Pergamon

Tetrahedron 57 (2001) 5061–5066

TETRAHEDRON

Experimental and theoretical studies on the oxidative addition of palladium(0) to β-chlorovinamidinium salts

Ian W. Davies,[a,*] Jimmy Wu,[a] Jean-François Marcoux,[a] Mark Taylor,[a] David Hughes,[a] Paul J. Reider[a] and Robert J. Deeth[b,*]

[a]*Department of Process Research, Merck & Co., Inc., R800-B263, P.O. Box 2000, Rahway, NJ 07065-0900, USA*
[b]*Inorganic Computational Chemistry Group, University of Warwick, Coventry, CV4 7AL, UK*

Dedicated to Professor Barry M. Trost, a master of reaction design and discovery, on the occasion of his 60th birthday

Received 25 January 2001; revised 21 February 2001; accepted 22 February 2001

Abstract—Boronic acids, esters and borinic anhydrides are partners in Suzuki–Miyaura cross-coupling reactions with a variety of β-chlorovinamidinium salts to give the desired β-arylvinamidinium salts in up to 88% yield. Reduction is a competing reaction pathway. DFT calculations on the intermediate palladium complex reveal that the Pd–C interaction is predominantly of σ-symmetry and the metal based LUMO is mainly d_{z^2} in character.

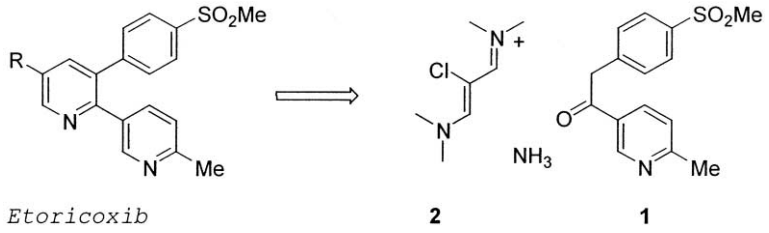
1. Introduction

Etoricoxib has been identified by Merck as a very potent and specific COX-2 inhibitor.[1] We have described how *etoricoxib* can be assembled by construction of the central pyridine ring (Scheme 1) from the readily accessible ketone **1**, the vinamidinium species **2** (CDT-phosphate) and ammonia.[2]

A wide range of other functionalized pyridines have also been prepared by extension of this methodology to substituted vinamidinium salts and aldehyde, ketone,[3] ester or acid enolates.[4] As a result of these studies, CDT-phosphate **2** has become available in commercial quantities. Vinamidinium salts have also been used very effectively by Gupton for the synthesis of pyrroles,[5] pyrimidines,[6] and pyrazoles.[7] Whilst vinamidinium salts typically react as electrophiles, they also behave as nucleophiles, e.g. nitration reactions.[8]

The synthetic potential of vinamidinium salts has not been fully realized—they are formally masked 1,3-dicarbonyls and their termini are easily differentiated. We were intrigued as to whether they would be able to participate in reactions other than with electrophiles or nucleophiles, e.g. transition metal cross-coupling reactions. Several laboratories have utilized positively charged substrates to promote the oxidative addition of palladium(0), most notably Moriarty (iodonium),[9] Genêt (diazonium)[10] and Liebeskind (sulfonium).[11] However, to our knowledge only a single study has examined palladium-catalyzed C–C cross-coupling reaction involving the transfer of an aryl cation.[12]

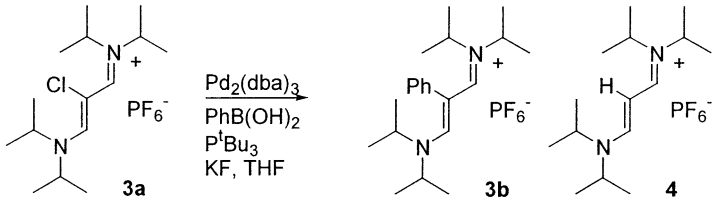
In this paper, we describe our preliminary observations on palladium-catalyzed cross-coupling reactions of β-chloro-vinamidinium salts. We also describe DFT calculations to characterize the structure and bonding of the unusual palladium(II) intermediate.



