The Novel Insertion of Imines into a Late-Metal−Carbon σ-Bond: Developing a Palladium-Mediated Route to Polypeptides

Rania D. Dghaym, Karin J. Yaccato, and Bruce A. Arndtsen*

*Department of Chemistry, McGill University, 801 Sherbrooke Street West,
Montreal, Quebec H3A 2K6, Canada*

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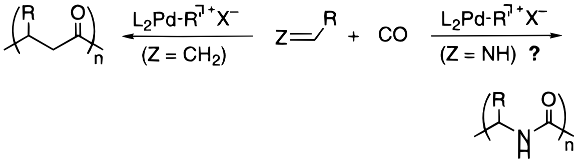
*Summary: The palladium complex (bipy)Pd(CH_3)$NCCH_3^+OTf^-$ (**2**; bipy = 2,2′-bipyridyl, OTf = OSO_2CF_3) has been found to undergo the novel sequential insertion of carbon monoxide and imine into the metal−carbon bond in a manner directly analogous to that observed in olefin/CO alternating copolymerizations. The structure of the insertion products, (bipy)$\overline{\text{Pd[C(Tol)HNRCO}}CH_3$]$^+OTf^-$, suggests that the unique combination of CO insertion, amide bond formation, carbonyl oxygen chelation, and resonance stabilization of the chelate ring provides the stabilization required for imine insertion to occur.*

The insertion polymerization of unsaturated substrates is among the most thoroughly investigated areas of metal catalysis.[1] Beginning with the discovery of Ziegler/Natta polymerization of ethylene and propylene, this field has expanded to provide important synthetic routes to a variety of poly(α-olefins) by utilizing electropositive metal catalysts.[2] More recent studies have shown that low-valent transition metals (e.g. Ni(II) or Pd(II)) can allow the incorporation of functionality into insertion polymerizations. Examples of the latter include polymerization of functionalized olefins[3] or the alternating copolymerization of olefins with CO.[4]

Despite this high degree of activity, insertion polymerizations have been studied almost exclusively with olefins as monomers. To our knowledge, the isoelectronic imines have not been reported to undergo analogous polymerizations. In fact, the single insertion of an imine into a well-defined metal−carbon σ-bond has only been reported with electropositive metal complexes, and this occurs to generate a robust metal−nitrogen bond which is inert toward subsequent insertions.[5−7] The lack of examples of imine insertions is surprising when one considers the potential utility of the polymerization products. Specifically, the extension of the olefin/CO copolymerizations to imine analogues would generate the poly-α-amide backbone of a polypeptide, providing a very attractive route to such materials (eq 1).[8]



(1)

The compatibility of the Pd(II) olefin/CO copolymerization catalysts toward heteroatoms[3,4] has stimulated our studies to determine if these systems would allow similar insertion reactions with imines. We report here that the insertion of imine into a late-metal−acyl bond can occur in a manner directly analogous to that of olefins, suggesting the viability of imines as insertion monomers. The factors that favor imine insertion, and structure of the insertion products, are described below.

The addition of Tol(H)C=NCH_3 (**1a**; 0.05 mmol) (Tol = p−$C_6H_4CH_3$) to (bipy)Pd(CH_3)$NCMe^+OTf^-$ (**2**;[9] 0.05 mmol) (bipy = 2,2′-bipyridyl, OTf = OSO_2CF_3) in CD_2Cl_2 (0.5 mL) results in the immediate liberation of acetonitrile and generation of the η^1-coordinated imine adduct (bipy)Pd(CH_3)(CH_3N=C(H)Tol)$^+$OTf$^-$ (**3a**) (Scheme 1). **3a** can be prepared independently by reaction of **1a** with (bipy)Pd(CH_3)Cl (**4**) and silver triflate in CD_2Cl_2 and isolated in >90% yield by precipitation with diethyl ether.[10] The spectroscopic data for **3a** show a significant shift in the resonances for the imine moiety upon coordination (^{1}H NMR: δ 8.24 (s, C*H*(Tol)) to δ 8.59; ^{13}C NMR δ 161.9 (*C*H(Tol)) to δ 171.6; $\nu_{C=N}$ 1652.3 to 1606.5 cm^{-1}), consistent with η^1 binding of **1a** to the Pd center.[11,12] Complexes **3b−d** can be prepared and isolated in a similar manner.

[⊗] Abstract published in *Advance ACS Abstracts*, December 15, 1997.

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[4] (a) Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663. (b) Sen, A. *Acc. Chem. Res.* **1993**, *26*, 303. (c) Rix, F. C.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **1996**, *118*, 4746 and references therein.

[5] Obora, Y.; Ohta, T.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1997**, *119*, 3745.

