

THE HECK REACTIONS OF ARYL BROMIDES IN IONIC LIQUIDS MEDIUM  
OF *N*-BUTYL-*N*-METHYLPYRROLIDINIUM  
TRIFLUOROMETHANESULFONATE

MOHAMAD HAFIZ BIN AHMAD TAJUDIN

A thesis submitted in fulfilment of the  
requirements for the award of the degree of  
Master of Science (Chemistry)

Faculty of Science  
Universiti Teknologi Malaysia

FEBRUARY 2006

## ABSTRACT

The application of the ionic liquids in the palladium catalyzed Heck reactions have been reported extensively, however, without proper evidence addressing the role of ionic liquids in the catalytic process. In this thesis, a new series of *N*-alkyl-*N*-methylpyrrolidinium trifluoromethanesulfonate salts (**46-52**) have been synthesized to study their potential as the alternative solvents for the Heck reaction, instead of using conventional molecular solvents. These salts were synthesized through quaternization reaction between *N*-methylpyrrolidine (**38**) with several alkyl iodides, followed by metathesis reaction with silver trifluoromethanesulfonate, to give the desired products (**46-52**) (yield: 72-96%) with melting points ranging from room temperature to 300°C. All the salts obtained were characterized by using <sup>1</sup>H and <sup>13</sup>C-NMR spectroscopies, CHN elemental analysis, melting point, density and molar conductivity. The effects of alkyl chains towards the melting points and molar conductivities of these salts (**46-52**) have been investigated. The *N*-butyl-*N*-methylpyrrolidinium trifluoromethanesulfonate, [Bmplim]CF<sub>3</sub>SO<sub>3</sub> (**49**), has been chosen as the solvent in the Heck reactions between methyl acrylate (**61**) and several types of aryl bromides (**56-60**) to give Heck adducts (**62-66**) with satisfactory yield between 37 to 97%. Parameters such as the types of bases, the amount of Pd catalyst loadings and the reaction temperatures were also studied in order to optimize the percentage conversion of respective Heck adducts (**62-66**). Results show that, the optimum condition to enhance the percentage conversion for this catalytic system is by using Et<sub>3</sub>N as base, Pd catalysts loading at 1.5mmol% and reaction temperature at 120°C, to achieve the calculated TONs of ~6667. With these conditions, the Heck adducts of reactive aryl bromides; 4-bromonitrobenzene (**56**), 4-bromoacetophenone (**57**) and bromobenzene (**58**) have achieved an extremely high percentage conversion (~100%). As for the unreactive aryl bromides; 4-bromoanisole (**59**) and 4-bromoaniline (**60**), the addition of PPh<sub>3</sub> was proved to be useful; however, leads to contamination from the by-product which results to problematical separation of the desired products (**62-66**). The ionic liquid of [Bmplim]CF<sub>3</sub>SO<sub>3</sub> (**49**), can be recycled up to three runs, without showing any distinct losses in its activities.

## ABSTRAK

Penggunaan cecair ionik dalam tindak balas Heck bermangkinkan paladium telah dilaporkan secara meluas, namun ianya tidak disertakan dengan bukti yang jelas tentang peranan cecair ionik dalam proses tindak balas pemangkinkan ini. Tesis ini melaporkan sintesis garam ionik baru bagi siri *N*-alkil-*N*-metilpirolidinium triflorometanasulfonat (**46-52**) untuk dikaji potensinya sebagai pelarut alternatif di dalam tindak balas Heck, selain daripada penggunaan pelarut molekul konvensional. Garam-garam ini disintesis melalui tindak balas pengkuateneran antara sebatian *N*-metilpirolidina (**38**) dengan beberapa alkil halida, diikuti dengan tindak balas metatesis dengan argentum triflorometanasulfonat, untuk memberikan hasil yang dikehendaki (**46-52**) (hasil: 72-96%), dengan takat lebur dalam julat suhu bilik ke 300°C. Kesemua garam ini kemudiannya dicirikan dengan menggunakan spektroskopi RMN <sup>1</sup>H and <sup>13</sup>C, analisis unsur CHN, takat lebur, ketumpatan dan kekonduksian molar. Kesan panjang rantai alkil terhadap takat lebur dan kekonduksian molar bagi garam-garam ini telah dikaji. Cecair ionik *N*-butil-*N*-metilpirolidinium triflorometanasulfonat [Bmplim]CF<sub>3</sub>SO<sub>3</sub> (**49**), telah dipilih sebagai pelarut dalam tindak balas Heck di antara metil akrilat (**61**) dengan beberapa jenis aril bromida (**56-60**) untuk memberikan aduk Heck (**62-66**) dengan perolehan hasil yang memuaskan, berjulat di antara 37 hingga 97%. Parameter seperti jenis bes, amaun mangkin Pd yang digunakan, dan suhu tindak balas turut dikaji bagi mengoptimumkan peratusan pertukaran bagi aduk Heck (**62-66**) terbabit. Keputusan menunjukkan bahawa keadaan paling optimum bagi meningkatkan peratusan pertukaran dalam sistem pemangkinkan bagi tindakbalas ini adalah dengan penggunaan Et<sub>3</sub>N sebagai bes, amaun Pd sebanyak 1.5mmol% dan suhu tindak balas pada 120°C bagi mencapai kiraan TONs sebanyak ~6667. Dengan menggunakan parameter-parameter ini, kesemua aduk Heck bagi aril bromida yang reaktif; 4-bromonitrobenzena (**56**), 4-bromoasetofenon (**57**) dan bromobenzena (**58**) telah berjaya mencapai peratusan pertukaran yang sangat tinggi (~100%). Bagi sebatian aril bromida yang tidak reaktif pula; 4-bromoanisol (**59**) dan 4-bromoanilina (**60**), penambahan PPh<sub>3</sub> didapati membantu meningkatkan peratusan pertukaran hasil, tetapi, pada masa yang sama, ia menyebabkan kehadiran bendasing yang membawa kepada masalah pengasingan aduk-aduk Heck (**62-66**) yang dikehendaki. Cecair ionik [Bmplim]CF<sub>3</sub>SO<sub>3</sub> (**49**) didapati boleh dikitar semula sehingga tiga kali penggunaan tanpa menunjukkan kehilangan yang jelas dalam aktivitinya.

