Molecular Library Obtained by Allene Insertion into the Pd−C Bond of Cyclopalladated Complexes: Biological and Pharmacological Evaluation

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Dedicated to Prof. J. Vicente, University of Murcia, on the occasion of his 60th birthday

Keywords: Allenes / Antibiotics / N-heterocycles / Nicotinic receptor / Palladium

A minilibrary of cationic N-heterocycles has been prepared and evaluated. The potential for the preparation was a result of the high versatility of palladium-mediated chemistry. The synthesis of the novel molecules was based on intramolecular quaternization of tertiary amine attached allylpalladium complexes. The steric and electronic factors of the reaction are discussed. The structures of the synthesized molecules made them candidates for precise biological and pharmacological evaluations. Of the various N-heterocyclic compounds, 2,2-dimethyl-3-methylenenaphtho[*def*]quinolizinium showed antibacterial activity at micromolar concentrations. This compound also proved to be a nanomolar competitive antagonist for the channel site of the nicotinic acetylcholine receptor.

Introduction

Among palladium-mediated syntheses, reactions involving cyclopalladated derivatives[1a−1c] open the route to molecular libraries that might be of interest to biologists or physicists. A huge number of cyclopalladated complexes have indeed been obtained by simple intramolecular C−H bond activation. Moreover, the palladium−carbon bond displays a richness of reactivity toward various substrates. The consequence is the potential for the synthesis of a wide range of novel organic or organometallic compounds. In line with this strategy, we have previously described the preparation of some imine-allylpalladium complexes and their intramolecular reaction behaviour.[2a−2c] We now wish to report on the application of the process to the preparation of a series of cationic N-heterocycles starting from cyclopalladated tertiary amines.[3a−3d] We chose to investigate the reactions between these organopalladium compounds and allenes, as such reactions seemed to afford the expected C−C and C−N bonds more readily than with other reactants. The palladium-mediated and -catalysed reactions of allenes have been reviewed recently.[4] Using a different strategy from ours, Larock and others[5a−5g] synthesized several N-heterocyclic compounds by means of a Pd^0-catalysed reaction between N-containing aryl units with *ortho*-iodo substituents and a selection of allenes.

The series of N-heterocyclic compounds prepared were evaluated as antibiotics and nicotinic acetylcholine receptor ligands. On the one hand, nosocomial infections[6] are a major problem in antibacterial therapy, and a problem only likely to be solved by the discovery of new active molecules. On the other hand, the finding of selective and powerful agonists and antagonists of the nicotinic acetylcholine receptor (nAChR)[7] might be of considerable therapeutic importance for the treatment of diseases such as congenital myasthenia gravis,[8] Alzheimer's syndrome and memory impairment.[9]

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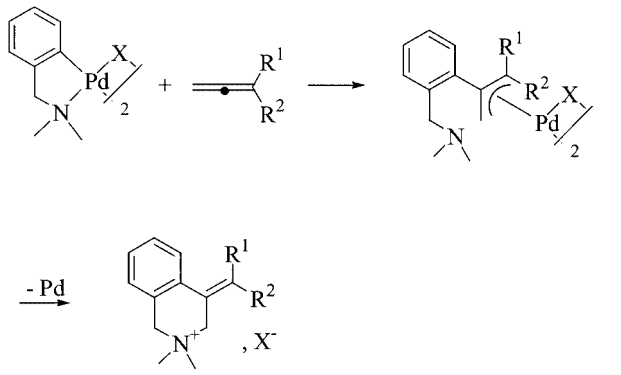
Results and Discussion

Synthesis

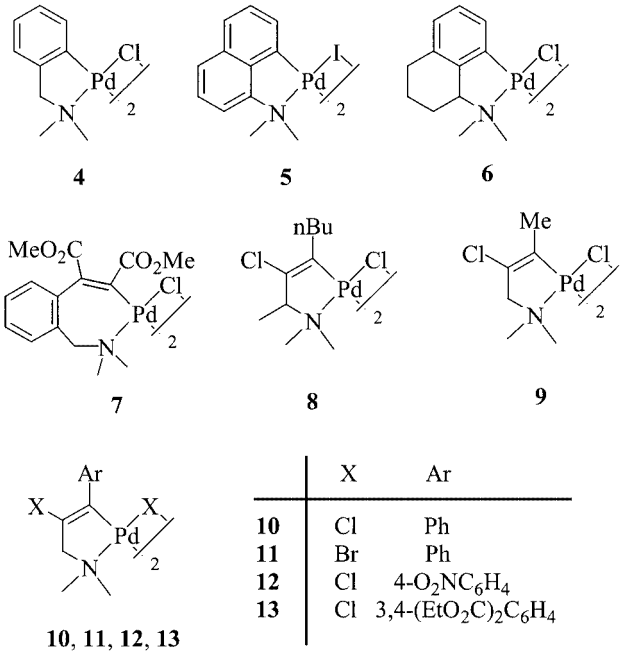
To perform an intramolecular reaction between the tertiary amines and the attached (η^3-allyl)palladium com-

  DOI: 10.1002/ejoc.200300776

plexes as depicted in Scheme 1, a series of cyclopalladated complexes (see Figure 1) was treated with three different allenes [3-methyl-1,2-butadiene (**1**), 3-methoxy-1,2-propadiene (**2**) and 1,2-heptadiene (**3**)].[2c]



Scheme 1



	X	Ar
10	Cl	Ph
11	Br	Ph
12	Cl	4-$O_2NC_6H_4$
13	Cl	3,4-$(EtO_2C)_2C_6H_4$

10, **11**, **12**, **13**

Figure 1. Structures of the various cyclopalladated starting complexes

The cyclopalladated benzyl- and naphthylamines **4**−**7** were prepared by described procedures,[10a−10e] while the cyclic [(dimethylamino)propene]palladium complexes **8**−**13** were synthesized by chloro- or bromopalladation of the corresponding propargylamines,[11] these in turn being prepared by standard procedures. Although the Mannich reaction was a good synthetic route to acetylenic amines, acetylenes bearing aryl-substituted groups were difficult to prepare. Sonogashira coupling[12a−12c] (providing complexes **12** and **13**) proved to be a useful alternative for the preparation of such propargylamines.

For the preparation of the N-heterocycles, procedure A was used in general, the cyclopalladated complexes and the allenes being allowed to react in CH_2Cl_2 or in MeOH. In some cases, however, this procedure failed or required longer times to be complete. From previous results,[2c] we also used procedure B: the reaction was performed in the presence of triphenylphosphane in MeOH or in PhCl. The yields of hexafluorophosphate salts were usually better, but the isolation of halide salts was required for the bacteriological assays. We thus selectively obtained the 3-alkylidenequinoliums **14**−**16,** benzo[*c*]azocinium **17** and 5-alkylideneaziniums **18**−**23** (see Figure 2). Compound **24** has been described previously.[2c] Such structures have hardly been encountered before in the literature.[13a−13g]

