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Generation of Tertiary and Quaternary Stereocenters *via* Palladium-Catalyzed Intramolecular Heck-type Reactions for the Stereocontrolled Synthesis of Pyrrolo[1,2-*b*]isoquinolines

Ane Rebolledo Azcargorta,[a] Estíbaliz Coya,[a] Iratxe Barbolla,[a] Esther Lete[a] and Nuria Sotomayor*[a]

Abstract:

The generation of quaternary and tertiary stereocenters on C-10 of the pyrroloisoquinoline skeleton through intramolecular Mizoroki-Heck reactions of 2-alkenyl substituted pyrroles and pyrrolidines has been studied. The cyclizations proceeded with moderate to good yields (up to 81%), although with low enantioselection when chiral phosphanes, such as (*R*)-BINAP, are used as ligands. However, enantiomerically pure 10-substituted pyrrolo[1,2-*b*]isoquinolines have been efficiently obtained through a diastereoselective approach using chiral non-racemic pyrrolidines as substrates, generating a tertiary stereocenter.

Introduction

The Mizoroki-Heck (M-H) reaction of aryl and vinyl halides with alkenes has developed into one of the most important carbon-carbon bond-forming reactions in organic synthesis.[1] The intramolecular variant represents an extremely powerful method for the construction of small and medium-size rings.[2] Particularly in recent years, this procedure has become an effective method for the formation of tertiary and quaternary stereocenters,[3] even in an asymmetric fashion.[4] In these cases, it is necessary to avoid the *syn* β-elimination of the hydride in the σ-alkylpalladium intermediate formed after the insertion of the arylpalladium to the alkene, so that the elimination takes place in another β' position and not on the carbon involved directly in bond formation. The method has been widely applied to adequately functionalized *N*-(*o*-iodophenyl)-2-alkylbut-2-enamides for the synthesis of oxindole derivatives.[5] A related procedure, that takes place with an unusual methoxide elimination, has been reported by Overman[6] in the preparation of an advanced intermediate in the synthesis of quadrigemine C. Six-membered rings with benzylic quaternary stereocenters have also been assembled by asymmetric intramolecular Mizoroki-Heck reaction. Thus, Shibasaki[7] reported a general method for synthesis of tetralin derivatives by cyclization of an aryl triflate bearing an internal (*Z*)-trisubstituted olefin with an allyl silyl ether moiety, whose utility was shown in the synthesis of an analgesic, (–)-eptazocine.

Although tertiary centre generation is usually less efficient, in 1990's Tietze showed that the regio-, diastereo- and enantioselective formation of carbocycles and heterocycles containing a tertiary carbon center can also be efficiently accomplished by a Heck reaction using either an allylsilane as the terminating group[8] or an alkene with a stereogenic center in the α-position.[9] In a similar way, Lautens[10] reported on palladium-catalyzed intramolecular cross-coupling reactions between an aryl iodide and allyl esters, leading to 2,4-disubstituted 1,2,3,4-tetrahydroquinolines with excellent diastereoselectivities as well as to various five- to seven-membered carbo- and heterocycles. The Mizoroki-Heck reaction also allows tertiary and quaternary center construction, leading to a β'-hydride elimination using cyclic alkenes[11] or cascade reactions.[12] Related tandem reactions have also been developed, where β-hydride elimination is avoided by an anion capture event.[13] In this context, we recently showed that the enantioselective palladium-catalyzed polyene cyclization can be successfully applied[14] to the construction of tetracyclic framework of Lycorine class of *Amaryllidaceae* alkaloids,[15] which exhibit a broad spectrum of pharmacological activity.[16] The pyrrolo[1,2-*b*]isoquinoline core is also the characteristic structural unit present in numerous biologically active compounds. Two examples are displayed in Figure 1. Phenanthroindolizidine alkaloids, as Tylophorine presents cytotoxic properties,[17] while Hypoestestatin 1[18] shows a promising antiviral activity.

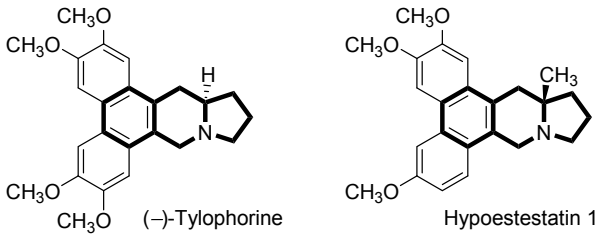

Figure 1. Representative alkaloids bearing a pyrrolo[1,2-*b*]isoquinoline core.

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Therefore, we decided to investigate further the scope of these Mizoroki-Heck intramolecular reactions towards the stereocontrolled synthesis of pyrrolo[1,2-*b*]isoquinolines. Thus, our first goal was to examine the possibility of generating quaternary and tertiary stereocenters on C-10 of the pyrroloisoquinoline skeleton. The substitution pattern on the alkene coupling partner will be studied. For that purpose we

selected 2-alkenylpyrroles as substrates in which the β-elimination is blocked by a substituent, or the β' elimination is favored by the introduction of a leaving group. The application to the formation of larger rings would also be studied (Figure 2). Besides, a diastereoselective approach was investigated, starting from chiral non-racemic pyrrolidines.

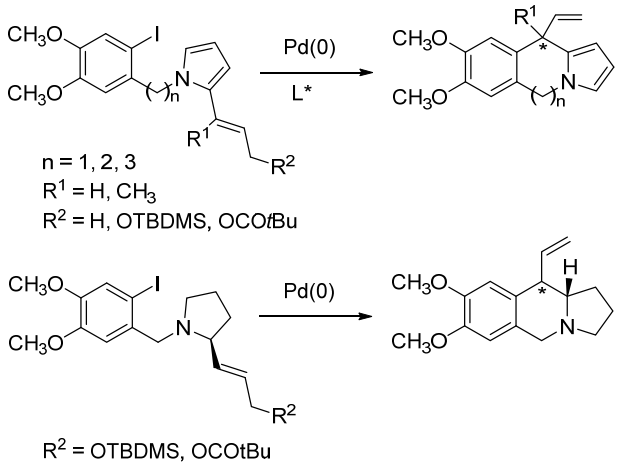
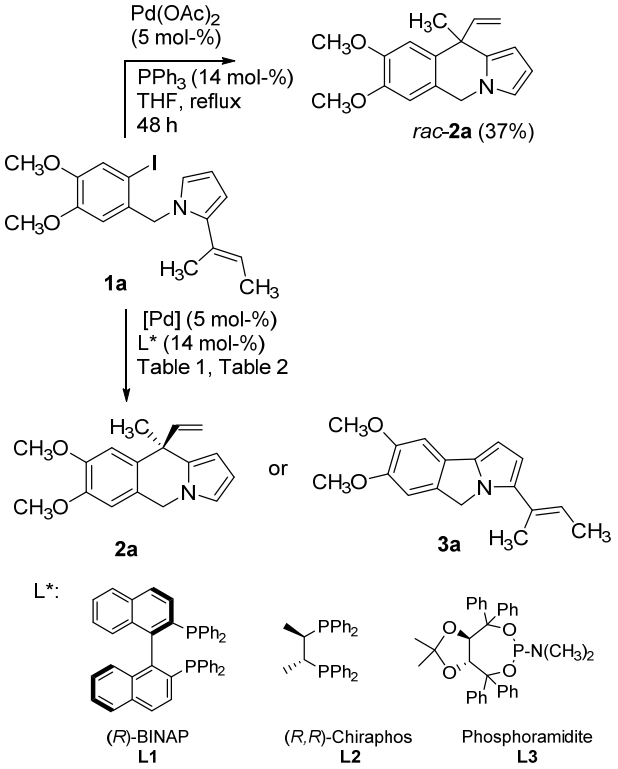


Figure 2.

