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Intramolecular Direct Arylation and Heck Reactions in the Formation of Medium-Sized Rings: Selective Synthesis of Fused Indolizine, Pyrroloazepine and Pyrroloazocine Systems

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Abstract: The intramolecular palladium-catalyzed reaction of *N*-(iodoarylalkyl)pyrroles can be applied for the selective synthesis of medium-sized rings by choosing the appropriate catalytic systems to direct the reaction to the alkene or to the pyrrole nucleus. These reactions can also be extended to the corresponding heteroaryl halides. Thus, reaction conditions have been established to access selectively to (hetero)fused indolizine, pyrroloazepine and pyrroloazocine systems.

Keywords: C–C coupling; direct arylation; Heck reaction; palladium

Introduction

Transition metal-catalyzed carbon-carbon bond-forming reactions represent important and useful synthetic methods in organic synthesis.[1] In this context, palladium-catalyzed coupling reactions[2] and, in particular, the Mizoroki–Heck reaction (M–H)[3] is of special relevance. These reactions have found wide application in the preparation of complex organic molecules, including heterocycles,[4] even in an asymmetric fashion, and are also applied in the chemical and pharmaceutical industries.[5]

The catalytic cycle of the M–H reaction has been studied in detail,[6] and it depends on the catalytic system and the presence of additives. Various types of palladium complexes have been reported to promote the vinylation of aryl halides, many of which follow the "classical" neutral Pd(0)/Pd(II) mechanism, as it is, for example, the case for $Pd(PPh_3)_4$.[7] In the case of $Pd(OAc)_2$/n PPh_3 ($n>2$) complexes, cationic $[ArPd(PPh_3)_2]^+$ species are to be considered as reactive intermediates in reactions performed with aryl halides in polar, aprotic solvents and at elevated temperatures.[8] When dppp is used instead of PPh_3, analogous electrophilic palladium(II) species have been reported for this catalytic system[9] although, in this case, the presence of thallium salts is necessary, as iodide ion scavenger.[10]

These electrophilic palladium(II) species have also been considered as reactive intermediates in direct arylation reactions of (hetero)arenes with aryl halides,[11] which initially were reported to occur *via* an S_EAr mechanism.[12] However, the fact that the reactivity has been shown to depend on C–H acidity,[13] not on (hetero)arene nucleophilicity, together with experimental and theoretical investigations,[14] led to the proposal of a concerted metalation–deprotonation (CMD) pathway for these direct arylation reactions.[15] In this mechanistic hypothesis, $Pd(OAc)_2$ is generally the transition metal precatalyst, and a carboxylate (or carbonate) anion plays a fundamental role in the C–H cleavage,[16] which occurs in the rate-determining step of this model simultaneously with carbon-palladium bond formation. In the CMD mechanism, the choice of an appropriate base represents an important element of catalyst design, so the influence of the anionic base and its counter cation on the outcome of the direct arylation should be taken into account.[17] Thus, CMD and nCMD (non-concerted metalation–deprotonation) mechanisms have been identified in the base-assisted, Pd-catalyzed direct arylation of oxazoles and thiole-4-carboxylates with aryl halides. Modulation of intrinsic basicity (K^+ *vs.* Cs^+) and ligand electronic effects were shown to be important for controlling the subtle CMD/nCMD competition.[18]

In this context, the reactivity and regioselectivity of palladium-catalyzed intermolecular direct arylation of several heterocycles, including pyrroles, have been studied.[11] Moreover, the intramolecular palladium coupling reaction onto pyrrole derivatives has also

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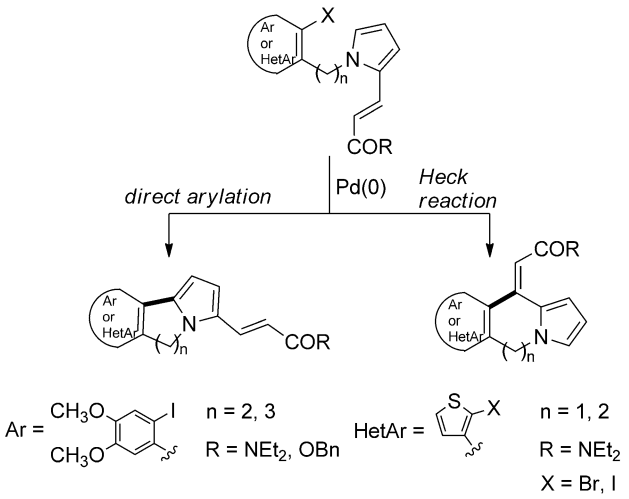

Figure 1.

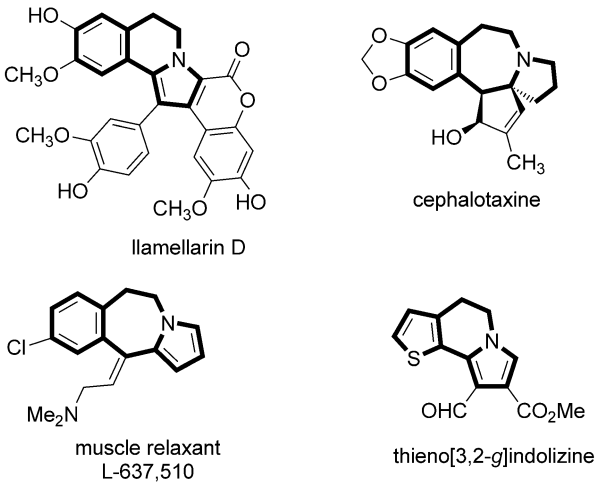

Figure 2. Examples of relevant bioactive structures bearing fused indolizine and pyrroloazepine framework.

been used in the synthesis of several types of nitrogen heterocycles.[19] However, since Mizoroki–Heck and direct arylation reactions share common reaction conditions, competition between the intramolecular M–H and direct arylation reactions could be established in (hetero)arenes bearing alkenes.[20] Thus, we have demonstrated[21] that the intramolecular palladium-catalyzed reaction of 2-alkenyl-substituted *N*-(*ortho*-iodobenzyl)pyrroles can be switched from the alkene (M–H reaction) to the pyrrole nucleus (direct arylation) by choosing the appropriate catalytic system, regardless of the nature of the substituent on the alkene. We proposed that the nature of the palladium intermediate species formed after the oxidative addition to the aryl halide determines the chemoselectivity of the reaction. The substitution patterns on the alkene do not affect the course of C-2 direct arylation of pyrrole derivative. This is one of the few examples of competition between intramolecular direct arylation and M–H reactions.[22]

Therefore, we decided to investigate further the scope of these types of intramolecular palladium-catalyzed reactions. Intramolecular Mizoroki–Heck and C–H activation reactions are well suited for the construction of five- and six-membered rings. However, there are few precedents for the formation of medium-sized rings, which usually require high catalyst loadings and high temperatures.[23–25]

Our first goal was to examine the effect of ring size on the competition, so we chose 2-alkenyl-substituted *N*-(*ortho*-iodophenylalkyl)pyrroles as substrates, modifying the linker between the nitrogen atom of the pyrrole ring and the aromatic ring. On the other hand, since C–H activation reactions, both in inter- and intramolecular versions, are mostly limited to coupling of aryl halides with (hetero)arenes, we also decided to investigate heteroaryl halides, such as thiophenes, as coupling partners (Figure 1). This approach would lead to a number of structurally diverse heterocyclic systems with biological relevance, such as pyrroloisoquinolines (anti-infertility and antitumor activities),[26] benzazepines (muscle relaxant, antihypertensive, and antipsychotic properties)[27] and benzazocines (antiviral agents),[28] and their heterofused analogues, as thienoindolizines (cardioprotectants and central nervous system agents).[29] Besides, these heterocyclic frameworks are found in several types of natural products, such as the lamellarin class of marine alkaloids,[30] *Cephalotaxus* alkaloids,[31] buflavine[32] or homoerythrinan alkaloids[33] (Figure 2).

Results and Discussion

We started studying the direct arylation reaction on pyrroles **1** and **2**[34] applying the conditions previously optimized for the formation of five-membered rings. As shown in Table 1 (Scheme 1), treatment of **1a** with $Pd(OAc)_2$ (2.5 mol%) in the presence of PPh_3 (10 mol%) and $(n\text{-Bu})_4NOAc$ in DMSO for 3 h gave only 35% of pyrroloisoquinoline **3a** (entry 1). The formation of the six-membered ring is slower than the formation of the five-membered ring,[35] so the reaction could be completed in a good yield (83%) when the reaction time was extended to 23 h (entry 2). Alternatively, an increase of the precatalyst loading to 5 mol% gave an excellent yield in 5 h (entry 3), that could be reduced to only two, if the reaction was carried out in DMF (entry 4). Analogously, the reaction required a longer time when $Pd(OAc)_2$ (2.5 mol%) was used in the presence of dppp (5 mol%) and TlOAc (entry 5) that could be reduced to 5 h using a 5 mol% of the precatalyst (entry 6).

