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Development of palladium catalysts for asymmetric hydroamination reactions*

King Kuok (Mimi) Hii

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, UK

Abstract: Our development of dicationic palladium(II) complexes for asymmetric hydroamination reactions, particularly the aza-Michael addition, is reviewed.

Keywords: asymmetric catalysis; hydroamination; palladium; amines; alkenes.

INTRODUCTION

The addition of N–H bonds to alkenes and alkynes (hydroamination reaction) is inherently prohibited by a large activation energy barrier. With prochiral alkenes, the reaction poses further challenges in regio- and stereoselectivity. The presence of certain electron-withdrawing substituents (e.g., CO_2R, CN) could activate the alkene, making it susceptible to nucleophilic attack at the β-position. Sometimes known as aza-Michael additions, these reactions may occur in the absence of catalysts. Nevertheless, they are mostly inert under ambient conditions, especially with highly substituted alkene and/or non-nucleophilic amine substrates.

As it is 100 % atom-economical and utilizes readily available and low-cost feedstocks, the hydroamination reaction is an extremely attractive process for the production of amines, given the prevalence of these compounds in practically every sector of the chemical industry. Because of this, the development of hydroamination catalysts has always been an important area of research. Recently, it has witnessed a considerable resurgence of interest, stimulated by important discoveries of several highly efficient and selective catalysts. In the last 5 years alone, it has been the subject of no less than 10 reviews [1] and numerous patent applications.

To date, the most active hydroamination catalysts are those derived from the early d- and f-block elements. Mostly applied to the intramolecular cyclization of aminoalkenes, these catalysts are capable of very high turnovers. Unfortunately, the oxophilicity of these compounds limits their applicability for large-scale synthesis—reactions are invariably conducted under a rigorously dry and inert atmosphere, employing special purified reagents and solvents. More crucially, their synthetic utility is also restricted, as certain functional groups are often not tolerated, e.g., acids, esters, and alcohols. In terms of asymmetric catalysis, enantioselectivities of ≥90 % have yet to be recorded, and no intermolecular examples are known.

In comparison, late transition-metal complexes tend to be catalytically less active, especially for the addition to unactivated olefins. However, they are generally more robust to air and moisture, and display better tolerance to functional groups. As asymmetric catalysts, they are also much more selective. The first landmark example was provided in 1997 by the group of Antonio Togni, who described

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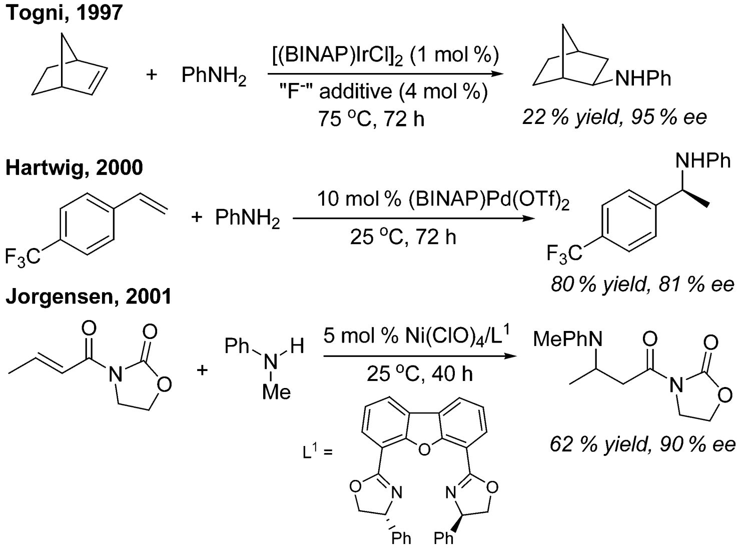
the use of an iridium–fluoride system to catalyze the addition of aniline to norbornene. Although an impressive ee of 95 % was achieved, the catalytic turnover was extremely (s)low, even after 3 days at 75 °C (Scheme 1) [2]. A second important breakthrough was reported by Kawatsura and Hartwig in 2000, where the enantioselective addition of aniline to vinylarenes was effected in the presence of $[(BINAP)Pd(OTf)_2]$ with ee's of up to 81 % [3]. Notably, these reactions required 3 days to afford a good yield, even though 10 mol % of the catalyst was used. A year later, Jørgenson et al. described the addition of secondary aromatic amines to α,β-unsaturated oxazolidinones with 90 % ee, catalyzed by a nickel perchlorate/bis-oxazolidine catalyst [4]. Once again, the reaction is very slow, even though the alkene substrate is fairly activated (this may be classified as an aza-Michael addition).



