Synthesis of the Azepinoindole Framework via Oxidative Heck (Fujiwara–Moritani) Cyclization

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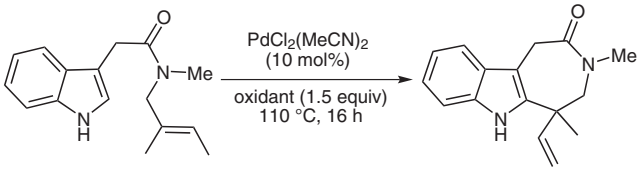
Abstract: A catalytic oxidative Heck (Fujiwara–Moritani) cyclization has been evaluated for construction of the azepinoindole framework starting from readily available 3-indoleacetic acid amides. The supporting role of the amide group in the substrate has been demonstrated necessary for the success of the cyclization.

Key words: C–H activation, Heck reaction, palladium, indoles, heterocycles

The palladium(II)-catalyzed oxidative Heck reaction involving C–H bond activation (Fujiwara–Moritani reaction) has been extensively studied[1] as an expedient alternative for the conventional Heck coupling in the direct alkenylation of arenes. This transformation is particularly synthetically interesting for rapid and selective functionalization of compounds containing the indole nucleus.[2] Considerable success has been achieved in the development of intermolecular alkenylation of indoles.[3] Remarkably efficient examples of the intramolecular catalytic oxidative Heck reaction have also been reported for annulation of indoles.[4] However, in all of these cases either a five- or a six-membered cycle is joined to the aromatic core via carbocyclization. On the other hand, methods using mostly stoichiometric amount of palladium have been elaborated for the synthesis of indoles fused with medium-sized N-containing rings, namely azepinoindoles[5] or azocinoindoles,[6] which are present in certain alkaloids. To the best of our knowledge, the catalytic oxidative Heck cyclization delivering the azepinoindole framework has been described only once for the synthesis of paullone derivatives.[7]

Despite this limited precedent success in the construction of medium-sized rings via oxidative Heck cyclization suitable conditions are sought for exploiting the reactivity of a supporting functionality.[3b,8] Hence the initial screening of reaction conditions was carried out on the example of the amide **1a** (Table 1) obtained by coupling of 3-indoleacetic acid and the corresponding allylamine in the presence of EDCI. The ortho-directing effect of the amide groups in oxidative Heck reaction has been unambiguously established for acylanilides.[8]

Table 1 Primary Set of Conditions



1a **2a**

Entry	Solvent	Oxidant	Yield (%)[a]
1	1,4-dioxane	BQ	20
2	1,4-dioxane	DTBQ	49
3	THF	DTBQ	53
4	THF	DMBQ	31
5	THF	NQ	traces
6	THF	duroquinone	n.r.[b]

[a] Isolated yield.
[b] No reaction.

Various combinations of palladium catalyst, oxidant, and solvent described in the literature[1] have been applied to the substrate **1a**. The first successful hit leading to the formation of the azepinoindolone **2a** was found using the combination of $PdCl_2(MeCN)_2$, BQ (*p*-benzoquinone), and 1,4-dioxane (Table 1, entry 1). No product formation was observed at a temperature lower than 110 °C. When *t*-BuO_2H or Bz_2O_2 were used as oxidants, the major isolated product was the amidoketone resulting from oxidation of the benzylic position in **1a**. $Pd(OAc)_2$ and $PdCl_2$ showed no catalytic activity, which in the case of $PdCl_2$ may be due its low solubility in 1,4-dioxane. The reaction turned very sluggish when MeCN, EtOAc, or toluene was used as a solvent leading to precipitation of palladium-black before any appreciable conversion of the starting material had been attained. Addition of the strongly coordinating polar solvents DMF, DMSO, or HMPA completely inhibited the reaction. LiCl or KOAc as additives produced the same effect.

