Development of new c-n bond formation strategies based on transition metal-catalyzed amidation and aziridination of activated c-h and c=c bonds

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**DEVELOPMENT OF NEW C–N BOND FORMATION
STRATEGIES BASED ON TRANSITION METAL-
CATALYZED AMIDATION AND AZIRIDINATION OF
ACTIVATED C–H AND C=C BONDS**

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iii

TABLE OF CONTENT

Abstract	v
Publications	vii
Abbreviations	viii

PART I

Chapter I	Transition Metal-Catalyzed Nitrogen Atom Transfer Reactions Mediated by Hypervalent Iodine(III) Reagents	
1.1	Introduction	1
1.2	C-H and C=C Bond Functionalization	2
1.3	Initial Advances in Transition Metal-Catalyzed Nitrogen Atom Transfer Reactions	5
1.4	Transition Metal-Catalyzed Nitrogen Atom Addition to C=C Bonds	8
1.5	Transition Metal-Catalyzed Nitrogen Atom Insertion into C-H Bonds	28
1.6	Proposed Work	42

PART II

Chapter II	Ruthenium(II) Porphyrin-Catalyzed Amidation of Aldehydes	
2.1	Introduction	44
2.2	Results and Discussion	46
2.3	Conclusion	59

Chapter III	Copper-Catalyzed Amidation of Aldehydes	
3.1	Introduction	61
3.2	Results and Discussion	62
3.3	Conclusion	80
Chapter IV	Copper-Catalyzed Amidation of 1,3-Dicarbonyl Compounds	
4.1	Introduction	81
4.2	Results and Discussion	82
4.3	Conclusion	95
PART III		
Chapter V	Copper Iodide-Catalyzed Aziridination of Alkenes and Amidation of Alkanes	
5.1	Introduction	97
5.2	Results and Discussion	99
5.3	Conclusion	110
Chapter VI	Copper -Catalyzed Amidation of Aromatic Heterocycles	
6.1	Introduction	112
6.2	Results and Discussion	113
6.3	Conclusion	131
Part IV		
Chapter VII	Experimental Section	132
Chapter VIII	References	204

ABSTRACT

The work in this thesis was undertaken in Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences in Nanyang Technological University from January 2006 to December 2009 under the supervision of Asst. Prof. Philip Wai Hong Chan.

The work of this thesis has been directed toward the establishing of new transition metal-mediated nitrogen atom transfer reactions to activated C–H and C=C bonds as a means to accessing nitrogen containing compounds of biological and materials interest in an efficient and selective manner. This thesis is divided into four parts:

- Part I consists of Chapter I, which gives an account of transition metal-catalyzed nitrogen transfer reactions mediated by hypervalent iodine(III) reagents. Progress in inter- and intramolecular aziridination of alkenes, as well as inter- and intramolecular amidation of saturated and aryl C–H bonds, and its application toward natural product synthesis will be discussed.
- Part II is aimed at exploring new substrates for the transition metal-catalyzed nitrogen atom transfer reactions. Chapter II details the establishment of a new catalytic method employing ruthenium(II) porphyrin as catalyst for the selective nitrogen atom insertion to the aldehydic C–H bond of aldehydes as a novel approach to amide bond synthesis. In Chapter III, a catalytic protocol that utilizes copper salts that are readily available from commercial sources, environmentally benign and cost-effective to effect the amidation of aldehydes is presented. This methodology is aimed at overcoming the limitations of the process posed by ruthenium(II) porphyrin catalysis. Mechanistic studies to delineate this amidation process will also be discussed. Chapter IV discusses the development of an enantioselective copper-catalyzed route to α -

hydroxy amino acids and 2-amino-1,3-diols *via* formal amidation of the α -C-H bond of β -keto esters and 1,3-dicarbonyl compounds.

- Part III is aimed at exploring the generality of these newly developed copper catalytic systems in terms of their reactivity and selectivity. Chapter V describes the application of copper iodide catalysis to known reactions such as inter- and intramolecular aziridination of alkenes as well as amidation of aryl alkanes. Chapter VI presents the copper-catalyzed amidation of aromatic heterocycles. A practical and straightforward method for the Ullmann coupling of azoles with aryl iodides to access the starting materials for the amidation of heteroarenes is discussed. The extension of this modified version of the Ullmann reaction to the coupling of phenols and thiols with aryl iodides is also presented.
- Part IV contains experimental data (Chapter VII) and references (Chapter VIII) pertaining to this thesis.

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1. "Practical Copper(I)-Catalysed Amidation of Aldehydes", Chang, J. W. W.; Ton, T. M. U.; Tania, S.; Taylor, P. C.; Chan, P. W. H. *Chem. Commun.* **2010**, 46, 922.
2. "Copper Iodide-Catalyzed Aziridination of Alkenes with Sulfonamides and Sulfamate Esters", Chang, J. W. W.; Ton, T. M. U.; Zhang, Z.; Xu, Y.; Chan, P. W. H. *Tetrahedron Lett.* **2009**, 50, 161.
3. "Copper-Catalyzed Ullmann Coupling under Ligand and Additive Free Conditions. Part 2: S-Arylation of Thiols with Aryl Iodides", Buranaprasertsuk, P.; Chang, J. W. W.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, 49, 2023.
4. "Copper-Catalyzed Ullmann Coupling under Ligand and Additive Free Conditions. Part 1: O-Arylation of Phenols with Aryl Halides", Chang, J. W. W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, 49, 2018.
5. "Highly Efficient Ruthenium(II) Porphyrin-Catalyzed Amidation of Aldehydes", Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, 47, 1138.
6. Practical Copper-Catalyzed N-Arylation of Nitrogen Heterocycles with Aryl Halides under Ligand and Additive Free Conditions", Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, 48, 245.

ABBREVIATIONS

Å	Angstrom
Ac	acetyl
acac	acetylacetonate
acacen	2,11-dihydroxy-4,9-dimethyl-5,8-diaza-2,4,8,10-dodecatratene
AnBOX	(<i>S,S</i>)-1,8-bis(4-(1-methylethyl)oxazolin-2-yl)anthracene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
bnp	1,1'-binaphthyl-2,2'-diyl phosphate
Boc	<i>tert</i> -butyloxycarbonyl
bp	4,7-diphenyl-1,10-phenanthroline
Bu	<i>n</i> -butyl
cHBOX	(<i>S,S</i>)-1,2-bis((<i>S</i>)-(4-phenyl)oxazolin-2-yl)cyclohexane
Cl ₃ terpy	4,4',4''-tri- <i>tert</i> -butyl-2,2':6'2''-terpyridine
cyclam	1,4,8,11-tetraazacyclotetradecane
DEAD	diethyl azodicarboxylate
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DTBM-SEGPPOS	5,5'-bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
esp	tetramethyl <i>m</i> -benzenedipropionic carboxylate
h	hour
H ₂ F ₂₀ -TPP	5,10,15,20-tetrakis-(pentafluorophenyl)-21 <i>H</i> ,23 <i>H</i> -porphyrin
H ₂ OEP	2,3,7,8,12,13,17,18-octaethyl-21 <i>H</i> ,23 <i>H</i> -porphyrin
H ₂ TDCPP	5,10,15,20-tetrakis-(2,6-dichlorophenyl) porphyrin
H ₂ TPP	5,10,15,20-tetrakis-(phenyl)-21 <i>H</i> ,23 <i>H</i> -porphyrin

H ₂ TTP	5,10,15,20-tetrakis-(4-methylphenyl)-21 <i>H</i> ,23 <i>H</i> -porphyrin
HPLC	high performance liquid chromatography
^{<i>i</i>} Pr	isopropyl
^{<i>i</i>} Pr ₃ tacn	1,4,7-triisopropyl-1,4,7-triazacyclononane
Mbs	methylbenzylsulfonyl
Me	methyl
MEOX	μ -(methyl 2-oxo-4-oxazolidinecarboxylate
min	minute
MPR	Merrifield [®] peptide resin
MS	molecular sieves
Ms	methanesulfonyl, mesyl
nap	<i>N</i> '-4-dimethyl- <i>N</i> -(2-oxopiperidin-3-yl)benzenesulfonamide
^{<i>n</i>} Hex	<i>n</i> -hexyl
NMR	Nuclear magnetic resonance
^{<i>n</i>} Pr	<i>n</i> -propyl
Ns	<i>p</i> -nitrobenzenesulfonyl, nosyl
nta	<i>N</i> -1,8-naphthoyl-alaninate
nttl	<i>N</i> -1,8-naphthoyl- <i>tert</i> -leucinate
Nu	nucleophile
OAc	acetoxy
oct	octanoate
OMe	methoxy
PEG	poly ethyleneglycol
Ph	phenyl

PhBOX	(<i>S,S</i>)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline)
Por	porphyrin
ppm	parts per million
PyBOX	2,6-bis[4-phenyl-2-oxazoliny]pyridine
rt	room temperature
SEGPPOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
Ses	trimethylethylsilylsulfonyl
tacn	triazacyclononane
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
^t Bu	<i>tert</i> -butyl
^t Bu ₃ tpy	4,4',4''-tri- <i>tert</i> -butyl-2,2':6'2''-terpyridine
tBuBOX	(<i>S,S</i>)-2,2'-isopropylidenebis(4- <i>tert</i> -butyl-2-oxazoline)
Tces	trichloroethylsulfonyl
TCPTAD	adamantan-1-yl-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetate
TCPTTL	<i>N</i> -tetrachlorophthaloyl- <i>tert</i> -leucinate
tfacam	trifluoroacetamide
TFPTTL	<i>N</i> -tetrafluorophthaloyl- <i>tert</i> -leucinate
THF	tetrahydrofuran
TLC	thin layer chromatography
Troc	2,2,2-trichloroethoxycarbonyl
Ts	<i>p</i> -toluenesulfonyl, tosyl
δ	delta
μ	micro

Chapter I. Transition Metal-Catalyzed Nitrogen Atom Transfer Reactions Mediated by Hypervalent Iodine(III) Reagents

1.1 Introduction

The vast majority of compounds, whether they be the building blocks of life to natural or synthetic products of biological and material interest, contain carbon-nitrogen bonds.¹ In addition, nitrogen-containing compounds have been shown to be invaluable building blocks in organic chemistry.² As such, the development of efficient and convenient synthetic strategies to nitrogen-containing functional groups is of fundamental importance in organic synthesis. Conventional synthetic methods to this ubiquitous compound class have generally relied upon addition or substitution of a nitrogen nucleophile to a carbon electrophile.³ Transition metal catalysis has also contributed significantly to the construction of C–N bonds by mediating reactions such as coupling of a wide variety of nitrogen nucleophiles with aryl and vinyl halides as well as hydroamination and diamination of π bonds of alkenes, allenes and alkynes.⁴ In general, these methodologies have often required activation of the electrophile through the pre-installation of reactive functional groups and in many cases, harsh reaction conditions that are required can lead to unwanted competitive side reactions. While this can be overcome through protection group chemistry, a consequence of this is the overall increase in the number of synthetic steps and resultant poor atom economy, which is undesirable when such methodologies are applied to the target synthesis of bioactive natural products and functional materials of current interest. Thus, new methods that can effect C–N bond formation by directly manipulating the carbon-hydrogen bonds of hydrocarbons would be of great synthetic value as such transformations hold the potential to overcome the limitations posed by traditional methodologies.

1.2 C-H and C=C Bond Functionalization

In recent years, transition metal-catalyzed carbon-hydrogen activation has gained considerable attention as a powerful and convenient synthetic strategy for carbon-carbon and carbon-heteroatom bond formation (Figure 1.1).⁵ The ability to selectively manipulate a specific C-H bond in the presence of other C-H bonds has provided an attractive atom-economical alternative to conventional strategies employing halogenated or metallated substrates. However, one of the key challenges in the field of C-H bond functionalization has remained the need to develop catalytic systems that are high yielding and general in terms of substrate scope and stereoselectivity.

Figure 1.1 Transition metal-catalyzed C-H bond functionalization.

Until recently, much of the work within this area of catalysis has been focused on developing transition metal-catalyzed carbenoid and oxygen atom transfer reactions to C=C and C-H bonds as versatile tools for carbon-carbon and carbon-oxygen bond formations.^{6,7} In the case of the former, this has typically involved the decomposition of a diazo compound to form the reactive carbene intermediate that subsequently adds to C=C bonds to form cyclopropanes or inserts into C-H bonds to give C-C coupling products.⁶ Similarly, the addition of an oxygen atom to a C=C bond or insertion into a C-H bond has been shown to proceed in the presence of stoichiometric amounts of oxidants such as iodosylbenzene (PhI=O), pyridine *N*-oxide and other peroxides to afford the

corresponding epoxides or alcohols.⁷ Such methodologies are well-established, shown to be highly selective and reported to have widespread applications in the synthesis of many natural products and bioactive compounds. In contrast, the analogous nitrogen atom transfer reactions have been less well developed despite their potential to provide a powerful and convenient synthetic route to amines and amine derivatives. Until recently, one reason for this lack of progress was noted to be due to the scarcity of easily accessible and suitable nitrogen sources to facilitate such transformations.

All this changed with a seminal report in 1975 by Yamada and co-workers detailing a straightforward and practical synthesis of (*p*-toluenesulfonyl)iminophenylidene (PhI=NTs) from (diacetoxyiodo)benzene (PhI(OAc)₂) and *p*-toluenesulfonamide (TsNH₂) (Scheme 1.1).⁸ In this work, a putative nitrene intermediate that was electrophilic in nature, was proposed to form *in situ* from decomposition of PhI=NTs.

Scheme 1.1 Synthesis of PhI=NTs.

The significant discovery of PhI=NTs and its analogues has since led to the advancement of transition metal-mediated nitrogen atom transfer reactions.^{9,10} Indeed, this has been elegantly demonstrated by the increasing use of this synthetic approach in the total synthesis of a variety of natural products and bioactive compounds, selected examples of which are shown in Figure 1.2.¹¹ The focal point of this introduction will be on the subsequent advances made in transition metal-catalyzed imino/nitrene transfer reactions mediated by hypervalent iodine(III) reagents.

Figure 1.2 Natural products synthesized *via* transition metal-catalyzed nitrogen atom transfer processes.

1.3 Initial Advances in Transition Metal-Catalyzed Nitrogen Atom Transfer Reactions

The unique property of $\text{PhI}=\text{NTs}$ as a nitrogen source was first explored by Breslow and Gellman who demonstrated its utility in inter- and intramolecular metal-imido/nitrene insertion processes.^{12,13} In this seminal work, the intermolecular amidation of cyclohexane with $\text{PhI}=\text{NTs}$ in the presence of either $[\text{Mn}(\text{TTP})\text{Cl}]$ **20** (H_2TTP = 5,10,15,20-tetrakis-(4-methylphenyl)-21*H*,23*H*-porphyrin) or $[\text{Fe}(\text{TTP})\text{Cl}]$ **21** as catalyst in CH_2Cl_2 was reported to give the insertion product *N*-cyclohexyl-*p*-toluenesulfonamide **22**, albeit in low yields of 3-7% (Scheme 1.2).¹²

Scheme 1.2 $[\text{Mn}(\text{TTP})\text{Cl}]$ **20** and $[\text{Fe}(\text{TTP})\text{Cl}]$ **21**-catalyzed amidation of cyclohexene.