Results and Discussion

We started studying the generation of a quaternary stereocenter using *N*-(*o*-iodobenzyl)pyrrolidine **1a**.[19] First, the reaction was tried in a racemic fashion. Thus, treatment of **1a** with $Pd(OAc)_2/PPh_3$ in THF at reflux gave racemic **2a**, although in poor yield (37%, Scheme 1). Having established that the formation of the quaternary centre was possible, we decided to optimize the reaction conditions for the enantioselective version. We started the optimization of conditions using (*R*)-BINAP, as it is one of the privileged ligands for this type of reaction[3,4] (Scheme 1, Table 1). Thus, treatment of **1a** with $Pd(OAc)_2$ (5 mol-%) in THF under reflux (Table 1, entry 1) led to a very low conversion, obtaining **2a** in a 5% yield. However, the enantioselectivity was promising (78% *ee*). The use of different solvents resulted in a loss of the enantioselectivity, while the yield did not improve significantly (entries 2-4). The use of DMF improved the yield of **2a** to 47%, but with a poor *ee* (18%) (entry 5). An increase or decrease of the temperature was not successful (entries 6 and 7). We continued using THF as solvent, as the enantioselectivity obtained was the best so far. The addition of PMP as a base, or nBu_4NI did not improve significantly the yield and the enantioselectivity dropped (entries 8-10 *vs* entry 1). The addition of thallium and silver salts was tried in order to drive the reaction to a cationic mechanism. The addition of TlOAc changed the chemoselectivity of the reaction affording pyrrolo[2,1-*a*]isoindole **3a** in excellent yields (entry 11). The same effect was observed by the addition of nBu_4NOAc (entry 12) and Ag_3PO_4 (entry 13). The formation of this compound was not unexpected, and resulted from a competitive direct arylation reaction of **1a** under conditions that would favor cationic palladium intermediates, or a CMD mechanism.[20]



Scheme 1. M-H reactions of **1a**. Generation of a quaternary centre.

The competition between these reactions (Mizoroki-Heck and direct arylation) has been studied by our group on related substrates.[21] A change in the palladium source, employing $Pd_2(dba)_3$ did not improve the results in terms of yield or enantioselectivity (entries 14-15), although in this case no formation of the arylation product **3a** was observed in the presence of silver salts. In a further attempt to improve both the yield and the enantioselectivity we decided to study the use of different ligands.[22] A bidentate phosphane [(*R,R*)-Chiraphos (**L2**)][23] and monodentate phosphoramidite **L3**[24] were selected (Scheme 1). We began trying the best reaction conditions in terms of enantioselectivity obtained for (*R*)-BINAP. Thus, treatment of **1a** with $Pd(OAc)_2$ in the presence of (*R,R*)-Chiraphos (**L2**) in THF under reflux afforded **2a** though with very poor yield (8%) and as a racemic mixture (Table 2, entry 1). The addition of PMP as base gave no reaction (entry 2), while the change in the solvent to DMF gave again low yield and *ee* (entry 3). The use of phosphoramidite **L3** gave better yields in the presence of PMP (up to 57% yield, entry 8), but again low enantioselectivities, in favor of the opposite enantiomer (up to –26% *ee*, entry 5).[25]

In view of these results, we decided to check the effect of the ring size in both the yield and the enantioselectivity of the reaction. However, when substrates **1b,c** (Scheme 2) were treated under the same reaction conditions used for **1a** in the racemic version (Table 3, entries 1 and 5), the pyrrolo[2,1-*a*]isoquinoline **3b** or benzo[*c*]pyrrolo[2,1-*a*]azepine **3c** were obtained in high yields, as a result of direct arylation reactions.

Table 1. Cyclization reactions of **1a** using (*R*)-BINAP (**L1**) as ligand.

Entry	[Pd]	Additive (1.1 equiv)	Solvent	Product	Yield (%)	*ee* (%)[a]
1	$Pd(OAc)_2$	-	THF[b]	**2a**	5	78
2	$Pd(OAc)_2$	-	toluene[c]	**2a**	9	14
3	$Pd(OAc)_2$	-	dioxane[c]	**2a**	11	3
4	$Pd(OAc)_2$	-	CH_3CN[b]	**2a**	11	15
5	$Pd(OAc)_2$	-	DMF[c]	**2a**	47	18
6	$Pd(OAc)_2$	-	DMF[d]	**2a**	8	36
7	$Pd(OAc)_2$	-	DMF[e]	**2a**	6	15
8	$Pd(OAc)_2$	PMP	THF[b]	**2a**	12	47
9	$Pd(OAc)_2$	*n*Bu_4NI	THF[b]	**2a**	3	32
10	$Pd(OAc)_2$	PMP/ *n*Bu_4NI	THF[b]	**2a**	4	8
11	$Pd(OAc)_2$	TlOAc	THF[b]	**3a**	99	-
12	$Pd(OAc)_2$	*n*Bu_4NOAc	THF[b]	**3a**	89	-
13	$Pd(OAc)_2$	Ag_3PO_4	THF[b]	**3a**	86	-
14	$Pd_2(dba)_3$	-	THF[b]	**2a**	14	4
15	$Pd_2(dba)_3$	AgOAc	DMF[c]	**2a**	10	15

[a] Determined by Chiral Stationary Phase HPLC (Chiralcel OZ3 2% hexane/*i*-PrOH). [b] Reflux. [c] 80 ºC. [d] 50 ºC. [e] 130 ºC.

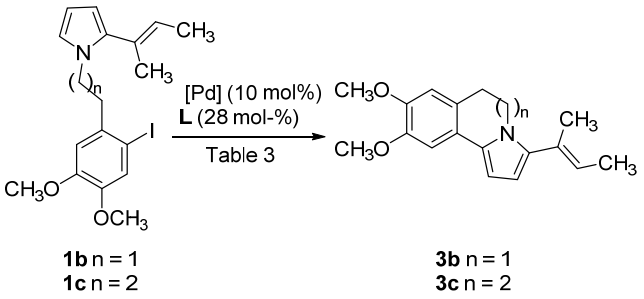
Table 2. Cyclization reactions of **1a** using **L2** and **L3** as ligands.

Entry	[Pd]	Ligand	Base	Solvent	2a Yield (%)	*ee* (%)[a]
1	$Pd(OAc)_2$	**L2**	-	THF[b]	8	-
2	$Pd(OAc)_2$	**L2**	PMP	THF[b]	-	
3	$Pd(OAc)_2$	**L2**	-	DMF[c]	5	22
4	$Pd(OAc)_2$[d]	**L3**	-	THF[b]	15	-25
5	$Pd(OAc)_2$[d]	**L3**	PMP	THF[b]	16	-26
6	$Pd(OAc)_2$[d]	**L3**	PMP	DMF[c]	24	-8
7	$Pd_2(dba)_3$[d]	**L3**	PMP	DMF[c]	45	-10
8	$Pd_2(dba)_3$[d]	**L3**	PMP	CH_3CN[b]	57	-21
9	$Pd_2(dba)_3$[d]	**L3**	PMP	THF[b]	42	-18
10	$Pd_2(dba)_3$[d]	**L3**	PMP	THF[e]	13	-24

[a] Determined by Chiral Stationary Phase HPLC (Chiralcel OZ3 2% hexane/*i*-PrOH). [b] Reflux. [c] 80 ºC. [d] 10 mol-% [Pd], 28 mol-% **L3**. [e] 40 ºC.

Similar results were obtained when (*R*)-BINAP (**L1**) or phosphoramidite **L3** were used, using $Pd(OAc)_2$ or $Pd_2(dba)_3$.

Pyrroles **1b** and **1c** showed to be less reactive than **1a**, and an increased catalyst loading was required (10 mol-% *vs* 5 mol-%) to obtain only partial conversions after 48 h, recovering starting material in most cases (Table 3). In the case of the formation of benzo[*c*]pyrrolo[2,1-*a*]azepine **3c**, inseparable mixtures with starting material **1c** were obtained, so the yield was estimated by ^{1}H-NMR (Table 3, entries 5-8). To fully characterize **3c**, the reaction was carried out under conditions that should favor the arylation reaction[21] [$Pd(OAc)_2$, PPh_3, *n*Bu_4NOAc in DMF], obtaining **3c** in 65% isolated yield. Thus, under the conditions tested, the formation of a 6 or 7 membered ring through a direct arylation process to obtain **3b,c** is favored over the formation of 7 or 8-membered rings and a quaternary center through a Mizoroki-Heck reaction. In this case, the ring size seems to be the key determinant factor in controlling selectivity.



1b n = 1
1c n = 2

3b n = 1
3c n = 2

Scheme 2. Cyclization reactions of reactions of **1b,c**.