The formation of the seven-membered ring of the pyrrolobenzazepine **4a** was significantly slower (en-

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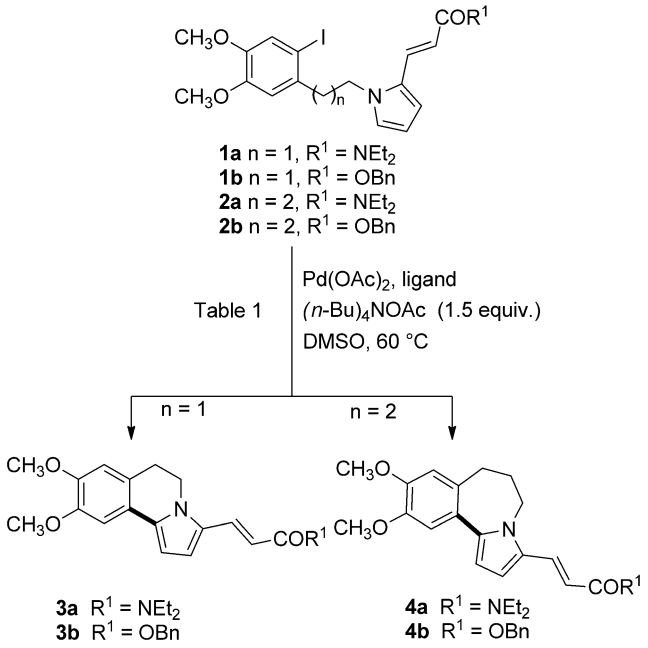
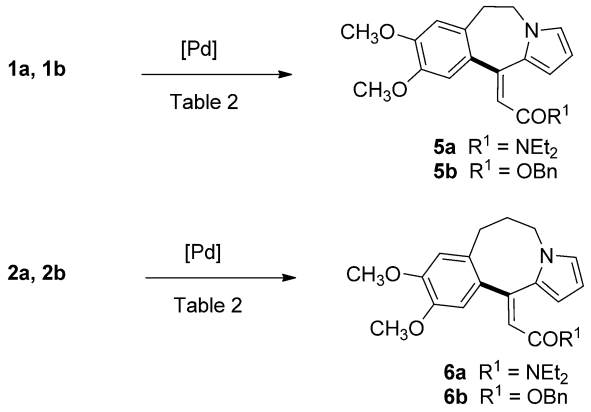
Table 1. Direct arylation of **1a**,**b** and **2a**,**b**. Synthesis of pyrroloisoquinolines **3** and pyrrolobenzazepines **4** (Scheme 1).

Entry	Substratae	$Pd(OAc)_2$ [mol%]	Ligand	Time [h]	Product	Yield [%]
1	**1a**	2.5	PPh_3[a]	3	**3a**	35
2	**1a**	2.5	PPh_3[a]	23	**3a**	83
3	**1a**	5	PPh_3[a]	5	**3a**	94
4	**1a**	5	PPh_3[a]	2[b]	**3a**	99
5	**1a**	2.5	dppp[c]	15	**3a**	63
6	**1a**	5	dppp[c]	5	**3a**	85
7	**1b**	5	PPh_3[a]	2	**3b**	84
8	**2a**	2.5	PPh_3[a]	65	**4a**	45
9	**2a**	5	PPh_3[a]	72	**4a**	60
10	**2a**	5	PPh_3[a]	1[b]	**4a**	84
11	**2a**	10	PPh_3[a]	48	**4a**	71
12	**2a**	2.5	dppp[c]	72	**4a**	20
13	**2a**	5	dppp[c]	96	**4a**	60
14	**2a**	10	dppp[c]	72	**4a**	70
15	**2b**	5	PPh_3[a]	2	**4b**	70

[a] 10 mol%.
[b] DMF was used as solvent.
[c] 5 mol%, TlOAc (1.2 equiv.) was also added.



Scheme 1.



Scheme 2.

tries 8 and 9, 11–14). In general, the formation of seven-membered rings by direct arylation requires a high catalyst loading or high temperatures, presumably due to the difficult formation of intermediate eight-membered palladacycles.[25] However, the pyrroloazepinone **4a** could be obtained in good yields by increasing the precatalyst loading to 5 or 10 mol% (entries 13 and 14), at 60 °C in DMSO. Interestingly, when DMF was used as solvent, at the same temperature, the reaction was completed in just 1 h with 5 mol% of palladium acetate (entry 10). The arylation reaction was faster in both cases with the ester derivatives, obtaining **3b** and **4b** in good yields with 5 mol% of $Pd(OAc)_2$ (entries 7 and 15).

We next moved to the optimization of the M–H reaction conditions to obtain selectively pyrroloazepines **5** and pyrroloazocines **6**. The application of the M–H reaction to the formation of seven- and eight-membered rings is not so general, and may lead to the formation of regioisomeric mixtures of products resulting from competing *endo* and *exo* cyclizations.[36] In our previous work,[21] we had shown that the M–H reaction occurred with complete regioselectivity for the formation of an isoquinoline ring when $Pd(PPh_3)_4$ was used. Thus, we took those reaction conditions as starting point. As shown in Table 2 (Scheme 2), pyrroloazepine **5a** was obtained in moderate yield with 3 mol% of the catalyst using Et_3N as base, and in the

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Table 2. Mizoroki–Heck reaction of **1a**,**b** and **2a**,**b**. Synthesis of pyrroloazepines **5** and pyrroloazocines **6** (Scheme 2).

Entry	Substrate	[Pd]	Ligand	Base	Additive	Solvent	Time [h]	Product	Yield [%]
1	**1a**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	CH_3CN	23	**5a**	64
2	**1a**	$Pd(PPh_3)_4$[d]	–	$NaHCO_3$[e]	$(n\text{-}Bu)_4NCl$[f]	CH_3CN	16	**5a**	77
3	**1a**	$Pd(PPh_3)_4$[a]	–	$NaHCO_3$[e]	$(n\text{-}Bu)_4NCl$[f]	DMF	3	**5a**	86
4	**1a**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	DMF	3	**5a**	91
5	**1a**	$Pd(dba)_2$[d]	PPh_3[g]	Et_3N[c]	–	DMF	6	**5a**	31[k]
6	**1a**	$Pd(dba)_2$[d]	$P(o\text{-}Tol)_3$[g]	Et_3N[c]	–	DMF	8	**5a**	86
7	**1a**	$Pd(dba)_2$[d]	$P(o\text{-}Tol)_3$[h]	Et_3N[c]	–	DMF	3	**5a**	67
8	**1a**	$Pd(dba)_2$[d]	PCy_3[g]	Et_3N[c]	–	DMF	29	**5a**	53[l]
9	**1a**	$Pd(dba)_2$[d]	$P(t\text{-}Bu)_3$[g]	Et_3N[c]	–	DMF	24	**5a**	77
10	**1a**	$Pd(dba)_2$[d]	$P(t\text{-}Bu)_3$[g]	Cy_2NMe[c]	–	DMF	5	**5a**	82
11	**1a**	$Pd_2(dba)_3$[i]	$P(t\text{-}Bu)_3$[j]	Cy_2NMe[c]	–	dioxane	168	**5a**	68
12	**1b**	$Pd(PPh_3)_4$[d]	–	$NaHCO_3$[e]	$(n\text{-}Bu)_4NCl$[f]	CH_3CN	6	**5b**	56
13	**2a**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	CH_3CN	25	**6a**	47[m]
14	**2a**	$Pd(PPh_3)_4$[d]	–	$NaHCO_3$[e]	$(n\text{-}Bu)_4NCl$[f]	CH_3CN	96	**6a**	27[m]
15	**2a**	$Pd(PPh_3)_4$[g]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	DMF	3	**6a**	80
16	**2a**	$Pd(dba)_2$[d]	$P(o\text{-}Tol)_3$[h]	Et_3N[c]	–	DMF	3	**6a**	53[n]
17	**2a**	$Pd(dba)_2$[d]	$P(t\text{-}Bu)_3$[g]	Cy_2NMe[c]	–	DMF	168	**6a**	32
18	**2b**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	CH_3CN	50	**6b**	31

[a] 3 mol%.
[b] 12 equiv.
[c] 2 equiv.
[d] 5 mol%.
[e] 2.5 equiv.
[f] 1.5 equiv.
[g] 10 mol%.
[h] 20 mol%.
[i] 0.5 mol%.
[j] 1 mol%.
[k] 30% of **3a** was obtained.
[l] 41% of **3a** was obtained.
[m] 36% of **4a** was obtained.
[n] 20% of **4a** was obtained.

presence of $(n\text{-}Bu)_4NCl$ in CH_3CN at reflux (entry 1). No formation of other regioisomers or the arylation product **3a** was detected by NMR. A change in the base to $NaHCO_3$ improved the yield (entry 2), but the best results were obtained when the reaction was carried out in DMF at 110 °C. Thus, **5a** was obtained in excellent yield in just 3 h using 3 mol% of the precatalyst (entries 3 and 4).