Regio- and Stereoisomerism

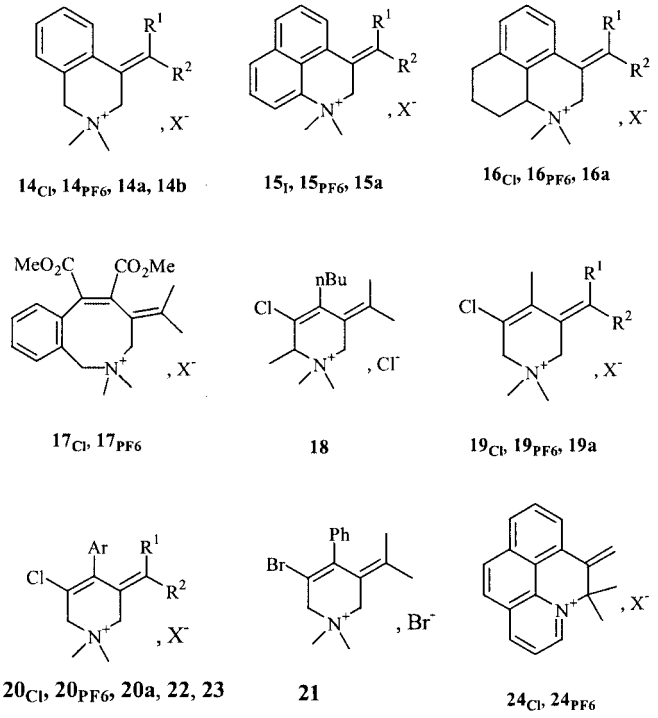
Two reactions performed in CH_2Cl_2 were repeated in MeOH. Whereas the cyclopalladated compound **10** had given rise to the formation of the 5-isopropylideneazinium **20** in CH_2Cl_2, the same reaction in MeOH yielded a 2:3 mixture of **20** and its regioisomer, the 5-methyleneazinium **20′**. From the organopalladium complex **9** in CH_2Cl_2 we obtained only the 5-(isopropylidene)trimethylazinium **19**, while in MeOH a 1:1 mixture of the two regioisomers [**19** and the 5-(methylene)pentamethylazinium **19′**] was obtained (see Scheme 2).

In MeOH the Pd−Cl bond of the (π-allyl)palladium intermediate is more prone to dissociation, resulting in a cationic Pd complex. The consequence is an increase in the positive charge at the more substituted terminus carbon of the π-allyl moiety. As a consequence, nucleophilic attack of the nitrogen atom at this carbon should be preferred. This behaviour has often been observed in related reactions.[5a][14a][14b] In the case of tertiary amine derivatives, however, N−C bond formation is hampered by the significant hindrance resulting from the occurrence of an $N^+Me_2-CMe_2$ unit, resulting in mixtures of regioisomers.

When the same reactions were performed in CH_2Cl_2, the previous electronic factors were much less important. The N−C bond formation between the tertiary amines and the allylpalladium units was mainly governed by steric repulsions between the more substituted allylic carbon and the dimethylamine fragment. This resulted in the selective formation of compounds **19** and **20**.

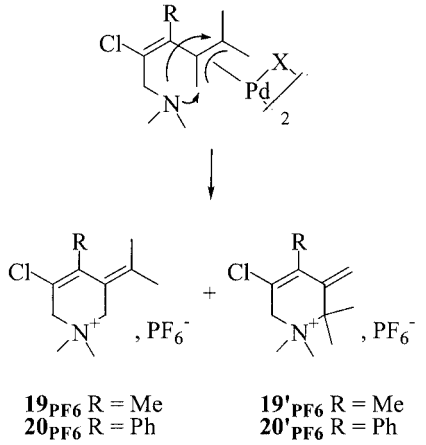
As depicted in Table 1, 3-methyl-1,2-butadiene (**1**) gave higher yields than 3-methoxy-1,2-propadiene (**2**) and 1,2-heptadiene (**3**). With these last two allenes an (*E*)/(*Z*) mixture of compounds was obtained, with the (*E*) isomer always predominant.

This result may be explained by the nature of the interactions between the fragment attached to the central allylic carbon atom and the substituents located at the terminus carbon atom of the allylic fragment (see Scheme 3). Indeed, it is well known that the allylpalladium complexes exist as equilibrium mixtures of both the *syn* and *anti* compounds. The thermodynamically favoured isomer is that with the R

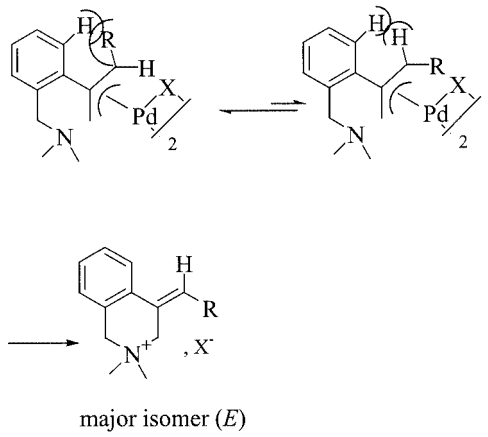


	X	R^1	R^2	Ar
14_{Cl}	Cl	Me	Me	
14_{PF6}	PF_6	Me	Me	
14a	PF_6	H	OMe	
14b	PF_6	H	nBu	
15_{I}	I	Me	Me	
15_{PF6}	PF_6	Me	Me	
15a	PF_6	H	OMe	
16_{Cl}	Cl	Me	Me	
16_{PF6}	PF_6	Me	Me	
16a	PF_6	H	OMe	
19_{Cl}	Cl	Me	Me	
19_{PF6}	PF_6	Me	Me	
19a	PF_6	H	OMe	
20_{Cl}	Cl	Me	Me	
20_{PF6}	PF_6	Me	Me	Ph
20a	PF_6	H	OMe	Ph
22	Cl	Me	Me	4-$O_2NC_6H_4$
23	Cl	Me	Me	3,4-$(EtO_2C)_2C_6H_4$

Figure 2. Structures of the various cationic N-heterocyclic compounds obtained



Scheme 2



Scheme 3

Table 1. Influence of the nature of the allene on the yield and on the stereochemistry

Compound	14	14a	14b	15	15a	19	19a	20	20a
Yield (%)	85	41	49	91	55	78	70	76	65
(*E*)/(*Z*)		11:1	20:1		15:2		2:1		E

fragment in the *syn* position. Despite this preference, the reaction usually takes place, for steric reasons, on the minor *anti* isomer; the (*E*) configuration is then obtained. Similar selectivities, though less clear-cut, have been observed by Larock.[5c]

In Vitro Susceptibility of Aerobic Bacteria

According to NCCLS guidelines, four reference strains were used: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 2913, *Bacillus subtilis* ATCC 6633 and *Enterococcus faecalis* ATCC 29212. In addition, two clinical strains were selected: *Micrococcus* sp. and *Corynebacterium* sp. With the cationic N-heterocycles prepared, no growth inhibition was observed by the diffusion[15a][15b] or dilution[16a,16b] methods with *E. coli*, *E. faecalis* or *B. subtilis* at any tested concentration. Growth inhibition was only observed for compound **24** at 150 mg with *Micrococcus* sp and *Corynebacterium* sp. The N-heterocycle **24** had a MIC[17] of 120 μM with *Micrococcus* sp, 240μM with *Corynebacterium*

sp and 1 mM with *S. aureus*. The compound was bactericidal[18] for *S. aureus* at 1 mM, while a decrease of 3 log units was achieved with *Corynebacterium* sp.

