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Intramolecular Palladium-Catalyzed Direct Arylation *vs.* Heck Reactions: Synthesis of Pyrroloisoquinolines and Isoindoles

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Abstract: The competition between C–H activation and Heck reactions has been studied on 2-alkenyl-substituted *o*-iodobenzylpyrroles. The reaction can be switched from the alkene to the pyrrole nucleus by choosing the adequate catalytic system, regardless of the nature of the substituent on the alkene, obtaining excellent yields of pyrrolo[1,2-*b*]isoquinolines or pyrrolo[2,1-*a*]isoindoles.

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

Introduction

Palladium-catalyzed coupling reactions of aryl and vinyl halides with alkenes have demonstrated to be extremely powerful methods for the construction of C–C bonds.[1] Since the important contribution made by Mizoroki and Heck in the early 1970s,[2] these transition metal-catalyzed transformations have found wide application in synthesis for preparing complex organic structures,[3] even in an asymmetric fashion.[4] In particular, intramolecular versions of the Mizoroki–Heck (MH) reaction have provided a very useful route to several types of heterocyclic systems.[5] In connection with our work on Parham-type cyclizations,[6] we have recently developed[7] an intramolecular carbolithiation for the synthesis of pyrrolo[1,2-*b*]isoquinolines, which represents the structural core of the lycorine class of *Amaryllidaceae* alkaloids[8] and the phenanthroindolizidine alkaloids.[9] Therefore, we decided to investigate the MH reaction as an alternative strategy for the synthesis of these compounds, since the same substrates, 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles, can be used in both types of intramolecular reactions. In addition, we were also intrigued by the possibility of a direct arylation reaction to take place on the C-2 pyrrole carbon to construct biaryl C–C bonds and give the corresponding isoindoles. Therefore, one of our challenges was to control the chemoselectivity associated with the intramolecular MH and C–H activation reactions (or direct arylation reaction).

Direct construction of biaryl C–C bonds by a Pd-catalyzed coupling of (hetero)arenes with aryl halides is a relatively clean and efficient method to generate the products in the most efficient and environmentally friendly way.[10] In this context, in 1990 Grigg[11] reported the first example of the palladium-catalyzed direct arylation of pyrrole using a tethered aryl iodide, the utility of which was demonstrated in the synthesis of the lamellarin class of marine natural products[12] or the pyrrolo[2,1-*a*]isoindolone nucleus of a novel series of potent Cdk4 inhibitors.[13] The potential of palladium-catalyzed functionalization of the pyrrole C–H function has also been shown by Trauner[14] in his synthesis of (±)-rhazinilam. Moreover, this intramolecular palladium coupling reaction onto pyrrole derivatives has been used in the synthesis of other nitrogen heterocycles, such as hetero-fused quinolones[15] and azepinones.[16] In a similar way, Lautens has reported the preparation of annulated nitrogen heterocycles *via* a one-pot palladium-catalyzed alkylation/norbornene-mediated direct arylation sequence.[17] Direct arylation of pyrroles has also been carried out using other types of aryl derivatives, such as iodine hipervalent reagents[18] or boronic acids.[19]

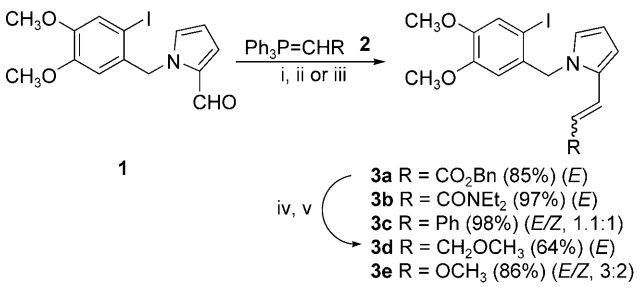
Herein we describe our results on the competition between the MH and direct arylation reactions on 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles with different substitution patterns on the alkene. We have

demonstrated that the cyclization may be switched from the isoquinoline to the isoindole nucleus by choosing the adequate catalytic system.

Results and Discussion

To investigate the competition between MH and C–H activation reactions, we prepared a series of 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles **3a–e** by Wittig reaction of aldehyde **1**[20] with the corresponding phosphorus ylides **2**, previously prepared (**2a**, R = CO_2Bn, **2b** R = $CONEt_2$), or generated *in situ* starting from the corresponding phosphomiun salt (**2c** R = Ph, **2e** R = OCH_3) (Scheme 1). When the reactions were carried out with stabilized ylides, compounds **3a, b** were isolated in good yields as single *E* stereoisomers. However, the reactions with ylides **2c, e** led to a mixture of both *E* and *Z* isomers, which could not be easily separated by column chromatography, so their ratio was calculated by ^{1}H NMR spectroscopy. Finally, **3d** was prepared by DIBALH reduction of **3a** to the corresponding alcohol and subsequent alkylation with MeI.

Our goal was to search for adequate catalytic systems to direct the intramolecular palladium-catalyzed reaction to the pyrrole ring or to the alkene. The catalytic cycle of the MH reaction has been studied in detail,[21] and it depends strongly on the catalytic system and the presence of additives. On the other hand, mechanistically the direct arylation of heteroarenes has been proposed to occur *via* oxidative addition of the transition metal into the aryl halide, followed by different pathways for the key carbon-carbon bond forming step.[10c] In this context, Fagnou[22] has recently reported that the concerted metalation-deprotonation (CMD) pathway,[23] first proposed by Echavarren and Maseras,[23d] accurately



Scheme 1. *Reagents and conditions:* (i) For **3a, b**: Ph_3P=$CHCO_2Bn$ or Ph_3P=$CHCONEt_2$, CH_2Cl_2, reflux, 4 days. (ii) For **3c**: $Ph_3P^+CH_2Ph$ Cl^- , *n*-BuLi, THF, 0 °C to −78 °C, 12 h. (iii) For **3e:** $Ph_3P^+CH_2OCH_3$ Cl^-, *t*-BuOK, toluene, room temperature, 5 h. (iv) For **3d**: DIBALH, toluene, −78 °C, 15 min; then MeOH, room temperature, 1 h. (v) NaH, THF, room temperature, 1.5 h; then MeI, room temperature, 16 h.

