Synthetic Methods

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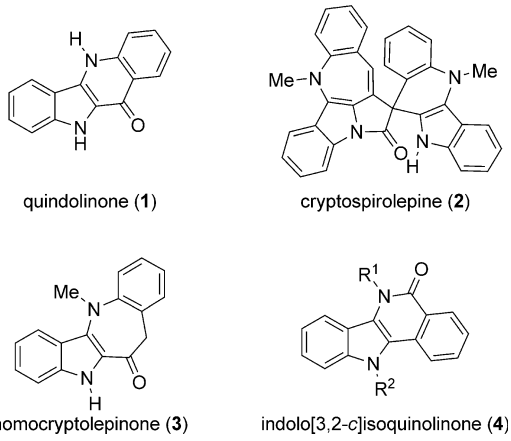
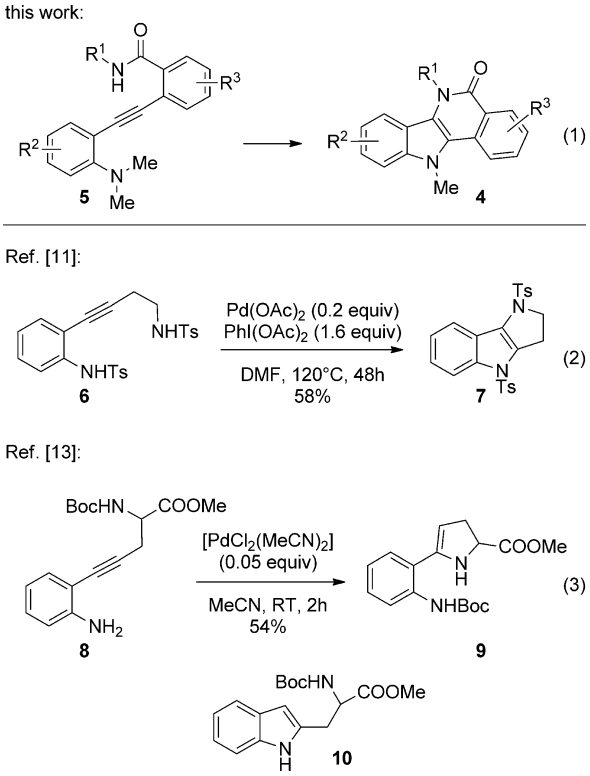
Palladium(II)-Catalyzed Intramolecular Diamination of Alkynes under Aerobic Oxidative Conditions: Catalytic Turnover of an Iodide Ion**

*Bo Yao, Qian Wang, and Jieping Zhu**

Polyheterocycles with an embedded 3-aminoindole moiety are found in a number of natural products (**1**–**3**)[1] and bioactive synthetic compounds (**4**, Scheme 1).[2] They show diverse biological activities, such as antimalarial, antimuscarinic, antibacterial, antiviral, antiplasmodial, antihypoglycemic, and PARP-inhibiting activities.[2,3] They are generally synthesized from 3-aminoindoles,[4] which are in turn prepared by multi-step processes.[5,6] As part of our ongoing research, which deals with palladium-catalyzed domino processes for the synthesis of heterocycles,[7] we became interested in the development of a one-pot synthesis of indolo[3,2-*c*]isoquinolinones (**4**) through a double intramolecular amination of internal alkynes **5** [Eq. (1), Scheme 2]. While the diamination of alkenes has been a field of intensive research for the past few years,[8,9] investigations on the diamination of alkynes remained rare.[10] Muñiz reported the only successful example of such a transformation, which occurred through the conversion of bis-tosylamide **6** to tetrahydropyrrolo[3,2-*b*]indole **7** [Eq. (2), Scheme 2].[11] The cyclization substrate **6** for this study was designed in such a way that neither regio- nor chemo-selectivity issues could occur during the cyclization.[12] On the other hand, with the aim to prepare isotryptophan **10**, Rutjes studied the cyclization of alkyne **8**, in which two different nucleophiles are tethered to the triple bond, and showed the initiation of the cyclization by the carbamate nitrogen atom rather than the aniline function, thus affording dihydropyrrole **9** after transacylation [Eq. (3), Scheme 2].[13] We set out to study the cyclization of **5** with the knowledge that the reactivity of an amide functionality versus that of an aniline nitrogen atom can be modulated,[14] although they are distinctly different. We report herein the efficient conversion of **5** into indolo[3,2-*c*]isoquinolinones (**4**) through a sequential amination/N-demethylation/amidation process under Pd-catalyzed oxidative conditions. We spectroscopically characterized a key palladacycle intermediate, furthermore we report conditions for the in situ generation of nBu$_4$NI, thus allowing the use of only a catalytic amount of this reagent for the removal of the N-Me group for the first time.



