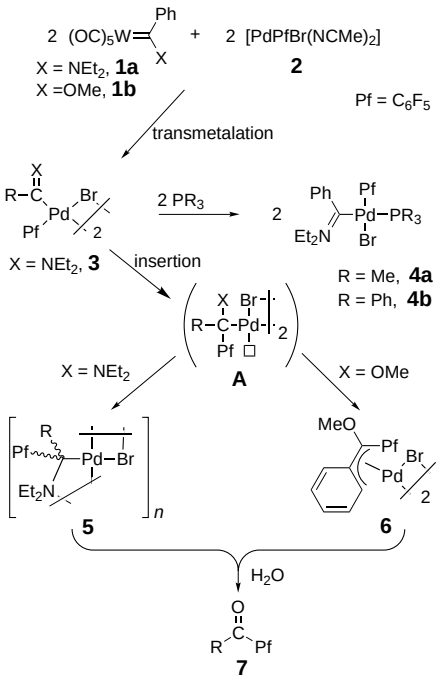
Observation of the Direct Products of Migratory Insertion in Aryl Palladium Carbene Complexes and Their Subsequent Hydrolysis**

Ana C. Albéniz,* Pablo Espinet,* Raúl Manrique, and Alberto Pérez-Mateo

The use of carbene ligands in palladium-catalyzed processes, presumably involving "[PdR(carbene)$_n$]" intermediates, is becoming increasingly important.[1] In this context, the understanding of the reactivity of these species, including the interactions between precursors of palladium carbenes,[2] becomes relevant. The formation of coupling products (R–carbene)$^+$ (R = alkyl) from alkyl palladium carbene complexes bearing heterocyclic carbenes C(NR$'_2$)$_2$ has been studied before, and theoretical calculations have discounted an alkyl-migration mechanism in favor of a concerted reductive elimination process.[3] We hypothesized that the course of the reaction might be different for other systems with more electrophilic carbene ligands. The use of aryl in place of alkyl ligands should also facilitate a migratory insertion mechanism, and the use of fluorinated aryl groups might facilitate the observation of intermediates and products. Compared with the rather stable palladium carbene complexes in which the less electrophilic carbene ligands are stabilized by two amino groups (C(NR$'_2$)$_2$),[4] those with carbene ligands stabilized by only one amino group (CR″(NR$'_2$)) are still rare.[5] Other heteroatom (for example, CR″(OR′)) or nonheteroatom ((CR$''_2$)) palladium carbenes are very elusive species, although often proposed as intermediates in many Pd-catalyzed reactions.[6] We report here the unprecedented direct observation of migratory insertion of carbene ligands into a Pd–aryl bond. The Pd complexes containing the hydrocarbyl ligand formed by insertion can be identified spectroscopically and by their hydrolysis products. In the case of CR″(NR$'_2$) carbenes, the migratory insertion occurs on isolable and characterizable compounds.

The transformations discussed herein are summarized in Scheme 1. Transmetalation of the carbene ligand from [W(CO)$_5$(CPhX)] (X = NEt$_2$, **1a**; X = OMe, **1b**) to [PdBrPf(NCMe)$_2$] (Pf = C$_6$F$_5$, **2**) leads eventually, at very different rates, to the migratory insertion products **5** and **6**. Both **5** and **6** undergo hydrolysis to afford the ketone **7**.

The transfer of a carbene between W and Pd centers has been previously used in the preparation of some palladium diamino carbenes[7] and, along with the extension described here for monoaminocarbenes, seems a convenient synthetic route. The possible competition of a Pd-catalyzed carbene dimerization is not evident under controlled stoichiometric conditions.[2]



Scheme 1. Synthesis, pentafluorophenyl migratory insertion, and hydrolysis of palladium carbene complexes.