## TABLE OF CONTENTS

<b>CHAPTER</b>	<b>TITLE</b>	<b>PAGE</b>
	<b>TITLE PAGE</b>	
	<b>DECLARATION</b>	ii
	<b>DEDICATION</b>	iii
	<b>ACKNOWLEDGEMENT</b>	iv
	<b>ABSTRACT</b>	v
	<b>ABSTRAK</b>	vi
	<b>TABLE OF CONTENTS</b>	vii
	<b>LIST OF TABLES</b>	xi
	<b>LIST OF FIGURES</b>	xii
	<b>LIST OF SCHEMES</b>	xiii
	<b>LIST OF SYMBOLS / ABBREVIATIONS / NOTATION / TERMINOLOGY</b>	xiv
	<b>LIST OF APPENDICES</b>	xv
<b>1</b>	<b>INTRODUCTION</b>	
	1.1 General Introduction	1
	1.2 Background of Research and Problem Statement	2
	1.3 Objectives of Research	4
	1.4 Scope of Research	5
	1.5 Thesis Outline	6

## 2 LITERATURE REVIEWS

2.1	Ionic Liquids	7
2.2	Combination of Cations and Anions	8
	2.2.1 Cations	8
	2.2.2 Anions	10
	2.2.3 Zwitterionic-Type Ionic Liquids	12
2.3	The Unique Properties of Ionic Liquids	13
	2.3.1 High stability	13
	2.3.2 Environmental Friendly	13
	2.3.3 Liquid-Crystalline Properties	14
2.4	Ionic Liquids as Solvent in Organic and Catalytic Reactions	14
2.5	The Heck Reactions	20
	2.5.1 Components of the Heck Reaction Medium	20
	2.5.2 Mechanism of the Heck Reaction	22

## 3 RESULTS AND DISCUSSION

3.1	The Synthesis of Ionic Liquids Derived from <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium Trifluoromethane sulfonate Series ( <b>46-52</b> )	25
	3.1.1 Quaternization and Metathesis Reactions	25
	3.1.2 Synthesis of <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium Trifluoromethanesulfonate Salts ( <b>46-52</b> ) from <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium Iodide Salts ( <b>39-45</b> )	27
	3.1.3 Characterization of <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium Trifluoromethanesulfonate Salts ( <b>46-52</b> )	33
	3.1.3.1 <sup>1</sup> H-NMR Spectroscopy Analysis	33
	3.1.3.2 <sup>13</sup> C-NMR Spectroscopy Analysis	35

3.1.3.3	CHN Elemental Analysis	38
3.2	The Heck Reactions	39
3.2.1	Characterization of the Heck Adducts ( <b>62-66</b> )	41
3.2.1.1	<sup>1</sup> H-NMR Spectroscopy Analysis	41
3.2.1.2	<sup>13</sup> C-NMR Spectroscopy Analysis	43
3.2.1.3	CHN Elemental Analysis	45
3.2.2	Studies on the Heck Reaction Parameters	46
3.2.2.1	The Effect of Bases	46
3.2.2.2	The Effect of Pd(OAc) <sub>2</sub> Catalysts Loadings	47
3.2.2.3	The Effect of Reaction Temperatures	48
3.2.2.4	Addition of Co-ligand	49
3.3	Recyclability of Ionic Liquids	50

## 4 EXPERIMENTAL

4.1	General Experimental Procedures	51
4.2	Chemicals	52
4.3	Preparation of Ionic Liquids	52
4.3.1	Preparation of <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium Iodide Salts ( <b>39-45</b> )	52
4.3.2	Preparation of <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium Trifluoromethanesulfonate Salts ( <b>46-52</b> )	53
4.4	Preparation of the Heck Adducts	55
4.4.1	Catalytic Reactions of Aryl Bromides ( <b>56-60</b> ) in Different Bases	57
4.4.2	Catalytic Reactions of Aryl Bromides ( <b>56-60</b> ) in Different Palladium Loadings	58

4.4.3	Catalytic Reactions of Aryl Bromides ( <b>56-60</b> ) at Different Temperatures	59
4.5	Recyclability of Ionic Liquids	60
<b>5</b>	<b>CONCLUSION AND SUGGESTION</b>	
5.1	Conclusion	62
5.2	Suggestion	65
	<b>SEMINARS AND PUBLICATIONS</b>	66
	<b>REFERENCES</b>	67
	<b>APPENDIX</b>	74

## LIST OF TABLES

TABLE NO.	TITLE	PAGE
3.1	Physical characterization of <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	28
3.2	<sup>1</sup> H-NMR data of the <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	33
3.3	<sup>13</sup> C-NMR data of the <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	36
3.4	CHN elemental analysis of the <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	38
3.5	<sup>1</sup> H-NMR data of the Heck adducts ( <b>62-66</b> )	41
3.6	<sup>13</sup> C-NMR data of the Heck adducts ( <b>62-66</b> )	43
3.7	CHN elemental analysis of the Heck adducts ( <b>62-66</b> )	45
4.1	Catalytic reactions of aryl bromides ( <b>56-60</b> ) in different bases	58
4.2	Catalytic reactions of aryl bromides ( <b>56-60</b> ) in different palladium loadings	59
4.3	Catalytic reactions of aryl bromides ( <b>56-60</b> ) at different temperatures	60
4.4	Recyclability test for ionic liquid of [Bmplim]CF <sub>3</sub> SO <sub>3</sub> ( <b>49</b> )	61



