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Palladium-mediated intramolecular C–N bond formation involving allyl substituted pyridines. Application to a novel strategy for the synthesis of the skeleton of berberinium derivatives

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This paper is dedicated to our friend Jean-Pierre Genêt on the occasion of his 60th birthday

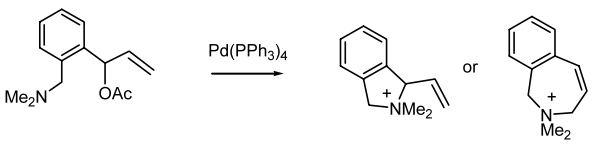
Abstract

The insertion of allenes in the Pd–C σ bond of cyclopalladated pyridine derivatives afforded (η^3-allyl) Pd complexes. The ideally located imine unit reacted selectively with the allyl functionality to yield a series of new cationic heterocycles. The process opened the route to a novel strategy for the synthesis of berberiniums, a class of molecules of pharmacological interest.

Keywords: Palladium-mediated synthesis; C–N bond formation; Allenes; Cyclopalladated complexes; Heterocyles; Berberiniums

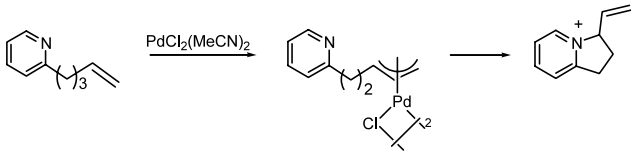
1. Introduction

Palladium has long been known as the most powerful tool for the formation of C–C or C–Y bonds (Y = heteroatom) [1]. However, as far as Y = N was concerned, this property has been mainly limited to those cases where the N atom was that of primary or secondary amines [2]. Only very few examples of either tertiary amines or secondary imines used in C–N bond synthesis have yet been reported. Our laboratory has been involved in such a project (Eq. (1)) as we found that intramolecular C–N bonds could be obtained with allyl substituted tertiary amines [3–7].



(1)

Whilst trying to perform a similar reaction with pyridines (Eq. (2)) *ortho*-substituted by an allyl functionality to afford quinolizinium compounds, we found that the reaction indeed took place, but with rather poor yields (< 10%) [8].



(2)

We thus decided to investigate whether more reliable routes would be achievable for the solution of this latter problem. As it appeared that the low yield of the heterocyclic compounds was mainly due to the formation of *ortho*-substituted pyridine complexes of palladium(II), we thought that we should rather look for π-allyl-Pd complexes bearing a pyridine ring whose N atom might be less prone to coordinate to the metal centre. A solution to this would be to place the pyridine unit at the central carbon of the allylic group rather than at one terminal carbon as we had in the previous studies. It is well known that the insertion of allenes into the

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Pd–C σ bonds affords η^3-allyl-palladium complexes in which the central carbon atom of the allylic group is substituted by the unit σ bonded to Pd in the starting material. We thus reasoned that cyclopalladated imines should be the ideal starting materials to afford, through reaction with allenes, such π-allyl moieties from which the imine unit would be ideally located to perform an intramolecular allylic substitution. We have already described the success of this simple strategy in preliminary forms [9,10]. In this paper we thus describe further studies connected to this reaction together with its application to the synthesis of the skeleton of berberinium derivatives.

2. Results and discussion

2.1. Syntheses

A series of symmetric or unsymmetric allenes **1**–**3** [11–15] have been reacted with a selection of cyclopalladated compounds **4a**–**7a** [16–19] having a pyridine unit coordinated to the palladium atom (Chart 1 and 2). Whereas **4a** and **5a** led directly to the organic products **4c** and **5c** respectively, in a few cases stable, isolable organometallic compounds were obtained as for, e.g. the reaction of **1**–**3** with **6a** and the reaction of **1** with **7a** (Scheme 1)

Combustion analysis and ^{1}H-NMR spectrometry established that these products were η^3-allyl–palladium complexes (see for example the chem. shifts of the terminal allylic protons, exp. section). They are intermediates in the normal course of the reaction. In consequence we reacted them further in methanol in the presence of three to four equivalents of triphenylphosphane to afford the cationic heterocyclic compounds **6e**, **6f**, **6g** and **7c**.

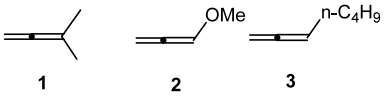


Chart 1.

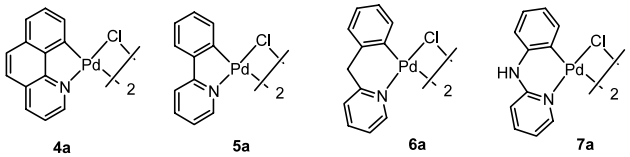
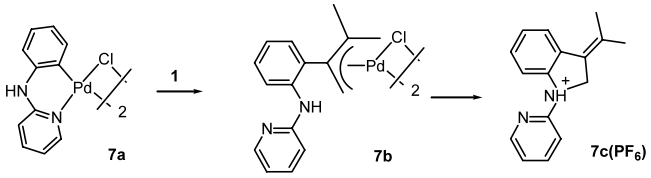
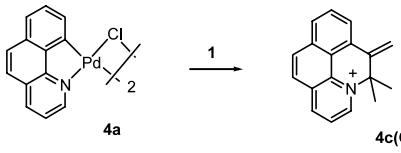


Chart 2.



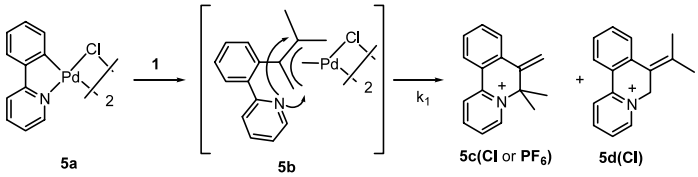
(3)

In CH_2Cl_2, complexes **4a** and **5a** were reacted with the appropriate allenes to yield the organic molecules **4c** and **5c** (Eq. (4) and Eq. (5), respectively).



(4)

Regardless whether these organopalladium intermediates were isolated or not, the reaction proceeds through the initial formation of a η^3-allyl–palladium complex. This intermediate results from the insertion of the allene into the Pd–C bond of the starting cyclopalladated complex. A carbon–carbon bond is formed between the previously metallated carbon and the central electrophilic carbon of the allene molecule. At this stage of the reaction, two types of nucleophilic attack of the intramolecular nitrogen on the metal–allyl complexe are possible (Eq. (5)). Thus, a mixture of two regioisomers may be obtained.