Nicotinic Receptor Binding Properties

The nicotinic acetylcholine receptor (nAChR)[19] contains a cation-selective ion channel, the opening of which is regulated by the binding of acetylcholine (ACh). In addition to that binding site for ACh and competitive antagonists such as tubocurare, nAChRs contain a distinct allosteric antagonist site located within the ion channel. The new N-heterocycles were tested on the two binding sites located on the nAChR from the *Torpedo marmarata* electric organ: the ACh and the NCB binding sites. Inhibition properties of the ACh binding site were derived from [^{125}I]-α-bungarotoxin initial rate binding inhibition with the tested ligands at 10 μM. Inhibition properties of the NBC binding site were determined from [^{3}H]-PCP binding inhibition at equilibrium with the tested ligands at 1 μM. The results are collected in Table 2.

Table 2. Inhibition of the ACh-binding site derived from [^{125}I]-α-bungarotoxin initial rate binding inhibition; inhibition of the NBC-binding site derived from [^{3}H]-PCP binding inhibition at equilibrium

Compound	ACh Binding site (%)	NBC Binding site (%)
14	33	37
15	49	72
16	24	75
17	7	63
19	26	39
20	28	55
21	18	60
22	48	57
23	33	63
24	54	79

At 10 μM, three compounds inhibited about 50% of the ACh binding, while the other inhibited 30%. The eight-membered ring heterocycle **17** was the poorest inhibitor.[20] At 1 μM, most of the compounds inhibited more than 50% of the binding to NCB. Three compounds inhibited more than 70% of this binding. Protection constants (K_p) (see Table 3) were obtained from [^{125}I]-α-bungarotoxin initial rate binding inhibition by the three best ligands (10 nM to 0.5 mM) for the ACh binding site.[21] Inhibition constants (K_i) were determined from [^{3}H]-PCP binding inhibition at equilibrium by the three best ligands (10 nM to 0.5 mM) for the NBC binding site[22] (see Table 3).

Table 3. Protection constants (K_p) derived from [^{125}I]-α-bungarotoxin initial rate binding inhibition by the tested ligands (10 nM to 0.5 mM) for the ACh-binding site; inhibition constants (K_i) from [^{3}H]-PCP binding inhibition at equilibrium by the tested ligands (10 nM to 0.5 mM) for the NBC-binding site

Compound	ACh-Binding site K_p (μM)	NBC-Binding site K_i (μM)
15	55	1.6
16	−	1.5
22	59	−
24	72	0.5

The affinities for the NCB binding site were in the micromolar range, while the affinity for the ACh binding site was 50 times lower (ca. 50 μM). Compound **24** showed a high affinity for the NCB site (0.5 μM). Moreover, its affinity for the NCB binding site was two orders of magnitude (ratio of 144) higher than for the ACh site. All the N-heterocycles tested have a quaternary ammonium moiety, which may explain why they all show affinity for the two ACh and NCB binding sites. In the case of the ACh binding site, steric hindrance might explain the moderate affinity (ca. 50 μM). In the case of the NCB binding site, the more hydrophobic the molecule, the better the affinity, as well as the selectivity for this site in relation to that for the ACh site. This is especially true for compound **24**.

Conclusion

A series of quaternized N-heterocycles has been prepared by insertion of allenes into the Pd−C bonds of various cyclopalladated tertiary amines. Depending on the solvent and reactants, the C_2 unit insertion reaction was regio- and stereoselective. These selectivities were functions of both steric and electronic factors. The potential of the molecular library was examined in the field of life sciences; 2,2-dimethyl-3-methylenenaphto[*def*]quinolizinium displayed antibacterial activity, though at higher than usual antibiotic concentrations. Pharmacological measurements were more encouraging. Selective binding to the distinct binding sites of the nicotinic receptor was obtained with two molecules from the library, 2,2-dimethyl-3-methylenenaphto[*def*]quinolizinium showing an affinity (500 nM) similar to that of PCP, the reference ligand used in this study. This cationic N-heterocycle might be used as a lead for the design of new drugs in the future.

Experimental Section

General Remarks: Solvents (CH_2Cl_2, MeOH, Et_2O and hexane) were dried beforehand and distilled under argon. The different allenes were prepared as described previously.[2c] ^{1}H (300.13 or 200.13 MHz) and ^{13}C (75.47 or 50.32 MHz) NMR spectra were recorded with AC 300 or AC 200 Bruker instruments. The spectra were externally referenced to tetramethylsilane. The coupling constants are expressed in Hz. Abbreviations: Ar aromatic, br. broad, quat. quaternary. The amounts of crystallization solvent were determined by ^{1}H NMR spectroscopy. IR spectra were recorded on an IRFT Bruker instrument. Melting points were measured with a Köfler bank (melting points of hexafluorophosphate salts exceeded 250 °C). Combustion analyses were performed by the Service central de microanalyses du CNRS, Université Louis Pasteur, Strasbourg. The mass spectra were carried out by the Laboratoire de spectroscopie de masse de l'Université Louis Pasteur, Strasbourg.

(2-Butynyl)dimethylamine: The apparatus used to generate propyne[23] consists of a two-necked, round-bottomed, 500 mL flask

fitted with a magnetic stirring bar, a dropping funnel and a reflux condenser. The flask was charged with 1-butanol (180 mL) and potassium hydroxide (75 g), a gentle reflux being maintained. 1,2-Dibromopropane (67 g, 0.33 mol) was placed in the dropping funnel. In a second two-necked, round-bottomed flask, fitted with a magnetic stirring bar and a cold finger condenser, was placed a mixture of paraformaldehyde (6.3 g, 0.21 mol), dimethylamine (40% aqueous solution, 26 mL, 0.21 mol) and cuprous iodide (500 mg) in diglyme (35 mL). The temperature was maintained between 70 and 75 °C. The dibromide was added to the refluxing BuOH/KOH and the resulting propyne was bubbled under the surface of the second reaction mixture. The rate of addition of the dibromide was adjusted according to the rate of reflux of the propyne (b.p. −23 °C) at the cold finger (filled with dry-ice/acetone). The addition was complete in 3 hours. The material from the second flask was distilled, and the fraction boiling between 80 and 125 °C was collected. This distillate was treated with KOH, filtered and distilled again. A colourless liquid was obtained (10 g, yield 52%). B.p. 116−125 °C. ^{1}H NMR ($CDCl_3$): δ = 3.13 (q, ^5J = 2.4, 2 H, CH_2), 2.25 (s, 6 H, 2 NCH_3), 1.81 (t, ^5J = 2.4, 3 H, CH_3) ppm.

Dimethyl(3-phenyl-2-propynyl)amine: Anhydrous dimethylamine (13.4 g, 0.3 mol) was added to a stirred mixture of phenylacetylene (20.4 g; 0.2 mol), paraformaldehyde (6.6 g, 0.22 mol) and cuprous iodide (200 mg) in dioxane (40 mL, exothermic reaction). The reaction mixture was heated at reflux for 3 h, and the solvent was removed in vacuo. Distillation of the residue afforded a colourless liquid (28 g, yield 88%). B.p.$_5$ 114 °C. ^{1}H NMR ($CDCl_3$): δ = 7.46−7.38 (m, 2 H, Ar), 7.33−7.23 (m, 3 H, Ar), 3.45 (s, 2 H, NCH_2), 2.35 (s, 6 H, 2 NCH_3) ppm.