## LIST OF FIGURES

FIGURE NO.	TITLE	PAGE
1.1	General structure of the <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate salts	4
2.1	Some examples of the cations used in the preparation of ionic liquids	8
3.1	The effect of alkyl chains lengths towards the melting points of the <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoro methanesulfonate salts <b>(46-52)</b>	29
3.2	The effect of alkyl chains lengths towards the molar conductivities ( $\Lambda_M$ ) of the <i>N</i> -alkyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate salts <b>(46-52)</b>	30
3.3	The effect of different bases towards the Heck adducts <b>(62-66)</b>	46
3.4	The effect of different Pd loadings towards the Heck adducts <b>(62-66)</b>	47
3.5	The effect of different reaction temperatures towards the Heck adducts <b>(62-66)</b>	48

## LIST OF SCHEMES

SCHEME NO.	TITLE	PAGE
21	The dimerization of propene ( <b>20</b> ) in ionic liquid of [Bmim]Cl <i>via</i> the Dimersol / Difasol process	16
22	The polymerization of propene ( <b>20</b> ) in ionic liquid of [Emim]Cl <i>via</i> the Ziegler-Natta reaction	17
23	The Diels-Alder reaction between cyclopentadiene ( <b>23</b> ) and ethyl acrylate ( <b>24</b> ) in ionic liquid of [Bmim]PF <sub>6</sub>	18
24	The hydrogenation of pentene ( <b>27</b> ) to pentane ( <b>28</b> ) in ionic liquid of [Bmim]SbF <sub>6</sub>	18
25	The hydroformylation of 1-octene ( <b>29</b> ) in ionic liquid [Bmim]Cl-SnCl <sub>2</sub>	19
26	The Friedel-Crafts alkylation of benzene ( <b>32</b> ) with ethylene ( <b>33</b> ) in ionic liquid of [Emim]Cl	19
27	The reduction of Pd(OAc) <sub>2</sub> ( <b>35</b> ) to the active Pd(0) ( <b>36</b> ) Heckcatalyst	23
28	General mechanism of the Heckreaction	24
31	General method of quaternization and metathesis reactions for preparing <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	26
32	Synthesis of <i>N</i> -alkyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate salts ( <b>46-52</b> )	27
33	The Heckreactions between methyl acrylate ( <b>61</b> ) and several types of aryl bromides ( <b>56-60</b> )	39

**LIST OF SYMBOLS / ABBREVIATIONS / NOTATION / TERMINOLOGY**

[Bm <sub>4</sub> im] <sup>+</sup> CF <sub>3</sub> SO <sub>3</sub> <sup>-</sup>	-	<i>N</i> -butyl- <i>N</i> -methylpyrrolidinium trifluoromethanesulfonate
<sup>13</sup> C-NMR	-	Carbon nuclear magnetic resonance
<sup>1</sup> H-NMR	-	Proton nuclear magnetic resonance
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMI / Bmim	-	1-butyl-3-methylimidazolium
Bu <sub>4</sub> NCl	-	Tetrabutylammonium chloride
C20MIM	-	<i>N</i> -isocane- <i>N</i> '-methylimidazolium
CDCl <sub>3</sub>	-	Chloroform- <i>d</i> <sub>6</sub>
CHN	-	Carbon-Hydrogen-Nitrogen
DMF	-	<i>N,N</i> '-dimethylformamide
DMSO	-	Dimethylsulfoxide- <i>d</i> <sub>6</sub>
EMI / Emim	-	1-ethyl-3-methylimidazolium
Et <sub>3</sub> N	-	Triethylamine
NaHCO <sub>3</sub>	-	Sodium hydrogen carbonate
Na <sub>2</sub> CO <sub>3</sub>	-	Sodium carbonate
NaOAc	-	Sodium acetate
NTf <sub>2</sub> <sup>-</sup>	-	Bis(trifluoromethylsulfonyl)imide
RTIL	-	Room temperature ionic liquid
ScCO <sub>2</sub>	-	Supercritical carbon dioxide
TFSA(III)	-	Bis(trifluoromethanesulfonyl)amide
TONs	-	Turnover numbers

## LIST OF APPENDICES

APPENDIX	TITLE	PAGE
1	$^1\text{H}$ -NMR spectrum of <i>N,N</i> -dimethylpyrrolidinium trifluoromethanesulfonate ( <b>46</b> )	74
2	$^{13}\text{C}$ -NMR spectra of <i>N,N</i> -dimethylpyrrolidinium trifluoromethanesulfonate ( <b>46</b> ); (a) $^{13}\text{CH}$ , (b) DEPT135 and (c) DEPT90	75
3	$^1\text{H}$ -NMR spectrum of <i>N</i> -ethyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>47</b> )	76
4	$^{13}\text{C}$ -NMR spectra of <i>N</i> -ethyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>47</b> ); (a) $^{13}\text{CH}$ , (b) DEPT135 and (c) DEPT90	77
5	$^1\text{H}$ -NMR spectrum of <i>N</i> -methyl- <i>N</i> -propyl pyrrolidinium trifluoromethanesulfonate ( <b>48</b> )	78
6	$^{13}\text{C}$ -NMR spectra of <i>N</i> -methyl- <i>N</i> -propyl pyrrolidinium trifluoromethanesulfonate ( <b>48</b> ); (a) $^{13}\text{CH}$ , (b) DEPT135 and (c) DEPT90	79
7	$^1\text{H}$ -NMR spectrum of <i>N</i> -butyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>49</b> )	80
8	$^{13}\text{C}$ -NMR spectra of <i>N</i> -butyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>49</b> ); (a) $^{13}\text{CH}$ , (b) DEPT135 and (c) DEPT90	81

