroaromatic C−H bond by an aryl or alkenyl group have been established by employing transition-metal catalysis.[2] However, protocols for the alkylation of a heteroaromatic C−H bond are still limited to date.[3] Therefore, the development of direct C−H alkylation methods for heterocycles, especially of those which exert regioselectivities different from the simple Friedel−Crafts alkylation, is still highly demanded.

As a step toward this goal, we have recently developed a palladium-catalyzed direct 2-alkylation reaction of free *N*-H indoles by invoking a norbornene-mediated cascade C−H activation (Scheme 1).[4] In the presence of a Pd(II) catalyst, norbornene, and a base, an indole substrate reacts with a primary alkyl bromide to form a 2-alkyl substituted indole product regioselectively. The transformation tolerates a wide variety of functional groups on both components. Both electron rich and electron deficient indoles have been shown to be suitable substrates. *N*,*N*-Dimethylacetamide (DMA) has evolved as the optimal solvent and the addition of water has a positive effect on the reaction outcome. Various Pd(II) catalysts, such as $Pd(OAc)_2$ and $PdCl_2(MeCN)_2$, have shown similar catalytic activity in this reaction and no additional ligand is required. This reaction provides a straightforward route to 2-alkylated indole derivatives starting from simple substrates under mild and practical conditions.

Scheme 1. Palladium-Catalyzed Direct 2-Alkylation of Indole and Originally Proposed Reaction Mechanism



The 2-alkylation process was originally assumed to proceed according to the mechanism shown in the lower part of Scheme 1.[4] It was speculated that the reaction is initiated by the well-established C3-palladation of indole[5] and that a subsequent insertion of norbornene into the C3—Pd bond occurs to form intermediate $\mathbf{IN_1}$. As discovered by Catellani and co-workers,[6,7] the Pd(II) center was thought to activate under basic conditions the proximal C2—H bond by electrophilic palladation to transform intermediate $\mathbf{IN_1}$ to a C3-norbornene

Received: June 15, 2012
Published: August 22, 2012

dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

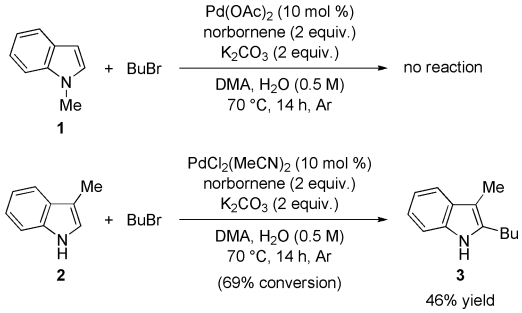
type palladacycle $\mathbf{IN_2}$, which after alkylation produces via 2-alkyl-3-indolylpalladium species $\mathbf{IN_3}$ the observed 2-alkylindole product together with the Pd(II) catalyst. The combination of the indole-palladium chemistry and the Catellani reaction allows for a successful cascade C−H activation cycle that regioselectively alkylates the less reactive C2 position of indole.

As an extension of this work, we sought to further study the detailed reaction mechanism of the Pd(II)-catalyzed direct 2-alkylation of indole. Our research along these lines led to the conclusion that the reaction does not follow the above-mentioned proposed mechanism. Rather our studies suggest a reaction mechanism, in which an *N*-norbornene type palladacycle, but not a C3-norbornene type palladacycle $\mathbf{IN_2}$, acts as the key intermediate. Therefore, a revised catalytic cycle is presented and the rate-determining step in the cycle was assigned by kinetic studies. In addition to the mechanistic investigations, we have exploited the synthetic utility of the indole 2-alkylation reaction by applying it to natural product total synthesis. Two indole alkaloids, goniomitine and aspidospermidine, were synthesized using the present reaction as key step. A new and concise strategy for the synthesis of *Aspidosperma* alkaloids has thus been established.

MECHANISTIC STUDIES

Motivation for the Mechanistic Study. To further explore the substrate compatibility of the indole alkylation reaction, we tested the reaction of *N*-methylindole (**1**) and 3-methylindole (**2**) with *n*-BuBr under the standard reaction conditions. It was found that *N*-methylindole failed to give any 2-alkylation product and remained intact after 14 h. In stark contrast, 3-methylindole exhibited unexpected reactivity under identical conditions and produced the 2-alkylation product **3** in a moderate yield (Scheme 2). Control experiment showed that this reaction did not proceed in the absence of norbornene.

Scheme 2. Reactions of *N*- and 3-Methylindole



The previously proposed reaction mechanism (Scheme 1) could not account for the experimental observations. According to the proposed mechanism, the N−H bond of indole is not involved in the reaction; thus, it is expected that **1** undergoes the same alkylation reaction as free *N*-H indole. On the other hand, the proposed mechanism requires C3-palladation of indole as the initiation step, which is incompatible with a 3-substituted indole. The successful alkylation of **2** contradicted this mechanistic interpretation. These results questioned the proposed catalytic cycle and prompted us to conduct detailed mechanistic studies on this reaction.

NMR Spectroscopic Study. The reactions employing indoles **1** and **2** suggested that the indole alkylation does not proceed via intermediates arising from a C3-palladation/norbornene insertion. To identify possible intermediate(s) involved in the catalytic process, NMR spectroscopic studies of the reaction mixture were conducted. The model 2-alkylation reaction of indole with BuBr was investigated. To simplify the reaction system for NMR analysis, an initial reaction was performed without addition of the alkylating reagent. A mixture of $PdCl_2(MeCN)_2$, indole, norbornene, KBr,[8] and K_2CO_3 in DMA with 0.5 M H_2O was allowed to react at 70 °C for 1 h. The resulting reaction mixture, after filtration, was directly subjected to ^{1}H NMR analysis. It was found that a new set of indole-based aromatic signals were generated (Figure 1a,b, red