Transmetalation with the carbene ligand CPh(NEt$_2$) affords **3** as an isolable yellowish solid.[8] The splitting of the bridging ligands with an equimolar amount of tertiary phosphane gives the monomeric derivatives **4**. Both **3** and **4** were characterized spectroscopically and by elemental analysis. The X-ray crystal structure of **4a** was determined (Figure 1). The carbene and pentafluorophenyl groups are in a *cis* arrangement (which suggests that they are the two ligands with the highest *trans* influence) and lie perpendicular to the palladium coordination plane. The bond lengths found in the carbene moiety

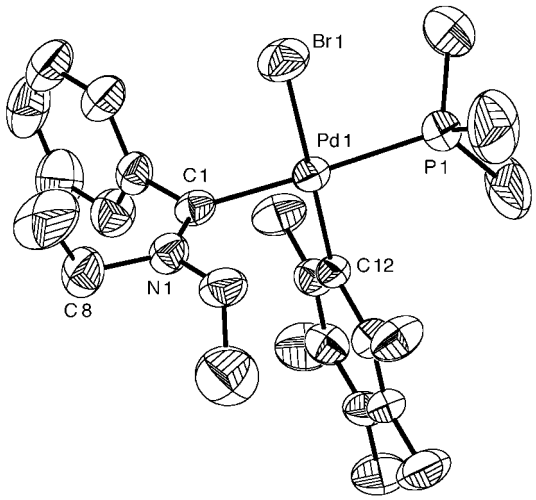


Figure 1. Molecular structure of **4a** (ORTEP plot, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Pd1-C1 2.030(5), C1-N1 1.291(6), Pd1-C12 2.016(5); Pd1-C1-N1 125.0(4), C1-N1-C8 124.3(4).

[*] Dr. A. C. Albéniz, Prof. P. Espinet, R. Manrique, A. Pérez-Mateo
Departamento de Química Inorgánica
Facultad de Ciencias, Universidad de Valladolid
Prado de la Magdalena s/n, 47005 Valladolid (Spain)
Fax: (+34) 983-42-013
E-mail: espinet@qi.uva.es

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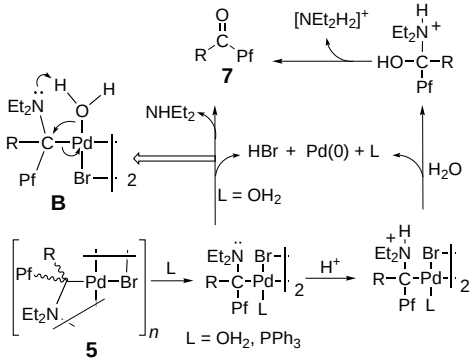
reflect the important donation of the lone pair of electrons on the amino group to the carbene carbon atom: the C=N bond length is consistent with a double bond, and the Pd1–C1 bond is a single one, very similar in length to the Pd–C12 bond. Pd complexes featuring two different monodentate auxiliary ligands (for example, [PdXRLL′]) are extremely rare, as they show a tendency to rearrange to mixtures of the symmetric complexes.

Complexes **3** and **4** decompose in $CDCl_3$ (very slowly) by migratory insertion. Kinetic experiments carried out with different starting concentrations of **4b** indicate that it disappears by a unimolecular process. The final product of the reaction is the hydrolysis product Pf(Ph)C=O (**7**). An intermediate aminoalkyl palladium complex **5** accumulates in solution during the course of the decomposition of **3**. Compound **5** is clearly observed in the ^{19}F NMR spectrum, where signals corresponding to the F_{ortho} atom of a C-bound Pf group (ca. $\delta = -135$ ppm) along with the spectral pattern of the ketone **7** slowly appear at the expense of the signals of complex **3** (Pf bound to Pd, ca. $\delta = -110$ ppm). Concomitant *trans*/*cis* isomerization of **3** is also observed, but both isomers react to give **5** and **7**.[8, 9] The exact structure of **5** could not be determined because of the impossibility of isolating it as a pure species, but it must accomplish tetracoordination from the unsaturated putative intermediate **A** by forming Br and aminocarbene double bridges. The structures of stoichiometrically related tetrapalladium oligomers ($n = 4$) are well established.[10] The hydrolysis reaction, which takes several days, possibly occurs on a de-coordinated transient species in equilibrium (**A**) by acid-catalyzed protonation of the appended amino group and external attack of adventitious water in the NMR tube (Scheme 2). Once initiated by traces of acid,