9	<sup>1</sup> H-NMR spectrum of <i>N</i> -methyl- <i>N</i> -pentyl pyrrolidinium trifluoromethanesulfonate ( <b>50</b> )	82
10	<sup>13</sup> C-NMR spectra of <i>N</i> -methyl- <i>N</i> -pentyl pyrrolidinium trifluoromethanesulfonate ( <b>50</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	83
11	<sup>1</sup> H-NMR spectrum of <i>N</i> -hexyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>51</b> )	84
12	<sup>13</sup> C-NMR spectra of <i>N</i> -hexyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>51</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	85
13	<sup>1</sup> H-NMR spectrum of <i>N</i> -heptyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>52</b> )	86
14	<sup>13</sup> C-NMR spectra of <i>N</i> -heptyl- <i>N</i> -methyl pyrrolidinium trifluoromethanesulfonate ( <b>52</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	87
15	<sup>1</sup> H-NMR spectrum of methyl 4-nitrocinnamate ( <b>62</b> )	88
16	<sup>13</sup> C-NMR spectra of methyl 4-nitrocinnamate ( <b>62</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	89
17	<sup>1</sup> H-NMR spectrum of methyl 4-acetoxycinnamate ( <b>63</b> )	90
18	<sup>13</sup> C-NMR spectra of methyl 4-acetoxycinnamate ( <b>63</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	91
19	<sup>1</sup> H-NMR spectrum of methyl cinnamate ( <b>64</b> )	92
20	<sup>13</sup> C-NMR spectra of methyl cinnamate ( <b>64</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	93
21	<sup>1</sup> H-NMR spectrum of methyl 4-methoxycinnamate ( <b>65</b> )	94
22	<sup>13</sup> C-NMR spectra of methyl 4-methoxycinnamate ( <b>65</b> ); (a) <sup>13</sup> C{ <sup>1</sup> H} (b) DEPT135 and (c) DEPT90	95
23	<sup>1</sup> H-NMR spectrum of methyl 4-aminocinnamate ( <b>66</b> )	96

24	<sup>13</sup> C-NMR spectra of methyl 4-aminocinnamate <b>(66)</b> ; (a) <sup>13</sup> CH <sub>3</sub> (b) DEPT135 and (c) DEPT90	97
25	The Heck reaction between 4-bromoanisole <b>(59)</b> with methyl acrylate <b>(61)</b> in [B <sub>3</sub> plim]CF <sub>3</sub> SO <sub>3</sub> <b>(49)</b> ; (a) without PPh <sub>3</sub> and (b) with PPh <sub>3</sub>	98
26	The Heck reaction between 4-bromoaniline <b>(60)</b> with methyl acrylate <b>(61)</b> in [B <sub>3</sub> plim]CF <sub>3</sub> SO <sub>3</sub> <b>(49)</b> ; (a) without PPh <sub>3</sub> and (b) with PPh <sub>3</sub>	99

## **CHAPTER 1**

### **INTRODUCTION**

#### **1.1 General Introduction**

The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances is the main goal of green chemistry [1]. The identification of environmentally benign solvents and separation processes is one of the most active research areas in this field today. Most traditional chemical processes use large quantities of organic solvents, because of their volatility, flammability and toxicity are incompatible with the aims of green chemistry. An ideal solvent for green chemistry should have low volatility, be chemically and physically stable, easy to handle, recyclable and reusable. Recently, possible replacements for traditional solvents that are more compatible with the aims of green chemistry are ionic liquids.

Ionic liquids are simply liquids composed entirely of ions [2]. They have garnered increasing interest in the last few years as novel solvents for synthesis, separations, electrochemistry and process chemistry. Organic ionic liquids were known for almost a century, but it was only during the last decade or so that they

emerged as important materials with a growing application base sufficient to sustain interest in their development.

## 1.2 Background of Research and Problem Statement

The Heck reaction has been studied intensively and numerous excellent surveys on a wide variety of different aspects of this reaction have been published [3], including; i) the development of ligands for this reaction, ii) advances in mechanistic studies, iii) the reactivity and the selectivity of the reactions, and iv) application in natural products synthesis. This thesis will discuss the latter topic, in which the use of ionic liquids as the solvent in the Heck reactions of aryl bromides.

Although there have been numerous reports on the use of ionic liquids in the Heck reactions [4-6], the fundamental studies of the relationship between the properties of ionic liquids and the improved performance compared to the conventional solvents are still rare. For example, many studies have found that the reaction rates, conversions and selectivities are enhanced to different degrees, though the reason why the ionic liquids show higher efficiency or specificity in the reaction is still an open question.

Moreover, there appears to be some confusion concerning the reactivity of aryl halides. In many studies, reactive aryl iodides substrates are routinely used to test the efficiency of a novel catalytic system, when it has been clearly demonstrated that even unligated palladium precursors can easily achieved extremely high turnover numbers (TONs), where most of them were up to millions [7]. Furthermore, the couplings of different types of aryl halides with methyl acrylate have very different rate-determining steps. This has important implication for the development of catalysts for the activation of unreactive aryl halides such as bromides and



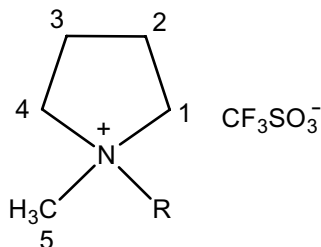
chlorides. Despite numerous reports of catalytic systems with impressive TONs, the majority of these studies were performed using electron-poor aryl halides, typically 4-bromoacetophenone and electron-poor olefins such as acrylates and styrenes.

The current challenge lies in the development of catalytic systems that will activate unreactive aryl halides towards Heck catalysis, especially aryl bromides and chlorides where the TONs still remain in the lower hundreds. Although certain aspects of this thesis have been covered by previous researchers [8, 9], a study addressing the Heck reactions of aryl bromides is considered to be particularly timely.

