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2016

Li, X. -R., Chew, R. J., Li, Y., & Leung, P. -H. (2016). Investigation of Functional Group Effects on Palladium Catalysed Asymmetric P–H Addition. *Australian Journal of Chemistry*, 69(5), 499-504.

<https://hdl.handle.net/10356/84714>

<https://doi.org/10.1071/CH15577>

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Investigation of Functional Group Effects on Palladium Catalyzed Asymmetric P-H Addition

Xi-Rui Li,^A Renta Jonathan Chew,^A Yongxin Li^A and Pak-Hing Leung^{A,B}

^A Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

^B Corresponding author. Email: pakhing@ntu.edu.sg

In memory of Emeritus Professor Brice Bosnich for his contributions to the field of organophosphorus chemistry and in catalysis. LPH is grateful to Professor Bosnich for his guidance during his stay at the University of Toronto and the University of Chicago

The pincer catalyzed asymmetric P-H addition of diphenylphosphine to 3-benzylidene-2,4-pentadione is herein reported. Albeit successful in catalyzing a series of similar substrates, unexpected chelation of the dione substrate to CP and CN palladacycle catalyst resulted in inactivation of catalyst with adjacent coordination sites. Protected phosphine adducts were isolated and characterized, providing critical insights to the choice of catalyst for structurally distinct functional groups borne by the substrate.

Manuscript received: xx xx 2015.

Manuscript accepted: xx xx 2015.

Published online: xx xx 2015.

Introduction

The past decades have witnessed exponential growth and development of transition metal (TM) complexes in industry and in research.^[1] Carbometallated palladium complexes, commonly known as palladacycles have emerged to be ubiquitous (pre)catalysts and resolving agents. Since the first palladacycle was prepared by Cope in the 1960s,^[2] there have been substantial reports on their preparation, properties, as well as the classes of reactions in which they mediate.^[3] To date, they have been demonstrated to be efficient catalysts in a wide variety of reactions, ranging from a) cross coupling reactions including the Suzuki-Miyaura,^[4] Heck,^[5] Sonogashira reactions;^[6] b) rearrangement reactions;^[7] c) annulations;^[8] d) hydrofunctionalizations.^[9]

The classes of palladacycles known today are notably the CY type complexes, analogs of the Hermann-Beller palladacycle;^[10] and the YCY class complexes, better known as pincer complexes (Figure 1). One of the first applications of chiral CY-type palladacycles was in the resolution of P-stereogenic phosphines.^[11] Following intensive studies with modification in the structural backbone of the fundamental palladacycle (**1**), Wild and co-workers successfully employed a naphthylamine analog (**2**) as exceedingly efficient resolving agents for dissymmetric phosphines^[12] and arsines.^[12b,13] The enhanced efficiency of **2** as a chiral derivatizing agent versus its benzylamine predecessor was established to be due to improved chiral induction to the coordination sites, owing to the rigid conformation of the organometallic ring (Figure 2).^[14] Bosnich *et al.* showed that however, the aromaticity of highly conjugated and sterically demanding analogs (10,10'-di-hydroxy-9,9'-biphenylanthryl) can be disrupted upon metal complexation (Figure 3).^[15] Pincer complexes on the other hand were pioneered by Moulten and Shaw in the 1970s. They have proven to be highly versatile catalysts,^[16] as chemical sensors, and in dendrimer chemistry.^[17]

Chiral phosphines, a critical feature in metal-mediated asymmetric catalysis have to a great extent driven the rapid

Figure 1: General classification of established palladacycles.

Figure 2: Improved efficacy of palladacycle **2** as a chiral derivatizing agent versus its benzylamine analog **1**.

Figure 3: Disruption of aromaticity in sterically demanding auxiliary upon complexation with palladium.

development of synthetic methodologies over the past century.^[18] On top of their conventional roles as ligands, they are also efficient organocatalysts in a number of chemical transformations.^[19] Despite their significance, conventional synthetic methodologies often dictate the use of chiral starting materials or auxiliaries, rendering such approaches wasteful and cumbersome. The ideal solution would be their direct preparation via catalysis, effectively achieving 100% atom-economy with minimal wastage *via* the addition of phosphines to prochiral substrates. Moreover, this facilitates the syntheses of phosphines bearing various functionalities (esters, amides, *etc.*) as they are valuable alternatives to typical ligands due to their distinct coordinative and stereoelectronic properties.

Realizing the perpetual demand for optically active and more importantly, unprotected phosphines, our group have in recent years achieved the palladacycle (**3**) catalyzed asymmetric hydrophosphination (AHP) of a variety of Michael acceptors. Substrates including α,β -unsaturated (di)ketones,^[20] imines,^[21] diesters,^[22] ketoamides,^[9c] phthalimides^[9d] and alkenylisoxazoles^[23] are suitable electrophiles, generating a library of free, enantioenriched phosphines bearing C- and/or P-stereogenic centers. The established methodology could further be utilized in the preparation of optically pure pincer auxiliaries/complexes (**4**) as traditional approaches often involve tedious synthetic methodologies or mechanical resolutions (Figure 4).^[24]

Figure 4: Phosphapalladacycles employed in the AHP reaction.