Scheme 1.

* Corresponding authors. Tel.: +1-732-594-3174; fax: +1-732-594-1499; e-mail: ian_davies1@merck.com

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00350-7



Scheme 2.

2. Results and discussion

2.1. Suzuki–Miyaura coupling

For our starting point, we chose to investigate the Fu conditions recently reported for the cross-coupling of aryl chlorides.[13] For an initial experiment, the reaction worked remarkably well. Coupling of β-chlorovinamidinium **3a** led to the formation of the β-phenylvinamidinium **3b** in 70% assay yield. In addition to the desired compound, the reduced compound **4** was obtained in up to 24% assay yield (Scheme 2).[14]

Previous studies have implicated 'Pd–H' in the reduction of aryl chlorides in the Suzuki–Miyaura reaction.[15] Control experiments revealed that palladium was not required for the competitive reduction to **4**. After excluding palladium, further experiments implicated phosphine/boronic acid or KF/boronic acid. Either combination led to significant reduction and the use of wet reagents further promoted the reduction pathway. Substituting the phenylboronic acid by $B(OH)_3$ and KI for KF further enhanced the reduction. These results led to the hypothesis that an electrophile (H^+)/nucleophile partnership was involved in the reduction. These observations were exploited and a very efficient method for the preparation of the parent vinamidinium salts was developed using HI or pTSA/PPh_3.[16]

The effect of base was examined in the reaction and the fluoride bases were clearly superior to phosphates or carbonates (Table 1). The palladium/ligand ratio chosen was 1:1 Pd:P^{t}Bu$_3$, based on Fu's observations for the Suzuki–Miyaura reaction (vide infra).

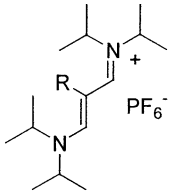
The effect of solvent was also briefly examined using KF as the base (Table 2).

$Pd_2(dba)_3$ was superior to $Pd(NCMe)_2Cl_2$. Other ligands examined included the Hermann–Beller palladacycles,[17] phosphites, Buchwald biphenylphospines,[18] chelating *N*-heterocyclic carbenes,[19] Genêt (palladium acetate),[10] and 'ligandless'[20] conditions, but in all cases the Fu conditions gave far superior results.

Table 1. Cross-coupling of **3a** using 2 equiv. $PhB(OH)_2$, Pd_2dba_3, P^{t}Bu$_3$, THF, 100°C, 0.5 M, 12 h

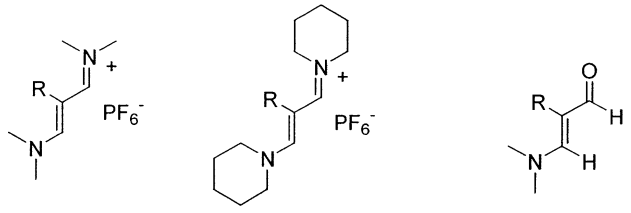
Entry	Base	**3a** (%)	**4** (%)
1	KF	70	24
2	CsF	61	37
3	Cs_2CO_3	24	62
4	K_3PO_4	27	40

An electronic effect of the boronic acid was not observed in this reaction.[21] In the case of vinamidinium **3a**, the 4-OMe and 4-F phenylboronic acids coupled to give **3c** (49%) and **3d** (46%) at essentially the same rate and efficiency. Presumably, the oxidative addition to **3a** is rate limiting.



R = 4-MeO-C$_6$H$_4$ 3c
R = 4-F-C$_6$H$_4$ 3d

The dimethyl- and dipiperidinylvinamidiniums **5a** and **6a** coupled with similar efficiency using the optimized conditions. Hydrolysis was a complication in the case of the dimethylvinamidiniums **5a** and **b** and the corresponding vinylogous amides **7** and **8** were observed in up to 20% yield.[22]