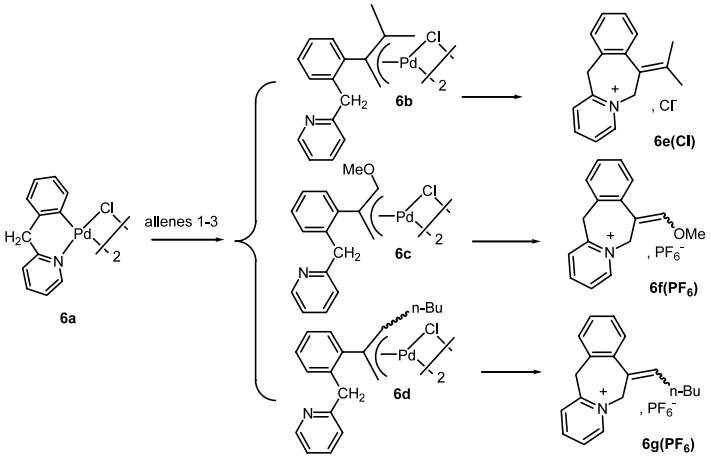


(5)

The cationic heterocycles we obtained arose indeed selectively from these two types of reactions. In the case of the benzoquinoleine and phenylpyridine ligands, six-membered rings **4c** and **5c**, bearing a 3-ethylidene substituent were formed. Starting with the benzylpyridine ligand, we obtained the seven-membered rings **6e**, **6f** and **6g**, bearing various substituted 3-ethylidene units. The five-membered heterocycle **7c** resulted from the attack of the nitrogen of an aminopyridine ligand. Such heterocyclic structures are without precedent in the literature.

2.2. Regioselectivity

We have been able to select the best conditions under which it was possible to observe the formation of the two possible regioisomers. Instantaneous formation of the η^3-allyl–palladium **5b** was observed by ^{1}H-NMR spectrometry after mixing the cyclopalladated phenylpyridine **5a** and butadiene **1** in CH_2Cl_2. The limiting step



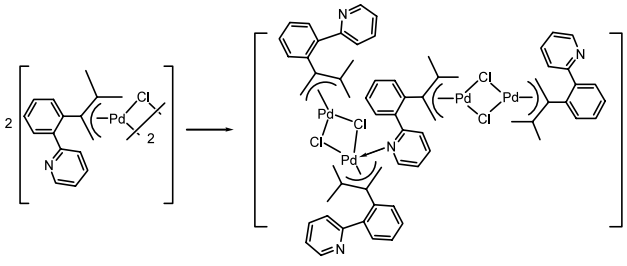
Scheme 1.

of the process was the disappearance of the complex **5b**. The formation of the 3-ethylidene–quinolizinium **5c** and of its regioisomer **5d** were also followed versus time (see Fig. 1).

As the hypothesis of a first order disappearance of the metal–allyl complex **5b** was unsatisfactory (see Fig. 2), we tested a second order reaction. With this latter hypothesis, a good linear correlation between **1/5b** and time was obtained, leading to the rate constant $k_1 = 180 \pm 10\ \mathrm{mM}^{-1}\ \mathrm{s}^{-1}$ (see Fig. 3).

Thus, it seems that some kind of association should occur between two molecules of **5b** prior to the depalladation reaction. Ryabov et al. [20] has shown that the reactions of organopalladium dimers with nucleophiles such as pyridine, alkynes or alkenes are in each case first-order in the palladium dimers and in the nucleophiles. As in our case the only nucleophile present in the reaction mixture is the pyridine fragment of the molecule **5b** we suggest that one pyridine nitrogen atom of one molecule of **5b** interacts with the palladium center of another molecule of **5b** akin to the intermediates postulated by Ryabov (Scheme 2).

Concerning the isomeric heterocycles, they were formed in a constant ratio **5c/5d** $= 3.0 \pm 0.1$. This result implies that the process is under kinetic control, the two regioisomers being formed through two parallel pathways. The rate constants ratio k_2/k_3 equals the products ratio (see experimental part). It was thus possible to



Scheme 2.

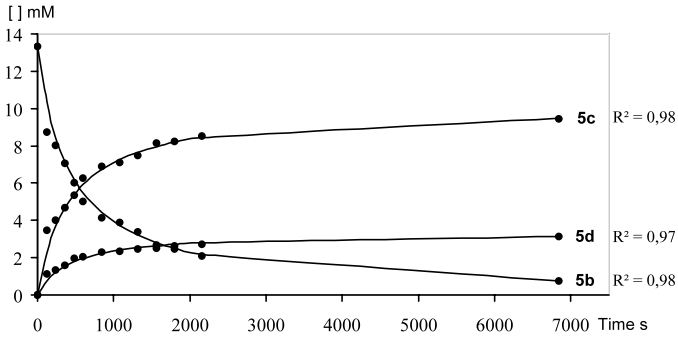


Fig. 1. Kinetics of the Eq. (5) in CH_2Cl_2.

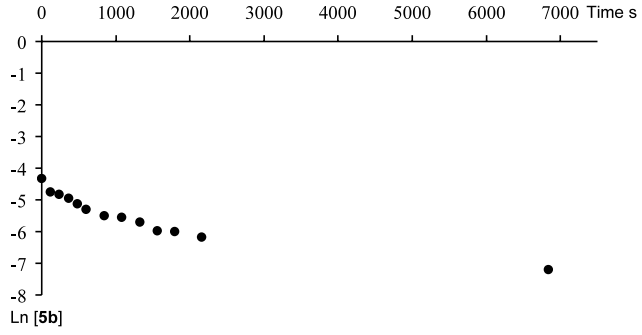


Fig. 2. Log evolution of the concentration of **5b** in Eq. (5).

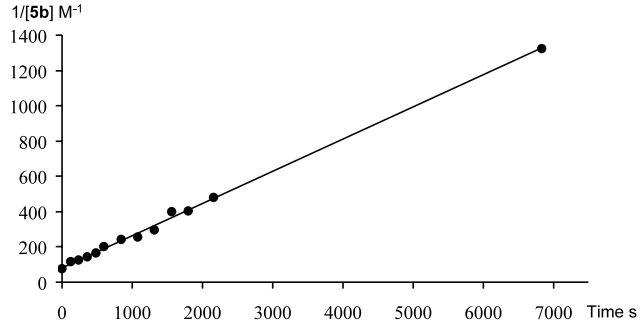


Fig. 3. Reciprocal evolution of the concentration of **5b** in Eq. (5).

simulate the kinetics of the disappearance of the intermediate **5b** and the formation of the products **5c** and **5d**. The obtained curves fit nicely with the experimental data as shown by their R^2 values that are close to 1.