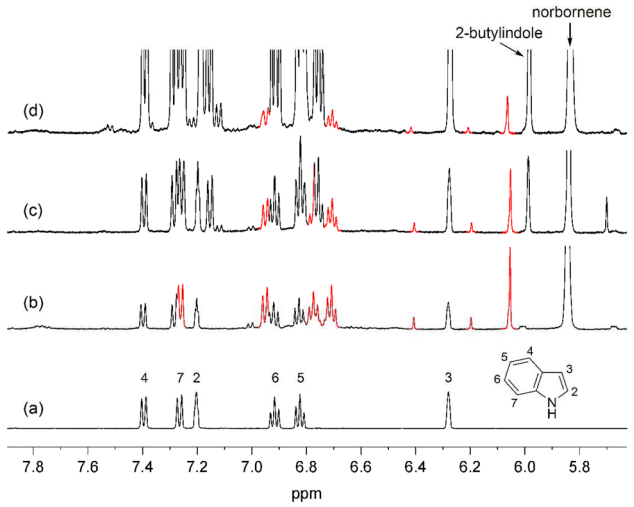


Figure 1. 500 MHz ^{1}H NMR spectra at room temperature in DMA with 0.5 M H_2O. Red peaks refer to the newly generated species in the reaction system. Conditions: (a) indole; (b) indole (0.053 M), $PdCl_2(MeCN)_2$ (0.057 M), norbornene (0.40 M), KBr (0.054 M), and K_2CO_3 (0.41 mmol·mL^{-1}) after 1 h at 70 °C; (c) indole (0.11 M), $PdCl_2(MeCN)_2$ (0.042 M), norbornene (0.19 M), BuBr (0.23 M), and K_2CO_3 (0.39 mmol·mL^{-1}) after 50 min at 70 °C; (d) indole (0.20 M), $PdCl_2(MeCN)_2$ (0.024 M), norbornene (0.41 M), BuBr (0.47 M), and K_2CO_3 (0.40 mmol·mL^{-1}) after 1.5 h at 70 °C.

signals). The new signals included four benzene C−H signals and the C3−H signal at 6.05 ppm, but signals corresponding to *N*-H and C2−H were lacking. New aliphatic peaks with similar intensity also emerged (not shown in the spectrum).

Subsequently, a crude ^{1}H NMR spectrum of the alkylation reaction mixture in the presence of BuBr was recorded (Figure 1c). To ensure a sufficient intensity of the intermediate peaks, 40 mol % of $PdCl_2(MeCN)_2$ catalyst was used. The spectrum showed the existence of the same intermediate, which was the major intermediate species during the alkylation reaction. Finally, ^{1}H NMR analysis of the crude reaction mixture with a normal catalyst loading (12 mol %) showed the same intermediate peaks (Figure 1d) albeit with lower intensity.

The NMR analyses seemed to indicate that indole, norbornene, and the palladium catalyst form a primary intermediate without participation of the alkylating reagent (Figure 1b). This intermediate appears to be the major intermediate throughout the reaction (Figure 1c,d) and seems to play a role in the following alkylation steps. The NMR spectra suggested that the intermediate was a norbornene-embedded C2-palladation product (due to the absence of the C2−H signal and appearance of new aliphatic signals) different from the previously proposed intermediate $\mathbf{IN_2}$ (due to the absence of the *N*-H signal and the presence of the C3−H

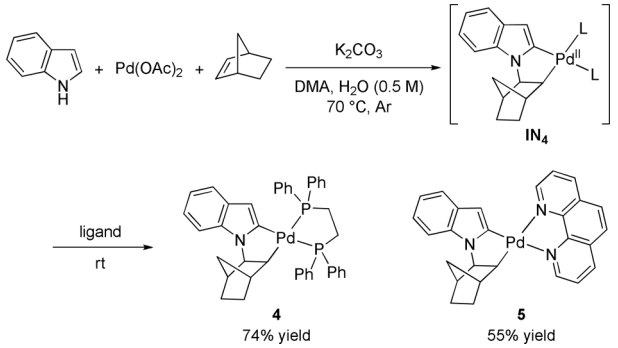
dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

signal). Further efforts to separate and characterize this intermediate were undertaken to elucidate its structure.

Separation and Characterization of the Key Palladacycle Intermediate. Although the primary intermediate could be directly observed by NMR, attempts to characterize it in pure form were unsuccessful due to purification problems. After an aqueous workup procedure and removal of the solvent, a dark-brown solid was obtained, which proved to be a complex mixture by NMR analysis. Attempts to purify this product by recrystallization or column chromatography failed. It seemed that the observed intermediate aggregated during the workup procedure, possibly due to weak ligands on the palladium center (MeCN, DMA, H_2O, etc.). To solve this problem, we tried to apply a bidentate ligand to form a stable and separable monomeric complex.

It was found that, after the reaction of indole, norbornene, and $Pd(OAc)_2$, upon addition of 1,2-bis(diphenylphosphino)-ethane (dppe) or 1,10-phenanthroline, new complexes **4** and **5** formed cleanly. These complexes were obtained in pure form after column chromatography (Scheme 3) and could be

Scheme 3. Synthesis of Palladacycle Complexes



analytically characterized. Two-dimensional NMR spectra and HRMS analyses established the palladacycle structure of the two complexes, in which the indole nitrogen atom is bound to the norbornene moiety and the C3 carbon atom remains unsubstituted. This structure assignment was unambiguously confirmed by an X-ray single crystal structure of the 1,10-phenanthroline complex **5**[9] (Figure 2). On the basis of these observations, the intermediate species observed by NMR was tentatively assigned structure $\mathbf{IN_4}$. The structure is in agreement with the recorded ^{1}H NMR spectrum, in which a C3−H signal was observed but *N*-H and C2−H signals could not be detected (Figure 1).

The results, together with the NMR spectroscopic studies, indicated that the *N*-norbornene type palladacycle $\mathbf{IN_4}$, rather than the previously proposed C3-norbornene type palladacycle $\mathbf{IN_2}$, was the major palladium species during the catalytic process. This *N*-norbornene type palladacycle is assumed to be generated by a cascade C−H activation process involving *syn*-aminopalladation of norbornene and subsequent *ortho*-C−H activation.