Homogeneous catalysis offers many advantages such as high selectivity, low investment cost and flexible operations under mild condition with easy mixing and heat removal. The quests for new catalyst immobilization or recovery strategies to facilitate its reuse are incessant. An approach which has been industrially applied is the use of liquid-liquid two-phase systems wherein the catalyst is immobilized in a polar liquid phase, and water operates as the second phase [10]. This approach is effective towards organic products, which are poorly miscible. Although the use of water has been largely developed, it still has some limitations; it may be coordinating towards the active metal centre, react with the metal-carbon bond or low solubility for some reactants [11]. Moreover, the high consumption of the expensive palladium catalyst makes it a relatively impractical process on an industrial scale. Therefore, recycling the catalyst is a key objective.

To overcome these problems, this research is intended to answer some curiosities, if not all, regarding the application of ionic liquids in the Heck reaction by introducing a new series of ionic liquids of *N*-alkyl-*N*-methylpyrrolidinium trifluoromethanesulfonate salts, R[Mplim]CF<sub>3</sub>SO<sub>3</sub> (Figure 1.1), as the solvent for this fascinating reaction. Furthermore, the discussion will be based on the optimization of the ionic liquids system rather than modification of the complicated catalyst precursors. The purpose of this thesis is therefore to present the underlying principles

and outcomes of the latest efforts to activate these more difficult substrates for Heck catalysis, thus highlighting the challenges in this highly competitive area.



**Figure 1.1** General structure of the *N*-alkyl-*N*-methylpyrrolidinium trifluoro methanesulfonate salts

### 1.3 Objectives of Research

There are three key objectives of this research. Firstly, to synthesize a new series of room temperature ionic liquids (RTILs) derived from the *N*-alkyl-*N*-methyl pyrrolidinium cation, R[Mplim]<sup>+</sup> and the trifluoromethanesulfonate anion, CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>. Secondly, to apply these ionic liquids as the solvents to replace the conventional organic solvent in the Heck reactions of several aryl bromides with different reactivities. Finally, to determine the optimum conditions for the reaction to proceed in the ionic liquid mediums by varying the parameters of the reaction; the bases, palladium catalyst loadings, reaction temperatures and addition of co-ligand.

## 1.4 Scope of Research

The first objective was achieved by reacting *N*-methylpyrrolidine (**38**) with several alkyl iodides through the quaternization process to produce a series of iodide salts (**39-45**). Next, these iodide salts (**39-45**) underwent anion-exchange with silver trifluoromethanesulfonate through the metathesis reaction to obtain the desired ionic liquids (**46-52**). These ionic liquids (**46-52**) were then characterized by using the digital melting point apparatus, the conductivity meter, the proton and carbon NMR spectroscopies and the CHN elemental analysis.

For the second objective, the ionic liquid which gave the highest yield and purity was chosen as the solvent in the palladium-catalyzed Heck reactions. In this reaction, methyl acrylate (**61**) was reacted with five aryl bromides with different reactivity; 4-bromonitrobenzene (**56**), 4-bromoacetophenone (**57**), bromobenzene (**58**), 4-bromoanisole (**59**) and 4-bromoaniline (**60**), respectively. The Heck adducts (**62-66**) were then characterized by using the digital melting point apparatus, the proton and carbon NMR spectroscopies and the CHN elemental analysis.

Finally, the third objective was achieved by conducting all the experiments in various combination of the reaction components; bases ( $\text{Et}_3\text{N}$ ,  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$  and  $\text{NaOAc}$ ), Pd catalyst loadings (1.0, 1.5 and 2.0 mmol%) and reaction temperatures (80, 100 and 120°C). The percentage conversion rate of the Heck adducts (**62-66**) were determined from the proton NMR spectra. The system which gave the highest conversion rate for the entire Heck adducts (**62-66**) was considered as the optimum reaction conditions.

## **1.5 Thesis Outline**

This thesis is divided into 5 main chapters. The main idea and objectives of this thesis are described in Chapter 1, followed by a concise discussion on literature reviews in Chapter 2. Chapter 3 provides the discussion on the findings of the experiments, while the experimental methods were described in Chapter 4. Finally, Chapter 5 provides the summary of all the chapters and suggestions for the future works.

## REFERENCES

1. Matlack, A.S. *Introduction to Green Chemistry*. New York: Marcel Dekker, Inc. 2001
2. Welton, T. Ionic Liquids in Catalysis. *Coord. Chem. Rev.* 2004. 248(21-24): 2459-2477.
3. Whitcombe, N.J., Hii, K.K. and Gibson, S.E. Advances in the Heck Chemistry of Aryl Bromides and Chlorides. *Tetrahedron*. 2001. 57(35): 7449-7476.
4. Calò, V., Nacci, A., Lopez, L. and Mannarini, N. Heck Reaction in Ionic Liquids Catalyzed by a Pd-benzothiazole Carbene Complex. *Tet. Lett.* 2000. 41(46): 8973-8976.
5. Howarth, J. and Dallas, A. Moisture Stable Ambient Temperature Ionic Liquids: Solvents for the New Millenium. 1. The Heck Reaction. *Molecules*. 2000. 5(6): 851-855.
6. Okubo, K., Shirai, M. and Yokoyama, C. Heck Reactions in Non-Aqueous Ionic Liquid Using Silica Supported Palladium Complex Catalysts. *Tet. Lett.* 2002. 43(39): 7115-7118.
7. Qadir, M., Möchel, T. and Hii, K.K. Examination of Ligand Effects in the Heck Arylation Reactions. *Tetrahedron*. 2000. 56(40): 7975-7979.
8. Riermeier, T.H. Zapf, A. and Bellar, M. Palladium Catalyzed C–C- and C–N- Coupling Reactions of Aryl Chlorides. *Top. Catal.* 1997. 4(3-4): 301-309.
9. Iyer, S., Kulkarni, G.M. and Ramesh, C. Mizoroki-Heck Reactions, Catalysis by Nitrogen Ligand Pd Complexes and Activation of Aryl Bromides. *Tetrahedron*. 2004. 60(9): 2163-2172.

