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The Journal of Organic Chemistry 2019 84 (16), 10183-10196

DOI**: 10.1021/acs.joc.9b01357**

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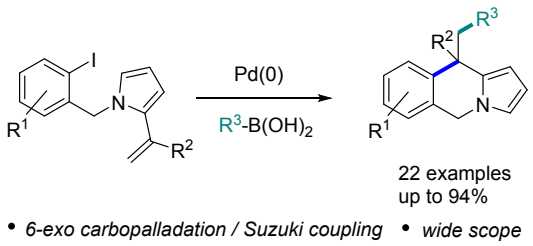
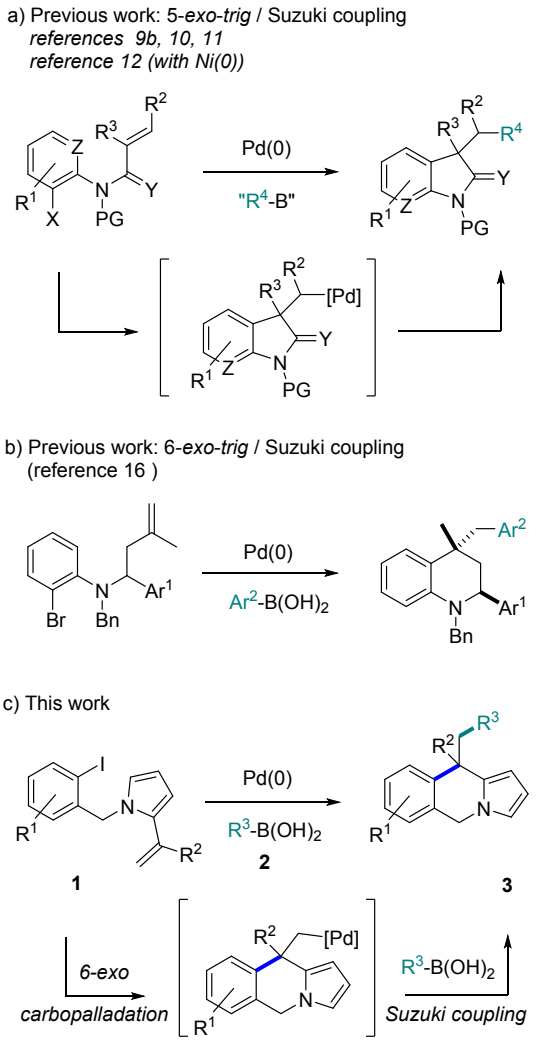


Abstract. A convergent route to pyrrolo[1,2-*b*]isoquinolines with a quaternary center at C-10 has been developed, that implies a sequential Pd(0)-catalyzed carbopalladation followed by cross-coupling reaction with boronic acids. The adequate catalytic system and experimental conditions, with and without the use of phosphane ligands, have been selected to control the chemoselectivity of the process, allowing a 6-*exo*-carbopalladation to generate a quaternary center, and avoiding a direct Suzuki coupling. A variety of electron rich and electron deficient arylboronic acids can be used providing an efficient route to substituted pyrrolo[1,2-*b*]isoquinolines in moderate to good yields (up to 94%, 22 examples).

Introduction

Cascade reactions play an important role in modern synthetic organic chemistry.[1] In particular, palladium-catalyzed carbopalladation initiated domino reactions (cascade cyclizations) are powerful carbon-carbon bond-forming processes for the construction of functionalized carbocycles and heterocycles with quaternary stereocenters.[2] The ideal starting point is an intramolecular Heck reaction,[3] i.e. the initiation is the oxidative insertion of Pd(0) in carbon-(pseudo)halide bonds, followed by the intramolecular carbopalladation of an 1,1-disubstituted alkene, to direct the carbopalladation to the most substituted position preventing β-hydride elimination. The termination step may be another cross-coupling reaction (Heck, Suzuki, Stille, Sonogashira, etc.).[4] For example, the generated *σ*-alkylpalladium (II) species may undergo an insertion with an alkene in an inter- or intramolecular way (second Heck reaction), so carbopalladation is repeated one or several times.[5] In the context of our interest in intramolecular palladium-catalyzed reactions,[6] we have achieved the enantioselective synthesis of the tetracyclic framework of Lycorane alkaloids via a Heck-Heck cascade reaction.[7] Another termination approach for these palladium-catalyzed cascade reactions is the Suzuki coupling,[8] where the *σ*-alkylpalladium (II) intermediate reacts with boronic acids or esters to produce cross-coupling product. Since Grigg's seminal work (Scheme 1a, PG = SO_2Ph, Bn; X = I, Y = H_2, O; Z = CH, R^2 = H, R^3 = Me),[9] these domino Heck/Suzuki cascade reactions have been widely exploited for the formation of five-membered rings. Thus, domino 5-*exo*-*trig* intramolecular carbopalladation-cross coupling reactions with various organoboranes provide access to functionalized 3,3-disubstituted azaindolines (Scheme 1a, PG = Ts; X = Br, Y = H_2; Z = N; R^2 = H, R^3 = Me)[10] and oxindoles (Scheme 1a, PG = Me; X = I, Y = O; Z = CH; R^2 = Ph, Ar, R^3 = Me)[11] bearing quaternary stereocenters. In the latter case, the diasterocontrol in the *syn* palladation step allowed the stereoespecific generation of two vicinal stereocenters. A similar Ni-catalyzed Heck/Suzuki cascade reaction has been recently applied to the synthesis of oxindoles (Scheme 1a, PG = Me, Bn; X = OTf, OPiv, Cl, Br, I; Y = O; Z = CH; R^2 = H, R^3 = Me.[12] Moreover, this cascade reaction is not limited to carbopalladation of alkenes, but can also be applied to alkynes, as exemplified in the synthesis of alkylidene substituted indenes,[13] benzofurans[14] or

cyclopenta[*b*]indoles,[15] which are interesting kinase inhibitor precursors. The *E/Z* selectivity of the alkylidene formation is also determined in the *5-exo-dig syn* carbopalladation step. However, to the best of our knowledge, the diastereoselective synthesis of 3,4,4-trisubstituted tetrahydroquinolines *via* a 6-*exo-trig* carbopalladation/Suzuki coupling of adequately functionalized *o*-bromoanilines (Scheme 1b)[16] is one of the few of examples of the construction of six-membered rings.[17] Therefore, we decided to explore the domino palladium-catalyzed intramolecular Heck/Suzuki coupling cascade, employing *o*-iodobenzylpyrroles **1** with an alkene in the proper position and boronic acids (Scheme 1c). Herein, we report a convergent route to pyrrolo[1,2-*b*]isoquinolines, which combines the cyclization by carbopalladation followed by the cross-coupling reaction with a boronic acid, and allows the straightforward preparation of a wide variety of derivatives bearing a quaternary stereocenter.



Scheme 1. Carbopalladation - Suzuki cascade.

Pyrrolo[1,2-*b*]isoquinoline is a common structural motif among many biologically active alkaloids, such as the lycorine class of Amaryllidaceae alkaloids[18] and the phenanthroindolizidine alkaloids,[19] and in many molecules exhibiting useful therapeutic properties. Some examples are displayed in Figure 1. Lycorine and Galanthine exhibit anticancer, acetylcholinesterase (AChE) inhibitory, antiplasmodial, or neuroprotective activities[20] while Tylophorine and Hypoestestatin 1 present cytotoxic properties and antiviral activity.[21] Among the synthetic pyrrolo[1,2-*b*]isoquinolines, the 10-amino derivatives are also used as AChE inhibitors for anti-amnesic action in the treatment of Alzheimer's disease, senile dementia, or other conditions characterized by memory loss,[22] while the 1,2-bis(hydroxymethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinolines and their bis(alkylcarbamates) exhibit significant antitumor activity and are able to induce DNA interstrand cross-linking.[23] Therefore, the development of new methodologies for the synthesis of pyrrolo[1,2-*b*]isoquinolines that allows the preparation of a wide variety of derivatives, could be useful in future studies of structure-activity relationships for drug development.

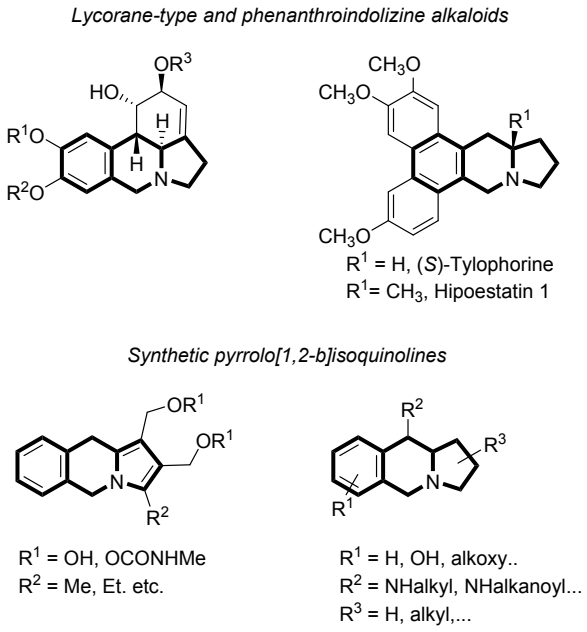


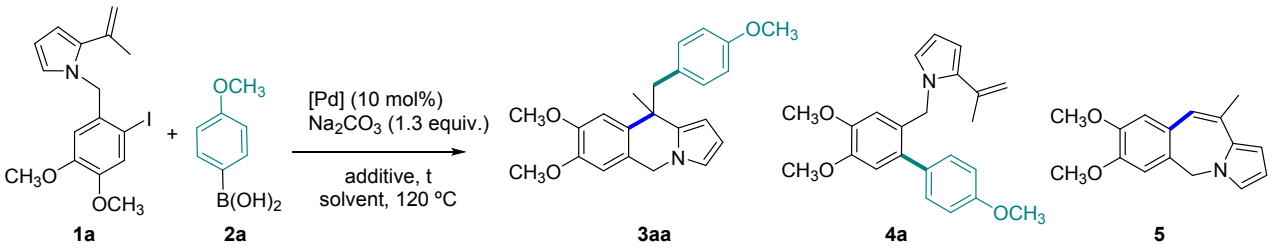
Figure 1. Selected bioactive compounds that contain fused pyrrolo[1,2-*b*]isoquinoline frameworks