If the *in situ* generated palladacycle $\mathbf{IN_4}$ was treated with BuBr instead of a bidentate ligand at 70 °C, 2-butylindole was generated in 53% yield within 0.5 h. This result together with the results presented in Scheme 2 support a reaction mechanism, in which $\mathbf{IN_4}$ acts as the key active palladacycle intermediate in the 2-alkylation process. It was assumed that $\mathbf{IN_4}$ reacts with alkyl bromide via oxidative addition, reductive

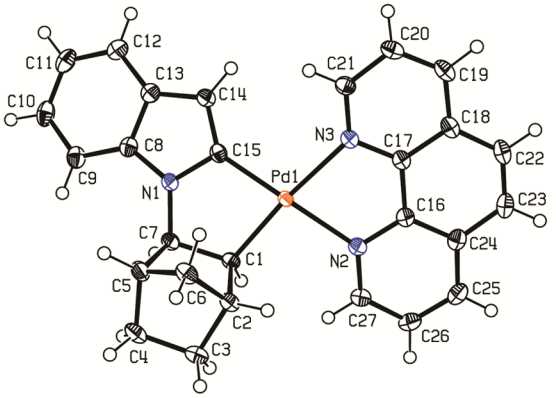
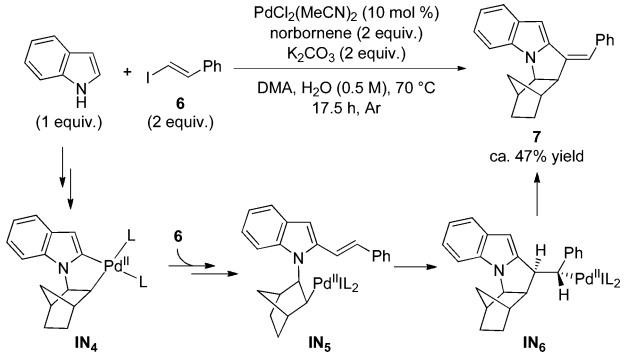


Figure 2. ORTEP style plot of compound **5**·$CDCl_3$ in the solid state. Thermal ellipsoids are drawn at the 50% probability level. $CDCl_3$ is omitted for clarity. Selected bond lengths (Å) and bond angles (°): Pd1−N2 2.1239(13), Pd1−N3 2.1471(13), Pd1−C1 2.0392(16), Pd1−C15 1.9774(15); N2−Pd1−N3 78.47(5), C1−Pd1−C15 82.60(6).

elimination, and subsequent steps to furnish the 2-alkylindole product, which are similar to the steps in the Catallani reaction.[7] A palladacycle of the $\mathbf{IN_2}$ type was not observed and is probably not involved in the reaction.

Intramolecular Trapping of the Intermediate. Previously we found that the C(sp^2)−I bond in an aryl iodide could be employed to generate a 2-arylated indole derivative.[4] Much to our surprise, in a test reaction employing *β*-iodostryene (**6**) as the electrophile, a polycyclic indole derivative **7** with an embedded norbornene moiety was isolated (Scheme 4) instead of the expected 2-alkenylation product.

Scheme 4. Intramolecular Heck-Trapping Reaction



The product is believed to be formed by an intramolecular Heck-type reaction following a normal norbornene-mediated 2-alkenylation process. A plausible mechanism for its formation is depicted in Scheme 4. The conversion starts with the formation of palladacycle $\mathbf{IN_4}$. Subsequently, intermediate $\mathbf{IN_4}$ and iodoalkene **6** undergo oxidative addition and reductive elimination to form the 2-alkenylated species $\mathbf{IN_5}$. Because of the close proximity of the norbornene−Pd bond and the newly attached C=C bond, an intramolecular carbopalladation occurs to generate the pentacyclic palladium intermediate $\mathbf{IN_6}$. Subsequent *β*-hydride elimination leads to product **7**.

The formation of the intramolecular trapping product **7** provides additional evidence for the involvement of nitrogen-norbornene type intermediates in the catalytic process. The *N*-norbornene type palladium intermediates can be observed at an

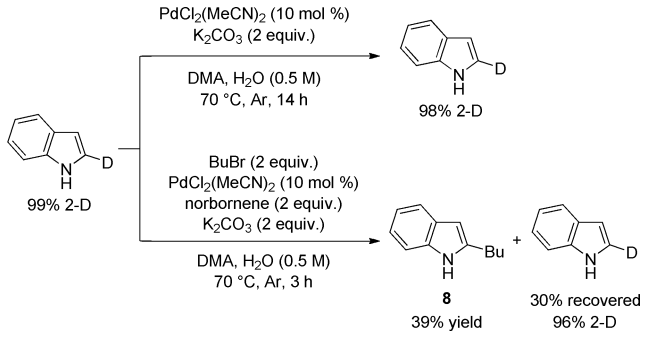
dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

early stage (i.e., before C2-functionalization) and trapped at a late stage of the reaction (i.e., after the C2-functionalization step), implying that this type of intermediates are involved throughout the catalytic cycle and play a key role in the reaction. Therefore, this result further supported that $\mathbf{IN_4}$ is the key palladacycle intermediate reacting with alkyl bromide to achieve the 2-alkylation on indole.

Deuterium Labeling Experiment. At this stage, further attention was paid to the key palladacycle intermediate $\mathbf{IN_4}$. A reaction employing 2-deuterated indole was conducted to probe the reversibility of the norbornene-mediated cascade C−H activation leading to $\mathbf{IN_4}$. If the formation of $\mathbf{IN_4}$ was involved in an equilibrium, the reverse reaction from $\mathbf{IN_4}$ to indole would decrease the C2-deuterium incorporation of the remaining indole substrate. Alternatively, an irreversible formation of $\mathbf{IN_4}$ would not decrease the percentage of C2-deuterium incorporation in the unconverted indole substrate.

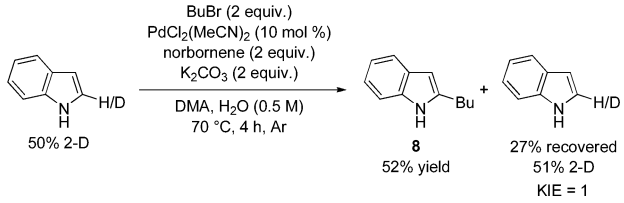
In a control experiment, treatment of 2-D-indole with a catalytic amount of $PdCl_2(MeCN)_2$ in DMA (0.5 M H_2O) at 70 °C in the presence of K_2CO_3 for 14 h did not result in loss of deuterium at carbon atom C2 of indole, indicating that there is no reversible direct C2-palladation of indole by the Pd(II) catalyst (Scheme 5). In a second experiment, the reaction of 2-D-indole with butyl bromide was conducted under standard conditions. The reaction was stopped after 3 h, when 39% of the 2-butylation product was generated at ca. 70% conversion (Scheme 5). The recovered indole substrate, as shown by ^{1}H NMR, had 96% 2-deuterium incorporation, indicating no loss of 2-deuterium within the limits of experimental error. This observation is consistent with an irreversible formation of palladacycle $\mathbf{IN_4}$ by an norbornene-mediated cascade C−H activation.