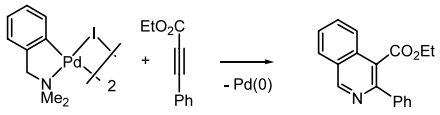
The previous reaction, when performed in MeOH, led only to the formation of the regioisomer **5c**, which is the less congested isomer (and thus the most stable one) as shown in Scheme 3.

However, if the previous kinetic results are of general scope, a kinetic point of view has to be considered. Compounds **4c** and **5c** result from the attack of the pyridine ligand on the more substituted, i.e. the more electrophilic, extremity of the allyl unit. On the other hand (compounds **6e**, **6f**, **6g** and **7c**), the same attack will lead to a crowded transition state and therefore attack of the less substituted carbon is that time preferred.

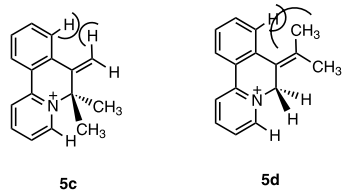
2.3. Palladium-mediated synthesis of berberiniums

Berberines are tetracyclic alkaloids [21]. This class of molecules present the peculiarity of containing a pyridine cycle whose nitrogen atom is shared between two rings, as it is the case in the above described compounds. Many berberines display interesting biological and/or pharmacological activities, like anti-inflammatory [22,23], antibacterial [24], immunostimulant [25], antioxidant [26]. Since Haworth and coworkers first synthesis [27], synthetic strategies have been developed using a Mannich reaction [28] or a photochemical process [29].

Application of the insertion of an allene into the Pd–C bond of a cyclopalladated pyridine derivative opens the possibility to plan a new synthesis. Cycle C might be obtained by this new reaction. On the other hand, the starting isoquinoline might result from the insertion of an internal alkyne in the Pd–C bond of a cyclometallated benzylamine, a reaction previously studied in our laboratory [30].

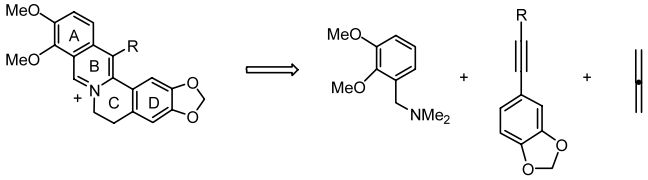


This will lead to an unprecedented synthesis of berberines as it will be performed via two successive C–H bond activation reactions which are mediated by stoichiometric amounts of palladium(II) complexes.



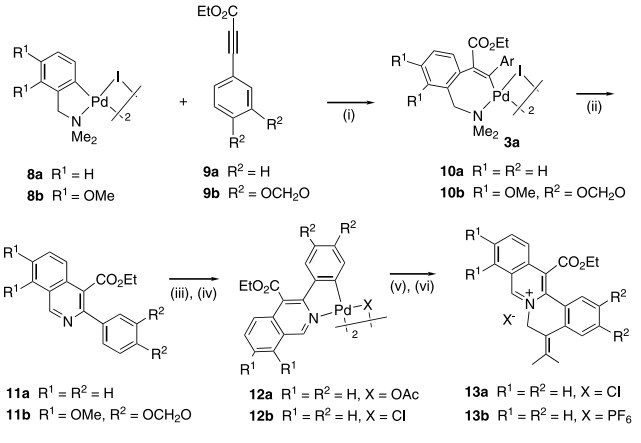
5c 5d

Scheme 3.



As depicted in Scheme 4, compound **11a** was synthesised in 78% yield by refluxing the organopalladium complex **10a** in PhCl, according to published procedure. [30] Only one regioisomer was obtained. [31] Since the formation of cycle B is the most critical one of this new process, we decided to perform it with the properly substituted substrates **8b** and **9b**. The insertion compound **10b**, obtained in CH_2Cl_2, was not further purified. It was directly refluxed in PhCl in the presence of catalytic amounts of pyridine to yield the 3-phenylisoquinoline derivative **11b** as the main product. Its isolation was, however, more tedious than **11a** as it required two successive chromatographies (overall yield 20%). Compared to a recent synthesis of cycle B in the berberines series, this yield is low. However our synthesis is convergent and might be useful for labscale syntheses [32]. It originates from a peculiar process of amino-dealkylation and aromatisation of the insertion intermediate **10b**.

The reaction of the isoquinoline **11a** in acetic acid with palladium acetate afforded **12a** in 97% yield. A subsequent metathesis with lithium chloride led to the quantitative formation of **12b**. The insertion of butadiene **1** into the Pd–C bond of the latter yielded the η^3-allylpalladium derivative **12c** as a stable solid (92%). The tetracyclic compound **13a** was obtained from **12c** through thermal demetallation at 80 °C in PhCl. Finally the 6-ethoxycarbonyl-3-isopropylidene-dibenzo(d,h) quinolizinium was isolated from **13a** as its PF_6 salt **13b** in 87% yield.



(i) CH_2Cl_2, RT, 4h; (ii) PhCl/Δ; (iii) $Pd(OAc)_2/CH_2Cl_2$; (iv) LiCl/acetone; (v) dimethylallene/CH_2Cl_2; (vi) PhCl/Δ

Scheme 4.

3. Conclusion

Built-in allyl–palladium complexes of pyridine derivatives have been reacted intramolecularly to yield a new series of cationic heterocyclic compounds. The reaction was regioselective with the respect to the structure of the starting material. Kinetic studies favoured kinetic over thermodynamic control of the course of the reaction. The process has been successfully applied to a novel synthesis of berberiniums.

4. Experimental

Solvents (dichloromethane, methanol, diethyl ether and hexane) were dried and distilled under argon. ^{1}H- (300.13 or 200.13 MHz) and ^{13}C- (75.47 or 50.32 MHz) NMR spectra were recorded on AC 300 or AC 200 Brüker instruments. Chemical shifts are expressed in ppm relative to TMS, the coupling constants in Hz. Abbreviations: Ar aromatic, br broad, quat. quaternary, Py pyridine. The number of H atoms at the carbon atoms was determined through DEPT experiments. The amounts of residual solvents have been measured by ^{1}H-NMR. IR spectra were recorded on an IRFT Brüker. The positions of the absorption bands are given in cm^{-1}. 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.