5a R = Cl
5b R = Ph

6a R = Cl
6b R = Ph

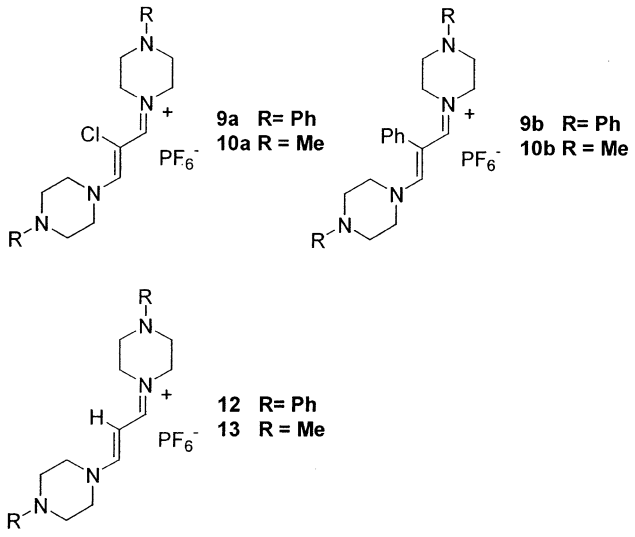
7 R = Cl
8 R = H

With this information in hand and the proposed mechanism of reduction, it seemed possible to design substrates that had lower basicity/nucleophilicity and, hence, lower propensity for reduction. The *N*-phenyl and *N*-methyl piperazines **9a** and **10a** were prepared by straightforward displacement reaction of CDT-phosphate at 100°C in toluene.[16]

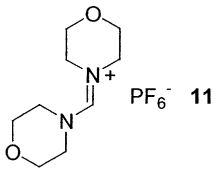
We were unable to obtain the desired product using morpholine and the formamidine **11** was isolated in ~35% yield following recrystallization from acetone. The *N*-Ph and *N*-Me piperazines **9a** and **10a** were recovered

Table 2. Cross-coupling of **3a** using 2 equiv. $PhB(OH)_2$, 5 mol% Pd_2dba_3, P^{t}Bu$_3$, KF, 100°C, 0.5 M, 12 h

Entry	Solvent	**3a** (%)	**4** (%)
1	THF	70	24
2	Dioxane	65	30
3	Toluene	18	32
4	CH_3CN	45	55
5	DMF	35	50



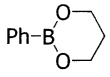
unchanged from the HI or the pTSA/PPh_3 conditions inspiring confidence that they would behave as ideal substrates.



Phenylboronic acid coupled to give **9b** in 59% yield—significantly the reduced vinamidinium **12** was observed in 39% yield (Table 3). The *N*-methyl derivative behaved similarly and the coupled product **10b** was obtained in 68% yield. Control experiments in these cases revealed that palladium was essential for the generation of the reduced vinamidiniums **12** and **13**! Hence, there are two distinct mechanistic pathways that are competitive with the desired cross-coupling pathway.

Using the *N*-phenyl piperazine, a range of aryl–boron species were examined as partners. Triphenylborane only led to decomposition with only 30% **9a** remaining after 6 h. The boronic ester led to substantial levels of the reduction product. The diphenylborinic anhydride proved to be optimal and gave the coupled product **7b** in 86% assay yield together with the reduction product **12** in 12% assay yield. The rate and yield were significantly higher using the borinic anhydride. The desired product **7b** was isolated in ~75% yield following work-up and recrystallization from acetone. Borinic anhydrides have previously been used to prepare a range of boron heterocycles, e.g. 1,3,5,2-oxadiazaborane,[23] but we have been unable to find a report of their use in palladium-catalyzed cross-coupling reactions. There is currently an effort to expand the range of organoboron coupling partners and the borinic anhydrides may have a role here.[24] We are currently examining their behavior and stoichiometry with more conventional aryl-substrates. We have not yet ruled out the possibility of transfer from diphenylborinic acid.

Table 3. Cross-coupling of **9a** using 5 mol% Pd_2dba_3, P^tBu_3, KF, THF, 100°C, 0.5 M, 6 h

Entry	Organoboron	**9b** (%)	**12** (%)
1	$PhB(OH)_2$	59	39
2	Ph_3B	0	0
3		21	59
4	$Ph_2B–O–BPh_2$	86	12

With our optimal substrate and boron partner in hand we reinvestigated the palladium/ligand stoichiometry (Table 4). A palladium/phosphine ratio of 1:1.5 is optimal and is in accord with the formal oxidative addition of a 12e Pd–P^tBu_3 fragment that is believed to be the active species using the Fu conditions.