Scheme 1. Natural and synthetic compounds with an embedded 3-aminoindole moiety.



Scheme 2. Diamination of alkynes. Ts = 4-toluenesulfonyl, DMF = *N*,*N*-dimethylformamide, Boc = *tert*-butoxycarbonyl.

[*] Dr. B. Yao, Dr. Q. Wang, Prof. Dr. J. Zhu
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: http://lspn.epfl.ch

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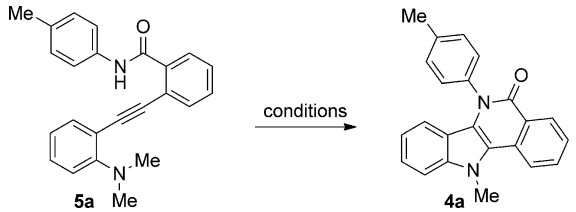
Pd-catalyzed Cacchi cyclizations of *o*-(1-alkynyl)anilines[15] and of *o*-(1-alkynyl)benzamides[16,17] are two well-studied processes. Both reactions were generally performed under basic and non-oxidative conditions. However, Pd^0 is expected to be produced in the reductive elimination step, therefore a suitable external oxidant is required in order to complete the catalytic cycle and to realize the reaction sequence we envisioned. The potential pitfall of this approach is the high sensitivity of aniline and especially the resulting indole to oxidative conditions, and, to the best of our knowledge, the Cacchi indole synthesis has thus never been performed under such conditions. Indeed, auto-oxidation of a 3-aminoindole derivative was a key step exploited in the total synthesis of (−)-mersicarpine described by Fukuyama and co-workers.[18] In addition, the order of cyclization can impact the outcome of the reaction significantly. If the reaction was to be initiated by amidopalladation of the amide function, then both 5-*exo* and 6-*endo* cyclization could take place with either the nitrogen or the oxygen atom of the amide as nucleophilic centers,[16] thus complicating the outcome of the reaction significantly.

The easily accessible diarylacetylene **5a** was used as a substrate to test the feasibility of our projected diamination process (Table 1). Following the seminal work of Larock and co-workers on the use of tetrabutylammonium iodide as a nucleophile for removal of the N-methyl group from the presumed indolium intermediate,[19] the double cyclization of **5a** was performed in different solvents in the presence of $Pd(OAc)_2$ (0.1 equiv), nBu$_4$NI (1.0 equiv), and an oxidant. Some conclusions could be drawn from the results: 1) The reaction worked in MeCN, DMF, and DMSO, with the latter being the solvent of choice (entries 1–4). 2) $Cu(OAc)_2$ is a competent oxidant both stoichiometrically (entry 1) and catalytically in combination with molecular oxygen as terminal oxidant (entries 2–4). 3) The addition of HOAc to the reaction mixture increased the yield of **4a** significantly (entry 2 vs. entry 3). 4) The reaction proceeded efficiently in DMSO in the presence of acetic acid (2.0 equiv) both under oxygen atmosphere (entries 5–7)[20] and simply under air atmosphere without the need to use $Cu(OAc)_2$ as co-oxidant (entries 8–12). Overall, **5a** was converted to **4a** in 84% yield of isolated product under optimized conditions (entry 8; $Pd(OAc)_2$ (0.1 equiv), nBu$_4$NI (1.0 equiv), HOAc (2.0 equiv), air atmosphere (1.0 atm) in DMSO at 50°C (conditions A)). The structure of **4a** was determined without ambiguity by X-ray crystallographic analysis (see the Supporting Information).