Results and Discussion

We started our study using 2-iodobenzylpyrrole **1a** as substrate, in the presence of (*p*-methoxyphenyl)boronic acid (**2a**) (Table 1).[24] The nature of the intermediate palladium(II) species would be crucial for the rate of carbopalladation to compete successfully with the rate of an early Suzuki cross-coupling (Scheme 1c). Therefore, the first challenge was to control the chemoselectivity by the adequate choice of the catalytic system and/or experimental conditions. We first focused on the use of catalytic systems in the absence of phosphane ligands. Besides the economical and environmental reasons for the development and application of phosphane-free catalytic systems, we reasoned that these conditions could be, in principle, suitable for the sterically more demanding generation of a quaternary stereocenter. Previous work on related reactions (Scheme 1a,b) had shown that complete conversions could be obtained in the absence of phosphane ligands using various palladium precatalysts.[10] On the other hand, moderate to excellent conversions have been obtained as well in the presence of phosphane ligands.[9b, 11] Interestingly, the presence of a phosphane has been shown to be required for the 6-*exo* cyclization cascade,[9b,16] with complete loss of reactivity in its absence.[16] However, in our case, using $Pd(OAc)_2$ and sodium carbonate as the base in DMF, the reaction took place sluggishly, recovering unreacted **1a** (24%) after 48 hours at 120 ºC. The major product isolated was pyrroloisoquinoline **3aa**, although in a low yield (entry 1). Under these conditions, the reaction was not selective, as two by-products, biaryl **4a** and pyrroloazepine **5** were isolated from the reaction mixture. This result shows the feasibility of the cascade reaction using a phosphane-free catalytic system, but also shows the difficulty of performing the 6-*exo* carbopalladation process for the generation of a quaternary center, as both the direct Suzuki coupling of **2a** with the aryl iodide to form **4a** and the 7-*endo* palladation/β-elimination leading to **5** compete effectively. Consequently, we focused on the optimization of reaction conditions to favor the 6-*exo* carbopalladation reaction vs. the 7-*endo* process and the direct Suzuki coupling (Table 1). In the presence of water, the reaction was completed in 48 h, but only to increase the amount of isolated **4a** (entry 2). The addition of nBu$_4$NCl (1 equiv) dramatically increased the reaction rate,[25] that was completed in 2 h, but the reaction was not selective. In this case, direct Suzuki coupling was the

major pathway (**4a**), with also a significant amount of the 7-*endo* Heck pathway (entry 3). Lowering the temperature to 90 ºC resulted in a much slower reaction, with almost no selectivity, isolating the three reaction products in comparable yields (entry 4). In the absence of water, using DMF as solvent, **3aa** was isolated as the major compound (entry 5) and, finally, the addition of 2 equivalents of nBu$_4$NCl completely suppressed the direct Suzuki pathway, isolating **3aa** as the major compound (entry 6). The presence of halide anions has been shown to increase the rates of some of the steps of the catalytic cycle of the Heck reaction,[25] while an increasing concentration of halide anions has the opposite effect on the transmetalation step of the Suzuki reaction.[26] Thus, the use of a higher concentration of this additive may slow down the direct Suzuki coupling allowing the 6-*exo* carbopalladation to occur at a competitive rate. However, the use of 3 equivalents, or the change to nBu$_4$NI or nBu$_4$NOAc did not improve the isolated yield of **3aa** (entries 7-9). We then modified the palladium precatalyst (entries 10-12) and the solvent (entries 13-15), obtaining moderate isolated yields of **3aa**. Interestingly, in the presence of PPh$_3$, the Suzuki coupling was the major pathway (28 % of **4a**), despite the use of nBu$_4$NCl, obtaining a low yield of **3aa** (25%) (entry 11). Unfortunately, the 7-*endo* Heck pathway could not be completely suppressed under any of the reaction conditions tested. For these reactions, the overall isolated yield is rather low due to the difficulties associated with the separation and purification of compounds by chromatography, but no formation of other products was detected by ^{1}H-NMR of the crude reaction mixtures.

Table 1. Carbopalladation/Suzuki sequence on **1a**. Optimization of reaction conditions with phosphane-free catalytic systems



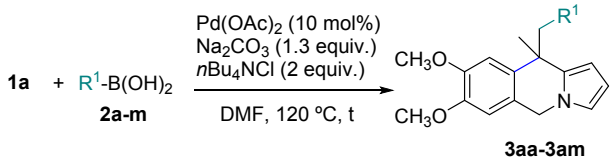
1a **2a** **3aa** **4a** **5**

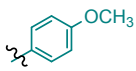
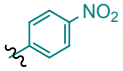
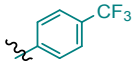
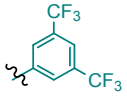
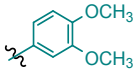
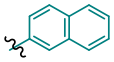
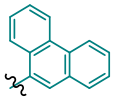
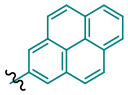
entry	[Pd]	Additive (equiv)	Solvent	Time (h)	**3aa**[a]	**4a**[a]	**5**[a]
1	$Pd(OAc)_2$	-	DMF	48[b]	34	4	23
2	$Pd(OAc)_2$	-	DMF/H_2O[c]	48	30	12	21
3	$Pd(OAc)_2$	*n*-Bu_4NCl (1)	DMF/H_2O[c]	2	22	33	26
4	$Pd(OAc)_2$	*n*-Bu_4NCl (1)	DMF/H_2O[c,d]	48[e]	27	27	29
5	$Pd(OAc)_2$	*n*-Bu_4NCl (1)	DMF	1	47	7	19
6	$Pd(OAc)_2$	*n*-Bu_4NCl (2)	DMF	1	56	-	13
7	$Pd(OAc)_2$	*n*-Bu_4NCl (3)	DMF	1	52	-	7
8	$Pd(OAc)_2$	*n*-Bu_4NI (1)	DMF	1	51	-	16
9	$Pd(OAc)_2$	*n*-Bu_4NOAc (2)	DMF	1	10	-	14
10	$Pd(TFA)_2$	*n*-Bu_4NCl (2)	DMF	2	46	9	11
11	$Pd(PPh_3)_4$	*n*-Bu_4NCl (2)	DMF	9	25	28	15
12	$Pd_2(dba)_3 \cdot CHCl_3$	*n*-Bu_4NCl (2)	DMF	4	42	-	10
13	$Pd(OAc)_2$	*n*-Bu_4NCl (2)	Toluene[f]	2	34	-	21
14	$Pd(OAc)_2$	*n*-Bu_4NCl (2)	THF[f]	5	52	-	17
15	$Pd(OAc)_2$	*n*-Bu_4NCl (2)	Dioxane[f]	1	56	-	25
16	$Pd(OAc)_2$	*n*-Bu_4NCl (2)	CH_3CN[f]	2	40	-	29

[a]Yield (%) of isolated pure compound. Reactions were carried out in a 0.3 mmol scale. [b]76% conversion. [c]DMF:H_2O 80:20. [d]90 ºC. [e]84% conversion. [f] Reflux

With the best reaction conditions in hand (Table 1 entry 6, Table 2 entry 1), we extended the reaction to the use of different boronic acids **2b-m** (Table 2).

Table 2. Extension of phosphane-free reaction to boronic acids **2a-m**.



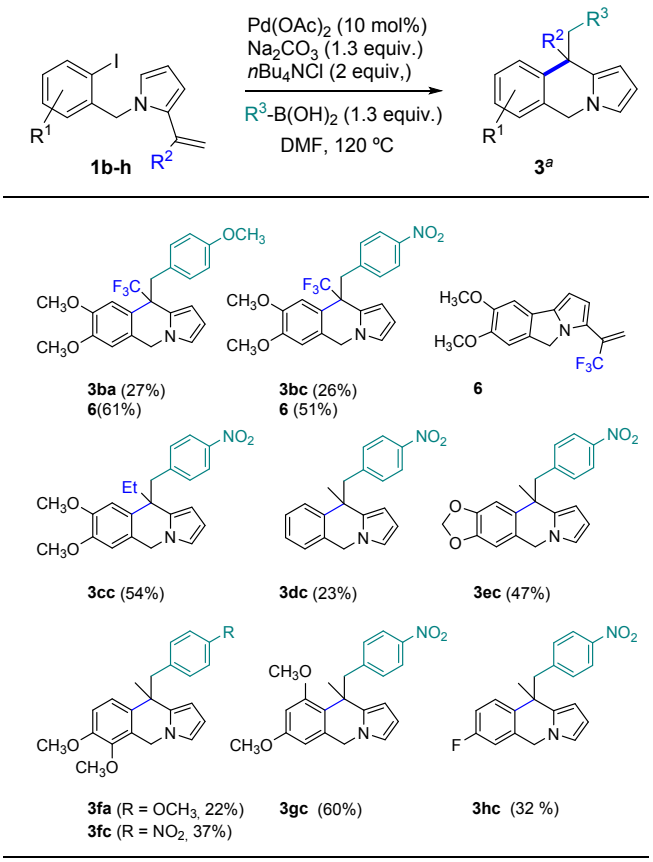
Entry	R^1	Time (h)	Product	Yield (%)[a]
1		1	**3aa**	56[b]
2		2	**3ab**	54
3		1	**3ac**	60[b]
4		2	**3ad**	52
5		1	**3ae**	38[b]
6		1	**3af**	47[b]
7		4	**3ag**	46[c]
8		1	**3ah**	53
9		1	**3ai**	63
10		1	**3aj**	70
11		48	**3ak**	15[d]
12		48	**3al**	21[e]
13		2	**3am**	37

[a]Yield (%) of isolated pure product. Reactions were carried out in a 0.3 mmol scale. [b]11-17% of **5** was also isolated. [c]19% of **3ag** was obtained when phenyl boronic acid pinacol ester was used instead of **2g**. [d] 76% conversion. [e]Potasium trifluorovinyl borate was used. 89% conversion

Moderate to good yields of pyrrolosiquinolines **3aa-3aj** were obtained when electron rich, electron deficient or even polycyclic aryl boronic acids were used. Minor amounts of the pyrroloazepine **5** were detected by NMR that in some of the experiments was isolated and quantified (entries 1, 3, 5, 6), but no formation of the direct Suzuki coupling was detected. A lower yield of **3ag** was obtained when phenyl boronic acid pinacol ester was used instead of **2g** (19% vs 46%, entry 7)**.** However the reaction with thiophen-3-ylboronic acid **2k** was much slower (48 h), recovering 24% of starting material and giving only a low yield of **3ak**, (entry 11). Alkenes could also be coupled with this procedure, although with a lower yield (entries 12, 13).

Next, we studied the extension to 2-iodobenzylpyrroles **1b-h**, with different substitution patterns on the aromatic ring and the alkene. It is interesting that when an electron-withdrawing group, such as CF_3, is incorporated in the alkene (**1b**, $R^2 = CF_3$), the intramolecular direct arylation of the aryl iodide with pyrrole C-5 position becomes the major pathway leading to **6** as the major compound (Table 3). Thus, **3ba** and **3bc** were obtained only in low yields. This type of reactivity has been shown to be competitive in Heck reactions with related substrates, using Pd/phosphane catalytic systems, specially when a cationic mechanism is favored.[6b,27] In this case, formation of pyrrolo[2,1-*a*]isoindoles was not observed when the alkene is substituted with an alkyl group, and **3cc** was obtained from **1c**, (R^2 = Et) with similar yield. The reaction could also be extended to benzylpyrroles with different substitution patterns on the aromatic ring (**1d-h**), obtaining the corresponding pyrroloisoquinolines with moderate to good yields (Table 3). However, benzylpyrroles **1** bearing electron rich aromatic rings led to better yields of **3**.

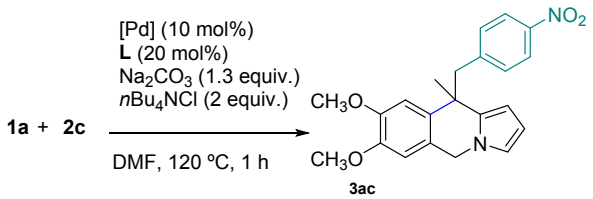
Table 3. Synthesis of pyrroloisoquinolines **3**.

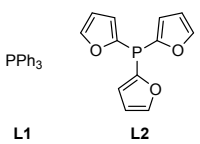


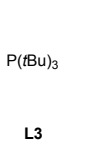
[a]Yield (%) of isolated pure product. Reactions were carried out in a 0.3 mmol scale.

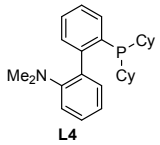
At this point, we have shown that is it possible to carry out the 6-*exo*-*trig* carbopalladation/Suzuki cascade using a phosphane-free catalytic system. However, the overall yields obtained are moderate in many cases, as the competitive 7-*endo* cyclization/elimination leading to **5** could not be completely suppressed under these conditions. Although we had previously shown that the formation of quaternary stereocenters *via* Heck reaction was possible on related substrates in the presence of phosphane ligands,[27] the use of $Pd(PPh_3)_4$ on the coupling of **1a** with **2a** led to a non-selective reaction (Table 1, entry 11). With these precedents, we carried out a further optimization of the reaction conditions, studying the effect of a phosphane ligand, using the reaction of **1a** with boronic acid **2c** (Table 4), which had given a moderate yield of **3ac** under the phosphane-free reaction conditions (60%, Table 2, entry 3).

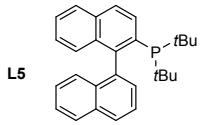
Table 4. Optimization of reaction conditions in the presence of phosphanes.