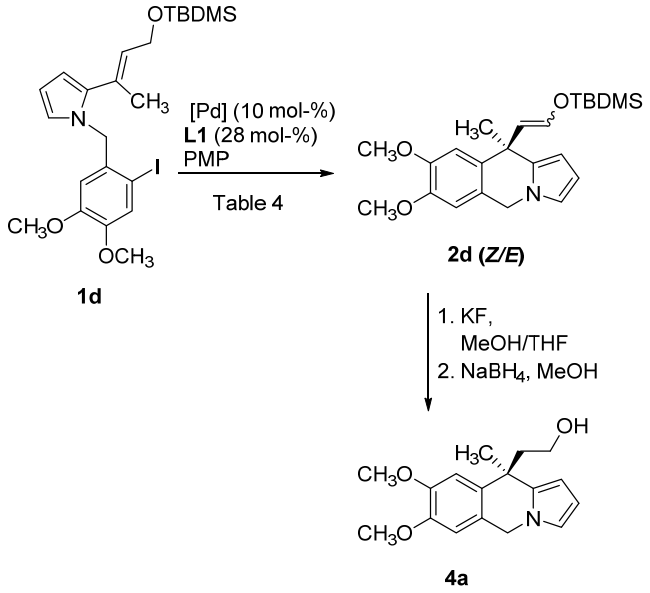
Table 3. Cyclization reactions of **1b,c**

Entry	1	[Pd]	Ligand	Base	Solvent	3, Yield (%)
1	**1b**	$Pd(OAc)_2$	PPh_3	Et_3N	THF[a]	**3b**,93
2	**1b**	$Pd(OAc)_2$	**L1**	-	THF[a]	**3b**, 60[b]
3	**1b**	$Pd_2(dba)_3$	**L1**	-	DMF[c]	**3b**, 55[b]
4	**1b**	$Pd_2(dba)_3$	**L3**	PMP	CH_3CN[a]	**3b**, 27[d]
5	**1c**	$Pd(OAc)_2$	PPh_3	Et_3N	THF[a]	**3c**, 66[e]
6	**1c**	$Pd(OAc)_2$	**L1**	-	THF[a]	**3c**, 17[e]
7	**1c**	$Pd_2(dba)_3$	**L1**	-	DMF[c]	**3c**, 32[e]
8	**1c**	$Pd_2(dba)_3$	**L3**	PMP	CH_3CN[a]	**3c**, 19[e]

[a] Reflux [b] Isolated yield for a 40% conversion [c] 80 ºC. [d] Isolated yield for a 50% conversion [e] Estimated by ^{1}H NMR

In view of the difficulties found for the efficient generation of a quaternary center, we selected pyrrole **1d** (Scheme 3) in which the β'-hydride elimination could be favored by the introduction of a silyl protected allylic alcohol, which, after cyclization, would lead to the formation of an enol ether.[7] The racemic version of the reaction was tested first, and treatment of **1d** with $Pd(PPh_3)_4$ provided the racemic silyl enol ether **2d** as 10:90 mixture of *Z:E* diastereomers in high yield (81%, Table 4, entry 1), which was

derivatized through deprotection with KF in MeOH/THF, followed by reduction with $NaBH_4$ obtaining alcohol **4** in an excellent yield (95%).



Scheme 3. M-H reactions of **1d**. Generation of a quaternary centre

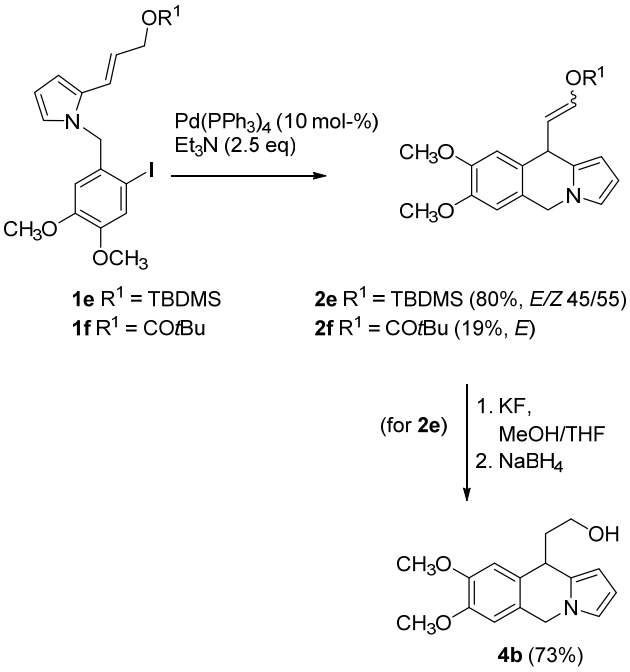
Table 4. Cyclization reactions of **1d** using (*R*)-BINAP (**L1**) as ligand

Entry	[Pd]	Solvent	2d , Yield (%) (*Z*/*E*)	4a, Yield (%)	*ee* (%)[a]
1	$Pd(PPh_3)_4$[b]	Toluene[c]	81 (10/90)	95	-
2	$Pd(OAc)_2$	THF[c]	-	-	-
3	$Pd(OAc)_2$	DMF[d]	38 (8/92)	89	2
4	$Pd(OAc)_2$	CH_3CN[c]	61 (19/81)	79	11
5	$Pd_2(dba)_3$	CH_3CN[c]	65 (11/89)	75	6
6	$Pd_2(dba)_3$	CH_3CN[c,e]	65 (34/66)	80	18

[a] Determined by Chiral Stationary Phase HPLC (Chiralcel ADH 10% hexane/*i*-PrOH) for **4a**. [b] No (*R*)-BINAP (**L1**) was used. Et_3N was used as a base. [c] Reflux. [d] 80 ºC. [e] Ag_3PO_4 was used instead of PMP.

Unfortunately, when the reaction was carried out in the presence of (*R*)-BINAP and PMP in different solvents, using both $Pd(OAc)_2$ and $Pd_2(dba)_3$, the reaction afforded moderate yields of **2d** (up to 65%), but low enantioselectivities (Table 4, entries 3-5).[25] No reaction took place in THF (entry 2). The addition of a silver salt gave a slight increase of the enantioselectivity and, in this case, no competitive arylation reaction was observed (entry 6).

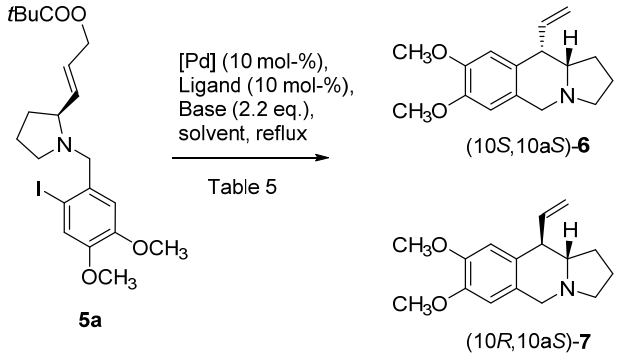
We continued using analogous substrates in order to promote generation of a tertiary stereocenter *via* β'-hydride elimination with retention of the leaving group. The tertiary stereocenter could be efficiently generated by reaction of **1e** under standard conditions (Scheme 4), obtaining **2e** as a mixture of *E*:*Z* diastereomers in good yield (80%), that could be deprotected and the resulting aldehyde reduced to obtain 10-hydroxyethylpyrroloisoquinoline **4b** in good yield. Unfortunately, when the reaction was carried out with $Pd(OAc)_2$ or $Pd_2(dba)_3$ in the presence of (*R*)-BINAP using different solvents (toluene, acetonitrile, DMF, DMA), bases (PMP, Cy_2NMe, Et_3N) under different conditions, the formation of **2e** could be observed by ^1H NMR, but together with unreacted starting material and complex mixtures of products that were not separated. The protecting group was changed to pivalate (**1f**), in order to favor the elimination of the leaving group. However, in the racemic version, the reaction of **1f** in DMF afforded a mixture of products, obtaining only the enol pivalate **2f** in low yield (19%, Scheme 4) as a single diastereoisomer, once again from a β'-hydride elimination. Different reaction conditions were tested, but in all cases the reaction was not selective, and gave low yields of **2f.**



Scheme 4. M-H reactions of **1e,f**. Generation of a tertiary centre

Thus, it has been shown that, for this type of substrates, the intramolecular Heck pathway can be optimized by modifying the substitution on the alkene, incorporating a protected allylic alcohol to favor the β'-hydride elimination. Both quaternary and tertiary stereocentres can be generated, although the enantioselective versions are not efficient. Besides, when the procedure is applied to the pyrrole derivatives, the direct arylation pathway may be competitive with the Heck reaction even under conditions that would favor a cationic mechanism, as it has been shown for **1a-c**. In fact, when **1e** was treated with $Pd(OAc)_2/PPh_3$ in the presence of *n*BuNOAc, the corresponding pyrrolo[2,1-*a*]isoindole, resulting from the direct arylation

reaction, was obtained as a the only product in high yield.[26] In this context, the electronic nature of the aryl halide coupling partner may also be important to drive the reaction through the Heck or direct arylation pathway. In previous works, we had observed that the substitution pattern on the aryl ring did not have a strong influence on the yield of the Heck reaction for the formation of quaternary stereocenters, although electron rich aromatic rings gave the best results.[14] However, when electron deficient heteroaryl halides (2-bromo or 2-iodoquinolines o pyridines) were tested in related reactions for the generation of tertiary stereocenters, under the above described conditions for **1a-e,** the selectivity could not be controlled, obtaining mixtures of Heck and arylation products.[26]