Despite the success, there remain certain limitations on the classes of substrates that **3** can efficiently catalyze. An example would be the addition of phosphorus nucleophiles to poorly activated Michael acceptors. While the AHP of chalcones and its analogs proceeded smoothly,^[20] additions to α,β -unsaturated monoesters, amides and benzylideneacetone (**5**) however proved to be challenging. A solution would be the introduction of activating functionalities (AF) (*i.e.* diesters,^[22] phthalimides^[9d]) to increase the electrophilicity of the β carbon, therefore allowing the desired AHP reaction to proceed (Figure 5). Applying the same strategy, an additional acetyl group was introduced to **5** with high hopes of achieving success in the P-H addition reaction. However, it was intriguing to note that the reaction proceeded sluggishly with palladacycle **3**; yet gave significantly improved conversions within short reaction times with catalyst **4**. As such, it was critical to unravel the underlying factors behind the observations so as to gain unprecedented understanding of the influence of functional group(s) on the catalyst and the associated chemical reactivities.

Figure 5: Introduction of activating groups to poorly activated Michael acceptors.

Results and Discussions

From an electronic viewpoint, the di-acetyl activated olefin (**6**) is considerably more activated than the diester analog (Figure 5) as electronic contribution by oxygen to the carbonyl functionality reduces esters' electron withdrawing capabilities. Thus, it was surprising that the latter afforded enantioenriched phosphine adducts at low temperatures with catalytic amounts of **3b**^[22] while the reaction between diphenylphosphine (Ph₂PH) and **6** ironically proceeded sluggishly even with raised temperatures (rt) and prolonged reaction times. It was also intriguing to observe only minute conversions even when stoichiometric amounts of azapalladacycle **3a** were employed as the promoter. Seeking the underlying factors for the unforeseen outcomes, thorough literature review subsequently revealed the tendency of acetylacetone (acac) to form

kinetically stable *O,O*-chelates with metallacycles in solution and in the solid state.^[25] As such, it was evident that CY-type palladacycles (**3**) were ineffective in catalyzing or mediating the desired P-H addition owing to **6** functioning as an effective catalyst poison (Figure 6).

Figure 6: Catalyst inactivation owing to formation of stable chelates between palladacycles **3** and the substrate.

Determined to achieve the syntheses of chiral acetylacetone-functionalized phosphines, a palladacycle bearing a single-coordination site (**4**) was employed as the catalyst in hopes of circumventing potential complications arising from the substrate's chelate effect. Fortuitously, the reaction proceeded smoothly with (*S,S*)-**4**, affording distinct signals at 5.8 and -13.8 ppm when subjected to ³¹P{¹H} NMR spectroscopic analysis upon reaction completion. Optimization of reaction conditions by varying the solvents and temperatures showed that THF produced the best conversion and enantioselectivity (Table 1, entry 1). While a reduction in operating temperatures improved the obtained enantiomeric excesses (*ee*), significantly longer reaction times were required for the reaction to go to completion. In addition, it is observed that the ratios of the obtained products varies depending on the solvents employed.

Table 1: Optimization of reaction conditions for (*S,S*)-**4** catalyzed asymmetric hydrophosphination of **6** with diphenylphosphine (Ph₂PH)^[a]

Entry	Solvent	T (°C)	Time (h)	Conv. (%) ^[b]	<i>ee</i> (%) ^[c]
1	THF	RT	4	83	58
2	CH ₂ Cl ₂	RT	24	82	6
3	acetone	RT	6	83	39
4	CHCl ₃	RT	24	80	5
5	CHCl ₃	-40	120	42	22

^[a] Reaction conditions: **6** (0.1 mmol), Ph₂PH (0.1 mmol), degassed solvent (5 mL). ^[b] Conversions are based on the sum of signals of **7** and **8** arising from the ³¹P{¹H} NMR spectrum of the crude products. ^[c] Enantiomeric excess (*ee*) are obtained from chiral HPLC analyses of the sulphurized products.

Treatment of the crude product mixture (**7,8**) with enantiopure (*R*)-**3a** gave unidentified signals at 44, 46, 48 ppm. However, stirring the mixture with silica subsequently affords diastereomeric adducts (**9**) with only two apparent signals at 56 and 59 ppm. Crystallization of the diastereomeric mixture followed by X-ray crystallographic analyses revealed a phosphine-enolate chelate, with the newly formed stereogenic center bearing a *R* configuration (Figure 7). Comparison of the carbon-oxygen bond lengths in **9** (C-O = 1.30 Å, C=O = 1.24 Å) reaffirms our observations that tautomers have indeed been obtained. Isolation of the major diastereomer (56 ppm) by flash chromatography and subsequent treatment with aqueous potassium cyanide (KCN) to liberate the bound phosphine surprisingly afforded 2 signals at 5.8 and -13.8 ppm (Scheme 1). This provides critical experimental evidence to support our postulations that a tautomeric mixture was obtained after the initial hydrophosphination reaction. In addition, the observed variation in product ratios in different solvent systems can now

Figure 7: Molecular structure and absolute stereochemistry of chelate **9** with 50% thermal ellipsoids shown. Hydrogen atoms except those on the chiral centre are omitted for clarity.^[26]

Scheme 1: Coordination studies revealing keto-enol tautomeric products prior and after coordination to palladacycle (*R*)-**3**.

be well understood since the degree of tautomerization is dependent on the solvents' properties.