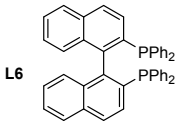












entry	[Pd]	L	3ac[a]	5[a]
1	$Pd(OAc)_2$	**L1**	70	4
2	$Pd(OAc)_2$	**L2**	74	9
3	$Pd(OAc)_2$	**L2**[b,c]	67	8
4	$Pd(OAc)_2$	**L3**	70	6
5	$Pd(OAc)_2$	**L4**	65	4
6	$Pd(OAc)_2$	**L5**	66	9
7	$Pd(OAc)_2$	**L6**[d]	53	12
8	$Pd(dba)_2$	**L2**[e]	79	-
9	$Pd_2(dba)_3.CHCl_3$	**L2**	86 (94)[f]	-
10	$Pd_2(dba)_3.CHCl_3$	**L2**[g,h]	30	33
11	$Pd_2(dba)_3.CHCl_3$	**L2**[i]	29	18

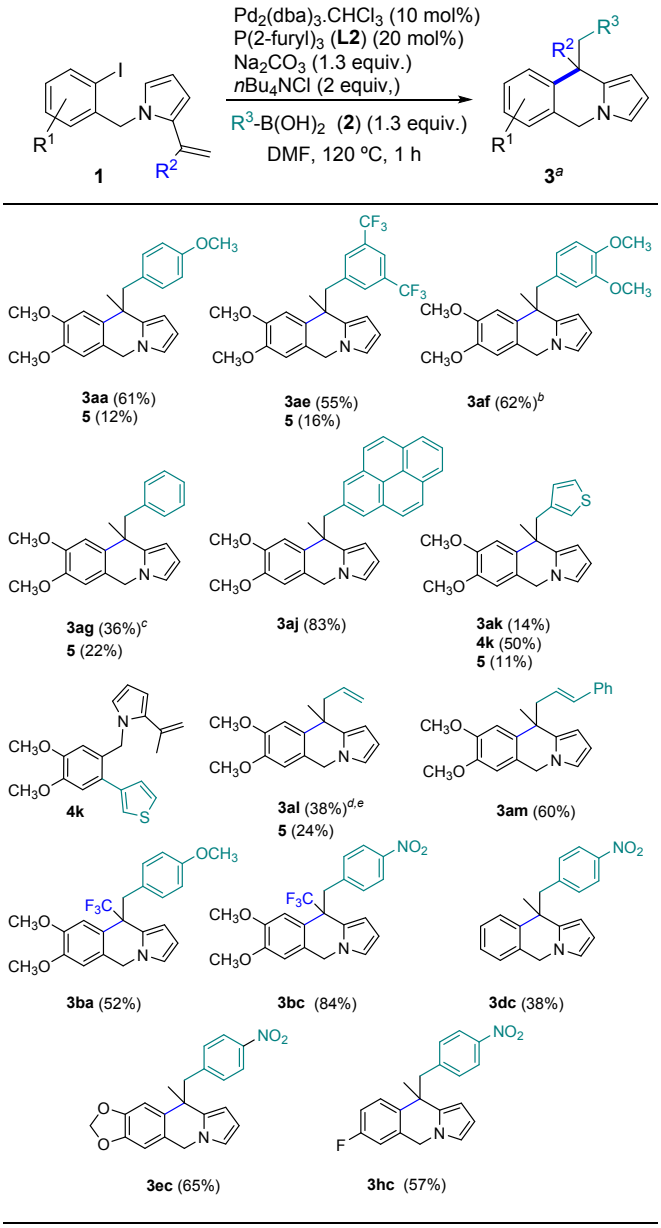
[a]Yield (%) of isolated pure product. Reactions were carried out in a 0.3 mmol scale. [b] 28% of **L2** was used. [c] Reaction time: 3 h. [d] Reaction time: 24 h. [e] Reaction time: 4 h. [f] The reaction was performed in a 1.32 mmol scale (506 mg of **1a**).[g] Reaction time: 48 h. [h] nBu_4NCl was not used. [i] Ag_3PO_4 was used as base instead of Na_2CO_3.

We were pleased to find that the reaction took place efficiently using the same reaction conditions in the presence of various phosphanes (20 mol%), such as triphenylphosphane (**L1**) (Table 4, entry 1),

tri(furan-2-yl)phosphane (**L2**) (Table 4, entry 2) or tri-*tert*-butylphosphane (**L3**) (Table 4, entry 4). Although, the formation of the 7-*endo* Heck product (**5**) could not be completely avoided (4-9% of **5** was isolated as by-product), the use of phosphane ligands led to the formation of **3ac** with an increased yield (70-74%). The use of a higher amount of the phosphane led to a slower reaction with a lower isolated yield of **3ac** (entry 3). The choice of the phosphane ligand has been shown to have a determinant effect on the *endo*/*exo* selectivity in related Heck cyclizations.[28] However, minor amounts of **5** (entries 5 and 6) were also isolated when the reaction was carried out in the in the presence of DavePhos (**L4**) and TrixiePhos (**L5**). The reaction using *rac*-BINAP (**L6**) was less efficient, and required 24 h to obtain a moderate yield of **3ac** (entry 7). The formation of the *endo* adduct **5** could be completely avoided changing the palladium source. Thus, the use of bis(dibenzylidene)palladium(0) with tri(furan-2-yl)phosphane (**L2**) gave **3ac** in good yield, with complete selectivity (entry 8). Finally, the reaction was more efficient when tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (86%, entry 9). The reaction could be carried out in a 0.5 gram scale (1.3 mmol of **1a**) also in high yield (94%, entry 9). The use of nBu$_4$NCl is still neccesary, as a much slower (48 h) and non selective reaction is took place when in its absence (entry 10), obtaining **5** as the major product, although no direct Suzuki coupling product was detected under these conditions. The change of the base for a silver salt (Ag_3PO_4) also resulted in a selectivity loss (entry 11).

Once the reaction conditions were optimized, we tested the use of selected boronic acids **2**. As shown in Tables 4 and 5, in most of the cases (**3aa**, **3ac**, **3ae**, **3af**, **3aj**, **3al**, **3am**), the results could be significantly improved with respect to the yield obtained with the phosphane-free catalytic system (see Table 2). However, in some of the cases, minor ammounts of **5** were also isolated (Table 5, 11-16%). In the case of **3ag**, a lower yield (36%) was obtained, isolating also the *endo*-Heck cyclization product **5** (22%). The reaction with thiophen-3-ylboronic acid **2k** gave again a low yield of **3ak** (15% Table 2 *vs*. 14% Table 5,), although under these conditions the main reaction pathway was the direct Suzuki coupling, obtaining **4k** with a 50% yield. The coupling with alkenes was also significantly improved (Table 5, **3al** and **3am**).

Table 5. Synthesis of pyrroloisquinolines **3** using **L2** as ligand

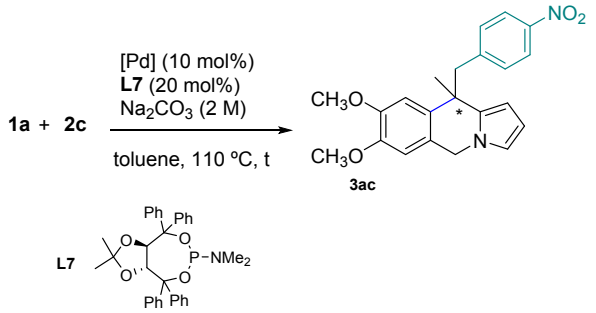


[a]Yield (%) of isolated pure product. Reactions were carried out in a 0.3 mmol scale. [b] Reaction time: 4 h. [c] Reaction time: 6 h.[d]Potasium trifluorovinyl borate was used. [e]Reaction time: 24 h.

Significantly, the use of the phosphane ligand completely changed the chemoselectivity when **1b** (R^2 = CF_3) was reacted with **2a** and **2c**. Thus, the direct arylation pathway leading to **6** (Table 3) was completely suppressed and 10b-trifluoromethylsubstituted pyrroloisoquinolines **3ba** and **3bc** were obtained in good yields (Table 5). This result probably reflects the change from a cationic (phosphane-free) to a neutral pathway for the initial carbopalladation step. The use of **1d**, **1e** and **1h** gave also

improved yields of the expected pyrroloisoquinolines **3dc**, **3ec** and **3hc**. (Table 5). In view of these results, we explored the possibility of an enantioselective version of the reaction, in the presence of chiral non-racemic phosphanes. In this context, we have reported an enantioselective Heck-Heck cascade using related substrates, showing that it is possible to control the enantioselectivity of the carbopalladation step using (*R*)-BINAP.[7] However, it was not possible to induce stereocontrol using (*R*)-BINAP or other chiral non-racemic phosphane ligands for the generation of quaternary stereocenters through Heck reactions on related alkenylpyrroles.[27] Once again, we selected the reaction of **1a** with **2c** as a model for optimization of the reaction conditions. Although different ligands, solvents and reaction conditions have been tested, only modest enantioselectivities (up to 44% *ee*) have been obtained so far. Some selected results are shown on Table 6 (see the Supporting Information for additional essays). We found that phosphoramidite **L7** led to the best results in terms of enantioselectivity, using palladium acetate in toluene, although with low conversion (Table 6, entries 1 and 2). The reaction is more efficient in DMF, but with no stereocontrol (Table 6, entries 4-6). On the other hand, *n*-Bu_4NCl accelerates the reaction, but leads to an almost racemic compound (entries 4 and 5). In the absence of *n*-Bu_4NCl, using solid Na_2CO_3 in DMF the reaction is much slower (entry 6), and does not proceed at all in toluene (see SI, Table S2). The reactivity could be recovered using an aqueous solution of base (Table 6, entries 1-3 and 7). The use of a more concentrated base (10 M) led to an improved *ee*, but with a lower conversion (Table 6, entry 2). In the absence of *n*-Bu_4NCl, the reaction was again non-selective, isolating the direct Suzuki coupling product **4c** as a by-product (see SI). The use of $Pd_2(dba)_3 \cdot CHCl_3$ led to improved yields, but with lower enantioselection (Table 6, entries 5 and 7) (see SI).

Table 6. Chiral phosphane **L7** mediated reaction of **1a**



entry	[Pd]	time	**3ac**[a]	*ee*[b]
1	$Pd(OAc)_2$	48	63[c]	34
2	$Pd(OAc)_2$	48[d]	28[c]	44
3	$Pd(OAc)_2$	24[e,f]	61	4
4	$Pd(OAc)_2$	3[g]	64[c]	<2
5	$Pd_2(dba)_3{\cdot}CHCl_3$	1[e,f,g]	86	6
6	$Pd_2(dba)_3{\cdot}CHCl_3$	48[f,g]	23	6
7	$Pd_2(dba)_3{\cdot}CHCl_3$	24	72	22

[a]Yield (%) of isolated pure product.[b]Determined by chiral stationary phase HPLC (Chiralcel ADH). Due to the low *ee* the configuration could not be determined. [c]**4c** was isolated as by product (see SI). [d]Na_2CO_3 (10 M aq. solution) was used. [e]*n*Bu_4NCl (1 equiv) was used as additive. [f]Solid Na_2CO_3 was used. [g]DMF was used as solvent.