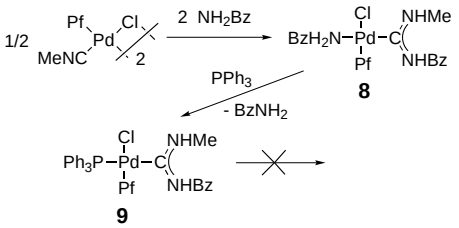


Scheme 2. Hydrolysis of palladium complexes containing a nucleophilic end group in the hydrocarbene ligand.

the hydrolysis produces HBr which further facilitates the reaction. In the case of $L = H_2O$, intramolecular hydrolysis by the more acidic coordinated water (intermediate **B**) is plausible. These proposals are supported by the following observations: 1) deliberate addition of water to a solution of **3** at the start hardly affects the rate of formation of **5**, but greatly increases its hydrolysis, 2) addition of water to an NMR solution rich in **5** results in its hydrolysis within hours, compared with days for a reference sample, 3) addition of PPh_3 to an NMR solution rich in **5** also accelerates noticeably its hydrolysis compared with a reference sample (PPh_3 should coordinate better than water, hindering the formation of **B**, while displacing and favoring the formation of decoordinated amino group). Consistently, **4b** also gives **7** (very slowly), but no inserted intermediate is observed.

No intermediate palladium carbene could be detected with the carbene ligand CPh(OMe), even at low temperatures. The migratory insertion on an unstable palladium carbene analogous to **3** apparently proceeds very fast in this case to give the benzylic derivative **6**, which then hydrolyzes to **7** and the ketal $Pf(Ph)C(OMe)_2$. The intermediate alkyl complex **A** (Scheme 1, X = OMe) is stabilized by coordination of the double bond to give **6**. Complex **6** decomposes quickly in solution at room temperature, but can be isolated as a crude yellowish solid (unpurified with some reaction by-products) by working at low temperatures. It was identified spectroscopically by NMR spectroscopy. Its ^1H NMR spectrum shows the very characteristic high-field shift for the aromatic proton involved in an η^3 Pd-bound benzylic moiety ($\delta = 5.55$ ppm).[11] We propose an *anti*-Pf stereochemistry for the C-1 allylic carbon atom on the basis of the ^{19}F NMR spectrum of **6**.[12] The observation of the ketal $Pf(Ph)C(OMe)_2$ as a solvolysis product arises from preferential reaction of **6** with methanol, which is generated as a by-product in this reaction and is more nucleophilic than water.

Diaminocarbene derivatives should be less prone to give this reaction pattern. To test this premise, the pentafluorophenyl diaminocarbene derivative [PdPfBr{C(NHMe)(NHCH$_2$Ph)}(PPh$_3$)] (**9**), which is analogous to **4b**, was synthesized (Scheme 3).[13] No change was observed in the NMR spectrum of a solution of **9** in $CDCl_3$ over 20 days at room temperature; **4b** gives **7** under the same conditions (23% decomposition after 10 days). A solution of **9** kept at 50 °C for 10 days also remains unchanged.



Scheme 3. Synthesis of palladium diaminocarbene complexes.

In summary, a migratory insertion reaction has been described for aryl carbene complexes of palladium. The reaction is intramolecular and is favored by the interaction of an electrophilic carbene carbon atom with the π-electron density of the aryl group and, as the structure of **4a** shows, both groups are appropriately oriented in the ground state. The electrophilicity of the carbene carbon atom is modulated by its substituents: $(C(NR'_2)_2) \ll (CR''(NR'_2)) < CR''(OR')$. The π-electron density on the C_{ipso} atom of the pentafluorophenyl group is lower than in a phenyl ring and the migratory insertion is expected to be slower. As a result, pentafluorophenyl monoaminocarbenes of palladium are stable enough to be characterized, but still sufficiently reactive to provide a nice picture of the migratory insertion reaction.