Scheme 5. M-H reactions of **5a**. Diastereoselective generation of a tertiary centre

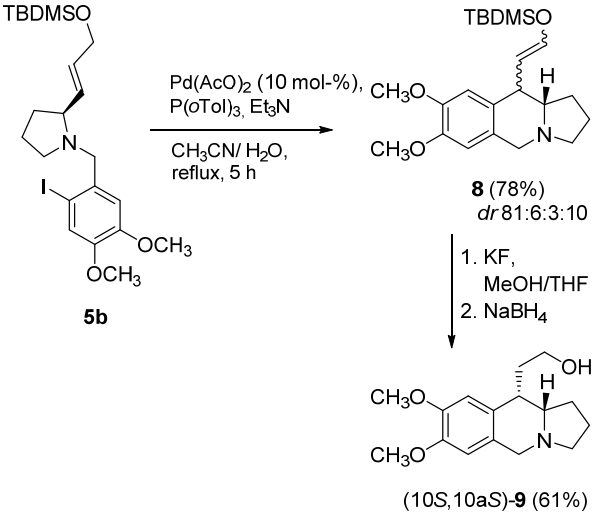
Table 5. Cyclization of **5a.**

Entry	[Pd]	Ligand	Base	Solvent	Yield (%)[a]	Ratio 6/7[b]
1	$Pd(PPh_3)_4$	-[c]	$NaHCO_3$	CH_3CN	16[d]	66:34
2	$Pd(OAc)_2$	P(*o*Tol)$_3$	Et_3N	CH_3CN	51[e]	83:17
3	$Pd(OAc)_2$	P(*o*Tol)$_3$	Et_3N	CH_3CN:H_2O	53[f]	78:22
4	$Pd(OAc)_2$	P*t*Bu$_3$	Et_3N	CH_3CN:H_2O	32[f]	78:22
5	$Pd(OAc)_2$	PCy$_3$	Et_3N	CH_3CN:H_2O	45[f]	78:22
6	$Pd(OAc)_2$	DavePhos	Et_3N	CH_3CN:H_2O	51[f]	76:24
7	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN:H_2O	32[f]	66:34
8	$Pd(OAc)_2$	dppp	Et_3N	CH_3CN:H_2O	51[f]	50:50
9	$Pd(OAc)_2$	P(*o*Tol)$_3$	$BuNMe_2$	CH_3CN:H_2O	35[f]	72:28
10	$Pd(OAc)_2$[g]	P(*o*Tol)$_3$	Et_3N	CH_3CN:H_2O	46[h]	79:21
11	$Pd_2(dba)_3$[g]	P(*o*Tol)$_3$	Et_3N	CH_3CN:H_2O	53[f]	82:18
12	$Pd_2(dba)_3$[g]	P(*o*Tol)$_3$	$BuNMe_2$	CH_3CN:H_2O	34[i]	77:23

[a] Isolated yield of the mixture. [b] Determined by GC-MS [c] nBu_4NCl (1.5 eq.) was also used. [d] 48 h. [e] 72 h. [f] 5 h. [g] 5 mol-%. [h] 22 h. [i] 6 h.

In view of these results we decided to study the obtention of enantiomerically pure pyrroloisoquinolines using a diastereoselective approach. We started studying the cyclizations of **5a**, obtained in enantiomerically pure form from L-prolinal.[19]

In this case, with a good leaving group, β'–pivalate elimination was observed by treatment with $Pd(PPh_3)_4$ and $NaHCO_3$ in acetonitrile, obtaining a 66:34 mixture of diastereomers **6**:**7**, in low yield (Scheme 5, Table 5, entry 1). No β'–hydride elimination product was detected. The use of a bulkier phosphane, such as tri-*ortho*-tolylphosphane, was required to obtain an increase in the diastereoselectivity and the yield (entry 2). The change of the solvent to a mixture of acetonitrile:H_2O shortened the reaction time to 5 h, with only a slight decrease of the diastereoselectivity (entry 3). Other phosphanes (entries 4-8) and bases (entry 9) were tried, but the yield or the diastereoselectivity were not improved. A decrease of the catalyst loading to 5 mol-% resulted in a slower reaction (22 h, entry 10). The use of $Pd_2(dba)_3$ gave similar results (entries 11-12). Both diastereomers have been isolated and characterized separately and the stereochemistry was assigned using NOESY experiments. In addition, the configuration of each diastereomer was unambiguously established by X-Ray diffraction techniques for each diastereomer, confirming a (10*S*,10a*S*)[27] configuration for the major diastereomer **6**, and a (10*R*,10a*S*)[28] configuration for the minor diastereomer **7**.



Scheme 6. M-H reaction of **5b**.Diastereoselective generation of a tertiary centre

Interestingly, when the leaving group capability was decreased by changing the protecting group of the alcohol to TBDMS, under the same conditions, β'–hydride elimination occurred (Scheme 6). Thus, enantiopure pyrrolidine **5b** gave silyl enol ether **8** in high yield (78%) as a mixture of diastereomers that correspond to (*E*)- and (*Z*)-enol configuration, for both (10*S*,10a*S*) (major) and (10*R*,10a*S*) (minor) diastereomers (Scheme 6). The silyl enol ether mixture **8** was deprotected and the resulting aldehyde was reduced to alcohol **9**, obtained finally as a single diastereomer in a 61% yield.

Conclusions

The stereocontrolled generation of a quaternary stereocenter through the Mizoroki-Heck reaction of 2-alkenylpyrrole **1a** to access to 10-disubstituted pyrrolo[1,2-*b*]isoquinoline **2a** is not effective. (*R*)-BINAP has provided the best results in terms of enantioselection, obtaining **2a** with a reasonable enantioselectivity (up to 78% *ee*) with $Pd(OAc)_2$, but in low yield. Attempts to improve the yield (up to 47%) resulted in a loss of enantioselectivity. The use of additives as silver or thallium salts, to try to increase the enantioselection through a cationic mechanism, in our case favored the arylation reaction, when $Pd(OAc)_2$ is used as pre-catalyst. The direct arylation reaction is also the preferred reaction pathway when the formation of larger ring is attempted from alkenyl pyrroles **1b,c**. However, the formation of tertiary and quaternary centers through M-H reaction is favored when a silyl protected allylic alcohol moiety is used as a coupling partner. Thus, pyrroloisoquinolines **2d** and **2e** can be obtained in good yields (80-81%), through selective β'-hydride elimination, although it was not possible to induce stereocontrol using (*R*)-BINAP. Finally, enantiomerically pure 10-substituted pyrrolo[1,2-*b*]isoquinolines have been efficiently obtained through a diastereoselective approach using chiral non-racemic pyrrolidines as substrates, generating a tertiary stereocenter. A change in the protecting group allows the selective β'-hydride elimination (when TBDMS is used) or β'-leaving group elimination (when pivalate is used).

Experimental Section

General 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 or at 500 MHz for ^{1}H and 125.7 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). Selective NOE or NOESY experiments were performed when necessary. Mass spectra were recorded under chemical ionization (CI) at 230 eV, under Electrospray ionization (ESI) or MALDI ionization. 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) or on alumina (70-230 mesh). 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.

(*R*)-7,8-Dimethoxy-10-methyl-10-vinyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (2a). (Table 1, entry 1) $Pd(OAc)_2$ (2.8 mg, 0.01 mmol) was added to a mixture of **1a** (96.6 mg, 0.24 mmol), (*R*)-BINAP (21.2 mg, 0.03 mmol) in dry THF (5 mL). The mixture was refluxed for 48 h, and allowed to cool down to r.t. The reaction mixture was then diluted with EtOAc (50 mL), washed with saturated aq. solution of NH_4Cl (30 mL) and H_2O (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, Hexane/EtOAc 8/2) to afford **2a** as a solid (3 mg, 5%): $[\alpha]_D^{20}$: + 33 7 (c = 1, CH_2Cl_2). mp.: 108-110 °C (Hexane/EtOAc). IR (ATR): *v* = 1700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.67 (s, 3H, CH_3), 3.89 (s, 6H, 2 × OCH_3), 4.85 (dd, *J* = 17.2, 1.1 Hz, 1H, CH=C*H*$_a$H$_b$), 4.96 (d, *J* = 15.9 Hz, 1H, H$_{5a}$), 5.02 (d, *J* = 15.9 Hz, 1H, H$_{5b}$), 5.04 (dd, *J* = 10.2, 1.1 Hz, 1H, CH=CH$_a$*H*$_b$), 5.94 (dd, *J* = 17.2, 10.2 Hz, 1H, C*H*=CH$_a$H$_b$), 6.00 (dd, *J* = 3.4, 1.7 Hz, 1H, H$_1$), 6.18-6.21 (m, 1H, H$_2$), 6.70-6.72 (m, 2H, H$_3$, H$_6$), 6.92 (s, 1H, H$_9$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = 26.0 (CH_3), 42.5 (C$_{10}$), 47.3 (CH_2), 56.0 (2 × OCH_3), 103.3 (C$_1$), 108.4 (C$_2$), 109.1 (C$_6$), 109.4 (C$_9$), 111.5 (CH=*C*H$_2$), 118.3 (C$_3$), 124.4 (C$_{5a}$), 132.6 (C$_{10b}$), 134.5 (C$_{9a}$), 144.4 (*C*H=CH$_2$), 147.5 (C$_7$), 148.3 (C$_8$) ppm. MS (CI): *m*/*z* (%) = 270 (100) [MH]$^+$, 269 (39) [M]$^+$, 254 (8). HRMS (CI): calcd. for $C_{17}H_{20}NO_2$ [MH]$^+$ 270.1494; found: 270.1501. The enantiomeric excess was determined by HPLC to be 78%, [Chiralcel OZ3, hexane/*iso*-propanol 98:2, 1 mL/min, *tr* (minor) = 9.4 min (11%), *tr* (major)= 10.1 min (89 %)].