In conclusion, it has been shown that *N*-(2-iodobenzyl)-2-(alkenyl)-1*H*-pyrroles **1** undergo cyclization through a 6-*exo* carbopalladation process to generate a quaternary center. The resulting σ-alkylpalladium can be trapped with arylboronic acids to generate C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines **3**. A phosphane free precatalytic system can be used in order to favor the 6-*exo* carbopalladation reaction *vs*. the direct Suzuki coupling, although the 7-*endo* process is competitive in some cases. Nevertheless, the 7-*endo* process can be suppressed in the presence of phosphane ligands, such as tri(furan-2-yl)phosphane (**L2**). In combination with $Pd_2(dba)_3.CHCl_3$, this phosphane ligand leads in most cases to a significant increase in the yields of the pyrroloisoquinolines **3**. Using both procedures, the presence of *n*-Bu_4NCl is crucial to allow the 6-*exo* carbopalladation to occur at a

competitive rate, avoiding the direct Suzuki coupling. Electron rich and electron deficient arylboronic acids can be used, although coupling with alkenyl or heteroaryl (thiophenyl) boronic acids provide lower yields. The use of chiral non racemic phosphanes, such as phosphoramidite **L7** gave only low enantioselectivities. Overall, this domino process allows the synthesis of interesting pyrrolo[1,2-*b*]isoquinolines, a common structural motif among biologically active alkaloids.

Experimental Section

General experimental methods. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained using an ATR. NMR spectra were recorded at 20-25 ˚C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C in $CDCl_3$ solutions. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Mass spectra were recorded under electron impact (EI) at 70 eV or with an ESI^+ source. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230-400 mesh). Chiral stationary phase HPLC was performed using Chiralcel ADH column (0.46 cm × 25 cm) in isocratic elution mode (hexane/i-propanol 9/1, 1 mL/min). All solvents used in reactions were anhydrous and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 ˚C) and purged with argon. Palladium catalysts were commercially available, and were used without further purification: $Pd(OAc)_2$: 98% purity, $Pd(TFA)_2$: 97% purity; $Pd(PPh_3)_4$: 99% purity; $Pd_2(dba)_3 \cdot CHCl_3$: 97% purity.

Synthesis of 1-(*o*-iodobenzyl)-2-alkenylpyrroles 1a-h. Substrates **1a-h** were prepared following the procedure described in the Supporting Information. Thus, acylpyrroles **8a-c** were alkylated with *o*-iodobenzylbromides **7a-f** to obtain 2-acyl-*N*-benzylpyrroles **9a-h**. Subsequent Wittig reation afforded **1a-g** in good yields.

Alkylation reactions. Synthesis of 2-acyl-*N*-benzylpyrroles 9a-h. General procedure. 2-Acylpyrrole **8** (1 mmol) was added over a suspension of powdered KOH (2 mmol) in DMSO (3 mL). The mixture was stirred at rt for 2 h, the corresponding bromide **7a-f** (1.2 mmol) was added, and the reaction mixture was stirred until the reaction was completed. H_2O (5 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography afforded the corresponding 2-acylpyrroles **9a-h**.

1-[1-(2-Iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl]ethan-1-one (9a).[27] According to general procedure, **8a** (854 mg, 7.82 mmol) was treated with benzylbromide **7a** (3.34 g, 9.39 mmol) and KOH (1.03 g, 15.65 mmol) in DMSO (20 mL). The mixture was stirred at rt for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **9a** as a white solid (2.45 g, 81%). mp (Hexane/EtOAc): 121-124 °C; IR (ATR): 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.64 (s, 3H), 3.82 (s, 3H), 5.51 (s, 2H), 6.16-6.18 (m, 1H), 6.25 (s, 1H), 6.85-6.86 (m, 1H), 7.00-7.02 (m, 1H), 7.22 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 55.6, 56.1, 56.9, 86.2, 108.6, 111.1, 120.3, 121.5, 130.0, 130.3, 132.9, 148.8, 149.6, 188.4 ppm; MS (CI) *m/z* (rel intensity): 386 (MH^+,65), 276 (71), 259 (100). HRMS (CI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found, 386.0237.

2,2,2-Trifluoro-1-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (9b). According to general procedure, **8b** (1.09 g, 6.66 mmol) was treated with benzylbromide **7a** (2.84 g, 7.99 mmol) and KOH (439 mg, 6.66 mmol) in DMSO (30 mL). The mixture was stirred at rt for 2 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **9b** as a white solid (2.51 g, 86 %): mp (petroleum ether/EtOAc): 93-95 ºC; IR (ATR): 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.85 (s, 3H), 5.51 (s, 2H), 6.27 (s, 1H), 6.32 (dd, J = 4.3, 2.5 Hz, 1H), 7.07 (m, 1H), 7.26 (s, 1H), 7.30-7.33 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 55.7, 56.2, 57.5, 86.6, 110.8, 111.1, 117.0 (q, J = 290.5 Hz), 121.8, 124.4, 124.6 (q, J = 4.0 Hz), 131.4, 134.0, 149.2, 149.8, 169.9 (q, J = 35.4 Hz) ppm; MS (ESI) *m/z* (rel intensity): 440

(MH$^+$, 31), 314 (12), 313 (100). HRMS (ESI-TOF): calcd. for $C_{15}H_{14}F_3INO_3$ [MH$^+$] 439.9965; found, 439.9978.

1-(1-(2-Iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)propan-1-one (9c). According to general procedure, **8c** (194 mg, 1.57 mmol) was treated with benzylbromide **7a** (674 mg, 1.89 mmol) and KOH (208 mg, 3.15 mmol) in DMSO (5 mL). The mixture was stirred at rt for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **9c** as a yellow solid (475 mg, 76%): mp (petroleum ether/EtOAc): 114-116 ºC; IR (ATR): 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, J = 7.4 Hz, 3H), 2.78 (q, J = 7.4 Hz, 2H), 3.60 (s, 3H), 3.78 (s, 3H), 5.49 (s, 2H), 6.14 (dd, J = 4.1, 2.6 Hz, 1H), 6.19 (s, 1H), 6.83 (dd, J = 2.6, 1.7 Hz, 1H), 6.99 (dd, J = 4.1, 1.7 Hz, 1H), 7.19 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 9.2, 32.4, 55.7, 56.2, 56.9, 86.1, 108.7, 110.1, 119.4, 121.6, 129.9, 130.0, 133.2, 148.8, 149.7, 191.9 ppm; MS (ESI) *m/z* (rel intensity): 400 (MH$^+$, 36), 274 (13), 273 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{19}INO_3$ [MH$^+$] 400.0404; found, 400.0413.

1-(1-(2-Iodobenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (9d).[29]According to general procedure, **8a** (933 mg, 8.55 mmol) was treated with benzylbromide **7b** (3.05 g, 10.25 mmol) and KOH (1.13 g, 17.09 mmol) in DMSO (30 mL). The mixture was stirred at rt for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **9d** as a white solid (2.32 g, 83 %): mp (Petroleum ether /EtOAc): 95-97 °C; IR (ATR): 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.56 (s, 2H), 6.24 (dd, J = 4.1, 2.6 Hz, 1H), 6.47 (dd, J = 7.8, 1.6 Hz, 1H), 6.84-6.85 (m, 1H), 6.90-6.96 (m, 1H), 7.06 (dd, J = 4.1, 1.7 Hz, 1H), 7.17-7.22 (m, 1H), 7.83 (dd, J = 7.8, 1.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$): δ 27.3, 57.8, 97.6, 108.9, 120.4, 127.2, 128.6, 129.0, 130.5, 130.5, 139.3, 140.8, 188.2 ppm; MS (ESI) *m/z* (rel intensity): 326 (MH$^+$, 100), 199 (10). HRMS (ESI-TOF): calcd. for $C_{13}H_{13}INO$ [MH$^+$] 326.0036; found, 326.0048.

1-(1-((6-Iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-1*H*-pyrrol-2-yl)ethan-1-one (9e). According to general procedure, **8a** (2.46 g, 22.56 mmol) was treated with benzylbromide **7c** (9.20 g, 27.07 mmol) and KOH (2.98 g, 45.12 mmol) in DMSO (50 mL). The mixture was stirred at rt for 4 h. After work up,

purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **9e** as a yellow solid (6.95 g, 84 %): mp (Petroleum ether/EtOAc): 123-125 °C; IR (ATR): 1650, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 5.49 (s, 2H), 5.91 (s, 2H), 6.09 (s, 1H), 6.23 (dd, J = 4.1, 2.6 Hz, 1H), 6.87 (dd, J = 2.6, 1.7 Hz, 1H), 7.05 (dd, J = 4.1, 1.7 Hz, 1H), 7.26 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.3, 57.4, 85.5, 101.7, 107.8, 108.9, 118.5, 120.4, 130.2, 130.4, 134.2, 147.7, 148.8, 188.4 ppm; MS (ESI) *m/z* (rel intensity): 370 (MH^+, 100), 243 (10). HRMS (ESI-TOF): calcd. for $C_{14}H_{13}INO_3$ [MH^+] 369.9935; found, 369.9942.

1-(1-(6-Iodo-2,3-dimethoxybenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (9f). According to general procedure, **8a** (741 mg, 6.79 mmol) was treated with benzylbromide **7d** (2.91 g, 8.15 mmol) and KOH (897 mg, 13.58 mmol) in DMSO (30 mL). The mixture was stirred at rt for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **9f** as a colorless oil (1.82 g, 69 %): IR (ATR): 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.63 (s, 3H), 3.81 (s, 3H), 5.71 (s, 2H), 6.01 (dd, J = 4.0, 2.7 Hz, 1H), 6.45-6.47 (m, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 4.0, 1.6 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.6, 51.9, 55.9, 61.0, 90.3, 108.1, 114.7, 120.0, 128.0, 131.0, 133.0, 134.7, 149.0, 153.3, 188.6 ppm; MS (ESI) *m/z* (rel intensity): 386 (MH^+, 100), 277 (41), 259 (14). HRMS (ESI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found, 386.0253.

1-(1-(2-Iodo-6-methoxybenzyl)-1H-pyrrol-2-yl)ethan-1-one (9g). According to general procedure, **8a** (35.6 mg, 0.33 mmol) was treated with benzylbromide **7e** (140 mg, 0.39 mmol) and KOH (43 mg, 0.65 mmol) in DMSO (10 mL). The mixture was stirred at rt for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **9g** as a white solid (94.3 mg, 75%): mp (petroleum ether/EtOAc): 142-144 °C; IR (ATR): 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.63 (s, 3H), 3.85 (s, 3H), 5.57 (s, 2H), 5.70 (d, J = 2.7 Hz, 1H), 6.21 (dd, J = 4.0, 2.6 Hz, 1H), 6.32 (d, J = 2.7 Hz, 1H), 6.85 (dd, J = 2.6, 1.7 Hz, 1H), 7.03 (dd, J = 4.0, 1.7 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 55.3, 56.5, 58.1, 78.6, 97.3, 104.9, 108.8, 120.3,

130.5, 130.5, 142.9, 158.8, 161.4, 188.3 ppm; MS (ESI) *m/z* (rel intensity): 386 (MH^+, 90), 259 (100). HRMS (ESI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found, 386.0255.

1-(1-(5-Fluoro-2-iodobenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (9h). Acetylpyrrole **8a** (179 mg, 1.64 mmol) was added over a suspension of powdered NaH (131 mg, 3.28 mmol) in dry DMF (10 mL) and the mixture was stirred at 60 ºC for 30 min. Benzyl bromide **7f** (620 mg, 1.97 mmol) was added and the reaction mixture was stirred at 60 ºC for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **9h** as a white solid (556 mg, 99%): mp (Petroleum ether/EtOAc): 122-124 °C; IR (ATR): 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.51 (s, 2H), 6.08-6.11 (m, 1H), 6.26 (dd, J = 4.1, 2.6 Hz, 1H), 6.68-6.71 (m, 1H), 6.88 (dd, J = 2.6, 1.7 Hz, 1H), 7.07 (dd, J = 4.1, 1.7 Hz, 1H), 7.75-7.78 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 57.7, 89.5 (d, J = 3.4 Hz), 109.2, 114.3 (d, J = 23.9 Hz), 116.2 (d, J = 22.1 Hz), 120.6, 130.3, 130.5, 140.3 (d, J = 7.3 Hz), 143.4 (d, J = 7.3 Hz), 163.6 (d, J = 247.4 Hz), 188.3 ppm; MS (ESI) *m/z* (rel intensity): 344 (MH^+, 100), 302 (24), 235 (8), 217 (10). HRMS (ESI-TOF): calcd. for $C_{13}H_{12}FINO$ [MH^+] 343.9942; found, 343.9957.