The low yield of **2a** with BQ as oxidant was ascribed to the unwanted reactivity of BQ as an electrophile, particularly, as a strong Michael acceptor. Therefore, we tested a number of substituted benzoquinones: NQ (1,4-naphthoquinone), DMBQ (2,4-dimethyl-1,4-benzoquinone), DTBQ (2,4-di-*tert*-butyl-1,4-benzoquinone), and duro-

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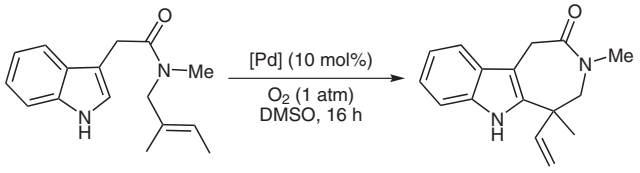
quinone. These should be more stable against nucleophilic attack owing to steric hindrance introduced by the substituents. Indeed, switching to DTBQ resulted in more than two-fold increase of the yield (Table 1, entry 2). THF was found to be a slightly superior solvent than 1,4-dioxane in terms of yield (Table 1, entry 3). However, at the current stage of work this difference was negligible.

Formation of **2a** was also observed in a totally different catalytic system employing DMSO as the solvent at 110 °C, $Pd(OAc)_2$ as catalyst, and O_2 as oxidant (Table 2, entry 1). This combination for direct O_2-coupled catalytic turnover was independently discovered in 1990s by the groups of Hiemstra and Larock and was applied widely for oxidative heterocyclization reactions.[9]

Table 2 Secondary Set of Conditions



Entry	Catalyst	Temp (°C)	Additive	Yield (%)[a]
1	$Pd(OAc)_2$	110	none	22
2	$Pd(OAc)_2$	110	DTBQ[b]	37
3	$Pd(MeCN)_4(BF_4)_2$	80	DTBQ[b]	37

[a] Isolated yield.
[b] DTBQ (40 mol%).

The presence of 40 mol% DTBQ improved the reaction outcome (Table 2, entry 2). No reaction occurred in the absence of O_2, thus, DTBQ clearly is not responsible for the oxidation of palladium(0) in this case. However, BQ has been reported to play several major roles in C–C bond-forming palladium -catalyzed reactions involving C–H activation[10] apart from being an oxidant. It may act as a ligand, stabilizing active palladium species during the catalytic cycle,[11] as well as a promoter of C–C bond formation,[12,8a] and most importantly, of the C–H activation step.[13] The change of the catalyst for the cationic complex $Pd(MeCN)_4(BF_4)_2$ allowed to conduct the reaction at a lower temperature (entry 3). This result is consistent with the fact, that cationic palladium intermediates are often more reactive than the analogous neutral species in Heck reaction.[14] However, no improvement of the yield was observed even upon increasing the loading of DTBQ to 100%. Therefore, the previously established conditions (Table 1, entry 3) were utilized as primary for further elaboration.

A number of compounds **3a**–**f** (Figure 1) with structural resemblance to **1a** was tested as substrates for the cyclization. No reaction was observed in any of these cases, which allows drawing certain conclusions. Thus, the substrate has to contain a free NH-indole core (e.g., compounds **3a**,**b** have no free NH-indole). The amide group of **1a**, clearly induces palladation via an ortho-directing effect, since compounds **3c** and **3e** with a shifted amide group position fail to cyclize. The 2-picolyl group in **3d**, reported to induce palladation in oxidative Heck reaction of indole,[3b] is not functional under our conditions. The case of compound **3f**, bearing no amide group, but potentially capable[15] of forming a six-membered palladacycle, also proves the exclusive effect of the amide function.