Dimethyl[3-(3,4-diethoxycarbonylphenyl)-2-propynyl]amine: A mixture of diethyl 4-bromophthalate[24] (8.1 g, 27 mmol), propargyldimethylamine (2.7 g, 32 mmol), bis(triphenylphosphane)palladium dichloride (18 mg), cuprous iodide (36 mg) and triphenylphosphane (36 mg) in triethylamine (30 mL) was heated under reflux for 4 hours.[12a−12c] Diethyl ether (50 mL) was then added, and the resulting solution was washed twice with aqueous sodium hydroxide solution (20%, 40 mL). Drying with MgSO4 and evaporation of the solvent afforded a yellow oil (7.62 g, yield 95%). ^{1}H NMR ($CDCl_3$): δ = 7.82−7.50 (m, 3 H, Ar), 4.37 (q, ^3J = 7.1, 2 H, OCH_2), 4.35 (q, ^3J = 7.1, 2 H, OCH_2), 3.48 (s, 2 H, NCH_2), 2.36 (s, 6 H, 2 NCH_3), 1.37 (t, ^3J = 7.1, 3 H, CH_3), 1.36 (t, ^3J = 7.1, 3 H, CH_3) ppm.

Dimethyl[3-(4-nitrophenyl)-2-propynyl]amine: The ligand was prepared as above.[12a−12c] Quantitative yield. ^{1}H NMR ($CDCl_3$): δ = 8.18 (d, ^3J = 8.9, 2 H, Ar), 7.56 (d, ^3J = 8.9, 2 H, Ar), 3.51 (s, 2 H, NCH_2), 2.39 (s, 6 H, 2 NCH_3) ppm.

Cationic Heterocycles Synthesis. General Procedure A: a) A solution of **5** (82 mg, 0.13 mmol) and 3-methyl-1,2-butadiene **1** (23 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) was stirred for 16 h at room temp. After filtration through a Celite pad, the filtrate was evaporated to dryness, leaving a brownish yellow residue. Extraction with water and addition of 1 equivalent of KPF_6 (49 mg, 0.26 mmol) yielded a white precipitate. This was dried in vacuo.

Compound 15$_{PF6}$: Yield 91 mg, 91%. $C_{17}H_{20}F_6NP$: calcd. C 53.26, H 5.22, N 3.66; found C 53.59, H 5.22, N 3.59. ^{1}H NMR ([D$_6$]acetone): δ = 8.26 (d, ^3J = 7.8, 1 H, Ar), 8.21 (d, ^3J = 8.3, 1 H, Ar), 8.08 (d, ^3J = 8.2, 1 H, Ar), 7.87 (d, ^3J = 7.2, 1 H, Ar), 7.80−7.74 (m, 2 H, Ar), 4.97 (s, 2 H, $=CH_2$), 3.92 (s, 6 H, NCH_3), 2.32 [s, 3 H, $C(CH_3)_2$], 2.29 [s, 3 H, $C(CH_3)_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 143.2, 141.4, 134.8, 131.4, 130.0, 128.1, 127.6, 127.2, 126.1, 122.9, 118.9, 118.5 (Ar + olefinic), 65.8 (CH_2), 55.3 (NCH_3), 23.1 and 21.8 [C(CH_3)$_2$] ppm.

Hexafluorophosphate 15a: The compound was obtained from 3-methoxy-1,2-propadiene (**2**); recrystallization from CH_2Cl_2/diethyl ether, yield 55 mg, 55%. $C_{16}H_{18}F_6NOP$ + 1/2CH_2Cl_2: calcd. C 46.32, H 4.44, N 3.27; found C 45.99, H 4.21, N 2.89. 15:2 Mixture of (*E*) and (*Z*) isomers as measured by ^{1}H NMR spectroscopy. ^{1}H NMR ([D$_6$]acetone, (*E*) isomer, characteristic signals): δ = 8.41 (dd, ^3J = 7.5, ^4J = 0.9, 1 H, Ar), 8.21 (t, ^3J = 7.3, 1 H, Ar), 8.05 (d, ^3J = 8.3, 1 H, Ar), 7.08 (s, 1 H, CHOCH$_3$), 4.69 (s, 2 H, NCH_2), 4.06 (s, 3 H, OCH_3), 3.83 (s, 6 H, NCH_3) ppm; [(*Z*) isomer, characteristic signals]: δ = 7.91 (d, ^3J = 8.8, 1 H, Ar), 4.88 (s, 2 H, NCH_2), 4.03 (s, 3 H, OCH_3); 3.90 (s, 6 H, NCH_3) ppm.

Compound 16$_{PF6}$: Yield 84 mg, 83%. $C_{17}H_{24}F_6NP$: calcd. C 52.71, H 6.20, N 3.62; found C 52.75, H 6.16, N 3.50. ^{1}H NMR ([D$_6$]acetone): δ = 7.41−7.37 (m, 2 H, Ar), 7.20 (t, ^3J = 4.4, 1 H, Ar), 4.90 (dd, ^3J = 10.7, 6.2, 1 H, NCH), 4.62 (s, 2 H, NCH_2), 3.57 (s, 3 H, NCH_3), 2.84 (s, 3 H, NCH_3), 2.95−2.71 (m, 2 H, CH_2Ar), 2.70−2.55 (m, 1 H, α CH_2), 2.25−1.78 (m, 3 H, α+β CH_2), 2.11 [s, 3 H, C(CH_3)$_2$] and 1.96 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 138.8, 136.6, 133.4, 128.7, 128.5, 127.4, 127.3, 119.6 (Ar + olefinic), 69.7 (NCH), 66.7 (NCH_2), 52.6, 44.7 and 28.6 (CH_2), 23.2 and 23.1 (NCH_3), 21.2 and 20.9 [C(CH_3)$_2$] ppm.

Compound 17$_{PF6}$: Yield 83 mg, 65%. $C_{20}H_{26}F_6NO_4P$ + H_2O: calcd. C 47.34, H 5.52, N, 2.76; found C 47.26, H 5.12, N 2.69. ^{1}H NMR ([D$_6$]acetone): δ = 7.84 (dd, ^3J = 7.6, ^4J = 1.7, 1 H, Ar), 7.67−7.54 (m, 3 H, Ar), 4.91 (d, ^2J = 13.5, 1 H, NCH), 4.72 (t, ^2J = 14.0, 2 H, NCH_2), 4.22 (d, ^2J = 13.5, 1 H, NCH), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.70 (s, 3 H, NCH_3), 3.12 (s, 3 H, NCH_3), 1.83 [s, 3 H, C(CH_3)$_2$], 1.59 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 167.8 and 165.5 (*C*O), 147.7, 142.1, 137.4, 136.5, 136.0, 131.6, 130.5, 128.8, 128.2, 117.4 (Ar + olefinic), 66.1 and 63.5 (NCH_2), 56.8 and 49.2 (OCH_3), 53.2 and 53.0 (NCH_3), 22.1 and 21.2 [C(CH_3)$_2$] ppm. IR (KBr pellet): $\tilde{\nu}$ = 1723, 1706 (CO) cm^{-1}.

b) A solution of 3-methyl-1,2-butadiene (**1**, 53 mg, 0.78 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of **10** (250 mg, 0.37 mmol) in CH_2Cl_2 (10 mL). The colour of the solution changed rapidly from yellow to black. Stirring was continued at room temp. for an additional 2 h to ensure complete reaction. The mixture was filtered through a Celite pad and the solvent was removed in vacuo. After the addition of water (5 mL), the resulting solution was filtered and KPF_6 (180 mg, 1 mmol) was added, affording **20** as a pale yellow solid. This was filtered, washed with Et_2O and dried in vacuo.