Scheme 5. Reactions of 2-Deuteroindole



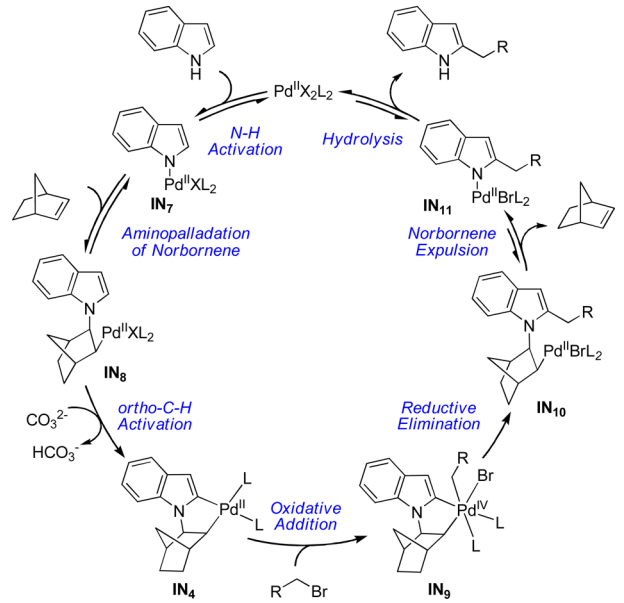
Kinetic Isotope Effect. By employing 2-deuteroindole as the substrate, the kinetic isotope effect (KIE) of the 2-alkylation reaction was measured to gain some insight into the cascade C−H activation step. Since deuterium labeling experiments proved the formation of palladacycle intermediate $\mathbf{IN_4}$ to be irreversible, a competition experiment using equal molar amounts of indole and 2-deuteroindole was expected to provide a potential primary KIE for the formation of palladacycle $\mathbf{IN_4}$ (Scheme 6). The k_H/k_D value was obtained by ^{1}H NMR analysis of unconverted indole starting material. It was found that the recovered indole showed a 51% 2-deuterium incorporation, indicating that almost no primary KIE was observed for this reaction. The lack of a primary KIE is consistent with a palladation mechanism, in which the C−H bond cleavage does not take place during the rate-determining step.[10] This is in agreement with the *ortho*-C−H activation step of the Catellani chemistry, in which the cleavage of the C−H bond is also not rate-determining.[7d]

Scheme 6. Competition Experiment for Determining a Primary KIE



A Revised Catalytic Cycle. Taking the results of the above mechanistic studies together, it is evident that the norbornene-mediated 2-alkylation of indole does not proceed via the originally proposed mechanism (Scheme 1), and a revised catalytic cycle can be drawn (Scheme 7). This catalytic cycle consists of two major stages: (1) irreversible formation of palladacycle $\mathbf{IN_4}$ by norbornene-mediated C−H activation and (2) reaction of $\mathbf{IN_4}$ and the alkyl bromide to complete the C2-alkylation of indole. Stage 1 is supported by the NMR spectroscopic study, by the synthesis and characterization of the palladacyclic complexes, and by the deuterium labeling experiments. The palladacycle intermediate $\mathbf{IN_4}$ is believed to be formed by *N*-palladation of indole (i.e., N−H activation of indole), *syn*-aminopalladation of norbornene, and *ortho*-C−H palladation via intermediates $\mathbf{IN_7}$ and $\mathbf{IN_8}$, respectively. Stage 2 of the mechanism is evidenced by the reaction of the *in situ* generated palladacycle $\mathbf{IN_4}$ with BuBr, the intramolecular trapping reaction (formation of **7**), and by the observed reactivity of 3-substituted indole in this 2-alkylation reaction. Similar to the Catellani reaction,[7d] the alkylation process is believed to take place through oxidative addition of the alkyl bromide to the Pd(II) center to generate Pd(IV) intermediate $\mathbf{IN_9}$, reductive elimination on the Pd(IV) center to form $\mathbf{IN_{10}}$, and norbornene expulsion to form 2-alkyl-*N*-palladaindole $\mathbf{IN_{11}}$. Hydrolysis of $\mathbf{IN_{11}}$ delivers the final 2-alkylindole product and regenerates the Pd(II) catalyst.

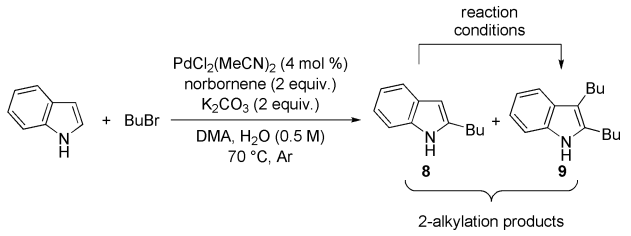
Scheme 7. Revised Catalytic Cycle



dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

Kinetic Studies. With the reasonable catalytic cycle in mind, we conducted kinetic studies on a model indole alkylation reaction (Scheme 8) to probe the concentration

Scheme 8. Model Reaction for Kinetic Studies



dependence of primary reaction components (indole, BuBr, norbornene, and palladium catalyst). It was hoped that kinetic studies would further support the mechanism and would also provide further insight into the nature of the proposed key intermediate $\mathbf{IN_4}$.

The progress of the model reaction was monitored by gas chromatography, and the obtained reaction time-course revealed monotonic increase in the concentrations of both product **8** and overalkylation byproduct **9**. The lack of an induction period enabled us to obtain kinetic parameters by the initial-rate method.[11] Since both product **8** and byproduct **9** were generated from the beginning and an independent reaction showed that **8** can be converted to **9** under the reaction conditions,[12] we took the total concentration of **8** and **9** as product concentration. The plot of ([**8**] + [**9**]) versus time showed a linear relationship during the initial period and the initial rate of the 2-alkylation was derived from the slope of this line.