Fluoride promoted cross-coupling of siloxanes[25] or silanes[26] represents an attractive alternative to Suzuki–Miyaura or Stille coupling. We have briefly investigated coupling of **9a** with these methods using phenylsiloxane or 1-phenyl-1-methylsilacyclobutane in the presence and absence of P^tBu_3. In the case of the silacyclobutane, only the reduced compound **11** was observed. In the case of phenylsiloxane, only decomposition (with no reduction) was observed.

We have previously reported that **3c**, **5a**, and **5b** exist in the 'W' conformation as determined by X-ray crystallographic analysis. X-Ray crystallographic analysis of **9a** also revealed a 'W' conformation (Fig. 1). Based on these data it seems reasonable to assume that the intermediate palladium(II) complex also contains the vinamidinium in the 'W' conformation.

2.2. DFT calculations

Since the intermediate palladium(II) complex is rather unique, we were intrigued as to the nature of the vinamidinium–metal interaction. Computational methods were employed to generate a fundamental understanding of the palladium complex and not as a prelude to further reaction optimization.

Assuming a 1:1 Pd/phosphine composition of the catalyst, DFT calculations were carried out on the simplified model system $[PdCl(PH_3)\{C(CHNH_2)_2\}]^+$. Although the initial oxidative addition is expected to generate a *cis*-chloro complex (relative to the Pd–C bond), all possible arrangements were considered. The formally low-spin d^8 Pd center strongly favors square planar coordination, but since there are only three ligands present, T-shaped structures result. The three possibilities are, relative to the Pd–C bond, all *cis*

Table 4. Cross-coupling of **9a** using 2 equiv. $Ph_2–B–O–BPh_2$, 5 mol% Pd_2dba_3, P^tBu_3, KF, 100°C, 0.5 M, 6 h

Entry	P^tBu_3	**9b** (%)	**12** (%)
1	1:1	86	12
2	1:1.5	88	11
3	1:2	85	15
4	1:0	3	6

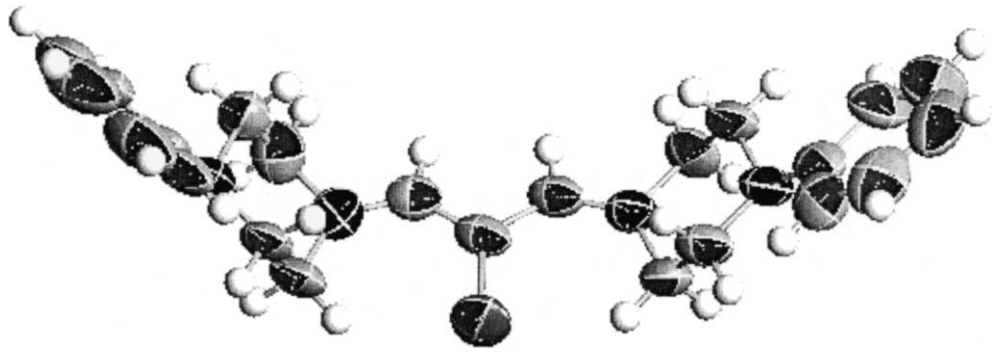
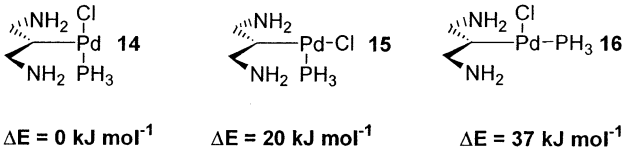


Figure 1. ORTEP of **9a**; thermal ellipsoids represent 50% probability.

(**14**), *cis* PH_3/*trans* Cl (**15**) and *cis* Cl/*trans* PH_3 (**16**).