(*E*)- and (*Z*)-10-[2-(*t*Butyldimethylsilyloxy)vinyl]-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (2d). (Table 4, entry 1) Et_3N (0.08 mL, 0.55 mmol) and $Pd(PPh_3)_4$ (25.70 mg, 0.02 mmol) were added to a solution of **1d** (116.10 mg, 0.22 mmol) in dry toluene (5 mL) and the mixture was heated under reflux for 16 h. The solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 4/6) obtaining **2d** as *Z*- and *E*-diastereoisomers, that could be separated and fully characterized. **(*Z*)-2d** (7.10 mg, 8% yield): colorless oil. IR (ATR): v = 1650 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 0.05 (s, 6H, Si*Me*$_2$*t*Bu), 0.79 (s, 9H, SiMe$_2$*tBu*), 1.74 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.64 (d, *J* = 6.4 Hz, 1H, C*H*=CH-OSi), 5.02 (s, 2H, 2×H$_5$), 6.02 (dd, *J* = 3.4, 1.7 Hz, 1H, H$_1$), 6.15 – 6.19 (m, 1H, H$_2$), 6.22 (d, *J* = 6.4 Hz, 1H, CH=C*H*-OSi), 6.61 – 6.65 (m, 1H, H$_3$), 6.66 (s, 1H, H$_6$), 7.08 (s, 1H, H$_9$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = -5.5 (Si*Me*$_2$*t*Bu), 18.0 (SiMe$_2$*C*(CH$_3$)$_3$), 25.4 (SiMe$_2$C(*CH*$_3$)$_3$), 30.6 (CH_3), 40.1 (C$_{10}$), 47.2 (C$_5$), 56.0, 56.1 (2 × OCH_3), 102.7 (C$_1$), 108.0 (C$_2$), 108.7 (C$_6$), 109.9 (C$_9$), 115.3 (*C*H=CHOSi), 117.3 (C$_3$), 123.0 (C$_{5a}$), 135.4 (C$_{9a}$), 137.4 (C$_{10a}$), 139.0 (CH=*C*HOSi), 147.1 (C$_8$), 148.2 (C$_7$) ppm. MS (ESI): *m*/*z* (%) = 401 (MH$^+$ + 1, 27); 400 (MH$^+$, 100). HRMS (ESI): calcd. for $C_{23}H_{34}NO_3Si$ [MH]$^+$ 400.2308; found: 400.2307. **(*E*)-2d** (63.80 mg, 73% yield): colorless oil. IR (ATR): v = 1650 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 0.12 (s, 6H, Si*Me*$_2$*t*Bu), 0.92 (s, 9H, SiMe$_2$*tBu*), 1.63 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.97 (d, *J* = 15.1 Hz, 1H, H$_{5a}$), 5.02 (d, *J* = 15.1 Hz, 1H, H$_{5b}$), 5.21 (d, *J* = 12.1 Hz, 1H, C*H*=CHOSi), 6.02 (dd, *J* = 3.5, 1.7 Hz, 1H, H$_1$), 6.09 (d, *J* = 12.1 Hz, 1H, CH=C*H*OSi), 6.18 (dd, *J* = 3.5, 2.8 Hz, 1H, H$_2$), 6.68 – 6.71 (m, 2H, H$_3$, H$_6$), 6.99 (s, 1H, H$_9$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = -5.1 (Si*Me*$_2$*t*Bu), 18.4 (SiMe$_2$*C*(CH$_3$)$_3$), 25.8 (SiMe$_2$C(*CH*$_3$)$_3$), 27.5 (*C*H$_3$), 39.4 (C$_{10}$), 47.2 (C$_5$), 56.0, 56.1 (2 x OCH_3), 103.2 (C$_1$), 107.9 (C$_2$), 109.1, 109.2 (C$_6$, C$_9$), 118.2 (C$_3$), 119.5 (*C*H=CHOSi), 124.2 (C$_{5a}$), 134.1 (C$_{9a}$), 135.6 (C$_{10a}$), 140.5 (CH=*C*HOSi), 147.4 (C$_8$), 148.3 (C$_7$) ppm. MS (ESI): *m*/*z* (%) = 401 (MH$^+$ + 1, 28); 400 (MH$^+$, 100). HRMS (ESI): calcd. for $C_{23}H_{34}NO_3Si$ [MH]$^+$ 400.2308; found: 400.2301.

***(E)*- and (*Z*)-10-[2-(*t*Butyldimethylsilyloxy)vinyl]-7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (2e).** Et_3N (0.06 mL, 0.45 mmol) and $Pd(PPh_3)_4$ (21.0 mg, 0.02 mmol) were added to a solution of **1e** (92.2 mg, 0.18 mmol) in dry toluene (5 mL) and the mixture was heated under reflux for 16 h. The solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography (silica gel, hexane/CH_2Cl_2 3/7) obtaining **2e** as *Z*- and *E*-diastereoisomers, that could be separated and fully characterized. **(*Z*)-2e** (24.8 mg, 36% yield): colorless oil. IR (ATR): v = 1650 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 0.22 (s, 6H, Si*Me*$_2$*t*Bu), 0.98 (s, 9H, SiMe$_2$*tBu*), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.67 (dd, *J* = 9.5, 5.7 Hz, 1H, C*H*=CHOSi), 5.02 - 5.10 (m, 2H, 2H$_5$), 5.23 (d, *J* = 9.5 Hz, 1H, H$_{10}$), 5.98 - 6.04 (m, 1H, H$_1$), 6.22 (t, *J* = 3.0 Hz, 1H, H$_2$), 6.53 (d, *J* = 5.7 Hz, 1H, CH=C*H*OSi), 6.68 – 6.73 (m, 2H, H$_3$, H$_6$), 6.94 (s, 1H, H$_9$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = -5.3 (Si*Me*$_2$*t*Bu), 18.3 (SiMe$_2$*C*(CH$_3$)$_3$), 25.7 (SiMe$_2$C(*CH*$_3$)$_3$), 32.6 (C$_{10}$), 47.2 (C$_5$), 55.8, 56.0 (2 x OCH_3), 103.8 (C$_1$), 108.2 (C$_2$), 108.7 (C$_6$), 110.8 (C$_9$), 111.8 (*C*H=CH-OSi), 117.9 (C$_3$), 123.2 (C$_{5a}$), 129.1 (C$_{9a}$), 131.3

(C_{10a}), 139.7 (CH=*C*H-OSi), 147.4 (C_8), 148.2 (C_7) ppm. MS (ESI): *m*/*z* (%) = 386 (MH^+, 100), 385 (40), 370 (19). HRMS (ESI): calcd. for $C_{22}H_{32}NO_3Si$ $[MH]^+$ 386.2151; found: 386.2128. **(*E*)-2e** (30.3 mg, 44% yield): yellow oil. IR (ATR): v = 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.21 (s, 6H, Si*Me*$_2$*t*Bu), 0.98 (s, 9H, SiMe$_2$*tBu*), 3.89 (s, 6H, 2 × OCH_3), 4.38 (d, *J* = 9.3 Hz, 1H, H_{10}), 4.97 - 5.07 (m, 2H, $2H_5$), 5.11 (dd, *J* = 11.9, 9.3 Hz, 1H, C*H*=CHOSi), 5.99 - 6.04 (m, 1H, H_1), 6.22 (t, *J* = 3.0 Hz, 1H, H_2), 6.47 (d, *J* = 11.9 Hz, 1H, CH=C*H*OSi), 6.69 – 6.74 (m, 2H, H_3, H_6), 6.91 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = -5.2 (Si*Me*$_2$*t*Bu), 18.4 (SiMe$_2$*C*(CH_3)$_3$), 25.7 (SiMe$_2$C(*C*H_3)$_3$), 37.1 (C_{10}), 47.2 (C_5), 55.9, 56.0 (2 × OCH_3), 104.4 (C_1), 108.2 (C_2), 108.8 (C_6), 110.7 (C_9), 112.4 (*C*H=CH-OSi), 118.3 (C_3), 123.6 (C_{5a}), 129.0 (C_{9a}), 131.3 (C_{10a}), 142.6 (CH=*C*H-OSi), 147.6 (C_8), 148.1 (C_7) ppm. MS (ESI): *m*/*z* (%) = 386 (MH^+, 100), 385 (38), 228 (34). HRMS (ESI): calcd. for $C_{22}H_{32}NO_3Si$ $[MH]^+$ 386.2151; found: 386.2130.