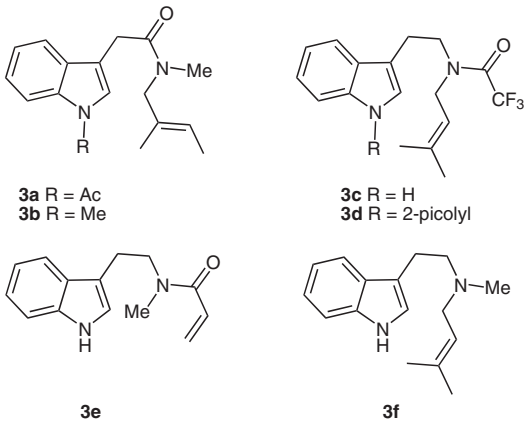
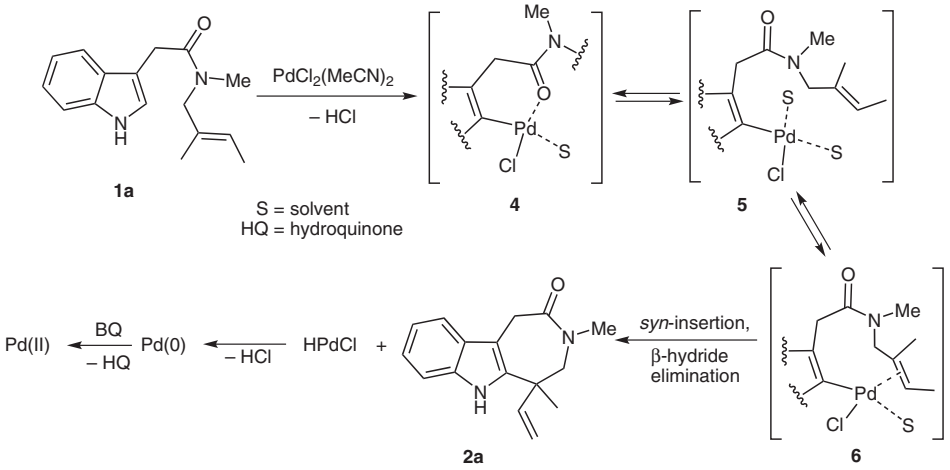


Figure 1



Scheme 1

The described experimental facts enabled us to sketch a possible mechanism (Scheme 1) for the cyclization of **1a** under the primary conditions with *p*-benzoquinone as an oxidant. The key intermediate forming after coordination of palladium(II) to the amide group should be the palladacycle **4**. Strongly coordinating solvents (MeCN, DMF, DMSO, HMPA) would be dominating in the ligand sphere of palladium(II) and, thus, would prevent palladation via **4** suppressing the overall reaction, which indeed is observed. On the other hand, formation of the intermediate **5** requires solvent to be capable of displacing the amide group in **4**. This assumption is consistent with the fact that weakly coordinating solvents (EtOAc, toluene) slow down the reaction. The fact that palladacycles obtained from indoles bearing a strong coordinating N-group do not engage in coupling, as described by Ricci et al.,[3b] also favors this hypothesis. Finally, the π-complex **6** is formed with the relative alignment of the olefin double bond and the C–Pd bond being crucial[14] for the cyclization regioselectivity. The given mechanistic rationalization limits the role of *p*-benzoquinone to reoxidation[16] of palladium(0) to palladium(II) and is hardly applicable to the combination $Pd(OAc)_2$/DMSO/O_2/DTBQ.

A number of substrates **1b–j** were prepared for evaluation of the cyclization scope (Table 3). In all cases the primary set of conditions (Table 1, entry 3) was applied first, changing the oxidant if necessary.