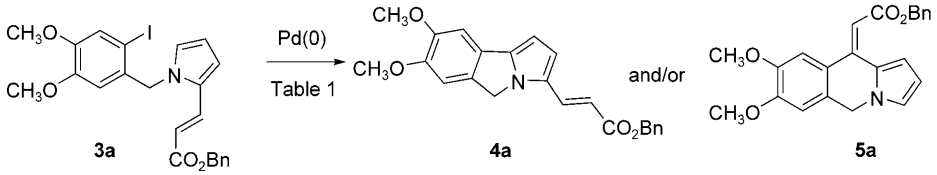
predicts both the relative rate and the regioselectivity of palladium-catalyzed direct arylation of electron-rich heteroarenes, which have been more commonly proposed to react *via* an SEAr pathway.[24]

With this in mind, we tested the first intramolecular Pd-catalyzed coupling reaction on 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrrole **3a** (R = CO_2Bn), using different catalytic systems in order to optimize the reaction conditions (Table 1).

Initial efforts to effect the carbon-carbon coupling reaction from compound **3a** employed the Jeffery[25] conditions: $Pd(OAc)_2$ (10 mol%), PPh_3 (40 mol%), $(n\text{-}Bu)_4NCl$ and $NaHCO_3$ in acetonitrile at 60 °C. Gratifyingly, the direct arylation product, pyrrolo[2,1-*a*]isoindole **4a** was obtained as major product. The dihydropyrrolo[1,2-*b*]isoquinoline **5a**, formed by intramolecular MH reaction, was also isolated as minor product (8% yield) (Table 1, entry 1). The reaction in DMF at 60 °C was equivalent to that in acetonitrile (entry 2), and superior to the reaction in less polar solvents. A series of palladium sources and ligands were screened in an effort to develop a cleaner reaction. Changing the ammonium salt [$(n\text{-}Bu)_4NOAc$ instead of $(n\text{-}Bu)_4NCl$, entry 3] increased the yield of isoindole derivative **4a** to a 92% in only 3 h. Similar results were obtained using NEt_3 as base or even in the absence of base (entries 4 and 5). Decreasing the catalyst loading in the original $Pd(OAc)_2/PPh_3$ system also led to good yield (90%) with 100% conversion (entry 7). Bidentate phosphines, such as dppp, could also be used for direct arylation when using TlOAc as additive (entries 8–10). The chemoselectivity could be shifted to the electron-deficient alkene with this catalytic system in the absence of TlOAc, and with $(n\text{-}Bu)_4NI$ as iodide anion source, obtaining the pyrroloisoquinoline **5a** though in moderate yield. Similar yields of **5a** were obtained using $Pd(PPh_3)_4$ as catalyst under classical conditions [$(n\text{-}Bu)_4NCl$ $NaHCO_3$ in acetonitrile under reflux]. Thus, $Pd(OAc)_2$ (2.5 mol%), PPh_3(10 mol%), using $(n\text{-}Bu)_4NOAc$ as additive in DMSO at 60 °C, emerged as the catalyst that offered the optimal balance of reaction rate and selectivity for C-functionalization over MH reaction, together with dppp (5 mol%) in the presence of TlOAc (1.2 equiv.).

Thus, we extended the procedure to benzylpyrroles **3b–e** that incorporate alkenes both with electron-withdrawing and electron-donating groups. As shown on Table 2, in all cases the reaction with $Pd(OAc)_2/PPh_3/(n\text{-}Bu)_4NOAc$ was completely selective towards the direct arylation reaction, obtaining the pyrroloisondoles **4b–e** in excellent yields. It is interesting to point out the relevance of the ammonium salt. When $(n\text{-}Bu)_4NCl$ was used instead,[26] the reaction was not selective, furnishing variable yields of the MH reaction, products **5b–d** (5–20%), showing the importance of the presence of acetate ions on the mechanism. As

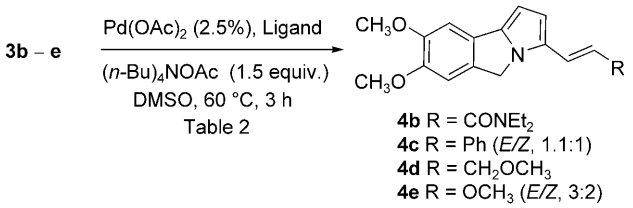
Table 1. MH reaction or direct arylation of **3a**.



Entry	Pd	Ligand	Additive	Base	Solvent	Time [h]	**4a** [%]	**5a** [%]
1	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NCl	$NaHCO_3$	CH_3CN	8	73	8
2	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NCl	$NaHCO_3$	DMF	8	70	8
3	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NOAc	$NaHCO_3$	DMF	3	92	–
4	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NOAc	Et_3N	DMF	3	94	–
5	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NOAc	–	DMF	3	93	–
6	$Pd(OAc)_2$[a]	PPh_3[b]	Bu_4NOAc	–	DMSO	3	97	–
7	$Pd(OAc)_2$[c]	PPh_3[b]	Bu_4NOAc	–	DMSO	3	90	–
8	$Pd(OAc)_2$[c]	dppp[d]	Bu_4NCl	TlOAc	DMSO	6	86	–
9	$Pd(OAc)_2$[c]	dppp[d]	–	TlOAc	DMSO	9	80	–
10	$Pd(OAc)_2$[c]	dppp[d]	Bu_4NOAc	TlOAc	DMSO	3	85	
11	$Pd(OAc)_2$[c]	dppp[d]	Bu_4NI	–	CH_3CN	24	–	40
12	$Pd(PPh_3)_4$[c]	–	Bu_4NCl	$NaHCO_3$	CH_3CN	16	–	42

[a] 10 mol%.
[b] 40 mol%.
[c] 2.5 mol%.
[d] 5 mol%.