Compound 20$_{PF6}$: Yield 230 mg, 76%. $C_{16}H_{21}ClF_6NP$: calcd. C 47.13, H 5.19, N 3.43; found C 47.13, H 5.26, N 3.39. ^{1}H NMR ([D$_6$]acetone): δ = 7.53−7.22 (m, 5 H, Ar), 4.49 (s, 4 H, NCH_2), 3.43 (s, 6 H, NCH_3), 1.93 [s, 3 H, C(CH_3)$_2$], 1.22 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 145.9, 138.9, 137.0, 122.2, 119.8 ($C_{quat.}$), 130.1, 129.4, 128.9 (CH_{Ar}), 65.8 and 63.6 (NCH_2), 52.9 (NCH_3), 24.0 and 23.4 [C(CH_3)$_2$] ppm.

When the reaction was performed in MeOH, the result was a 2:3 mixture of **20** and its regioisomer **20′**; total yield 80%. **20′:** ^{1}H NMR ([D$_6$]acetone): δ = 7.53−7.22 (m, 5 H, Ar), 5.73 and 4.99 (2s, 2 H, $=CH_2$), 4.79 (s, 2 H, NCH_2), 3.39 (s, 6 H, NCH_3), 1.83 (s, 6 H, CH_3) ppm.

Compound 20a: The compound was obtained from the 3-methoxy-1,2-propadiene (**2**); yield 195 mg, 65%. $C_{15}H_{19}ClF_6NOP$: calcd. C

43.97, H 4.67, N 3.42; found C 43.84, H 4.68, N 3.51. ^{1}H NMR ([D$_6$]acetone): δ = 7.49−7.45 (m, 3 H, Ar), 7.37−7.28 (m, 2 H, Ar), 6.22 (s, 1 H, C*H*OCH$_3$), 4.56 (s, 2 H, NC*H*$_2$), 4.52 (s, 2 H, NC*H*$_2$), 3.72 (s, 3 H, OC*H*$_3$), 3.55 (s, 6 H, NC*H*$_3$) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 154.4 (*C*HOCH$_3$), 153.1, 134.8, 128.5, 115.2 ($C_{quat.}$), 130.2, 129.5, 129.4 (*C*H$_{Ar}$), 65.4 and 58.7 (N*C*H$_2$), 61.7 (O*C*H$_3$), 52.6 (N*C*H$_3$) ppm.

Compound 19$_{PF6}$: Yield 200 mg, 78%. $C_{11}H_{19}ClF_6NP$: calcd. C 38.22, H 5.54, N 4.05; found C 37.08, H 5.41, N 3.91. ^{1}H NMR ([D$_6$]acetone): δ = 4.36 (s, 2 H, NC*H*$_2$), 4.32 (br. s, 2 H, NC*H*$_2$), 3.35 (s, 6 H, NC*H*$_3$), 2.18 (t, ^5J = 2.0, 3 H, CC*H*$_3$), 2.06 [s, 3 H, C(C*H*$_3$)$_2$], 1.98 [s, 3 H, C(C*H*$_3$)$_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 143.9, 132.2, 121.7, 120.7 ($C_{quat.}$), 65.7 and 63.5 (N*C*H$_2$), 52.9 (N*C*H$_3$), 24.2, 23.2 and 20.1 (*C*H$_3$) ppm.

When the reaction was performed in MeOH, a 1:1 mixture of **19** and its regioisomer **19′** was obtained in a total yield of 80%. **19′:** ^{1}H NMR ([D$_6$]acetone): δ = 5.78 and 5.77 (2s, 2 H, =C*H*$_2$), 4.52 (br. s, 2 H, NC*H*$_2$), 3.34 (s, 6 H, NC*H*$_3$), 2.15 (t, ^5J = 1.8, 3 H, CC*H*$_3$), 1.78 (s, 6 H, C*H*$_3$) ppm.

Compound 19a: This compound was obtained from 3-methoxy-1,2-propadiene (**2**). Yield 180 mg, 70%. $C_{10}H_{17}ClF_6NOP$: calcd. C 34.55, H 4.93, N 4.03; found C 34.29, H 4.80, N 3.90. 2:1 mixture of (*E*) and (*Z*) isomers as measured by ^{1}H NMR spectroscopy. ^{1}H NMR ([D$_6$]acetone); (*E*) isomer: δ = 6.56 (s, 1 H, C*H*OCH$_3$), 4.34 (m, 4 H, NC*H*$_2$), 3.84 (s, 3 H, OC*H*$_3$), 3.31 (s, 6 H, NC*H*$_3$), 2.23 (t, ^5J = 2.0, 3 H, CC*H*$_3$) ppm; (*Z*) isomer: δ = 7.01 (s, 1 H, C*H*OCH$_3$), 4.36 (m, 4 H, NC*H*$_2$), 3.86 (s, 3 H, OC*H*$_3$); 3.39 (s, 6 H, NC*H*$_3$), 2.05 (t, ^5J = 1.8, 3 H, CC*H*$_3$) ppm.

c) The cyclopalladated complex **6** (500 mg, 0.8 mmol) and 3-methyl-1,2-butadiene (**1**, 2.5 equiv., 134 mg, 2 mmol) in dichloromethane (20 mL) were stirred overnight at room temp. A black, heterogeneous mixture was obtained. The black metallic palladium produced was filtered off, and the yellow filtrate was concentrated and treated with water. After filtration of the resulting solution, water was evaporated, and the residue was dried in vacuo. The cationic heterocycle was recrystallized as a chloride salt from chloroform/diethyl ether.

Compound 16$_{Cl}$: Yield 288 mg, 65%. M.p. 144−145 °C. $C_{17}H_{23}ClN$ + 2H$_2$O: calcd. C 65.05, H 9.00, N 4.46; found C 65.70, H 8.33, N 4.38. ^{1}H NMR (CDCl$_3$): δ = 7.39−7.28 (m, 2 H, Ar), 7.14 (dd, ^3J = 6.9, 1 H, Ar), 4.94 (d, ^2J = 14.6, 1 H, NC*H*), 4.74 (dd, ^3J = 9.5, ^3J = 6.7, 1 H, NC*H*), 4.62 (d, ^2J = 14.6, 1 H, NC*H*), 3.80 (s, 3 H, NC*H*$_3$), 2.88 (s, 5 H, NC*H*$_3$ and ArC*H*$_2$), 2.63 (m, 1 H, α C*H*), 2.21 (m, 1 H, α C*H*), 2.10 [s, 3 H, C(C*H*$_3$)$_2$], 2.02 [s, 3 H, C(C*H*$_3$)$_2$], 1.83 (m, 2 H, β C*H*$_2$) ppm. ^{13}C NMR (CD$_3$OD): δ = 138.0, 136.7, 133.0, 126.6, 118.9 ($C_{quat.}$), 128.2, 126.9 (*C*H$_{Ar}$), 69.3 (N*C*H), 66.5 (N*C*H$_2$), 52.8 and 44.6 (N*C*H$_3$), 28.6 (Ar*C*H$_2$), 23.6 and 22.3 [C(*C*H$_3$)$_2$], 23.4 and 20.6 (*C*H$_2$) ppm. IR (KBr pellet): ν̃ = 1637 (C=C) cm^{-1}.