Wittig Reaction. Synthesis of 2-alkenylpyrroles 1a-g. General procedure: Potassium *tert*-butoxide (2 mmol) was added to a solution of methyltriphenylphosphonium bromide (2 mmol) in dry THF (10 mL) at 0 ºC. The reaction mixture was stirred at room temperature under argon for 30 min and then cooled at 0 ºC. A solution of *N*-benzylpyrrole **9a-g** (1 mmol) in dry THF (10 mL) was added over 5 min and the mixture was heated under reflux for 24 h. The reaction mixture was allowed to reach room temperature and filtered under vacuum. The filtrate was diluted with Et_2O (5 mL) and sequentially washed with $NaHSO_3$ sat. (5 mL), Na_2CO_3 sat. (5 mL) and brine (5 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude was subjected to flash chromatography (silica gel) obtaining **1a-g.**

1-(2-Iodo-4,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1a). According to general procedure, **9a** (1.00 g, 2.61 mmol) in dry THF (20 mL) was treated with potassium *tert*-butoxide (598 mg, 5.22 mmol) and methyltriphenylphosphonium bromide (1.90 g, 5.22 mmol) in dry THF (20 mL).

After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded *N*-benzylpyrrole **1a** as a yellow solid (856 mg, 86%): mp (petroleum ether /EtOAc): 96-98 °C; IR (ATR): 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.62 (s, 3H), 3.85 (s, 3H), 4.73 (s, 1H), 4.98-4.99 (m, 1H), 5.08 (s, 2H), 6.00 (s, 1H), 6.20-6.23 (m, 1H), 6.25-6.27 (m, 1H), 6.64-6.65 (m, 1H), 7.24 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 55.7, 56.2, 56.2, 84.2, 108.2, 109.2, 110.6, 112.1, 121.4, 123.9, 133.5, 134.8, 135.3, 148.8, 149.7 ppm; MS (ESI) *m/z* (rel intensity): 384 (MH^+, 17), 276 (100), 256 (54). HRMS (CI): calcd. for $C_{16}H_{19}INO_2$ [MH^+] 384.0455; found, 384.0442.

1-(2-Iodo-4,5-dimethoxybenzyl)-2-(3,3,3-trifluoroprop-1-en-2-yl)-1*H*-pyrrole (1b). According to general procedure, **9b** (818 mg, 1.86 mmol) in dry THF (20 mL) was treated with potassium *tert*-butoxide (418 mg, 3.72 mmol) and methyltriphenylphosphonium bromide (1.33 g, 3.72 mmol) in dry THF (20 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **1b** as a yellow solid (490.6 mg, 60%): mp (petroleum ether/EtOAc): 72-74 °C; IR (ATR): 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.85 (s, 3H), 5.01 (s, 2H), 5.38 (dd, J = 3.5, 1.7 Hz, 1H), 5.95-5.97 (m, 2H), 6.26 (dd, J = 3.8, 2.8 Hz, 1H), 6.41-6.43 (m, 1H), 6.74 (dd, J = 2.8, 1.7 Hz, 1H), 7.23 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 55.6, 55.7, 56.2, 84.3, 108.8, 110.4, 112.0, 120.9 (q, J = 5.4 Hz), 121.4, 122.8 (q, J = 273.9 Hz), 124.9, 125.2, 130.4 (q, J = 31.6 Hz), 132.7, 148.9, 150.0 ppm; MS (ESI) *m/z* (rel intensity): 438 (MH^+, 100). HRMS (ESI-TOF): calcd. for $C_{16}H_{16}F_3INO_2$ [MH^+] 438.0172; found, 438.0182

2-(But-1-en-2-yl)-1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrole (1c). According to general procedure, **9c** (195 mg, 0.49 mmol) in dry THF (5 mL) was treated with potassium *tert*-butoxide (110 mg, 0.98 mmol) and methyltriphenylphosphonium bromide (350 mg, 0.98 mmol) in dry THF (10 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **1c** as a colorless oil (139.0 mg, 72 %): IR (ATR): 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (t, J = 7.4 Hz, 3H), 2.35 (q, J = 7.4 Hz, 2H), 3.62 (s, 3H), 3.85 (s, 3H), 4.80-4.81 (m, 1H), 5.04-5.05 (m, 3H), 6.00 (s, 1H), 6.19-6.23 (m, 2H), 6.63-6.65 (m, 1H), 7.23 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 13.2, 30.4, 55.7, 55.8, 56.2, 84.3, 108.2, 108.6, 110.6, 111.5, 121.4, 123.4,

133.7, 134.7, 141.8, 148.7, 149.8 ppm; MS (ESI) *m/z* (rel intensity): 398 (MH^+, 100), 277 (56), 242 (10). HRMS (ESI-TOF): calcd. for $C_{17}H_{21}INO_2$ [MH^+] 398.0611; found, 398.0614.

1-(2-Iodobenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1d). According to general procedure, **9d** (603 mg, 1.85 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (416 mg, 3.71 mmol) and methyltriphenylphosphonium bromide (1.32 g, 3.71 mmol) in dry THF (20 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **1d** as a colorless oil (556 mg, 93 %): IR (ATR): 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 4.69 (s, 1H), 4.98-4.99 (m, 1H), 5.18 (s, 2H), 6.26-6.33 (m, 2H), 6.53-6.56 (m, 1H), 6.67-6.68 (m, 1H), 6.96-7.02 (m, 1H), 7.25-7.30 (m, 1H), 7.86-7.89 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 56.7, 96.5, 108.3, 109.1, 111.9, 124.0, 127.5, 128.8, 129.0, 134.7, 135.3, 139.2, 141.0 ppm. MS (ESI) *m/z* (rel intensity): 324 (MH^+, 100). HRMS (ESI-TOF): calcd. for $C_{14}H_{15}IN$ [MH^+] 324.0244; found, 324.0250.

1-((6-Iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1e). According to general procedure, **9e** (661 mg, 1.79 mmol) in dry THF (20 mL) was treated with potassium *tert*-butoxide (402 mg, 3.58 mmol) and methyltriphenylphosphonium bromide (1.28 g, 3.58 mmol) in dry THF (20 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **1e** as a yellow solid (427 mg, 65 %): mp (Petroleum ether/EtOAc): 114-116 °C; IR (ATR): 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H), 4.69 (s, 1H), 4.97-4.98 (m, 1H), 5.06 (s, 2H), 5.93 (s, 2H), 6.05 (s, 1H), 6.22-6.27 (m, 2H), 6.62-6.63 (m, 1H), 7.26 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 56.5, 84.0, 101.7, 108.0, 108.3, 109.2, 111.8, 118.4, 123.9, 134.5, 134.6, 135.2, 147.7, 149.0 ppm; MS (ESI) *m/z* (rel intensity): 368 (MH^+, 100), 261 (28). HRMS (ESI-TOF): calcd. for $C_{15}H_{15}INO_2$ [MH^+] 368.0142; found, 368.0152.

1-(6-Iodo-2,3-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1f). According to general procedure, **9f** (599 mg, 1.56 mmol) in dry THF (20 mL) was treated with potassium *tert*-butoxide (351 mg, 3.11 mmol) and methyltriphenylphosphonium bromide (1.12 g, 3.11 mmol) in dry THF (20 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded

N-benzylpyrrole **1f** as a yellow solid (508.3 mg, 85 %): mp (petroleum ether/EtOAc): 54-56 °C; IR (ATR): 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 3.57 (s, 3H), 3.87 (s, 3H), 5.16 (s, 1H), 5.29-5.30 (m, 1H), 5.35 (s, 2H), 6.07-6.10 (m, 1H), 6.19-6.21 (m, 1H), 6.37-6.39 (m, 1H), 6.72 (d, J = 8.6 Hz, 1H), 7.60 (s, J = 8.6 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.4, 51.0, 56.0, 60.7, 90.2, 107.4, 107.7, 113.3, 114.5, 121.1, 134.1, 134.7, 135.6, 136.2, 148.8, 153.4 ppm; MS (ESI) *m/z* (rel intensity): 384 (MH+, 100), 277 (14), 242 (20). HRMS (ESI-TOF): calcd. for $C_{16}H_{19}INO_2$ $[MH^+]$ 384.0455; found, 384.0462.

1-(2-Iodo-3,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1g). According to general procedure, **9g** (283 mg, 0.73 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (165 mg, 1.47 mmol) and methyltriphenylphosphonium bromide (524 mg, 1.47 mmol) in dry THF (10 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded *N*-benzylpyrrole **1g** as a colorless oil (184.9 mg, 66 %): IR (ATR): 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H), 3.64 (s, 3H), 3.89 (s, 3H), 4.69 (s, 1H), 4.96-4.97 (m, 1H), 5.17 (s, 2H), 5.75 (d, J = 2.7 Hz, 1H), 6.23-6.29 (m, 2H), 6.36 (d, J = 2.7 Hz, 1H), 6.67 (t, J = 2.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 55.4, 56.5, 57.2, 77.1, 97.6, 104.7, 108.2, 109.0, 111.8, 124.2, 134.8, 135.2, 143.3, 158.7, 161.6 ppm; MS (ESI) *m/z* (rel intensity): 384 (MH+, 100), 257 (42), 242 (56). HRMS (ESI-TOF): calcd. for $C_{16}H_{19}INO_2$ $[MH^+]$ 384.0455; found, 384.0465.

1-(5-Fluoro-2-iodobenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (1h). According to general procedure, **9h** (204 mg, 0.59 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (133 mg, 1.19 mmol) and methyltriphenylphosphonium bromide (424 mg, 1.19 mmol) in dry THF (10 mL). After work up, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **1h** as a colorless oil (188 mg, 93 %): IR (ATR): 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 4.66 (s, 1H), 4.99-5.00 (m, 1H), 5.14 (s, 2H), 6.25-6.33 (m, 3H), 6.68 (dd, J = 2.7, 1.9 Hz, 1H), 6.73-6.80 (m, 1H), 7.78-7.83 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 56.5, 88.7 (d, J = 3.0 Hz), 108.7, 109.4, 111.9, 115.1 (d, J = 24.2 Hz), 116.4 (d, J = 22.0 Hz), 123.9, 134.6, 135.2, 140.3 (d, J = 7.7 Hz), 143.6 (d, J = 7.1 Hz), 163.8 (d, J = 248.1 Hz) ppm; MS (ESI) *m/z* (rel

intensity): 342 (MH^+, 85), 160 (33), 158 (100). HRMS (ESI-TOF): calcd. for $C_{14}H_{14}FIN$ [MH^+] 342.0149; found, 342.0161

Domino carbopalladation-Suzuki reaction on 1. Synthesis of pyrrolo[1,2-*b*]isoquinolines 3. General procedure A (Phosphane free catalytic system). $Pd(OAc)_2$ (0.1 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **1** (1 mmol), boronic acid **2** (1.3 mmol), sodium carbonate (1.3 mmol) and tetrabutylammonium chloride (2 mmol) in DMF (3 ml). The mixture was stirred at 120 ºC for the time indicated in each case. H_2O (15 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification by column chromatography (silica gel) of the resulting residue afforded the corresponding pyrroloisoquinoline **3**.

General procedure B (with phosphane L2). $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **1** (1 mmol), boronic acid **2** (1.3 mmol), sodium carbonate (1.3 mmol), tri(furan-2-yl)phosphane (**L2**) (0.2 mmol) and tetrabutylammonium chloride (2 mmol) in DMF (3 ml). The mixture was stirred at 120 ºC for 1 h. The corresponding pyrroloisoquinoline **3** was obtained after work-up and chromatographic purification as indicated in General procedure A.