Table 2. Direct arylation of **3b–e**. Synthesis of pyrroloisoindoles **4b–e**.



Entry	Substrate	Ligand	Base	Product	Yield [%]
1	**3b**	PPh_3[a]	–	**4b**	84
2	**3b**	dppp[b]	TlOAc[c]	**4b**	96
3	**3c**	PPh_3[a]	–	**4c**	92
4	**3c**	dppp[b]	TlOAc[c]	**4c**	96
5	**3d**	PPh_3[a]	–	**4d**	90
6	**3d**	dppp[b]	TlOAc[c]	**4d**	60
7	**3e**	PPh_3[a]	–	**4e**	70
8	**3e**	dppp[b]	TlOAc[c]	**4e**	86

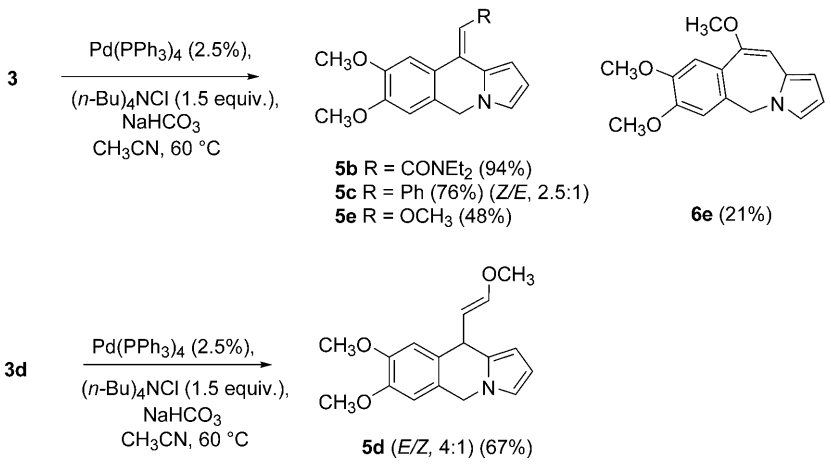
[a] 10 mol%.
[b] 5 mol%.
[c] 1.2 equiv.

shown on Table 2, the use of dppp/TlOAc gave comparable yields.

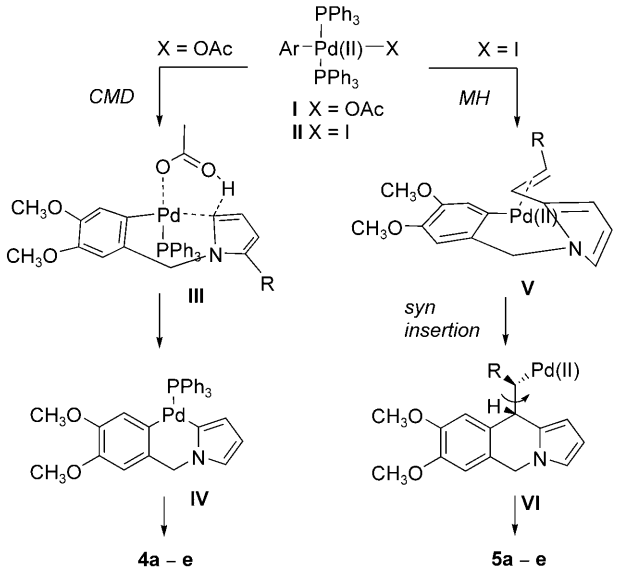
Although the direct arylation of pyrroles with aryl iodides has been reported,[10–19] the reaction described herein can be carried out in the presence of alkenes (both electron-rich and poor) by choosing the adequate catalytic system, avoiding the competing MH reaction. This is one of the few examples of competition between intramolecular direct arylation and MH reactions.[27]

We then extended the procedure for the MH reaction. The optimal reactions conditions were determined to be $Pd(PPh_3)_4$ (2.5 mol%), $(n\text{-}Bu)_4NCl$, and $NaHCO_3$ in acetonitrile at 60 °C, as shown on Table 1 for **3a**. Under these conditions, the reactions proceeded with complete +chemo and regioselectivity on the alkene in favor of the *exo* cyclization product to afford the pyrroloisoquinolines **5b–d** in good yields. Only in the case of **3e**, a minor *endo* product, the pyrrolobenzazepine **6e** (21%) was obtained (Scheme 2).

To explain the change in the chemoselectivity it is necessary to understand the intermediate palladium species involved in the catalytic cycles, which have been studied in detail by Jutand.[28] Thus, when $Pd(OAc)_2/n\,PPh_3$ ($n>2$) is used, *trans* complex **I** (X = OAc) is formed, while the intermediate species for $Pd(PPh_3)_4$ is **II** (X = I), with an iodide ligand (Scheme 3).[28] On the other hand, it has also been found[29] that the acetate ion is easily dissociable, and equilibrium could be established between *trans*-$ArPd(PPh_3)(OAc)$ species **I**, and cationic $[ArPd(PPh_3)]^+$ 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 SEAr pathway could be suggested. However, Fagnou[23b] has reported that, on direct arylation reactions, the reactivity depended on C–H acidity, not on arene nucleophilicity. Thus, a



Scheme 2. MH reaction of **3b–e**. Synthesis of pyrroloisoquinolines **5b–e**.



Scheme 3. Proposed CMD and MH mechanisms.

concerted metalation-deprotonation (CMD) pathway,[23]involving proton abstraction by the acetate ion could be proposed (Scheme 3). This mechanism would explain the selective arylation even in the presence of an electron-rich alkene, such as **3e** (Table 2, entries 7 and 8) and the improvement of the chemoselectivity towards the direct arylation when a source of acetate ions, such as $(n\text{-Bu})_4$NOAc is added (Table 1, entries 1–3).