Interestingly, the direct arylation reaction was competitive when $Pd(dba)_2$ in the presence of PPh_3 was used, obtaining a mixture of **5a** and **3a** (entry 5). The nature of the ligand has been shown to have an important effect both in the reactivity and in the regioselectivity of Heck and arylation reactions.[22c,d] Thus, this loss of regioselectivity could be avoided using tri-*ortho*-tolylphosphane as ligand, leading to a good yield of **5a** (entries 6 and 7). On the other hand we studied also the bulky trialkylphosphanes (tri-*tert*-butylphosphane and tricyclohexylphosphane). These ligands are known to stabilize highly reactive coordinatively unsaturated palladium species, and have been used to perform room temperature Heck reactions.[37]

In our case, when **1a** was treated with $Pd(dba)_2$/PCy_3 using Et_3N as the base in DMF at 130 °C, the arylation product **3a** was isolated (41%) together with the desired M–H product **5a** (53%) (entry 8). The use of tri-*tert*-butylphosphane as ligand afforded chemoselectively **5a** in good yield (77%) (entry 9). The reaction was more efficient with $P(t\text{-}Bu)_3$ on changing the base to Cy_2NMe (entry 10). Moreover, it was possible to obtain selectively the pyrroloazepine **5a** in 68% yield by employing a low catalyst loading (0.5 mol%) (entry 11), albeit with a longer reaction time. The formation of the eight-membered ring of the pyrrolobenzazocine **6a** with $Pd(PPh_3)_4$ was slower (entries 13 and 14) and non-selective as in both cases the arylation product **4a** was also isolated. However, pyrrolobenzazocine **6a** could be obtained in good yield (80%) by increasing the catalyst loading to 10 mol% (entry 15) at 110 °C in DMF. No formation of the other regioisomer or the arylation product **4a** was detected. In this case, the use of bulky phosphanes did not improve the results (entries 16 and 17). It was also possible to control the chemoselectivity with the ester deriva-

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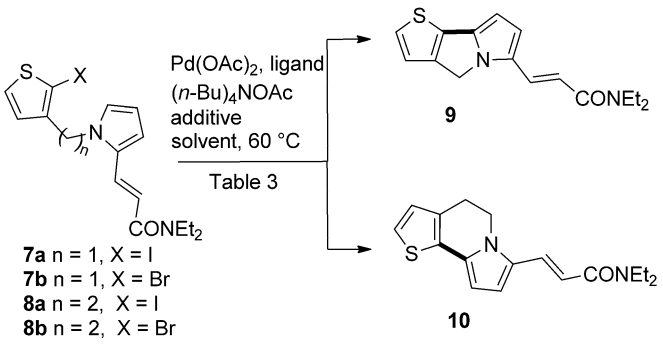
Table 3. Direct arylation of **7a**,**b** and **8a**,**b**. Synthesis of thienopyrrolizine **9** and thienoindolizine **10** (Scheme 3).

Entry	Substrate	$Pd(OAc)_2$ [mol%]	Ligand	Time [h]	Solvent	Product	Yield [%]
1	**7a**	5	PPh_3[a]	23	DMSO	**9**	11
2	**7a**	5	PPh_3[a]	23	DMF	**9**	52
3	**7a**	10	PPh_3[a]	4	DMF	**9**	73
4	**7b**	10	PPh_3[a]	4	DMF	**9**	45
5	**7b**	10	PPh_3[a]	16	DMF	**9**	93
6	**7a**	5	dppp[b]	27	DMSO	**9**	30
7	**8a**	5	PPh_3[a]	23	DMSO	**10**	61
8	**8a**	5	PPh_3[a]	6	DMF	**10**	65
9	**8a**	10	PPh_3[a]	6	DMF	**10**	85
10	**8b**	10	PPh_3[a]	6	DMF	**10**	71
11	**8a**	5	dppp[b]	27	DMSO	**10**	66

[a] 10 mol%.
[b] 5 mol%, TlOAc (1.2 equiv.) was also added.



Scheme 3.

tives, obtaining **5b** and **6b** in moderate yields (entries 12 and 18).

Our next goal was to investigate the use of heteroaryl halides as coupling partners in these types of reactions. For this purpose, we selected the structures represented in Scheme 3, to study the influence of the size of the ring formed ($n=1$, 2), and the nature of the halogen atom.

We started by studying the direct arylation reaction on thiophenes **7a**,**b** and **8a**,**b**[34] on applying the conditions previously optimized for the formation of five-membered rings.[21] As shown on Table 3, treatment of **7a** with $Pd(OAc)_2$ (5 mol%) in the presence of PPh_3 (10 mol%) and $(n\text{-Bu})_4NOAc$ in DMSO for 23 h gave only 11% of the thienopyrrolizine **9** (entry 1), recovering unreacted starting material. The use of DMF resulted in a faster reaction, obtaining **9** in moderate yield (entry 2). An increase of pre-catalyst loading provided the best result for the iodinated thiophene **7a** obtaining **9** in 73% isolated yield (entry 3). Under these conditions, the brominated substrate **7b** was less reactive and required a longer time (16 *vs.* 4 h), obtaining the thienopyrrolizine **9** in excellent yield (93%) (entries 4 and 5).

Analogously, the thienoindolizine **10** was obtained in good yield under similar conditions starting from iodide **8a** (entry 7). The change of the solvent enhanced the reaction rate, and an increase of the pre-catalyst loading to 10 mol% gave an excellent yield of thienoindolizine **10** (entries 8 and 9). In this case, the reaction of the brominated thiophene **8b** (entry 10) gave a similar result. The use of dppp as ligand in the presence of TlOAc did not improve these results (entries 6 and 11).

We next moved to the optimization of the Mizoroki–Heck reaction (Table 4, Scheme 4). Thus, we took the best reaction conditions obtained for the *N*-(*ortho*-iodoarylakyl)pyrroles as a starting point. As shown in Table 4, only small amounts of **11** were obtained with 3 mol% of the catalyst using Et_3N as base, and in the presence of $(n\text{-Bu})_4NCl$ in DMF at 110 °C, recovering unreacted starting material (entry 1). An increase of catalyst loading did not improve the results, neither did changes of the base and the solvent (entries 2 and 3). Only traces of the thienoindolizine **11** were obtained when employing a bulky ligand (entry 5). No improvement was observed using bromide **7b** (entries 4 and 6). However, the pyrroloazepine **12** could be obtained in moderate yield under the standard conditions, although in this case the competitive arylation reaction was observed, isolating **10** as a by-product (entry 7). The change of the solvent to CH_3CN changed completely the chemoselectivity of the reaction giving the arylation product **10** in excellent yield (entry 8), while not observing the formation of **12**. The use of bulky ligands did not improve the results (entries 10 and 11). Interestingly the use of $Pd(OAc)_2$ in the presence of dppp using Et_3N as a base and $(n\text{-Bu})_4NI$ as additive in CH_3CN provided the benzazepine **12** as the major compound (entry 12).

The change in the chemoselectivity could be explained according to the intermediate palladium species involved in the catalytic cycles. As has been mentioned, in the case of $Pd(OAc)_2/n\,PPh_3$ ($n>2$) complexes, and equilibrium could be established between

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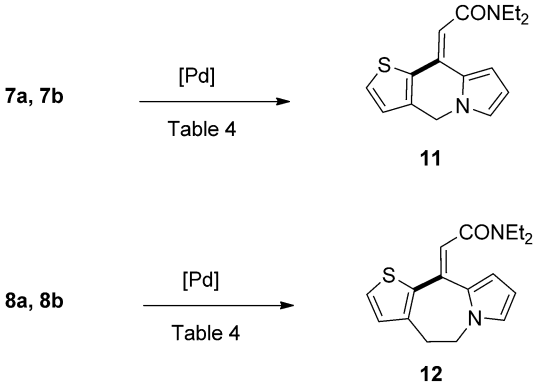
Table 4. Mizoroki–Heck reactions of **7a**,**b** and **8a**,**b** (Scheme 4).