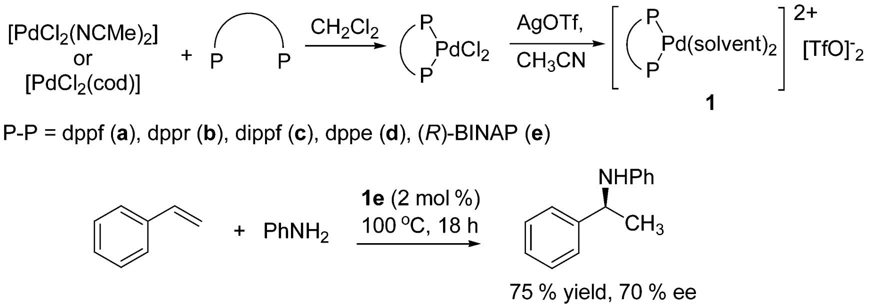
Scheme 1 Asymmetric hydroamination reactions catalyzed by late transition-metal complexes (prior to 2001).

Prior to our investigations, these were the only asymmetric reactions known to be catalyzed by late transition metals. This paper will describe our research efforts in this area since 2001, and important advances that have guided us in our quest.

RESULTS AND DISCUSSION

Our aim is to develop robust hydroamination catalysts that can be employed in air at low catalyst loading, yet deliver high turnovers and selectivity. Postulating that an electrophilic metal center could provide a Lewis acidic site for the activation alkenes and/or amines, the catalytic activity of a class of dicationic (diphosphine)palladium complexes **1** was examined. The catalysts were prepared by halide abstraction from dichloro-complexes, employing silver triflate in acetonitrile (Scheme 2). Left in air, the coordinating solvent exchanges readily with atmospheric moisture, to furnish $[(diphosphine)Pd(OH_2)(NCMe)]^{2+}[TfO]^-_2$ as crystalline solids [5].

These complexes catalyzed the regioselective addition of aniline to styrene at temperatures above 80 °C. The five complexes displayed different turnovers, thus revealing important correlation of the ligand's structure with catalytic activity. With the most active catalyst **1a**, catalytic loading may be reduced to 0.25 mol % without any depreciation in yield or regioselectivity. With the chiral complex **1e**, the product was obtained in 75 % yield in 18 h, employing just 2 mol % of catalyst. More importantly, the product was found to possess an ee of 70 %, which compared favorably with the enantioselectivity ob-

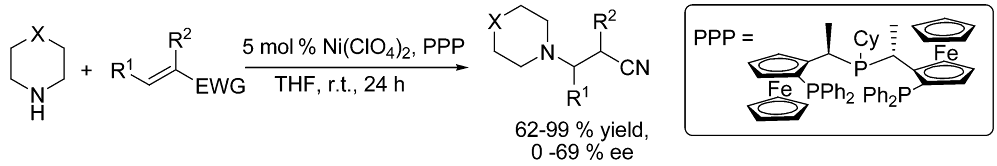


Scheme 2

served earlier for the addition to 2-vinylnaphthalene catalyzed by [(BINAP)Pd(OTf)$_2$] (64 % ee) [3]. This implied that enantioselectivity of this process need not be compromised by elevated temperatures.

We found that these complexes can also catalyze the addition of dibutylamine, piperidine, and aniline to activated acyclic olefins such as acrylates, crotonate, cinnamate, and acrylonitrile at low catalytic loadings (2 mol %) [6]. Addition of amines to these activated olefins are particularly interesting, as they afford highly valuable β-amino acid derivatives [7]. Initially, our attempts to induce enantioselectivity in these systems (with **1e**) were not particularly successful. Frustratingly, low/no enantiomeric excesses were observed in the products.

About this time, the Togni group communicated their results on the cationic nickel-catalyzed addition of aliphatic amines to these olefins (Scheme 3). The reactions were also found to proceed with low to moderate enantioselectivity. Using the tridentate "Pigiphos" phosphine ligand, the addition of morpholine to crotonitrile was achieved with an ee of 69 % [8]. Comparing this with the previous result obtained by Jørgensen [4], we postulated that high enantioselectivity may be achieved by introducing a 1,3-dicarbonyl moiety to the olefin substrate. By forming a stable chelate to the metal center, stereodifferentiation between enantiofaces may be enhanced (Fig. 1).



Scheme 3 Cationic Ni-catalyzed addition of cyclic alkylamines to activated olefins.

