Faculty of Resource Science and Technology

The Amine-Carbonyl Reaction and their Role in Catalysis

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DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Malaysia Sarawak. Except where due acknowledgements have been made, the work is that of the author alone. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

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Signature

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ABSTRACT

The metal catalyzed carbon-carbon bond formation reactions are among the most important and useful methods for organic synthesis. During the past century, significant progress has been made in this field to develop an ideal catalyst for cross-coupling chemistry. This can be achieved by changing the types of ligands coordinated to the metal center due to the catalytic properties of the metal complexes is usually a combination of the steric environment that the ligands impart, in addition to their electronic influence on the metal center. In this project, two series of diimine compounds bearing electron donating and electron withdrawing substituent (R-DAB) were synthesized by condensation reaction and then reacted with the dichlorobis(acetonitrile)palladium(II) precursor, [$PdCl_2(MeCN)_2$], to form palladium(II) diimine, [$PdCl_2$(R-DAB)], complex. The catalytic efficiency of [$PdCl_2$(R-DAB)] complexes in Sonogashira cross-coupling reaction was examined by reacting methyl-4-bromobenzoate and 2-methylbut-3-yn-2-ol for 5 hours under nitrogen condition at 70 °C. The initial hypothesis of this work was the strong *trans*-effect from diimine ligand in [$PdCl_2$(R-DAB)], which can enhance the rate of reductive elimination and subsequently promote the formation of cross-coupling product. Unfortunately, the results showed that the [$PdCl_2$(R-DAB)] complexes were incapable to induce the cross-coupling reaction. In order to increase the electron density on the palladium metal center and consequently accelerate the reactivity rate of cross-coupling reaction, palladium(II) diamine complex were synthesized based on structural modification of [$PdCl_2$(R-DAB)]. However, these complexes were also unable to perform the catalytic reaction by forming palladium black within 10 minutes of the reaction. The reasons for failure of all of the palladium complexes to catalyze Sonogashira cross-coupling reactions is due to the energy level of LUMO is much higher than the 3*d*-orbitals of phosphorus which restrict the effectiveness of

back-bonding and prevent the oxidative addition from happening as well as resulting the formation of palladium black particle after terminal alkyne was added into the reaction. In addition, a direct C-H/N-H oxidative coupling of primary and secondary amine with glyoxal was developed. This reaction can be achieved by using 4 equivalents of $CuCl_2 \cdot 2H_2O$ as the oxidant, Cs_2CO_3 (1.3 equiv) and CF_3COOH (1.0 equiv) as the additives in MeTHF at 70 °C for 5 hours under N_2 atmosphere. The yield was increased from 20% in the beginning to 70% under the aforementioned conditions. This transformation is also well tolerated for a series of aniline substrates with a wide variety of substitution patterns and functionalities. This protocol can be easily scaled up which demonstrate the practicality of this transformation and this can be applicable in the field of organic synthesis and medicinal chemistry.

Keywords: Diimine compound, catalytic efficiency, Sonogashira cross-coupling, Oxidative coupling

Tindakbalas Amina-Karbonil dan Peranannya dalam Pemangkinan

ABSTRAK

Tindak balas pembentukan ikatan karbon-karbon yang dimangkinkan oleh logam adalah antara kaedah yang paling penting dan berguna untuk sintesis organik. Sepanjang abad yang lalu, kemajuan yang ketara telah dicapai dalam bidang ini untuk mengembangkan pemangkin ideal bagi tindak balas gandingan silang. Ini dapat dicapai dengan mengubah jenis ligan yang diselaraskan ke pusat logam kerana sifat pemangkin kompleks logam biasanya merupakan gabungan persekitaran sterik yang diberikan oleh ligan, selain pengaruh elektronik mereka pada pusat logam. Dalam projek ini, dua siri sebatian diimina yang mengandungi pengganti penderma elektron dan pengganti penarik elektron (R-DAB) telah disintesis melalui tindak balas kondensasi dan kemudian bertindak balas dengan pendahulu [$PdCl_2(MeCN)_2$] untuk membentuk kompleks [$PdCl_2$(R-DAB)]. Kecekapan pemangkin [$PdCl_2$(R-DAB)] kompleks dalam tindak balas gandingan silang Sonogashira dikaji dengan bertindak balas metil-4-bromobenzoat dan 2-metilbut-3-yn-2-ol selama 5 jam dalam keadaan nitrogen pada suhu 70 °C. Hipotesis awal kerja ini adalah kesan trans ligan yang kuat dalam [$PdCl_2$(R-DAB)] dapat meningkatkan kadar penyingkiran reduktif dan seterusnya mendorong pembentukan produk gandingan silang. Malangnya, keputusan menunjukkan bahawa kompleks [$PdCl_2$(R-DAB)] tidak mampu mendorong pembentukan tindak balas gandingan silang. Untuk meningkatkan ketumpatan elektron di pusat logam paladium dan seterusnya mempercepatkan kadar kereaktifan tindak balas gandingan silang, kompleks diamina palladium(II) disintesis berdasarkan modifikasi struktur [$PdCl_2$(R-DAB)]. Walau bagaimanapun, kompleks itu juga tidak dapat memangkin gandingan silang dengan membentuk paladium hitam dalam masa 10 minit dari tindak balas. Sebab kegagalan semua kompleks paladium untuk memangkinkan tindak balas gandingan silang