Concentration Dependence of the Initial Rate on Each Reaction Component. The order of each component employed in the alkylation reaction was determined by the initial-rate method. Since the reaction is heterogeneous (K_2CO_3 is only slightly soluble in the reaction media), we first measured the initial rates of the model reaction with different amounts of K_2CO_3 (0.2−0.6 mmol/mL reaction volume, i.e., 1−3 equiv. versus indole). It was found that the initial rate did not change as a function of the K_2CO_3 loading, indicating that the phase transfer of base is not rate-determining (see Supporting Information for details). This allowed us to gain useful mechanistic information from the rate-dependence measurements.

The dependence of the alkylation rate on [indole] was found to be of negative order, indicating that indole has an inhibition effect on the reaction (Figure 3). The nonlinear dependence fits to an equation describing off-cycle binding interaction between indole and the active palladium species (vide infra).

The dependence of the initial rate on the concentration of both [BuBr] and $[PdCl_2(MeCN)_2]$ was found to be first-order (Figures 4 and 5). However, the rate dependence on [Pd] deviates from first-order at higher [Pd] (16−24 mM, the order of [Pd] was found to be ca. 0.5).[13] The dependence of the alkylation rate on [norbornene] was found to be zero-order (Figure 6).

The above-mentioned kinetic results support a rate-determining step in which both the Pd catalyst and alkyl bromide are involved and they rule out the C−H activation as the rate-determining step. Given the revised catalytic cycle proposed in Scheme 7, it is clear that the rate-determining step

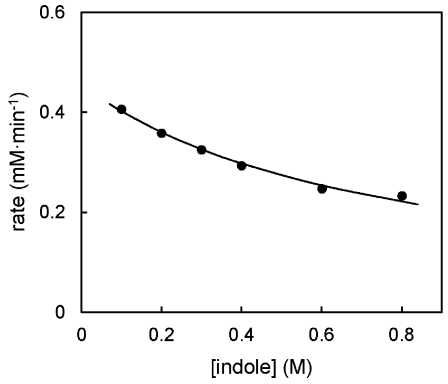


Figure 3. Initial rate as a function of [indole]. Conditions: [indole] = 0.1−0.8 M, $[PdCl_2(MeCN)_2]$ = 8.0 mM, [BuBr] = 0.40 M, [norbornene] = 0.40 M, K_2CO_3 0.40 mmol·mL^{-1}, DMA with 0.5 M H_2O, 70 °C.

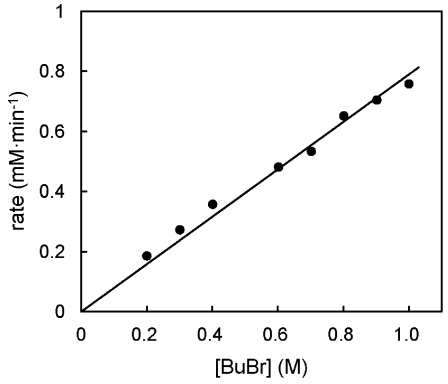


Figure 4. Initial rate as a function of [BuBr]. Conditions: [BuBr] = 0.2−1 M, $[PdCl_2(MeCN)_2]$ = 8.0 mM, [indole] = 0.20 M, [norbornene] = 0.40 M, K_2CO_3 0.40 mmol·mL^{-1}, DMA with 0.5 M H_2O, 70 °C.

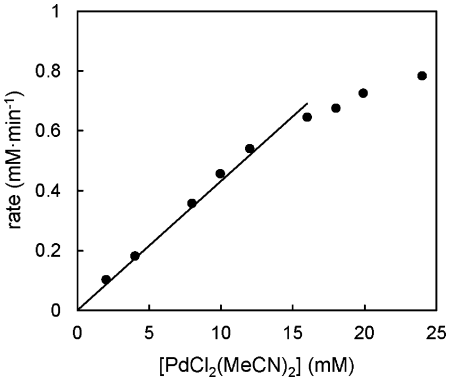


Figure 5. Initial rate as a function of [Pd]. Conditions: $[PdCl_2(MeCN)_2]$ = 2−24 mM, [indole] = 0.20 M, [BuBr] = 0.40 M, [norbornene] = 0.40 M, K_2CO_3 0.40 mmol·mL^{-1}, DMA with 0.5 M H_2O, 70 °C.

is not the formation of $\mathbf{IN_4}$, but the reactions involving $\mathbf{IN_4}$ and the alkyl bromide (oxidative addition or reductive elimination). Although the present kinetic data do not provide direct evidence to support either step as rate-determining, the oxidative addition of $\mathbf{IN_4}$ is more likely to be rate-determining based on the following considerations: (1) it is generally accepted in organopalladium(IV) chemistry that the reductive elimination on a Pd(IV) center is facile;[14] (2) experiments

dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

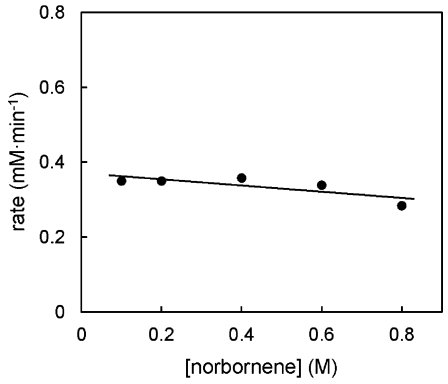


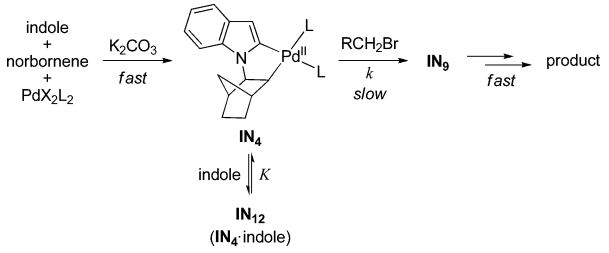
Figure 6. Initial rate as a function of [norbornene]. Conditions: [norbornene] = 0.1−0.8 M, $[PdCl_2(MeCN)_2]$ = 8.0 mM, [indole] = 0.20 M, [BuBr] = 0.40 M, K_2CO_3 0.40 mmol·mL^{-1}, DMA with 0.5 M H_2O, 70 °C.

showed that bulkier alkyl bromides (e.g., *iso*-butyl bromide) exhibit a decreased alkylation reactivity compared with *n*-butyl bromide,[4] which is consistent with a mechanism, in which oxidative addition is rate-determining and reductive elimination is not.