Entry	Substrate	[Pd]	Ligand	Base	Additive	Solvent	Time [h]	Product	Yield [%]
1	**7a**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	DMF	8	**11**	5
2	**7a**	$Pd(PPh_3)_4$[d]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	DMF	7	**11**	14
3	**7a**	$Pd(PPh_3)_4$[e]	–	$NaHCO_3$[f]	$(n\text{-}Bu)_4NCl$[g]	CH_3CN	16	–	–
4	**7b**	$Pd(PPh_3)_4$[e]	–	$NaHCO_3$[f]	$(n\text{-}Bu)_4NCl$[g]	CH_3CN	16	–	–
5	**7a**	$Pd(dba)_2$[e]	$P(t\text{-}Bu)_3$[d]	Cy_2NMe[c]	–	DMF	11	**11**	<5
6	**7b**	$Pd(dba)_2$[e]	$P(t\text{-}Bu)_3$[d]	Cy_2NMe[c]	–	DMF	11	**11**	<5
7	**8a**	$Pd(PPh_3)_4$[a]	–	Et_3N[b]	$(n\text{-}Bu)_4NCl$[c]	DMF	8	**12**	45[i]
8	**8a**	$Pd(PPh_3)_4$[a]	–	$NaHCO_3$[f]	$(n\text{-}Bu)_4NCl$[g]	CH_3CN	16	**10**	87
9	**8b**	$Pd(PPh_3)_4$[a]	–	$NaHCO_3$[f]	$(n\text{-}Bu)_4NCl$[g]	CH_3CN	16	**12**	17
10	**8a**	$Pd(dba)_2$[e]	$P(t\text{-}Bu)_3$[d]	Cy_2NMe[c]	–	DMF	11	**12**	27[j]
11	**8b**	$Pd(dba)_2$[e]	$P(t\text{-}Bu)_3$[d]	Cy_2NMe[c]	–	DMF	11	**10**	15
12	**8a**	$Pd(OAc)_2$[d]	dppp[e]	Et_3N[f]	$(n\text{-}Bu)_4NI$[h]	CH_3CN	24	**12**	46[k]

[a] 3 mol%.
[b] 12 equiv.
[c] 2 equiv.
[d] 10 mol%.
[e] 5 mol%.
[f] 2.5 equiv.
[g] 1.5 equiv.
[h] 10 equiv.
[i] 23% of **10** was obtained.
[j] 41% of **10** was obtained.
[k] 26% of **10** was obtained.



Scheme 4.

trans-$ArPd(PPh_3)_2(OAc)$ species formed after oxidative addition, and cationic $[ArPd(PPh_3)_2]^+$ species in polar aprotic solvents. Thus, a mechanism involving an electrophilic palladium(II) species that would react preferentially at the more electron-rich pyrrole nucleus through an S_EAr pathway could be suggested.

However, a concerted metalation–deprotonation (CMD) pathway, involving proton abstraction by the acetate ion could also be proposed.[15–17] This mechanism would explain the selective arylation when a source of acetate ions, such as $(n\text{-}Bu)_4NOAc$, is added. Thus, it has been shown that the arylation reaction can be efficiently extended to the synthesis of six- and seven-membered rings, of pyrroloisoquinolines **3a**,**b** and pyrrolobenzazepines **4a**,**b**, although the reaction requires longer reaction times compared to the formation of five-membered rings reported previously.[21] This can be attributed to the more difficult formation of seven- and eight-membered palladacycle intermediates. However, an increase on the catalyst loading to 5 mol% and a switch of solvent to DMF has allowed the efficient synthesis of these heterocycles. Under similar reaction conditions the arylation of the pyrrole nucleus with the thiophenyl halide is slower. If the formation of the isoquinoline ring system of **3a** and the thienoindolizine ring system of **10** are compared, the reaction of the thiophene moiety requires longer reaction times (6 *vs.* 2 h) and higher catalyst loadings (10 mol% *vs.* 5 mol%) to reach completion. This may suggest that the palladium(II) species formed after oxidative addition is less reactive in the case of the thiophene ring.

On the other hand, the Mizoroki–Heck reaction to obtain the benzazepine and benzazocine skeletons of **5a**,**b** and **6a**,**b** can be carried out selectively with $Pd(PPh_3)_4$, presumably through a "classical" neutral mechanism, as stated above. However, the formation of the eight-membered ring is more difficult. The Mizoroki–Heck reactions with thiophenyl halides **7a**,**b** and **8a**,**b** have not been so effective. In this case, the seven-membered ring of **12** is obtained with better yield than the six-membered ring of **11**, although, again, in both cases the reactivity of the intermediate palladium(II) species towards the alkene seems to be lower.

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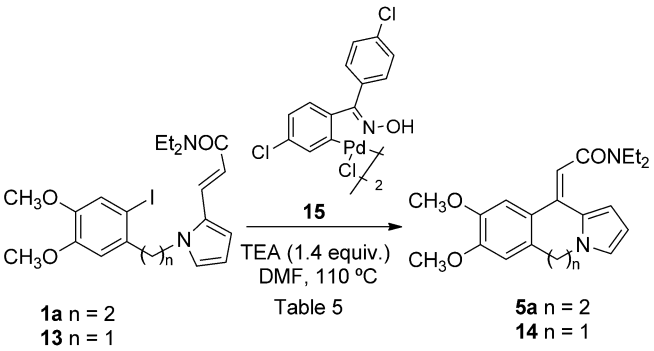


Scheme 5.

Besides, in these cases, under "classical" conditions that would lead to a neutral mechanism, the formation of the six-membered arylation product **10** is competitive with the formation of azepine **12**.

In view of these results, we decided to explore other catalytic systems in order to achieve a selective Mizoroki–Heck reaction. In this context, oxime-based palladacycles are very efficient and versatile pre-catalysts for a wide range of useful and well known C–C coupling processes.[38] Thus, we decided to study the intramolecular Mizoroki–Heck reaction using palladacycle **15** for the formation of six- and seven-membered rings of pyrroloazepine **5a** and pyrroloisoquinoline **14**[21] (Scheme 5, Table 5).

Table 5. Mizoroki–Heck reactions of **1a** and **13** catalyzed by palladacycle **15** (Scheme 5).

Entry	Substrate	**15** [mol%]	Time [h]	Product	Yield [%]
1	**1a**	10^{-2}	46	–	–[a]
2	**1a**	10^{-1}	75	**5a**	32
3	**1a**	1	7	**5a**	74
4	**1a**	5	8	**5a**	31
5	**13**	10^{-2}	24	–	–[a]
6	**13**	10^{-1}	76	–	–[a]
7	**13**	1	7	**14**	36
8	**13**	5	4	**14**	46

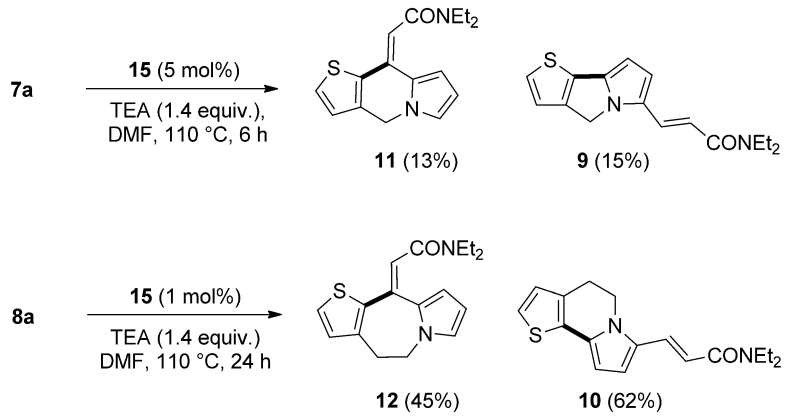
[a] Starting material was recovered.

The formation of the seven-membered ring required an increase of the catalyst loading to 1 mol% providing the pyrrolobenzazepine **5a** in good yield (entry 3). No reaction or low conversion was obtained with lower catalyst loadings (entries 1 and 2). On the other hand, the use of a higher catalyst loading (5 mol%) did not improve the results (entry 4). It has been shown that an increase of the catalyst loading may diminish the reaction rate, as the formation of inactive aggregates of Pd(0) black may be favoured at higher concentrations.[38b] The formation of the six-membered ring of pyrroloisoquinoline **14** was less efficient, obtaining only moderate yields (entries 7 and 8).