(*E*)-2-(7,8-Dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)vinyl pivalate (2f). Et_3N (0.64 mL, 4.61 mmol) and $Pd(PPh_3)_4$ (21.30 mg, 0.02 mmol) were added to a solution of **1f** (178.20 mg, 0.37 mmol) in dry DMF (15 mL) and the mixture was heated at 110 ºC for 5 h. The crude was eluted with EtOAc (20 mL) and was washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL) and then, with water (3 × 10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/Et_2O 6/4) obtaining product **2f** as a yellow oil (24.90 mg, 19% yield). This compound was unstable to column chromatography in both silica gel and neutral alumina. IR (ATR): v = 1740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.24 (s, 9H, COC(C*H*$_3$)$_3$), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.60 (d, *J* = 8.7 Hz, 1H, H_{10}), 4.98-5.13 (m, 2H, 2×H_5), 5.52 (dd, 1H, *J* = 12.3, 8.7 Hz, C*H*=CHOCO*t*Bu), 6.03-6.05 (m, 1H, H_1), 6.23 (t, *J* = 3.0 Hz, 1H, H_2), 6.70-6.75 (m, 2H, H_3, H_6), 6.84 (s, 1H, H_9), 7.18 (d, *J* = 12.3 Hz, 1H, CH=C*H*OCO*t*Bu) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = 26.9 (C(*C*H_3)$_3$), 37.3 (C_{10}), 38.7 (*C*(CH_3)$_3$), 47.1 (C_5), 56.1, 56.2 (2 × OCH_3), 104.7 (C_1), 108.5 (C_2), 109.1 (C_6), 111.26 (C_9), 116.72 (*C*H=CHOCO*t*Bu), 118.59 (C_3), 123.74 (C_{10a}), 127.3 (C_{5a}), 129.5 (C_{9a}), 136.7 (CH=*C*HOCO*t*Bu); 148.0, 148.4 (C_8, C_7), 175.7 (*CO**t**Bu*) ppm. MS (CI): *m*/*z* (%) = 356 (MH^+, 100), 355 (72), 270 (30), 254 (37). HRMS (CI): calcd. for $C_{21}H_{26}NO_4$ $[MH]^+$ 356.1862; found: 356.1852.

(*E*)-3-(But-2-en-2-yl)-7,8-dimethoxy-5H-pyrrolo[2,1-*a*]isoindole (3a). (Table 1, entry 13) $Pd(OAc)_2$ (2.6 mg, 0.01 mmol) was added to a mixture of **1a** (91.7 mg, 0.23 mmol), (*R*)-BINAP (20.1 mg, 0.03 mmol) in dry THF (5 mL). The mixture was refluxed for 9 h, and allowed to cool down to r.t. The reaction mixture was then diluted with EtOAc (50 mL), washed with saturated aq. solution of NH_4Cl (30 mL) and H_2O (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, Hexane/EtOAc 8/2) to afford **3a** as a solid (55 mg, 89%): mp.: 118-121 °C (Hexane/EtOAc). IR (ATR): v = 1615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.87 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CH=CH$_3$C), 2.05 (s, 3H, CH$_3$CH=C*H*$_3$C), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.88 (s, 2H, H_5), 5.77 (q, *J* = 6.7 Hz, 1H, CH$_3$C*H*=CCH$_3$), 6.22 (d, *J* = 3.6 Hz, 1H, H_1), 6.30 (d, *J* = 3.6 Hz, 1H, H_2), 6.95 (s, 1H, H_6), 7.05 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = 13.9 (*C*H$_3$C=CH$_3$CH), 14.8 (CH$_3$C=*C*H$_3$CH), 52.0 (C_5), 56.0 (OCH_3), 56.3 (OCH_3), 97.1 (C_1), 102.2 (C_9), 106.9 (C_6), 110.5 (C_2), 117.0 (CH$_3$C=CH$_3$*C*H), 126.1 (C_{5a}), 127.9 (CH$_3$*C*=CH$_3$CH), 132.1 (C_{9a}), 132.7 (C_3), 139.3 (C_{9b}), 147.1 (C_7), 149.3 (C_8) ppm. MS (CI): *m*/*z* (%) = 270 (MH^+, 63) 269 (M^+, 100), 255 (24), 254 (11). HRMS (CI): calcd. for $C_{17}H_{20}NO_2$ $[MH]^+$ 270.1494; found: 270.1490.

(*E*)-3-(But-2-en-2-yl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (3b). (Table 3, entry 1) $Pd(OAc)_2$ (4.9 mg, 0.02 mmol), PPh_3 (15.8 mg, 0.06 mmol) and Et_3N (60 µL, 0.43 mmol) were added to a solution of **1b** (88.2 mg, 0.22 mmol), in dry THF (5 mL). The mixture was refluxed for 6 h, and allowed to cool down to r.t. The reaction mixture was then diluted with EtOAc (50 mL), washed with saturated aq. solution of NH_4Cl (30 mL) and H_2O (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, Hexane/EtOAc 9/1) to afford **3b** as a solid (57.4 mg, 93%): IR (ATR): v = 1510 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.80 (d, *J* = 6.8 Hz, 3H, CH$_3$C=CHC*H*$_3$), 1.98 (s, 3H, C*H*$_3$C=CHCH$_3$), 2.94 (t, *J* = 6.5 Hz, 2H, 2 × H_6), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.02 (t, *J* = 6.5 Hz, 2H, 2 × H_5), 5.30-5.53 (m, 1H, CH$_3$C=C*H*CH$_3$), 6.08 (d, *J* = 3.7 Hz, 1H, H_1), 6.38 (d, *J* = 3.7 Hz, 1H, H_2), 6.70 (s, 1H, H_7), 7.02 (s, 1H, H_{10}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = 14.1 (CH$_3$C=CH*C*H$_3$), 17.6 (*C*H$_3$C=CHCH$_3$), 29.3 (C_6), 42.0 (C_5), 55.9 (OCH_3), 56.0 (OCH_3), 102.1 (C_1), 106.0 (C_7), 107.4 (C_2), 111.2 (C_{10}), 123.0 (C_{10a}), 125.8 (C_{6a}), 126.8 (CH$_3$C=*C*HCH$_3$), 127.6 (CH$_3$*C*=CHCH$_3$), 130.0 (C_3), 136.8 (C_{10b}), 147.2, 148.2 (C_8, C_9) ppm. MS (ESI^+): *m*/*z* (%) = 285 (MH^++1, 16), 284 (MH^+, 100), 283 (M^+, 38). HRMS (ESI^+): calcd. for $C_{18}H_{22}NO_2$ $[MH]^+$ 284.1651; found: 284.1651.