4.1. 3-Methyl-1,2-butadiene *1*

Calcium chloride (93 g; 0.83 mol) was added in portions to a cold (0–5 °C) stirred mixture of concentrated hydrochloric acid (400 ml), 2-methyl-3-butyn-2-ol (70 g; 0.83 mol) and hydroquinone (0.75g). After addition, the cooling bath was removed and the stirring continued for 1 h. The top layer was separated, dried over sodium carbonate, and distilled under reduced pressure. All the material that distilled up to 40 °C under 110 mmHg was collected and distilled again. 3-Chloro-3-methyl-1-butyne was thus collected as a colourless liquid (b.p. 74–6 °C) (45.5 g; 53% yield). Lit. [11]: 75–6 °C. ^{1}H-NMR ($CDCl_3$): 2.48 (s, 1H, CH); 1.82 (s, 6H, 2 CH_3).

For the next step, the described procedure [12] was improved in the following way. Metallic zinc powder (52 g; 0.79 mol) was washed with aqueous 3% hydrochloric acid solution (4 × 40 ml), aqueous 2% copper sulfate solution (2 × 60 ml), ethanol (2 × 60 ml), and *n*-butanol (2 × 60 ml). The thus treated zinc was rinsed with 110 ml *n*-butanol in a two-neck round-bottom flask provided with a dropping funnel, a magnetic stirrer bar and a distillation head with Vigreux column (30 cm). 3-Chloro-3-methyl-1-butyne (40.5 g; 0.4 mol) was placed in the dropping funnel, 3 ml added to the zinc–butanol slurry and the mixture heated cautiously, with stirring, until the reaction started. Slow addition of the remaining propargyl chloride followed, controlled by the distilling rate of the allene (distilling temperature between 38 and 42 °C). The collected material was redistilled, giving a colourless liquid of b.p. 38–41 °C (19.5 g; 71% yield). Lit. [13]: 39.5–41 °C. [1]H-NMR ($CDCl_3$): 4.53 (septet, 2H, $^{5}J = 3.1$, CH_2); 1.70 (t, 6H, $^{5}J = 3.1$, 2 CH_3).

4.2. 3-Methoxy-1,2-propadiene *2*

Potassium *t*-butoxide (0.25 g, 2.5 mmol) was added to molecular sieve dried methyl propargyl ether (7 g, 0.1 mol). The mixture was heated to reflux for 3 h and then distilled under reduced pressure at r.t. to a dry-ice–acetone cooled trap. Redistillation afforded a colourless liquid of b.p. 50–2 °C (6.4 g, 91% yield). Lit. [14]: 50–2 °C. ^{1}H-NMR ($CDCl_3$): 6.74 (t, 1H, $^{4}J = 6$, CH); 5.45 (d, 2H, $^{4}J = 6$, CH_2); 3.39 (s, 3H, OCH_3).

4.3. 1,2-Heptadiene *3*

The compound was prepared as described previously [15].

The cyclopalladated compounds: bis [(2-pyridyl(h)naphtyl (κN, κC^{1})] di(μ-chloro) dipalladium **4a**, 16 bis [2-(2-pyridyl)phenyl (κN, κC^{1})] di(μ-chloro) dipalladium **5a** [17], bis [2-(2-pyridyl)methylphenyl (κN, κC^{1})] di(μ-chloro) dipalladium **6a** [18] and bis [2-pyridyl-2-aminophenyl (κN, κC^{1})] di(μ-chloro) dipalladium **7a** [19] were prepared according to published methods.

4.4. Synthesis of the heterocyclic compounds *4c*(PF_6), *5c*(PF_6), *4c*(Cl), *4c*(PF_6)

(a) A mixture of the cyclopalladated complex **4a** (320 mg, 0.5 mmol) and 2.5 equivalents of propadiene **1** (85 mg, 1.25 mmol) in 20 ml of dichloromethane was stirred for 1 h at r.t. A black heterogenous solution was observed. The black metallic palladium was removed by a filtration over a Celite pad. The yellow filtrate left was concentrated. On addition of hexane, a yellow precipitate was formed. After drying the latter under vacuum, the cationic heterocycle was obtained as a yellow powder. The product was fully characterized as its hexafluorophosphate salt, which was obtained by treating a water solution with one equivalent of KPF_6.

4.4.1. 2,2-Dimethyl-3-ethylidene-anthra(d,e,f)quinolizinium **4c**(PF_6)

Yield 75%. Anal. Calc. for $C_{18}H_{16}F_6NP$: C, 55.24; H, 4.09; N, 3.58. Found: C, 55.59; H, 3.80; N, 3.43%. ^{1}H-NMR (acetone-d_6): 9.90 (1H, d, $^3J = 6.3$, H_o–Py); 9.35 (1H, d, $^3J = 8.1$, Ar); 8.46–8.41 (2H, m, Ar); 8.38–8.30 (3H, m, Ar); 8.15 (1H, t, $^3J = 7.8$, Ar); 6.14 (2H, s, $=CH_2$); 2.16 (6H, s, 2 CH_3). MS (EI) Calc. for $C_{18}H_{16}N$: $m/z = 246$. Found: [M^+] 246.

(b) Compound **5c** was prepared via a similar procedure to that described for **4c**, starting from **5a** and using methanol instead of dichloromethane. The PF_6 salt was obtained directly by treating the methanol filtrate with one equivalent of KPF_6.

4.4.2. 2,2-Dimethyl-3-ethylidene-benzo(d)quinolizinium **5c**(PF_6)

Yield 51%. Anal. Calc. for $C_{16}H_{16}F_6NP$: C, 52.32; H, 4.36; N, 3.82. Found: C, 52.63; H, 4.26; N, 3.70%. ^{1}H-NMR (CD_3OD): 9.23 (1H, d, $^3J = 5.7$, H_o–Py); 8.66 (1H, dd, $^3J = 8.3$, $^4J = 1.5$, Ar); 8.57 (1H, td, $^3J = 7.9$, $^4J = 1.3$, Ar); 8.25 (1H, t, $^3J = 7.3$, Ar); 7.99 (1H, td, $^3J = 6.7$, $^4J = 1.6$, Ar), 7.84–7.66 (3H, m, Ar); 5.80 (2H, s, $=CH_2$); 1.91 (6H, s, CH_3). MS (EI) Calc. for $C_{16}H_{16}N$: $m/z = 222$. Found: [M^+] 222.