Analogously we studied the Mizoroki–Heck reaction in the thiophene derivatives **7a** and **8a** (Scheme 6). In both cases the reaction was non-selective. With iodide **7a**, almost equal amounts of arylation and Mizoroki–Heck products were obtained, with low conversion. The reaction of iodide **8a** was faster for the formation of the six-membered ring obtaining the arylation product **10** as the major compound. This is one of the few reported examples of the use of this type of oxime palladacycle in direct arylation reactions.[39]

Conclusions

The intramolecular palladium-catalyzed reaction of *N*-(arylalkyl)pyrroles can be applied for the selective synthesis of medium-sized rings by choosing the appropriate catalytic systems to direct the reaction to the alkene or to the pyrrole nucleus. Thus, $Pd(OAc)_2$ and PPh_3 or dppp provided selectively pyrrolo[2,1-*a*]isoquinolines **3a**,**b** and pyrrolo[1,2-*a*]benzazepines **4a**,**b** through arylation reactions. On the other hand, $Pd(PPh_3)_4$ drives the reaction to the alkene through a Mizoroki–Heck reaction, leading selectively to



Scheme 6.

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pyrrolo[1,2-*a*]benzazepines **5a**,**b** and pyrrolo[1,2-*a*]benzazocines **6a**,**b**. The formation of six-, seven- and eight-membered rings either by Mizoroki–Heck reaction and direct arylation requires longer reaction times and higher catalyst loadings than for the smaller rings.

These reactions can also be extended to heteroaryl halides. Although the direct arylation reaction is competitive even under neutral mechanism conditions, selective formation of heterofused systems, such as thieno[2,3-*a*]pyrrolizine **9**, thieno[3,2-*g*]indolizine **11**, thieno[3,2-*f*]indolizine **10** and pyrrolo[1,2-*d*]thieno-[2,3-*d*]azepine **12** can be achieved under the optimized conditions. The intramolecular Mizoroki–Heck reaction employing oxime-based palladacycle **15** allows the selective synthesis of pyrrolo[1,2-*a*]benzazepine and pyrrolo[1,2-*b*]isoquinoline skeletons using 1 mol% of **15**. On the contrary, the direct arylation reaction is the major reaction when thiophenyl halides are used.

Experimental Section

(*E*)-3-(8,9-Dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)-*N*,*N*-diethylacrylamide (3a) (Table 1, entry 4)

$Pd(OAc)_2$ (2.2 mg, 0.01 mmol) was added to a mixture of *N*-phenethylpyrrole **1a** (126 mg, 0.26 mmol), PPh_3 (6.9 mg, 0.02 mmol) and $(n\text{-}Bu)_4NOAc$ (122 mg, 0.39 mmol) in DMF (5 mL) and this mixture was stirred at 60 °C for 2 h. The reaction mixture was then diluted with 50 mL of EtOAc, washed with saturated NH_4Cl (30 mL) and H_2O (2×30 mL), dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography (silica gel, hexane/EtOAc = 2:8) gave **3a** as an oil; yield: 92 mg (99%). IR (neat): ν = 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.25 [m, 6H, $N(CH_2CH_3)_2$], 3.01 (t, J = 6.7 Hz, 2H, H-6), 3.42–3.47 [m, 4H, $N(CH_2CH_3)_2$], 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.12 (t, J = 6.7 Hz, 2H, H-5), 6.47 (d, J = 3.9 Hz, 1H, H-1), 6.58 (d, J = 14.9 Hz, 1H, =CH-CO), 6.70 (d, J = 3.9 Hz, 1H, H-2), 6.71 (s, 1H, H-10), 7.01 (s, 1H, H-7), 7.70 (d, J = 14.9 Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.3 (CH_3), 15.1 (CH_3), 29.3 (C-6), 40.9 (C-5), 41.1 (NCH_2CH_3), 42.1 (NCH_2CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 104.4 (C-1), 106.3 (C-7), 110.3 (C-2), 111.1 (C-10), 112.2 (=CH-CO), 121.7 (C-10a), 123.3 (C-6a), 129.6 (C-3), 129.7 (=CH-Ar), 133.4 (C-10b), 148.0, 148.3 (C-8, C-9), 166.2 (CO); MS (230 eV, CI): m/z (%) = 355 (58) $[MH]^+$, 354 (100) $[M]^+$, 340 (10), 282 (17), 255 (6); HR-MS (CI): m/z = 355.2020, calcd. for $C_{21}H_{27}N_2O_3$ $[MH]^+$: 355.2022.

(*E*)-Benzyl-3-(8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3-yl)acrylate (3b) (Table 1, entry 7)

$Pd(OAc)_2$ (2.1 mg, 0.01 mmol) was added to a mixture of *N*-phenethylpyrrole **1b** (132 mg, 0.25 mmol), PPh_3 (4.7 mg, 0.02 mmol) and $(n\text{-}Bu)_4NOAc$ (84 mg, 0.26 mmol) in DMSO and this mixture was stirred at 60 °C for 2 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 6:4) gave **3b** which was crystallized from hexane/EtOAc as a yellow solid; yield: 81 mg (84%); mp (hexane/EtOAc) 122–125 °C. IR (neat): ν = 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.02 (t, J = 6.7 Hz, 2H, H-6), 3.89 (s, OCH_3), 3.91 (s, OCH_3), 4.11 (t, J = 6.7 Hz, 2H, H-5), 5.24 (s, 2H, CO_2CH_2Ph), 6.21 (d, J = 15.5 Hz, 1H, =CH-CO), 6.76 (d, J = 4.05 Hz, 1H, H-1), 6.72 (s, 1H, H-7), 6.76 (d, J = 4.05 Hz, 1H, H-2), 7.02 (s, 1H, H-10), 7.30–7.43 (m, 5H, $COCH_2Ph$), 7.68 (d, J = 15.5 Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.5 (C-6), 41.05 (C-5), 56.0, 56.1 (OCH_3), 66.0 (CO_2CH_2Ph), 105.1 (C-1), 106.5 (C-10), 111.1 (C-7), 111.3 (=CH-CO), 113.0 (C-2), 121.3 (C-10a), 123.5 (C-6a), 128.1 ($COCH_2Ph$), 128.2 ($COCH_2Ph$), 128.5 ($COCH_2Ph$), 128.7 (C-3), 132.1 (=CH-Ar), 134.6 (C-10b), 136.4 ($COCH_2Ph$), 148.4 (C-8, C-9), 167.7 (CO); MS (230 eV, CI): m/z (%) = 390 (100) $[MH]^+$, 389 (52) $[M]^+$, 375 (16), 299 (24), 282 (12), 256 (18), 243 (17), 230 (40), 229 (33), 91 (38); HR-MS (CI): m/z = 390.1690, calcd. for $C_{24}H_{24}NO_4$ $[MH]^+$: 390.1705.

(*E*)-3-(9,10-Dimethoxy-6,7-dihydro-5*H*-benzo[*c*]-pyrrolo[1,2-*a*]azepin-3-yl)-*N*,*N*-diethylacrylamide (4a) (Table 1, entry 10)

$Pd(OAc)_2$ (2.1 mg, 0.01 mmol) was added to a mixture of *N*-phenylpropylpyrrole **2a** (93 mg, 0.18 mmol), PPh_3 (5.0 mg, 0.02 mmol) and $(n\text{-}Bu)_4NOAc$ (88 mg, 0.28 mmol) in DMF (5 mL) and this mixture was stirred at 60 °C for 1 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 2:8) gave **4a** as an oil; yield: 56 mg (84%): IR (neat): ν = 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.26 [m, 6H, $N(CH_2CH_3)_2$], 2.20–2.26 (m, 2H, H-6), 2.60 (t, J = 7.1 Hz, 2H, H-7), 3.47–3.51 [m, 4H, $N(CH_2CH_3)_2$], 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.94 (t, J = 6.6 Hz, 2H, H-5), 6.28 (d, J = 3.9 Hz, 1H, H-1), 6.60 (d, J = 14.9 Hz, 1H, =CH-CO), 6.69 (d, J = 3.9 Hz, 1H, H-2), 6.76 (s, 1H, H-11), 6.92 (s, 1H, H-8), 7.61 (d, J = 14.9 Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.3 (CH_3), 15.1 (CH_3), 29.9 (C-6), 32.2 (C-7), 41.2 (NCH_2CH_3), 41.7 (C-5), 42.3 (NCH_2CH_3), 56.0 (OCH_3), 56.1 (OCH_3), 107.6 (C-1), 109.6 (C-2), 111.5 (C-11), 112.5 (=CH-CO), 112.7 (C-8), 125.6 (C-11a), 130.3 (C-7a), 130.4 (=CH-Ar), 130.5 (C-3), 138.8 (C-11b), 147.8, 148.6 (C-9, C-10), 166.3 (CO); MS (230 eV, CI): m/z (%) = 369 (88) $[MH]^+$, 368 (100) $[M]^+$, 354 (14), 297 (10), 296 (33), 256 (12), 243 (8); HR-MS (CI): m/z = 369.2182, calcd. for $C_{22}H_{29}N_2O_3$ $[MH]^+$: 369.2178.