Intramolecular metal-imido/nitrene insertion of 2,5-diisopropylbenzenesulfonyliminoiodinane **23** by a variety of catalysts was shown to be more efficient, furnishing the corresponding cyclic sulfonamide adduct **24** in up to 86% yield based on HPLC analysis (Scheme 1.3).¹³ Among the catalysts screened, the highest yield obtained was with $\text{Rh}_2(\text{OAc})_4$, which was coincidentally also reported to be among one of the most efficient catalysts in studies on metal-carbenoid transfer reactions to alkenes, affording cyclopropanes.¹⁴

Scheme 1.3 Transition metal-catalyzed intramolecular C-H insertion of iminoiodinane **23**

(cyclam = 1,4,8,11-tetraazacyclotetradecane).

Mansuy and co-workers subsequently communicated that intermolecular alkene aziridination catalyzed by iron(III) and manganese(III) porphyrin complexes could be accomplished.¹⁵ Reactions of a variety of aromatic alkenes **26** with PhI=NTs in the presence of either the manganese(III) porphyrin **20** or iron(III) porphyrins **21** and **28** as catalyst were shown to proceed smoothly and afford the corresponding aziridines **27-Ts** in 16-90% yields (Scheme 1.4).

Scheme 1.4 Manganese(III) and iron(III) porphyrin-catalyzed intermolecular aziridination of alkenes (H₂TDCPP = 5,10,15,20-tetrakis-(2,6-dichlorophenyl)-21*H*,23*H*-porphyrin).

Iron(III) porphyrin complexes were shown to convert aliphatic alkenes to their respective aziridines in moderate yields but with low to moderate chemo- and regioselectivity as demonstrated by the reaction of *cis*-2-hexene **29** (Table 1.1, entries 1-2).¹⁶ A re-examination of this protocol revealed that manganese(III) porphyrin catalysts were more selective toward insertion at the allylic C–H bond of alkenes although the transformation still suffered from low product yields and regioselectivity (entries 3-4).¹⁷

In both the aziridination and amidation processes reported by Mansuy and co-workers, the reactions were postulated to occur *via* formation of high valent complexes [M(V)=NTs] **35** or [M(IV)-NTs] **36** (Scheme 1.5, M = Mn or Fe).^{16,17} This was followed by a hydrogen abstraction/radical rebound process to give the carboradical intermediates **37** or **39**. Transfer of the NTs moiety to these putative radicals gave the respective products **31a-d** or **41**.

Table 1.1 Iron(III) and manganese(III) porphyrin-catalyzed reaction of *cis*-2-hexene **29** with PhI=NTs.

Entry	Catalyst	Yield (%)	
		Aziridines 30	Allylic amides 31
1	[Fe(TPP)(ClO ₄)] 32 ^a	12	20
2	[Fe(TDCPP)(ClO ₄)] 28	35	13
3	[Mn(TPP)(ClO ₄)] 33	<2	37
4	[Mn(TDCPP)(ClO ₄)] 34	11	26

^a H₂TPP = 5,10,15,20-tetrakis-(phenyl)-21*H*,23*H*-porphyrin

In general, these early works by the groups of Breslow and Mansuy were plagued by several drawbacks that included the need for an excess amount of substrate, lack of catalyst generality in terms of substrate scope, and low to moderate chemo- and regioselectivity. Coupled with low to moderate product yields, this lessened their utility in organic synthesis. Nevertheless, the mechanistic studies reported by these seminal works provided valuable insights on these processes that enabled further advances in this field, particularly in terms of understanding and improving the efficiency and selectivity of new catalyst systems.

Scheme 1.5. Proposed mechanism for iron(III) and manganese(III) porphyrin-catalyzed imido/nitrene transfer reactions.

1.4 Transition Metal-Catalyzed Nitrogen Atom Addition to C=C Bonds

1.4.1 Intermolecular Aziridination of Alkenes with PhI=NTs

It was not until the beginning of the 1990s when Evans and co-workers reported the next significant advance in this area of chemistry.^{18,19} In their work, copper(I) and copper(II) salts were shown to be superior to other metal complexes for the aziridination process. The reaction of a wide variety of substituted alkenes with PhI=NTs in the presence of copper catalysts such as Cu(MeCN)₄ClO₄, Cu(acac)₂ (acac = acetylacetonate) or Cu(OTf)₂ were reported to afford the aziridine products in 30-95% yields (Table 1.2, entries 1-3). A notable feature of this reported method was that no allylic amidation products were obtained for reactions with alkenes containing an aliphatic side chain, which implied copper had a low propensity to catalyze C-H insertion reactions. Evans and co-workers also suggested that the aziridination process was most likely to occur in a concerted manner *via* a copper(II) oxidation state. The earliest application of this copper-catalyzed aziridination methodology in natural product synthesis was subsequently demonstrated by the groups of Hudlicky and Overman in their respective total synthesis of pancrastatin **1** and (-)-hispidospermidin **2** (Scheme 1.6)^{11q-s}.

Scheme 1.6 Synthesis of (a) pancrastitatin **1** and (b) (-)-hispidospermidin **2**.

In 1993, Pérez and co-workers described the synthesis and utility of $[\text{Tp}'\text{Cu}(\text{C}_2\text{H}_4)]$ **42a** (Tp' = hydrotris(3,5-dimethyl-1-pyrazolyl)borate, Figure 1.3a) for aziridinations of alkenes with $\text{PhI}=\text{NTs}$.²⁰ In these reactions, the corresponding aziridine products were reported to be afforded in 40-90% yields (Table 1.2, entry 4). Following this work, Hutchings and co-workers detailed the use of the copper-exchanged zeolite $[\text{CuHY}]$ **43** (Y = zeolite) as a heterogeneous catalyst for this reaction (Table 1.2, entry 5).²¹ In this work, reactions with $\text{PhI}=\text{NTs}$ were shown to proceed smoothly within the intracrystalline space of the zeolite and afforded the desired aziridination products in 44-90% yields.

Figure 1.3 Copper and iron catalysts used in aziridination of alkenes with $\text{PhI}=\text{NTs}$.

Table 1.2 Transition metal-catalyzed intermolecular aziridination of alkenes with $\text{PhI}=\text{NTs}$.

Entry	Catalyst	Yield (%)	Ref.
1	$\text{Cu}(\text{MeCN})\text{ClO}_4$	45-90	18, 19
2	$\text{Cu}(\text{acac})_2$	30-95	18, 19
3	$\text{Cu}(\text{OTf})_2$	40-92	19
4	$[\text{Tp}^+\text{Cu}(\text{C}_2\text{H}_4)]$ 42a	40-90	20
5	$[\text{CuHY}]$ 43	44-90	21
6	$[(^i\text{Pr}_3\text{tacn})\text{Cu}(\text{OTf})_2]$ 44	25-96	22
7	copper(I) β -diketiminate 45	14-98	23
8	copper(I) pyridinophane 46	59-96	24
9	$[\text{Ru}(\text{TPP})(\text{NTs})_2]$ 48a or $[\text{Ru}(\text{OEP})(\text{NTs})_2]$ 48b	66-85	25
10	$\text{AgNO}_3 + ^t\text{Bu}_3\text{tpy}$ 50	66-91	27
11	$[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})(\text{BF}_4)]$ 52	7-85	28
12	$[\text{Fe}(\text{Cl}_3\text{terpy})]$ 53	68-97	29
13	$\text{Fe}(\text{OTf})_2$	24-90	30

As these copper-catalyzed methodologies still suffered from poor substrate scope and moderate to high catalyst loading, introduction of nitrogen-based ligands was envisaged to increase both the catalyst reactivity and substrate tolerance. In this context, copper complexes such as $[(^i\text{Pr}_3\text{tacn})\text{Cu}(\text{OTf})_2]$ **44** ($^i\text{Pr}_3\text{tacn}$ = 1,4,7-triisopropyl-1,4,7-

triazacyclononane),²² copper(I) β -diketiminate **45**²³ and copper(I) pyridinophane **46**²⁴ were applied to alkene aziridination (Figure 1.3b-d; Table 1.2 entries 6-8). They were shown to be effective for reactions of alkenes with PhI=NTs, affording the desired products in good to excellent yields.

In an attempt to provide an insight on the mechanism in these aziridination reactions, Che and co-workers communicated the synthesis and spectroscopic characterization of the bis(tosyl)imidoruthenium(VI) porphyrin complexes [Ru(TPP)(NTs)₂] **48a** and [Ru(OEP)(NTs)₂] **48b** (H₂OEP = 2,3,7,8,12,13,17,18-octaethyl-21*H*,23*H*-porphyrin).²⁵ Both ruthenium(II) complexes were shown to undergo stoichiometric imido/nitrene group transfer reactions with alkenes to give the corresponding aziridines in 66-85% yields (Table 1.2, entry 9). Extensive mechanistic studies revealed that these complexes were likely to be the reactive species in the aziridination process.²⁶ Moreover, the reaction was postulated to proceed *via* a stepwise mechanism with rate-determining formation of carboradical intermediate **49**.

Scheme 1.7 Plausible mechanism for [Ru(Por)(CO)]-catalyzed aziridination of *cis*-alkenes (Por = porphyrin).

He and Cui reported the first example of a disilver(I,I)-catalyzed aziridination of alkenes (Table 1.2, entry 10). The combination of AgNO₃ and ^tBu₃tpy **50** (^tBu₃tpy = 4,4',4''-tri-*tert*-butyl-2,2':6'2''-terpyridine) was shown to form the active species [Ag₂(^tBu₃tpy)₂(NO₃)₂] **51** *in situ* that mediated the aziridination of alkenes with

PhI=NTs.²⁷ In these reactions, the aziridine products were furnished in good to excellent yields. Notably, no competitive insertion byproducts were observed for reactions of alkenes containing an aliphatic side chain.

More recently, Hossain and co-workers revealed that the Lewis acidic iron complex $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})(\text{BF}_4)]$ **52** (Figure 1.3e) could facilitate aziridination of a variety of alkenes in product yields of 7-85% (Table 1.2, entry 11).²⁸ However, the substrate scope of this catalyst was found to be limited to phenyl substituted alkenes. On the other hand, Che and co-workers showed that alkene aziridination in the presence of $[\text{Fe}(\text{Cl}_3\text{terpy})_2]$ **53** (Cl_3terpy = 4,4',4''-tri-*tert*-butyl-2,2':6'2''-terpyridine, Figure 1.3f) as catalyst was applicable to a wider range of starting alkenes and gave the corresponding products in 68-97% yields (Table 1.2, entry 12).²⁹ This work was followed by a report by Bolm and co-workers, who demonstrated a $\text{Fe}(\text{OTf})_2$ -catalyzed version of this reaction that gave the corresponding products in moderate to good yields of 24-90% (Table 1.2, entry 13).³⁰

1.4.2 Intermolecular Aziridination of Alkenes with Other Iminoiodinanes

Despite the potential shown by dirhodium(II,II) catalysis to effect intramolecular C–H insertion of **3** mentioned earlier in Section 1.3, the use of the Group 9 metal as catalyst in alkene aziridinations with PhI=NTs have been reported to be less successful. Evans and co-workers showed that aziridination of styrene with PhI=NTs using $\text{Rh}_2(\text{OAc})_4$ as catalyst led to formation of *N*-tosyl-2-phenylaziridine **27a** in 48% yield.¹⁹ The laboratory of Müller noted a similar result with the same catalyst and substrate (Scheme 1.8).³¹

Scheme 1.8 $\text{Rh}_2(\text{OAc})_4$ -catalyzed aziridination of styrene with PhI=NTs.

Interestingly, when Müller and co-workers switched the nitrene precursor from PhI=NTs to (*p*-nitrobenzenesulfonyl)iminophenylidiodine (PhI=NNs), aziridination of a variety of aromatic alkenes in the presence of $\text{Rh}_2(\text{OAc})_4$ was shown to proceed in yields up to 85% (Scheme 1.9).^{31,32} In this work, reactions of alkenes with aliphatic substituents with PhI=NNs was shown to be less efficient, affording the corresponding products in moderate yields of 27-54%. In addition, mechanistic studies suggested that the aziridination process to proceed *via* reaction of the alkene with a putative metallonitrene intermediate in a concerted manner.³³ In their studies, no evidence for a radical pathway was found.

Scheme 1.9 $\text{Rh}_2(\text{OAc})_4$ -catalyzed aziridination of alkenes with PhI=NNs .

In 1999, Dodd and Dauban described the utility of a non-arylsulfonamide-based iminoiodine as a nitrogen source.³⁴ In reactions mediated by CuOTf or $\text{Cu}(\text{OTf})_2$, aziridination of a series of alkenes with (trimethylsilyl)ethanesulfonyl iminophenylidiodine (PhI=NSes) were shown to afford the corresponding aziridines in 33-68% yields (Scheme 1.10). In these reactions, the product yields were found to be comparable to those afforded for the analogous copper-catalyzed reactions of alkenes with PhI=NTs . To demonstrate the synthetic applications of this approach, the removal of the *Ses* moiety with TASF (TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate) was shown to occur under ambient conditions. Moreover, the facile aziridine ring opening by a variety of nucleophiles such as sodium borohydride and

arylthiophenols was also reported to proceed smoothly and give the corresponding 1,2-difunctionalized amines **55** in good yields of up to 90%.

Scheme 1.10 Copper-catalyzed aziridination with $\text{PhI}=\text{NSes}$ followed by (a) deprotection or (b) ring opening by nucleophiles.

As a continuation of their work on $\text{Fe}(\text{OTf})_2$ -catalyzed alkene aziridinations with $\text{PhI}=\text{NTs}$, Bolm and co-workers revealed that 5-methyl-2-pyridinesulfonyliminoiodinane ($\text{PhI}=\text{NSO}_2\text{Py}$) was also a suitable nitrene source.³⁵ In this work, reactions of alkenes with $\text{PhI}=\text{NSO}_2\text{Py}$ in the presence of quinaldinic acid and ethylmethyylimidazolium bis((trifluoromethyl)sulfonyl) amide (emim BTA) was shown to furnish the aziridine products in 36->95% yields (Scheme 1.11).

Scheme 1.11 $\text{Fe}(\text{OTf})_2$ -catalyzed aziridination of alkenes with $\text{PhI}=\text{NSO}_2\text{Py}$.

1.4.3 Intermolecular Aziridination of Alkenes with Sulfonamides in the Presence of a Hypervalent Iodine(III) Oxidant

While iminoiodinanes have been extensively used to convert alkenes to the corresponding aziridines, one of the major drawbacks of using such reagents has been their synthesis, which can be time consuming and arduous.⁹ⁱ Furthermore, iminoiodinanes have been shown to have a short shelf-life and be potentially explosive, thus limiting their applications to large scale synthesis.

In 2001, Dodd, Dauban and co-workers reported that $\text{Cu}(\text{MeCN})_4\text{PF}_6$ was a suitable catalyst for the intermolecular aziridination of a range of alkenes with various sulfonamides in the presence of $\text{PhI}=\text{O}$ as oxidant.³⁶ In these reactions, the corresponding aziridines were afforded in 40-78% yields, comparable to literature yields employing $\text{PhI}=\text{NTs}$ as the nitrene source (Table 1.3, entry 1). Under the reported reaction conditions, it was surmised that the iminoiodinane was formed *in situ* from TsNH_2 and $\text{PhI}=\text{O}$, and reacted rapidly with the catalyst to form a putative reactive copper imido/nitrene species. Notably, while $\text{PhI}=\text{O}$ has been extensively used for the analogous epoxidation of alkenes, control experiments demonstrated that $\text{C}=\text{C}$ bond epoxidation by $\text{PhI}=\text{O}$ with the copper catalyst and in the absence of sulfonamides was sluggish (<10% yield).