Compound 14$_{Cl}$: Yield 250 mg, 54%. M.p. > 250 °C. $C_{14}H_{20}ClN$ + H$_2$O: calcd. C 65.70, H 8.67, N 5.47; found C 64.30, H 8.57, N 5.39. ^{1}H NMR (CDCl$_3$): δ = 7.47 (d, ^3J = 7.8, 1 H, Ar), 7.36 (td, ^3J = 7.8, ^4J = 1.5, 1 H, Ar), 7.30−7.24 (m, 2 H, Ar), 4.88 (s, 2 H, NC*H*$_2$), 4.54 (s, 2 H, NC*H*$_2$), 3.64 (s, 6 H, NC*H*$_3$), 2.18 [s, 3 H, C(C*H*$_3$)$_2$], 2.12 [s, 3 H, C(C*H*$_3$)$_2$] ppm. ^{13}C NMR (CDCl$_3$): δ = 139.7, 132.0 ($C_{quat.}$), 128.9, 128.3, 128.0, 127.5 (*C*H$_{Ar}$), 64.9 and 64.3 (N*C*H$_2$), 52.9 (N*C*H$_3$), 23.8 and 22.8 [C(*C*H$_3$)$_2$] ppm. IR (KBr pellet): ν̃ = 1637 (C=C) cm^{-1}.

Compound 15$_I$: Yield 445 mg, 76%. M.p. 214−215 °C. $C_{17}H_{20}IN$: calcd. C 55.90, H 5.52, N 3.83; found C 56.03, H 5.50, N 3.63. ^{1}H NMR (CDCl$_3$): δ = 8.36 (d, ^3J = 7.9, 1 H, Ar), 7.97 (d, ^3J = 8.2, 1 H, Ar), 7.85 (dd, ^3J = 7.8, ^4J = 1.4, 1 H, Ar), 7.69−7.60 (m, 3 H, Ar), 5.00 (s, 2 H, NC*H*$_2$), 4.13 (s, 6 H, NC*H*$_3$), 2.43 [s, 3 H, C(C*H*$_3$)$_2$], 2.23 [s, 3 H, C(C*H*$_3$)$_2$] ppm. ^{13}C NMR (CDCl$_3$): δ = 143.7, 141.1, 134.1, 129.7, 122.4, 118.1 ($C_{quat.}$), 130.7, 127.6, 126.9, 126.5, 126.2, 119.5 (*C*H$_{Ar}$), 65.5 (N*C*H$_2$), 55.4 (N*C*H$_3$), 23.7 and 23.6 [C(*C*H$_3$)$_2$] ppm. IR (KBr pellet): ν̃ = 1638 (C=C) cm^{-1}.

Compound 17$_{Cl}$: Yield 468 mg, 77%. M.p. 160−161 °C. $C_{20}H_{26}ClNO_4$ + 2H$_2$O: calcd. C 57.75, H 7.27, N 3.36; found C 57.90, H, 6.97, N 2.76. ^{1}H NMR (CDCl$_3$): δ = 8.16 (dd, ^3J = 5.9, 1 H, Ar), 7.60−7.48 (m, 3 H, Ar), 5.10 (d, ^2J = 13, 1 H, NC*H*), 5.03 (d, ^2J = 13, 1 H, NC*H*), 4.39 (d, ^2J = 13.4, 1 H, NC*H*), 3.97 (s, 3 H, NC*H*$_3$), 3.87 (s, 6 H, OC*H*$_3$), 3.65 (d, ^2J = 13.4, 1 H, NC*H*), 3.36 (s, 3 H, NC*H*$_3$), 1.84 (1s, 3 H, C(C*H*$_3$)$_2$], 1.60 [s, 3 H, C(C*H*$_3$)$_2$] ppm. ^{13}C NMR (D$_2$O): δ = 169.3 and 167.1 (CO), 149.2, 140.8, 136.9, 135.3, 127.6, 114.6 ($C_{quat.}$), 135.2, 130.9, 130.1, 127.6 (*C*H$_{Ar}$) 65.4 and 62.7 (N*C*H$_2$), 56.2 and 48.5 (O*C*H$_3$), 53.7 and 53.6 (N*C*H$_3$), 21.3 and 20.5 [C(*C*H$_3$)$_2$] ppm. IR (KBr pellet): ν̃ = 1734 and 1706 (CO), 1631 (C=C) cm^{-1}.

Chloride 18: Yield 335 mg, 82%. $C_{15}H_{27}ClN$ + 2H$_2$O: calcd. C 54.87, H 9.52, N 4.27; found C 54.81, H 9.46, N 4.14. ^{1}H NMR ([D$_6$]acetone): δ = 4.43 (q, ^3J = 6.1, 1 H, NC*H*), 4.38 (d, ^2J = 13.0, 1 H, NC*H*), 4.20 (d, ^2J = 13.0, 1 H, NC*H*), 3.36 (s, 3 H, NC*H*), 3.13 (s, 3 H, NC*H*$_3$), 2.68 (t, 2 H, α C*H*$_2$), 2.04 [s, 3 H, C(C*H*$_3$)$_2$], 1.98 [s, 3 H, C(C*H*$_3$)$_2$], 1.70 (d, 3 H, NCHC*H*$_3$), 1.56−1.28 (m, 4 H, β and γ C*H*$_2$), 0.89 (t, ^3J = 7.0, 3 H, δ C*H*$_3$) ppm. ^{13}C NMR ([D$_6$]acetone): δ = 137.7, 132.1, 121.7 114.0 ($C_{quat.}$), 65.7 (N*C*H), 57.9 (N*C*H$_2$), 48.7 and 43.9 (N*C*H$_3$), 27.4, 25.4 and 18.2 (*C*H$_2$), 20.1 and 19.4 [C(*C*H$_3$)$_2$], 10.1 (NCH*C*H$_3$), 9.28 (*C*H$_3$) ppm.

General Procedure B

a) Under argon, the cyclopalladated complex **4** (70 mg, 0.13 mmol), 3-methyl-1,2-butadiene (**1**) (22 mg, 0.32 mmol) and triphenylphosphane (240 mg, 0.9 mmol) in methanol (15 mL) were stirred at room temp. for 2 hours. A fine yellow precipitate of [Pd(PPh$_3$)$_4$] was obtained. After filtration, the remaining solution was evaporated to dryness, leaving a yellow, oily residue. The addition of one equivalent of KPF$_6$ to a water solution of this oil yielded the expected heterocyclic compound as a solid.

Compound 14$_{PF6}$: 77 mg, 85%. $C_{14}H_{20}F_6NP$: calcd. C 48.41, H 5.76, N 4.03; found C 48.66, H 5.73, N 3.94. ^{1}H NMR ([D$_6$]acetone): δ = 7.48 (d, ^3J = 7.5, 1 H, Ar), 7.42 (td, ^3J = 6.5, ^4J = 1.8, 1 H, Ar), 7.37−7.26 (m, 2 H, Ar), 4.67 (s, 2 H, NC*H*$_2$), 4.36 (s, 2 H, NC*H*$_2$), 3.39 (s, 6 H, NC*H*$_3$), 2.14 [s, 3 H, C(C*H*$_3$)$_2$], 2.04 [s, 3 H, C(C*H*$_3$)$_2$] ppm. ^{13}C NMR ([D$_6$]acetone): δ = 140.1, 133.0, 129.8, 128.8, 128.6, 128.0, 119.8 (Ar + olefinic), 65.1 and 64.4 (N*C*H$_2$), 53.0 (N*C*H$_3$), 23.8 and 22.5 [C(*C*H$_3$)$_2$] ppm.