(*E*)-Benzyl-3-(9,10-dimethoxy-6,7-dihydro-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepin-3-yl)acrylate (4b) (Table 1, entry 15)

$Pd(OAc)_2$ (5.7 mg, 0.02 mmol) was added to a mixture of *N*-phenylpropylpyrrole **2b** (132 mg, 0.25 mmol), PPh_3 (6.6 mg, 0.02 mmol) and $(n\text{-}Bu)_4NOAc$ (116 mg, 0.37 mmol) in DMSO (5 mL) and this mixture was stirred at 60 °C for 2 h 30 min. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 4:6) gave **4b** as yellow solid which was crystallized from hexane/EtOAc; yield: 70 mg (70%): mp (hexane/EtOAc) 128–130 °C. IR (neat): ν = 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (t, J =

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6.8 Hz, 2H, H-6), 2.62 (t, J=7.1 Hz, 2H, H-7), 3.86–3.95 (m, 8H, 2×OCH_3, H-5), 5.24 (s, 2H, CO_2CH_2Ph), 6.22 (d, J=15.6 Hz, 1H, =CH-CO), 6.32 (d, J=3.9 Hz, 1H, H-1), 6.75 (d, J=3.9 Hz, 1H, H-2), 6.78 (s, 1H, H-8), 6.93 (s, 1H, H-11), 7.30–7.44 (m, 5H, $COCH_2Ph$), 7.67 (d, J=15.6 Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=30.3 (C-7), 32.2 (C-6), 41.9 (C-5), 56.0 (2×OCH_3), 66.1 (CO_2CH_2Ph), 108.2 (C-1), 111.3 (C-11), 111.5 (=CH-CO), 112.2 (C-2), 112.6 (C-8), 125.2 (C-7a), 128.0 ($COCH_2Ph$), 128.1 ($COCH_2Ph$), 128.5 ($COCH_2Ph$), 128.9 (C-3), 130.4 (C-11a), 132.8 (=CH-Ar, 136.4 ($COCH_2Ph$), 140.3 (C-11b), 147.7 (C-8), 148.7 (C-9), 167.7 (CO); MS (230 eV, CI): m/z (%)=404 (100) $[MH]^+$, 403 (42) $[M]^+$, 313 (14), 296 (11), 272 (15), 270 (14), 258 (13), 257 (12), 244 (40), 243 (27), 229 (13), 91 (25); HR-MS (CI): m/z=404.1844, calcd. for $C_{25}H_{26}NO_4$ $[MH]^+$: 404.1862.

(*Z*)-2-(8,9-Dimethoxy-5*H*-benzo[*d*]pyrrolo[1,2-*a*]-azepin-11(6*H*)-ylidene)-*N*,*N*-diethylacetamide (5a) (Table 2, entry 4)

$Pd(PPh_3)_4$ (7.9 mg, 0.006 mmol) was added to a mixture of *N*-phenethylpyrrole **1a** (109 mg, 0.22 mmol), (n-Bu)$_4$NCl (106 mg, 0.45 mmol) and Et_3N (0.4 mL, 2.71 mmol) in dry DMF (5 mL) and the mixture was stirred at 110 °C under argon 3 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc=2:8) gave **5a** as a yellow solid which was crystallized from hexane/EtOAc; yield: 71 mg (91%); mp (hexane/EtOAc) 168–171 °C. IR (neat):: ν=1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, J=7.1 Hz, 3H, NCH_2CH_3), 1.12 (t, J=7.1 Hz, 3H, NCH_2CH_3), 3.12–3.14 (m, 2H, H-6), 3.33 (q, J=7.1 Hz, 2H, NCH_2CH_3), 3.42 (q, J=7.1 Hz, 2H, NCH_2CH_3), 3.87 (s, 6H, OCH_3), 4.21–4.24 (m, 2H, H-5), 5.95 (s, 1H, CH=C), 6.07–6.08 (m, 1H, H-2), 6.38 (dd, J=3.7, 1.7 Hz, 1H, H-1), 6.61–6.62 (m, 1H, H-3), 6.68 (s, 1H, H-10), 7.01 (s, 1H, H-7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.3 (NCH_2CH_3), 13.6 (NCH_2CH_3), 33.0 ($ArCH_2$), 38.9 (NCH_2CH_3), 42.7 (NCH_2CH_3), 48.9 (CH_2N), 56.1 (OCH_3), 56.3 (OCH_3), 108.4 (C-2), 111.5, 111.6, 111.7 (C-1, C-10, C-7), 122.6 (CH=), 123.3 (C-3), 127.8 (C-6a), 128.7 (CH=C), 133.3 (C-10a), 136.5 (C-11), 148.0, 148.6 (C-9, C-10), 168.6 (CO); MS (230 eV, CI): m/z (%)=355 (100) $[MH]^+$, 354 (70) $[M]^+$, 310 (9), 283 (22), 282 (93), 256 (14), 255 (55), 242 (18); HR-MS (CI): m/z=355.2027, calcd. for $C_{21}H_{27}N_2O_3$ $[MH]^+$: 355.2022; anal. calcd. for $C_{21}H_{26}N_2O_3$: C 71.16, H 7.39, N 7.90; found: C 70.75, H 7.46, N 7.65.

(*Z*)-Benzyl 2-(8,9-Dimethoxy-5*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepin-11(6*H*)-ylidene)acetate (5b) (Table 1, entry 12)

$Pd(PPh_3)_4$ (13.7 mg, 0.01 mmol) was added to a mixture of *N*-phenethylpyrrole **1b** (121 mg, 0.23 mmol), (n-Bu)$_4$NCl (83 mg, 0.35 mmol) and $NaHCO_3$ (49 mg, 0.58 mmol) in dry CH_3CN (5 mL) and the mixture was heated to reflux for 3 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc=7:3) gave **5b** (oil) as a mixture of diastereomers *Z*/*E* 1:0.7 as established by ^{1}H NMR; yield: 51 mg (56%); data of the mixture are given. IR (neat): ν=1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.10–3.21 (m, 2H, H-6 both isom), 3.69 (s, 3H, OCH_3 isom *E*), 3.87 (s, 3H, OCH_3 isom *Z*), 3.88 (s, 3H, OCH_3 isom *Z*), 3.90 (s, 3H, OCH_3 isom *E*), 4.16–4.20 (m, 2H, H-5 isom *E*), 4.23–4.27 (m, 2H, H-5 isom *Z*), 5.08 (s, 2H, CH_2Ph isom *E*), 5.18 (s, 2H, CH_2Ph isom *Z*), 5.96 (s, 1H, CH=C isom *Z*), 6.14 (dd, J=3.6, 2.8 Hz, 1H, H-2 isom *E*), 6.16 (dd, J=3.6, 2.8 Hz, 1H, H-2 isom *Z*), 6.39–6.42 (m, 2H, H-1 isom *E*, CH=C isom *E*), 6.51 (dd, J=3.6, 1.7 Hz, H-1 isom *Z*), 6.66–6.70 (m, 3H, H-7 isom *Z*, H-3 both isom), 6.72 (s, 1H, H-10 isom *E*), 6.79 (s, 1H, H-7 isom *E*), 6.87 (s, 1H, H-10 isom Z), 7.23–7.37 (m, 5H, HPh both isom); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=32.2 (C-6 both isom), 55.9 (OCH_3 both isom), 56.1 (OCH_3 both isom), 48.8 (C-5 isom *Z*), 49.8 (C-5 isom *E*), 65.8 (CH_2Ph isom *E*), 66.1 (CH_2Ph isom *Z*), 108.6 (C-2 isom *E*), 108.7 (C-2 isom *Z*), 109.4 (C-1 isom *E*), 110.7 (C-10 isom *Z*), 110.8 (C-10 isom *E*), 111.7 (C-7 isom *Z*), 113.5 (H-1 isom *Z*), 115.5 (CH=C isom *E*), 117.5 (CH=C isom *Z*), 124.3 (C-2 isom *Z*), 125.6 (C-3 isom *E*), 127.4 (C-6a isom *Z*), 127.9 (CPh4 isom *Z*), 128.0 (CPh4 isom *E*), 128.1 (CPh3 isom *Z*), 128.2 (C-10c isom *Z*), 128.3 (CPh3 isom *E*), 128.4 (CPh2 isom *Z*/*E*), 128.5 (C11 isom *E*), 129.6 (C-10a isom *E*), 131.7 (C-6a isom *E*), 133.8 (C-10a isom *Z*), 136.1 (CPh1 isom *Z*/*E*), 147.1 ($COCH_3$ isom *E*), 147.3 (C-11 isom *Z*), 147.8 ($COCH_3$ isom *Z*), 148.7 (C-10b isom *E*), 149.0 ($COCH_3$ isom *Z*), 149.2 ($COCH_3$ isom *E*), 166.0 (CO isom *E*), 166.8 (CO isom *Z*); MS (230 eV, CI): m/z (%)=390 (100) $[MH]^+$, 100), 389 (23) $[M]^+$, 372 (12), 284 (12), 282 (41), 256 (11), 244 (10), 91 (13); HR-MS (CI): m/z=390.1687, calcd. for $C_{24}H_{24}NO_4$ $[MH]^+$: 390.1705.