Following this work, Du Bois and co-workers disclosed that $[\text{Rh}_2(\text{tfacam})_4]$ **56** (tfacam = trifluoroacetamide, Figure 1.4a) could catalyze intermolecular aziridination of alkenes.^{37,38} In the presence of the dirhodium(II,II) catalyst, trichloroethoxysulfonamide (TcesNH_2), $\text{PhI}(\text{OAc})_2$ and MgO , aziridination of a variety of alkenes were shown to furnish the desired aziridines in 57-95% yields (Table 1.3, entry 2). Notably, in substrates containing an allylic $\text{C}-\text{H}$ bond, the reaction was reported to proceed selectively and give the aziridine adduct as the sole product.

Prior to the work of Bolm and co-workers with $\text{PhI}=\text{NSO}_2\text{Py}$, Chang and co-workers showed that $[\text{Cu}(\text{tfac})_2]$ **57** (tfac = trifluoroacetylacetonate) mediated the aziridination of alkenes with 5-methyl-2-pyridinesulfonamide (PySO_2NH_2) and $\text{PhI}(\text{OAc})_2$ (Table 1.3, entry 3).³⁹ The corresponding aziridines were obtained in 44-84% yields. In this work, the driving force for this process was proposed to be the coordination of the copper nitrene species **58** to the nitrogen atom of the pyridine (Figure 1.4b).

Table 1.3 Transition metal-catalyzed aziridination of alkenes with nitrogen sources in the presence of a hypervalent iodine(III) oxidant.

Entry	Catalyst	R^5NH_2	Oxidant	Yield (%)	Ref.
1	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	TsNH_2 , SesNH_2 or $\text{MbsNH}_2^{\text{a}}$	$\text{PhI}=\text{O}$	40-78	36
2	$[\text{Rh}_2(\text{tfacam})_4]$ 56	TcesNH_2	$\text{PhI}(\text{OAc})_2$	65-95	37, 38
3	$[\text{Cu}(\text{tfac})_2]$ 57	PySO_2NH_2	$\text{PhI}(\text{OAc})_2$	44-84	39
4	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	Sulfonimidamide 59	$\text{PhI}=\text{O}$	35-96	40
5	$\text{Rh}_2(\text{OAc})_4$	Sulfonimidamide 59	$\text{PhI}(\text{OAc})_2$	17-66	41
6	$\text{AgNO}_3 + ^i\text{Bu}_3\text{tpy}$ 50	TsNH_2	$\text{PhI}(\text{OAc})_2$	30-90	42
7	$[\text{Au}(^i\text{Bu}_3\text{tpy})(\text{OTf})]$ 60	NsNH_2	$\text{PhI}(\text{OAc})_2$	37-95	43
8	$[\text{IPrCu}(\text{DBM})]$ 61	TcesNH_2	$\text{PhI}=\text{O}$	35-82	44

^a Mbs = methylbenzylsulfonyl

Dauban, Dodd and co-workers also revealed that aziridination of alkenes with *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **59** (Figure 1.4c), a chiral iminoiodinane precursor, in the presence of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and $\text{PhI}=\text{O}$ generated the corresponding aziridines in 35-96% yields and diastereomeric excesses (de) up to 60% (Table 1.3, entry 4).⁴⁰ Following this work, Müller and co-workers in collaboration with Dauban, Dodd and co-workers demonstrated that reaction of alkenes with sulfonimidamide **59** in the presence of $\text{Rh}_2(\text{OAc})_4$ also proceeded smoothly, affording the products in moderate yields of 17-66% and up to 82% de (Table 1.3, entry 5).⁴¹

Figure 1.4 (a) $[\text{Rh}_2(\text{tfacam})_4]$ **56**, (b) Copper nitrene species **58**, (c) sulfonimidamide **59** and (d) $[\text{IPrCu}(\text{DBM})]$ **61**.

At about the same time, He and Cui reported that the “ $\text{AgNO}_3 + \text{'Bu}_3\text{tpy}$ **50**” catalytic system was effective for the reaction of alkenes with TsNH_2 and $\text{PhI}(\text{OAc})_2$ (Table 1.3, entry 6).⁴² This was closely followed by works from the same group detailing aziridination of a variety of alkenes with sulfonamides in the presence of $[\text{Au}(\text{'Bu}_3\text{tpy})(\text{OTf})]$ **60** and $\text{PhI}(\text{OAc})_2$ (Table 1.3, entry 7).⁴³ In this work, the corresponding aziridines were obtained in moderate to excellent yields of 37-95%. However, the latter procedure was shown to only work well for activated alkenes; aziridination of simple aliphatic alkenes failed to give any desired products.

More recently, Apella and co-workers demonstrated that the *N*-heterocyclic carbene (NHC) copper complex $[\text{IPrCu}(\text{DBM})]$ **61** (IPr = 1,3-bis(2,6-diisopropylphenyl)-1*H*-

imidazolium cation, DBM = dibenzoylmethane, Figure 1.4d) could effect aziridination of aliphatic alkenes with PhI=O and TcesNH_2 .⁴⁴ In this work, the reaction was shown to proceed smoothly to afford the corresponding aziridine products in moderate to high yields (Table 1.3, entry 8). The aziridination of cyclic alkenes such as cyclopentene and cyclohexene were also demonstrated to work well and give the aziridine products in moderate yields.

1.4.4 Intermolecular Asymmetric Aziridination of Alkenes

As a part of an ongoing program on copper-catalyzed aziridinations, Evans and co-workers discovered that the use of CuOTf in tandem with the chiral bis(oxazoline) ligand **PhBOX 62a** (**PhBOX** = (*S,S*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline), Figure 1.5a) could mediate the asymmetric intermolecular aziridination of *trans*-cinnamate esters in product yields up to 89% and enantiomeric excesses (ee) up to 97% (Table 1.4, entry 1).⁴⁵ However, upon closer inspection, the reaction was found not to be general - while high ee values could be attained, different types of starting materials often required a specific chiral bis(oxazoline) ligand and solvent combination to maintain high enantioselectivities.

Figure 1.5 Chiral ligands used in copper-catalyzed enantioselective aziridination reactions.

At about the same time, Jacobsen and co-workers detailed the same reaction catalyzed by CuOTf and the dichloro-substituted Schiff base ligand **63** (Figure 1.5b).⁴⁶ Despite a low turnover number, formation of the aziridine products were reported to be afforded in high ee values up to >98% (Table 1.4, entry 2). This process was shown to work well for *cis*-alkenes, complementing the findings of Evans and co-workers that was reported to work well for *trans* substrates. Moreover, mechanistic studies suggested that a copper(III)-nitrene species was a plausible reactive intermediate in a copper(I)/copper(III) catalytic cycle.

Following initial works on heterogeneous copper-catalyzed aziridinations, Hutchings and co-workers showed that the introduction of enantioselectivity could be achieved by using chiral bis(oxazoline) ligands.⁴⁷ The reaction of styrene with PhI=NTs in the presence of [CuHY] **43**, PhBOX **62a** and PhI=NTs depicted in Scheme 1.8 was reported to furnish aziridine **27a** in 78% yields and 61% ee. Interestingly, when the nitrene source was switched to PhI=NNs, an improved product ee value of 90% was obtained.⁴⁸ This was in contrast with previous reports showing PhI=NNs as a poor nitrogen source in copper-catalyzed aziridination reactions.

Scott and co-workers reported that when *trans*-cinnamate esters were subjected to PhI=NTs in the presence of Cu(MeCN)₄BF₄ and chiral diimine **64** (Figure 1.5c), the corresponding aziridines were afforded in 32-89% yields and with ee values of 88-98% (Table 1.4, entry 3).⁴⁹ In this work, it was postulated that chiral induction occurred *via* a concerted process that was promoted by ancillary binding of the carbonyl group of the cinnamate ester to the metal center. The laboratory of Chan and co-workers reported a similar catalytic system, employing Cu(MeCN)₄ClO₄ as catalyst in combination with diimine **65** (Figure 1.5d) as ligand to furnish the chiral products in 22-92% yields and up to 97% ee (Table 1.4, entry 4).⁵⁰

Table 1.4 Transition metal-catalyzed asymmetric aziridination of alkenes.

Entry	Catalyst	Yield (%)	Ee (%)	Ref.
1	CuOTf + 62a	16-89	19-97	45
2	CuOTf + 63	50-79	30->98	46
3	Cu(MeCN)BF ₄ + 64	32-89	88-98	49
4	Cu(MeCN) ₄ ClO ₄ + 65	22-92	11-97	50
5	Cu(MeCN) ₄ ClO ₄ + 62b	55-94	<74	51
6	CuOTf + 66/67	38-92	68->99	52-54
7	68	9-28	7-61	56
8	[Mn(Por*)(MeOH)(OH)] 69a	43-73	40-68	57, 58
9	[Ru(Por*)(CO)(EtOH)] 69b	72-91	<39	58
10	[Ru(salen)(PPh ₃) ₂] 70	64-84	45-83	59
11	[Rh ₂ (-)-(bnp) ₄] 71	74-80	55-73	31, 33
12	Fe(OTf) ₂ + 62	40-75	<40	35

Another asymmetric copper-catalyzed aziridination process was reported by Che and co-workers in 2004.⁵¹ In this work, it was shown that the combination of Cu(MeCN)₄ClO₄ and tBuBOX **62b** (tBuBOX = (*S,S*)-2,2'-isopropylidenebis(4-*tert*-butyl-2-oxazoline), Figure 1.5a) could mediate the enantioselective reaction of aryl-substituted alkenes with various sulfonamides in the presence of PhI(OAc)₂ (Table 1.4, entry 5). The corresponding chiral aziridines were obtained in good to excellent yields of up to 94% and with ee values up to 74%.

More recently, Xu and co-workers communicated the utility of bis(oxazoline) copper(I) complexes as catalysts for the aziridination of chalcones. Interestingly, the anthracene-derived bis(oxazoline) ligand AnBOX **66** (AnBOX = (*S,S*)-1,8-bis(4-(1-methylethyl)oxazolin-2-yl)anthracene, Figure 1.5e) was shown to be the most suitable chiral ligand for reactions of electron-rich chalcones.⁵² In contrast, the enantioselective aziridination of electron-poor chalcones was shown to proceed well with the cyclohexane-derived variant cHBOX **67** (cHBOX = (*S,S*)-1,2-bis((*S*)-(4-phenyl)oxazolin-2-yl)cyclohexane, Figure 1.5f).⁵³ The products of these transformations were obtained in 38-92% yields and with ee values of 68->99% (Table 1.4, entry 6). Subsequently, this catalyst and ligand combination was also shown to mediate the aziridination of 1,3-dienes with PhI=NTs to afford vinyl aziridines in yields up to 73% and with up to >99% regioselectivity, >99% diastereoselectivity and 80% enantioselectivity.⁵⁴

Asymmetric induction in the aziridination process had also been attempted with other metal catalysts. In 1992, Burrows and co-workers demonstrated achiral manganese(III) Schiff base complexes could catalyze the reaction of styrene with PhI=NTs to give *N*-tosyl-2-phenylaziridine **27a** shown in Scheme 1.8 in 46% yield.⁵⁵ However, the use of chiral manganese(III) complexes in this reaction only led to low product yields and no asymmetric induction. On the other hand, when Katsuki and co-workers applied the chiral manganese (III) Schiff base complex **68** as catalyst (Figure 1.6a), asymmetric aziridination of styrene with PhI=NTs was shown to afford the corresponding chiral product in 28% yield and 61% ee (Table 1.4, entry 7).⁵⁶

Che and co-workers disclosed the synthesis of the chiral *D₄*-manganese(III) porphyrin complex [Mn(Por*)(MeOH)(OH)] **69a** (H₂Por* = 5,10,15,20-tetrakis(1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracen-9-yl)-21*H*,23*H*-porphyrin, Figure 1.6b).^{57,58} This chiral complex was shown to catalyze aziridination of styrene derivatives with PhI=NTs

and furnished the products in 43-73% yields and modest ee values of 40-68% (Table 1.4, entry 8). However, in instances where the substrates contained an allylic C-H bond, C-H insertion was found to be predominant and furnish the allyl amides in 73-76% yields. Spectroscopic monitoring of the aziridination reaction suggested that it proceeded *via* a Mn(IV) reactive intermediate, which was postulated to be [Mn(IV)-PhINTs]complex adduct of **69a**.

Figure 1.6 Chiral catalysts employed in enantioselective intermolecular aziridinations.

When the metal center was switched to ruthenium, the chiral ruthenium(II) porphyrin complex **69b** (Figure 1.6b) was shown to catalyze aziridination of aromatic alkenes and afford the products in 72-91% yields albeit with lower enantioselectivity (Table 1.4, entry 9).⁵⁸ Further studies revealed that the chiral ruthenium(II) Schiff base complex **70** (Figure 1.6c) was more enantioselective for the aziridination process, giving the corresponding products in moderate to good yields and ee values up to 83% (Table 1.4, entry 10).⁵⁹

Following their works on achiral aziridinations, an evaluation of chiral dirhodium(II,II) complexes by Müller and co-workers revealed that asymmetric aziridination of alkenes to be less effective.^{31,33} The best result was obtained with [Rh₂((-)-bnp)₄] **71** (bnp = 1,1'-binaphthyl-2,2'-diyl phosphate, Figure 1.6d), which furnished the products in good yields of 74-80% and ee values up to 73% (Table 1.4, entry 11).

The efficiency of chiral bis(oxazoline) ligands was further demonstrated by their utility in $\text{Fe}(\text{OTf})_2$ -catalyzed aziridinations.³⁵ Preliminary studies from the laboratory of Bolm and co-workers reported that the aziridination of styrene by chiral iron(II) complexes gave the aziridine **27a** in moderate yields of 40-75% and with moderate ee values up to 40% (Table 1.4, entry 12).

1.4.5 Intermolecular Aziridination of Silyl Enol Ethers

Works directed toward the aziridination of silyl enol ethers as a means to accessing α -amino acids and α -amino ketones have also been investigated. Following their work on copper-catalyzed alkene aziridinations, Evans and co-workers reasoned that aziridination of silyl enol ethers **72** followed by ring-opening of the aziridine in a tandem manner would furnish the corresponding α -amino compounds **74** (Scheme 1.12).¹⁹ In their seminal work, $\text{Cu}(\text{MeCN})_4\text{ClO}_4$ was shown to catalyze aziridination of silyl enol ethers **72** with $\text{PhI}=\text{NTs}$ smoothly and give the corresponding α -amino ketones **74** in 53-75% yields. In contrast, the analogous amidations of silyl ketene acetals under the same reaction conditions was shown to be less efficient, giving product yields of 27-45%.

Scheme 1.12 Tandem aziridination/ring opening of silyl enol ethers.

Bolm and co-workers demonstrated that an iron-catalyzed version of this process could also be accomplished.³⁰ When the substrates **72** were exposed to $\text{Fe}(\text{OTf})_2$ and $\text{PhI}=\text{NTs}$, the corresponding α -amino ketones **74** were attained in moderate to good yields of 46-72%.