7,8-Dimethoxy-10-(4-methoxybenzyl)-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3aa). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**2a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3aa** as an oil (66 mg, 61 %): IR (ATR): 2970, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.87 (d, J = 12.5 Hz, 1H), 2.99 (d, J = 12.5 Hz, 1H), 3.65-3.72 (m, 1H) 3.72 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 4.60 (d, J = 15.4 Hz, 1H), 6.16-6.29 (m, 4H), 6.46-6.55 (m, 4H), 6.97 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.8, 41.1, 46.8, 53.6, 55.1, 55.9, 56.1, 102.6, 108.2, 108.2, 108.6, 112.6, 117.6, 125.1, 130.2, 131.0, 131.9, 135.0, 147.4, 148.2, 158.2 ppm; MS (ESI) *m/z* (rel intensity): 364 (MH^+, 100), 242

(12). HRMS (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found, 364.1920. [**5** (9 mg, 12 % was isolated as a by product. See spectroscopic data below]

10-(4-Fluorobenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ab). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-fluorophenylboronic acid (**2b**) (55 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ab** as an oil (56.1 mg, 54 %): IR (ATR): 2965, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 2.88 (d, J = 12.5 Hz, 1H), 3.00 (d, J = 12.5 Hz, 1H), 3.64 (d, J = 15.4 Hz, 1H), 3.86 (s, 3H), 3.93 (s, 3H), 4.62 (d, J = 15.4 Hz, 1H), 6.14 (dd, J = 3.6, 1.7 Hz, 1H), 6.19-6.26 (m, 3H), 6.43 (s, 1H), 6.50 (dd, J = 2.7, 1.7 Hz, 1H), 6.61-6.67 (m, 2H), 6.96 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.0, 41.0, 46.6, 53.6, 55.9, 56.1, 102.6, 108.0, 108.3, 108.4 (d, J = 7.8 Hz), 113.8 (d, J = 20.8 Hz), 117.6, 124.9, 131.3, 131.4, 133.7 (d, J = 3.2 Hz), 134.5, 147.5, 148.2, 161.7 (d, J = 244.2 Hz) ppm; MS (ESI) *m/z* (rel intensity): 352 (MH^+, 100), 350 (10), 243 (13). HRMS (ESI-TOF): calcd. for $C_{22}H_{23}FNO_2$ [MH^+] 352.1707; found, 352.1713.

7,8-Dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ac). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (506 mg, 1.32 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (134 mg, 0.13 mmol), 4-nitrophenylboronic acid (**2c**) (284 mg, 1.7 mmol), sodium carbonate (180 mg, 1.7 mmol), tri(furan-2-yl)phosphane (**L2**) (60.2 mg, 0.26 mmol) and tetrabutylammonium chloride (723 mg, 2.60 mmol) in DMF (4 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9:1) afforded **3ac** as an oil (470 mg, 94 %): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 3H), 3.05 (d, J = 12.1 Hz, 1H), 3.16 (d, J = 12.1 Hz, 1H), 3.68 (d, J = 15.7 Hz, 1H), 3.87 (s, 3H), 3.97 (s, 3H), 4.66 (d, J = 15.6 Hz, 1H), 6.18 (dd, J = 3.6, 1.7 Hz, 1H), 6.27 (dd, J = 3.6, 2.7 Hz, 1H), 6.41-6.45 (m, 3H), 6.50 (dd, J = 2.7, 1.7 Hz, 1H), 7.02 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ

27.7, 41.0, 46.6, 54.2, 55.9, 56.2, 103.1, 108.1, 108.2, 108.7, 117.9, 122.2, 124.3, 130.6, 130.5, 133.6, 146.0, 146.6, 147.8, 148.5 ppm; MS (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (23). HRMS (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found, 379.1658.

7,8-Dimethoxy-10-methyl-10-(4-trifluoromethylbenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ad). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1a** (115 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-trifluoromethylphenylboronic acid (**2d**) (74.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h.. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ad** as an oil (63.1 mg, 52 %): IR (ATR): 2935, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 3H), 2.97 (d, J = 12.3 Hz, 1H), 3.09 (d, J = 12.3 Hz, 1H), 3.66 (d, J = 15.5 Hz, 1H), 3.87 (s, 3H), 3.93 (s, 3H), 4.64 (d, J = 15.5 Hz, 1H), 6.16-6.17 (m, 1H), 6.26 (t, J = 3.1 Hz, 1H), 6.40-6.45 (m, 3H), 6.50-6.52 (m, 1H), 6.95 (s, 1H), 7.21 (d, J = 7.9 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 40.9, 46.6, 54.0, 55.9, 56.1, 102.9, 108.1, 108.4, 117.8, 123.9 (q, J = 3.8 Hz), 124.4 (q, J = 271.9 Hz), 124.7, 128.4 (q, J = 32.3 Hz), 130.2, 131.1, 134.2, 142.2, 147.7, 148.3 ppm; MS (ESI) *m/z* (rel intensity): 402 (MH^+, 100), 243 (7). HRMS (ESI-TOF): calcd. for $C_{23}H_{23}F_3NO_2$ [MH^+] 402.1675; found, 402.1682.

10-(3,5-bis(Trifluoromethy)lbenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ae). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31 mg, 0.03 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (**2e**) (101 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (14 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silicagel, petroleum ether/ethyl acetate 9/1) afforded **3ae** as an oil (77.5 mg, 55%): IR (ATR): 2940, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.99 (d, J = 12.3 Hz, 1H), 3.12 (d, J = 12.3 Hz, 1H), 3.46 (d, J = 15.9 Hz, 1H), 3.84 (s, 3H), 3.96 (s, 3H), 4.64 (d, J = 15.9 Hz, 1H), 6.18 (dd, J = 3.6, 1.7 Hz, 1H), 6.27 (dd, J = 3.6, 2.7 Hz,

1H), 6.40 (s, 1H), 6.46 (dd, J = 2.7, 1.7 Hz, 1H), 6.61-6.62 (m, 2H), 7.01 (s, 1H), 7.62 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.9, 40.9, 46.2, 54.0, 56.0, 56.3, 103.1, 108.2, 108.8, 118.0, 119.9 (sept, J = 3.9 Hz), 123.2 (q, J = 272.7 Hz), 124.3, 130.0, 130.1 (q, J = 33.0 Hz), 133.0, 140.5, 148.2, 148.8 ppm; MS (ESI) *m/z* (rel intensity): 470 (MH^+, 100), 360 (11). HRMS (ESI-TOF): calcd. for $C_{24}H_{22}F_6NO_2$ [MH^+] 470.1549; found, 470.1553. [**5** (12.2 mg, 16%) was isolated as a by product. See spectroscopic data below]

10-(3,4-Dimethoxybenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3af). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 3,4-dimethoxyphenylboronic acid (**2f**) (71 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3af** as an oil (72.8 mg, 62 %): IR (ATR): 2935, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (s, 3H), 2.85 (d, J = 12.4 Hz, 1H), 2.98 (d, J = 12.4 Hz, 1H), 3.51 (s, 3H), 3.54 (d, J = 15.4 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 3.96 (s, 3H), 4.57 (d, J = 15.4 Hz, 1H), 5.72 (d, J = 2.0 Hz, 1H), 5.87 (dd, J = 8.1, 2.0 Hz, 1H), 6.17 (dd, J = 3.6, 1.7 Hz, 1H), 6.27 (dd, J = 3.6, 2.7 Hz, 1H), 6.42 (s, 1H), 6.46-6.49 (m, 2H), 7.02 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.1, 41.2, 46.7, 54.2, 55.4, 55.8, 55.9, 56.2, 102.5, 108.0, 108.3, 108.5, 109.9, 112.9, 117.5, 121.9, 125.2, 130.6, 131.7, 134.8, 147.4, 147.5, 147.6, 148.2 ppm; MS (ESI) *m/z* (rel intensity): 394 (MH^+, 86), 242 (11). HRMS (ESI-TOF): calcd. for $C_{24}H_{28}NO_4$ [MH^+] 394.2013; found, 394.2017.

10-Benzyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ag). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), phenylboronic acid (**2g**) (47.5 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 4 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ag** as a

solid (45.8 mg, 46%): mp (petroleum ether/EtOAc): 98-100 °C; IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.90 (d, J = 12.3 Hz, 1H), 3.02 (d, J = 12.3 Hz, 1H), 3.61 (d, J = 15.3 Hz, 1H), 3.85 (s, 3H), 3.91 (s, 3H), 4.59 (d, J = 15.3 Hz, 1H), 6.15 (dd, J = 3.6, 1.7 Hz, 1H), 6.25 (dd, J = 3.6, 2.6 Hz, 1H), 6.28-6.32 (m, 2H), 6.43 (s, 1H), 6.50 (dd, J = 2.7, 1.7 Hz, 1H), 6.92-6.98 (m, 3H), 7.06-7.11 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.9, 41.0, 46.7, 54.3, 55.9, 56.1, 102.6, 108.1, 108.2, 108.6, 117.6, 125.1, 126.1, 127.1, 130.1, 131.7, 134.9, 137.9, 147.4, 148.1 ppm; MS (ESI) *m/z* (rel intensity): 334 (MH^+, 100), 243 (11). HRMS (ESI-TOF): calcd. for $C_{22}H_{24}NO_2$ [MH^+] 334.1802; found, 334.1813.

7,8-Dimethoxy-10-methyl-10-(naphthalen-2-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ah). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), naphthalen-2-ylboronic acid (**2h**) (67.1 mg 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ah** as an oil (61 mg, 53%): IR (ATR): 3010, 1275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), 3.06 (d, J = 12.4 Hz, 1H), 3.18 (d, J = 12.4 Hz, 1H), 3.47 (d, J = 15.4 Hz, 1H), 3.83 (s, 3H), 3.91 (s, 3H), 4.50 (d, J = 15.4 Hz, 1H), 6.19 (dd, J = 3.6, 1.7 Hz, 1H), 6.27-6.29 (m, 1H), 6.36 (s, 1H), 6.41 (dd, J = 8.4, 1.7 Hz, 1H), 6.45-6.47 (m, 1H), 6.75 (s, 1H), 6.98 (s, 1H), 7.35-7.43 (m, 3H), 7.49-7.52 (m, 1H), 7.70-7.73 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.8, 41.1, 46.8, 54.4, 55.9, 56.1, 102.7, 108.2, 108.3, 108.6, 117.7, 124.9, 125.2, 125.4, 126.2, 127.3, 127.6, 128.6, 128.7, 131.8, 132.0, 132.9, 134.8, 135.5, 147.4, 148.2 ppm; MS (ESI) *m/z* (rel intensity): 384 (MH^+, 100), 242 (23). HRMS (ESI-TOF): calcd. for $C_{26}H_{26}NO_2$ [MH^+] 384.1958; found, 384.1964.

7,8-Dimethoxy-10-methyl-10-(phenanthren-9-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ai). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1a** (115 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), phenanthren-9-ylboronic acid (**2i**) (86.8 mg 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1

mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ai** as an oil (82.6 mg, 63%): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (s, 3H), 3.48-3.56 (m, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 4.43 (d, J = 15.5 Hz, 1H), 6.19-6.23 (m, 3H), 6.35-6.36 (m, 1H), 6.69 (s, 1H), 6.95 (s, 1H), 7.23-7.28 (m, 1H), 7.43-7.60 (m, 5H), 8.58-8.61 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.2, 41.2, 47.1, 49.5, 56.0, 56.2, 102.8, 108.2, 108.6, 109.1, 118.0, 122.2, 122.4, 124.5, 125.3, 125.4, 125.7, 126.1, 126.3, 128.3, 129.5, 129.6, 131.3, 131.8, 132.3, 132.4, 135.2, 147.6, 148.3 ppm; MS (ESI) *m/z* (rel intensity): 434 (MH^+, 100), 242 (59). HRMS (ESI-TOF): calcd. for $C_{30}H_{28}NO_2$ [MH^+] 434.2115; found, 434.2119.

