Enabling Ligand Screening for Palladium-Catalysed Enantioselective Aza-Michael Addition Reactions

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Abstract: The bis(trifluoromethanesulfonate)palladium(II) dihydrate complex, Pd(OTf)2·2H2O (1), is an active palladium(II) precursor for the generation of dicationic palladium(II) catalysts. Parallel ligand screening is enabled for the first time, and twenty-four chiral ligands were evaluated for the asymmetric aza-Michael addition of aromatic amines to α,β-unsaturated N-alkenoylimides and carbamates. Enantioselectivities of >99% can be obtained. Catalytic precursors generated from 1 using the new protocol have been identified.

Keywords: asymmetric catalysis; conjugate addition; hydroamination; ligand effects; palladium

Introduction

Enantioselectivity of a catalytic process is dependent on the attainment of a kinetically favourable transition state, which is often highly sensitive to stereoelectronic effects exerted by the ligand and substrate(s). Invariably, judicious modification of a ligand’s structure is necessary to accommodate substrate changes. The problem is alleviated to a certain extent by the increasing commercial availability of chiral ligands, as well as the advent of easy-to-synthesise modular ligands, driven and complemented by advances in high-throughput experimentation techniques and laboratory automation.[1] Ideally, a catalyst is prepared in situ by mixing a metal precursor with the requisite ligand prior to the introduction of substrates. However, this is only feasible if the system does not generate competing catalytic species that can interfere with the intended reaction pathway.

Previously, we demonstrated that [R-(BINAP)Pd-(solvate)]2+[TIO]+ (I) catalyses the addition of aromatic amines to α,β-unsaturated N-oxazolidinones (2), carbamates (3) and imides (4) with excellent yields and enantioselectivities (Scheme 1).

Dicationic palladium complexes are generally prepared by halide abstraction from the corresponding ligated palladium(II) dihalides using silver salts.[6] Occasionally, the halide abstraction is performed in situ,[7] but this still requires the preparation of (diphosphine)PdX2, and the presence of silver cation in the reaction mixture is not always desirable. Most importantly, the introduction of different ligands is an expensive and time-consuming process. As the aza-Michael reactions are highly sensitive to the steric and electronic structures of the substrates, we wanted to develop a method for ligand screening that will facilitate the identification of more active and/or selective catalysts. Herein, we describe a method of generating these catalysts in situ, and subsequent ligand screening in these aza-Michael addition reactions.

Results and Discussion

Preliminary examination of Pd precursors for the addition of aniline to butenoyl-N-imide 4a was conducted us-

Scheme 1. Asymmetric aza-Michael reactions catalysed by palladium complex 1.
ing the ligand (R)-BINAP (Table 1). Unsurprisingly, none of the common palladium(0) or palladium(II) complexes containing strongly coordinating anionic ligands was found to be active under these conditions (entries 1–5). Interestingly, while palladium(II) acetate initiated some product formation, palladium(II) trifluoroacetate was completely inactive (entries 6 and 7). Ultimately, bis(trifluoromethanesulfonato)palladium(II) provided a result comparable to that obtained with complex 1, and the system appeared to be insensitive to the M:L ratio (entries 8–10).

The additions of the aromatic amines to substrates 3 and 4 were subsequently re-examined and the results were compared to that obtained previously with the isolated complex (Table 2). Indeed, the reaction outcomes proved to be largely similar. In most cases, ee enhancement was obtained with the new catalyst system; in two cases, optically pure products can be attained (entries 2 and 5).

These results demonstrate that Pd(OTf)2·2H2O can be used to generate catalytically active dicationic palladium(II) triflate complexes in situ without involving extraneous reagents, thus enabling parallel ligands screening. Subsequently, twenty-four commercially available chiral ligands were evaluated in parallel, for the addition of anilines to the Michael acceptor 4a (Table 2). The results show that the highest product yields are generally afforded by diphosphine ligands. Also, those with biaryl-derived chirality are by far the most selective: Among these, five ligands gave enantioselectivity of ≥ 90% (BINAP, Tol-BINAP, C3-Tunephos, Difluorphos and CTH-Phos). Remarkably, the reaction is fairly insensitive to electronic effects of these biaryl ligands.