[6] Products consistent with imine insertion into a M−COR bond have been suggested in several systems; however, the imine insertion step into the metal−acyl is only postulated: (a) Alper, H.; Amaratunga, S. *J. Org. Chem.* **1982**, *47*, 3595. (b) Reduto, A. C.; Hegedus, L. S. *Organometallics* **1995**, *14*, 1586. (c) Muller, F.; van Koten, G.; Vrieze, K.; Heijdenrijk, D. *Organometallics* **1989**, *8*, 33.

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[8] Polypeptide syntheses: Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 113.

[9] Rülke, R. E.; Delis, J. G. P.; Groot, A. M.; Elsevier: C. J.; van Leeuwen, P. W. N. M.; Vrieze, K.; Goubitz, K.; Schenk, H. *J. Organomet. Chem.* **1996**, *422*, 109.

[10] The spectroscopic and elemental analysis data for **3a−d**, **5a−d**, and **6a−c** are provided in the Supporting Information.

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Table 1. Imine Binding Constants for 3a−d

R	K_{eq}[a]	ΔH (kcal/mol)[b]	ΔS (cal/mol)[b]
CH_3	9.3×10^{-6}	8.6 (±0.5)	6.0 (±2)
$PhCH_2$	7.1×10^{-5}	8.7 (±0.9)	10 (±3)
Ph	2.9×10^{-3}	6.6 (±0.3)	10 (±1)
tBu	1.4×10^{-3}	6.1 (±0.2)	7.2 (±0.5)

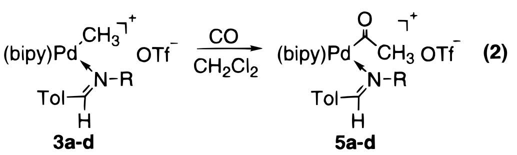
[a] Measured by ^{1}H NMR at 30 °C for **3a−d** + $CD_3CN \leftrightarrow$ **2** + **1a−d**. [b] From plot of K_{eq} vs $1/T$ from 25 to 75 °C.

In contrast to olefins, which have been shown to undergo rapid insertion into Pd−CH_3 bonds at ambient temperatures,[13] complexes **3a−d** show no evidence for imine insertion, even upon heating at 130 °C for >48 h in the presence of excess imine. Since insertion processes often involve the generation of a π-bonded complex,[7] the η^1 binding of the imines in **3a−d** could potentially hinder their insertion. However, dissolution of **3a−d** (0.05 mmol) in CD_3CN (1.0 mL) results in the immediate formation of an equilibrium mixture of the imine complex and the solvated species (bipy)PdCH_3($NCCD_3$)$^+$ (Table 1), demonstrating that imine η^1 binding is reversible at ambient temperatures.

Examination of simple bond enthalpies may provide an explanation for this difference between olefin and imine insertions with $L_2Pd(CH_3)^+ X^-$ and suggests a possible method to enhance the insertion propensity of imines. Typical imine insertion reactions with electropositive metal complexes occur with a regiochemistry to generate a strong M−N bond.[5] However, the analogous reaction with **3a−d** would result in the formation of a weaker late-transition-metal−nitrogen σ-bond,[14] implying there would be less of a driving force for this process. This could result in a reversal of imine insertion regiochemistry with **3a−d** (i.e. M−C + C=N → M−C−N−C). However, simple bond energetics predict that imine insertion with the latter regiochemistry is actually *endothermic* (ca. +1 kcal/mol).[15,16] Thus, unlike olefins,[17] imine insertion thermodynamics can be significantly affected by the nature of the metal center and in general are predicted to be less favored with late-metal complexes. Interestingly, the above calculations also imply that the insertion polymerization of imines would be an energetically unfavorable process.

The thermodynamics of imine insertion with late-metal complexes, as well as imine polymerization, are dramatically altered when carbon monoxide is also inserted into the metal−carbon bond. In this case, imine insertion could occur into a metal-acyl with a regiochemistry to generate a strong amide bond (M−COR + C=N → M−C−N−COR), with the latter providing a significant driving force for the reaction (ca. −17 kcal/mol).[15] Since this alternating insertion of CO and imine would also result in the generation of a peptide backbone (eq 1), the viability of these insertion steps is explored below.

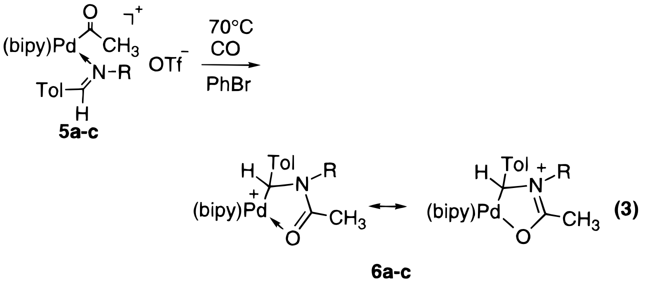
Addition of 1 atm of CO to **3a−d** in CD_2Cl_2 results in the quantitative formation of the CO insertion products (bipy)Pd($COCH_3$)(RN=C(Tol)H)$^+$OTf$^-$ (**5a−d**; eq 2).