Table 1: Optimization of reaction conditions for the double cyclization of **1a**.[a]



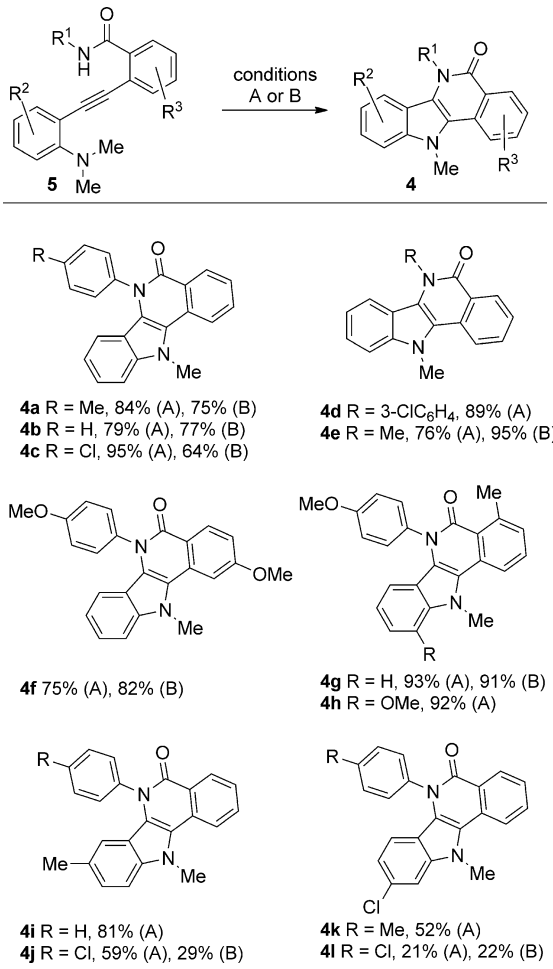
5a **4a**

Entry	$Pd(OAc)_2$ [mol%]	Oxidant (equiv)	HOAc [equiv]	Solvent	Yield [%][b]
1	10	$Cu(OAc)_2$ (2.0)[c]	–	MeCN	50
2	10	$Cu(OAc)_2$ (0.1)[d]	–	DMF	19
3	10	$Cu(OAc)_2$ (0.1)[d]	1.0	DMF	59
4	10	$Cu(OAc)_2$ (0.05)[d]	1.0	DMSO	79
5	10	O_2	1.0	DMSO	77
6	10	O_2	2.0	DMSO	78
7	10	O_2	3.0	DMSO	(84)
8	10	air	2.0	DMSO	(84)
9[e]	5	air	2.0	DMSO	72
10[e]	5	air	2.0[g]	DMSO	72
11[f]	10	air	1.0[h]	DMSO	73
12	5	air	2.0[h]	DMSO	(75)[i]

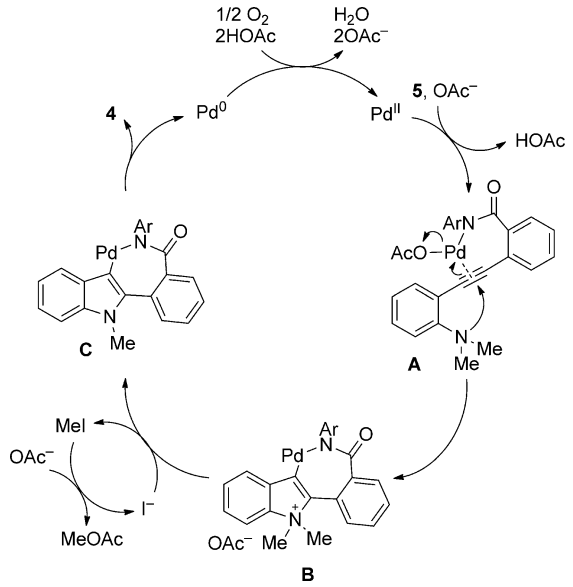
[a] Reaction conditions: A solution of **5a** (0.05 mmol), $Pd(OAc)_2$, oxidants, nBu$_4$NI (1.0 equiv), and HOAc in solvents (2.0 mL) was heated at 50°C under argon, air or oxygen atmosphere (1 atm) for 12 h. [b] Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard, yields of isolated products in parenthesis. [c] Under Ar atmosphere (1 atm). [d] Under O_2 atmosphere (1 atm). [e] 24 h. [f] 86 h. [g] 0.4 equiv of nBu$_4$NI was used. [h] 0.1 equiv of nBu$_4$NI was used. [i] Reaction was performed at 80°C.