Other C2-symmetric diphosphine ligands are less selective (DIOP, Phanephos). The Solvias family of diphosphines also offered low enantioselectivities: Josi-
phos and Walphos induced the highest conversions. One of the Walphos ligands (W002) offered opposite stereo-control (R), suggesting a possible synergistic effect between the elements of chirality. Use of the aminodiphosphines was less successful; Taniaphos led to lower product yield, while Mandyphos ligands gave the lowest yields with a complete loss of selectivity. BOX and BINOL ligands, previously shown to be effective in Lewis acid-catalysed processes, are incompatible with cationic palladium in this instance, showing low turnover with little/no selectivity.

A solution of Pd(OTf)$_2$·2H$_2$O and BINAP in dichloromethane was found to contain two catalytic precursors [Eq. (1)], the expected mono-ligated bis-aqua complex 5 ($\delta_P = +34$ ppm) with an associated observed molecular ion at $m/z = 877$ [corresponding to a molecular composition of [Pd(BINAP)(OTf)]$^+$.], and a novel bis-ligated complex 6 ($\delta_P = +18$ ppm), identifiable by a characteristic mass ion at $m/z = 1499$ [[Pd(BINAP)$_2$(OTf)]$^+$.].

$$\begin{align*}
\text{Pd(OTf)$_2$·2H}_2\text{O} + \text{BINAP} &\rightarrow \text{Pd(OTf)$_2$·2H}_2\text{O} + \text{BINAP} \\
& \rightarrow \text{[Pd(BINAP)(OTf)]}^+ + \text{[Pd(BINAP)$_2$(OTf)]}^+
\end{align*}$$

The formation of the complexes is dependent on the reaction conditions – complex 5 can be isolated by performing the reaction in the presence of a small amount of acetonitrile. Conversely, complex 6 may be obtained...
The geometry at the palladium centre is distorted square planar with a marked tetrahedral twist, [Pd(P(1),P(2)) and [Pd(O(1),O(2))] being inclined by ca. 16° (the twists for the two independent dications in NATTEH are ca. 8° and 18°). With the two trans ligands being identical [i.e., both water, Pd−O(1) 2.141(3) and Pd−O(2) 2.138(3) Å], the Pd−P binding of the binap ligand is symmetric [Pd−P(1) 2.2376(11), Pd−P(2) 2.2367(11) Å]; the bite angle is 91.39(4)°. By contrast, in each of the two independent dications in NATTEH the bonding is more asymmetric with Pd−P distances of 2.183(3) and 2.256(3) Å and Pd−O bond lengths of 2.18(1) and 2.26(1) Å for dication A, whilst for dication B the Pd−P distances are 2.177(3) and 2.241(3) Å with Pd−O bond lengths of 2.18(1) and 2.24(1) Å.

The single crystal X-ray analysis of 6 revealed a chiral structure (the absolute structure was determined unambiguously from the X-ray data; see Experimental Section) with two R-BINAP ligands coordinated to a distorted square planar palladium centre (Figure 3), the two triflate counterions being non-coordinating. The dication has molecular C_2 symmetry about an axis that passes through the metal centre and bisects the naphthalene-naphthalene bond in each of the diphosphine ligands. Interestingly, the Pd−P coordination distances for the two BINAP ligands are noticeably different (Table 2); whereas the P(1)/P(2) ligand coordinates symmetrically [Pd−P(1) 2.4271(13), Pd−P(2) 2.4352(14) Å], the coordination of the P(3)/P(4) ligand is distinctly asymmetric with one bond shorter and one longer than those seen for the P(1)/P(2) ligand [Pd−P(3) 2.4043(14), Pd−P(4) 2.4678(13) Å]. It is not immediately apparent why this should be the case. The associated P−P−P bite angles for the two chelating BINAP ligands are 86.43(5) and 85.99(4)° for the P(1)/P(2) and P(3)/P(4) ligands, respectively. There is a noticeable tetrahedral twist in the metal coordination plane, the [Pd,P(1),P(2)] and [Pd,P(3),P(4)] planes being inclined by ca. 13°.