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Experimental Section

All manipulations were carried out by using Schlenk techniques. Complexes **1a**,[14] **1b**,[15] **2**,[16] and **8**[13] were prepared according to literature methods. All palladium carbene complexes gave satisfactory elemental analyses. Only selected spectroscopic data are included. For full experimental details see the Supporting Information.

trans-**3**: Equimolar amounts of **1a** and **2** were mixed in MeCN and stirred for 18 h at room temperature. The solvent was evaporated to dryness and the residue was extracted with $CHCl_3$. The resulting yellow solution was filtered through activated carbon, concentrated (ca. 2 mL), and Et_2O was added. The solution was cooled to $-20\,^{\circ}C$ to afford **3** as a yellow solid. Yield 58 %. *trans*-**3** is a 1.3:1 mixture of *syn* (**3**) and *anti* (**3′**) isomers in solution. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38-6.77$ (5H; Ph, **3**/**3′**), 5.23 (dq, $J = 14.4$, 7.2 Hz, 1H; C*H*H, **3′**), 5.13 (m, 1H; CH*H*, **3′**), 5.11 (q, 2H; CH_2, **3**), 3.55 (dq, $J = 14.4$, 7.2 Hz, 1H; C*H*H′, **3**/**3′**), 3.42 (dq, $J = 14.4$, 7.2 Hz, 1H; CH*H*′, **3**/**3′**), 1.56 (t, $J = 7.2$ Hz, 3H; CH_3, **3**), 1.52 (t, $J = 7.2$ Hz, 3H; CH_3, **3′**), 1.02 (t, $J = 7.2$ Hz, 3H; CH_3', **3′**), 1.01 ppm (t, $J = 7.2$ Hz, 3H; CH_3', **3**); ^{19}F NMR (282 MHz, $CDCl_3$, 253 K): $\delta = -164.0$ (m, 1F; *m*-Pf, **3′**), -163.8 (m, 1F; *m*-Pf, **3**), -162.6 (m, 1F; *m*-Pf, **3**), -162.3 (m, 1F; *m*-Pf, **3′**), -160.1 (t, 1F; *p*-Pf, **3**), -160.0 (t, 1F; *p*-Pf, **3′**), -117.9 (m, 1F; *o*-Pf, **3′**), -117.5 (m, 2F; *o*-Pf, **3**), -117.1 ppm (m, 1F; *o*-Pf, **3′**); $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$, 253 K): $\delta = 229.24$ (s; Pd–C, **3′**), 228.89 ppm (s; Pd–C, **3**).

cis-**3**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.74-7.14$ (m, 5H; Ph), 5.32 – 4.93* (2H; CH_2), 3.60* (2H; CH_2'), 1.64 (t, $J = 7.2$ Hz, 3H; CH_3), 1.09 ppm (m, 3H; CH_3'); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -165.00$ (m, 2F; *m*-Pf), -162.82 (t, 1F; *p*-Pf), -116.65 ppm (m, 2F; *o*-Pf). *Signal overlaps with signals of the *trans* isomers.

Complexes **4a** and **4b** were obtained by the addition of a stoichiometric amount of the phosphane to a solution of **3** in CH_2Cl_2. After 1 h at room temperature, the solvent was evaporated to dryness and *n*-hexane was added to afford, after cooling at $-20\,^{\circ}C$, pale orange solids.