Hexafluorophosphate 14a: The heterocycle was obtained from 3-methoxy-1,2-propadiene (**2**); yield 31 mg, 41%. $C_{13}H_{18}F_6NOP$ + 1/2CH_2Cl_2: calcd. C 41.39, H 4.89, N 3.58; found C 40.90, H 4.56, N 3.34. 11:1 mixture of (*E*) and (*Z*) isomers as measured by ^{1}H NMR spectroscopy. ^{1}H NMR ([D$_6$]acetone, (*E*) isomer, characteristic signals): δ = 8.25 (d, ^3J = 7.9, 1 H, Ar), 7.42 (td, ^3J = 7.6, ^4J = 1.6, 1 H, Ar), 7.33 (td, ^3J = 7.6, ^4J = 1.3, 1 H, Ar), 7.26 (dd, ^3J = 7.6, ^4J = 0.8, 1 H, Ar), 6.78 (s, 1 H, C*H*OCH$_3$), 4.88 (s, 2 H, NC*H*$_2$), 4.34 (s, 2 H, NC*H*$_2$), 3.96 (s, 3 H, OC*H*$_3$), 3.38 (s, 6 H, NC*H*$_3$) ppm; [(*Z*) isomer, characteristic signals]: δ = 7.75 (d, ^3J = 8.8, 1 H, Ar), 7.51 (t, 1 H, Ar), 4.84 and 4.52 (2s, 4 H, NC*H*$_2$), 3.93 (s, 3 H, OC*H*$_3$), 3.43 (s, 6 H, NC*H*$_3$) ppm.

Hexafluorophosphate 14b: This compound was obtained from 1,2-heptadiene (**3**). Yield 48 mg, 49%. $C_{16}H_{24}F_6NP$: calcd. C 51.20, H 6.40, N 3.73; found C 50.26, H 6.09, N 3.59. 20:1 mixture of (*E*) and (*Z*) isomers as measured by ^{1}H NMR spectroscopy. ^{1}H NMR ([D$_6$]acetone, (*E*) isomer, characteristic signals): δ = 7.93 (d, ^3J = 7.6, 1 H, Ar), 7.50−7.37 (m, 2 H, Ar), 7.30 (d, ^3J = 6.4, 1 H, Ar), 6.81 (t, ^4J = 7.6, 1 H, C*H*), 4.92 (br. s, 2 H, NCH_2), 4.66 (br. s, 2 H, NCH_2), 3.45 (s, 6 H, NCH_3), 2.43−2.36 (m, 2 H, α CH_2), 1.59−1.36 (m, 4 H, β and γ CH_2), 0.94 (t, ^3J = 7.2, 3 H, δ CH_3) ppm; [(*Z*) isomer, characteristic signals]: δ = 7.78 (br. d, 1 H, Ar), 6.13 (br. t, 1 H, C*H*), 4.94 (br. s, 2 H, NCH_2), 4.43 (br. s, 2 H, NCH_2), 3.43 (s, 6 H, NCH_3) ppm.

Hexafluorophosphate 16a: The compound was obtained from 3-methoxy-1,2-propadiene (**2**); yield 54 mg, 53%. $C_{16}H_{22}F_6NOP$: calcd. C 49.36, H 5.66, N 3.60; found C 49.61, H 5.63, N 3.44. 1:1 mixture of (*E*) and (*Z*) isomers as measured by ^{1}H NMR spectroscopy. ^{1}H NMR ([D$_6$]acetone, (*E*) isomer, characteristic signals): δ = 8.11 (d, ^3J = 8.0, 1 H, Ar), 6.70 (s, 1 H, C*H*OCH$_3$), 4.56 (d, ^2J = 13.2, 1 H, NC*H*), 4.22 (d, ^2J = 13.2, 1 H, NC*H*), 3.94 (s, 3 H, OCH_3), 3.02 (s, 3 H, NCH_3), 3.01 (s, 3 H, NCH_3) ppm; [(*Z*) isomer, characteristic signals]: δ = 7.54 (d, ^3J = 7.9, 1 H, Ar), 7.43 (s, 1 H, C*H*OCH$_3$), 4.73 (d, ^2J = 13.8, 1 H, NC*H*), 4.37 (d, ^2J = 13.8, 1 H, NC*H*), 3.91 (s, 3 H, OCH_3), 3.59 (s, 3 H, NCH_3), 3.54 (s, 3 H, NCH_3) ppm.

b) 3-Methyl-1,2-butadiene (**1**, 0.105 g, 1.5 mmol) was added to the palladacycle **12** (0.484 g, 0.5 mmol) dissolved in chlorobenzene (5 mL). After 15 min, triphenylphosphane (1.04 g, 4 mmol) was added, and the mixture was stirred overnight. Addition of hexane (15 mL) afforded a yellow precipitate, which was filtered and extracted with water (2 × 5 mL). After filtration, the water extract was evaporated in vacuo, leaving an almost colourless solid. Recrystallization from acetone/MeOH gave colourless crystals.

Chloride 22: Yield 150 mg, 44%. M.p. > 250 °C. $C_{16}H_{20}Cl_2N_2O_2$: calcd. C 55.99, H 5.87, N 8.16; found C 55.70, H 6.14, N 8.12. ^{1}H NMR (D$_2$O): δ = 8.31 (d, ^3J = 8.9, 2 H, Ar), 7.61 (d, ^3J = 8.9, 2 H, Ar), 4.40 (s, 2 H, NCH_2), 4.34 (s, 2 H, NCH_2), 3.29 (s, 6 H, NCH_3), 1.89 [s, 3 H, C(CH_3)$_2$], 1.24 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]DMSOo): δ = 146.7, 144.6, 143.7, 133.6, 123.2, 118.5 ($C_{quat.}$), 130.6, 123.6 (*C*H$_{Ar}$), 63.8 and 61.2 (N*C*H$_2$), 51.3 (N*C*H$_3$), 23.9 and 23.1 [C(*C*H$_3$)$_2$] ppm.

Compound 19$_{Cl}$: The heterocycle was directly crystallized from water; yield 85 mg, 36%. M.p. 235 °C (dec.). $C_{11}H_{19}Cl_2N$: calcd. C 55.94, H 8.11, N 5.93; found C 55.95, H 8.20, N 5.97. ^{1}H NMR (D$_2$O): δ = 4.15 (br. s, 2 H, NCH_2), 4.07 (s, 2 H, NCH_2), 3.14 (s, 6 H, NCH_3), 2.16 (t, ^5J = 1.9, 3 H, CCH_3), 2.01 [s, 3 H, C(CH_3)$_2$], 1.91 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 141.6, 130.1, 121.0, 119.7 ($C_{quat.}$), 63.6 and 61.1 (N*C*H$_2$), 51.0 (N*C*H$_3$), 23.8 and 23.2 [C(*C*H$_3$)$_2$], 19.5 (*C*H$_3$) ppm.