As part of an effort to examine the catalytic capability of chiral $[\text{Ru}(\text{salen})\text{PPh}_3]$ **70**, Che and co-workers applied this catalyst to the asymmetric amidation of silyl enol ethers.⁵⁹ In this study, the corresponding α -amino ketones were furnished in 72-85% yields and with up to 97% ee.

In 2007, Hashimoto and co-workers described the enantioselective amidation of silyl enol ethers **72** with $\text{PhI}=\text{NNs}$ in the presence of $[\text{Rh}_2((S)\text{-TFPTTL})_4]$ **75** (TFPTTL = *N*-tetrafluorophthaloyl-*tert*-leucinate).^{11f} It was reported that the corresponding α -amino ketones **74** were obtained in 80-95% yields and 47-95% ee. Notably, the synthetic utility of this methodology was demonstrated by the formal synthesis of (-)-metazocine **3** (Scheme 1.13).

Scheme 1.13 Synthesis of (-)-metazocine **3**.

1.4.6 Intramolecular Aziridination of Alkenes

In 2000, Dodd, Dauban and co-workers communicated the synthesis of iminoiodinanes containing a pendant alkene moiety **77** (Scheme 1.14).⁶⁰ When these compounds were treated with CuOTf or $\text{Cu}(\text{OTf})_2$, the intramolecular cyclization occurred smoothly to give the corresponding bicyclic compounds **78a** in 31-80% yields.

Scheme 1.14 Copper-catalyzed intramolecular cyclization of iminoiodinanes **77**.

Subsequent studies by the same group demonstrated that this transformation could also be effected in a one pot manner directly from unsaturated sulfonamides **76a** or sulfamate esters **76b** (Scheme 1.15).^{36,61} In this work, the aziridination of substrates **76a** and **76b** was shown to proceed in the presence of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and $\text{PhI}=\text{O}$, giving the corresponding bicyclic compounds in 50-94% yields. Moreover, the introduction of tBuBOX **62b** to this process successfully rendered the reaction enantioselective, furnishing the corresponding chiral products in 24-86% yields and 34-84% ee.⁶² This seminal finding removed the need to synthesize and isolate the iminoiodinanes **77** prior to reaction, enabling intramolecular transformations of a variety of substrates that were previously limited by the strongly basic conditions of iminoiodinane synthesis.

Scheme 1.15 $\text{Cu}(\text{MeCN})_4\text{PF}_6$ -catalyzed intramolecular amidation of unsaturated sulfonamides **76a** and sulfamate esters **76b**.

Rojas and co-workers demonstrated the tandem intramolecular aziridination/ring-opening of allal 3-carbamates **79** (Scheme 1.16a).⁶³ The reaction was shown to proceed in the presence of $\text{Rh}_2(\text{OAc})_4$, $\text{Cu}(\text{MeCN})_4\text{PF}_6$ or $\text{Cu}(\text{acac})_2$ as catalyst, $\text{PhI}=\text{O}$ and MgO and furnished the corresponding products **81** in up to 75% yields. At about the same time, Padwa and co-workers described $\text{Rh}_2(\text{OAc})_4$ -catalyzed cyclization of indolyl-substituted carbamate **82** (Scheme 1.16b).⁶⁴ Both transformations were proposed to occur *via* different mechanisms with the former proceeding *via* the metal-aziridine complex **80** while the latter *via* the metal-free zwitterionic intermediate **83**.

Scheme 1.16 Intramolecular aziridination of carbamate esters.

In 2003, Che and co-workers reported that intramolecular aziridination of unsaturated sulfonamides **76a** catalyzed by $\text{Rh}_2(\text{OAc})_4$ in the presence of $\text{PhI}(\text{OAc})_2$ and Al_2O_3 as base gave the corresponding bicyclic aziridines **78a** in product yields up to 98%.⁶⁵ It was also shown that the enantioselective version of this reaction using $[\text{Rh}_2((4S)\text{-MEOX})_4]$ **85** ($\text{MEOX} = \mu\text{-(methyl 2-oxo-4-oxazolidinecarboxylate)}$), Figure 1.7a) afforded the desired products in up to 95% yields and moderate to good ee values of 55-76%.⁶⁶

Figure 1.7 Catalysts used in intramolecular aziridination of alkenes.

Du Bois and co-workers subsequently disclosed that dirhodium(II,II)-catalyzed intramolecular aziridination of unsaturated sulfamate esters **76b** proceeded in a

stereospecific manner (Scheme 1.17).^{38,67} In this work, substrate cyclization was proposed to occur in the presence of $[\text{Rh}_2(\text{tfacam})_4]$ **56** or $[\text{Rh}_2(\text{oct})_4]$ **86** (oct = octanoate, Figure 1.7b) *via* a chair-like transition state. The corresponding bicyclic products **78b** were afforded in good to excellent yields up to 92%. The synthetic utility of this dirhodium(II,II)-catalyzed intramolecular cyclization of homoallylic sulfamate esters was highlighted by its application to the total synthesis of (-)-agelastatin A **4** (Scheme 1.17).^{11a}

Scheme 1.17 Synthesis of (-)-agelastatin A **4**.

Che and co-workers showed that reaction of sulfonamides **76a** with $\text{PhI}(\text{OAc})_2$ in the presence of $[\text{Ru}(\text{F}_{20}\text{-TPP})(\text{CO})]$ **88a** ($\text{H}_2\text{F}_{20}\text{-TPP}$ = 5,10,15,20-tetrakis-(pentafluorophenyl)-21*H*,23*H*-porphyrin, Figure 1.7c) afforded the corresponding bicyclic products in up to 87% yields and with high turnover numbers up to 2014.⁶⁸ However, substrates containing allylic or benzylic C–H bonds were shown to give the insertion product in competition with the aziridine, suggesting a lack of selectivity of the ruthenium catalyst. When chiral ruthenium(II) porphyrin **69b** was used as catalyst, product yields up to 65% was obtained but almost no chiral induction was found (9% ee). In addition, Che and co-workers reported that $[\text{Fe}(\text{Cl}_3\text{terpy})_2]$ **53** could catalyze intramolecular aziridination of unsaturated sulfonamides in product yields of 86–96%.²⁹

1.5 Transition Metal-Catalyzed Nitrogen Atom Insertion into C–H Bonds

1.5.1 Intermolecular Amidation of Saturated C–H Bonds

Despite the discovery that the amidation adduct could be furnished from C–H bond amidation with $\text{PhI}=\text{NTs}$ in the presence of dirhodium(II,II), iron(III) and manganese(III) complexes as catalyst and as a side product in studies on aziridination of allylic and benzylic compounds, subsequent progress in this area initially remained sparse.^{9h} Following the seminal works of Breslow and Gellman, the next major advance came more than a decade later in a report by Müller and co-workers.³¹ In this work, it was shown that selective amidation of cyclohexene with $\text{Rh}_2(\text{OAc})_4$ and $\text{PhI}=\text{NNs}$ furnished the allylic amide **89** in 70% yield (Scheme 1.18). Notably, this process was shown to occur with near complete suppression of the aziridine **90**.

Scheme 1.18 $\text{Rh}_2(\text{OAc})_4$ -catalyzed amidation of cyclohexene.

Müller and co-workers also demonstrated that the same catalytic system could effect C–H insertion at the benzylic and ethereal positions of other types of substrates (Table 1.5, entry 1).⁶⁹ These reactions were shown to proceed smoothly and afford the corresponding products in low to good yields up to 84%. In addition, mechanistic experiments revealed that the process was similar to that proposed for dirhodium(II,II)-catalyzed aziridinations.

Following this, Che and co-workers described the synthesis of the bis(tosylamido)ruthenium(III) complex $[\text{Ru}(\text{Me}_3\text{tacn})(\text{NHTs})_2(\text{OH})]$ **91** (Me_3tacn = 1,4,7-trimethyl-1,4,7-triazacyclononane, Figure 1.8a) and showed it to efficiently catalyze intermolecular amidation of allylic and benzylic substrates with $\text{PhI}=\text{NTs}$ (Table 1.5,

entry 2).⁷⁰ The corresponding amides were obtained in 30-72% yields although the turnover for this reaction was low. Interestingly, the amidation process was also reported to proceed with stoichiometric amounts of complex **91** with AgClO_4 as an oxidant. This suggested that oxidation of **91** *via* deprotonation of amido ligands generated the reactive $\text{Ru}=\text{NTs}$ species.

Further studies by the laboratory of Che and co-workers revealed that stoichiometric amidation of hydrocarbons by $[\text{Ru}(\text{TPP})(\text{NTs})_2]$ **48a** and $[\text{Ru}(\text{OEP})(\text{NTs})_2]$ **48b** also proceeded smoothly, affording the corresponding products in 52-88% yields (Table 1.5, entry 3).²⁶ Mechanistic studies suggested that this process was most likely to involve formation of the carboradical intermediate **93** (Scheme 1.19).

Scheme 1.19 Proposed mechanism for amidation of alkanes catalyzed by **24a** and **24b**.

Che and co-workers also demonstrated the utility of $[\text{Ru}(\text{F}_{20}\text{-TPP})(\text{CO})]$ **88a** and $[\text{Mn}(\text{F}_{20}\text{-TPP})\text{Cl}]$ **88b**, as well as $[\text{Ru}(\text{Me}_3\text{tacn})(\text{OTf})_3 \cdot \text{H}_2\text{O}]$ **94** and $[\text{Ru}(6,6'\text{-Cl}_2\text{bpy})_2\text{Cl}_2]$ **95** ($6,6'\text{-Cl}_2\text{bpy}$ = 6,6'-dichloro-2,2'-bipyridine) in C-H bond amidation (Table 1.5, entries 4-9).^{71,72} In these reactions, the corresponding amides were furnished in up to 93% product yields in the presence of $\text{PhI}=\text{NTs}$ or $\text{PhI}(\text{OAc})_2$ with various sulfonamides. Notably, a product turnover as high as 2600 was reported when complex **88b** was employed as catalyst.

Table 1.5 Transition metal-catalyzed amidation of alkanes.

Entry	Catalyst	Nitrogen Source	Yield (%)	Ref.
1	$\text{Rh}_2(\text{OAc})_4$	$\text{PhI}=\text{NNs}$	13-84	69
2	$[\text{Ru}(\text{Me}_3\text{tacn})(\text{NHTs})_2(\text{OH})]$ 91	$\text{PhI}=\text{NTs}$	30-72	70
3	$[\text{Ru}(\text{TPP})(\text{NTs})_2]$ 48a or $[\text{Ru}(\text{OEP})(\text{NTs})_2]$ 48b	-	52-88	26
4	$[\text{Ru}(\text{F}_{20}\text{-TPP})(\text{CO})]$ 88a or $[\text{Mn}(\text{F}_{20}\text{-TPP})\text{Cl}]$ 88b	$\text{PhI}=\text{NTs}$	13-92	71
5	$[\text{Mn}(\text{F}_{20}\text{-TPP})\text{Cl}]$ 88b	$\text{PhI}(\text{OAc})_2 + \text{RNH}_2$	72-92	71
6	$[\text{Ru}(\text{Me}_3\text{tacn})(\text{OTf})_3 \cdot \text{H}_2\text{O}]$ 94	$\text{PhI}=\text{NTs}$	80-93	72
7	$[\text{Ru}(6,6'\text{-Cl}_2\text{bpy})_2\text{Cl}_2]$ 95	$\text{PhI}=\text{NTs}$	81-92	72
8	$[\text{Ru}(\text{Me}_3\text{tacn})(\text{OTf})_3 \cdot \text{H}_2\text{O}]$ 94	$\text{PhI}(\text{OAc})_2 + \text{RNH}_2$	80-89	72
9	$[\text{Ru}(6,6'\text{-Cl}_2\text{bpy})_2\text{Cl}_2]$ 95	$\text{PhI}(\text{OAc})_2 + \text{RNH}_2$	80-85	72
10	$[\text{Tp}^{\text{Br}_3}\text{Cu}(\text{MeCN})]$ 42b	$\text{PhI}=\text{NTs}$	10->98	73, 74
11	$[\text{Rh}_2(\text{esp})_2]$ 96	$\text{PhI}(\text{O}_2\text{C}^t\text{Bu})_2 +$ TcesNH_2	50-74	75, 76
12	$[\text{Co}(\text{acacen})]$ 97	$\text{PhI}=\text{NTs}$	40-70	77
13	$[\text{Ag}_2(\text{bp})_2]$ 98	$\text{PhI}=\text{NNs}$	25-71	78
14	$[\text{Tp}^{*,\text{Br}}\text{Ag}]$ 99	$\text{PhI}=\text{NTs}$	65-90	79

Figure 1.8 Catalysts employed in intermolecular amidation reactions.

In 2003, Pérez and co-workers reported that the copper(I)-homoscorpionate complex $[\text{Tp}^{\text{Br}_3}\text{Cu}(\text{MeCN})]$ **42b** (Tp^{Br_3} = hydrotris(3,4,5-tribromo-1-pyrazolyl)borate) could mediate amidation at the primary C–H bond of toluene and mesitylene in high yields of >95%.⁷³ The reactions of substrates containing benzylic, allylic or ethereal C–H bonds with $\text{PhI}=\text{NTs}$ in the presence of **42b** was also shown to proceed smoothly and give the corresponding products in moderate to excellent yields (Table 1.5, entry 10).⁷⁴

Du Bois and co-workers demonstrated that the dirhodium(II,II) catalyst $[\text{Rh}_2(\text{esp})_2]$ **96** (esp = tetramethyl *m*-benzenedipropionic carboxylate, Figure 1.8c) could mediate amidation of alkanes containing a benzylic or tertiary C–H bond in the presence of TcesNH_2 and bis(*tert*-butylcarbonyloxy)iodobenzene ($\text{PhI}(\text{O}_2\text{C}^t\text{Bu})_2$) as oxidant (Table 1.5, entry 11).^{75,76} In this work, the corresponding products were obtained in 50–74% yields. Extensive studies also suggested the intermolecular amidation reaction was mechanistically analogous to the intramolecular version with both processes occurring *via* a dirhodium-nitrene intermediate that inserted directly into the C–H bond of the substrate.

Cenini and co-workers described amidation of allylic C–H bonds with the cobalt(II) Schiff base complex [Co(acacen)] **97** (acacen = 2,11-dihydroxy-4,9-dimethyl-5,8-diaza-2,4,8,10-dodecatratene, Figure 1.8d).⁷⁷ The reaction was demonstrated to proceed efficiently and give the corresponding amides in 40–70% yields (Table 1.5, entry 12).

In the laboratory of He and co-workers, it was demonstrated that [Ag₂(bp)₂] **98** (bp = 4,7-diphenyl-1,10-phenanthroline, Figure 1.8e) was effective for intermolecular amidation of alkanes with PhI=NNs (Table 1.5, entry 13).⁷⁸ In particular, amidation of benzylic substrates gave the corresponding amides in 25–71% yields. Notably, amidation of unreactive substrates such as cycloalkanes and mesitylene were also shown to be facile in furnishing the corresponding products albeit in lower yields of 25–40%. In this work, it was hypothesized that a concerted process may have been most likely *via* formation of a disilver(II)-nitrene species with the nitrene moiety bridging two silver(II) ions. This was in sharp contrast to that proposed by Pérez and co-workers for intermolecular amidation of alkanes catalyzed by [Tp^{*.Br}Ag] **99** (Tp^{*.Br} = hydrotris(3,5-dimethyl-4-bromo-1-pyrazolyl)borate, Figure 1.8f, entry 14 in Table 1.5).⁷⁹ In these latter reactions, the C–N bond forming process was postulated to proceed *via* a stepwise radical pathway that afforded the corresponding amides in 65–90% yields.