(*Z*)-2-(9,10-Dimethoxy-6,7-dihydrobenzo[*d*]-pyrrolo[1,2-*a*]azocin-12(5*H*)-ylidene)-*N*,*N*-diethylacetamide (6a) (Table 2, entry 15)

$Pd(PPh_3)_4$ (25 mg, 0.02 mmol) was added to a mixture of *N*-phenylpropylyrrole **2a** (108 mg, 0.21 mmol), (n-Bu)$_4$NCl (102 mg, 0.43 mmol) and Et_3N (0.36 mL, 2.61 mmol) in 5 mL of dry DMF and the mixture was stirred at 110 °C for 3 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc=1:9) gave **6a** as a white solid; yield: 64 mg (80%); mp (hexane/EtOAc) 166–168 °C. IR (neat): ν=1645 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (t, J=7.1 Hz, 3H, NCH_2CH_3), 1.20 (t, J=7.1 Hz, 3H, NCH_2CH_3), 1.71–1.79 (m, 2H, H-6), 2.52 (t, J=6.2 Hz, 2H, H-7), 3.37 (q, J=7.1 Hz, 2H, NCH_2CH_3), 3.48 (q, J=7.1 Hz, 2H, NCH_2CH_3), 3.64–3.71 (m, 2H, H-5), 3.91 (s, 2H, OCH_3), 5.80 (s, 1H, CH=C), 6.11–6.14 (m, 1H, H-2), 6.54–6.56 (m, 1H, H-1), 6.56–6.59 (m, 2H, H-3, H-11), 7.06 (s, 1H, H-8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.2 (NCH_2CH_3), 13.9 (NCH_2CH_3), 29.9 (C-7), 32.8 (C-6), 38.8 (NCH_2CH_3), 42.5 (NCH_2CH_3), 45.4 (C5), 55.9 (OCH_3), 56.1 (OCH_3), 108.6 (C-2), 111.7 (C-11), 112.2 (C-8), 112.9 (C-3), 122.0 (CH=C), 124.5 (C-1), 129.9 (C-7a), 130.9 (C-12a), 131.8 (C-11a), 135.8 (C-12), 147.3, 149.6 (C-9, C-10), 169.3 (CO); MS (230 eV, CI) m/z (%)=369 (100) $[MH]^+$, 368 (52) $[M]^+$, 297 (18), 296 (61), 269 (28); HR-MS (CI): m/z=369.2178, calcd. for $C_{22}H_{29}N_2O_3$ $[MH]^+$: 369.2178.

(*Z*)-Benzyl 2-(9,10-dimethoxy-6,7-dihydrobenzo[*d*]-pyrrolo[1,2-*a*]azocin-12(5*H*)-ylidene)acetate (6b) (Table 2, entry 18)

$Pd(PPh_3)_4$ (9.5 mg, 0.008 mmol) was added to a mixture of *N*-phenylpropylpyrrole **2b** (143 mg, 0.24 mmol), (n-Bu)$_4$NCl

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(127 mg, 0.54 mmol) and Et_3N (0.5 mL) in dry CH_3CN (5 mL) and the mixture was heated under reflux for 50 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 8:2) gave **6b** as an oil; yield: 34 mg (31%): IR (neat): $\nu = 1710\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.81–1.88$ (m, 2H, H-6), 2.72 (t, $J = 6.7$ Hz, 2H, H-7), 3.43–3.58 (m, 2H, H-5), 3.71 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.98 (s, 2H, CO_2CH_2Ph), 6.16 (dd, $J = 3.8$, 2.6 Hz, 1H, H-2), 6.51 (s, 1H, CH=C), 6.63 (s, 1H, H11), 6.60–6.67 (m, 1H, H-1), 6.72 (s, 1H, H-8), 6.81 (dd, $J = 3.8$, 1.7 Hz, 1H, H-3), 7.13–7.41 (m, 5H, $COCH_2Ph$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 29.5$ (C-7), 32.8 (C-6), 46.5 (C-5), 55.7, 55.9 ($2 \times OCH_3$), 65.6 (CO_2CH_2Ph), 108.5 (C-2), 110.5 (C-11), 111.2 (C-3), 113.0 (CH=C), 113.3 (C-1), 127.5 (C-12a), 127.9 ($COCH_2Ph$), 128.2 ($COCH_2Ph$), 128.3 ($COCH_2Ph$), 129.5 (C-7a), 132.1 (C-11a), 136.3 ($COCH_2Ph$), 147.0 (C-8), 148.1 (C-9), 149.8 (C-12), 166.3 (CO); MS (230 eV, CI): m/z (%) = 404 (100) $[MH]^+$, 403 (23) $[M]^+$, 298 (12), 296 (41), 270 (14), 107 (13), 93 (21). 91 (41); HR-MS (CI): $m/z = 404.1845$, calcd. for $C_{25}H_{26}NO_4$ $[MH]^+$: 404.1862.

(*E*)-*N*,*N*-Diethyl-3-(4*H*-thieno[2,3-*a*]pyrrolizin-6-yl)-acrylamide (9) (Table 3, entry 5)

$Pd(OAc)_2$ (6.1 mg, 0.02 mmol) was added to a mixture of **7b** (97.9 mg, 0.26 mmol), PPh_3 (8.3 mg, 0.02 mmol) and (n-Bu)$_4$NOAc (105 mg, 0.40 mmol) in dry DMF (5 mL) and was heated at 60 °C over 16 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 6:4) afforded **9** as an oil; yield: 70 mg (93%). IR (neat): $\nu = 1635\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.19–1.24$ [m, 6H, $N(CH_2CH_3)_2$], 3.45–3.50 [m, 4H, $N(CH_2CH_3)_2$], 4.83 (s, 2H, H-4), 6.20 (d, $J = 3.7$ Hz, 1H, H-8), 6.51 (d, $J = 15.0$ Hz, =CH-CO), 6.61 (d, $J = 3.7$ Hz, 1H, H-7), 7.05 (d, $J = 4.9$ Hz, 1H, H-3), 7.24 (d, $J = 4.9$ Hz, 1H, H-2), 7.65 (d, $J = 15.0$ Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.3$ (NCH_2CH_3), 15.0 (NCH_2CH_3), 41.2 (NCH_2CH_3), 42.3 (NCH_2CH_3), 49.2 (C-4), 99.5 (C-7), 110.6 (C-8), 117.3 (=CH-CO), 121.0 (C-3), 126.5 (C-2), 127.8 (C-6), 130.7 (=CH-Ar), 134.1 (C-3a), 137.6 (C-8a), 144.3 (C-8b), 166.2 (CO); MS (230 eV, CI): m/z (%) = 287 (100) $[MH]^+$, 286 (52) $[M]^+$, 214 (33), 187 (7), 174 (7); HR-MS (CI): m/z = 287.1217, calcd. for $C_{16}H_{19}N_2OS$ $[MH]^+$: 287.1218.