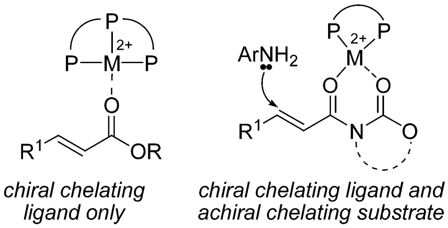
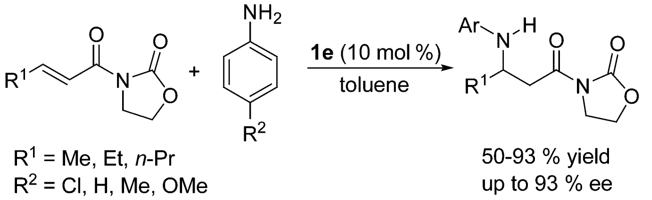


Fig. 1

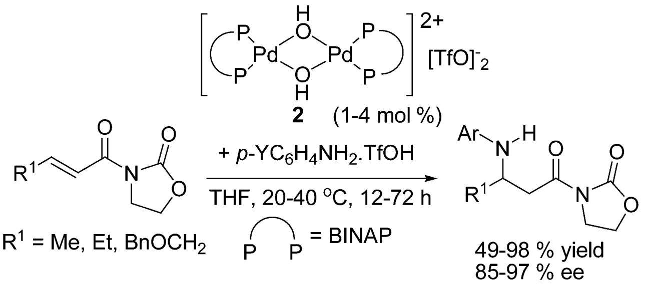
Adopting butenoyl-*N*-oxazolidinone as the olefin substrate, we were delighted to find that the addition of aniline proceeded with an enantioselectivity of 93 %, catalyzed by complex **1e** (Scheme 4) [9]. Although a high catalyst loading is required (10 mol %), the reaction proceeded in a relatively short period of time (18 h).



Scheme 4 Enantioselective addition of aromatic amines to α,β-unsaturated-*N*-oxazolidinones.

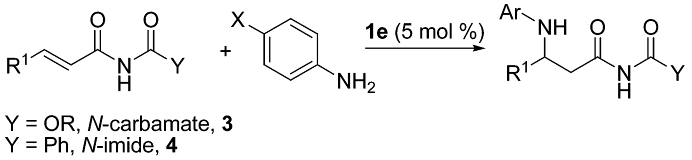
Modifying the substituents (R^1 and R^2) on both substrates, some interesting observations were made on the scope and limitations of the reaction: (i) There is no apparent correlation between the nucleophilicity of the amine and reactivity, as might be expected for Lewis acid-catalyzed processes; (ii) The rate of reaction is retarded by extending the alkyl substituent (R^1). Elevated temperatures were required, which led to a corresponding deterioration in ee; (iii) Addition of electron-rich toluidine and anisidine proceeded at much lower selectivity than corresponding reactions with aniline and *p*-chloroaniline.

Reasoning that nucleophilic amines undergo uncatalyzed reactions and also deactivate the palladium catalyst by amine coordination, Sodeoka et al. subsequently reported an improvement to these reactions by employing trifluoromethanesulfonate salt of the amine, in combination with a μ-hydroxyl-palladium-BINAP complex **2**, to regulate the generation of free amine for catalysis (Scheme 5) [10]. Using the new protocol, extremely high enantioselectivity can be achieved, not only for the addition of electron-rich anisidine, but also benzylamines.



Scheme 5 Amine salt-controlled enantioselective addition of aromatic amines to alkenoyl-*N*-oxazolidinones.

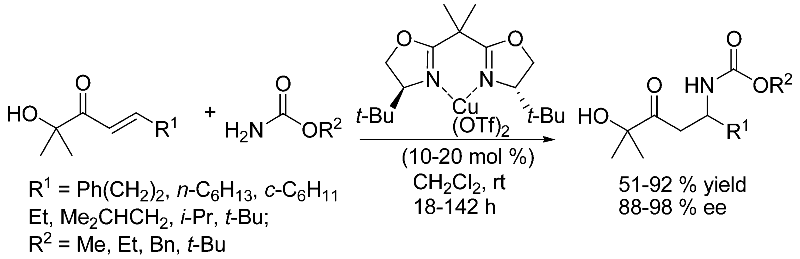
Meanwhile, having established the chelating moiety of the olefin substrate as the key stereo-controlling element, we proceeded to examine the effect exerted by the terminal carbonyl group on the achiral template, by replacing the oxazolidinone ring with structurally similar acyclic carbamate [11] and imide [12] moieties (Scheme 6).



Scheme 6 Addition of primary aromatic amines to other Michael acceptors containing chelating templates.