The relative energies correlate with an increasing *trans* influence in the sequence Cl<P<C. Thus, the lowest energy arrangement occurs when there is no ligand *trans* to the strongest (i.e. Pd–C) bond. For the remaining two isomers, the Cl group has the lowest *trans* influence and, thus, does not compete very strongly with the Pd–C bond. The ground state destabilization is, therefore, smaller than when Ph_3, with its higher *trans* influence, is opposite the vinamidinium ligand. However, in the subsequent step, where a second Pd–C bond is formed, the worst position, both structurally and energetically, would be opposite the existing Pd–C bond. Presumably, the complex rearranges in order both to bring the two carbon ligands into closer proximity as well as to reduce the ground state destabilization by placing the new Pd–C bond *trans* to a ligand with a lesser *trans* influence.

A common feature of the structures of **14**–**16** is that the W configuration of the vinamidinium ligand would lead to severe steric interactions with the other ligands if the vinamidinium and PdCPCl planes were coplanar. Instead, the steric strain is relieved by the vinamidinium being perpendicular to the coordination plane. This has virtually no electronic consequences, since, as described below, the Pd–C interaction is predominantly of σ symmetry which, therefore, permits free rotation around the Pd–C bond (Fig. 2).

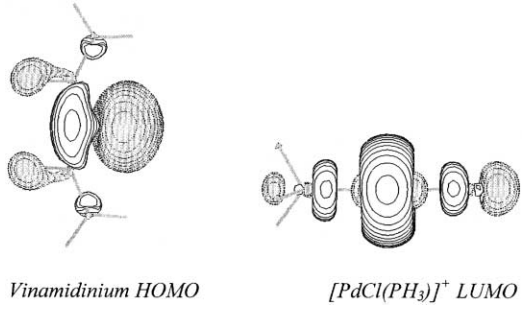


Figure 2. Frontier orbital analysis of $[PdCl(PH_3)\{C(CHNH_2)_2\}]^+$.

The ligand HOMO is employed to form the Pd–C σ bond and interacts strongly with the metal-based LUMO which is mainly Pd d_{z^2} character.

As for the remaining metal–ligand bonding, there are six π electrons and five π orbitals on the vinamidinium ligand, hence the lowest three orbitals are filled and ϕ_4 is the ligand LUMO (Fig. 3).

However, the ϕ_4 is not able to form a strong metal–ligand interaction with the Pd-based HOMO, since the former has a node on the central carbon. The LUMO thus has local Pd–C δ symmetry, but located on carbon atoms some distance from the metal (Fig. 4).

The picture is emphasized by analyzing the Pd–C bond energy which can be broken down into its symmetry components via an ADF fragment calculation. To avoid spurious electrostatic contributions, the dichloro complex $[PdCl_2\{C(CHNH_2)_2\}]$ was used. This is divided into two neutral fragments, $PdCl_2$ and $C(CHNH_2)_2$, which assigns a nominal negative charge to the donor carbon and, thus, treats the Pd–C interaction formally as a dative bond. The complex has C_{2v} symmetry with the *Z* axis aligned along the Pd–C direction. The bond energy decomposition scheme separates the overall interaction into a 'steric' part and an orbital part. The former term models the interactions arising from bringing the charge clouds of the two fragments from infinity up to their bonded conformation, but keeping them orthogonal (i.e. zero overlap), while the latter term models the (normally attractive) interactions which result when the two charge clouds are allowed to overlap. The orbital term

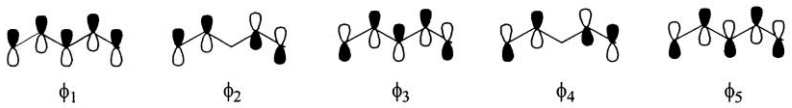
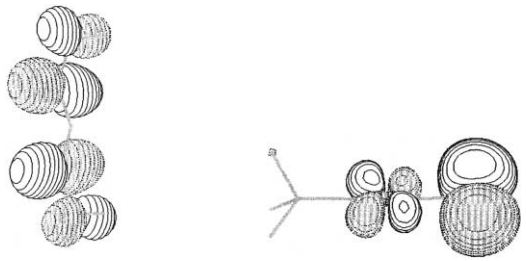


Figure 3. Schematic representation of the vinamidinium π-type orbitals.