A similar CMD mechanism could be proposed when dppp is used instead of PPh_3, as analogous palladium species have been reported for this catalytic system.[30] In this case, the presence of thallium salts is necessary, as iodide ion scavenger.[31]

Conversely, catalytic species **II** (X = I) would favor a Heck-type α,β-insertion reaction.[21] In this case, the anchimeric assistance of the iodide anion to remove a proton in an intermediate such as **III** would be much more difficult to take place, and the only catalytic reaction would be a Heck-type *via* a neutral mechanism, preferentially in the β-position (with the only exception of the minor formation of **6e**) of the more electron-deficient alkene, therefore affording an intermediate **VI**. After rotation, *syn* palladium hydride elimination would give the Z configuration of the double bond on **5a–c** and **5e**. The minor formation of pyrroloisoquinolines in the presence of $(n\text{-Bu})_4$NCl (Table 1, entries 1 and 2) could be attributed to the formation of a chloride coordinated palladium species, as reported by Jutand,[28c] that would react through a Heck mechanism.

This alternative Heck reaction mechanism could also explain the formation of pyrroloisoquinoline **5a** with $Pd(OAc)_2$/dppp when a source of iodide is used (Bu_4NI) instead of acetate (Table 1, entry 11), through the formation of an iodide coordinated species analogous to **II**, that would react through a neutral pathway.

Conclusions

In conclusion, we have demonstrated that the intramolecular palladium-catalyzed reaction of 2-alkenyl-substituted *N*-(*o*-iodobenzyl)pyrroles can be switched from the alkene to the pyrrole nucleus by choosing the adequate catalytic system. In fact, the nature of the X ligand on the palladium intermediate species (X = OAc, I) determines the chemoselectivity of the reaction. The reactions employ only 2.5 mol% of commercially available catalyst to effect 5-*exo-trig* direct arylation or 6-*exo-trig* MH cyclizations to generate pyrrolo[2,1-*a*]isoindoles or dihydropyrrolo[1,2-

b]isoquinolines, respectively. The substitution patterns on the alkene do not affect the course of C-2 direct arylation of pyrrole derivative. The selectivity of the reactions appears to be controlled by the catalytic system

Experimental Section

Intramolecular Palladium-Catalyzed Direct Arylation. Synthesis of Pyrroloisoindoles 4a–e; General Procedure

$Pd(OAc)_2$ (2.5 or 10.0 mol%) was added to a mixture of *N*-benzylpyrrole **3a–e** (1 mmol), PPh_3 (10 or 40 mol%) and $(n\text{-}Bu)_4NOAc$ (1.5 mmol) in 5 mL of dry DMSO. Next, the mixture was stirred at 60 °C under argon until TLC showed complete reaction. The reaction mixture was then diluted with 50 mL of AcOEt, washed with saturated NH_4Cl (1× 30 mL) and H_2O (2×30 mL), dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, hexane/AcOEt) to give the corresponding pyrroloisoindoles **4a–e**.

(*E*)-Benzyl 3-(7,8-dimethoxy-5*H*-pyrrolo[2,1-*a*]isoindol-3-yl)acrylate (4a): According to the general procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3a** (201 mg, 0.40 mmol), PPh_3 (10.5 mg, 0.04 mmol) and $(n\text{-}Bu)_4NOAc$ (181 mg, 0.60 mmol) in DMSO and this mixture was stirred at 60 °C for 3 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **4a** which was crystallized from Et_2O as a green solid; yield: 142 mg (97%); mp 148–150 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.92$ (s, 3H), 3.94 (s, 3H), 4.89 (s, 2H), 5.25 (s, 2H), 5.97 (d, $J = 15.8$ Hz, 1H), 6.31 (d, $J = 3.9$ Hz, 1H), 6.67 (d, $J = 3.9$ Hz, 1H), 6.97 (s, 1H), 7.08 (s, 1H), 7.33–7.45 (m, 5H), 7.66 ppm (d, $J = 15.8$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 51.2$ (CH_2), 56.1 (CH_3), 56.2 (CH_3), 66.0 (CH_2), 99.9 (CH), 102.8 (CH), 106.5 (CH), 109.2 (CH), 120.8 (CH), 124.9 (C), 126.3 (C), 128.1 (CH), 128.2 (CH), 128.5 (CH), 133.3 (C), 133.6 (CH), 136.4 (C), 144.0 (C), 148.4 (C), 149.5 (C), 167.8 ppm (C); IR (KBr): $\upsilon = 2930$, 1701, 1615 cm^{-1}; MS (EI): *m/z* (%) = 376 (26) $[M+1]^+$, 375 (100) $[M]^+$, 285 (10), 284 (50), 256 (44), 241 (44), 240 (13), 226 (18), 224 (12), 196 (19), 91 (52); anal. calcd (%) for $C_{23}H_{21}NO_4$: C 73.60, H 5.60, N 3.73; found: C 73.39, H 5.55, N 3.81.