(*E*)-3-(But-2-en-2-yl)-9,10-dimethoxy-6,7-dihydro-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepine (3c). $Pd(OAc)_2$ (6.5 mg, 0.03 mmol), PPh_3 (15 mg, 0.06 mmol) and *n*Bu_4NOAc (132 mg, 0.43 mmol) were added to a solution of **1c** (121 mg, 0.28 mmol), in dry DMF (5 mL). The mixture stirred at 60 ºC for 48 h, and allowed to cool down to r.t.. The reaction mixture was then diluted with EtOAc (50 mL), washed with saturated aq. solution of NH_4Cl (20 mL) and H_2O (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The oil crude was purified by flash column chromatography (silica gel, Hexane/EtOAc 9:1) to afford **3c** as a solid (54.2 mg, 65%) (This sample still contains a mixture with **1c** in a 4:1 ratio): IR (ATR): v = 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.82 (d, *J* = 6.8 Hz, 3H, CH$_3$C=CHC*H*$_3$), 2.01 (s, 3H, C*H*$_3$C=CHCH$_3$), 2.17-2.30 (m, 2H, 2 × H_6) 2.72 (t, *J* = 7.0 Hz, 2H, 2 × H_7), 3.82 (t, *J* = 6.1 Hz, 2H, 2 × H_5), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.51-5.61 (m, 1H, CH$_3$C=C*H*CH$_3$), 6.12 (d, *J* = 3.6 Hz, 1H, H_1), 6.24 (d, *J* = 3.6 Hz, 1H, H_2), 6.77 (s, 1H, H_8), 6.96 (s, 1H, H_{11}) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): *δ* = 14.1 (CH$_3$C=CH*C*H$_3$), 17.1 (*C*H$_3$C=CHCH$_3$), 30.7 (C_6), 32.8 (C_7), 43.1 (C_5), 55.9 (OCH_3), 56.0 (OCH_3), 105.4 (C_1), 106.5 (C_8), 111.5 (C_2), 112.6 (C_{11}), 122.6 (C_{11a}), 126.7 (C_{7a}), 128.1 (CH$_3$C=*C*HCH$_3$), 129.7 (CH$_3$*C*=CHCH$_3$) 136.1 (C_3), 138.2 (C_{11b}), 147.7, 147.8 (C_9, C_{10}) ppm. MS (ESI^+): *m*/*z* (%) = 299 (MH^++1, 17), 298 (MH^+, 100), 297 (M^+, 11). HRMS (ESI^+): calcd. for $C_{19}H_{24}NO_2$ $[MH]^+$ 298.1807; found: 298.1808.

2-(7,8-Dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)etanol (4a). (Table 4, entry 6, 3 step procedure from **1d**) (*R*)-BINAP (27.7 mg 0.04 mmol), Ag_3PO_4 (135.7 mg, 0.32 mmol) and $Pd_2(dba)_3.CHCl_3$ (16.4 mg, 0.02 mmol) were subsequently added to a solution of **1d** (83.8 mg, 0.16 mmol) in dry CH_3CN (5 mL) under an inert atmosphere, and the reaction mixture was heated under reflux for 4 h. After that time, the mixture was diluted with EtOAc (20 mL), filtered through celite and washed with a saturated aqueous solution of NH_4Cl (10 mL) and H_2O (2 × 10 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/CH_2Cl_2 4/6) obtaining the silyl enol ethers **2d** (41.2 mg, 65% yield) as a 34:66 mixture of diastereomers. To a solution of this mixture in dry THF (5 mL), KF (0.30 mL of a 1 M solution in MeOH, 0.30 mmol) was added *via* canula under an inert atmosphere. The reaction was stirred for 4 h at room temperature. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the

lack of stability of the aldehyde intermediate. The so-obtained aldehyde (29.40 mg, 0.10 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (7.80 mg, 0.21 mmol) was added portion wise at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. H_2O (10 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining **4a** as a white solid (23.7 mg, 80% two steps): $[\alpha]_D^{20}$: -3.2 (c = 0.5, CH_2Cl_2). mp: 125-126 °C (Hexane/EtOAc). IR (ATR): v = 3385, 1515 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CH_3), 2.05 – 2.18 (m, 2H, CH_2CH_aH$_b$OH), 3.35 (dt, J = 11.1, 6.5 Hz, 1H, CH$_2$CH_aH$_b$OH), 3.42 (dt, J = 11.1, 6.5 Hz, 1H, - CH$_2$CH$_a$$H_b$OH), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.04 (d, J = 15.6 Hz , 1H, H_{5a}), 5.10 (d, J = 15.6 Hz , 1H, H_{5b}), 6.07 (dd, J = 3.5, 1.7 Hz, 1H, H_1), 6.22 - 6.26 (m, 1H, H_2), 6.65 – 6.72 (m, 2H, H_3, H_6), 6.94 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.7 (CH_3), 37.7 (C_{10}), 47.0 (C_5), 47.6 (*C*H$_2$CH$_2$OH), 55.9, 56.1 (2 × OCH_3), 60.1 (CH$_2$*C*H$_2$OH), 102.4 (C_1), 108.2 (C_9), 108.6 (C_2), 108.8 (C_3), 118.3 (C_6), 123.3 (C_{5a}), 132.7 (C_{9a}), 135.0 (C_{10a}), 147.6 (C_8), 148.5 (C_7) ppm. MS (CI): *m*/*z* (%) = 289 (17), 288 (MH^+, 100). HRMS (ESI): calcd. for $C_{17}H_{22}NO_3$ $[MH]^+$ 288.1600; found: 288.1610. The enantiomeric excess was determined by HPLC to be 18% [Chiralcel ADH, hexane: *i*-PrOH 90:10, 1 mL/min, t_r (*major*)= 35.5 min (59%), t_r (*minor*)= 58.4 min (41%)].

2-(7,8-Dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)ethan-1-ol (4b). To a solution of **2e** (diastereomeric mixture, 56.0 mg, 0.15 mmol) in dry THF (5 mL), KF (0.44 mL of a 1 M solution in MeOH, 0.44 mmol) was added *via* canula under an inert atmosphere. The reaction was stirred for 5 h at room temperature. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the lack of stability of the aldehyde intermediate. The so-obtained aldehyde (38.8 mg, 0.14 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (16.2 mg, 0.43 mmol) was added portion wise at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. H_2O (10 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining **4a** as a white solid (28.60 mg, 73% two steps): IR (ATR): v = 3515, 1515 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.81 – 1.90 (m, 1H, CH_aH$_b$CH$_2$OH), 1.95 – 2.04 (m, 1H, CH$_a$$H_bCH_2$OH), 3.66 – 3.72 (m, 2H, CH$_a$H$_b$CH_2OH), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.18 – 4.25 (m, 1H, H_{10}), 4.98 (d, J = 15.3 Hz, 1H, H_{5a}), 5.06 (d, J = 15.3 Hz , 1H, H_{5b}), 6.03 (dd, J = 3.3, 1.5 Hz, 1H, H_1), 6.17 - 6.22 (m, 1H, H_2), 6.70 – 6.74 (m, 2H, H_3, H_6), 6.83 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 36.1 (C_{10}), 41.0 (*C*H$_2$CH$_2$OH), 47.3 (C_5), 56.0, 56.1 (2 × OCH_3), 60.5 (CH$_2$*C*H$_2$OH), 103.8 (C_1), 108.2 (C_2), 109.2 (C_6), 111.1 (C_9), 118.4 (C_3), 124.1 (C_{5a}), 130.1 (C_{9a}), 130.7 (C_{10a}), 147.5 (C_8), 148.3 (C_7) ppm. MS (ESI): *m*/*z* (%) = 274 (MH^+, 100), 273 (M^+, 6), 272 (32). HRMS (CI): calcd. for $C_{16}H_{20}NO_3$ $[MH]^+$ 274.1443; found: 274.1451.