(c) The cyclopalladated complex **4a** (0.8 mmol) and 2.5 equivalents of propadiene **1** (134 mg, 2 mmol) in 20 ml of dichloromethane were stirred overnight at RT. A black heterogenous solution was obtained. The black metallic palladium so formed was filtered. The yellow filtrate left was concentrated and redissolved in water. After filtration over paper, water was evaporated and the residue dried under vacuum. The cationic heterocycle as a chloride salt was recrystallized from chloroform–diethyl ether.

4c(Cl): 32% yield. Anal. Calc. for $C_{18}H_{16}ClN \cdot 2H_2O$: C, 68.02; H, 5.07; N, 4.40. Found: C, 67.49; H, 5.33; N, 4.10%. ^{1}H-NMR (CD_3OD): 9.76 (1H, d, $^3J = 6.3$, H_o–Py); 9.22 (1H, dd, $^3J = 8.1$, $^4J = 0.9$, Ar); 8.33–8.18 (5H, m, Ar); 8.10 (1H, t, $^3J = 7.9$, Ar); 6.08 and 6.08 (2H, 2s, $=CH_2$); 2.06 (6H, s, 2 CH_3). ^{13}C-NMR (CD_3OD): 141.6; 135.8; 134.0; 131.4; 129.6; 118.3 ($C_{quat.}$); 145.6; 141.3; 132.5; 130.9; 129.0; 125.2; 124.8; 123.9 ($CH_{aromatic}$); 117.3 ($=CH_2$); 70.6 (NC); 26.3 (CH_3). IR (KBr pellet): 1626 (C=C).

5c(Cl): 50% yield. Anal. Calc. for $C_{16}H_{16}ClN + H_2O$: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.15; H, 6.15; N, 4.89%. ^{1}H-NMR ($CDCl_3$): 10.40 (1H, d, $^3J = 6.5$, H_o–Py); 8.53–8.49 (3H, 2m, Ar); 8.07 (1H, d, $^3J = 7.3$, Ar); 7.73–7.65 (3H, m, Ar), 5.82 and 5.81 (2H, 2s, $=CH_2$); 2.07 (6H, s, 2 CH_3). ^{13}C-NMR (D_2O): 151.0; 143.8; 136.5; 127.0 ($C_{quat.}$); 147.6; 142.3; 136.7; 132.7; 128.9; 128.7; 128.0 ($CH_{aromatic}$); 119.4 ($=CH_2$); 71.4 (NC); 28.1 (CH_3). IR (KBr pellet): 1619 (C=C).

4.5. Isolation of the (η^3-allyl) Pd complexes **6b,c,d** and **7b**

To a suspension of starting cylopalladated complex **6a** (1 mmol) in CH_2Cl_2 (20 ml) was added dropwise a solution of 2.5 equivalents of allene in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h at r.t.: a clear yellow solution containing a light black palladium deposit was obtained. After filtration over Celite, the yellow filtrate was concentrated (ca. 5 ml) and hexane added to precipitate a pale yellow solid corresponding to the (η^3-allyl) Pd complex, **6b**.

6b: obtained from **1**. 87% yield. Anal. Calc. for $C_{17}H_{18}ClNPd$: C, 54.81; H, 5.08; N, 3.60. Found: C, 55.18; H, 5.14; N, 3.40%.^{1}H-NMR ($CDCl_3$ + Py-d_5): 8.48 (1H, d, $^3J = 4.6$, H_o–Py); 7.92 (1H, d, $^3J = 6.7$, Ar); 7.51 (1H, td, $^3J = 8.4$, $^4J = 1.5$, Ar); 7.27–7.19 (3H, m, Ar); 7.06 (1H, t, $^3J = 5.2$, Ar); 6.93 (1H, d, $^3J = 7.7$, Ar); 4.25 and 4.12 (2H, 2d, $^2J = 15.6$, CH_2); 3.46 and 3.42 (2H, 2 br s, allylic H); 1.34 and 1.04 (6H, 2 s, $C(CH_3)_2$).

6c (*syn* isomer): obtained from **2**; 86% yield. Anal. Calc. for $C_{16}H_{16}ClNOPd$: C, 52.30; H, 4.86; N, 3.49. Found: C, 52.67; H, 4.88; N, 3.31%. ^{1}H-NMR ($CDCl_3$ + Py-d_5): 8.52 (1H, d, $^3J = 4.5$, H_o–Py); 8.02 (1H, dd, $^3J = 6.5$, $^4J = 2.2$, Ar); 7.53 (1H, td, $^3J = 7.6$, $^4J = 1.7$, Ar); 7.34–7.26 (3H, m, Ar); 7.10 (1H, t, $^3J = 6.1$, Ar); 6.99 (1H, d, $^3J = 7.8$, Ar); 5.79 (1H, br s, $CHOCH_3$); 4.39 and 4.33 (2H, 2d, $^2J = 16.4$, CH_2); 3.46 (3H, br s, OCH_3); 3.31 and 2.70 (2H, 2 s, allylic H).

6d: obtained from **3**; 83% yield; 3:1 mixture of *syn* and *anti* isomers as measured by ^{1}H-NMR. Anal. Calc. for $C_{19}H_{22}ClNPd$: C, 56.16; H, 5.42; N, 3.45. Found: C, 55.99; H, 5.39; N, 3.37%. ^{1}H-NMR ($CDCl_3$ + Py-d_5): *Z* isomer (characteristic signals) 8.53 (1H, d, $^3J = 3.0$, H_o–Py); 7.32–7.24 (4H, m, Ar); 6.94 (1H, d, $^3J = 7.8$, Ar); 4.50 (1H, br t, CH); 3.83 and 3.63 (2H, 2 br s, allylic H); E isomer (characteristic signals) 7.18–7.08 (4H, m, Ar); 7.00 (1H, d, $^3J = 7.9$, Ar); 3.96 (1H, br t, CH); 3.44 and 3.06 (2H, 2 br s, allylic H).