1.5.2 Asymmetric Intermolecular Amidation of Saturated C–H Bonds

One of the earliest examples of enantioselective C–N bond formation was reported by Che and co-workers. In this work, chiral manganese(III) and ruthenium(II) porphyrin complexes **69a** and **69b** were found to be effective for the enantioselective intermolecular amidation of aryethanes with PhI=NTs, affording the corresponding amides in up to 91% yields and 45–58% ee (Scheme 1.20a).^{58,80} In addition, the amidation of chlorosteryl acetate **100** with either PhI=NTs or PhI(OAc)₂ and TsNH₂ by either **69a** or **69b** were also

shown to give the corresponding amino-substituted steroid adduct **101** as a mixture of α - and β -isomers in up to 4.2:1 selectivity (Scheme 1.20b).

Scheme 1.20 Amidation of (a) C–H bonds and (b) chlorosteryl acetate **100**.

Katsuki and co-workers revealed that the chiral manganese(III) Schiff base complex **102** (Figure 1.9a) could mediate enantioselective amidation of benzylic and allylic C–H bonds (Scheme 1.20a).⁸¹ In this work, the amidation products were afforded in moderate yields of 42-74% and 41-89% ee. Mechanistic studies implied that the C–N bond forming process followed the H-abstraction/radical rebound pathway, similar to that proposed by Che and co-workers for the analogous ruthenium(II) and manganese(III) porphyrin-catalyzed reactions.

Figure 1.9 Chiral catalysts employed in enantioselective intermolecular C–H insertion reactions.

Preliminary experiments from Müller and co-workers revealed that amidation of indane with $\text{PhI}=\text{NNs}$ catalyzed by $[\text{Rh}_2(-)(\text{bnp})]_4$ **71** afforded the corresponding amide in 71% yield but in low enantioselectivity of 31% (Scheme 1.21).³² This was followed by a report from the groups of Müller and Dauban and Dodd that showed $[\text{Rh}_2((S)\text{-nttl})_4]$ **103a** ($\text{nttl} = N\text{-}1,8\text{-naphthoyl-}tert\text{-leucinate}$, Figure 1.9b) could mediate intermolecular amidation of arylalkanes with sulfonimidamides **59** and $\text{PhI}(\text{O}_2\text{C}^t\text{Bu})_2$ (Scheme 1.20a).⁸² Through this approach, product yields of 62–93% and excellent diastereoselectivities ($\geq 93\%$ de) were achieved. In instances where the aliphatic substrate contained a $\text{C}=\text{C}$ bond, the corresponding allyl amides were reported to be obtained in good yields of 55–75% but with lower de values of 38–50%. Notably, no aziridine products were observed in these reactions. Moreover, amidation of unreactive hydrocarbons were shown to occur in good yields of 65–69%. An extensive study showed that $[\text{Rh}_2((S)\text{-nta})_4]$ **103b** ($\text{nta} = N\text{-}1,8\text{-naphthoyl-alaninate}$, Figure 1.9b) was superior to $[\text{Rh}_2((S)\text{-nttl})_4]$ **103a** in terms of catalytic activity, substrate scope, diastereoselectivity and regioselectivity.⁸³

Scheme 1.21 $[\text{Rh}_2(-)(\text{bnp})]_4$ -catalyzed amidation of indane.

More recently, Hashimoto and co-workers showed $[\text{Rh}_2((S)\text{-TCPTTL})_4]$ **104** (TCPTTL = $N\text{-tetrachlorophthaloyl-}tert\text{-leucinate}$, Figure 1.9c) was an efficient catalyst for the amidation of benzylic C-H bonds with $\text{PhI}=\text{NNs}$ with 52–88% product yields and ee values up to 84% obtained (Scheme 1.22).⁸⁴ In addition, this catalyst was shown to facilitate the tandem hydrosilylation/allylic amidation of cyclohexenone to give the β -amino ketone **105**, a key intermediate toward the total synthesis of (–)-pancracine **5**.^{11b}

Scheme 1.22 Synthesis of (-)-pancracine **5**.

Davies and co-workers reported that $[\text{Rh}_2((S)\text{-TCPTAD})_4]$ **106** (TCPTAD = adamantan-1-yl-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetate, Figure 1.9c) could mediate amidation of aryl alkanes with NsNH_2 and $\text{PhI}(\text{OAc})_2$ (Scheme 1.20a).⁸⁵ The desired products were furnished in 65-95% yields and up to 94% ee.

1.5.3 Intramolecular Amidation of Saturated C–H Bonds

In these reactions reported by Du Bois and co-workers, intramolecular C–H insertion of carbamate esters **107a** and sulfamate esters **110a** were shown to proceed in the presence of $\text{Rh}_2(\text{OAc})_4$ or $[\text{Rh}_2(\text{tpa})_4]$ **109** (tpa = triphenylacetic acid, Figure 1.10a, Scheme 1.23 and Table 1.6, entry 1).^{86,87} On the other hand, as is typical in dirhodium(II,II) catalysis, cyclization of **107b–c** and **110b–c** was found to work well with $[\text{Rh}_2(\text{oct})_4]$ **86** or $[\text{Rh}_2(\text{esp})_2]$ **96** as catalyst.^{88–92}

Scheme 1.23 Dirhodium(II,II)-catalyzed intramolecular amidation of (a) carbamate esters **107** and (b) sulfamate esters **110**.

In general, the intramolecular C–H insertion process was reported to be highly selective, giving the corresponding five- or six-membered ring compounds as the sole product.^{67,93} For instance, in the cyclization of **110a**, formation of the five-membered ring **112a** resulting from insertion into the β C–H was not observed, although this could be achieved in the absence of the γ C–H bond. This selectivity was attributed to preservation of the N–S–O bond angle of the sulfamate starting material in the product **111a**.⁸⁷ The reactions were also proposed to occur *via* a chair-like transition state, in which equatorial C–H insertion (Scheme 1.24, route *a*) was preferred to axial C–H insertion (route *b*). This proposed pathway also accounted for the high degree of diastereocontrol of cyclization. Moreover, the rate determining step of this process was proposed to be the formation of the iminoiodinane although this intermediate could not be detected.

Scheme 1.24 $\text{Rh}_2(\text{II,II})$ -catalyzed intramolecular cyclization of sulfamate esters *via* a chair-like transition state.

By utilizing the chiral dirhodium(II,II) catalyst $[\text{Rh}_2((S)\text{-TFPTTL})_4]$ **75** shown in Scheme 1.13, Hashimoto and co-workers reported the enantioselective cyclization of sulfamate esters **110a** in the presence of $\text{PhI}(\text{OAc})_2$ could be accomplished in product yields up to 87% and with ee values up to 48% (Table 1.6, entry 2).⁹⁴ An improvement of the enantioselectivity (up to 99% ee) in this reaction was subsequently reported by Du

Bois and co-workers with $[\text{Rh}_2((S)\text{-nap})_4]$ **114** (nap = *N*'-4-dimethyl-*N*-(2-oxopiperidin-3-yl)benzenesulfonamide, Figure 1.10b) as catalyst (Table 1.6, entry 3).⁹⁵

Figure 1.10 Catalysts used in intramolecular C–H insertion reactions.

While dirhodium(II,II) complexes have proven to be efficient for intramolecular amidation reactions, other transition metal catalysts were also reported to be suitable catalysts for this transformation. Che and co-workers demonstrated that $[\text{Ru}(\text{F}_{20}\text{-TPP})(\text{CO})]$ **88a** could mediate intramolecular amidation of sulfamate esters **110a** in the presence of Al_2O_3 (Table 1.6, entry 4).⁹⁶ The corresponding products were obtained in 52–88% yields and with high regioselectivity and almost complete diastereoselectivity. Similarly, when the chiral ruthenium(II) porphyrin **69** was employed as catalyst, intramolecular amidation of these substrates proceeded smoothly to give the corresponding *N*-heterocycles in 40–77% yields and 70–87% ee (Table 1.6, entry 5).

Following this work, Che and co-workers reported that the chiral manganese(III) Schiff base complex **102** mediated enantioselective intramolecular amidation of sulfamate esters **110a** under mild conditions in yields of up to 92% (Table 1.6, entry 6).⁹⁷ The products were shown to be obtained exclusively *cis* in configuration and with ee values up to 79%. The same group also highlighted that $[\text{Fe}(\text{Cl}_3\text{terpy})_2]$ **53** could catalyze the intramolecular amidation of sulfamate esters **110a** and afford the corresponding sulfamidates in 84–90% yields (Table 1.6, entry 7).²⁹

Table 1.6 Transition metal-catalyzed intramolecular amidation of sulfamate esters **90a**.

Entry	Catalyst	Yield (%)	Ec(%)	Ref.
1	Rh ₂ (OAc) ₄ or Rh ₂ (oct) ₄ 86	60-91	-	86, 87
2	[Rh ₂ ((S)-TFPTTL) ₄] 75	30-87	<48	94
3	[Rh ₂ ((S)-nap) ₄] 114	45-98	56-99	95
4	[Ru(F ₂₀ -TPP)(CO)] 88a	52-88	-	96
5	[Ru(Por*)(CO)] 69b	40-77	70-87	96
6	Mn(III) complex 102	18-92	27-79	97
7	[Fe(Cl ₃ terpy)] 53	84-90	-	29
8	AgNO ₃ + ^t Bu ₃ tpy 50	53-90	-	98
9	[Ag ₂ (bp) ₂] 98	75-90	-	78
10	Ru(II) complex 115	42-84	75-92	99

In 2007, He and co-workers showed amidation of a variety of carbamate and sulfamate esters catalyzed by “AgNO₃ + ^tBu₃tpy **50**”.⁹⁸ The corresponding cyclic adducts were obtained in good to excellent yields of 53-90% (Table 1.6, entry 8). Moreover, they found that when [Ag₂(bp)₂] **98** was employed as catalyst, cyclization of substrates which were previously shown to be low yielding with the “AgNO₃ + ^tBu₃tpy **50**” catalytic approach, proceeded smoothly and afforded the corresponding products in 75-90% yields (Table 1.6, entry 9).⁷⁸

More recently, Blakey and co-workers reported that the chiral cationic ruthenium(II) complex **115** (Figure 1.10c) in combination with AgOTf, PhI(OCO^tBu)₂ and MgO

mediated the asymmetric intramolecular amidation of sulfamate esters **110a** (Table 1.6 entry 10).⁹⁹ Substrates containing benzylic or allylic C–H bonds were shown to undergo cyclization, giving the corresponding oxathiazinanes in 42–84% yields and 75–92% ee.

1.5.4 Amidation of Aryl C–H Bonds

In contrast to the myriad of works on transition metal-mediated imido/nitrene transfer reactions to C=C bonds of alkenes and C–H bonds of alkanes, the analogous transformations with aryl C–H bonds are sparse in the literature, presumably due to the associated high bond dissociation energy of the aryl C–H bonds.^{5b} In this regard, a notable achievement is that by Pérez and co-workers who demonstrated [$\text{Tp}^{\text{Br}_3}\text{Cu}(\text{MeCN})$] **42b** was an effective catalyst for imido/nitrene insertion into the C–H bond of aromatic compounds (Scheme 1.25a).⁷⁴ The reaction of benzene and chlorobenzene was noted to proceed smoothly and afford the corresponding products in moderate to good yields although the latter gave a mixture of the *ortho*- and *para*-substituted *N*-tosylaniline products *o*-**116** and *p*-**116**. Moreover, when pyridine was subjected to the reaction conditions, *ortho*- and *N*-amidation occurred to furnish *o*-**117** and *N*-**117** in 35% and 65% yields, respectively (Scheme 1.25b).

Scheme 1.25 [$\text{Tp}^{\text{Br}_3}\text{Cu}(\text{MeCN})$]-catalyzed amidation of aromatic substrates.

This was followed by a report by Che's group showing that $[\text{Ru}(\text{TTP})(\text{CO})]$ **47a** could mediate amidation of aromatic heterocycles with $\text{PhI}=\text{NTs}$ (Scheme 1.26).¹⁰⁰ These reactions afforded the mono- and diamidated heteroarenes in moderate to good yields of 34-84% and complete regioselectivity.

Scheme 1.26 $[\text{Ru}(\text{TTP})(\text{CO})]$ -catalyzed amidation of heteroarenes.

In 2006, Che and co-workers disclosed $\text{Pd}(\text{OAc})_2$ -catalyzed amidation of aryl C–H bonds *via* a C–H activation/nitrene insertion process (Scheme 1.27).¹⁰¹ In this work, amidation of substrates containing oxime or pyridine directing groups with a variety of amides in the presence of $\text{Pd}(\text{OAc})_2$ and $\text{K}_2\text{S}_2\text{O}_8$ as oxidant was shown to give the corresponding *ortho*-insertion products **121** in 88-96% yields.

Scheme 1.27 $\text{Pd}(\text{OAc})_2$ -catalyzed intermolecular amidation.

At about the same time, Sanford and co-workers reported C–H insertion of the palladacycle **122** (Scheme 1.28).¹⁰² In this study, it was found that the C–H bond of the *N*-chelated ligand reacted with $\text{PhI}=\text{NTs}$ in a stepwise manner to give the palladium(II) complex **125** in low to moderate yields.

Scheme 1.28 Imido/nitrene insertion into palladacycle **120**.

An intramolecular strategy to form carbazoles **127** was disclosed by Gaunt and co-workers (Scheme 1.29).¹⁰³ The reaction of 2-phenylaniline derivatives **126** was shown to undergo intramolecular C–H insertion in the presence of $\text{Pd}(\text{OAc})_2$ and $\text{PhI}(\text{OAc})_2$, furnishing the corresponding carbazoles in 50–96% yields. The reaction was postulated to proceed *via* a Pd(II)/Pd(IV) catalytic cycle involving a trinuclear cyclopalladation complex.

Scheme 1.29 $\text{Pd}(\text{OAc})_2$ -catalyzed intramolecular amidation to furnish carbazoles.

He and co-workers reported that direct nitrogen atom insertion of a nitrogen group into an aryl C–H bond could be carried out with AuCl_3 and $\text{PhI}=\text{NNs}$ (Scheme 1.30).¹⁰⁴ In this work, amidation of methyl-substituted benzene derivatives gave the corresponding *N*-nosylprotected aniline derivatives in 61–90% yields. It was proposed that the selectivity toward aryl C–H bond insertion was due to the formation of the arylgold(III) species **128**.

Scheme 1.30 AuCl_3 -catalyzed amidation of mesitylene.

1.6 Proposed Work

The work of this thesis has been directed toward providing new methodologies that would enable the delivery of nitrogen-containing compounds of biological and materials interest from direct amidation of activated C–H bonds in an efficient and selective manner. In particular, this will include the establishing of new nitrogen atom transfer reactions that explore the scope of other functional groups that have received little or no previous attention.