Table 3 Investigation of the Cyclization Scope

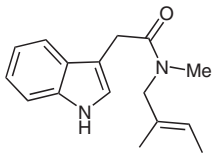
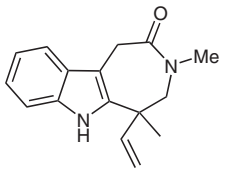
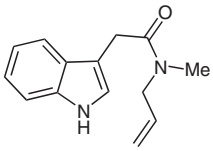
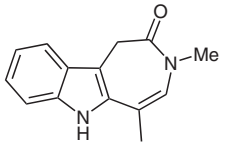
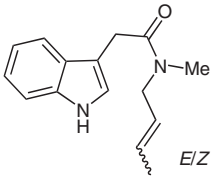
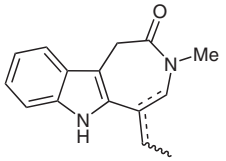
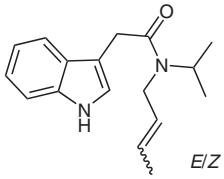
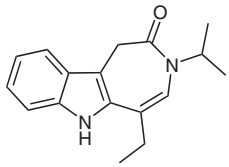
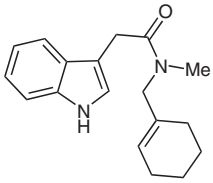
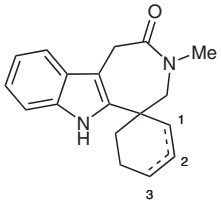
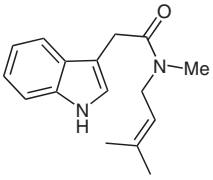
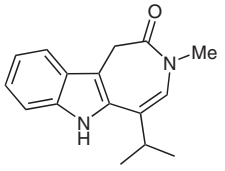
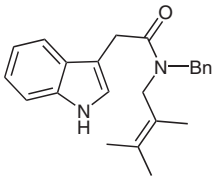
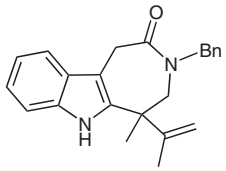
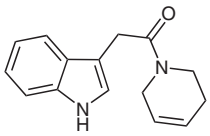
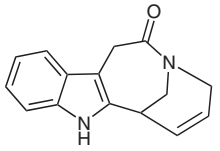
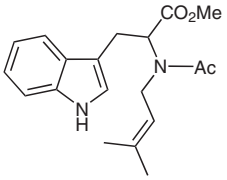
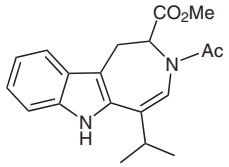
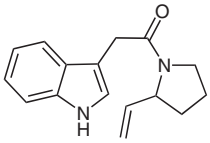
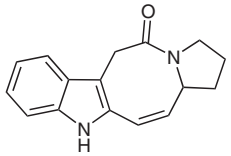
Entry	Substrate	Oxidant	Solvent	Product	Yield (%)[a]
1	**1a** 	DTBQ	THF	**2a** 	53
2[b]	**1b** 	none	MeCN	**2b** 	40
3		DMBQ	THF		35
4	**1c**  *E*/*Z* ~ 9:1	DTBQ	THF	**2c** 	25[c]
5		DMBQ			55[d]
6	**1d**  *E*/*Z* ~ 9:1	DTBQ	THF	**2d** 	n.r.
7		DMBQ			13
8	**1e** 	DTBQ	THF	**2e** 	40[e]
9	**1f** 	DTBQ	1,4-dioxane	**2f** 	14
10			THF		56

Table 3 Investigation of the Cyclization Scope (continued)

Entry	Substrate	Oxidant	Solvent	Product	Yield (%)[a]
11	**1g** 	*p*-benzoquinone[f]	THF	**2g** 	n.r.
12[g]		O_2/DTBQ	DMSO		36
13	**1h** 	*p*-benzoquinone[f]	THF	**2h** 	n.r.
14[g]		O_2/DTBQ	DMSO		20
15	**1i** 	DMBQ	THF	**2i** 	17 (28)[h]
16	**1j** 	DMBQ	THF	**2j** 	20

[a] Isolated yields reproduced on three consecutive runs.
[b] $PdCl_2(MeCN)_2/AgBF_4$ (1.5 equiv), 80 °C, 15 min.
[c] *endo* 17%/*exo* 8%.
[d] *endo* 38%/*exo* 17%.
[e] Ratio of $\Delta^{1,2}/\Delta^{2,3}$ = ~1:19.
[f] BQ or DMBQ, or DTBQ.
[g] DMSO, $Pd(MeCN)_4(BF_4)_2$ (10 mol%), O_2 (1 atm, balloon), DTBQ (40 mol%), 80–90 °C.
[h] Based on the recovered starting material.