7b: obtained from **1** as a beige solid with a 78% yield. Anal. Calc. for $C_{16}H_{17}ClN_2Pd$: C, 51.66; H, 4.86; N, 7.16. Found: C, 51.71; H, 4.89; N, 6.72%. ^{1}H-NMR ($CDCl_3$ + Py-d_5): 8.15 (1H, br s, NH); 7.91 (1H, br s, H_o–Py); 7.63–7.40 (2H, m, Ar); 7.31 (1H, d, $^3J = 6.4$, Ar); 7.09 (1H, br t, Ar); 6.83–6.62 (2H, m, Ar); 3.66 and 3.62 (2H, 2 broad s, allylic H); 1.40 and 1.21 (6H, 2 br s, $C(CH_3)_2$).

4.6. Depalladation reaction of the (η^3-allyl) Pd complexes, synthesis of the heterocyclic compounds: **7c**(PF_6), **6e**(Cl), **6f**(PF_6), **6g**(PF_6) and **7c**(PF_6)

(a) Under an argon atmosphere, triphenylphosphane (0.63 g, 2.4 mmol) was added to a solution of **7b** (0.26 g, 0.34 mmol) in 25 ml of methanol. After stirring for 10

min, the fine yellow precipitate formed was removed by a filtration over Celite. The orange yellow filtrate was evaporated to dryness. The residue was extracted with 5 ml of dichloromethane. Precipitation using hexane afforded derivative **7c** as a pale yellow solid. The PF_6 salt was obtained by reacting a water solution of **7c** with KPF_6.

4.6.1. 2-H-3-Isopropylidene-1-(2-pyridyl)indolinium 7c(PF_6)

Yield 63%. Anal. Calc. for $C_{16}H_{17}F_6N_2P$: C, 50.26; H, 4.45; N, 7.33. Found: C, 50.36; H, 4.55; N, 7.26%. ^{1}H-NMR (acetone-d_6): 10.23 (1H, br s, NH); 8.50 (1H, d, $^3J = 6.5$, H_o–Py); 8.15–8.10 (1H, m, Ar); 7.56 (1H, d, $^3J = 8.9$, Ar); 7.37–7.35 (3H, m, Ar); 7.28 (1H, td, $^3J = 6.8$, $^4J = 1.2$, Ar); 7.24–7.18 (1H, m, Ar); 5.39 (2H, br s, NCH_2); 2.14 and 1.99 (6H, 2s, $C(CH_3)_2$). ^{13}C-NMR (acetone-d_6): 151.1; 143.1; 141.2; 141.0; 137.0; 132.0; 130.6; 128.7; 126.4; 124.0; 120.9; 119.2; 116.5 (Ar+olefinic); 60.4 (NCH_2); 22.5 and 20.5 ($C(CH_3)_2$).

4.6.2. 5-Isopropylidene-dibenzo(a,d)azepizinium 6e(Cl)

Yield 53%. Anal. Calc. for $C_{17}H_{18}ClN + 1/10\ CH_2Cl_2$: C, 72.80; H, 6.40; N, 4.90. Found: C, 73.14; H, 6.17; N, 4.92%. ^{1}H-NMR ($CDCl_3$): 10.18 (1H, d, $^3J = 5.7$, H_o–Py); 8.30 (1H, t, $^3J = 7.6$, Ar); 7.94 (1H, d, $^3J = 7.4$, Ar); 7.88 (1H, t, $^3J = 6.6$, Ar); 7.30–7.18 (4H, m, Ar); 6.14 (2H, s, NCH_2); 4.55 (2H, s, CH_2); 2.13 and 1.82 (6H, 2s, $C(CH_3)_2$). ^{13}C-NMR (CD_2Cl_2): 157.5; 147.3; 146.4; 138.5; 137.0; 133.5; 131.5; 129.0–128.3; 126.9; 124.5; (Ar+olefinic); 62.6 (NCH_2); 40.5 (CH_2); 23.4 and 21.1 ($C(CH_3)_2$). MS (EI) Calc. for $C_{17}H_{18}N$: $m/z = 236$. Found: [M^+] 236.

(b) **6f**(PF_6) was obtained from compound **6c**. The reaction and primary separation were performed as for **7c**. An oily residue was obtained which was extracted in water. The cationic heterocycle was precipitated by addition of one equivalent of potassium hexafluorophosphate. After a filtration, the white solid was extracted with 2 ml of acetone. The solvent was evaporated to dryness. The pale yellow residue left was then washed with ether and dried in vacuo.

4.6.3. 5-Methoxyethylidene-dibenzo(a,d)azepizinium 6f(PF_6)

Yield 42%; 3:1 mixture of *E* and *Z* isomers as measured by ^{1}H-NMR. Anal. Calc. for $C_{16}H_{16}F_6NOP$: C, 50.13; H, 4.18; N, 3.66. Found: C, 50.26; H, 4.01; N, 3.52%. ^{1}H-NMR (acetone-d_6): *Z* isomer (characteristic signals) 9.17 (1H, d, $^3J = 6.2$, H_o–Py); 7.53 (1H, d, $^3J = 8.8$, Ar); 7.12 (1H, s, $CHOCH_3$); 5.96 (2H, s, NCH_2); 4.96 (2H, s, CH_2); 3.96 (3H, s, OCH_3); *E* isomer (characteristic signals): 9.25 (1H, d, $^3J = 6.1$, H_o–Py); 8.66 (1H, t, $^3J = 7.8$, Ar); 8.31 (1H, d, $^3J = 7.7$, Ar); 8.23 (1H, dd, $^3J = 7.9$, $^4J = 1.4$, Ar); 8.16 (1H, t, $^3J = 7.4$, Ar); 7.40 (1H, d, $^3J = 6.3$, Ar); 7.06 (1H, s, $CHOCH_3$); 5.84 (2H, s, NCH_2); 5.02 (2H, s, CH_2); 3.90 (3H, s, OCH_3).