The nature of the chelating template evidently has a modulating effect on the overall reactivity and selectivity of these reactions. Using *N*-imide **4** as the Michael acceptor, the enantioselectivity of the reactions were relatively insensitive to the electronic structure of the aromatic amine, ranging between 73–89 % for the addition to the butenoyl, 51–63 % to pentenoyl, and 55–70 % to hexenoyl derivatives. In contrast, the addition of primary aromatic amines to *N*-carbamates **3** was particularly facile and enantioselective. For the addition of 4-chloroaniline, optically pure products (>99 % ee) were obtained quantitatively by employing just 2 mol % of the palladium catalyst. Overall, high enantioselectivities of >80 % were obtained in most cases, with two notable exceptions—the addition of the anisidine to the pentenoyl and hexenoyl olefin substrates proceeded with low ee's of 16 and 17 %, respectively.

The concept of using an acyclic chelating template for aza-Michael additions has since been adopted by Palomo et al. to great effect. Employing a hydroxy-ketone as a mode of chelation to the metal center, addition of carbamates to the α'-hydroxy enones proceeded in impressive ee's in the presence of an Evan's bis-oxazoline copper catalyst (Scheme 7) [13].



Scheme 7 Cu(II)-catalyzed enantioselective addition of carbamates to α'-hydroxyketones.

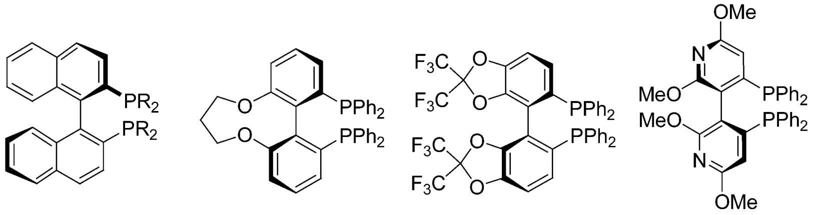
Having examined the effect of the achiral chelating template, we began to investigate the catalytic activity and selectivity bestowed by the ligand in these systems. To facilitate ligand screening, we ideally like to generate a catalyst in situ, i.e., by mixing a metal precursor with the requisite ligand prior to the introduction of substrates, preferably without any extraneous reagents/ligands. Using BINAP as the ligand, a number of palladium precursors was screened for the addition of aniline to butenoyl *N*-imide **4** (R^1 = Me). This led us to identify $Pd(OTf)_2 \cdot 2H_2O$ as a superior precursor [14]. Subsequently, the addition of the aromatic amines to **3** and **4** were re-examined (Table 1). The results proved to be striking—in most cases, significant ee enhancement was obtained with the new catalyst system. Additionally, optically pure products were obtained in two cases (entries 2 and 3) [15].

Table 1 Comparative yields and enantioselectivities obtained with different catalytic systems (Scheme 6).

Entry	Y	R^1	X	Yield/%[a]	ee/%[a]
1	*t*-BuO	Me	H	89 (>99)	97 (97)
2	*t*-BuO	Me	Cl	82 (>99)	>99 (>99)
3	*t*-BuO	Et	Cl	61 (92)	>99 (85)
4	*t*-BuO	*n*-Pr	Cl	45 (90)	92 (89)
5	Ph	Me	H	86 (84)	91 (89)
6	Ph	Me	Cl	81 (88)	81 (73)
7	Ph	Et	H	86 (75)	80 (63)
8	Ph	Et	Cl	75 (70)	60 (54)
9	Ph	Et	Me	22 (70)	79 (59)

[a] Result obtained with the catalyst generated in situ from $Pd(OTf)_2{\cdot}2H_2O$ and BINAP. Value in parenthesis corresponds to result obtained with isolated complex **1e**.

Subsequently, a number of commercially available chiral ligands were evaluated for the addition of aniline to the Michael acceptor **4** (R^1 = Me) [14]. Key structural aspects essential for high enantioselectivity were rapidly identified from this small ligand screen: Highest yields are afforded by diphosphine ligands, and highest selectivity is associated with those with chirality derived from a biaryl unit. Among these, five ligands gave enantioselectivity of ≥90 % in the addition of aniline to substrate **4**, where R^1 = Me (Chart 1).