(*E,Z*)-3-(7,8-Dimethoxy-5*H*-pyrrolo[2,1-*a*]isoindol-3-yl)-*N*,*N*-diethylacrylamide (4b): According to the general procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3b** (210 mg, 0.45 mmol), PPh_3 (10.5 mg, 0.04 mmol) and $(n\text{-}Bu)_4NOAc$ (202 mg, 0.67 mmol) in DMSO and this mixture was stirred at 60 °C for 1.5 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 80%) gave **4b** as an oil as an isomeric mixture *Z*/*E* in a 1/3 ratio; yield: 129 mg (84%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.12$ (t, $J = 7.0$ Hz, 6H isomer *Z*), 1.20–1.28 (m, 6H isomer *E*), 3.39 (c, $J = 7.0$ Hz, 4H isomer *Z*), 3.49–3.52 (m, 4H isomer *E*), 3.89 (s, 3H isomer *Z*), 3.92 (s, 6H isomers *Z* and *E*), 3.94 (s, 3H isomer *E*), 4.78 (s, 2H isomer *Z*), 4.90 (s, 2H isomer *E*), 5.82 (d, $J = 12.5$ Hz, 1H isomer *Z*), 6.19 (d, $J = 3.7$ Hz, 1H isomer *Z*), 6.27 (d, $J = 3.7$ Hz, 1H isomer *E*), 6.42 (d, $J = 15.3$ Hz, 1H isomer *E*)*, 6.44 (d, $J = 12.5$ Hz, 1H isomer *Z*)*, 6.65 (d, $J = 3.7$ Hz, 1H isomer *E*), 6.77 (d, $J = 3.7$ Hz, 1H isomer *Z*), 6.92 (s, 1H isomer *Z*), 7.01 (s, 2H isomer *E* and *Z*), 7.06 (s, 1H isomer *E*), 7.67 ppm (d, $J = 15.3$ Hz, 1H isomer *E*) (*designates partially overlapped signals); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 13.3$ (CH_3 isomer *Z*), 15.0 (CH_3 isomer *E*), 41.1 (CH_2 isomer *Z*), 42.2 (CH_2 isomer *E*), 48.9 (CH_2 isomer *Z*), 50.4 (CH_2 isomer *E*), 56.1 (CH_3 isomers *Z* and *E*), 99.0 (CH isomer *Z*), 99.3 (CH isomer *E*), 102.6 (CH isomer *Z*), 102.7 (CH isomer *E*), 106.9 (CH isomer *E*), 107.1 (CH isomer *Z*), 110.4 (CH isomer *E*), 115.5 (CH isomer *Z*), 116.5 (CH isomer *Z*), 117.2 (CH isomer *E*), 122.3 (CH isomer *Z*), 125.7 (C isomer *E*), 125.8 (C isomer *Z*), 126.6 (C isomer *Z*), 127.4 (C isomer *E*), 131.0 (CH isomer *E*), (132.3 (C isomer *Z*), 132.7 (C isomer *E*), 139.7 (C isomer *Z*), 142.2 (C isomer *E*), 147.6 (C isomer *Z*), 148.0 (C isomer *E*), 149.4 (C isomer *Z*), 149.6 (C isomer *E*), 166.3 (C isomer *E*), 168.0 ppm (C isomer *Z*); IR ($CHCl_3$): $\upsilon = 2995$, 1625 cm^{-1}; MS (EI): *m/z* (%) = 341 (18) $[M+1]^+$, 340 (47) $[M]^+$, 241 (29), 240 (55), 226 (20), 224 (15), 196 (22), 91 (70); HR-MS (EI+): *m/z* = 340.1787, calcd. for $C_{20}H_{24}N_2O_3$ (M^+): 340.1787.

(*E,Z*)-7,8-Dimethoxy-3-styryl-5*H*-pyrrolo[2,1-*a*]isoindole (4c): According to the general procedure, $Pd(OAc)_2$ (9 mg, 0.04 mmol) was added to a mixture of *N*-benzylpyrrole **3c** (200 mg, 0.45 mmol), PPh_3 (47 mg, 0.18 mmol) and $(n\text{-}Bu)_4NOAc$ (203 mg, 0.67 mmol) in DMSO and this mixture was stirred at 60 °C for 6 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **4c** as an oil as an isomeric mixture *Z*/*E* in a 1/1.1 ratio; yield: 131 mg 892%). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.88$ (s, 3H isomer Z), 3.93 (s, 6H), 3.96 (s, 3H isomer *E*), 4.53 (s, 2H isomer *Z*), 4.97 (s, 2H isomer *E*), 6.14 (d, $J = 3.7$ Hz, 1H isomer *Z*), 6.28 (d, $J = 3.6$ Hz, 1H isomer *E*)*, 6.29 (d, $J = 3.7$ Hz, 1H isomer *Z*)*, 6.39 (d, $J = 12.1$ Hz, 1H isomer *Z*), 6.44 (d, $J = 12.1$ Hz, 1H isomer *Z*), 6.49 (d, $J = 3.6$ Hz, 1H isomer *E*), 6.72 (d, $J = 16.4$ Hz, 1H isomer *E*), 6.87 (s, 1H isomer *Z*), 7.01 (s, 2H isomer *Z* and *E*), 7.06 (d, 1H isomer *E*)*, 7.07 (s, 1H isomer *E*)*, 7.20–7.49 ppm (m, 10H) (*designates partially overlapped signals); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 49.3$ (CH_2 isomer *Z*), 50.8 (CH_2 isomer *E*), 56.1 (CH_3), 56.2 (CH_3), 97.9 (CH isomer *Z*), 98.5 (CH isomer *E*), 102.2 (CH isomer *Z*), 102.3 (CH isomer *E*), 106.8 (CH isomer *Z*), 106.9 (CH isomer *E*), 112.8 (CH isomer *Z*), 114.2 (CH isomer *E*), 118.7 (CH isomer *E*), 118.9 (CH isomer *Z*), 123.0 (CH isomer *E*), 125.7 (C), 125.9 (C), 126.4 (CH isomer *Z*), 126.7 (CH isomer *E*), 127.0 (CH isomer *Z*), 128.3 (CH isomer *Z*), 128.4 (CH isomer *Z*), 128.6 (CH isomer *E*), 128.7 (CH), 132.4 (C), 138.1 (C isomer *E*), 138.2 (C isomer *Z*), 138.5 (C isomer *Z*), 140.5 (C isomer *E*), 147.2 (C isomer *Z*), 147.5 (C isomer *E*), 149.2 (C isomer *Z*), 149.4 ppm (C isomer *E*); IR ($CHCl_3$): $\upsilon = 2932$, 1626 cm^{-1}; MS (EI): *m/z* (%) = 318 (13) $[M + 1]^+$, 317 (58) $[M]^+$, 303 (21), 302 (100), 274 (45), 273 (63), 272 (19), 259 (17), 258 (16), 230 (27), 228 (31), 215 (17); anal. calcd. (%) for $C_{21}H_{19}NO_2$: C 79.49, H 5.99, N 4.41; found: C 79.33, H 5.86, N 4.26.