4.6.4. 5-Hexylidene-dibenzo(a,d)azepizinium 6g(PF_6)

Yield 26%; 8:1 mixture of *E* and *Z* isomers as measured by ^{1}H-NMR. ^{1}H-NMR (acetone-d_6): *Z* isomer (characteristic signals): 6.31 (1H, br t, CH); 5.88 (2H, br s, NCH_2); 2.41–2.24 (2H, m, α CH_2); 0.79 (3H, t, δ CH_3); E isomer (characteristic signals): 9.25 (1H, d, $^3J = 6.1$, H_o–Py); 8.64 (1H, td, $^3J = 7.9$, $^4J = 1.4$, Ar); 8.32 (1H, d, $^3J = 7.9$, Ar); 8.12 (1H, td, $^3J = 6.6$, $^4J = 1.4$, Ar); 6.37 (1H, t, $^4J = 7.4$, CH); 6.08 (2H, br s, NCH_2); 4.94 (2H, br s, CH_2); 2.60–2.53 (2H, m, α?CH2); 0.97 (3H, t, $^3J = 7.2$, δ CH_3).

4.7. bis[(2-Dimethylaminomethyl-3,4-dimethoxy)phenyl(κN, κC^1)]di(μ-iodo)dipalladium 8b

This compound was obtained by metathesis, performed on the chloro analog [33] in acetone and presence of excess of sodium iodide (i.e. four equivalents of NaI per Pd atom). Anal. Calc. for $C_{22}H_{32}I_2N_2O_4Pd_2$: C, 30.90; H, 3.77; N, 3.28. Found: C, 30.10; H, 3.62; N, 3.04%. ^{1}H-NMR ($CDCl_3$+Py-d_5): 6.42 (1H, d, $^3J = 8.3$, H_6); 5.38 (1H, d, $^3J = 8.3$, H_5); 4.11 (2H, s, NCH_2); 3.79 and 3.75 (6H, 2s, OCH_3); 3.10 (6H, s, NCH_3).

4.7.1. Ethyl 3,4-methylendioxyphenylpropiolate 9b

1,1-Dibromo-2-(3,4-methylendioxyphenyl)ethane (4.5 g, 14.7 mmol), prepared with a 88% yield according to Corey [34], was treated with 3.5 equivalents of methyllithium in THF at −78 °C. The yellow solution, when returned to RT, became red. This latter was cooled to −78 °C and 2.2 equivalents of ethyl chloroformate added to it. The following day, the solution was quenched at 0 °C by addition of aqueous sodium bicarbonate. After diethyl ether extraction, the crude product was chromatographied over SiO_2 (eluent Hex–Et_2O 20%) to give 1.6 g substance **9b** (yield 50%).

M.p. (Hex): 86; lit. 83.5–84.4 [35,36]; Anal. Calc. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.95; H, 4.56%. ^{1}H-NMR ($CDCl_3$): 7.18 (1H, dd, $^3J = 8.0$, $^4J = 1.6$, H_5); 7.03 (1H, d, $^4J = 1.6$, H_2); 6.82 (1H, d, $^3J = 7.7$, H_6); 5.04 (2H, s, OCH_2O); 4.31 (2H, q, $^3J = 7.1$, OCH_2); 1.37 (3H, t, $^3J = 7.1$, CH_3). ^{13}C-NMR ($CDCl_3$): 154.2 (CO); 150.0 and 147.6 (C_1, C_3, C_4); 128.8; 112.5 and 108.7 (C_2, C_5, C_6); 101.8 (OCH_2O); 86.5 and 79.7 ($C_{1'}$, $C_{2'}$); 62.0 (OCH_2) and 14.1 (CH_3).

4.7.2. 7,8-dimethoxy-4-ethoxycarbonyl-3-(3,4-methylendioxyphenyl) isoquinoline 11b

Compound **8b** (500 mg, 0.58 mmol) was dissolved in 50 ml of dichloromethane. Propiolate **9b** (250 mg, 1.15 mmol) in 150 ml of CH_2Cl_2 was added dropwise to the previous solution under vigorous stirring. Stirring was continued until next day and the solvent evaporated.

Chlorobenzene (50 ml) and five drops of pyridine were then added and the mixture refluxed for 4 h. After evaporation of the volatiles, the crude product was first filtered over SiO_2 with a CH_2Cl_2–MeOH 5–10% eluent, then flash chromatographed over Al_2O_3 with a CH_2Cl_2–MeOH 0.5–5%) gradient to yield 88 mg (20%) of the isoquinoline derivative **11b**.

M.p. (AcOEt–Hex): 195; Anal; Calc. for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 65.10; H, 4.75; N, 3.51%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.52 (1H, s, H_1); 7.31 (1H, d, $^3J = 8.3$, H_6); 6.92 (1H, d, $^3J = 8.3$, $H_{5'}$); 6.86 (1H, dd, $^3J = 6.1$, $^4J = 1.7$, $H_{6'}$); 6.85 (1H, d, $^4J = 1.7$, $H_{2'}$); 6.53 (1H, d, $^3J = 8.1$, H_5); 6.08 (2H, s, OCH_2O); 4.15 (2H, q, $^3J = 7.1$, OCH_2); 3.93 and 3.78 (6H, 2s, OCH_3); 2.00 (H_2O); 1.07 (3H, t, $^3J = 7.1$, CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz): 169.3 (CO); 166.0 (C_3); 151.4, 149.2, 148.1, 136.3, 128.1, 126.2, 124.9, 121.2 (C_4, C_7, C_8, C_{10}, $C_{1'}$, $C_{3'}$, $C_{4'}$); 146.9, 124.2, 119.5, 110.2, 108.7, 100.4 (C_1, C_5, C_6, $C_{2'}$, $C_{5'}$, $C_{6'}$); 101.9 (OCH_2O); 61.7 (OCH_2); 56.0 and 44.2 (OCH_3); 13.9 (CH_3). MS (EI) Calc. for $C_{21}H_{19}NO_6$: $m/z = 381.4$. Found: [M^+] 381.2; [$M^+ - 29$]; [$M^+ - 71$].

4.7.3. Cyclopalladated phenylisoquinoline *12a*

To a solution of 3-phenylisoquinoline **11a** prepared by published procedure [30] (1.2 g, 4.5 mmol) in 40 ml of acetic acid, was added one equivalent of palladium acetate (1.02 g). The mixture was stirred for 1 day at r.t. leading to an orange solution and a greenish solid. The solid was filtered and washed with water, methanol and ether. After drying, the solid was obtained as a yellow powder (1.95 g, 97% yield).