R = Ph, *R*-**BINAP**
86 %, 91 % ee
R = Tol, *R*-**Tol-BINAP**
79 %, 90 % ee

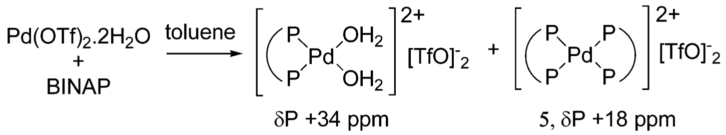
R-**C3-Tunephos**
79 %, 90 % ee

R-**Difluorphos**
83 %, 91 % ee

R-**CTH-P-Phos**
81 %, 93 % ee

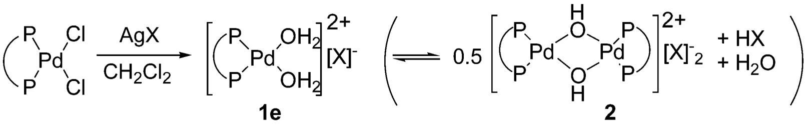
Chart 1

The nature of the dicationic palladium complex generated from $Pd(OTf)_2{\cdot}2H_2O$ was subsequently examined. By mixing an equimolar amount of the metal precursor and BINAP in toluene, the formation of the bis-aqua complex **1e**.OTf was clearly identifiable by its ^{31}P resonance signal (+34 ppm) and mass ion [m/z 877, $(BINAP)Pd(OTf)^+$]. Additionally, the formation of a bis-ligated complex **5** was also observed (Scheme 8), indicated by its distinctive resonance ^{31}P signal at +18 ppm, supported by a corresponding mass ion [m/z 1499, $(BINAP)_2Pd(OTf)^+$]. The complex may also be isolated exclusively from a 1:2 mixture of Pd:L.



Scheme 8 Dicationic complexes generated from $Pd(OTf)_2 \cdot 2H_2O$ precursor.

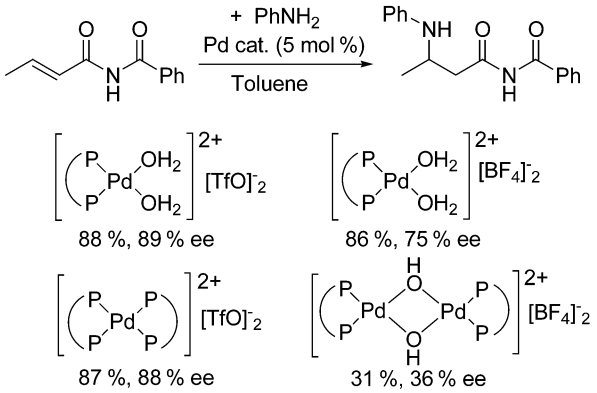
Next, the comparative catalyst activities of different cationic palladium complexes were investigated. Both complexes **1e** and **2** may be synthesized by the halide abstraction method, with slight variations in the reaction conditions and counteranion employed [16]. Using a mixed acetone–water solvent system, the addition of silver tetrafluoroborate to $(BINAP)PdCl_2$ generates a mixture of the bis-aqua complex **1e**.BF_4 (δP +34 ppm), as well as the dimeric μ-hydroxyl-bridged palladium complex **2**.BF_4 (δP +29.3 ppm) in a dynamic equilibrium—the addition of molecular sieves or base favors the formation of **2** (Scheme 9).



Scheme 9 Different dicationic Pd(II) complexes generated from halide abstraction.

Notably, if silver trifluoromethanesulfonate was used, we only observed the formation of the monomeric bis-aqua complex **1e**.OTf, in the absence of molecular sieves/base. The apparent stability of the monomeric complex is attributed to the existence of four contiguous hydrogen bonds between the coordinated water and trifluoromethanesulfonate counteranion [14,17].

Four different cationic palladium complexes (**1e**.BF_4, **1e**.OTf, **2**.BF_4, and **5**) were isolated and used as catalysts in the addition of aniline to butenoyl-*N*-imide (Scheme 10). The result showed that **1e**.OTf is more selective than **1e**.BF_4. Presumably, the reduced stability of **1e**.BF_4 led to the some formation of complex **2**.BF_4, which catalyzed a slower, less selective process. Rather surprisingly, complex **5** displayed identical catalytic activity to the monomeric **1e**.OTf. We speculate that one of the BINAP ligands in complex **5** dissociates/exchanges with the substrate under catalytic conditions to initiate catalytic turnover.



Scheme 10 Catalytic activity of different dicationic Pd complexes.

SUMMARY

We have successfully developed a class of cationic palladium complexes that are able to catalyze the addition of aryl amines to α,β-unsaturated acid derivatives with high enantioselectivity. These reactions are practically simple, and allowed access to optically active *N*-aryl-β-amino acid derivatives. The nature of stereochemical control of these catalyst systems is currently being investigated. Concurrently, we are also developing different catalysts for hydroamination reactions involving different classes of substrates. These results will be reported in due course.

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