(*E*)-7,8-Dimethoxy-3-(3-methoxyprop-1-enyl)-5*H*-pyrrolo-[2,1-*a*]isoindole (4d): According to the general procedure, $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3d** (165 mg, 0.40 mmol), PPh_3 (12 mg,

0.04 mmol) and nBu$_4$NOAc (181 mg, 0.60 mmol) in DMSO and this mixture was stirred at 60 °C for 6 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **4d** as an oil; yield: 115 mg (90%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.39 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 4.11 (dd, J = 6.4, 1.2 Hz, 2H), 4.89 (s, 2H), 5.89 (dt, J = 16.1, 6.4 Hz, 1H), 6.22 (d, J = 3.6 Hz, 1H), 6.35 (d, J = 3.6 Hz, 1H), 6.57 (d, J = 16.1 Hz, 1H), 6.97 (s, 1H), 7.06 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 50.7 (CH_2), 56.2 (CH_3), 57.7 (CH_3), 73.8 (CH_3), 98.0 (CH), 102.5 (CH), 107.0 (CH), 113.8 (CH), 120.2 (CH), 123.4 (CH), 126.1 (C), 127.7 (C), 132.5 (C), 140.2 (C), 147.5 (C), 149.6 ppm (C); IR ($CHCl_3$): υ = 2920, 2826, 1643 cm^{-1}; MS (EI): m/z (%) = 285 (29) [M]$^+$, 254 (100), 210 (10), 91 (47); HR-MS (EI+): m/z = 285.1265, calcd. for $C_{17}H_{19}NO_3$ (M^+): 285.1365.

(*E,Z*)-7,8-Dimethoxy-3-(2-methoxyvinyl)-5*H*-pyrrolo[2,1-*a*]isoindole (4e): According to the general procedure, $Pd(OAc)_2$ (9 mg, 0.04 mmol) was added to a mixture of *N*-benzylpyrrole **3e** (159 mg, 0.40 mmol), PPh_3 (42 mg, 0.16 mmol) and (n-Bu)$_4$NOAc (181 mg, 0.60 mmol) in DMSO and this mixture was stirred at 60 °C for 7 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **4e** as a oil as a isomeric mixture Z/E in a 2/3 ratio; yield: 76 mg (70%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.69 (s, 3H isomer *E*), 3.80 (s, 3H isomer *Z*), 3.90 (s, 6H), 3.94 (s, 6H), 4.74 (s, 4H), 5.21 (d, J = 6.7 Hz, 1H isomer *Z*), 5.80 (d, J = 13.0 Hz, 1H isomer *E*), 6.06 (d, J = 6.7 Hz, 1H isomer *Z*), 6.16 (d, J = 3.4 Hz, 1H isomer *Z*)*, 6.18 (d, J = 3.4 Hz, 1H isomer *Z*)*, 6.21 (d, J = 3.5 Hz, 1H isomer *E*), 6.57 (d, J = 3.5 Hz, 1H isomer *E*), 6.92 (d, J = 13.0 Hz, 1H isomer *E*)*, 6.92 (s, 1H isomer *Z*)*, 6.95 (s, 1H isomer *E*)*, 7.02 (s, 1H isomer *Z*)*, 7.03 ppm (s, 1H isomer *E*)* (*designates partially overlapped signals); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 49.0 (CH_2 isomer *Z*), 50.0 (CH_2 isomer *E*), 56.1 (CH_3), 56.3 (CH_3), 56.6 (CH_3 isomer *Z*), 60.5 (CH_3 isomer *E*), 95.6 (CH isomer *Z*), 97.0 (CH isomer *E*), 97.6 (CH isomer *Z*), 98.0 (CH isomer *E*), 102.1 (CH isomer *Z*), 102.3 (CH isomer *E*), 107.0 (CH isomer *Z*), 107.1 (CH isomer *E*), 108.9 (CH isomer *Z*), 112.4 (CH isomer *E*), 125.8 (C isomer *Z*), 126.4 (C isomer *E*), 126.8 (C isomer *Z*), 127.2 (C isomer *E*), 131.9 (C isomer *Z*), 132.2 (C isomer *E*), 137.0 (C isomer *Z*), 138.0 (C isomer *E*), 144.9 (CH isomer *Z*), 146.6 (CH isomer *E*), 146.9 (C), 149.3 ppm (C); IR ($CHCl_3$): υ = 2920, 1649, 1279 cm^{-1}; MS (EI): m/z (%) = 271 (20) [M]$^+$, 256 (29), 212 (15), 123 (11), 111 (15), 109 (16), 97 (23), 95 (28), 93 (11), 85 (65), 83 (26), 83 (100), 81 (32), 79 (13), 71 (30), 70 (11); HR-MS (EI+): m/z = 271.1208, calcd. for $C_{16}H_{17}NO_3$ (M^+): 271.1208.

Intramolecular Heck Reactions. Synthesis of Pyrroloisoquinolines 5a–e: General Procedure

$Pd(PPh_3)_4$ (2.5 mol%) was added to a mixture of *N*-benzylpyrrole (1 equiv.), (n-Bu)$_4$NCl (1.5 equiv.) and $NaHCO_3$ (2.5 equiv.) in 5 mL of dry CH_3CN. Next, the mixture was stirred at reflux under argon until TLC showed complete reaction. The reaction mixture was then diluted with 50 mL of AcOEt, washed with saturated NH_4Cl (1 × 30 mL) and H_2O (2 × 30 mL), dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, hexane/AcOEt) to give the corresponding pyrroloisoquinolines.