Bromide 21: Direct crystallization from water; yield 160 mg, 41%. M.p. > 250 °C. $C_{16}H_{21}Br_2N$: calcd. C 49.64, H 5.47, N 3.62; found C 49.40, H 5.66, N 3.60. ^{1}H NMR (D$_2$O): δ = 7.51−7.33 (m, 5 H, Ar), 4.43 (s, 2 H, NCH_2), 4.29 (s, 2 H, NCH_2), 3.23 (s, 6 H, NCH_3), 1.88 [s, 3 H, C(CH_3)$_2$], 1.20 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 143.3, 139.7, 137.7, 119.4, 113.7 ($C_{quat.}$), 129.0, 128.4, 127.9 (*C*H$_{Ar}$), 65.2 and 61.3 (N*C*H$_2$), 51.1 (N*C*H$_3$), 23.4 and 23.2 [C(*C*H$_3$)$_2$] ppm.

Chloride 23: Recrystallization from acetone/CH_2Cl_2; yield 200 mg, 45%. M.p. 220 °C (dec.). $C_{22}H_{29}Cl_2NO_4$: calcd. C 59.73, H 6.61, N 3.17; found C 59.62, H 6.51, N 3.16. ^{1}H NMR (CDCl$_3$): δ = 7.73 (d, ^3J = 8.0, 1 H, Ar), 7.51 (d, ^4J = 1.5, 1 H, Ar), 7.39 (dd, ^3J = 8.0, ^4J = 1.5, 1 H, Ar), 4.77 (s, 2 H, NCH_2), 4.64 (s, 2 H, NCH_2), 4.35 (q, ^3J = 7.0, 2 H, OCH_2), 4.34 (q, ^3J = 7.0, 2 H, OCH_2), 3.70 (s, 6 H, NCH_3), 2.02 [s, 3 H, C(CH_3)$_2$], 1.35 (t, 6 H, 2 CH_3), 1.21 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR (CDCl$_3$): δ = 167.0 (CO), 145.6, 140.5, 134.2, 132.8, 131.6, 123.3, 118.2 ($C_{quat.}$), 131.8, 129.4, 129.3 (*C*H$_{Ar}$), 65.0 and 62.6 (N*C*H$_2$), 61.9 and 61.8 (O*C*H$_2$), 52.2 (N*C*H$_3$), 24.7 and 24.1 [C(*C*H$_3$)$_2$], 14.1 (*C*H$_3$) ppm.

c) 3-Methyl-1,2-butadiene (**1**, 0.105 g, 1.5 mmol) was added to a stirred suspension of the cyclopalladated complex **10** (0.336 g, 0.5 mmol) in 5 mL of PhCl. A brown precipitate appeared. After 3 min, triphenylphosphane (1.04 g, 4 mmol) was added, and the precipitate dissolved, giving a dark solution. This slowly deposited a new precipitate. Filtration after 30 min and washing with chlorobenzene and hexane afforded a colourless solid after drying. It was recrystallized from chloroform/diethyl ether.

Compound 20$_{Cl}$: Yield 215 mg, 72%. M.p. 230 °C (dec.). $C_{16}H_{21}Cl_2N$: calcd. C 64.43, H 7.10, N 4.70; found C 64.46, H 7.36, N 4.68. ^{1}H NMR (D$_2$O): δ = 7.67−7.35 (m, 5 H, Ar), 4.33 (s, 2 H, NCH_2), 4.28 (s, 2 H, NCH_2), 3.25 (s, 6 H, NCH_3), 1.91 [s, 3 H, C(CH_3)$_2$], 1.23 [s, 3 H, C(CH_3)$_2$] ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 143.4, 137.7, 135.2, 121.4, 118.2 ($C_{quat.}$), 129.0, 128.4, 127.9 (*C*H$_{Ar}$), 63.8 and 61.3 (N*C*H$_2$), 51.2 (N*C*H$_3$), 23.4 and 23.2 [C(*C*H$_3$)$_2$] ppm.

Bacteriological Tests

Stock solutions were obtained by dissolving the N-heterocycles in water at concentrations of 200 mg/L and 2 mg/L. The solutions were subsequently sterilized by membrane filtration (Millex 0.22 μm Millipore), and stored in sterile sealed glass vials at 4 °C. Sterile disks were soaked with the different molecule solutions and dried at 20 °C for 24 h. Antibacterial activity was tested by the diffusion method[15a][15b] with soaked disks on Mueller-Hinton agar inoculated with different bacteria strains (according to CA-SFM guidelines)[25a][25b] and by the dilution method[16a][16b] in Mueller-Hinton broth in order to determine the minimum inhibitory concentration (MIC)[17] and the minimal bactericidal concentration (MBC).[18] Plates and tubes were incubated in air at 35 °C for 18 to 20 hours. Bacterial *inoculum* was standardized by using direct suspensions of colonies from overnight growth in saline adjusted to a turbidity matching the 0.5 McFarland standard, and diluted to obtain a density of 10^4 CFU/mL for the diffusion method and 10^5 CFU/mL for the dilution method. Purity and *inoculum* density as well as percentage of viable bacteria in limpid tubes were checked by plate counting on sheep blood agar. Broth containing no molecule solution was inoculated with each selected bacterial strain as a control for organism viability (growth control) in the dilution method. Disks soaked with sterile water were used as control in the diffusion method.

Binding Properties to the Nicotinic Receptor

Materials: [^{3}H]-Phencyclidine ([^{3}H]-PCP) and [^{125}I]-α-bungarotoxin ([^{125}I]-BgTx) were purchased from New England Nuclear. Live *Torpedo marmorata* were obtained from the Biological Station of Roscoff (France). Pepstatine, aprotinine, PMSF, proadifen, carbamylcholine (Carb), and *d*-tubocurarine chloride were purchased from Sigma.

Membrane preparation: AChR-rich membrane fragments were purified from frozen *T. marmorata* electric organ.[26] Specific [^{125}I]-α-bungarotoxin binding activities were determined by the DEAE filter disc procedure and typically ranged from 1.5 to 2 nmol of [^{125}I]-α-bungarotoxin bound per mg of protein.[27] Protein determination was achieved by a modified Lowry method.[28]

Agonist-Binding Site: Ligand inhibition constants at the agonist-binding site were determined from the decrease in initial binding rate of [^{125}I]-α-BgTx to nAChR-rich membranes (2 nM α-BgTx binding sites). After preincubation of *Torpedo* membrane with ligand in PBS pH 7.2 for 30 min, [^{125}I]-αBgTx (2 nM) was added and the suspension was incubated for 6 min at 25 °C, filtered through Millipore HAWP and counted. Competing ligands were tested at 10 μ M and at a range of concentrations (10 nM to 0.5 mM) for the best ligands.

NCB-Binding Site: Association constants of ligands for the non-competitive blocking of the (NCB) binding site were determined by competition experiments at equilibrium (45 min preincubation) with [^{3}H]-PCP (1 nM) and ligand on desensitized AChRs (68 nM [^{125}I]-αBgTx binding sites, 30 min preincubation with 0.1 mM Carb at 25 °C). The suspensions were filtered through GF-B (Whatman) and counted. Competing ligands were tested at 1 μM and in the 10 nM to 500 nM concentration range for the three best ligands.

Acknowledgments

Prof. Henri Monteil and Prof. Maurice Goeldner are gratefully acknowledged for their contributions. Financial supports of this work has been provided by the CNRS, the Ministère de la Recherche et de la Technologie (fellowship to J. C.), COFECUB (Brazil, project 188/96, fellowship to R. K.) and CAPES (Brazil, fellowship to G. E.).

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Received December 11, 2003