(2)

These compounds show spectral features similar to those of previously prepared palladium−acyl complexes,[4c,10] including the presence of *COCH$_3$* in the ^{1}H NMR (δ 2.10−2.34 (s)), ^{13}C NMR (δ 228.5−230.0), and IR (ν_{CO} 1680−1694 cm^{-1}). The imine ligands in **5a−d** have ^{1}H and ^{13}C NMR resonances only slightly shifted from those in **3a−d**, suggesting a similar η^1-bonding mode.

As with the Pd−methyl complexes, the imine acyl complexes **5a−d** do not undergo imine insertion at room temperature. However, warming of complex **5a** to 70 °C in PhBr or CH_3CN for 6 h results in the formation of the new palladium complex **6a**. This compound has been characterized as the novel product of imine insertion: (bipy)Pd[C(Tol)HN(CH_3)COCH$_3$]$^+$OTf$^-$ (eq 3).



(3)

Monitoring the ^{1}H NMR (d_5-PhBr) of **5a** at 95 °C shows the clean first-order formation of **6a**, with new resonances for NCH_3 (δ 2.83 (s)) and $COCH_3$ (δ 2.30 (s)), and the former imine hydrogen shifted upfield to δ 5.04 (s). The latter is consistent with the reduction of the C=N double bond, which is confirmed by the upfield shift in the ^{13}C NMR of the imine carbon from δ 172.3 to 69.2. Both **5b** and **5c** show similar behavior upon heating to 70 °C. The more sterically encumbered imine complex **5d** does not undergo insertion under these conditions and decomposes at temperatures above 120 °C.

The formulation of **6a−c** as imine insertion products was confirmed by X-ray structural determination of complex **6b**.[18] This shows that insertion has occurred with the predicted regiochemistry, in which a pal-

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(11) Knight, D. A.; Dewey, M. A.; Stark, G. A.; Bennet, B. K.; Arif, A. M.; Gladysz, B. K. *Organometallics* **1993**, *12*, 4523.

(12) Mononuclear complexes with side-on π-bound imines have only been reported with strong back-bonding early metals: (a) Durfee, L. D.; Hill, J. E.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1990**, *9*, 75. (b) Buchwald, S. L.; Watson, R. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.

(13) Killian, C. M.; Tempel, D. J.; Johnson, L. K.; Brookhart, M. *J. Am. Chem. Soc.* **1996**, *118*, 11664.

(14) Bryndza, H. E.; Tam, W. *Chem. Rev. (Washington, D.C.)* **1988**, *88*, 1163.

(15) Calculated from standard C=X and C−X bond enthalpies.[16a] These calculations do not take into account any potential differences in M−C bond energies or the effect of C=X substituents.[16b]

(16) (a) Sandorfy, C. *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; Wiley: New York, 1970; p 1. (b) Wiberg, K. B.; Nakaji, D. Y.; Morgan, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 3527.

(17) Insertion of olefins into a M−C bond would generate an analogous M−C bond (M−C + C=C → M−C−C−C) and is exothermic (ca. −20 kcal/mol).[15]

(18) Crystallographic data for_**6b**.PhBr: $C_{34}H_{31}BrF_3N_3O_4PdS$, mw = 820.99, triclinic, space group $\bar{P}1$, pale yellow plates, $a = 13.146(3)$ Å, $b = 13.827(5)$ Å, $c = 11.022(3)$ Å, $\alpha = 67.390(10)°$, $\beta = 84.130(10)°$, $\gamma = 68.660(10)°$, $V = 1721.0(9)$ Å,^{3} $Z = 2$, $D_c = 1.584$ g cm^{-3}, $\mu = 1.314$ mm^{-1}, R (R_w) = 0.0717 (0.1330), GOF = 0.991, $T = 293$ K. Full details of the crystallographic analysis of **6b** are described in the Supporting Information.