Thus, the aim of this project has been involved in establishing new transition metal-catalyzed protocols for the selective nitrogen atom insertion to the aldehydic C–H bond of aldehydes as a novel approach to amide bond synthesis (Figure 1.11). In addition, attention has also been focused on the development of an efficient and enantioselective route to α -hydroxy amino acids and 2-amino-1,3-diols *via* formal amidation of the α -C–H bond of β -keto esters and 1,3-dicarbonyl compounds. It is envisaged that the newly-established reaction processes will be general in terms of substrate scope, reactivity and selectivity. In tandem with these works, new catalytic systems that are readily available from commercial sources, environmentally benign and cost-effective will also be developed to effect these novel organic transformations. The generality of these new catalytic methods in terms of their reactivity and selectivity will be evaluated by examining their applicability to other known reactions such as aziridination of alkenes as well as amidation of alkanes and aromatic heterocycles.

Figure 1.11 Transition metal-catalyzed nitrene transfer reactions.

Chapter II. Ruthenium(II) Porphyrin-Catalyzed Amidation of Aldehydes

2.1 Introduction

The installation of the amide bond functionality is of immense interest in organic synthesis due to the prevalence of this structural motif in a myriad of compounds of biological, pharmaceutical, and materials interest.¹ Conventional methods to this ubiquitous class of nitrogen containing compounds have heavily relied upon the coupling of activated carboxylic acid and amine precursors.^{3,105,106} Although shown to be exceptionally efficient for the synthesis of small peptides, many classes of amides, including those found in many natural products, bioconjugates, and pharmaceutical targets, and the lability of the activated carboxylic acid derivatives, pose significant challenges to these amide bond forming methodologies.

In view of these shortcomings, the establishment of alternative amide bond formation strategies has been actively pursued.¹⁰⁷ Some of these methodologies include the modified Staudinger reaction,¹⁰⁸ hydrative amide synthesis from alkynes and azides,¹⁰⁹ aminocarbonylation of alkenes, alkynes and aryl halides with amines,¹¹⁰ hydration of nitriles,¹¹¹ Beckmann rearrangements of oximes¹¹² and oxidative amidation of alcohols¹¹³ with amines with amines. One approach that has also gained recent attention is the direct manipulation of the aldehydic C–H bond with amines in the presence of a transition metal catalyst under oxidative conditions.^{114,115} According to the seminal reports by Li,^{114e} Beller^{114f} and others, these catalytic systems are surmised to involve the formation of a carbinolamine intermediate that undergoes metal-catalyzed oxidation to furnish the amide product. However, catalytic systems that can effect amide bond formation of a wide range of aldehydes via a nitrogen atom insertion process have remained sparse.

In this context and attracted by recent works showing ruthenium(II) porphyrin complexes to be efficient catalysts in C–H bond amidation reactions with PhI=NTs as the nitrogen source as mentioned earlier in Chapter I, we envisioned that a “[Ru] + PhI=NTs” strategy could hold promise as the basis for developing a new approach for amide bond synthesis. Herein, we report the first chemoselective ruthenium(II) porphyrin-catalyzed amidation of a wide range of aldehydes with PhI=NTs as the nitrogen source that proceeded in product yields up to 99% (Scheme 2.1).¹¹⁶

Scheme 2.1 [Ru(TTP)(CO)]-catalyzed amidation of aldehydes.

While insertions of a putative reactive metal-nitrene/imido species to C–H bonds of alkanes and, more recently, C–H bonds of benzene and heteroarenes have been extensively examined as discussed in Section 1.5 of Chapter I, to our knowledge, the analogous nitrogen atom transfer reactions to the aldehydic C–H bond has until recently, remained unexplored. During the completion of this work, Chan and co-workers described the analogous Rh₂(esp)₂-catalyzed amidation of aldehydes with a variety of sulfonamides in the presence of PhI(O₂C^tBu)₂ as oxidant and ⁱPrOAc as solvent (Scheme 2.2).¹¹⁷

Scheme 2.2 Rh₂(esp)₂-catalyzed amidation of aldehydes.

It also noteworthy to highlight that the acylsulfonamides obtained in this work are themselves a class of biologically active compounds of current therapeutic interest.¹¹⁸ Acylsulfonamides **132-134** shown in Figure 2.1, for example, have been reported to exhibit potent HCV NS5B polymerase allosteric inhibitory,^{118a} anti-inflammatory,^{118b} and antitumor activity,^{118d} respectively.

Figure 2.1 Bioactive compounds containing the acylsulfonamide moiety.

2.2 Results and Discussion

2.2.1 Ruthenium(II) Porphyrin-Catalyzed Amidation Reaction

The porphyrin ligands and ruthenium(II) porphyrin complexes used in this work were prepared following literature procedures as shown in Schemes 2.3 and 2.4.¹¹⁹ Synthesis of H₂TTP **135a** involved reaction of equimolar quantities of pyrrole with *p*-tolualdehyde in refluxing propionic acid for 30 min. A simple work-up *via* filtration afforded the desired product as purple crystals in 20% yield. *Meso*-5,10,15,20-tetrakis(phenyl)-21*H*,23*H*-porphyrin (H₂TPP) **135b** was synthesized in a similar manner from the condensation of pyrrole and benzaldehyde. In this instance the purple crystals of **135b** were furnished in 16% yield.

An alternative method was employed for the synthesis of H₂F₂₀-TPP **135c**.¹²⁰ Condensation of 1 equiv of pyrrole and 1 equiv of pentafluorobenzaldehyde was carried out in CHCl₃ at room temperature in the presence of BF₃·OEt₂ for 1.5 h. This was

followed by oxidation with *p*-chloranil at reflux for 1 h. Upon work-up, the solids were collected and dried *in vacuo* to give **135c** as purple crystals in 13% yield.

Scheme 2.3 Synthesis of porphyrins **135a-c**.

In general, treatment of equimolar amounts of $\text{Ru}_3(\text{CO})_{12}$ and ligands **135a-c** in decalin at reflux for 20 h gave a deep red solution that was purified *via* flash column chromatography using neutral alumina (Scheme 2.4). Subsequent recrystallization in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ gave the corresponding ruthenium(II) porphyrin complexes as red purple crystals. In this manner, $[\text{Ru}(\text{TTP})(\text{CO})]$ **47a** and $[\text{Ru}(\text{F}_{20}\text{-TPP})(\text{CO})]$ **88a** were obtained in 91% and 61% yields from the respective reactions of $\text{Ru}_3(\text{CO})_{12}$ with **135a** and **135c**. However, repeated attempts toward the complexation of $\text{Ru}_3(\text{CO})_{12}$ with **135b** was found to be unsuccessful and the ligand **135b** was recovered in almost quantitative yield from the reaction mixture in all instances.

Preparation of $\text{PhI}=\text{NTs}$ was carried out according to the procedure reported by Yamada and co-workers.⁸ The reaction of $\text{PhI}(\text{OAc})_2$ with TsNH_2 in a 1:1 molar ratio was carried out in the presence of KOH in MeOH for 4-6 h. Filtration of the reaction mixture afforded $\text{PhI}=\text{NTs}$ as a pale yellow solid in 92% yield.

Scheme 2.4 Synthesis of ruthenium(II)porphyrin complexes.

With the ruthenium(II) catalysts and PhI=NTs in hand, we chose to begin our study by focusing our attention on developing a catalytic system that would effect amide bond formation regardless of the aliphatic or aromatic nature of the aldehyde starting material. In this regard, we examined the amidation of isovaleraldehyde **130a** as a model substrate to establish the reaction conditions (Table 2.1). This revealed treatment of 1 equiv of **130a** with PhI=NTs (2 equiv) and 10 mol% of [Ru(TTP)(CO)] **47a** as catalyst in CH₂Cl₂ at room temperature for 30 min gave the best result, furnishing 3-methyl-*N*-tosylbutanamide **131a** as the sole product in 94% yield (entry 1). Notably, under these conditions, no byproduct that could be attributed to amidation at the tertiary C–H bond of **130a** was detected. A comparable yield of 93% of the *N*-acylsulfonamide product **131a** was obtained on increasing the amount of PhI=NTs to 4 equiv (entry 2). In contrast, a slightly lower product yield of 82% was afforded when the amount of PhI=NTs was decreased to 1 equiv (entry 3). Similarly, decreasing the catalyst loading to 1 or 5 mol% with 4 equiv of PhI=NTs also resulted in lower product yields (entries 4-5). In contrast, the analogous reactions with [Ru(F₂₀-TPP)(CO)] **88a** or Rh₂(OAc)₄ as catalyst gave **131a** in markedly lower product yields of 31-58%. (entries 6-7). In addition, when PhI=NTs

Table 2.1 Optimization of reaction conditions^a

Entry	PhI=NTs (equiv)	Catalyst	Yield (%) ^b
1	2	[Ru(TTP)(CO)] 47a	94
2	4	[Ru(TTP)(CO)] 47a	93
3	1	[Ru(TTP)(CO)] 47a	82
4 ^c	4	[Ru(TTP)(CO)] 47a	76
5 ^d	4	[Ru(TTP)(CO)] 47a	80
6	2	Rh ₂ (OAc) ₄	31
7	2	[Ru(F ₂₀ -TPP)(CO)] 88a	58
8	- ^e	[Ru(TTP)(CO)] 47a	24
9 ^f	2	-	- ^g

^a Unless otherwise stated, all reactions were carried out in CH₂Cl₂ (2 mL) with catalyst:**130a** molar ratio = 1:10 at room temperature for 30 min. ^b Isolated yield. ^c Reaction conducted with 1 mol% of catalyst. ^d Reaction conducted with 5 mol% of catalyst. ^e Reaction conducted with PhI(OAc)₂ and TsNH₂ in place of PhI=NTs with **130a**:PhI(OAc)₂:TsNH₂ molar ratio = 1:1.25:1.5 at room temperature for 24 h. ^f Reaction was carried out in the absence of catalyst. ^g No reaction based on TLC and ¹H NMR analysis of the crude reaction mixture.

was replaced with the combination of PhI(OAc)₂ (1.25 equiv) and TsNH₂ (1.5 equiv), the reaction was shown to be less effective, furnishing the desired product in 24% yield after 24 h (entry 8). No reaction was also observed by TLC and ¹H NMR analysis of the crude mixture when **130a** was subjected to PhI=NTs in the absence of catalyst (entry 9).

To define the scope of the [Ru(TTP)(CO)]-catalyzed amidation reactions, we applied this process to a series of aliphatic and aromatic aldehydes **130b-β** (Table 2.2). In general, these reactions afforded the corresponding *N*-acylsulfonamides **131b-β** in good to excellent yields (40-99%). The amidation of aldehydes containing a variety of alkyl groups **130b-k** were shown to furnish the corresponding products in near quantitative yields (entries 1-10). Notably, for reactions of aliphatic aldehydes **130d** and **130f-h** also containing a tertiary carbon center, C–N bond formation was found to occur chemoselectively at the aldehyde functional group, which is consistent with our earlier findings for the amidation of **130a** (entries 3 and 5-7). Furthermore, in instances where it was envisioned that the presence of a benzylic C–H bond in the substrate would lead to competitive side reactions as in **130i** and **130j**, the corresponding adducts **131i** and **131j** were furnished as the sole product in good to excellent yields (entries 8-9). The reaction of aldehyde containing an alkyl bromide functionality **130k**¹²¹ was also demonstrated to proceed smoothly to afford **131k** in a high yield of 98% (entry 10). Similarly, when substrates bearing a pendant alkene bond were subjected to standard reaction conditions, no products resulting from aziridination at the C=C bond or amidation at the allylic C–H bond were detected (entries 13-15). In these latter reactions, *N*-acylsulfonamides **131n-p** were afforded as the sole product in 91-99% yield. On the other hand, steric effects of the aliphatic aldehyde could play a role since a bulky group, such as *tert*-butyl, provided the corresponding product **131e** in moderate yield (entry 4).

The [Ru(TTP)(CO)]-catalyzed amidation of benzaldehyde **130q** and aromatic aldehydes **130r-s** containing a *para*-substituted electron donating group on the benzene ring were also found to proceed well. Under the standard conditions, the corresponding *N*-acylsulfonamides **131q-s** were afforded in excellent yields of 92-96% (entries 16-18).

Table 2.2 [Ru(TTP)(CO)]-catalyzed amidation of aldehydes **130b- β^a**

$ \begin{array}{c} \text{R}-\text{CHO} \\ \text{130} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt, 30 min}]{\begin{array}{c} [\text{Ru}(\text{TTP})(\text{CO})] \text{ 47a (10 mol\%)} \\ \text{PhI=NTs (2 equiv)} \end{array}} \begin{array}{c} \text{R}-\text{C(=O)-NHTs} \\ \text{131} \end{array} $				
Entry	Aldehyde	Product	Yield(%) ^b	
1	130b	131b , R = Et	97	
2		131c , R = ⁿ Hex	97	
3	130d		86	
4	130e	131e , R = ^t Bu	60	
5	130f	131f , n = 1	91	
6			99	
7	130h	131h , n = 4	97	
8	130i	131i , n = 1, R = Ph	86	
9		131j , n = 2, R = Ph	68	
10	130k		96	
11	130l	131l , n = 2, R = CO ₂ Me	- ^c	
12			- ^c	
13		131n , R ¹ = ⁿ Pr, R ² = H	99	
14	130o		91	
15			99	
16	130q	131q , X = H	93	
17		131r , X = Me	92	
18	130s		96	
19	130t	131t , X = Cl	- ^d	

Table 2.2 (continued)

Entry	Aldehyde	Product	Yield(%) ^b
20	130u	131u , X = Br	- ^d
21	130v	131v , X = NO ₂	- ^c
22	130w	131w	68
23	130x	131x	28
24	130y	131y , X = O	93
25	130z	131z , X = S	76
26	130a	131a , X = NH	- ^c
27	130β	131β	- ^c

^a All reactions were carried out at room temperature for 30 min with **47a**:**130**: PhI=NTs molar ratio = 1:10:20. ^b Isolated yield. ^c No reaction based on TLC and ¹H NMR analysis of the crude reaction mixture. ^d Pure product not isolated.

In contrast, while reactions of benzaldehyde derivatives **130t** and **130u** containing electron withdrawing substituent at the *para* position of the benzene ring were found to proceed smoothly with >99% conversion based on TLC and ¹H NMR analysis of the crude mixture, isolation of the corresponding products **131t** and **131u** were found to be problematic (entries 19-20). Despite repeated attempts to purify these compounds, they could not be isolated in their respective pure forms. In both instances, the *N*-acylsulfonamide was obtained as an inseparable mixture with TsNH₂ and trace amounts

of the ruthenium(II) catalyst. This contrasted to the amidation of 1-naphthaldehyde **130w** with PhI=NTs, which gave the corresponding **131w** in 68% isolated yield (entry 22).

The present procedure was also shown to efficiently amidate aldehydes with a pendant furan or thiophene functionality, furnishing the corresponding amidated adducts **131y** and **131z** in 93 and 76% yield respectively (entries 24-25). This is noteworthy as such compounds are common structural motifs in a myriad of bioactive natural and pharmaceutical products. On the other hand, amidation of pyrrole-2-carboxaldehyde **130a** with PhI=NTs did not proceed (entry 26). Under the standard conditions, reactions of *p*-nitrobenzaldehyde **130v** and pyridine-3-carboxaldehyde **130β** were also found to give no product formation (entries 21 and 27). In addition, the presence of an ester or alkynyl moiety as in **130l**¹²² and **130m** was shown prevent amidation (entries 11-12). Analysis of the crude reaction mixture *via* TLC and ¹H NMR revealed that no product was formed and the starting aldehydes were recovered almost quantitatively. These latter reactions, thus, suggested that a drawback of the current method is that it is limited to aldehyde substrates containing functional groups that cannot take part in strong coordination with the metal catalyst.