Finally, in the last part of the present study, the catalytic activity of complexes 5 and 6 were assessed for the ad-
dation of aniline to 4a. Rather surprisingly, identical results were obtained – complex 5 gave 88% yield, 89% ee, whilst complex 6 afforded the product in 87% yield and 88% ee. Given that these results are similar to that obtained with complex 1, this observation suggests that complex 6 undergoes dissociation of one of the BINAP ligands, to generate the catalytically active moniligated complex 5. This is supported by the X-ray crystal data, which suggest weaker binding of one of the BINAP ligands in complex 6.

**Conclusion**

In summary, we have demonstrated that Pd(OTf)$_2$·2 H$_2$O can be used as a precursor in the rapid constitution of asymmetric hydroamination catalysts. Hence, identification of enantioselective ligands may be accomplished by parallel screening. In this work, important structural aspects for high enantioselectivity were elucidated for the aza-Michael addition of aromatic amines to N-imide, and different catalytic precursors were isolated and identified.

**Experimental Section**

**Typical Catalytic Reaction**

In a glove box, Radley's reaction tubes were charged with Pd(OTf)$_2$·2 H$_2$O (6 mg), an appropriate amount of the corresponding ligand and a magnetic stirrer. Each tube was then fitted with a PTFE screw cap with integrated gas inlet valve ports. In a glove box, Radley F%- vs reaction tubes were charged with aniline to 4a.

**X-Ray Crystallographic Study**

Crystal data for [C$_{6}$H$_4$P$_2$Pd](CF$_3$SO$_3$)$_2$·0.5 CH$_3$Cl$_2$, M = 1105.67, triclinic, P1 (no. 2), a = 11.2080(8), b = 13.4496(12), c = 16.6057(12) Å, $\alpha$ = 98.7877(7), $\beta$ = 105.4866(6), $\gamma$ = 98.9467(6)°, V = 2331.3(3) Å$^3$, Z = 2, $D_c$ = 1.575 g·cm$^{-3}$, $\mu$(Mo-K$\alpha$) = 0.690 mm$^{-1}$, $T$ = 173 K, yellow plate-like needles, Oxford Diffraction Xcalibur 3 diffractometer; 15356 independent measured reflections, $F^2$ refinement, $R_1$ = 0.101, $\omega R_2$ = 0.266, 13562 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 66°]. 625 parameters. CCDC 266252.

**Crystal data for 6:** [C$_{6}$H$_4$P$_2$Pd](CF$_3$SO$_3$)$_2$·0.5 CH$_3$Cl$_2$, M = 1729.34, orthorhombic, P2$_2$2$_1$2 (no. 18), a = 19.7973(5), b = 30.2266(8), c = 13.3181(3) Å, V = 7969.6(3) Å$^3$, Z = 4, $D_c$ = 1.441 g·cm$^{-3}$, $\mu$(Mo-K$\alpha$) = 0.470 mm$^{-1}$, $T$ = 173 K, yellow block-like needles, Oxford Diffraction Xcalibur 3 diffractometer; 27409 independent measured reflections, $F^2$ refinement, $R_1$ = 0.079, $\omega R_2$ = 0.134, 15615 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$], 1061 parameters. The absolute structure of 6 was determined by a combination of R-factor tests [$R_1^\prime$ = 0.0785, $R_2^\prime$ = 0.0811] and by use of the Flack parameter $x^r = +0.02(2)$, $x = +0.98(2)$. CCDC 286581.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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**References and Notes**


[8] As far as we are aware, Pd(OTf)$_2$·2 H$_2$O has only been directly employed once before in an asymmetric aldol process, but yield and ee were very low: A. Yanagisawa, *Adv. Synth. Catal.* 2006, 348, 587 – 592. © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim asc.wiley-vch.de

[9] Addition to N-Boc carbamate esters in the present study were conducted in a lower amine:3 ratio (1:1.1) than that employed previously (1:1.5), which could account for the lower yields. The limited solubility of Pd(OTf)$_2$ in toluene could also be a contributing factor.