10. Cornils, B. Industrial Aqueous Biphasic Catalysis: Status and Directions. *Org. Process Res. And Dev.* 1998. 2(2): 121-127.
11. Olivier, H. Recent Developments in the Use of Non-Aqueous Ionic Liquids for Two-Phase Catalysis. *J. Mol. Catal. A: Chem.* 1999. 146(1-2): 285-289.
12. Earle, M.J. and Seddon K.R. Ionic Liquids. Green Solvents for the Future. *Pure Appl. Chem.* 2000. 72(7): 1391-1398.
13. Yang, Z. and Pan, W. Ionic Liquids: Green Solvents for Nonaqueous Biocatalysis. *Enzyme Microb. Technol.* 2005. 37(1): 19-28.
14. Chemical & Engineering News. Eyes on Ionic Liquids. *Science / Technology.* May 15. 2000. 78(20): 37-50.
15. Jork, C., Kristen, C., Pieraccini, D., Stark, A. Chiappe, C., Beste, Y.A. and Arlt, W. Tailor-Made Ionic Liquids. *J. Chem. Thermodyn.* 2005. 37(6): 537-558.
16. Welton, T. Room Temperature Ionic Liquids. Solvent for Synthesis and Catalysis. *Chem. Rev.* 1999. 99(8): 2071-2084.
17. Wasserscheid, P. and Keim, W. Ionic Liquids – New “Solution” for Transition Metal Catalysis. *Angew. Chem. Int. Ed. Engl.* 2000. 39(21): 3772-3789.
18. Forsyth, S., Golding, J., Mac Farlane, D.R. and Forsyth, M. *N*-methyl-*N*-alkylpyrrolidinium Tetrafluoroborate Salts: Ionic Solvents and Solid Electrolytes. *Electrochim. Acta.* 2001. 46(10-11): 1753-1757.
19. Matsumoto, H., Matsuda, T. and Miyazaki, Y. Room Temperature Molten Salts Based on Trialkylsulfonium Cations and Bis(trifluoromethylsulfonyl) imide. *Chem. Lett.* 2000. 29(12): 1430-1431.
20. Varma, R.S. and Namboodri, V.V. An Expedient Solvent-Free Route to Ionic Liquids Using Microwaves. *Chem. Commun.* 2001. 7: 643-644.
21. Chauvin, Y., Olivier, H. and De Souza. *Catalytic Composition for Biphasic Catalysis, in Particular Using Nickel Complexes, and a Process for the Oligomerization of Olefins.* US Patent 5723712. 1998.
22. Bósmann, A., Franciéo, G., Janssen, E., Solinas, M., Leitner, W. and Wasserscheid, P. Activation, Tuning and Immobilization of Homogeneous Catalysts in an Ionic Liquid / Compressed CO<sub>2</sub> Continuous-Flow System. *Angew. Chem. Int. Ed. Engl.* 2001. 40(14): 2697-2699.

23. Earle, M.J., McCormac, P.B. and Seddon, K.R. Regioselective Alkylation in Ionic Liquids. *Chem. Commun.* 1998. 20: 2245-2246.
24. Seddon, K.R. Ionic Liquids for Clean Technology. *J. Chem. Technol. Biotechnol.* 1997. 68(4): 351-356.
25. Mac Farlane, D.R., Sun, J., Golding, J., Meakin, P. and Forsyth, M. High Conductivity Molten Salts Based on the Imide Ion. *Electrochim. Acta.* 2000. 45(8-9): 1271-1278.
26. Larsen, A.S., Holbrey, J.D., Tham, F.S. and Reed, C.A. Designing Ionic Liquids: Imidazolium Melts with Inert Carborane Anions. *J. Am. Chem. Soc.* 2000. 122(30): 7264-7272.
27. Mac Farlane, D.R., Golding, J., Forsyth, S., Forsyth, M. and Deacon, G.B. Low Viscosity Ionic Liquids Based on Organic Salts of the Dicyanamide Anion. *Chem. Commun.* 2001. 16: 1430-1431.
28. Yoshizawa, M., Hirao, M., Ito-Akita, K. and Ohno, H. Ion Conduction in Zwitterionic-Type Molten Salts and Their Polymers. *J. Mater. Chem.* 2001. 11(4): 1057-1062.
29. Koel, M. Physical and Chemical Properties of Ionic Liquids Based on the Dialkylimidazolium Cation. *Proc. Est. Acad. Sci. Chem.* 2000. 49(3): 145-155.
30. Poole, C.F. Chromatographic and Spectroscopic Methods for the Determination of Solvent Properties of Room Temperature Ionic Liquids. *J. Chromatogr. A.* 2004. 1037(1-2): 49-82.
31. Carmichael, H. Making Waves. *Chemistry in Britain.* 2000. January: 36-38.
32. Zhao, D., Wu, M., Kou, Y. and Min, E. Ionic Liquids: Application in Catalysis. *Catal. Today.* 2002. 74(1-2): 1-33.
33. Holbrey, J.D. and Seddon, K.R. Ionic Liquids. *Clean Products and Processes.* 1999. 1: 223-236.
34. Chauvin, Y., Olivier-Bourbigou, H. and Oligomerisation of n-butenes Catalysed by Nickel Complexes Dissolved in Organo-Chloroaluminate Ionic Liquids. *J. Cat.* 1997. 165(2): 275-278.
35. Carlin, R.T. and Wilkes, J.S. Complexation of  $Cp_2MCl_2$  in a Chloroaluminate Molten-Salt – Relevance to Homogenous Ziegler-Natta Catalysis. *J. Mol. Catal.* 1990. 63(2): 125-129.