Vinamidinium LUMO *$[PdCl(PH_3)]^+$ HOMO*

Figure 4. Frontier orbital analysis of $[PdCl(PH_3)\{C(CHNH_2)_2\}]^+$.

can be broken down by symmetry. Here, a_1 interactions correspond to the Pd–C σ-type interaction which at -422 kJ mol^{-1} are much larger than the π-type interactions which appear as b_1 (-41 kJ mol^{-1}) and b_2 (-29 kJ mol^{-1}) contributions. The steric term includes both Pauli repulsion and the electrostatic energy. For $[PdCl_2\{C(CHNH_2)_2\}]$, these two virtually cancel, leaving a total 'steric' electronic energy of only -5 kJ mol^{-1}.

3. Summary

We have demonstrated the first oxidative addition of Pd(0) to a β-chlorovinamidinium salt. The *N*-Ph piperazine derivatives couple in up to 88% yield using diphenylborinic anhydride. Two distinct reduction mechanisms are competitive with the desired reaction pathway. DFT calculations on the proposed palladium(II) intermediate indicate a significant *trans* effect of the vinamidinium ligand. The Frontier MO analysis of the complex reveals the Pd–C interaction is predominantly of σ symmetry which, therefore, permits free rotation around the Pd–C bond. The ligand HOMO is employed to form the Pd–C σ bond and interacts strongly with the metal-based LUMO which is mainly Pd d_{z^2} character.

4. Experimental

Melting points are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Mass spectral analyses were performed by M-Scan, Inc., West Chester, PA. Water content was determined by Karl Fischer titration. Compounds **2**, **3a**, **9a**, and **10a** were prepared according to the literature procedures.[16,27]

4.1. General procedure for Suzuki–Miyaura coupling

To a #15 pressure tube (Aldrich) were added the β-chlorovinamidinium **9a** (1.50 g, 2.77 mmol), palladium–dibenzylideneacetone complex (0.125 g, 0.14 mmol), and diphenylborinic anhydride (2.16 g, 6.23 mmol, Aldrich) followed by potassium fluoride (0.05 g, 8.30 mmol). Tetrahydrofuran (5 mL) was added and the mixture was degassed by bubbling through a stream of dry nitrogen. Tri-tertbutylphosphine (0.05 g, 0.2 mmol) was added and the pressure tube was capped and the mixture was heated in an oil bath at 100°C for 6 h. The mixture was cooled to ambient, diluted with acetonitrile and filtered through solka floc. The filtrate was concentrated to dryness and diluted with dichloromethane. The solids were removed by filtration and the filtrate was concentrated to a light brown oil. The oil was triturated with hexane/ethyl acetate (1:1) and the solids were recrystallized from acetone to give **9a** (1.22 g, 76%) as an off-white solid.

4.1.1. 2-Chloro-1,3-bis(*N′*-phenyl-*N*-piperazine)trimethinium hexafluorophosphate (9a), obtained as a light yellow solid (acetone): mp 217–221°C; ^{1}H NMR (400 MHz, DMF-d^7): 3.4–3.55 (8H, m), 3.95–4.05 (4H, m), 4.45–5.55 (4H, m), 6.84 (2H, t, *J*=7.5 Hz), 7.04 (4H, d, *J*=7.5 Hz), 7.31 (4H, t, *J*=7.5 Hz), 8.17 (2H, s), ^{13}C NMR (100 MHz, DMF-d^7): δ 47.9, 48.8, 49.6, 57.6, 92.1, 116.3, 120.2, 129.4, 150.6, 159.5. Anal. Calcd for $C_{15}H_{31}F_6N_2P$: C, 51.5; H, 5.2; N, 10.4. Found: C, 51.1; H, 5.2, N, 10.3.