To gain an insight into the possible mechanism of the present reaction, we conducted a deuterium-labelling experiment. As shown in Scheme 2.5, treating a CH₂Cl₂ solution containing benzaldehyde-*α*-*d*₁ **130q-d₁** with 10 mol% of [Ru(TTP)(CO)] catalyst and PhI=NTs as the nitrogen source at room temperature for 1 h gave *N,N*-*d*₁-tosylbenzamide **131q-d₁** in 90% yield and with a deuterium content of 76% incorporated at the nitrogen atom, as determined by ¹H NMR analysis and verified by mass spectrometry of the crude mixture obtained.

Scheme 2.5 [Ru(TTP)(CO)]-catalyzed amidation of **130q-d₁**.

This finding led us to tentatively speculate that the mechanism for the present ruthenium-catalyzed aldehyde amidation reaction to proceed by C–H bond functionalization (Scheme 2.6). In a manner similar to that proposed by Che,^{26,68,97,123} DuBois,^{76,93} Sanford^{5c} and others,^{69,78} the high oxidation state metal complex [Ru(TTP)(NTs)₂] **48a** is thought to initially form from reaction of [Ru(TTP)(CO)] with PhI=NTs. As shown in Scheme 2.5, subsequent transfer of the imido/nitrene group from this newly formed intermediate by either direct insertion or hydrogen atom abstraction/radical rebound is thought to give the amide product **131**.

Scheme 2.6 Tentative mechanism for [Ru(TTP)(CO)]-catalyzed amidation of aldehydes with PhI=NTs.

2.2.2 Polymer-Supported Ruthenium(II) Porphyrin-Catalyzed Amidation of Aldehydes

The problems encountered in attempting to separate *N*-acylsulfonamides **131t** and **131u** derived from amidation of the corresponding aromatic aldehydes containing an electron withdrawing group with PhI=NTs led us to explore the possibility of addressing this issue through a heterogenous approach.¹²⁴ We reasoned the development of such a method would also enable recycling of the ruthenium(II) porphyrin catalyst and is thus attractive in view of the current demands for more atom-economical and efficient catalytic processes. With this in mind, we turned our attentions to examining polymer-supported ruthenium(II) porphyrin systems.¹²⁵ In particular, we were drawn to the use of solid supports such as Merrifield's peptide resin (MPR) and Wang's resin which have found wide applications in the immobilization of metal complexes for the purpose of catalyst recycling.¹²⁶ These types of catalysts have been shown to be stable, easy to handle and easily separable from the reaction mixture *via* a simple filtration step. Moreover, the catalytic activities of these polymer-bound metal catalysts have been shown to be sustainable over several reaction cycles. Additionally, we examined the use of soluble polymer supports due to the ability of such heterogenous catalysts, typically covalently linked to poly(ethylene glycol) (PEG) as support, to be soluble in many organic solvents and could be easily separated from the reaction mixture *via* precipitation with diethyl ether.¹²⁷

For this purpose, we synthesized the unsymmetrical ruthenium(II) porphyrin complex **136** following reported procedures.^{125b} *Meso*-5,10,15-tris(4-tolyl)-20-(4-hydroxyphenyl) porphyrin **135d** was formed from condensation of pyrrole (4 equiv), *p*-tolualdehyde (3 equiv) and *p*-hydroxybenzaldehyde (1 equiv) in propionic acid at reflux for 30 min (Scheme 2.7). Filtration of the reaction mixture gave purple crystals of **135d** in 3% yield.

Subsequent complexation of **135d** with $\text{Ru}_3(\text{CO})_{12}$ in decalin under reflux conditions for 20 h afforded complex **136** in 83% yield.

Scheme 2.7 Synthesis of ruthenium(II) porphyrin complex **136**.

Treatment of the ruthenium(II) complex **136** with MPR in DMF in the presence of K_2CO_3 at reflux gave the heterogenous catalyst **137** (Scheme 2.8).^{125b} In this work, two MPR-linked catalysts with different loadings of **137** were prepared; **137-1** (2 $\mu\text{mol/g}$) and **137-2** (50 $\mu\text{mol/g}$) with metal loadings determined by atomic absorption spectrometry.

Scheme 2.8 Synthesis of MPR-supported ruthenium(II) porphyrin catalyst **137**.

On the other hand, Mitsunobu reaction of ruthenium(II) porphyrin **136** with Wang's resin in the presence of triphenylphosphine (PPh_3) and diethylazodicarboxylate (DEAD) in THF at room temperature were shown to afford **138** with a catalyst loading of 0.1 mmol/g (Scheme 2.9).¹²⁸

Scheme 2.9 Synthesis of Wang's resin-supported ruthenium(II) porphyrin catalyst **138**.

In this work, PEG was converted to the corresponding mesylate **139** via reaction with dimethylsulfonylchloride in the presence of trioctylamine in CH_2Cl_2 at room temperature for 20 h (Scheme 2.10).¹²⁹ Subsequent reaction of the resultant mesylate **139** with **136** in DMF the presence of K_2CO_3 at 60°C for 6 h gave **140** at 0.1 mmol/g catalyst loading.^{125a}

Scheme 2.10 Synthesis of PEG-supported ruthenium(II) porphyrin **140**.

With the polymer-supported ruthenium(II) catalysts in hand, we proceeded to investigate the catalytic properties of these complexes with isovaleraldehyde **130a** as a model substrate (Table 2.3). When **137-1** (10 mg) was subjected to **130a** (0.5 mmol) and $\text{PhI}=\text{NTs}$ (2 equiv) in CH_2Cl_2 at room temperature for 18 h, a low product yield of 17% was obtained (entry 1). In this reaction, no side products were isolated and the remaining starting material was recovered. We next attempted to increase the catalyst loading and found that doubling the amount of the catalyst **137-1** to 20 mg did not improve the yield

of the reaction significantly (entry 2). Surprisingly, a further increment of catalyst to 50 mg resulted in a decrease in product yield (entry 3). This led us to surmise that the poor activity of **137-1** could be attributed to the low loading of 2 μmol of the ruthenium(II) porphyrin per gram of the resin. Indeed, when we subjected 10 mg of **137-2** (50 $\mu\text{mol/g}$) to our reaction conditions, the acylsulfonamide **131a** was furnished in an improved yield of 40% (entry 4). Increasing the catalyst loading to 50 mg or 100 mg led to further improvements in product yields (entries 5-6). However, in both instances, leaching of the catalyst into the reaction mixture could be observed. The reaction mixtures were found to be brownish in color, indicative of the presence of the metal, as opposed to colorless or pale yellow solutions in previous works. The use of metal scavengers has been reported to remove ruthenium catalysts from reaction products.¹³⁰ While this method would be provide a possible solution to this problem, it would also make the current methodology less effective.

In this work, reaction of **130a** with PhI=NTs with Wang's resin-supported ruthenium(II) porphyrin catalyst **138** at various loadings was also examined under the standard reaction conditions. It was found that reaction with 10 mg of **138** as catalyst furnished the desired product **131a** in a low yield of 25% (entry 7). However, a five-fold increase of catalyst loading did not translate to significant improvement in yield as **131a** was afforded in a yield of 33% (entry 8). We then switched to PEG-supported ruthenium(II) porphyrin **140** as catalyst and found that the analogous reactions with catalyst loadings of 20 mg or 50 mg also gave the corresponding amide **131a** in low yields of 23-31% (entries 9-10). In all cases, the unreacted starting aldehyde was recovered quantitatively.

Table 2.3 Polymer-supported ruthenium(II) porphyrin catalyzed amidation of **130a**^a

Entry	Catalyst ^b	Yield (%) ^c
1	137-1 (10 mg)	17
2	137-1 (20 mg)	19
3	137-1 (50 mg)	11
4	137-2 (10 mg)	40
5	137-2 (50 mg)	50 ^d
6	137-2 (100 mg)	44 ^d
7	138 (10 mg)	25
8	138 (50 mg)	33
9	140 (20mg)	23
10	140 (50mg)	31

^a Reactions were carried out in CH₂Cl₂ at room temperature for 18 h with **130a**:PhI=NTs molar ratio = 1:2 in the presence of polymer-supported ruthenium porphyrin catalyst. ^b Values in parenthesis indicate amount of catalyst used. ^c Isolated yield. ^d Catalyst leaching observed.

2.3 Conclusion

In summary, we have developed a highly efficient ruthenium(II)-catalyzed strategy for the direct amidation of aldehydes using PhI=NTs as a nitrogen source. The method was shown to be applicable to a wide range of aldehydes. It is high yielding and chemoselective with amidation only occurring at the aldehydic C–H bond of the starting

aldehyde. This was exemplified by the complete absence of side-product formation from amidation of the tertiary, benzylic or allylic carbon center of substrates containing such reactive sites. Similarly, no aziridination products could be detected in reactions of starting materials containing a C=C bond. On the other hand, the method was shown to be limited to substrates bearing functional groups not capable of strongly coordinating with the ruthenium catalyst and suffered from the inability to isolate the product in reactions with *para*-substituted benzaldehyde derivatives containing electron withdrawing groups. Attempts to address this latter drawback by a heterogenous approach that utilized ruthenium(II) porphyrin catalysts immobilized on three different polymer supports was shown to be unsuccessful. The results revealed that the heterogenous ruthenium(II) porphyrin catalysts examined gave low product yields and catalyst leaching was observed at higher catalyst loading.

Chapter III. Copper-Catalyzed Amidation of Aldehydes

3.1 Introduction

Copper complexes have re-emerged as efficient and ecologically benign catalysts in nitrogen atom transfer reactions in recent years. For instance, Lebel and co-workers demonstrated that $[\text{Cu}(\text{pyridine})_4(\text{BF}_4)_2]$ **142a** mediated intermolecular aziridination of alkenes with trichloroethyl *N*-tosyloxycarbamate **141** to give the corresponding aziridines in moderate yields of 51-68% (Scheme 3.1).^{131a}

Scheme 3.1 $[\text{Cu}(\text{pyridine})_4(\text{BF}_4)_2]$ -catalyzed intermolecular aziridination of alkenes.

Subsequent works from the respective groups of Lebel and Fleming showed that unsaturated *N*-tosyloxycarbamates **76c** could undergo intramolecular aziridination in the presence of $[\text{Cu}(\text{pyridine})_4(\text{OTf})_2]$ **142b** or CuOTf as catalysts (Scheme 3.2).¹³¹ More recently, Appella and co-workers also described efficient copper-catalyzed aziridination of alkenes with TcesNH₂ in the presence of PhI=O, as discussed in Section 1.4.3 of Chapter I.

Scheme 3.2 Copper-catalyzed intramolecular aziridination of *N*-tosyloxycarbamates **76c**.

In the previous chapter, we described the ruthenium(II) porphyrin-catalyzed amidation of aldehydes with $\text{PhI}=\text{NTs}$. In that work, the practicality of the new amidation method was shown to be limited by the inability to purify reactions with aromatic aldehydes containing electron withdrawing groups. An attempt to rectify this problem by examining a heterogenous ruthenium porphyrin-catalyzed approach was also shown to be unsuccessful. In this regard, we became interested in examining the feasibility of using copper catalysis as a means to readdress such problems in the aldehyde amidation process. Herein, we report a copper-catalyzed methodology for the reaction of a variety of aldehydes with $\text{PhI}=\text{NTs}$ or Chloramine-T trihydrate ($\text{TsNClNa}\cdot 3\text{H}_2\text{O}$) as nitrogen source that proceeded in yields up to 99%.¹³² A study that delineates the possible mechanism of aldehyde amidation process is also presented.

Scheme 3.3 Copper(I)-catalyzed amidation of aldehydes **130**.

3.2 Results and Discussion

We chose isovaleraldehyde **130a** as our model substrate so as to provide a direct comparison of catalytic activities between a copper-catalyzed approach with that of the analogous $[\text{Ru}(\text{TTP})(\text{CO})]$ -catalyzed reactions. Table 3.1 shows our initial evaluation of copper salts as catalyst. We found that treatment of 1 equiv of **130a** with 2 equiv of $\text{PhI}=\text{NTs}$ in the presence of 10 mol% of CuOTf and powdered 4 Å molecular sieves in CH_2Cl_2 at room temperature for 18 h gave 3-methyl-*N*-tosylbutanamide **131a** as the sole product in 50% yield (entry 1). Notably, no byproduct from the amidation of the tertiary carbon center of **130a** was formed in this process. The analogous reaction with $\text{Cu}(\text{OTf})_2$

Table 3.1 Screening of copper salts^a

Reaction scheme: **130a** (4-methylpentanal) reacts with copper catalyst (10 mol%), PhI=NTs (2 equiv) in CH₂Cl₂ with 4 Å MS at rt for 18 h to form **131a** (4-methylpentanamide).

Entry	Catalyst	Yield (%) ^b
1	[Cu(OTf)] ₂ ·PhMe	50
2	Cu(OTf) ₂	36
3	CuI	87
4 ^c	CuI	67
5 ^d	CuI	52
6	CuBr	43
7	CuCl	18
8	CuOAc	43

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with catalyst:**130a**:PhI=NTs molar ratio = 1:10:20.

^b Isolated yield. ^c Reaction was carried out with 1 equiv of PhI=NTs. ^d PhI=NTs was replaced with 2 equiv of PhI=O and 2 equiv of TsNH₂.

as catalyst was shown to furnish **131a** in a lower yield of 36% (entry 2). The comparison of reactivity of CuOTf and Cu(OTf)₂ led us to select a range of copper(I) salts for further investigation. This revealed that the use of 10 mol% of copper iodide as catalyst gave the best result (entry 3). Under these conditions, **131a** was afforded as the sole product in 87% yield. On the other hand, a lower product yield was obtained when the reaction was repeated with 1 equiv of PhI=NTs (entry 4). Similarly, the reaction was demonstrated to afford the desired product **131a** in a lower yield of 52%, when PhI=NTs was replaced

with $\text{PhI}=\text{O}$ and TsNH_2 (entry 5). However, in this instance, no side-products were isolated; the remaining starting materials were recovered. Our finding of a lower product yield suggests the lower reactivity of copper iodide as a catalyst. Other copper(I) halide salts such as CuBr and CuCl were also shown to be less efficient catalysts, giving **131a** in markedly lower product yields of 18-43% (entries 6-7). Similarly, repeating the reaction with CuOAc as catalyst was found to result in the formation of **131a** in a lower product yield (entry 8). We next turned our attention to evaluate the generality of copper iodide as catalyst *via* an initial examination of substrate scope (Table 3.2). This showed that treatment of propionaldehyde **130b** with $\text{PhI}=\text{NTs}$ under reaction conditions furnished the corresponding amidated adduct **131b** in a low yield of 18% (entry 1). Repeating the reaction with heptanal **130c** gave the *N*-acylsulfonamide **131c** in a slightly higher yield of 48% (entry 2). We postulated that the low product yields could be attributed to the possibility of either starting aldehydes **130b** and **130c** or products **131b** and **131c** strongly coordinating to the copper center, thus deactivating the catalyst. This was supported by our findings for reactions of sterically bulky substrates such as cyclopentanecarboxaldehyde **130g** and cyclohexanecarboxaldehyde **130h**, which were found to give markedly higher product yields (entries 3-4).¹³³ Aldehyde complexes of copper salts have also been reported by Davis and Green. Thus, we envisaged that reactions of aldehydes **130b** and **130c** at higher catalyst loadings would afford the desired products with improved yields. With this in mind, the amidations of substrates **130b** and **130c** were repeated with a stoichiometric amount of copper iodide. In both instances, the corresponding acylsulfonamides **131b** and **131c** were obtained in 85 and 83% yields, respectively, thereby supporting our initial hypothesis.