(*Z*)-Benzyl 2-(7,8-dimethoxypyrrolo[1,2-*b*]isoquinolin-10-ylidene)acetate (5a): According to the general procedure, $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3a** (226 mg, 0.45 mmol), (n-Bu)$_4$NCl (167 mg, 0.60 mmol) and $NaHCO_3$ (94 mg, 1.12 mmol) in CH_3CN and this mixture was stirred at reflux for 16 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **5a** as an oil; yield: 71 mg (42%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.92 (s, 3H), 3.93 (s, 3H), 5.06 (s, 2H), 5.24 (s, 2H), 6.18 (s, 1H), 6.34 (t, J = 3.9 Hz, 1H), 6.72 (s, 1H), 6.90 (s, 1H), 7.21 (s, 1H), 7.33–7.46 (m, 5H), 7.51 ppm (t, J = 2.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 47.8 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 65.9 (CH_2), 107.0 (CH), 107.6 (CH), 108.3 (CH), 109.5 (CH), 115.3 (CH), 122.6 (CH), 125.5 (C), 125.6 (C), 126.1 (C), 128.1 (CH), 128.5 (CH), 128.6 (CH), 136.1 (C), 139.2 (C), 148.6 (C), 150.1 (C), 166.2 ppm (C); IR ($CHCl_3$): υ = 2932, 1731, 1602 cm^{-1}; MS (EI): m/z (%) = 376 (16) [M + 1]$^+$, 375 (59) [M]$^+$, 300 (31), 277 (15), 256 (21), 243 (17), 242 (25), 241 (100), 240 (69), 224 (14), 210 (14), 196 (18), 167 (17), 151 (22), 149 (20), 111 (15), 108 (17), 107 (17), 97 (23), 91 (76), 85 (24), 83 (28) 79 (19), 77 (18); HR-MS (EI+): m/z = 375.0523, calcd. for $C_{23}H_{21}NO_4$ (M+): 375.0515.

(*Z*)-2-(7,8-Dimethoxypyrrolo[1,2-*b*]isoquinolin-10-ylidene)-*N*,*N*-diethylacetamide (5b): According to the general procedure, $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3b** (187 mg, 0.40 mmol), (n-Bu)$_4$NCl (167 mg, 0.60 mmol) and $NaHCO_3$ (84 mg,1.00 mmol) in CH_3CN and this mixture was stirred at reflux for 16 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 90%) gave **5b** which was crystallized from Et_2O as a brown solid; yield: 129 mg (94%); mp 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.00 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 3.33 (c, J = 7.1 Hz, 2H), 3.52 (c, J = 7.1 Hz, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 5.06 (s, 2H), 6.21 (s, 2H), 6.57 (s, 1H), 6.68 (s, 1H), 6.77 (s, 1H), 7.20 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 12.5 (CH_3), 14.1 (CH_3), 39.0 (CH_2), 42.7 (CH_2), 47.4 (CH_2), 55.9 (CH_3), 106.8 (CH), 108.4 (CH), 108.7 (CH), 109.7 (CH), 111.9 (CH), 120.6 (CH), 123.9 (C), 124.5 (C), 125.9 (C), 128.1 (C), 148.5 (C), 149.4 (C), 169.1 ppm (C); IR (KBr): υ = 2972, 1610 cm^{-1}; MS (EI): m/z (%) = 341 (7) [M+1]$^+$, 340 (26) [M]$^+$, 269 (15), 268 (73), 242 (20), 241 (100), 240 (15), 224 (11); HR-MS (EI+): m/z = 340.1781, calcd. for $C_{20}H_{24}N_2O_3$ (M+): 340.1787.

(*E,Z*)-10-Benzylidene-7,8-dimethoxy-5,10-dihydropyrrolo-[1,2-*b*]isoquinoline (5c): According to the general procedure, $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3c** (200 mg, 0.45 mmol), (n-Bu)$_4$NCl (188 mg, 0.67 mmol) and $NaHCO_3$ (94 mg,1.12 mmol) in CH_3CN and this mixture was stirred at reflux for 48 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **5c** as an oil as an isomeric mixture Z/E in a 2.5/1 ratio; yield: 108 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.33 (s, 3H isomer *E*), 3.90 (s, 3H isomer *E*), 3.93 (s, 3H isomer *Z*), 3.99 (s, 3H isomer *Z*), 5.07 (s, 2H isomer *E*), 5.10 (s, 2H isomer *Z*), 5.90 (t, J = 1.5 Hz, 1H isomer *Z*), 6.07 (t, J = 2.6 Hz, 1H isomer *Z*), 6.29 (t, J = 2.7 Hz, 1H isomer *E*), 6.52 (t, J = 1.6 Hz, 1H

isomer *E*), 6.71 (s, 1H isomer *E*), 6.73 (s, 2H isomer *Z*), 6.80 (d, $J=1.4$ Hz, 1H isomer *E*), 6.93 (s, 1H isomer *E*), 6.97 (s, 1H isomer *Z*), 7.08 (s, 1H isomer *E*), 7.21 (t, $J=7.3$ Hz, 1H isomer *E*), 7.26–7.39 (m, 9H isomer *Z* and *E*), 7.51 ppm (d, $J=7.6$ Hz, 2H isomer *Z*); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta=47.8$ (CH_2 isomer *Z*), 48.0 (CH_2 isomer *E*), 55.0 (CH_3 isomer *E*), 55.8 (CH_3 isomer *E*), 56.0 (CH_3 isomer *Z*), 56.1 (CH_3 isomer *Z*), 102.2 (CH isomer *E*), 106.6 (CH isomer *Z*), 108.4 (CH isomer *Z*), 108.6 (CH isomer *Z* and *E*), 109.4 (CH isomer *E*), 111.8 (CH isomer *E*), 119.4 (CH isomer *Z*), 119.5 (CH isomer *E*), 120.4 (CH isomer *Z*), 121.4 (CH isomer *E*), 123.6 (C isomer *Z*), 123.9 (C isomer *E*), 125.6 (C isomer *E*), 126.4 (CH isomer *Z*), 126.6 (CH isomer *E*), 126.7 (C isomer *Z*), 126.8 (C isomer *Z*), 127.0 (C isomer *Z*), 128.3 (CH), 128.9 (CH), 129.2 (C isomer *E*), 132.2 (C isomer *E*), 138.4 (C isomer *E*), 138.7 (C isomer *Z*), 146.8 (C isomer *E*), 148.3 (C isomer *E*), 148.5 (C isomer *Z*), 148.7 ppm (C isomer *Z*); IR ($CHCl_3$): $\upsilon=2932$, 1602, 1261 cm^{-1}; MS (EI): *m/z* (%) = 317 (100) $[M]^+$, 316 (33), 302 (13), 285 (17), 243 (11), 242 (18), 241 (12), 230 (13), 228 (13); HRMS (EI+): *m/z* = 317.1420, calcd. for $C_{21}H_{19}NO_2$ (M^+): 317.1416.