Sonogashira adalah kerana tahap tenaga LUMO jauh lebih tinggi daripada fosforus 3d-orbital yang menghadkan keberkesanan ikatan belakang dan menghalang penambahan oksidatif daripada berlaku serta mengakibatkan pembentukan paladium hitam setelah alkuna terminal ditambahkan ke dalam tindak balas. Sebagai tambahan, C-H/N-H gandingan oksidatif langsung amina primer dan sekunder dengan glioksal telah dikembangkan. Tindak balas ini dapat dicapai dengan menggunakan 4 setara $CuCl_2 \cdot 2H_2O$ *sebagai pengoksidaan,* Cs_2CO_3 *(1.3 setara) dan* CF_3COOH *(1.0 setara) sebagai bahan tambah dalam MeTHF pada 70 °C selama 5 jam di bawah atmosfera nitrogen. Hasil meningkat dari 20% pada permulaan hingga 70% dalam keadaan yang disebutkan di atas. Transformasi ini juga bertoleransi dengan baik terhadap substrat anilin yang mempunyai pelbagai corak penggantian dan fungsi. Protokol ini dapat ditingkatkan dengan mudah bagi menunjukkan praktikal transformasi ini serta diguna dalam bidang sintesis organik dan kimia perubatan.*

Kata kunci: *Sebatian diimina, kecekapan pemangkin, silang gandingan Sonogashira, gandingan oksidatif*

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LIST OF ABBREVIATIONS

δ	chemical shift in part per million
° C	degrees Celsius
Å	Ångström
^{13}C NMR	carbon nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
Ar	aryl group
$CDCl_3$	deuterated chloroform
CF_3	fluoroform
CHN	carbon, hydrogen, nitrogen
cm	centimeter
cm^{-1}	reciprocal centimetre
CMe_3	isobutane
Cy-DAB	*N*,*N*-Dicyclohexyl-1,4-diazabutadiene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
equiv.	equivalent
E_a	activation energy
Et_3N	triethylamine

EtOH	ethanol
FTIR	fourier transform infrared
g	gram
GC	gas chromatography
GCMS	gas chromatography mass spectrometer
h	hour
H_2O	water
HCl	hydrochloric acid
HCOOH	formic acid
Hz	hertz
iPr	isopropyl
iPrOH	isopropanol
J	coupling constant
KBr	potassium bromide
m	meta
Me	methyl
MeOH	methanol
mg	milligrams
mL	millilitres
mmol	millimoles
nm	nanometer
NMe_2	dimethylamine
NMR	nuclear magnetic resonance
m.p	melting point
NO_2	nitro

o	ortho
OAc	acetate
OMe	methoxy
p	para
Pd	palladium
$[PdCl_2(PPh_3)_2]$	dichlorobis(triphenylphosphine)palladium(II)
Ph	phenyl
PPh_3	triphenylphosphine
ppm	part per milion
p-TsOH	*p*-toluenesulfonic acid
r.t.	room temperature
R	alkyl group
R-DAB	1,4-disubstituted-1,4-diaza-1,3-butadiene
s	singlet
t	triplet
^tBu	tert-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilance
TsOH	p-toluenesulfonic acid
UV	ultraviolet
UV-Vis	ultraviolet-visible

CHAPTER 1

INTRODUCTION

1.1 Introduction to catalysis

Catalysis is the increase of the rate in a chemical reaction due to the participation of an additional substance called catalyst (Hagen, 2015). With the presence of a catalyst, a reaction can occur faster with less energy. Importantly, catalyst is not consumed in the reaction, hence it often is needed in tiny amount since it can be reactivated (recycled) in the reaction (Kakaei et al., 2019). According to Figure 1.1, a catalyst increases the rate of a chemical reaction by forming bonds with the adsorbents (A and B) and letting them react with each other to make the product (P). Then, the product can desorb from the catalyst and the catalyst is recovered in its original form at the end of the reaction cycle (Chorkendorff & Niemantsverdriet, 2017).

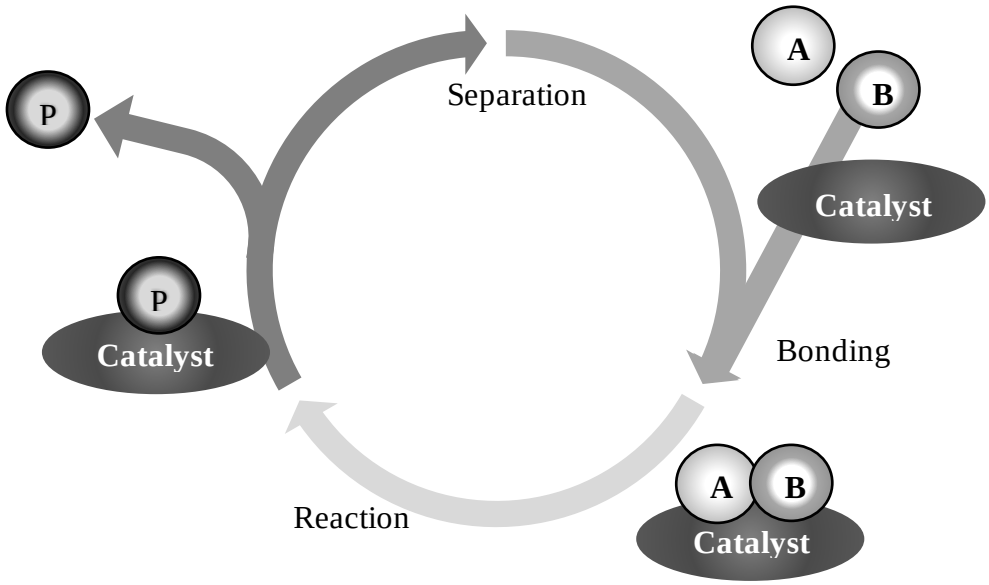

Figure 1.1: General mechanism of a catalytic reaction