4a: Yield 50 %. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.30-6.80$ (5H; Ph), 4.75 (q, $J = 7.3$ Hz, 2H; CH_2), 3.36 (dq, $J = 13.6$, 6.8 Hz, 1H; C*H*H′), 3.51 (dq, $J = 13.6$, 6.8 Hz, 1H; CH*H*′), 1.54 (t, $J = 6.8$ Hz, 3H; CH_3), 1.19 (t, $J = 9.6$ Hz, 9H; PCH_3), 1.08 ppm (t, $J = 6.8$ Hz, 3H; CH_3'); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -163.82$ (m, 1F; *m*-Pf), -162.89 (m, 1F; *m*-Pf), -160.80 (t, 1F; *p*-Pf), -116.51 ppm (m, 2F; *o*-Pf); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): $\delta = -17.34$ ppm (d, $^4J_{F,P} = 7.87$ Hz); $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$, 263 K): $\delta = 244.27$ ppm (d, $^2J_{C,P} = 151.3$ Hz; Pd–C).

4b: Yield 69 %. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.58-6.95$ (20H; Ph), 4.93 (q, $J = 7.0$ Hz, 2H; CH_2), 3.62 (dq, $J = 13.8$, 6.9 Hz, 1H; C*H*H′), 3.42 (dq, $J = 13.8$, 6.9 Hz, 1H; CH*H*′), 1.62 (t, $J = 6.9$ Hz, 3H; CH_3), 1.11 ppm (t, $J = 6.9$, 3H; CH_3'); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -164.63$ (m, 1F; *m*-Pf), -163.19 (m, 1F; *m*-Pf), -162.41 (t, 1F; *p*-Pf), -117.20 (m, 1F; *o*-Pf), -116.42 ppm (m, 1F; *o*-Pf); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): $\delta = 21.73$ ppm (d, $^4J_{F,P} = 7.15$ Hz); $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$, 263 K): $\delta = 241.62$ ppm (d, $^2J_{C,P} = 142.4$ Hz; Pd-C).

5: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.76-7.63$ (5H; Ph), 4.75 (q, $J = 7.2$ Hz, 2H; CH_2), 4.62 (q, $J = 7.2$ Hz, 2H; CH_2'), 1.67 (t, 3H; CH_3), 1.38 ppm (t, 3H; CH_3'); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -155.90$ (m, 2F; *m*-Pf), -142.88 (t, 1F; *p*-Pf), -134.78 ppm (m, 2F; *o*-Pf).

6: A solution of **1b** and **2** in THF was stirred at room temperature for 40 min. Compound **6** was obtained by evaporation to dryness and addition of Et_2O at $-20\,^{\circ}C$. Yield 32 %. ^1H NMR (300 MHz, $CDCl_3$, 263 K): $\delta = 8.15-7.30$ (m, 4H; Ph), 5.55 (m, 1H; *benz*-η^3-Ph), 3.51 ppm (s, 3H; OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$, 263 K): $\delta = -160.64$ (m, 2F; *m*-Pf), -150.55 (t, 1F; *p*-Pf), -135.93 (br, 1F; *o*-Pf), -127.54 ppm (br, 1F; *o*-Pf).

7: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$ (m, 2H; *o*-Ph), 7.70 (m, 1H; *p*-Ph), 7.54 ppm (m, 2H; *m*-Ph); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -160.28$ (m, 2F; *m*-Pf), -150.88 (t, 1F; *p*-Pf), -140.30 ppm (m, 2F; *o*-Pf).

$Pf(Ph)C(OMe)_2$: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (m, 2H; *m*-Ph), 7.46 (m, 1H; *p*-Ph), 7.34 (m, 2H; *o*-Ph), 3.23 ppm (6H; OCH_3); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -162.48$ (m, 2F; *m*-Pf), -155.01 (t, 1F; *p*-Pf), -139.35 ppm (m, 2F; *o*-Pf).