Thus, the allylamine amide **1b** failed to cyclize in the presence of DTBQ. Nevertheless, the corresponding product **2b** was obtained using stoichiometric amount of palladium(II) (Table 3, entry 2)[5] revealing the principal possibility of cyclization. Switching to DMBQ (Table 3, entry 3) allowed catalytic conversion of **1b** to **2b** with a comparable efficiency. The example of **1b** gave us a sound proof for a complex role of *p*-benzoquinone in the reaction. DTBQ was also less efficient than DMBQ in the case of **1c** (Table 3, entries 4, 5) containing a disubstituted double bond. The corresponding product **2c** was obtained as a separable mixture of *endo*- and *exo*-cyclic double bond isomers. The presence of a bulky isopropyl substituent in **1d** otherwise analogous to **1c** led to a significant decrease of the yield (Table 3, entry 7). Amide **1e** was cyclized under the optimal primary conditions with a satisfactory yield (Table 3, entry 8). The product azepinoindolone **2e** was isolated as a chromatographically inseparable mixture of double bond isomers. The example of **1f** containing a trisubsituted double bond reveals a peculiar solvent effect. Namely, THF (Table 3, entry 10) is far more superior to 1,4-dioxane (Table 3, entry 9), even though in the case of **1a** (Table 1, entries 2, 3) there was almost no difference between these solvents. Heavier double bond substitution in **1g** renders the latter inert under primary reaction conditions (Table 3, entry 11). However, the corresponding azepinoindolone **2g** could be obtained applying the secondary set of conditions (Table 3, entry 12). Interestingly, when conducted without DTBQ reaction of **1g** led to a complete degradation of the starting material. Application of the secondary condition set was also fruitful in the case of amide **1h** successfully leading to the teracycle **2h** (Table 3, entry 14). We also decided to test tryptophan derivative **1i** as a substrate for the cyclization under our conditions. The results previously reported for the stoichiometric oxidative Heck cyclization of this compound in $Pd(OAc)_2$/DMSO/O_2 system strongly suggest that the methoxycarbonyl group may induce palladation.[6a] Indeed, we managed to obtain the azepinoindol **2i** using DMBQ as an oxidant (Table 3, entry 15). However, the yield did not exceed 17% due to the incomplete conversion, which failed to improve even with an additional amount of catalyst. Low conversion was plaguing the similar reported transformation as well.[6a] Perhaps this is a consequence of the less efficient palladation step, which has to proceed via a seven-membered intermediate instead of a six-membered **4** (Scheme 1). In contrast to all aforementioned substrates amide **1j** afforded the azocino-

indolone **2j**. This outcome should be the consequence of a different pattern for coordination of the double bond on palladium(II) in the intermediate **6** determined by the structure of the substrate. Under the secondary set of conditions **1j** underwent complete decomposition.

In summary, we have developed an approach towards azepino[4,5-*b*]indol-2-ones via oxidative Heck cyclization of readily accessible 3-indoleacetic acid amides. The initially speculated crucial role of the amide function as a supporting group has been confirmed. It has also been demonstrated, that the nature of the solvent and the structure of the *p*-benzoquinone ensure the success of the cyclization. Despite the moderate efficiency of the developed method, the discovered effects may be helpful in the further development of novel applications of the oxidative Heck reaction in general.

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 or Bruker 400 instruments with TMS as an internal standard at 298 K unless otherwise stated. High-resolution mass spectra (EI) were recorded on Kratos MS50TC and Kratos Mach III system.

Oxidative Heck Cyclization Under Primary Conditions; General Procedure

Amide **1** (0.2 mmol), $PdCl_2(MeCN)_2$ (5 mg, 10 mol%), and the *p*-benzoquinone [1.5 equiv; either DTBQ (66 mg) or DMBQ (40 mg)] were loaded into a screw-cap vial equipped with a stir bar. The vial was evacuated and flushed back with argon. Anhyd THF (4 mL) was added, the vial was sealed under argon, and kept with stirring at 110 °C (oil bath temperature). After 16 h, the reaction mixture was filtered through a short pad of Celite. The filtrate was evaporated with silica gel under reduced pressure. The residue was subjected to column chromatography on silica gel.

2a

Prepared from **1a** (51 mg) with DTBQ; yield: 27 mg (53%); eluent: hexane–EtOAc (1:3); R_f = ~0.21.