An alternate approach to facilitate isolation and characterization of the phosphine products is the utilization of gold(I) halides as protecting agents. While the approach appear similar to coordination with palladium complexes (**2**), gold(I) however possess only one coordination site, thus effectively eliminating any potential chelate effects. X-ray analyses of the gold-phosphine complex revealed that the keto isomer was the sole product with no tautomerization observed even after purification with silica chromatography (Figure 8). Albeit obtaining racemic crystals, comparisons of the C=O bond lengths in the gold-phosphine complex showed that they are practically identical at 1.21 Å. On the other hand, distinct differences in the carbon-oxygen bond lengths in **9** (C-O = 1.30 Å, C=O = 1.24 Å) reinforces the experimental findings of product tautomerization and the associated coordination modes

Figure 8: Molecular structure of the gold(I)-phosphine adduct with 50% thermal ellipsoids.^[26]

with palladium.

Conversely, protection of the crude phosphine adducts (**7,8**) by sulphurization initially produced signals at 48 and 50 ppm (**10,11**). While seemingly analogous to protection *via* complexation with gold(I), it was found that tautomerization of the phosphine-enol adduct to the thermodynamically favorable keto isomer **11** (50 ppm) ensued upon purification on silica gel (Scheme 2). The methine proton (CO-CHC-CO) as observed in the proton NMR of **11** ($\delta=5.21$) substantiates the formation of the more stable di-keto tautomer.

Scheme 2: Silica induced tautomerization of sulphurized phosphine adducts.

A mechanistic cycle for the pincer catalyzed hydrophosphination reaction is proposed. As secondary phosphines possess high affinities to palladium, diphenylphosphine readily displaces the weakly bound acetate ion. Unlike palladacycles which possess adjacent coordination sites, pincer **4** binds preferentially to a single molecule of diphenylphosphine even in the presence of chelating bidentates. While this may appear insignificant, the unique affinities of various substrates to the catalyst are in fact critical for the desired nucleophilic attack in this study. The free acetate ion subsequently deprotonates the bound phosphine which is acidified due to metal complexation. This generates a highly reactive phosphido species which adds to the olefin via a outer sphere mechanism. Proton transfer from acetic acid followed by displacement of the product by unreacted diphenylphosphine regenerates the active catalyst (Scheme 3).

Scheme 3: Proposed catalytic cycle for the Pd-pincer catalyzed hydrophosphination of 3-benzylidenepentane-2,4-dione.

Conclusion

In summary, the intricate relationship between how various functional groups borne on the substrate can influence the performance of selected palladacycle catalysts is explored in this study, providing valuable insights on the choice of catalyst for structurally distinct substrates. The employment of a mono-coordination site palladium pincer catalyst circumvents catalyst inactivation by the starting material, facilitating the first known asymmetric preparation of phosphines bearing a diketone functionality. While the *ee* values obtained are at best moderate, modifications to the pincer catalyst could potentially engender improvements in the obtained results. A plausible mechanistic cycle has been proposed for the asymmetric hydrophosphination reaction.

Experimental

All reactions were carried out under a positive pressure of nitrogen using standard Schlenk techniques. Commercially available reagents and solvents were purchased and used without further purification. When necessary, solvents should be freshly degassed before use. Column chromatography was conducted on Silica gel 60 (Merck or Grace Division Discovery Science's (Davisil)). $^{31}\text{P}\{^1\text{H}\}$, ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on Bruker ACF 400 or 500 spectrometers. High Resolution Mass spectroscopy (LC-HRMS) was performed using a Finnigan MAT95XP spectrometer. Chiral HPLC was conducted using a Agilent Technologies Series 1200 spectrometer, equipped with a DIACEL Chiralpak IC column; Conditions: Eluent= Hexane:IPA (19:1), Flow rate= 1 mL/min; temperature= 21.5 °C.

General Procedure for the (*S,S*)-4 catalyzed asymmetric hydrophosphination reaction

3-benzylidene-2,4-pentadione (**6**) (0.02 g, 0.1 mmol) was added to the solution of PCP pincer catalyst (*S,S*)-4 (1.0 mg, 0.03 equiv.) and diphenylphosphine (1.0 equiv.) and stirred in the specified solvent (5 mL), temperature and time. The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy, and the conversions calculated using the sum of integrals of tautomeric products **7** (-13.8 ppm) and **8** (5.8 ppm).

Supplementary Material

Spectroscopic data and experimental details are available in the supplementary material on the Journal's website..

Acknowledgement

The authors wish to thank Nanyang Technological University (NTU) for supporting this project (MOE-RG-02/14). X.-R. Li and R. J. Chew are grateful for the research scholarships awarded by NTU.

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[26] CCDC 1424966 (Figure 7) and 1424965 (Figure 8) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.