4.1.2. 2-Phenyl-1,3-bis(*N′*-phenyl-*N*-piperazine)trimethinium hexafluorophosphate (9b), mp 232–233°C; ^{1}H NMR (400 MHz, CD_3CN): δ 2.90–2.99 (4H, br. s), 3.00–3.09 (4H, br. s), 3.29–3.35 (4H, br. s), 3.70–3.79 (4H, br. s), 6.80–6.95 (6H, m), 7.17–7.25 (4H, m), 7.38 (2H, br. s), 7.45–7.60 (5H, m). ^{13}C NMR (100 MHz, CD_3CN): δ 47.1, 47.9, 49.3, 56.8, 105.3, 116.2, 120.2, 129.1, 129.4, 129.7, 131.1, 132.9, 150.2, 161.8. ^{19}F NMR (376.2 MHz, CD_3CN): δ −73.3 (d, *J*=708 Hz). Calcd for $C_{29}H_{33}N_4$ *m/z* 437.2705, found *m/z* 437.2696.

4.1.3. 2-Chloro-1,3-bis(*N′*-methyl-*N*-piperazine)trimethinium hexafluorophosphate (10a), mp 154–157°C; ^{1}H NMR (400 MHz, DMF-d^7): δ 2.28 (6H, s), 2.50–2.63 (8H, m), 3.72–3.82 (4H, m), 4.29–4.42 (4H, m), 8.01 (2H, br. s). ^{13}C NMR (100 MHz, DMF-d^7): 44.8, 47.6, 54.3, 55.0, 91.5, 159.1. Anal. Calcd for $C_{13}H_{24}ClF_6N_4P$: C, 37.46; H, 5.80; N, 13.44. Found: C, 37.29; H, 5.74; N, 13.27.

4.1.4. 2-Phenyl-1,3-bis(*N′*-methyl-*N*-piperazine)trimethinium hexafluorophosphate (10b), mp 182–185°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (4H, t, *J*=5 Hz), 2.23 (6H, s), 2.56 (4H, t, *J*=5 Hz), 2.86 (4H, t, *J*=5 Hz), 3.66 (4H, t, *J*=5 Hz), 7.20–7.30 (2H, m), 7.40–7.48 (3H, m), 7.67 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.5, 47.3, 54.0, 55.2, 57.4, 104.8, 129.7, 130.0, 130.9, 133.2, 163.0. Anal. Calcd for $C_{19}H_{29}F_6N_4P$: C, 49.78; H, 6.38; N, 12.22. Found: C, 49.75; H, 6.32; N, 12.01.

4.1.5. Formamidine (11), mp 245–250°C (decomp.) (acetone). NMR data were collected at 265 K due to extensive line broadening/exchange at 300 K. ^{1}H NMR (500 MHz, CD_3CN, 265 K): δ 3.44–3.51 (4H, m), 3.54–3.63 (4H, m), 3.68–3.79 (8H, m), 7.48 (1H, s). ^{13}C NMR (125 MHz, CD_3CN, 265 K): δ 48.8, 52.8, 66.1, 66.6, 155.3. ^{31}P NMR (202.5 MHz, CD_3CN, 265 K): δ 96.9 (heptet, *J*=708 Hz). $C_9H_{17}N_2O_2$ requires *m/z* 185, found *m/z* 185. Anal. Calcd for $C_9H_{17}F_6N_2O_2P$: C, 32.74; H, 5.19; N, 8.48. Found: C, 32.83; H, 5.05, N, 8.44.

4.1.6. 1,3-Bis(*N′*-phenyl-*N*-piperazine)trimethinium hexafluorophosphate (12), mp 252–254°C; ^{1}H NMR (400 MHz, CD_3CN): δ 3.20–3.40 (8H, m), 3.68–3.81 (8H, m), 5.64 (1H, t, *J*=12 Hz), 6.91 (2H, t, *J*=7 Hz), 6.99 (4H, d, *J*=8 Hz), 7.30 (4H, t, *J*=8 Hz), 7.59 (2H, t, *J*=12 Hz). ^{13}C

NMR (100 MHz, CD_3CN) δ 46.3, 48.0, 49.2, 54.2, 89.3, 116.4, 120.3, 129.1, 150.3, 161.4. Anal. Calcd for $C_{23}H_{29}F_6N_4P$: C, 54.54; H, 5.77; N, 11.06. Found: C, 54.10; H, 5.70; N, 10.88.