The intriguing initial-rate dependence on [indole] might be understood by considering indole as an inhibitory ligand. Negative dependence of a primary substrate in a catalytic reaction is uncommon, and this type of substrate inhibition often suggests off-cycle binding between the substrate and the catalytically active species that decreases the effective catalyst concentration within the cycle.[15]

In this reaction, it is reasonable to attribute the observed substrate inhibition to the off-cycle binding between $\mathbf{IN_4}$ and indole. A kinetic model can be tentatively established based on this assumption and on the revised catalytic cycle (Scheme 9).

Scheme 9. Kinetic Model of the Reaction



A rate law derived from this model accounts for the observed kinetic features of this reaction (eq 1),[16] and the nonlinear fit of the curve shown in Figure 4 gives a K value of 1.3 ± 0.1 M^{-1}. The small equilibrium constant suggests that indole acts as a weak inhibitory ligand in the alkylation reaction.

$$\text{rate} = k[\mathbf{IN_4}][RCH_2Br] = \frac{k[RCH_2Br][Pd]_{total}}{K[\text{indole}] + 1} \quad (1)$$

The decreased order of [Pd] at high catalyst concentration suggests the active Pd species may aggregate or decompose during the reaction, as observed in other Pd-catalyzed reactions.[17] However, at present it is not possible to give a clear picture of this process nor to quantify it.

To summarize the mechanistic section, a revised catalytic cycle for the direct indole 2-alkylation reaction was established with an emphasis on *N*-norbornene type intermediate $\mathbf{IN_4}$ as the key intermediate. A rate-determining oxidative addition of the alkyl bromide to the Pd(II) center in $\mathbf{IN_4}$ is suggested by kinetic studies. To the best of our knowledge, there has so far not been any clear evidence for a palladaheterocycle in Catellani-type alkylation reactions.[7,18] The present reaction represents a new reaction category among these reactions. As disclosed in the mechanistic study, the ability of the present catalytic system to achieve 2-alkylation on a 3-substituted indole greatly extends its synthetic power (Scheme 2). This feature enables a new access to 2,3-disubstituted indole derivatives and was applied to indole alkaloid synthesis.

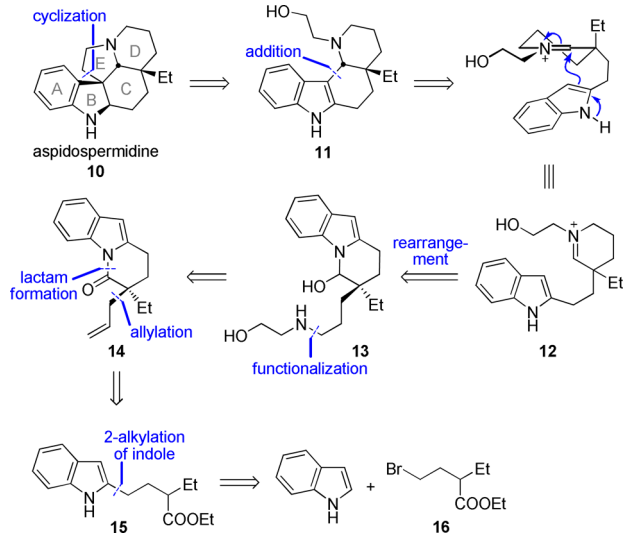
■ SYNTHETIC APPLICATIONS

Indole alkaloids compose an important class of natural products due to their unique structures and biological activities.[19] To date, tremendous efforts have been devoted to the total synthesis of indole alkaloids, and many elegant strategies have been developed to construct their core structure.[20] The direct 2-alkylation reaction of indoles enables a direct access to 2-alkylindole derivatives from indole and an alkyl bromide. Therefore, it was expected that a new and more straightforward synthetic strategy could be realized by applying this method to indole alkaloid synthesis.

Total Synthesis of Aspidospermidine. The *Aspidosperma* family is one of the largest groups of indole alkaloids.[21] As a representative member of this alkaloid family, aspidospermidine has attracted attention from the synthetic community since the 1960s[22] due to its unique pentacyclic skeleton with four contiguous stereocenters. To date, a number of successful synthetic routes have been established, and the general strategies to construct the multisubstituted dihydroindole core include Fischer indole synthesis,[22b,23c,f−h,24j,m−r] Pictet-Spengler reaction/rearrangement,[23a,b,i,24a] and intramolecular cyclization of an aniline-type intermediate.[23d,e,24c,h,k,l] With the indole 2-alkylation method in hand, we planned to develop an approach to this alkaloid family by a direct coupling of the indole core and the alkyl subunit.

Retrosynthetic analysis suggested that the AB rings of aspidospermidine can originate from indole (Scheme 10). For the construction of the CDE ring system, the E ring was planned to be created by base-induced cyclization of alcohol **11**

Scheme 10. Retrosynthetic Analysis of Aspidospermidine

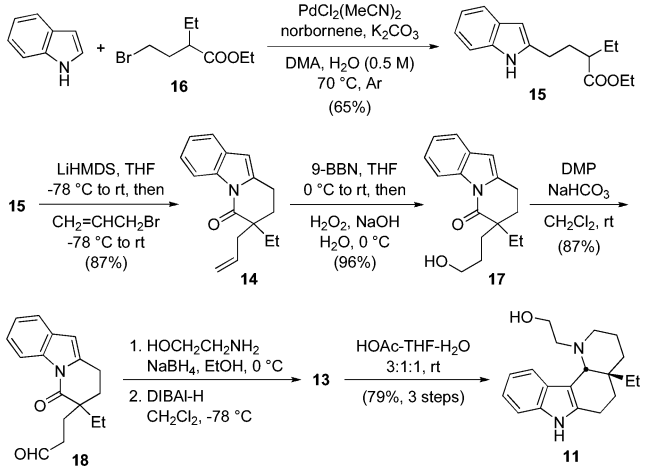


dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

after conversion of the hydroxyl group to a good leaving group.[23d,24e] Alcohol **11** was supposed to be obtained from hemiaminal **13** by an acid-catalyzed rearrangement via cyclic iminium ion **12**,[24e,25] with contemporary formation of the C and D rings. Hemiaminal **13** could be derived from α-allyl-δ-lactam **14** by functionalization of the C=C bond and reduction of the lactam carbonyl group. Finally, lactam **14** was planned to be synthesized by base-induced cyclization and α-allylation of indole derivative **15**, which can be easily prepared from indole and alkyl bromide **16**[26] by the indole 2-alkylation reaction.