^{1}H NMR (400 MHz, DMSO-d_6, 327 K): δ = 10.55 (s, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.01–7.07 (m, 1 H), 6.95–7.00 (m, 1 H), 6.02 (dd, *J* = 10.6, 17.4 Hz, 1 H), 5.16 (dd, *J* = 1.2, 10.6 Hz, 1 H), 4.93 (dd, *J* = 1.2, 17.4 Hz, 1 H), 3.72–3.81 (m, 3 H), 3.67 (d, *J* = 15.0 Hz, 1 H), 2.95 (s, 3 H), 1.45 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.47, 141.94, 136.77, 135.27, 127.62, 122.06, 119.53, 118.17, 116.10, 110.47, 104.20, 59.28, 43.44, 37.42, 32.44, 23.84.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{18}N_2O$: 254.1419; found: 254.1428.

2b

Prepared from **1b** (46 mg) with DMBQ; yield: 16 mg (35%); eluent: hexane–EtOAc (1:1); R_f = ~0.21.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.15 (s, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.11–7.16 (m, 1 H), 7.02–7.07 (m, 1 H), 6.32 (d, *J* = 1.2 Hz, 1 H), 3.45 (s, 2 H), 3.01 (s, 3 H), 2.21 (d, *J* = 1.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.25, 138.11, 134.65, 127.46, 126.14, 122.39, 119.46, 118.23, 115.76, 111.74, 106.97, 36.36, 33.08, 18.44.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}N_2O$: 226.1106; found: 226.1110.

***endo*-2c**

Prepared from **1c** (48 mg) with DMBQ; yield: 18 mg (38%); eluent: hexane–EtOAc (2:3); R_f = ~0.33.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.10–7.21 (m, 2 H), 6.11 (s, 1 H), 3.56 (s, 2 H), 3.11 (s, 3 H), 2.57 (q, *J* = 7.4 Hz, 2 H), 1.15 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.09, 137.64, 132.86, 126.33, 126.30, 122.85, 122.13, 119.95, 118.48, 110.94, 109.14, 36.51, 33.10, 26.06, 14.45.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_2O$: 240.1263; found: 240.1267.

***exo*-2c**

Prepared from **1c** (48 mg) with DMBQ; yield: 8 mg (17%); eluent: hexane–EtOAc (2:3); R_f = ~0.12. An analytically pure sample was obtained after recrystallization from EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.52 (d, *J* = 7.9 Hz, 1 H), 7.27 (d, *J* = 7.9 Hz, 1 H), 7.14–7.19 (m, 1 H), 7.06–7.11 (m, 1 H), 5.95 (q, *J* = 7.0 Hz, 1 H), 4.31 (s, 2 H), 3.96 (s, 2 H), 3.04 (s, 3 H), 1.97 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.55, 136.16, 134.38, 128.21, 127.28, 122.51, 120.35, 119.27, 118.27, 111.17, 150.47, 47.17, 33.68, 33.06, 13.54.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_2O$: 240.1263; found: 240.1268.

2d

Prepared from **1d** (54 mg) with DMBQ; yield: 7 mg (13%); eluent: hexane–EtOAc (1:1); R_f = ~0.19.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.21–7.26 (m, 1 H), 7.15–7.20 (m, 1 H), 6.25 (s, 1 H), 4.92 (sept, *J* = 6.7 Hz, 1 H), 3.53 (s, 2 H), 2.63 (q, *J* = 7.6 Hz, 2 H), 1.20 (t, *J* = 7.6 Hz, 3 H), 1.18 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.69, 137.59, 132.94, 126.33, 123.91, 122.76, 120.79, 119.90, 118.54, 110.91, 109.59, 46.25, 33.71, 26.47, 20.71, 14.61.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{20}N_2O$: 268.1576; found: 268.1573.

2e

Prepared from **1e** (56 mg) with DTBQ; yield: 22 mg (40%); eluent: hexane–EtOAc (1:1); R_f = ~0.10. An analytically pure sample was obtained after recrystallization from DMSO.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.09–7.19 (m, 2 H), 5.98–6.04 (m, 1 H), 5.90–5.96 (m, 1 H), 3.93 (d, *J* = 16.1 Hz, 1 H), 3.88 (d, *J* = 16.1 Hz, 1 H), 3.85 (d, *J* = 14.8 Hz, 1 H), 3.58 (d, *J* = 14.8 Hz, 1 H), 3.14 (s, 3 H), 2.38–2.46 (m, 1 H), 2.29–2.36 (m, 2 H), 2.19–2.27 (m, 1 H), 2.01–2.10 (m, 1 H), 1.77–1.85 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6, 363 K): δ = 173.53, 141.45, 135.88, 127.68, 126.37, 125.14, 121.20, 118.87, 117.67, 111.18, 102.77, 53.48, 38.30, 36.97, 33.74, 32.46, 30.20, 22.58.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}N_2O$: 280.1576; found: 280.1589.