4.1.7. 1,3-Bis(*N'*-methyl-*N*-piperazine)trimethinium hexafluorophosphate (13), isolated as a light brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19 (6H, s), 2.35–2.50 (8H, m), 3.50–3.61 (8H, m), 5.45 (1H, t, J=12 Hz), 7.48 (2H, t, J=12 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.5, 46.3, 53.5, 54.6, 54.7, 89.3, 161.7. ^{19}F NMR (376.2, CD_3CN): δ −73.2 (d, J=708 Hz). $C_{11}H_{25}N_4$ requires *m/z* 237.2079. Found: *m/z* 237.2071.

4.2. Computational methods

All DFT calculations were carried out using the Amsterdam Density: Functional (ADF) code, version 2000.01. Geometries were optimized at the local density approximation level with no symmetry contraints using triple-ζ+polarization STO expansions on Pd (ADF basis IV) and double-ζ+polarization STO expansions on all other atoms (ADF basis III). The core orbitals up to 3*d* on Pd, 2*p* on P and Cl and 1*s* on N and C were frozen. Energies were computed using the Becke88/Perdew86 gradient corrected functional. Orbital plots were generated using ADFrom1.2 and MOLDEN 3.3.

References

1. (a) Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J.-Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, J. L.; Yound, R. N. *Bioorg. Med. Lett.* **1998**, *8*, 2777. (b) Riendeau, D.; Percival, M. D.; Brideau, C.; Charleson, S.; Dubé, D.; Ethier, D.; Falfueyret, J.-P.; Friesen, R. W.; Gordon, R.; Grieg, G.; Guay, J.; Mancini, J.; Ouellet, M.; Wong, E.; Xu, L.; Boyce, S.; Visco, D.; Girard, Y.; Prasit, P.; Zamboni, R.; Gresser, M.; Ford-Hutchinson, S. W.; Young, R. N.; Chan, C.-C. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 1.
2. Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 8415.
3. Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339.
4. Davies, I. W.; Marcoux, J.-F.; Reider, P. J. *Org. Lett.* **2001**, *3*, 209.
5. Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *J. Org. Chem.* **1990**, *55*, 4735.
6. Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689.
7. Kase, K.; Katayama, M.; Ishirara, T.; Yamanaka, H.; Gupton, J. T. *J. Fluor. Chem.* **1998**, *90*, 29.
8. Kucera, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1704.
9. Moriarty, R. M.; Epa, W. R. *Tetrahedron Letters* **1992**, *33*, 4095.
10. (a) Darses, S.; Jeffrey, T.; Brayer, J. L.; Demoute, J. P.; Genêt, J.-P. *Tetrahedron Letters* **1996**, *37*, 3857. (b) Darses, S.; Genêt, J.-P. *Tetrahedron Letters* **1997**, *38*, 4393.
11. Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.
12. Bicharin, B. M.; Valenciano, J.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **1999**, *1*, 545.
13. Littke, A. F.; Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
14. A reverse phase ion-pairing HPLC method was developed for analysis of vinamidinium salts using a YMC basic column and acetonitrile/4 mM heptane sulfonic acid sodium salt as mobile phase.
15. (a) Wolfe, J. P.; Singer, R. A.; Young, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.
16. (a) Davies, I. W.; Taylor, M.; Hughes, D.; Reider, P. J. *Organic Letters* **2000**, *2*, 3385. (b) Davies, I. W.; Taylor, M.; Marcoux, J.-F.; Wu, J.; Dormer, P.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 251.
17. Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. *J. Organometallic Chem.* **1999**, *576*, 23.
18. See for example: Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051. See also Ref. 14.
19. Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organometallic Chem.* **1998**, *557*, 93.
20. Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437.
21. In the reaction of *para*-substituted phenylboronates and a propargylic carbonate a positive ρ value (+0.73) has been observed: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
22. Arnold, S. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051.
23. Moehrle, H.; Bluhme-Hensen, K.; Middelhauve, B.; Mootz, D.; Wunderlich, H. *Z. Naturforsch.* **1991**, *46B*, 1219.
24. Molander, G. A.; Ito, H. *Org. Lett.* **2001**, *3*, 393.
25. Mowery, M.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1648.
26. Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495.
27. Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571.