The synthesis of aspidospermidine commenced with the 2-alkylation of indole with bromide **16** under standard conditions (Scheme 11). The 2-alkylindole product **15** was obtained in

Scheme 11. Synthesis of Key Aminoalcohol 11[a]

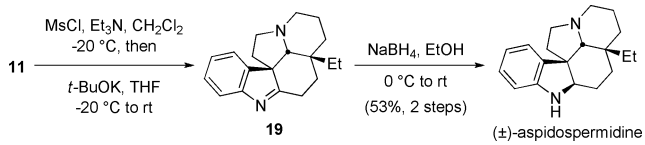


[a]9-BBN = 9-borabicyclo[3.3.1]nonane.

65% yield. Treatment of intermediate **15** with lithium hexamethyldisilazide (LiHMDS) and quenching the generated lactam enolate with allyl bromide afforded α-allyl-δ-lactam **14** in high yield. A hydroboration-oxidation sequence[27] of compound **14** gave alcohol **17**, which was oxidized to aldehyde **18** with Dess-Martin periodinane (DMP).[28] This aldehyde intermediate was transformed to the key aminoalcohol **11** by a three-step sequence. First, the 2-hydroxyethylamino group was installed by reductive amination of aldehyde **18** with ethanolamine and $NaBH_4$. Second, treatment with diisobutylaluminum hydride (DIBAl-H) at low temperature reduced the lactam carbonyl group to give hemiaminal **13**,[29] and finally, under mild acidic conditions, **13** was converted to the key aminoalcohol **11** in a diastereoselective fashion by acid-catalyzed rearrangement. Following this route, the ABCD ring system was established in seven steps.

Aminoalcohol **11** was treated with MsCl in the presence of Et_3N and then with *t*-BuOK to promote the intramolecular cyclization reaction.[23d] In this manner, the E ring of aspidospermidine was created and the pentacyclic system was established to give imine **19**.[30] The final step in the synthesis was accomplished by reducing imine **19** with $NaBH_4$,[23f] affording aspidospermidine in a moderate overall yield from tetracyclic intermediate **11** (Scheme 12). The total synthesis of racemic aspidospermidine was accomplished in nine steps from indole and bromide **16** and in an overall yield of 15%. The brevity of this synthetic route is largely attributed to the application of direct 2-alkylation of indole and the acid-

Scheme 12. Completion of the Synthesis



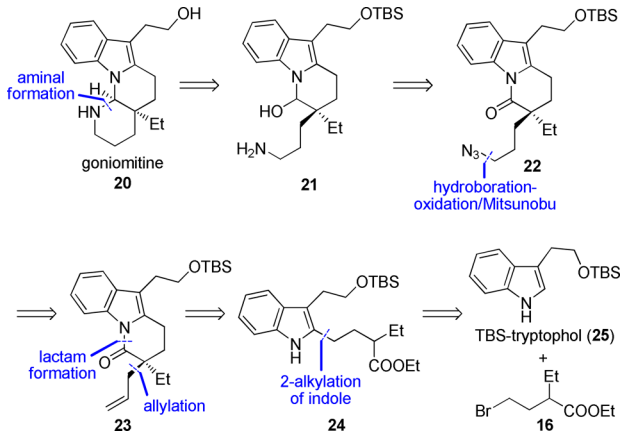
catalyzed skeletal rearrangement of the δ-lactam-derived hemiaminal intermediate.

The present route also represents formal syntheses of (±)-vincadifformine[23j] and (±)-quebrachamine,[24o] as both can be derived from imine **19** in one step by established methods.

Total Synthesis of Goniomitine. In addition to the C2-alkylation of an unsubstituted indole, the indole 2-alkylation method allows also to install an alkyl group to the C2-position of a 3-substituted indole (Scheme 2). This discovery greatly extends the synthetic utility of the present method, and therefore provides high potential for the total synthesis of another *Aspidosperma* alkaloid, goniomitine (**20**). Isolated in 1987, goniomitine is a significantly unique member of the *Aspidosperma* alkaloid family as it exhibits a rare octahydroindolo[1,2-*a*][1,8]naphthyridin scaffold and a 2-hydroxyethyl substituent at the C3-position of its indole core.[31] Goniomitine was found to display a promising antiproliferative activity in several tumor cell lines, and four total syntheses have been accomplished to date.[32]

Our retrosynthetic analysis suggested a short sequence starting from *O*-TBS-protected tryptophol[33] by using the direct 2-alkylation method (Scheme 13). The aminal functionality was

Scheme 13. Retrosynthetic Analysis of Goniomitine



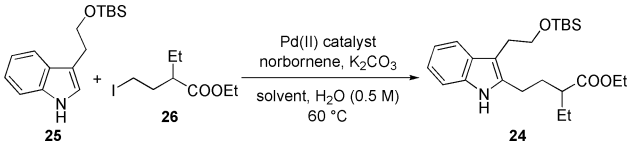
planned to be created by acid-catalyzed cyclization of hemiaminal intermediate **21**, which can be obtained by reduction of azide **22**. The azide functional group was supposed to be installed by hydroboration-oxidation[27] and Mitsunobu reaction[34] at the terminal end of the allyl group in lactam **23**. Similar to the synthesis of aspidospermidine, α-allyl-δ-lactam intermediate **23** was planned to be derived from indole derivative **24**. The key step was the 2-alkylation reaction of tryptophol derivative **25** with alkyl bromide **16**.

When we set out to conduct the planned 2-alkylation reaction of TBS-tryptophol **25** using alkyl bromide **16**, it was found that the reaction under standard conditions was rather sluggish. The reaction outcome indicated that the 3-substituted indole derivative was less reactive than indole itself and the

dx.doi.org/10.1021/ja3058138 | J. Am. Chem. Soc. 2012, 134, 14563−14572

original conditions were no longer suitable. Therefore, we replaced alkyl bromide **16** with the potentially more electrophilic iodide **26** and conducted an optimization study to achieve appropriate reaction conditions for the 2-alkylation of the 3-substituted indole substrate **25** (Table 1).