(*E,Z*)-7,8-Dimethoxy-10-(2-methoxyvinyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (5d): According to the general procedure, $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3d** (165 mg, 0.40 mmol), $(n\text{-Bu})_4NCl$ (167 mg, 0.60 mmol) and $NaHCO_3$ (84 mg,1.00 mmol) in CH_3CN and this mixture was stirred at reflux for 48 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 40%) gave **5d** as an oil as an isomeric mixture *Z*/*E* in a 1/4 ratio; yield: 77 mg (67%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=3.59$ (s, 3H), 3.71 (s, 3H), 3.88 (s, 6H isomer *Z*), 3.89 (s, 6H isomer *E*), 4.43 (d, $J=8.8$ Hz, 1H isomer *E*), 4.60 (dd, $J=9.5$, 6.0 Hz, 1H isomer *Z*), 4.86 (dd, $J=12.6$, 8.8 Hz, 1H isomer *E*), 5.00–5.07 (m, 4H isomer *E* and *Z*), 5.12 (d, $J=9.4$ Hz, 1H isomer *Z*), 6.02 (dd, $J=2.3$, 1.7 Hz, 2H isomer *E* and isomer *Z*), 6.20–6.23 (m, 3H isomer *E* and *Z*), 6.49 (d, $J=12.6$ Hz, 1H isomer *E*), 6.70–6.73 (m, 4H isomer *E* and *Z*), 6.90 (s, 1H isomer *E*), 6.94 ppm (s, 1H isomer *Z*); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta=33.2$ (CH isomer *Z*), 37.5 (CH isomer *E*), 47.2 (CH_2 isomer *E* and *Z*), 56.0 (CH_3 isomer *E* and *Z*), 59.8 (CH isomer *Z*), 103.7 (CH isomer *Z*), 104.3 (CH isomer *E*), 104.9 (CH isomer *E*), 108.2 (CH isomer *Z* and *E*), 108.4 (CH isomer *Z*), 108.9 (CH isomer *E* and *Z*), 111.0 (CH isomer *E* and *Z*), 118.0 (CH isomer *Z*), 118.3 (CH isomer *E*), 123.5 (C isomer *Z*), 123.7 (C isomer *E*), 129.0 (C isomer *E*), 129.1 (C isomer *Z*), 131.2 (C isomer *Z*), 131.3 (C isomer *E*), 147.4 (C isomer *E*), 147.5 (C isomer *Z*), 147.7 (CH isomer *E*), 148.2 (CH isomer *Z*), 148.7 ppm (CH isomer *E* and *Z*); IR ($CHCl_3$): $\upsilon=2932$, 2838 cm^{-1}; MS (EI): *m/z* (%) = 285 (47) $[M]^+$, 284 (29), 270 (20), 125 (14), 111 (21), 109 (15); HRMS (EI+): *m/z* = 285.1367. calcd. for $C_{17}H_{19}NO_3$ (M^+): 285.1365.

(*Z*)-7,8-Dimethoxy-10-(methoxymethylene)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (5e): According to the general procedure, $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) was added to a mixture of *N*-benzylpyrrole **3e** (167 mg, 0.45 mmol), $(n\text{-Bu})_4NCl$ (175 mg, 0.63 mmol) and $NaHCO_3$ (88 mg,1.05 mmol) in CH_3CN and this mixture was stirred at reflux for 48 h. After work-up, purification by column chromatography (silica gel, hexane/AcOEt 30%) gave **5e** as an oil; yield: 56 mg (48%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=3.87$ (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.06 (s, 2H), 6.32 (t, $J=3.5$ Hz, 1H), 6.64 (s, 1H), 6.70 (dd, $J=3.6$, 1.6 Hz, 1H), 6.71–6.72 (m, 2H), 6.95 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta=47.6$ (CH_2), 55.9 (CH_3), 60.8 (CH_3), 104.7 (CH), 106.6 (C), 107.5 (CH), 108.9 (CH), 109.2 (CH), 118.5 (CH), 121.7 (C), 123.5 (C), 125.8 (C), 141.6 (CH), 147.8 (C), 148.3 ppm (C); IR ($CHCl_3$): $\upsilon=2932$, 2838, 1637 cm^{-1}; MS (EI): *m/z* (%) = 271 (35) $[M]^+$, 256 (100), 228 (11), 192 (71), 190 (24), 125 (13), 123 (15), 111 (24), 109 (22), 97 (42), 95 (40); HR-MS (EI+): *m/z* = 271.1208, calcd. for $C_{16}H_{17}NO_3$ (M^+): 271.1195.

Together with **5e**, the 7,8,10-trimethoxy-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepine (**6e**) was isolated as a by-product; yield: 36 mg (21%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta=3.86$ (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.79 (s, 2H), 6.06 (dd, $J=3.4$, 1.6 Hz, 1H), 6.11 (s, 1H), 6.15 (t, $J=3.2$ Hz, 1H), 6.63 (t, $J=2.1$ Hz, 1H), 6.76 (s, 1H), 7.22 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta=$ 51.8 (CH_2), 55.5 (CH_3), 56.0 (CH_3), 96.0 (CH), 106.6 (CH), 108.6 (CH), 109.7 (CH), 110.9 (CH), 119.4 (CH), 127.9 (C), 128.1 (C), 129.0 (C), 148.4 (C), 149.4 (C), 152.5 ppm (C); IR ($CHCl_3$): $\upsilon=2949$, 1265 cm^{-1}; MS (EI): *m/z* (%) = 271 (29) $[M]^+$, 256 (100), 212 (15), 192 (75), 190 (15), 125 (22), 123 (13), 111 (28), 109 (21), 97 (35), 95 (43); HR-MS (EI+): *m/z* = 271.1190, calcd. for $C_{16}H_{17}NO_3$ (M^+): 271.1195.

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