2f

Prepared from **1f** (51 mg) with DTBQ; yield: 29 mg (57%); eluent: hexane–EtOAc (2:1); R_f = ~0.16.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.21–7.26 (m, 1 H), 7.15–7.9 (m, 1 H), 6.11 (d, *J* = 0.8 Hz, 1 H), 3.55 (s, 2 H), 3.13 (s, 3 H), 2.93 (sept, *J* = 6.7 Hz, 1 H), 1.27 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.39, 137.67, 132.87, 127.06, 126.16, 125.44, 122.80, 119.89, 118.43, 110.97, 109.57, 36.46, 33.02, 31.08, 22.53.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{18}N_2O$: 254.1419; found: 254.1418.

2i

Prepared from **1i** (66 mg) with DMBQ; yield: 11 mg (17%); eluent: hexane–EtOAc (2:3); R_f = ~0.35. During chromatography 26 mg of the starting amide **1i** was recovered (eluent: hexane–EtOAc, 2:3; R_f = ~0.14); recalculated yield of **2i**: 28% (brsm).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.17–7.22 (m, 1 H), 7.10–7.15 (m, 1 H), 6.52 (s, 1 H), 5.66 (t, *J* = 5.0 Hz, 1 H), 3.71 (dd, *J* = 5.7, 16.7 Hz, 1 H), 3.56 (s, 3 H), 3.22 (dd, *J* = 4.6, 16.7 Hz, 1 H), 2.91 (sept, *J* = 6.7 Hz, 1 H), 2.22 (s, 3 H), 1.32 (d, *J* = 6.7 Hz, 1 H), 1.25 (d, *J* = 6.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.13, 169.72, 135.36, 130.54, 128.59, 127.39, 123.48, 122.91, 119.80, 118.60, 113.03, 110.68, 56.10, 52.11, 30.11, 26.73, 23.24, 22.66, 22.10.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}N_2O_3$: 326.1630; found: 326.1637.

2j

Prepared from **1j** (50 mg) with DMBQ; yield: 10 mg (20%); eluent: hexane–EtOAc (1:4); R_f = ~0.11.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 7.15–7.19 (m, 1 H), 7.09–7.14 (m, 1 H), 6.39 (dd, *J* = 2.1, 11.9 Hz, 1 H), 5.59 (dd, *J* = 4.9, 11.9 Hz, 1 H), 5.00–5.05 (m, 1 H), 4.29 (d, *J* = 14.5 Hz, 1 H), 3.77 (d, *J* = 14.5 Hz, 1 H), 3.48–3.62 (m, 2 H), 2.08–2.18 (m, 1 H), 1.89–2.00 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.22, 135.57, 133.46, 131.42, 129.14, 123.99, 122.62, 119.48, 118.74, 111.39, 109.21, 56.69, 45.55, 33.96, 32.78, 23.12.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{16}N_2O$: 252.1263; found: 252.1276.

Oxidative Heck Cyclization Under Secondary Conditions; General Procedure

Amide **1** (0.2 mmol), $Pd(MeCN)_4(BF_4)_2$ (9 mg, 10 mol%), and DTBQ (18 mg, 40 mol%) were loaded into a round-bottom single-necked flask equipped with a stir bar. Anhyd DMSO (2 mL) was added and an O_2 balloon was attached to the neck via a three-port valve. The flask was evacuated and flushed back with O_2. After stirring for 16 h at elevated temperature (oil bath) under O_2 atmosphere, the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (20 mL), brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure with silica gel. The residue was subjected to column chromatography on silica gel.