9: Two atropisomers were found in solution at room temperature (1.25:1 ratio). Isomer 1: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61-7.26$ (20H; Ph), 6.70 (m, 1H; *H*NCH$_2$Ph), 5.72 (m, 1H; *H*NMe), 4.30 (d, $J = 5.0$ Hz, 2H; HNC*H*$_2$Ph), 3.56 ppm (d, $J = 4.4$ Hz, 3H; HNC*H*$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -163.48$ (m, 2F; *m*-Pf), -162.36 (t, 1F; *p*-Pf), -117.40 ppm (m, 2F; *o*-Pf); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): $\delta = 21.30$ ppm. Isomer 2: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61-7.26$ (20H; Ph), 6.49 (m, 1H; *H*NMe), 5.72 (m, 1H; *H*NCH$_2$Ph), 5.36 (d, $J = 5.2$ Hz, 2H; HNC*H*$_2$Ph), 2.77 ppm (d, $J = 4.9$ Hz, 3H; HNC*H*$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -163.37$ (m, 2F; *m*-Pf), -162.29 (t, 1F; *p*-Pf), -117.77 ppm (m, 2F; *o*-Pf); $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$): $\delta = 21.69$ ppm; $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): $\delta = 198.52$ ppm (d, $^2J_{P,C} = 146.4$ Hz; Pd–C, both isomers).

X-ray structural analysis of **4a:** a yellow prism ($0.2 \times 0.12 \times 0.05$ mm) obtained by slow evaporation of a solution in CH_2Cl_2 was mounted on the tip of a glass fiber. X-ray measurements were made using a Bruker SMART CCD area-detector diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Crystal data: $C_{20}H_{24}BrF_5NPPd$, $M_r = 590.68$, monoclinic $P2(1)/c$, $a = 9.168(6)$, $b = 19.028(12)$, $c = 13.969(9)$ Å, $\alpha = \gamma = 90$, $\beta = 102.235(13)^{\circ}$, $V = 2382(3)$ Å^3, $Z = 5$, $\rho_{calcd} = 2.059$ g cm^{-3}, $F(000) = 1460$; $\mu(Mo_{K\alpha}) = 3.211$ mm^{-1}. 9864 reflections were collected ($1.84^{\circ} < \theta > 21.69^{\circ}$). Intensities were integrated and the structure was solved by direct methods. Full-matrix least-squares refinement (on F^2) based on 2921 independent reflections converged with 267 variable parameters and no restraints. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were constrained to ideal geometries and refined with fixed isotropic displacement parameters. $R1 = 0.0316$, for $F^2 > 2\sigma(F^2)$; $wR2 = 0.0749$. GOF (F^2) = 0.937. The max/min residual electron density was 0.669/ – 0.336 e Å^3. CCDC-178512 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[8] Several geometrical isomers are possible for complexes **3**. In $CDCl_3$, **3** is a mixture of *trans-anti* and *trans-syn* isomers, which correspond to a *trans* arrangement of carbene moieties along the Pd ··· Pd axis and a relative *syn* or *anti* arrangement of the diethylamino groups relative to the coordination plane. The compound first formed is tentatively assigned (the assignment might be reversed) as *trans*-**3**, which (both isomers) slowly isomerizes to the *cis* (*syn* and *anti* isomers) and eventually undergoes hydrolysis when kept in solution for several days.
[9] Decomposition data for **3** (%) after seven days in $CDCl_3$ at room temperature: *trans*-**3** (25.9), *cis*-**3** (26.9), **5** (19.5), **7** (27.7).
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[12] The ^{19}F NMR spectrum of **6** shows two broad signals for the two inequivalent F_{ortho} atoms at $\delta = -135.93$ and -127.54 ppm, which indicate there is restricted rotation of the Pf group about the C–C bond, and hence the Pf group must be located in a sterically crowded position. The chemical shifts for these signals are consistent with a Pf group bound to a carbon atom and closely influenced by the metal center, which also points to an *anti* arrangement of the group.
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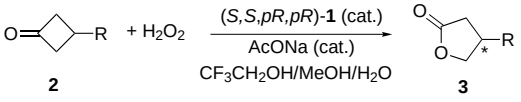
Asymmetric Baeyer – Villiger Reaction with Hydrogen Peroxide Catalyzed by a Novel Planar-Chiral Bisflavin**

Shun-Ichi Murahashi,* Satoshi Ono, and Yasushi Imada*

Metal-free organocatalytic reactions, especially enantioselective ones, have attracted increasing attention as a complement to metal-catalyzed and enzyme-catalyzed reactions.[1] Organocatalytic reactions have several advantages, for example, the availability of structural diversity of the catalysts in optically pure form and their stability under aerobic and aqueous conditions, and the catalysts are often more stable than enzymes.