(10*S*,10a*S*)-7,8-Dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (6) and (10*R*,10a*S*)-7,8-dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (7). (Table 5, entry 3) Et_3N (0.13 mL, 0.93 mmol), P(*o*Tol)$_3$ (13.5 mg, 0.04 mmol) and $Pd(OAc)_2$ (9.70 mg, 0.04 mmol) were added to a solution of **5a** (209.8 mg, 0.43 mmol) in CH_3CN:H_2O (10:1, 22 mL) under inert atmosphere. The reaction mixture was heated under reflux for 5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×10 mL) and the combined organic extracts were washed with saturated aqueous solution of NH_4Cl (3 × 10 mL) and dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, gradient of solvents: from EtOAc to EtOAc/MeOH 9.5/0.5) obtaining 78:22 mixture (GC/MS) of diastereoisomers **6:7** (59.6 mg, 53%). Both diastereoisomers **6** and **7** were separated by flash chromatography (silica gel, hexane/EtOAc 7/3 with a 2% of Et_3N) and each one crystallized from $CHCl_3$. Data for **6**: $[\alpha]_D^{20}$: +270.9 (c = 1.2, CH_2Cl_2). mp.: 60-61 °C ($CHCl_3$). IR (ATR): v = 2950, 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 – 1.86 (m, 4H, 2 × H_1, 2 × H_2), 2.13 – 2.25 (m, 1H, H_{3a}), 2.43 – 2.56 (m, 1H, H_{10a}), 3.19 – 3.27 (m, 1H, 1H_{3b}), 3.29 – 3.36 (m, 2H, H_{5a}, H_{10}), 3.84 (s, 6H, 2 × OCH_3), 4.07 (d, J = 14.3 Hz, 1H, H_{5b}), 5.05 (d, J = 9.7 Hz, 1H, CH$_a$=CH_bH$_c$), 5.10 (d, J = 17.2 Hz, 1H, CH$_a$=CH$_b$$H_c$), 5.93 (dt, J = 17.2, 9.7 Hz, 1H, CH_a=CH$_b$H$_c$), 6.54 (s, 1H, H_6), 6.60 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.8 (C_2), 26.5 (C_1), 47.5 (C_{10}), 55.1 (C_3), 55.8 (2 × OCH_3), 56.1 (C_5), 63.5 (C_{10a}), 109.0 (C_6), 112.4 (C_9), 115.3 (CH$_a$=*C*H$_b$H$_c$), 126.7 (C_{9a}), 129.3 (C_{5a}), 139.8 (*C*H$_a$=CH$_2$), 147.4 (C_7), 147.5 (C_8) ppm. MS (CI): *m*/*z* (%) = 260 (MH^+, 100); 259 (51); 258 (28); 191 (29); 190 (72). HRMS (CI): calcd. for $C_{16}H_{22}NO_2$ $[MH]^+$ 260.1651; found: 260.1646. Data for **7**: $[\alpha]_D^{20}$: - 22.5 (c = 0.8, CH_2Cl_2). mp.: 100-102 °C ($CHCl_3$). IR (ATR): v = 3072, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 – 1.66 (m, 1H, H_{1a}), 1.72 – 1.83 (m, 1H, H_{2a}), 1.84 – 1.94 (m, 1H, H_{2b}), 1.96 – 2.06 (m, 1H, 1H_{1b}), 2.09 – 2.18 (m, 1H, H_{10a}), 2.22 – 2.32 (m, 1H, H_{3a}), 3.23 (t, J = 9.5 Hz, 1H, H_{10}), 3.29 (t, J = 8.5 Hz, 1H, H_{3b}), 3.39 (d, J = 14.1 Hz, 1H, H_{5a}), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.04 (d, J = 14.1 Hz, 1H, H_{5b}), 5.18 – 5.32 (m, 2H, CH=CH_2), 5.67 (dt, J = 17.2, 9.5 Hz, 1H, C*H*=CH$_2$), 6.55 (s, 1H, H_6), 6.69 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.3 (C_2), 30.0 (C_1), 51.5 (C_{10}), 55.2 (C_3), 55.7 (C_5), 55.8 (OCH_3), 55.9 (OCH_3), 65.3 (C_{10a}), 109.3 (C_6), 111.2 (C_9), 117.6 (CH=*C*H$_2$), 126.8 (C_{9a}), 128.6 (C_{5a}), 139.3 (*C*H=CH$_2$), 147.4 (C_7), 147.5 (C_8). MS (CI): *m*/*z* (%) = 260 (MH^+, 100), 259 (43), 258 (27), 191 (28), 190 (73). HRMS (CI): calcd. for $C_{16}H_{22}NO_2$ $[MH]^+$ 260.1651; found: 260.1646.

(10*S*,10a*S*)-10-[(*E*)-2-(*t*Butyldimethylsilyloxy)vinyl]-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (8). Et_3N (0.05 mL, 0.36 mmol), P(*o*Tol)$_3$ (5.20 mg, 0.02 mmol) and $Pd(OAc)_2$ (3.80 mg, 0.02 mmol) were added to the a solution of **5a** (209.80 mg, 0.43 mmol) in CH_3CN:H_2O (10:1, 5 mL) under inert atmosphere. The reaction mixture was heated under reflux for 5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×10 mL) and the combined organic extracts were washed with saturated aqueous solution of NH_4Cl (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) obtaining the mixture of diastereomers **8** as yellow oil (49.8 mg, 0.13 mmol, 78% yield, (81:6:3:10). Only the major diastereoisomer was characterized. $[\alpha]_D^{20}$: +69.4 (c = 1.0, CH_2Cl_2). IR (ATR): v = 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 6H, Si*Me*$_2$*t*Bu), 0.90 (s, 9H, SiMe$_2$*tBu*), 1.73 – 1.81 (m, 4H, 2 × H_1, 2 × H_2), 2.15 – 2.28 (m, 1H, H_{3a}), 2.49 (m, 1H, H_{10a}), 3.14 – 3.23 (m, 2H, H_{10}, H_{3b}), 3.30 (d, J = 14.2 Hz, 1H, H_{5a}), 3.82 (s, 6H, 2 × OCH_3), 4.02 (d, J = 14.2 Hz, 1H, H_{5b}), 5.12 (dd, J = 12.0, 10.3 Hz, 1H, C*H*=CHOSi), 6.34 (d, J = 12.0 Hz, 1H, CH=C*H*OSi), 6.51 (s, 1H, H_6), 6.59 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = -5.2 (Si*Me*$_2$*t*Bu), 18.3 (SiMe$_2$C(*CH*$_3$)$_3$), 21.9, 26.7 (C_1, C_2), 25.7 (SiMe$_2$*C*(CH$_3$)$_3$), 41.5 (C_{10}), 55.2 (C_3), 55.7, 55.8 (2 × OCH_3), 55.9 (C_5), 63.9 (C_{10a}), 109.0 (C_6), 112.4 (C_9), 113.6 (*C*H=CHOSi), 126.4 (C_{9a}), 130.6 (C_{5a}), 140.6 (CH=*C*HOSi), 147.3, 147.4 (C_7, C_8) ppm. MS (CI): *m*/*z* (%) = 391 (28); 390 (MH^+, 100), 389 (20), 388 (78), 386 (15). HRMS (CI): calcd. for $C_{22}H_{36}NO_3Si$ $[MH]^+$ 390.2464; found 390.2455.

2-[(10*S*,10a*S*)-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]isoquinolin-10-yl]ethan-1-ol (9). To a solution of **8** (diastereomeric mixture, 50.0 mg, 0.13 mmol) in dry THF (5 mL), KF (0.64 mL of a 1 M solution in MeOH, 0.64 mmol) was added *via* canula under an inert

atmosphere. The reaction was stirred for 24 h at room temperature, and additional KF solution (0.64 mL of a 1 M solution in MeOH, 0.64 mmol) was added. The course of the reaction was followed by TLC. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the lack of stability of the aldehyde intermediate. The so-obtained aldehyde (35.3 mg, 0.13 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (9.7 mg, 0.26 mmol) was added portion wise at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. The reaction was quenched with H_2O (10 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) obtaining **9** as brown oil (21.7 mg, 61% two steps): $[\alpha]_D^{20}$: +66.9 (c = 1.0, CH_2Cl_2). IR (ATR): ν = 3330, 2930 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.69 – 1.79 (m, 1H, $CH_aH_bCH_aH_bOH$), 1.79 – 2.10 (m, 4H, 2 × H_1, 2 × H_2), 2.17 – 2.26 (m, 1H, $CH_aH_bCH_aH_bOH$), 2.27 – 2.36 (m, 1H, H_{3a}), 2.55 – 2.64 (m, 1H, H_{10a}), 2.89 – 2.95 (m, 1H, $CH_aH_bCH_aH_bOH$), 3.18 - 3.21 (m, 1H, H_{10}), 3.25 – 3.32 (m, 2H, H_{3b}, $CH_aH_bCH_aH_bOH$), 3.37 (d, *J* = 14.3 Hz, 1H, H_{5a}), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.11 (d, *J* = 14.3 Hz, 1H, H_{5b}), 6.53 (s, 1H, H_6), 6.58 (s, 1H, H_9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.3 (C_2), 25.5 (C_1), 33.0 (CH_2CH_2OH), 39.7 (C_{10}), 54.6 (C_3), 55.5 (C_5), 55.8, 55.9 (2 x OCH_3), 56.9 (CH_2CH_2OH), 62.6 (C_{10a}), 108.9 (C_6), 111.4 (C_9), 126.7 (C_{5a}), 128.7 (C_{9a}), 147.6, 147.9 (C_7, C_8) ppm. MS (ESI): *m*/*z* (%) = 279 (14), 278 (MH^+, 100). HRMS (ESI): calcd. for $C_{16}H_{24}NO_3$ $[MH]^+$ 278,1756; found: 278.1760.

Supporting Information: Synthesis and characterization of precursors **1a-f**, **5a-b**, details on additional reactions performed with **1e** and with electron deficient heteroaryl halides, copies of ^1H and ^{13}C NMR spectra of compounds described, X-Ray crystallographic data for **6** and **7**, and selected Chiral Stationary Phase HPLC traces (see footnote on the first page of this article).

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[28] CCDC 1062659 contains the supplementary crystallographic data for **7**. These data can be obtained from The Cambridge Crystallographic Data Centre (see supporting information)