7,8-Dimethoxy-10-methyl-10-(pyren-1-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3aj). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (115 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), pyren-1-ylboronic acid (**2j**) (96 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3aj** as an oil (114.2 mg, 83%): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.85 (d, J = 15.4 Hz, 1H), 3.68 (s, 3H), 3.72-3.73 (m, 2H), 3.91 (s, 3H), 4.20 (d, J = 15.4 Hz, 1H), 6.09 (s, 1H), 6.25-6.33 (m, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 7.51 (d, J = 9.4 Hz, 1H), 7.71 (d, J = 9.4 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.92-8.13 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.6, 41.7, 46.8, 50.5, 56.0, 56.3, 102.9, 108.2, 108.6, 109.0, 118.1, 123.4, 123.7, 124.2, 124.5, 124.6, 124.7, 125.5, 125.7, 126.2, 126.9, 127.5, 129.5, 129.9, 130.2, 130.6, 131.3, 132.0, 132.5, 134.8, 147.7, 148.4 ppm; MS (ESI) *m/z* (rel intensity): 458 (MH^+, 100), 242 (56). HRMS (ESI-TOF): calcd. for $C_{32}H_{28}NO_2$ [MH^+] 458.2115; found, 458.2123

7,8-Dimethoxy-10-methyl-10-(thiophen-3-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ak). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), thiophen-3-ylboronic acid (**2k**) (50 mg, 0.39 mmol),

sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ak** as an oil (14 mg, 14%): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.96 (d, J = 12.9 Hz, 1H), 3.05 (d, J = 12.9 Hz, 1H), 3.87 (s, 3H),* 3.92 (s, 3H),* 3.87-3.92 (m, 1H),* 4.70 (d, J = 15.4 Hz, 1H), 5.99 (dd, J = 4.9, 1.3 Hz, 1H), 6.13-6.18 (m, 2H), 6.24-6.26 (m, 1H), 6.48 (s, 1H), 6.54-6.55 (m, 1H), 6.90-6.92 (m, 2H) ppm (*overlapped); $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 40.6, 46.6, 48.3, 55.9, 56.1, 102.5, 108.1, 108.3, 108.5, 117.6, 122.5, 123.3, 124.7, 129.6, 131.7, 135.0, 138.4, 147.4, 148.1 ppm; MS (ESI) *m/z* (rel intensity): 340 (MH^+, 59), 243 (14), 242 (100). HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NO_2S$ [MH^+] 340.1366; found, 340.1372. [**5** (8 mg, 11%) and **4k** (50.6 mg, 50%) were isolated as by products. See spectroscopic data below]

10-Allyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3al). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (31.0 mg, 0.03 mmol), potasium trifluorovinylborate (52.2 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 24 h. After work up, purification by column chromatography (silicagel, petroleum ether/ethyl acetate 95:5) afforded **3al** as an oil (31.7, mg, 38%): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.50-2.53 (m, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 4.81-4.89 (m, 2H), 5.01 (d, J = 15.5 Hz, 1H), 5.08 (d, J = 15.5 Hz, 1H), 5.37-5.48 (m, 1H), 6.04 (dd, J = 3.5, 1.7 Hz, 1H), 6.23 (dd, J = 3.5, 2.7 Hz, 1H), 6.67-6.69 (m, 2H), 6.93 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 39.3, 47.3, 49.2, 56.0, 56.1, 102.6, 108.1, 108.8, 108.9, 117.4, 118.0, 124.0, 133.1, 134.8, 135.5, 147.4, 148.2 ppm; MS (ESI) *m/z* (rel intensity): 284 (MH^+, 100), 243 (51). HRMS (ESI-TOF): calcd. for $C_{18}H_{22}NO_2$ [MH^+] 284.1645; found, 284.1649. [**5** (16 mg, 24%) was isolated as by product. See spectroscopic data below]

10-Cinnamyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3am). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (31.0 mg, 0.03 mmol), (*E*)-styrylboronic acid (**2m**) (57.7 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3am** as an oil (64.5 mg, 60%): IR (ATR): 2970, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.55-2.68 (m, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 5.01 (s, 2H), 5.82 (dt, *J* = 15.8, 7.4 Hz, 1H), 6.09-6.14 (m, 2H), 6.26 (dd, *J* = Hz, 3.6, 2.7 Hz, 1H), 6.67 (s, 1H), 6.69 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.97 (s, 1H), 7.14-7.28 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.6, 39.8, 47.4, 49.0, 56.0, 56.1, 102.6, 108.2, 108.8, 108.8, 118.1, 124.1, 126.0, 126.5, 127.0, 128.4, 132.6, 133.0, 135.5, 137.6, 147.4, 148.2 ppm; MS (ESI) *m/z* (rel intensity): 360 (MH^+, 98), 243 (100). HRMS (ESI-TOF): calcd. for $C_{24}H_{26}NO_2$ [MH^+] 360.1958; found, 360.1964.

7,8-Dimethoxy-10-(4-methoxybenzyl)-10-(trifluoromethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3ba). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1b** (132 mg, 0.30 mmol) was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (31.0 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**2a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3ba** as an oil (64.7 mg, 52%): IR (ATR): 2960, 1510, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.60 (d, *J* = 14.4 Hz, 1H), 3.64 (s, 3H), 3.75 (d, *J* = 14.4 Hz, 1H), 3.86 (s, 3H,), 3.89 (s, 3H), 4.67 (d, *J* = 15.8 Hz, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 6.32-6.34 (m, 1H), 6.45-6.57 (m, 6H), 6.72-6.73 (m, 1H), 7.14 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 39.2, 46.7, 49.6 (q, *J* = 25.0 Hz), 55.0, 55.8, 56.0, 108.1, 108.2, 109.0, 111.7 (q, *J* = 2.6 Hz), 113.0, 119.5, 120.9, 124.3, 126.0, 127.0 (q, *J* = 284.6 Hz), 127.4, 130.8, 147.7, 148.8, 158.0 ppm; MS (ESI) *m/z* (rel intensity): 418 (MH^+, 100), 296 (23). HRMS

(ESI-TOF): calcd. for $C_{23}H_{23}F_3NO_3$ [MH^+] 418.1625; found, 418.1627. [Using General Procedure A, **6** (57.1 mg, 61%) was isolated as the major compound. See spectroscopic data below]

7,8-Dimethoxy-10-(4-nitrobenzyl)-10-(trifluoromethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3bc). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1b** (133 mg, 0.30 mmol) was treated with $Pd_2(dba)_3 \cdot CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/dichloromethane 9:1) afforded **3bc** as a solid (110 mg, 84%): IR (ATR): 2970, 1520, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.77-3.92 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.77 (d, J = 15.9 Hz, 1H), 5.04 (d, J = 15.9 Hz, 1H), 6.32-6.35 (m, 1H), 6.44-6.46 (m, 1H), 6.60 (s, 1H), 6.75-6.81 (m, 3H), 7.09 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 39.7, 46.7, 49.1 (q, J = 25.6 Hz), 55.8, 56.2, 108.4, 108.5, 109.4, 111.2 (q, J = 2.5 Hz), 119.9, 120.0, 122.8, 123.2, 126.0, 126.7 (q, J = 284.5 Hz), 130.5, 143.4, 146.6, 148.1, 149.3 ppm; MS (ESI) *m/z* (rel intensity): 433 (MH^+, 100), 296 (15). HRMS (ESI-TOF): calcd. for $C_{22}H_{20}F_3N_2O_4$ [MH^+] 433.1370; found, 433.1379. [Using General Procedure A, **6** (47 mg, 51%) was isolated as the major compound. See spectroscopic data below]

10-Ethyl-7,8-dimethoxy-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-b]isoquinoline (3cc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1c** (117 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3cc** as an oil (63.5 mg, 54%): IR (ATR): 2970, 1520, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.64 (t, J = 7.2 Hz, 3H), 2.36 (q, J = 7.2 Hz, 2H), 3.06 (d, J = 12.1 Hz, 1H), 3.19 (d, J = 12.1 Hz, 1H), 3.64 (d, J = 15.7 Hz, 1H), 3.85 (s, 3H), 3.97 (s, 3H), 4.64 (d, J = 15.7 Hz, 1H), 6.15 (dd, J =3.6, 1.7 Hz, 1H), 6.28-6.31 (m, 1H), 6.37-6.40 (m, 3H), 6.45-6.47 (m, 1H), 6.96 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H)

ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 9.0, 33.8, 46.1, 46.2, 54.4, 55.8, 56.2, 102.9, 108.0, 108.2, 109.0, 117.7, 122.1, 125.3, 127.6, 130.5, 131.8, 146.1, 146.4, 147.8, 148.7 ppm; MS (ESI) *m/z* (rel intensity): 393 (MH^+, 100), 257 (12). HRMS (ESI-TOF): calcd. for $C_{23}H_{25}N_2O_4$ [MH^+] 393.1809; found, 393.1815.

10-Methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3dc). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1d** (97.0 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 95:5) afforded **3dc** as an oil (36.6 mg, 38%): IR (ATR): 2935, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 3H), 3.08 (d, J = 12.3 Hz, 1H), 3.19 (d, J = 12.3 Hz, 1H), 3.85 (d, J = 15.9 Hz, 1H), 4.79 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 3.6, 1.7 Hz, 1H), 6.30 (dd, J = 3.6, 2.7 Hz, 1H), 6.44 (d, J = 8.7 Hz, 2H), 6.56 (dd, J = 2.7, 1.7 Hz 1H), 7.01-7.03 (m, 1H), 7.25-7.28 (m, 1H), 7.38-7.41 (m, 1H), 7.57-7.59 (m, 1H), 7.83 (d, J = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.2, 41.2, 47.0, 54.2, 103.3, 108.8, 118.1, 122.2, 125.4, 125.8, 126.7, 127.6, 130.7, 132.0, 133.7, 138.9, 145.9, 146.6 ppm; MS (ESI) *m/z* (rel intensity): 319 (MH^+, 100), 183 (14). HRMS (ESI-TOF): calcd. for $C_{20}H_{19}N_2O_2$ [MH^+] 319.1441; found, 319.1443.

10-Methyl-10-(4-nitrobenzyl)-5,10-dihydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-*b*]isoquinoline (3ec). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1e** (111 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 95/5) afforded **3ec** as a solid (70.6 mg, 65%): mp (petroleum ether/ethyl acetate): 179-181 ºC; IR (ATR): 2915, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 3.00 (d, J = 12.2 Hz, 1H), 3.13 (d, J = 12.2 Hz, 1H), 3.63 (d, J = 15.8

Hz, 1H), 4.61 (d, *J* = 15.8 Hz, 1H), 5.98 (d, *J* = 1.4 Hz, 1H), 6.03 (d, *J* = 1.4 Hz, 1H), 6.15 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.26 (dd, *J* = 3.6, 2.7 Hz, 1H), 6.41-6.49 (m, 4H), 7.02 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.8, 41.3, 47.0, 54.1, 101.3, 103.2, 105.3, 105.4, 108.8, 117.9, 122.2, 125.3, 130.6, 132.2, 133.5, 146.0, 146.3, 146.6, 147.5 ppm; MS (ESI) *m/z* (rel intensity): 363 (MH^+, 100), 269 (40), 227 (23). HRMS (ESI-TOF): calcd. for $C_{21}H_{19}N_2O_4$ [MH^+] 363.1339; found, 363.1346.

6,7-Dimethoxy-10-(4-methoxybenzyl)-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3fa). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1f** (111 mg, 0.29 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**2a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL). After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 95:5) afforded **3fa** as an oil (23.4 mg, 22 %): IR (ATR): 2935, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 2.79 (d, *J* = 12.4 Hz, 1H), 2.95 (d, *J* = 12.4 Hz, 1H), 3.40 (d, *J* = 16.6 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.90 (s, 3H), 4.91 (d, *J* = 16.6 Hz, 1H), 6.11-6.15 (m, 3H), 6.24 (dd, *J* = 3.5, 2.7 Hz, 1H), 6.49-6.54 (m, 3H), 6.93 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 26.6, 40.9, 42.4, 54.4, 55.1, 55.8, 60.1, 102.4, 108.2, 111.2, 112.6, 117.9, 120.7, 127.6, 130.2, 130.9, 133.1, 134.8, 144.0, 150.2, 158.2 ppm; MS (ESI) *m/z* (rel intensity): 364 (MH^+, 100), 242 (6). HRMS (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found, 364.1911.