In 1989 we demonstrated that 5-alkylated flavins can be used as organocatalysts for oxidations based on the precise kinetic study on the recycling step of flavoenzymes.[2] Thus, the flavin-catalyzed biomimetic oxidations of sulfides and amines with hydrogen peroxide occurs highly efficiently to give the corresponding sulfoxides and nitrones, respectively. A novel method for enantioselective oxidation with organocatalysts can be developed if one can design suitable chiral flavin catalysts. We report herein that a flavin-catalyzed asymmetric Baeyer – Villiger reaction of cyclobutanones can be performed with up to 74% *ee* [Eq. (1)].



2 3 (1)

Much attention has been focused on the asymmetric Baeyer – Villiger reaction, because this is the direct route to obtain optically active lactones from cyclic ketones.[3] Transition-metal catalysts in the asymmetric Baeyer – Villiger reactions of cyclic ketones have been studied extensively: copper with a combination of molecular oxygen and aldehyde,[4] platinum with H_2O_2,[5] titanium with *tert*-butyl hydroperoxide,[6] cobalt with urea · H_2O_2,[7] and magnesium[8] and aluminum[9] with cumene hydroperoxide; selectivities of up to 77% *ee* were observed. Enantioselective Baeyer – Villiger reactions have been also performed by using microbial whole cell cultures[10] as well as purified enzymes[11] with stoichiometric amounts of NADPH as a cofactor.

Catalytic Baeyer – Villiger reactions have been shown to occur in the presence of flavin catalyst,[12] which is similar to our catalyst.[2] Therefore, we wanted to design chiral flavin catalysts for enantioselective oxidation reactions. Planar-chiral flavins have been prepared and used for the asymmetric oxidation of sulfides.[13, 14] However, the synthesis of the catalysts is very tedious because of the need for optical resolution with preparative HPLC. To prepare chiral flavin catalysts simply without optical resolution, we designed planar-chiral C_2-symmetric bisflavinium perchlorate **1** (Scheme 1), in which each of the flavin moieties blocks one plane of the other flavin moiety. The bisflavin catalyst **1** was prepared in three steps without resolution. Treatment of (*S*,*S*)-1,2-diaminocyclohexane (**4**) with *o*-fluoronitrobenzene (**5**) gave (*S*,*S*)-1,2-bis[(2-nitrophenyl)amino]cyclohexane (**6**) in 77% yield. Catalytic hydrogenation of **6** over palladium on charcoal and subsequent treatment with 3-methylalloxan[15] gave C_2-symmetric bisflavin **7** in 90% yield [m.p. 223.5 – 224.6 °C; $[\alpha]_D^{25} = +401$ ($c = 0.20$ in $CHCl_3$)] in diastereomerically pure form. The stereochemistry was determined by difference NOE experiments of **7**;[16] irradiation of the H^b proton ($\delta = 8.38$ ppm) caused a 20% enhancement of the signal for H^a ($\delta = 7.30$ ppm) and caused no detectable enhancement of other signals on the cyclohexane ring, from

[*] Prof. Dr. S.-I. Murahashi
Department of Applied Chemistry, Faculty of Engineering
Okayama University of Science
1-1, Ridaicho, Okayama 700-0005 (Japan)
Fax: (+81) 86-256-9513
E-mail: murahashi@high.ous.ac.jp
Prof. Dr. Y. Imada, S. Ono
Department of Chemistry, Graduate School of Engineering Science
Osaka University
1-3, Machikaneyama, Toyonaka, Osaka 560-8531 (Japan)
Fax: (+81) 6-6850-6224
E-mail: imada@chem.es.osaka-u.ac.jp
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