If MeI were indeed formed, it would be converted to methyl acetate by reacting with acetate present in the reaction mixture. The ^{1}H NMR spectrum of the crude reaction mixture of the reaction performed in [D$_6$]DMSO supported this assumption (see the Supporting Information). As nBu$_4$NI was regenerated in this reaction, we wondered if the conversion of **5** to **4** could be realized in the presence of a catalytic amount of nBu$_4$NI. Gratefully, the reaction of **5a** in the presence of 10 mol% of nBu$_4$NI under otherwise identical conditions afforded **4a** in 73% yield, determined by ^{1}H NMR spectroscopy, after 86 hours (entry 11, Table 1). Through optimization of the reaction conditions (see the Supporting Information), we found that a slightly higher reaction temperature (80°C) was required in order to increase the overall catalytic efficiency. The optimized conditions included the performance of the reaction in DMSO at 80°C in the presence of $Pd(OAc)_2$ (0.05 equiv), nBu$_4$NI (0.1 equiv), and HOAc (2.0 equiv) under air atmosphere (conditions B). Tetracycle **4a** was isolated in 75% yield under these conditions (entry 12, Table 1).[21] With the optimum conditions in hands, the substrate scope of the reaction was next examined using both conditions A and B. Both N-methyl and N-aryl amides are good substrates for this reaction and a range of substituents, including a chlorine atom, were tolerated at different positions (Scheme 3), thus providing a handle for further functionalization.

Neither the desired tetracyclic product nor the iodinated intermediate was formed when the cyclization of **5c** was performed in the absence of $Pd(OAc)_2$ under otherwise identical conditions. The result ruled out the possibility of an iodine-mediated transformation.[22] In addition, treatment of a solution of **5g** in DMSO with a stoichiometric amount of $Pd(OAc)_2$, HOAc (2 equiv), and nBu$_4$NI (1.0 equiv) under argon atmosphere afforded the tetracyclic product **4g** in 93% yield. This control experiment indicated that, under our conditions, the diamination reaction went through a catalytic cycle involving Pd^{II}/Pd^0 species. Based on the above-mentioned experimental observations, a possible catalytic cycle was proposed for the reaction (Scheme 4). A sequence of events that involve the coordination of both alkyne and amide



Scheme 3. Substrate scope of the reaction. Conditions A: **5** (0.1 mmol) in DMSO (4.0 mL) was heated at 50 °C in the presence of $Pd(OAc)_2$ (0.1 equiv), nBu$_4$NI (1.0 equiv), and HOAc (2.0 equiv) under air atmosphere (1 atm) for 12 h. Conditions B: **5** (0.1 mmol) in DMSO (4.0 mL) was heated at 80 °C in the presence of $Pd(OAc)_2$ (0.05 equiv), nBu$_4$NI (0.1 equiv), and HOAc (2.0 equiv) in DMSO (4.0 mL) under air atmosphere (1.0 atm) for 12 h.



Scheme 4. Plausible reaction pathway for the double cyclization of **5** to **4**.

functionalities to the Pd^{II} species followed by deprotonation of the amide NH would afford σ,π-chelated Pd complex **A**. An *anti* addition of the tethered N,N-dimethylaniline to the triple bond through a formal 5-*endo*-dig mode would afford the σ-C-Pd^{II}-amide intermediate **B**, which upon S_N2 displacement with an iodide ion as nucleophile would provide intermediate **C** and MeI. Under the present reaction conditions, the acetate anion (AcO^-) converted MeI to methyl acetate with concurrent regeneration of the iodide ion, therefore allowing the use of only a catalytic amount of nBu$_4$NI to complete the reaction sequence. Reductive elimination from **C** gave product **4** and a Pd^0 species. Finally, oxidation of Pd^0 to Pd^{II} by molecular oxygen completed the catalytic cycle.[23]

To gain mechanistic insight, we attempted to isolate the putative σ-vinyl Pd complex **B**. Much to our delight, monitoring the reaction of **5g** with $Pd(OAc)_2$ (1.0 equiv) in [D$_6$]DMSO at room temperature indicated clean formation of a new compound, and the conversion was complete in three hours. This compound was identified as intermediate **B** from detailed spectroscopic studies (see the Supporting Information). Notably, the HRMS data found (489.0791) matched the calculated value for $[C_{25}H_{23}N_2O_2Pd]^+$ (489.0804). Intermediate **B**, which was stable at room temperature for a few hours, was readily converted to **4g** upon addition of nBu$_4$NI (2 equiv, RT, 3.5 h), thus indicating that **B** could indeed be an intermediate in the conversion of **5** to **4**. We noted that this intermediate can also be converted to **4g** upon prolonged heating at 50 °C, thus indicating that AcO^- can also act as nucleophile to remove the N-methyl group, although this reaction was less efficient than that with iodide ions.