6,7-Dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3fc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1f** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL). After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 9/1) afforded **3fc** as a solid (41.2 mg, 37%): mp (petroleum ether/ethyl acetate): 102-104 ºC; IR (ATR): 2940, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (s, 3H), 2.98 (d, *J* = 12.1 Hz, 1H), 3.13 (d, *J* = 12.1 Hz, 1H),

3.59 (d, J = 17.0 Hz, 1H), 3.73 (s, 3H), 3.91 (s, 3H), 4.96 (d, J = 17.0 Hz, 1H), 6.15 (dd, J = 3.7, 1.7 Hz, 1H), 6.26-6.28 (m, 1H), 6.40 (d, J = 8.6 Hz, 2H), 6.55-6.56 (m, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.6 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.3, 40.8, 42.5, 54.7, 55.8, 60.1, 103.0, 108.7, 111.6, 118.3, 120.7, 122.2, 126.7, 130.7, 131.9, 133.6, 144.1, 146.1, 146.6, 150.4 ppm; MS (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (15). HRMS (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found, 379.1659.

7,9-Dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3gc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **1g** (92.3 mg, 0.24 mmol) was treated with $Pd(OAc)_2$ (5.4 mg, 0.02 mmol), 4-nitrophenylboronic acid (**2c**) (52.3 mg, 0.31 mmol), sodium carbonate (33.2 mg, 0.31 mmol) and tetrabutylammonium chloride (134 mg, 0.48 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silicagel, petroleum ether/ethyl acetate 9/1) afforded **3gc** as an oil (54.7 mg, 60%): IR (ATR): 2935, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.09 (d, J = 12.1 Hz, 1H), 3.75-3.79 (m, 1H), 3.78 (s, 3H), 3.86 (d, J = 16.2 Hz, 1H), 3.96 (s, 3H), 4.73 (d, J = 16.2 Hz, 1H), 6.02 (d, J = 2.5 Hz, 1H), 6.24 (dd, J = 3.6, 1.7 Hz, 1H), 6.31-6.33 (m, 1H), 6.43-6.47 (m, 4H), 7.74 (d, J = 8.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ.28.9, 41.3, 46.8, 49.5, 55.2, 55.3, 98.6, 101.2, 103.1, 109.0, 116.6, 118.3, 122.1, 130.1, 133.6, 136.1, 146.2, 147.8, 159.0, 159.5 ppm; MS (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (14). HRMS (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found, 379.1654.

7-Fluoro-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (3hc). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **1h** (102 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**2c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L2**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After work up, purification by column chromatography (silica gel, petroleum ether/ethyl acetate 98/2) afforded **3hc** as a solid (57.7 mg, 57 %): mp (petroleum ether/ethyl acetate): 171-173 ºC; IR (ATR): 2935, 1515 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$): δ 1.91 (s, 3H), 3.03 (d, J = 12.2 Hz, 1H), 3.18 (d, J = 12.2 Hz, 1H), 3.78 (d, J = 16.3 Hz, 1H), 4.73 (d, J = 16.3 Hz, 1H), 6.20 (dd, J = 3.6, 1.7 Hz, 1H), 6.30 (dd, J = 3.6, 2.7 Hz, 1H), 6.43 (d, J = 8.7 Hz, 2H), 6.54 (dd, J = 2.7, 1.7 Hz, 1H), 6.72 (dd, J = 9.0, 2.7 Hz, 1H), 7.06-7.13 (m, 1H), 7.54 (dd, J = 8.8, 5.4 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 27.4, 40.9, 46.9 (d, J = 2.1 Hz), 54.3, 103.5, 109.0, 112.2 (d, J = 21.9 Hz), 114.8 (d, J = 21.0 Hz), 118.1, 122.4, 127.4 (d, J = 8.0 Hz), 130.7, 133.4, 134.2 (d, J = 7.7 Hz), 134.7 (d, J = 3.2 Hz), 145.7, 146.7, 161.1 (d, J = 246.4 Hz) ppm; MS (ESI) *m/z* (rel intensity): 337 (MH^+, 100), 201 (14). HRMS (ESI-TOF): calcd. for $C_{20}H_{18}FN_2O_2$ [MH^+] 337.1347; found, 337.1357.

2-(Prop-1-en-2-yl)-1-((4,4',5-trimethoxy-[1,1'-biphenyl]-2-yl)methyl)-1*H*-pyrrole (4a). (Table 1, entry 3)**.** $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **1a** (114 mg, 0.30 mmol), 4-methoxyphenylboronic acid **2a** (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in a mixture DMF/H_2O 8:2 (1 mL). The mixture was stirred at 120 ºC for 2 h. H_2O (5 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification by column chromatography (silica gel, petroleum ether/ethyl acetate 95/5) of the resulting residue afforded **4a** as a yellow oil (35.6 mg, 33 %): mp (petroleum ether/ethyl acetate): 77-79 ºC; IR (ATR): 2945, 1610, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 3.75 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.75 (s, 1H), 4.94-4.95 (m, 1H), 5.06 (s, 2H), 6.15-6.23 (m, 2H), 6.33 (s, 1H), 6.58-6.59 (m, 1H), 6.79 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.1, 49.6, 55.3, 55.9, 56.0, 107.7, 108.8, 110.4, 111.9, 113.3, 113.8, 123.7, 128.3, 130.3, 132.8, 132.9, 134.8, 135.6, 147.8, 148.5, 158.8 ppm; MS (ESI) *m/z* (rel intensity): 364 (MH^+, 5), 258 (12), 257 (100). HRMS (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found, 364.1901.

1-((4,5-Dimethoxy-4'-nitro-[1,1'-biphenyl]-2-yl)methyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (4c). Isolated as by-product in the reaction of **1a** with **2c** in the presence of phosphoramidite **L7** (Table 6, entry 1: 23%; entry 2: 7%) (See also SI): mp (petroleum ether/ethyl acetate): 145-147 ºC; IR (ATR):

2965, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 3.79 (s, 3H), 3.91 (s, 3H), 4.69 (s, 1H), 4.93-4.94 (m, 1H), 5.03 (s, 2H), 6.14-6.20 (m, 2H), 6.43 (s, 1H), 6.55-6.56 (m, 1H), 6.78 (s, 1H), 7.39 (d, J = 8.7 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.0, 49.4, 55.9, 56.1, 108.0, 109.0, 111.1, 112.0, 112.8, 123.4, 123.6, 128.2, 130.1, 130.9, 134.9, 135.6, 147.0, 147.2, 148.2, 149.5 ppm; MS (ESI) *m/z* (rel intensity): 379 (MH^+, 51), 272 (100), 226 (36). HRMS (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found, 379.1653.

1-(4,5-Dimethoxy-2-(thiophen-3-yl)benzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (4k). Isolated as by-product in the reaction of **1a** with **2k** using General Procedure B (Table 5) (See above): IR (ATR): 2935, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H), 3.75 (s, 3H), 3.88 (s, 3H), 4.76 (s, 1H,), 4.95-4.96 (m, 1H), 5.08 (s, 2H), 6.15 (dd, J = 3.6, 2.7 Hz, 1H), 6.21 (dd, J = 3.6, 1.8 Hz, 1H), 6.36 (s, 1H), 6.54 (dd, J = 2.7, 1.8 Hz, 1H), 6.84 (s, 1H), 7.03-7.05 (m, 2H), 7.37 (dd, J = 4.6, 3.3 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.1, 49.7, 55.9, 56.0, 107.7, 108.8, 110.9, 112.0, 113.1, 122.7, 123.4, 125.5, 128.0, 128.4, 128.7, 134.8, 135.6, 140.5, 147.9, 148.7 ppm; MS (ESI) *m/z* (rel intensity): 340 (MH^+, 10), 234 (10), 233 (100). HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NO_2S$ [MH^+] 340.1366; found, 340.1372.

7,8-Dimethoxy-11-methyl-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepine (5). Isolated as by-product in the reactions of **1a** (Tables 1, 2, 4 and 5) (See above): mp (petroleum ether/ethyl acetate): 136-138 ºC; IR (ATR): 2965, 1605, 1515, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.78 (s, 2H), 6.15 (dd, J = 3.6, 1.6 Hz, 1H), 6.22 (td, J = 3.5, 2.6 Hz, 1H), 6.70 (t, J = 2.1 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.80 (s, 1H), 7.00 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 24.2, 52.2, 56.0, 56.1, 107.4, 108.5, 110.0, 111.4, 120.2, 120.5, 128.3, 130.9, 131.3, 132.4, 148.2, 148.5 ppm; MS (ESI) *m/z* (rel intensity): 256 (MH^+, 100), 189 (8). HRMS (ESI-TOF): calcd. for $C_{16}H_{18}NO_2$ [MH^+] 256.1333; found, 256.1339.

7,8-Dimethoxy-3-(3,3,3-trifluoroprop-1-en-2-yl)-5*H*-pyrrolo[2,1-*a*]isoindole (6) Isolated as the major compound in the reactions of **1b** using General Procedure A (Table 3) (See above): mp

(petroleum ether/ethyl acetate): 123-125 ºC; IR (ATR): 2940, 1620, 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.95 (s, 3H), 4.85 (s, 2H), 5.54-5.56 (m, 1H), 5.78-5.79 (m, 1H), 6.27-6.28 (m, 1H), 6.58-6.60 (m, 1H), 6.96 (s, 1H), 7.06 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (75.5 MHz, $CDCl_3$): δ 51.8, 56.1, 56.3, 98.2, 102.4, 106.6, 110.7 (q, J = 5.9 Hz), 115.2 (q, J = 2.6 Hz), 122.5, 123.1 (q, J = 274.1 Hz), 125.4, 130.6 (q, J = 30.8 Hz), 132.4, 141.8, 148.0, 149.6 ppm; MS (ESI) *m/z* (rel intensity): 310 (MH^+, 100), 309 (32). HRMS (ESI-TOF): calcd. for $C_{16}H_{15}F_3NO_2$ [MH^+] 310.1049; found, 310.1053.

Synthesis of enantioenriched 3ac. (Table 6, entry 1). $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **1a** (115 mg, 0.30 mmol), 4-nitrophenylboronic acid (60.1 mg, 0.36 mmol), sodium carbonate (0.3 mL, 0.60 mmol, 2M in water) and phosphoramidite **L7** (32.4 mg, 0.06 mmol) in toluene (1 mL). The mixture was stirred at 110 ºC for 48 h. After work-up and column chromatography, **3ac** was obtained as a yellow solid (71.9 mg, 63 %). The enantiomeric excess was determined by HPLC to be 34% (SI, Figure S2) [Chiralcel ADH, Hexane/2-propanol 9:1, 1 mL/min, t_R (*minor*) = 9.1 min (32.93%), t_R (*major*) = 14.7 min (67.07%)]. [**4c** (26 mg, 23%) was isolated as by product].

Supporting Information Available. Scheme for the preparation of substrates **1a-h**. Additional essays for the chiral non-racemic phosphane ligand mediated reaction of **1a** with **2c**. Copies of ^1H and ^{13}C NMR spectra of compounds **1a-g, 3aa-hc, 4a, 4c, 4k, 5, 6**, **9a-h**. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgments. Ministerio de Economía y Competitividad (CTQ2016-74881-P), Gobierno Vasco (IT1045-16) and Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU are gratefully acknowledged for their financial support. IB wishes to thank Gobierno Vasco for a grant. Technical and human support provided by Servicios Generales de Investigación SGIker (UPV/EHU, MINECO, GV/EJ, ERDF and ESF) is also acknowledged.

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