(*E*)-3-(4,5-Dihydrothieno[3,2-*g*]indolizin-7-yl)-*N*,*N*-diethylacrylamide (10) (Table 3, entry 9)

$Pd(OAc)_2$ (51 mg, 0.02 mmol) was added to a mixture of **8a** (94 mg, 0.22 mmol), PPh_3 (5.8 mg, 0.02 mmol) and (n-Bu)$_4$NOAc (5.8 mg, 0.02 mmol) in dry DMF (5 mL) and was heated at 60 °C over 6 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 7:3) afforded **10** as an oil; yield: 56 mg (85%). IR (ATR): $\nu = 1630\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.18–1.25$ [m, 6H, $N(CH_2CH_3)_2$], 3.04 (t, $J = 7$ Hz, 2H, H-4), 3.47–3.50 [m, 4H, $N(CH_2CH_3)_2$], 4.16 (t, $J = 7$ Hz, 2H, H-5), 6.31 (d, $J = 3.9$ Hz, 1H, H-9), 6.60 (d, $J = 15.0$ Hz, 1H, =CH-CO), 6.66 (d, $J = 3.9$ Hz, 1H, H-8), 6.87 (d, $J = 4.9$ Hz, 1H, H-3), 7.08 (d, $J = 4.9$ Hz, 1H, H-2), 7.69 (d, $J = 15.0$ Hz, 1H, =CH-Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.2$ (NCH_2CH_3), 15.0 (NCH_2CH_3), 24.9 (C-4), 41.1 (NCH_2CH_3) 41.3 (C-5), 42.1 (NCH_2CH_3), 105.0 (C-8), 110.3 (C-9), 112.6 (=CH-CO), 122.2 (C-2), 126.7 (C-3), 129.2 (C-7), 129.7 (=CH-Ar), 129.8 (C-9a), 130.0 (C-3a), 131.1 (C-9b), 166.1 (CO); MS (230 eV, CI): m/z (%) = 301 (100) $[MH]^+$, 300 (58) $[M]^+$, 229 (18), 228 (28), 201 (7), 188 (6); HR-MS (CI): $m/z = 301.1368$, calcd. for $C_{17}H_{21}N_2OS$ $[MH]^+$: 301.1375.

(*E*)-*N*,*N*-Diethyl-2-{thieno[3,2-*f*]indolizin-9(4*H*)-ylidene}acetamide (11) (Table 4, entry 2)

$Pd(PPh_3)_4$ (27 mg, 0.02 mmol) was added to a mixture of **7a** (94 mg, 0.23 mmol), (n-Bu)$_4$NCl (107 mg, 0.46 mmol) and Et_3N (0.4 mL) in dry DMF (5 mL) and the mixture was stirred at 110 °C for 7 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 6:4) gave **11** as an oil; yield: 9.4 mg (14%). IR (ATR): $\nu = 1645\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.13$ (t, $J = 7.1$ Hz, 3H, NCH_2CH_3), 1.25 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3), 3.43 (q, $J = 7.1$ Hz, 2H, NCH_2CH_3), 3.56 (q, $J = 7.1$ Hz, 1H, NCH_2CH_3), 5.19 (s, 2H, H-4), 6.09 (s, 1H, =CH-CO), 6.30 (dd, $J = 3.9$, 2.8 Hz, 1H, H-7), 6.67 (dd, $J = 3.9$, 1.5 Hz, 1H, H-8), 6.84 (d, $J = 1.5$ Hz, 1H, H-6), 6.92 (d, $J = 5.1$ Hz, 1H, H-3), 7.24–7.27 (m, 1H, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.7$ (NCH_2CH_3), 14.3 (NCH_2CH_3), 39.1 (NCH_2CH_3), 42.8 (NCH_2CH_3), 46.0 (C-4), 108.8 (C-8), 110.3 (C-7), 110.4 (=CH-CO), 121.4 (C-6), 124.7 (C-8a), 125.1 (C-9a), 125.2 (C-3), 125.3 (C-2), 132.4 (C-3a), 134.9 (C-9), 168.3 (CO); MS (230 eV, CI): m/z (%) = 287 (100) $[MH]^+$, 286 (46) $[M]^+$, 273 (20), 214 (9); H-RMS (CI): $m/z = 287.1228$, calcd. for $C_{16}H_{19}N_2OS$ for $[MH]^+$: 287.1218.

(*E*)-*N*,*N*-Diethyl-2-{4*H*-pyrrolo[1,2-*a*]thieno[2,3-*d*]-azepin-10(5*H*)-ylidene}acetamide (12) (Table 4, entry 12)

$Pd(OAc)_2$ (5.4 mg, 0.02 mmol) was added to a mixture of **8a** (101 mg, 0.24 mmol), dppp (5.1 mg, 0.01 mmol), (n-Bu)$_4$NI (884 mg, 2.3 mmol) and Et_3N in dry CH_3CN (5 mL) and was heated at reflux over 24 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 6:4) afforded **12** as a solid; yield: 33 mg (46%), together with **10**; yield: 19 mg (26%).

Data for 12: mp (hexane/EtOAc) 114–116 °C. IR (ATR): $\nu = 1620\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.15$ Hz, 3H, NCH_2CH_3), 1.08 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3), 3.06–3.08 (m, 2H, H-4), 3.23 (q, $J = 7.1$ Hz, 2H, NCH_2CH_3), 3.37 (q, $J = 7.1$ Hz, 2H, NCH_2CH_3), 4.22–4.26 (m, 2H, H-5), 6.01 (dd, $J = 3.6$, 2.7 Hz, 1H, H-8), 6.32 (dd, $J = 3.6$, 1.7 Hz, 1H, H-9), 6.39 (s, 1H, =CH-CO), 6.61–6.63 (m, 1H, H-7), 6.76 (d, $J = 5.2$ Hz, 1H, H-3), 7.09 (d, $J = 5.2$ Hz, 1H, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.2$ (NCH_2CH_3), 13.5 (NCH_2CH_3), 31.8 (C-4), 38.7 (NCH_2CH_3), 42.4 (NCH_2CH_3), 47.1 (C-5), 107.5 (C-8), 111.8 (C-1), 122.0 (C-7, =CH-CO), 123.4 (C-2), 129.5 (C-9a), 129.7 (C-10a), 130.7 (C-3), 135.8 (C-3a), 137.0 (C-10), 167.8 (CO); MS (230 eV, CI): m/z (%) = 301 (91) $[MH]^+$, 300 (21) $[M]^+$, 256 (13), 230 (14), 229 (37), 228 (100), 201 (19), 188 (29), 116 (28): HR-MS (CI): $m/z = 301.1389$, calcd. for $C_{17}H_{21}N_2OS$ $[MH]^+$: 301.1375.

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(*Z*)-2-{7,8-Dimethoxypyrrolo[1,2-*b*]isoquinolin-10(5*H*)-ylidene}-*N*,*N*-diethylacetamide (14) (Table 5, entry 8)

Pd complex **15** (9.0 mg, 0.01 mmol) was added to a mixture of *N*-phenethylpyrrole **13**[21] (101 mg, 0.21 mmol) and Et_3N (0.04 mL) in 5 mL of dry DMF and the mixture was stirred at 110 °C for 4 h. Standard work-up, followed by column chromatography (silica gel, hexane/EtOAc = 1:9) gave **14** as a yellow solid which was crystallized from Et_2O; yield: 33 mg (46%); the data are coincidental to those reported:[21]; mp (Et_2O) 113–115 °C. IR (ATR): $\nu = 1610\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.1$ Hz, 3H, NCH_2CH_3), 1.23 (t, $J = 7.1$ Hz, 3H, NCH_2CH_3), 3.33 (q, $J = 7.1$ Hz, 2H, NCH_2CH_3), 3.52 (q, $J = 7.1$ Hz, 3H, NCH_2CH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H,OCH_3), 5.06 (s, 2H, H-5), 6.21 (bs, 2H, =CH-CO, H-1), 6.57 (bs, 1H, H-2), 6.68 (s, 1H, H-6), 6.77 (bs, 1H, H-3), 7.2 (s, 1H, H-9); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.5$ (NCH_2CH_3), 14.1 (NCH_2CH_3), 39.0 (NCH_2CH_3), 42.7 (NCH_2CH_3), 47.4 (C-5), 55.9 (2× OCH3), 106.8 (C-2), 108.4 (C-1), 108.7 (C-9), 109.7 (=CH-CO), 119.6 (C-6), 120.6 (C-3), 123.9 (C-5a), 124.5 (C-10a), 125.9 (C-9a), 128.1 (C-10), 148.5 (C-8), 149.7 (C-7), 169.1 (C=O).

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