The chemoselectivity we observed is different from that described by Rutjes and co-workers, who reported that amidopalladation occurred preferentially with the N-carbamate than with the aniline function [see Eq. (3), Scheme 2]. Strong coordination of the $ArNH_2$ function to Pd could be one of the reasons for this selectivity.[24] In our case, the ligation of DMSO (solvent) to $Pd(OAc)_2$ could hamper the coordination of the bulky N,N-dimethylamino group to Pd^{II}, thus leading to the observed chemoselectivity.[25] The observation that aminopalladation, which involves N,N-dimethylamino nitrogen as nucleophile, was favored over amidopalladation in the presence of HOAc, is counterintuitive at first glance. However, ^{1}H NMR titration of **5g** in [D$_6$]DMSO with two equivalents of HOAc at 50 °C and 80 °C, respectively, indicated that the N,N-dimethylamino group in **5g** was not protonated at all.[26]

In conclusion, we reported a novel Pd^{II}-catalyzed intramolecular diamination of alkynes under aerobic oxidative conditions for the construction of indolo[3,2-*c*]isoquinolinone. To the best of our knowledge, this study presented the first examples in which the cyclization of *o*-(1-alkynyl)benzamides and the Cacchi indole synthesis were combined and realized under oxidative conditions. The domino process proceeded in a highly ordered fashion, was regio- and chemo-

selective, and provided the first examples of the diamination of alkynes with two differentially protected amino functions. A palladacycle (**B**) was characterized and its intermediacy in the conversion of **5** to tetracycle **4** was demonstrated. In addition, we documented that, in the presence of HOAc, only a catalytic amount of nBu$_4$NI is required for removal of the N-methyl group, and we believe that the in situ generation of nBu$_4$NI described herein could be applicable in other related system.

Experimental Section

General procedure: A solution of **5a** (0.1 mmol), $Pd(OAc)_2$ (conditions A: 0.1 equiv; conditions B: 0.05 equiv), nBu$_4$NI (conditions A: 1.0 equiv; conditions B: 0.1 equiv) and HOAc (0.2 mmol) in DMSO (4 mL) was heated at 50 °C or 80 °C under air atmosphere (1.0 atm) for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel) to give **4a** (conditions A: 84%; conditions B: 75%). m.p.: 288–290 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (ddd, J = 8.1, 1.4, 0.5 Hz, 1H), 8.36 (m, 1H), 7.80 (ddd, J = 8.6, 7.2, 1.5 Hz, 1H), 7.56 (ddd, J = 8.2, 7.2, 1.0 Hz, 1H), 7.46–7.39 (m, 3H), 7.39–7.34 (m, 2H), 7.28 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 6.84 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H), 6.23–6.12 (m, 1H), 4.27 (s, 3H), 2.54 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5, 139.1, 138.8, 136.6, 132.4, 130.7, 130.7, 129.7, 128.6, 126.1, 125.4, 124.4, 122.0, 120.9, 120.3, 120.0, 119.4, 116.8, 109.3, 33.6, 21.6 ppm; ATR-IR: $\tilde{\nu}$ = 2987, 2973, 2901, 1630, 1609, 1566, 1383, 1234, 1068, 1058, 742, 690 cm^{-1}; ESI-MS: m/z 339 $[M+H]^+$; elemental analysis calcd (%) for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28; found: C, 81.37, H, 5.54; N, 8.13.

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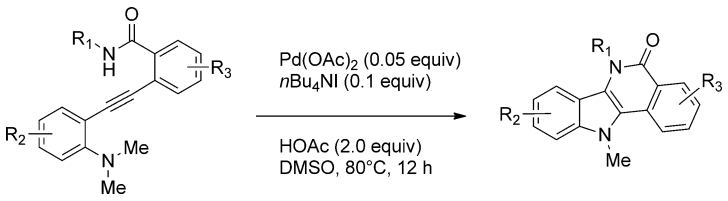
[27] CCDC-874091 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Synthetic Methods

B. Yao, Q. Wang, J. Zhu* ___ ■■■■–■■■■

Palladium(II)-Catalyzed Intramolecular Diamination of Alkynes under Aerobic Oxidative Conditions: Catalytic Turnover of an Iodide Ion



"I" did it: A sequential intramolecular amination/N-demethylation/amidation of internal acetylenes in the presence of a catalytic amount of $Pd(OAc)_2$ and nBu_4NI afforded indolo[3,2-*c*]isoquinolinones under mild aerobic conditions (see scheme, DMSO = dimethyl sulfoxide). The iodide ion was regenerated by reaction of in situ generated MeI with HOAc present in the reaction mixture.