36. Wasserscheid, P. and Welton, T. *Ionic Liquids in Synthesis*, Weinheim: Wiley-VCH Verlag. 2003
37. Chauvin, Y. and Musmann, L. and Olivier, H. A Novel Class of Versatile Solvents for Two-Phase Catalysis: Hydrogenation, Isomerization and Hydroformylation of Alkene Catalyzed by Rhodium Complexes in Liquid 1,3-dialkylimidazolium Salts. *Angew. Chem. Int. Ed. Eng.* 1995. 34(23-24): 2698-2700.
38. Mehnert, C.P., Cook, R.A., Dispenziere, N.C. and Mozeleski, E.J. Biphasic Hydroformylation Catalysis in Ionic Liquid Media. *Polyhedron*. 2004. 23(17): 2679-2688.
39. Yeung, K.S., Farkas, M.E., Qiu, Z. and Yang, Z. Friedel-Crafts Acylation of Indoles in Acidic Imidazolium Chloroaluminate Ionic Liquid at Room Temperature. *Tet. Lett.* 2002. 43(33): 5793-5795.
40. Heck, R.F. and Nolley, J.P. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions With Aryl, Benzyl and Styryl Halides. *J. Org. Chem.* 1972. 37(14): 2320-2322.
41. Hagiwara, H., Shimizu, Y., Hoshi, T., Suzuki, T., Ando, M., Ohkubo, K. and yokoyama, C. Heterogeneous Heck Reaction Catalyzed by Pd/C in Ionic Liquid. *Tet. Lett.* 2001. 42(26): 4349-4351.
42. Littke, A.F. and Fu, G.C. Heck Reactions in the Presence of P(*t*-Bu)<sub>3</sub>: Expanded Scope and Milder Reaction Conditions for the Coupling of Aryl Chlorides. *J. Org. Chem.* 1999. 64(1): 10-11.
43. Heck, R.F. Palladium-Catalyzed Reactions of Organic Halides with Olefins. *Acc. Chem. Res.* 1979. 12(4): 146-151.
44. Mo, J., Liu, S. and Xiao, J. Palladium-Catalyzed Regioselective Heck Arylation of Electron-Rich Olefins in a Molecular Solvent-Ionic Liquid Cocktail. *Tetrahedron*. 2005. 61(41): 9902-9907.
45. Zhao, S.F., Zhou, R.X. and Zheng, X.M. Heterogeneous Heck Reaction Catalyzed by a Series of Amine-Palladium(0) Complexes. *J. Mol. Catal. A: Chem.* 2004. 211(1-2): 139-142.
46. Shibasaki, M. Boden, C.D.J. and Kojima, A. The Assymmetric Heck Reaction. *Tetrahedron*. 1997. 53(22): 7371-7393.
47. Jeffery, T. On the Efficiency of Tetraalkylammonium Salts in Heck Type Reactions. *Tetrahedron*. 1996. 52(30):10113-10130.



48. Hegedus, L.S. Palladium(II)-Assisted Reactions of Monoolefins. *Tetrahedron*. 40(13): 2415-2434.
49. Ohff, M., Ohff, A. van der Boom, M.E. and Milstein, D. Highly Active Pd(II) PCP-Type Catalysts for the Heck Reaction. *J. Am. Chem. Soc.* 1997. 119(48): 11687-11688.
50. Mac Farlane, D.R., Meakin, P., Sun, J. Amini, N and Forsyth, M. Pyrrolidinium Imides: A New Family of Molten Salts and Conductive Plastic Crystal Phases. *J. Phys. Chem. B*. 1999. 103(20): 4164-4170.
51. Nair, V., Bindu, S. and Sreekumar, V. N-Heterocyclic Carbenes: Reagents, Not Just Ligands!. *Angew. Chem. Int. Ed.* 2004. 43(39): 5130-5135.
52. Exter, O. and Vřetečka, V. The Concept of Mesomeric Dipole Moment. *Tet. Letters*. 13(45): 4613-4616.
53. Mustaffa Shamsuddin, Sofian Ibrahim, Mohamad Hafiz Ahmad Tajudin, Hasnah Mohd Sirat and Zakaria Bahari (2003). Ionic Liquids: New Solvent for organic Reaction. *Proceedings of Annual Fundamental Science Seminar (AFSS)*. May 20-21. Johor Bahru, Johor: Institut Ibnu Sina (IIS), 87-91.
54. Sheldon, R. Catalytic Reactions in Ionic Liquids. *Chem. Commun.* 2001. 23: 2399-2407.
55. Bonhôte, P., Dias, A.P., Papageorgiou, N., K.Kalyanasundaram, K. and Grätzel, M. Hydrophobic, Highly Conductive Ambient-Temperature Molten Salts. *Inorg. Chem.* 1996. 35(5): 1168-1178.
56. Crosthwaite, J.M., Aki, S.N.V.K., Maginn, E.J., Brennecke, J.F. Liquid Phase Behavior of Imidazolium-Based Ionic Liquids with Alcohols: Effect of Hydrogen Bonding and Non-Polar Interactions. *Fluid Phase Equilib.* 2005. 228-229: 303-309.
57. Dzyuba, S.V. and Bartsch, R.A. New Room-Temperature Ionic Liquids With C<sub>2</sub>-Symmetrical Imidazolium Cations. *Chem. Commun.* 2001. 16: 1466-1467.
58. Sun, J., Mac Farlane, D.R. and Forsyth, M. A New Family of ionic Liquids Based on the 1-alkyl-2-methylpyrrolinium Cation. *Electrochim. Acta.* 2003. 48(12): 1707-1711.
59. Lu, W., Fadeev, A.G., Qi, B., Smela, E., Mattes, B.R., Ding, J., Spinks, G.M., Mazurkiewicz, J., Zhou, D., Wallace, G.G., Mac Farlane, D.R., Forsyth, S.A. and Forsyth, M. Use of Ionic Liquids for  $\pi$ -Conjugated Polymer Electrochemical Devices. August 9, 2002. *Science*. 297(5583): 983-987.