Table 1. Optimization Study for the 2-Alkylation of *O*-TBS-Tryptophol[a]



entry	conditions	t (h)	conv.[b]	yield[c]
1	$PdCl_2(MeCN)_2$, DMF, Ar	50	54%	36%
2	$PdCl_2(MeCN)_2$, DMF, O_2	48	66%	48%
3	$PdCl_2(MeCN)_2$, DMF/DMSO 9:1, O_2	26	73%	52%
4	$PdCl_2$, DMF/DMSO 9:1, O_2	26	85%	65%
5	$PdCl_2$, DMF/DMSO 9:1, air	26	84%	73%

[a]Conditions: **25** (1 equiv), **26** (4 equiv), norbornene (2 equiv), K_2CO_3 (4 equiv), 10 mol % Pd(II) catalyst, 0.5 M H_2O, 60 °C. [b]Calculated based on recovered starting material **25**. [c]Yield of isolated product **24** after column chromatography.

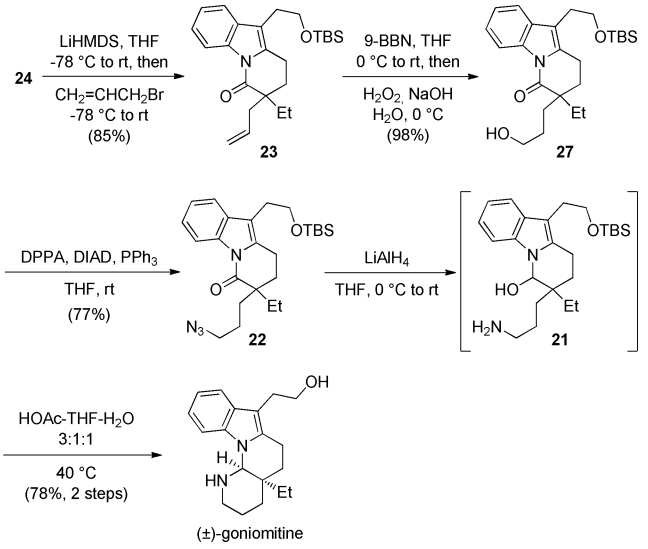
It was found that DMF was more suited than DMA as the solvent for this reaction, since the latter resulted in minor amounts of inseparable impurities in the product **24**. Preliminary experiment showed that the reaction did not reach full conversion after two days and only a low yield of 2,3-disubstituted indole product **24** was obtained (entry 1). Assuming undesired Pd(0) formation may be the reason for the slow conversion, we applied an oxygen atmosphere and found that both conversion and yield increased (entry 2). A mixed DMF–DMSO solvent system[5e] was found beneficial (entry 3) and $PdCl_2$ as catalyst turned out to be slightly better suited than $PdCl_2(MeCN)_2$ (entry 4). Finally, an air atmosphere was found to be optimal and the yield of 2,3-disubstituted indole **24** was increased to 73% in a reaction time of 26 h (entry 5).

Starting from key intermediate **24**, alcohol **27** was synthesized following a two-step sequence identical to the preparation of alcohol **17** in the total synthesis of aspidospermidine (Scheme 14). Mitsunobu reaction of alcohol **27** with diphenylphosphoryl azide (DPPA)[34] gave azide **22**. Treatment of **22** with $LiAlH_4$ resulted simultaneously in the reduction of the lactam to the respective hemiaminal and in the conversion of the azide to a primary amine. Finally, the generated intermediate **21** was treated under mild acidic conditions to promote the cyclic aminal formation as well as the deprotection of the silyl ether. Goniomitine was obtained diastereoselectively in high yield. Following this sequence, the total synthesis of racemic goniomitine was accomplished in seven steps from tryptophol and iodide **26** in an overall yield of 35%.

CONCLUSION

The regioselective direct 2-alkylation of the indole core by alkyl halides is highly demanded because 2-alkylindole derivatives serve as useful synthetic intermediates and building blocks. This

Scheme 14. Synthesis of Goniomitine[a]



[a]DIAD = diisopropyl azodicarboxylate.

transformation was realized by establishing a palladium-catalyzed norbornene-mediated cascade C–H activation of *N*-H indole derivatives. Initial synthetic studies revealed the scope and limitations of this reaction, and simultaneously triggered the mechanistic study to elucidate the reaction mechanism. Combining the information obtained from NMR studies, intermediate characterization, intramolecular trapping reaction, isotope labeling experiments, and kinetic studies, the previously proposed catalytic cycle was revised. The new catalytic cycle features an *N*-norbornene type palladacycle as the key intermediate and the oxidative addition of alkyl bromide to the Pd(II) center in this intermediate as the rate-determining step. The mechanistic findings render this reaction a yet unknown reaction type in the Catellani chemistry. The utility of this indole 2-alkylation method was demonstrated by total syntheses of two structurally different *Aspidosperma* alkaloids, aspidospermidine and goniomitine. The indole 2-alkylation reaction was the key step in both syntheses, and the construction of the molecular skeleton by an acid-catalyzed rearrangement of a hemiaminal intermediate also contributed to the conciseness of both routes. A new and general strategy to synthesize the *Aspidosperma* alkaloid has been established.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and NMR spectra for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

thorsten.bach@ch.tum.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

L.J. acknowledges the Alexander von Humboldt foundation for a postdoctoral fellowship.

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(8) The bromide anion exists in the alkylation reaction system as a byproduct. Therefore, in this NMR study, KBr was added to simulate the real reaction system. It was found that Br^- acted as a ligand for the observed intermediate, see Support Information for details.

(9) Single crystal X-ray structure determination of compound **5**·$CDCl_3$: red fragment, $C_{27}H_{23}N_3Pd{\cdot}CDCl_3$, M_r = 615.25; monoclinic, space group $P2_1/c$ (No. 14), a = 11.6211(5), b = 25.3321(12), c = 8.6027(4) Å, β = 103.6754(18)°, V = 2460.7(2) Å^3, Z = 4, λ(Mo Kα) = 0.71073 Å, μ = 1.104 mm^{-1}, ρ_{calcd} = 1.661 g·cm^{-3}, T = 123(1) K, F(000) = 1240, θ_{max}: 25.37°, R1 = 0.0171 (4373 observed data), wR2 = 0.0435 (all 4508 data), GOF = 1.085, 316 parameters, $\Delta\rho_{max/min}$ = 0.32/−0.41 e·Å^{-3}. For more details see Supporting Information. CCDC-885398.

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