2g

Prepared from **1g** (69 mg) at 90 °C; yield: 25 mg (36%); eluent: hexane–EtOAc (3:1); R_f = ~0.16.

^{1}H NMR (400 MHz, DMSO-d_6, 363 K): δ = 10.43 (s, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.25–7.39 (m, 6 H), 6.97–7.08 (m, 2 H), 5.01 (m, 1 H), 4.65–4.71 (m, 2 H), 4.47 (d, *J* = 15.3 Hz, 1 H), 3.93 (d, *J* = 15.7 Hz, 1 H), 3.87 (d, *J* = 15.7 Hz, 1 H), 3.82 (d, *J* = 15.2 Hz, 1 H), 3.57 (d, *J* = 15.2 Hz, 1 H), 1.72 (d, *J* = 0.8 Hz, 3 H), 1.48 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.43, 147.00, 137.92, 137.49, 135.24, 128.75, 128.04, 127.52, 127.48, 121.98, 119.44, 118.09, 115.25, 110.60, 103.92, 54.22, 51.13, 45.68, 32.59, 24.00, 19.99.

HRMS (EI): *m*/*z* calcd for $C_{23}H_{24}N_2O$: 344.1889; found: 344.1889.

2h

Prepared from **1h** (48 mg) at 80 °C; yield: 10 mg (20%); eluent: CH_2Cl_2–MeCN (2:1); R_f = ~0.26.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 1 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 7.04 (m, 1 H), 6.98–7.04 (m, 1 H), 6.02–6.10 (m, 1 H), 5.72–5.78 (m, 1 H), 4.50 (dd, *J* = 4.0, 17.3 Hz, 1 H), 4.43 (d, *J* = 14.2 Hz, 1 H), 4.10 (d, *J* = 15.0 Hz, 1 H), 3.62 (dd, *J* = 3.4, 14.2 Hz, 1 H), 3.44–3.55 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.48, 136.97, 135.17, 128.89, 128.03, 127.97, 121.15, 119.04, 117.82, 111.18, 101.81, 47.06, 44.30, 33.56, 32.13.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1106.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) For recent reviews on oxidative Heck (Fujiwara–Moritani) reaction, see: (a) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, 1399. (b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley-VCH: Weinheim, **2009**, 345–382.

(2) For a recent review on catalytic functionalization of indoles, see: Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.

(3) For examples on catalytic intermolecular oxidative Heck reactions of indoles, see: (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125. (b) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (c) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097.

(4) β-Carbolinones: (a) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919. (b) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625. Carbazoles: (c) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339. Indoles annulated with cyclopentane and cyclohexane: (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. Enantioselective variant: (e) Schiffner, J. A.; Machotta, A. B.; Oestreich, M. *Synlett* **2008**, 2271.

(5) Azepinoindole in *Iboga* alkaloids: (a) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. (c) Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334.

(6) Azocinoindole in *Deoxyisoaustamide* and *Okaramine N*: (a) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (b) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.

(7) Joucla, L.; Montagne, C.; Fournet, G.; Joseph, B. *Lett. Org. Chem.* **2005**, *2*, 707.

(8) (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (c) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874.

(9) (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (c) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 928. (d) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357.

(10) For a recent review on C–C bond-forming palladium-catalyzed reactions via C–H activation, see: Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

(11) Bäckvall, J. E. *Pure Appl. Chem.* **1992**, *64*, 429.
(12) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. Eur. J.* **2001**, *7*, 2481.
(13) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.
(14) For a detailed review on mechanisms of the Mizoroki–Heck Reaction, see: Jutand, A. *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley-VCH: Weinheim, **2009**, 1–50.
(15) For examples of similar palladacycles, see: (a) Vicente, J.; Saura-Llamas, I.; Bautista, D. *Organometallics* **2005**, *24*, 6001. (b) Motoyama, T.; Shimazaki, Y.; Yajima, T.; Nakabayashi, Y.; Naruta, Y.; Yamauchi, O. *J. Am. Chem. Soc.* **2004**, *126*, 7378.
(16) For a review on the role of benzoquinone and O_2 as oxidants in palladium-catalyzed reactions, see: Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149.