60. Sofian Ibrahim (2004). *Sintesis dan Penggunaan Cecair Ionik Terbitan N-metilpirolidina Dalam Tindak Balas Diels-Alder*. Universiti Teknologi Malaysia: M.Sc. Thesis.
61. Fuller, J., Carlin, R.T. and Osteryoung, R.A. The Room Temperature Ionic Liquid 1-ethyl-3-methylimidazolium Tetrafluoroborate: Electrochemical Couples and Physical Properties. *J. Electrochem. Soc.* 1997. 144(11): 3881-3885.
62. Hagiwara, R., Hirashige, T., Tsuda, T. and Ito, Y. Acidic 1-ethyl-3-methylimidazolium Fluoride: A New Room Temperature Ionic Liquid. *J. Fluorine Chem.* 1999. 99(1): 1-3.
63. Hagiwara, R. and Ito, Y. Room Temperature Ionic Liquids of Alkylimidazolium Cations and Fluoroanions. *J. Fluorine Chem.* 2000. 105(2): 221-227.
64. Anthony, J.L., Magnin, E.J. and Brennecke, J.F. Solution Thermodynamics of Imidazolium-Based Ionic Liquids and Water. *J. Phys. Chem. B.* 2001. 105(44): 10942-10949.
65. Gordon, C.M. New Developments in Catalysis Using Ionic Liquids. *Appl. Catal. A.* 2001. 222(1-2): 101-117.
66. Cammarata, L., Kazarian, S.G., Salter, P.A. and Welton, T. Molecular States of Water in Room Temperature Ionic Liquids. *Phys. Chem. Chem. Phys.* 2001. 3(23): 5192-5200.
67. Domanska, U., Marciniak, A. Solubility of 1-alkyl-3-methylimidazolium Hexafluorophosphate in Hydrocarbons. *J. Chem. Eng. Data.* 2003. 48(3): 451-456.
68. Najdanovic-Visak, V., Esperanca, J.M.S.S, Rebelo, L.P.N., da Ponte, M.N., Guedes, H.J.R., Seddon, K.R. and Szydowski. Phase Behaviour of room Temperature Ionic Liquid Solution: An Usually Large Co-Solvent Effects in (Water + Ethanol). *Phys. Chem. Chem. Phys.* 2002. 4(10): 1701-1703.
69. Gutowski, K.E., Broker, G.A., Willauer, H.D., Huddleston, J.G., Swatloski, R.P., Holbrey, J.D. and Rogers, R.D. Controlling the Aqueous Miscibility of Ionic Liquids: Aqueous Biphasic Systems of Water-Miscible Ionic Liquids and Water-Structuring Salts for Recycle, Metathesis, and Separations. *J. Am. Chem. Soc.* 2003. 125(22): 6632-6633.

70. Crosthwaite, J.M., Aki, S.N.V.K., Maginn, E.J., Brennecke, J.F. Liquid Phase Behavior of Imidazolium-Based Ionic Liquids with Alcohols. *J. Phys. Chem. B*. 2004. 108(16): 5113-5119.
71. Olivier-Bourbigou, H. and Magna, L. Ionic Liquids: Perspectives for Organic and Catalytic Reactions. *J. Mol. Catal. A: Chem.* 2002. 182-183: 419-437.
72. Littke, A.F. and Fu, G.C. Palladium Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem. Int. Ed.* 2002. 41(22): 4176-4211.
73. Scrivanti, A., Bertoldini, M., Matteoli, U., Beghetto, V., Antonaroli, S., Marini, A. and Crociani, B. Highly Efficient Heck Olefin Arylation in the Presence of Iminophosphine – Palladium(0) Complexes. 2005. *J. Mol. Catal. A: Chem.* 235(1-2): 12-16.
74. Hegedus, L.S. *Transition Metal in the Synthesis of Complex Organic Molecules*. Mill Valey, CA: University Science Books. 1994
75. Zhao, F., Bhanage, B.M., Shirai, M. and Arai, M. Heck Reactions of Iodobenzene and Methyl Acrylate with Conventional Supported Palladium Catalysts in the Presence of Organic and / or Inorganic Bases Without Ligands. *Chem. --Eur. J.* 2000. 6(5): 843-848.
76. Martin, W.B. and Kateley L.J. The Heck Reaction: A Microscale Synthesis Using a Palladium Catalyst. *J. Chem. Educ.* 2000. 77(6): 757-759.
77. Heidenreich, R.G., Krauter J.G.E., Pietsch, J. and Köhler, K. Control of Pd Leaching in Heck Reactions of Bromoarenes Catalyzed by Pd Supported on Activated Carbon. *J. Mol. Catal. A: Chem.* 2002. 182-183: 499-509.
78. Spencer, A. A Highly Efficient Version of the Palladium-Catalysed Arylation of Alkenes With Aryl Bromides. *J. Organomet. Chem.* 1983. 258(1): 101-108.
79. Sofian Ibrahim, Mustaffa Shamsuddin, Hasnah Mohd Sirat and Zakaria Bahari. Potensi Garam Piroldinium Sebagai Cecair Ion (2002). *Proceedings of 15<sup>th</sup> Malaysian Analytical Chemistry Symposium (SKAM-15)*. Sept 10-12. Minden, Penang: Universiti Sains Malaysia, *In Press*.
80. Callam, C.S. and Lowary, T.L. Suzuki Cross-Coupling Reactions: Synthesis of Unsymmetrical Biaryls in the Organic Laboratory. 2001. *J. Chem. Educ.* 78(7): 947-948.