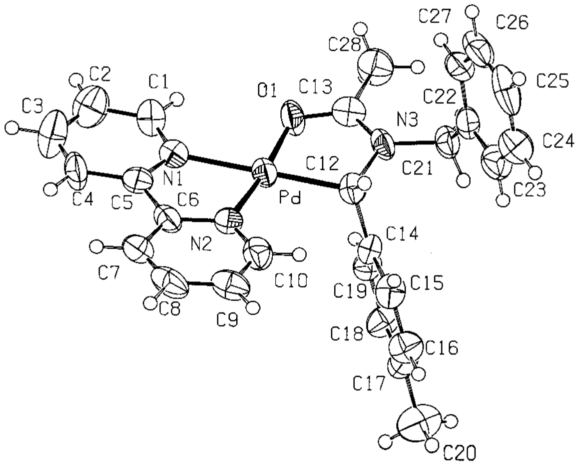
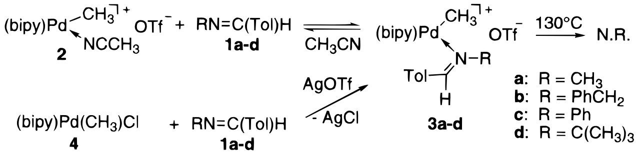


Figure 1. Molecular structure of **6b**. Selected bond lengths (Å) are as follows: Pd–O(1), 2.008(6); Pd–C(12), 2.022(8); O(1)–C(13), 1.265(10); N(3)–C(13), 1.328(11); N(3)–C(12), 1.498(10).

Scheme 1



ladium–carbon and amide bond are formed (Figure 1). The palladium center possesses square-planar geometry, with the amide carbonyl oxygen occupying the fourth coordination site. This chelation of the carbonyl group is directly analogous to that observed in palladium catalyzed CO/olefin copolymerization intermediates: $L_2\overline{\mathrm{Pd}[\mathrm{CR_2CR_2C}}\mathrm{OCH_3}]^+$.[4,19]

To our knowledge, this insertion of an imine into a late-metal–carbon σ-bond to generate a stable product has no precedent in the literature, although this process has been postulated in several instances, such as the insertion of imine into a iron-ketene complex.[6b] In addition, there are very few examples of imine insertions into a M–C bond to generate a new M–C σ-bond.[6] The latter is a feature of significant importance for utilizing imines as polymerization monomers, as it opens the possibility to multiple insertion processes. The fact that this reaction occurs only with the prior formation of the palladium-acyl ligand implies that amide bond formation is indeed an important feature for imine insertion (vide supra). The X-ray structure of **6b** supports this conclusion. This shows a planar amide nitrogen (sum of bond angles 359.9°), and a C(13)–N(1) bond length (1.328(11) Å) that is significantly shorter than the typical C–N single bond (1.47 Å),[15] indicating a high degree of π-conjugation in the C–N bond. This amide bond also stipulates the novel regiochemistry for insertion, as it requires the imine nitrogen to be bound to the acyl fragment. The chelation of the carbonyl oxygen in **6b** (Pd–O(1) = 2.008(6) Å) further facilitates the generation of a stable insertion product, through both occupying the vacant coordination site on Pd generated upon insertion and allowing for resonance stabilization of the positive charge between Pd and amide nitrogen (eq 3). In addition to these thermodynamic considerations, the inactivity of palladium–methyl complexes **3a–c** toward any reaction suggests the acyl ligand also significantly lowers the kinetic barrier toward imine insertion, though the nature of this stabilizing affect (i.e. a mechanism that involves π-conjugation during insertion or a direct nucleophilic attack of imine on the acyl carbonyl) is still under investigation. Note that none of these factors are available to imine insertions into simple metal–alkyl bonds, such as **3a–d**.

In conclusion, the insertion of an imine into a late-metal–carbon bond has been observed to be uniquely facilitated by the presence of an acyl ligand in **5a–c**. This reaction occurs upon prior insertion of CO into a palladium–carbon bond and results in the generation of a new Pd–C bond, suggesting the viability of a CO/imine copolymerization process. Indeed, the structures of the products of sequential CO and imine insertion (**6a–c**) are directly analogous to those obtained from CO/olefin copolymerization systems. Preliminary attempts to insert a subsequent CO and imine in **6a–c**, the putative next step in the copolymerization process, have not been successful, implying a greater degree of stabilization of metallacycles **6a–c** than those generated in CO and olefin copolymerizations. Nevertheless, similar phenomena have been noted with certain olefin/CO insertion intermediates and found to be affected by the nature of the olefin and ancillary ligands.[19] Efforts directed toward modifying these catalyst and imine properties to extend the imine/CO insertion chemistry into a poly-α-amide synthesis are in progress.

Acknowledgment. We thank Dr. Anne-Marie Lebuis for determination of the crystal structure of **6b** and ESTAC and NSERC for their financial support. R.D.D. thanks McGill University for the McFee Memorial Fellowship.

Supporting Information Available: Text giving synthesis details and characterization data for **3a–d**, **5a–d**, and **6a–c**, tables giving X-ray structural information for **6b**, and figures giving ^{1}H NMR spectra for **3a–d**, a plot of $-\ln(K_{eq})$ vs $1/T$ for **3a–d**, and kinetic plots for **6a–c** (26 pages). Ordering information is given on any current masthead page.

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