^{1}H-NMR ($CDCl_3$+Py-d_5): 9.37 (1H, s, H_o–Py); 7;99 (1H, d, $^3J = 8.2$, Ar); 7.83–7.78 (2H, m, Ar); 7.67–7.61 (1H, m, Ar); 7.35 (1H, dd, $^3J = 7.9$, $^4J = 1.1$, Ar); 7.05 (1H, $^3J = 7.6$, $^4J = 1.1$, Ar); 6.89 (1H, td, $^3J = 7.5$, $^4J = 1.2$, Ar); 6.27 (1H, d, $^3J = 7.7$, Ar); 4.60 (2H, q, $^3J = 7.1$, OCH_2); 2.02 (3H, s, OAc); 1.43 (3H, t, $^3J = 7.1$, CH_3).

A mixture of **12a** (0.73g, 0.83 mmol) and four equivalents of lithium chloride (0.14 g) in 30 ml of acetone was stirred at r.t. overnight, yielding a red solution and a yellow precipitate. After filtration, washing with diethylether and drying, a fine beige solid was obtained (**12b**: 0.68 g, 98% yield).

4.7.4. η^3-Allylpalladium complexe *12c*

A solution of propadiene **1** (0.14 g, 2.1 mmol) in 2 ml of CH_2Cl_2 was added at r.t. to a suspension of the cyclopalladate compound **12b** (0.68 g, 0.82 mmol) in 20 ml CH_2Cl_2. After 15 min, a yellow solution was obtained. It was stirred during 2 h. After filtration over Celite and concentration of the filtrate, a yellow solid was obtained by addition of hexane (**12c**: 0.73g, 92% yield).

Anal. Calc. for $C_{23}H_{22}ClNO_2Pd$: C, 56.79; H, 4.53; N 2.88. Found: C, 56.70; H, 4.43; N 2.76%.^{1}H-NMR ($CDCl_3$): 9.26 (1H, s, H_o–Py); 8.23 (1H, d, $^3J = 7.3$, Ar); 8.12 (1H, d, $^3J = 8.0$, Ar); 7.80 (1H, t, $^3J = 7.6$, Ar); 7.68 (1H, t, $^3J = 7.5$, Ar); 7.55–7.35 (3H, m, Ar); 4.16 (2H, q, $^3J = 7.1$, OCH_2); 3.74 and 3.40 (2H, 2s, allylic CH_2); 1.21 (3H, t, $^3J = 7.1$, CH_3); 1.08 and 1.02 (6H, 2s, $C(CH_3)_2$).

4.7.5. 6-Ethoxycarbonyl-3-isopropylidene-dibenzo(d,h)quinolizinium hexafluorophosphate *13b*

The allylpalladium compound **12c** (0.21g, 0.22 mmol) in 15 ml of PhCl was heated at 80 °C for 16 h, this leading to the formation of palladium black. After filtration over Celite and evaporation of the solvent, an orange residue of **13a** was obtained. Treatment with one equivalent in MeOH led to a beige solid (**13b**: 0.19g, 87% yield).

^{1}H-NMR (CD_3OD): 10.09 (1H, s, H_o–Py); 8.50 (1H, d, $^3J = 8.4$, Ar); 8.32–8.23 (2H, m, Ar); 8.11–8.05 (1H, m, Ar); 7.90 (1H, d, $^3J = 7.7$, Ar); 7.73–7.66 (2H, m, Ar); 7.57–7.52 (1H, m, Ar); 5.48 (2H, br s, NCH_2); 4.52 (2H, q, $^3J = 7.1$, OCH_2); 2.15 and 2.14 (6H, 2s, $C(CH_3)_2$); 1.27 (3H, t, $^3J = 7.1$, CH_3). MS (EI) Calc. for $C_{23}H_{22}NO_2$: $m/z = 344$. Found: [M^+] 344; [$M^+ - 1$]; [$M^+ - 2$].

4.8. Kinetic study of the reaction of *1* with the palladium complex *5a*

The cyclopalladated complex **5a** (119 mg, 0.2 mmol) was dissolved in 15 ml of dichloromethane. At time $t = 0$, 2.5 equivalents of propadiene **1** (34 mg, 0.5 mmol) were added. The yellow solution turned immediatly black. The kinetics was followed by sampling at regular time until 360 min. A last sample was made at $t = 1140$ min. The samples of 1 ml were obtained under a nitrogen flux with a syringe. They were then filtered over a celite pad in test tubes. Then the samples were evaporated under vacuum and stored in the freezer. To be analysed by ^{1}H-NMR, the samples were dissolved in 0.4 ml of $CDCl_3$ just before recording the different spectra.

^{1}H-NMR: η^3-allyl complex **5b**: 8.65 (1H, br s, H_o–Py); 8.13 (2H, br d, Ar); 7.35 (1H, br d, Ar); 7.25–7.00 (4H, m, Ar); 3.91 and 3.66 (2H, 2 br s, H allylic); 1.04 and 0.73 (6H, 2 br s, $C(CH_3)_2$).

5d (opposite regioisomer of **5c**): 10.45 (1H, d, $^3J = 6.1$, H_0–Py); 8.43 (1H, t, $^3J = 7.3$, Ar); 8.29 (1H, d, $^3J = 7.8$, Ar); 7.95 (1H, d, $^3J = 7.5$, Ar); 7.65–7.45 (3H, m, Ar); 5.78 (2H, s, NCH_2); 2.26 and 2.04 (6H, 2s, $C(CH_3)_2$).

[**5b**] = A; [**5c**] = B; [**5d**] = C.

Ln A and $1/A$ were quoted versustime.

The second curve was straight with a slope $k_1 = 180 \pm 10$ mM^{-1} s^{-1} and a correlation coefficient 0.998: the kinetic is second-order. The products ratio B/C was constant (3.0 ± 0.1) with time: **5c** and **5c′** are formed

with parallel rates (rate constants k_2 and k_3, respectively). In consequence the expression of the different rates are the following: $-\mathrm{d}A/\mathrm{d}t = k_1A^2$; $1/2\ \mathrm{d}B/\mathrm{d}t = k_2A^2$; $1/2\ \mathrm{d}C/\mathrm{d}t = k_3A^2$; leading to the integrate forms: $A = A_0/(1+k_1A_0t)$; $B = (2A_0k_2/k_1)[1-1/(1+k_1A_0t)]$; $C = (2A_0k_3/k_1)[1-1/(1+k_1A_0t)]$; $k_2 = 68 \pm 6\ \mathrm{mM}^{-1}\ \mathrm{s}^{-1}$; $k_3 = 22 \pm 2\ \mathrm{mM}^{-1}\ \mathrm{s}^{-1}$.

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