Table 3.2 Copper iodide-catalyzed amidation of aldehydes^a

$ \begin{array}{ccc} \text{R}-\text{CHO} & \xrightarrow[\text{4 \AA MS, CH}_2\text{Cl}_2, \text{rt, 18 h}]{\text{CuI (10 mol \%), PhI=NTs (2 equiv)}} & \text{R}-\text{CONHTs} \\ \mathbf{130} & & \mathbf{131} \end{array} $				
Entry	Aldehyde	Product	Yield (%) ^b	
			10 mol% CuI	1 equiv CuI
1	130b	131b , R = Et	18	85
2	130c	131c , R = ⁿ Hex	48	83
3	130g	131g , R = Cyclopentyl	87	– ^c
4	130h	131h , R = Cyclohexyl	96	– ^c

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with **130a**:PhI=NTs molar ratio = 1:2 with either 10 mol% CuI or 1 equiv CuI. ^b Isolated yield. ^c Reaction not carried out.

While we have shown that substrate or product coordination to the copper center could be resolved by the use of stoichiometric copper iodide, this was not a practical solution to this problem. Thus, we sought to address this issue by introducing ligands as a means to disrupt the substrate/product-catalyst interaction sufficiently to render the reaction catalytic. In particular, we intended to examine nitrogen-based ligands which are cheap and commercially available, or could be accessed in one step in a straightforward manner, from readily available starting materials.

With CuOTf as the copper salt, we next proceeded to screen a variety of nitrogen-based ligands in our test reaction with **130a** (Table 3.3). We found that treatment of isovaleraldehyde **130a** with 2 equiv PhI=NTs in the presence of combination of 10 mol% of CuOTf and 40 mol% of pyridine as ligand gave the best result, affording the adduct

Table 3.3 Screening of ligands^a

Entry	Ligand	Yield (%) ^b
1		85
2		60
3		45
4		39
5		37
6	143a , R ¹ = R ² = H	13
7	143b , R ¹ = F, R ² = H	28
8	143c , R ¹ = I, R ² = H	38
9	143d , R ¹ = NO ₂ , R ² = H	37
10	 142e , R ¹ = Cl, R ² = H	52
11	143f , R ¹ = Br, R ² = H	72
12	143g , R ¹ = Cl, R ² = Me	12
13	143h , R ¹ = Br, R ² = Me	60

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h. Catalyst:**143**:**130a**:PhI=NTs molar ratio was 1:1:10:10 for entries 3 & 6-13; 1:2:10:20 for entries 2 & 4-5; and 1:4:10:20 for entry 1. ^b Isolated yield.

131a in 85% yield (entry 1). In contrast, the use of 20 mol% of bipyridine in this reaction was shown to give the desired product in a lower yield of 60% (entry 2). Reaction of **130a** with 10 mol% of terpyridine as ligand was also demonstrated to be less efficient, furnishing the *N*-acysulfonamide **131a** in 45% yield (entry 3). Introduction of 20 mol% of diamine ligands such as phenylenediamine and ethylenediamine to the reaction conditions also proved detrimental to product yields (entries 4-5). A range of Schiff base ligands were also explored in this work. In general, we found that the use of the unsubstituted Schiff base ligand **143a** as well as those with *o*-, *p*-difluoro-, diiodo- and dinitro-substitution **143b-d** in the reaction of **130a** with PhI=NTs gave **131a** in low yields of 13-38% yields (entries 6-9). A slightly higher product yield of 52% was furnished on switching the Schiff base ligand to the *o*-, *p*-dichloro-substituted analogue **143e** (entry 10). Similarly, changing the ligand to the 3,5-dibromo-substituted Schiff base compound **143f** was shown to lead to a further increase in product yield (entry 11). In contrast, the use of the methoxy-protected Schiff base ligands **143g** and **143h** gave **131a** in lower product yields (entries 12-13).

Returning to the range of copper salts used in Table 3.1 confirmed that an increase in the yield of the product was found in all cases with the addition of 40 mol% of pyridine (Table 3.4). Once again, copper iodide was found to give the best result and afforded **131a** in 97% yield (entry 1), comparable to that obtained for the analogous reaction of **130a** with PhI=NTs catalyzed by ruthenium(II) porphyrin. When the catalyst loading of copper iodide was decreased to 5 mol%, a lower product yield of 70% was obtained (entry 2). Similarly, when the reaction was repeated with CuBr, CuCl and Cu(OTf)₂, lower product yields of 54-87% were obtained (entries 3-5). An examination of solvent effects revealed CH₂Cl₂ to be the best solvent (entry 6-9). When toluene or benzene was employed as solvents, slightly lower product yields of 86% were obtained (entries 6-7). In

Table 3.4 Catalyst and solvent screening^a

<div style="text-align: center;"> <p>130a</p> </div>			
Entry	Catalyst	Solvent	Yield (%) ^b
1	CuI	CH ₂ Cl ₂	97
2 ^c	CuI	CH ₂ Cl ₂	70
3	CuBr	CH ₂ Cl ₂	87
4	CuCl	CH ₂ Cl ₂	80
5	Cu(OTf) ₂	CH ₂ Cl ₂	54
6	CuI	PhMe	86
7	CuI	C ₆ H ₆	86
8	CuI	MeNO ₂	– ^d
9	CuI	MeCN	– ^d

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves at room temperature for 18 h with catalyst:pyridine:**130a**:PhI=NTs molar ratio = 1:4:10:20. ^b Isolated yield. ^c 5 mol% of catalyst was used. ^d No reaction observed based on TLC and ¹H NMR analysis of the crude reaction mixture.

contrast, repeating the reaction in more polar solvents such as MeCN and MeNO₂ was found to give no reaction (entries 8-9).

We next sought to challenge our method with an aromatic aldehyde substrate and selected benzaldehyde **130q** (Table 3.5). Under our optimized conditions with 10 mol% of copper iodide and 40 mol% of pyridine, this was found to lead to a high conversion but also significant formation of the imine byproduct **144q** (entry 1).¹³⁴ Table 3.5 shows how

this byproduct formation could be eliminated or minimized through two strategies. The first was by employing slow addition of aldehyde (entries 2-3). A solution of **130q** (1 equiv) in CH₂Cl₂ was introduced into the reaction containing a mixture of copper iodide, pyridine and PhI=NTs *via* syringe pump over 2 h at room temperature (entry 2). After stirring the reaction mixture at room temperature for another 16 h, the desired amide **131q** was obtained in 83% yield, and only 5% of **144q** was detected. Based on this outcome, we hypothesized that a longer addition time could fully eliminate imine formation. However, extending the addition time to 4 h resulted in a lower product yield (entry 3).

Table 3.5 Optimization of the reaction conditions for **130q**^a

$ \begin{array}{c} \text{Cul (10 mol\%)} \text{ pyridine (40 mol\%)} \\ \text{or CuCl (10 mol \%)} \\ \text{PhI=NTs or TsNCINa}\cdot\text{3H}_2\text{O} \\ \text{4 \AA MS, rt, 18 h} \\ \text{CH}_2\text{Cl}_2 \text{ or MeCN} \end{array} $				
Entry	Nitrene Source	Catalyst	Yield (%) ^b	
			131q	144q
1	PhI=NTs	CuI	75	25
2 ^c	PhI=NTs	CuI	83	5
3 ^d	PhI=NTs	CuI	60	8
4 ^e	TsNCINa·3H ₂ O	CuI	27	^f
5 ^e	TsNCINa·3H ₂ O	CuCl	93	^f

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with CuI:pyridine:**130q**:PhI=NTs molar ratio = 1:4:10:20. ^b Isolated yield. ^c **130q** was added over 2 h. ^d **130q** was added over 4 h. ^e Reactions were carried out in MeCN for 18 h with catalyst:**130q**:TsNCINa·3H₂O molar ratio = 1:10:20. ^f Not determined.

This could be attributed to decomposition of the putative copper-imido/nitrene complex or PhI=NTs in solution over time in view of the low concentrations of aldehyde. We believed that the intricate balance between concentration of aldehyde and reactive copper species could be crucial in this amidation process. The second approach was by switching the nitrene transfer reagent to $\text{TsNCINa}\cdot 3\text{H}_2\text{O}$ (entries 4-5).¹³⁵ In these latter reactions, CuCl was found to be more effective than copper iodide, giving **131q** in 93% yield, comparable to that obtained for analogous ruthenium(II) porphyrin-mediated reaction of **130q** with PhI=NTs .

To define the scope of the modified reaction conditions, we applied this process to a variety of aliphatic and aromatic aldehydes **130b-v** (Table 3.6). These substrates were assessed with either copper iodide (10 mol%), pyridine (40 mol%), PhI=NTs (2 equiv) and addition of the aldehyde diluted in CH_2Cl_2 over 2 h or with CuCl (10 mol%) and $\text{TsNCINa}\cdot 3\text{H}_2\text{O}$ (2 equiv). In general, these reactions furnished the corresponding *N*-acylsulfonamide products in moderate to excellent yields (30-99%), comparable to those afforded in the analogous $[\text{Ru}(\text{TTP})(\text{CO})]$ -catalyzed reactions. Under the standard reaction conditions, amidation of alkyl aldehydes **130b-c** and **130d-h** were shown to proceed smoothly with copper iodide and PhI=NTs to afford the corresponding amides **131a-c** and **131d-h** in 81-98% product yield (entries 1-6). Notably, reactions of aldehydes containing an unbranched alkyl group as in **130b** and **130c** with PhI=NTs were demonstrated to give the corresponding products **131b** and **131c** in high yields of 81% and 95%, respectively (entries 1-2). These results further supported our earlier hypothesis that the concentration of aldehyde in the reaction was a key factor in determining product yields, particularly in cases where coordination of sterically unhindered substrates or products to the catalyst played a potential role in the outcome of the reaction. In addition, for substrates **130d-h** containing a tertiary carbon center, the corresponding amides were

Table 3.6 Copper(I)-catalyzed amidation of **130b-a**^a

$ \begin{array}{ccc} \text{R}-\text{CHO} & \xrightarrow[\text{TsNCINa}\cdot 3\text{H}_2\text{O, MeCN, 18 h}]{\text{Cul (10 mol \%), pyridine (40 mol \%)}} & \text{R}-\text{C(=O)NHTs} \\ \text{130} & \text{or} & \text{131} \\ & \text{PhI=NHTs, 4 \AA MS, CH}_2\text{Cl}_2, 18 \text{ h} & \\ & \text{CuCl (10 mol \%)} & \end{array} $				
Entry	Aldehyde	Product	Yield(%) ^b	
1	130b	131b , R = Et	81	
2	130c	131c , R = ⁿ Hex	95	
3	130d	131d , R = ⁱ Pr	81	
4	130f	131f , <i>n</i> = 1	98	
5	130g	131g , <i>n</i> = 3	96	
6	130h	131h , <i>n</i> = 4	96	
7	130i	131i , <i>n</i> = 1, R = Ph	- ^c	
8	130j	131j , <i>n</i> = 2, R = Ph	- ^c (24)	
9	130n	131n , R ¹ = ⁿ Pr, R ² = H	34 (62)	
10	130o	131o , R ¹ = R ² = Me	65 (32)	
11	130r	131r , X = Me	93 (92) ^d	
12	130s	131s , X = OMe	65 (99) ^d	
13	130t	131t , X = Cl	47 (33) ^d	
14	130u	131u , X = Br	59 (64) ^d	
15	130v	131v , R = NO ₂	- ^c	
16	130w	131w	40 (99) ^d	
17	130x	131x	30 (31) ^d	

Table 3.6 (continued)

Entry	Aldehyde	Product	Yield(%) ^b
18	130z	131z , X = O	64 (-) ^c
19	130y	131y , X = S	- ^e
20	130a	131a , X = NH	- ^e

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with CuI:pyridine:**130**:PhI=NTs molar ratio = 1:4:10:20. ^b Isolated yield; values in parenthesis denote yields from reactions conducted with CuCl and TsNCINa.3H₂O in place of CuI and PhI=NTs with CuCl:**130**:TsNCINa.3H₂O molar ratio = 1:10:20 in MeCN. ^c No reaction observed based on TLC and ¹H NMR analysis of the crude reaction mixture. ^d Trace amounts of the corresponding imine also detected by ¹H NMR analysis of the crude mixture but not isolated. ^e No reaction detected based on TLC and ¹H NMR analysis with either CuI/pyridine/PhI=NTs or CuCl/ TsNCINa.3H₂O reaction systems.

furnished in 81-98% yields (entries 3-6). In these reactions, no C-H insertion at the tertiary carbon center was observed, which is consistent with our earlier findings for the copper iodide-catalyzed amidation of **130a** and the analogous [Ru(TTP)(CO)]-mediated reactions of aldehydes **130a-c** and **130d-h** with PhI=NTs. The amidation of aldehydes bearing a C=C bond as in **130n** and **130o** were also shown to give the corresponding adducts **131n** and **131o** in moderate yields of 34% and 65%, respectively, (entries 9-10). In these latter reactions, the *N*-acylsulfonamides **131n** and **131o** were obtained as the sole product, and no byproducts that could be attributed to the aziridination of the C=C bond were observed.

The copper iodide-catalyzed amidation of *p*-tolualdehyde **130r** was shown to proceed smoothly and afford **131r** in near quantitative yields of 93% (entry 11). In contrast, reaction of *p*-methoxybenzaldehyde **130s** was found to furnish **131s** in a lower yield of 65% (entry 12). The reaction of other benzaldehyde derivatives **130t** and **130u** containing electron withdrawing substituents at the *para*-position with PhI=NTs were also demonstrated to be less efficient, affording the corresponding acylsulfonamides **131t** and **131u** in lower yields of 47% and 59%, respectively (entries 13-14). When naphthaldehydes **130v** and **130w** were treated with PhI=NTs under reaction conditions, the corresponding products **131v** and **131w** were obtained in 40% and 30% yield, respectively (entries 16-17). Additionally, amidation of 2-furaldehyde **130z** with PhI=NTs was demonstrated to give **131z** in 64% yield (entry 18). In all reactions involving aromatic aldehydes, formation of trace quantities of the imine byproducts were observed based on ¹H NMR analysis.

The reactions of aldehydes **130j-a** with TsNCINa·3H₂O in the presence of 10 mol% of CuCl were also examined. Notably, near quantitative product yields were obtained in the amidation of *p*-methoxybenzaldehyde **130s** and 1-naphthaldehyde **130w** under these alternative reaction conditions (entries 12 and 16). An improvement in product yields were also observed for the reactions of **130n** and **130u** (entries 9 and 14). In contrast, other substrates examined in this study were found to furnish the corresponding acylsulfonamides in comparable or lower yields to that of the analogous copper iodide-catalyzed reactions. However, reactions of aldehyde substrates **130q**, **130y** and **130a** containing a *p*-nitrophenyl, thiophene and pyrrole moieties, respectively, with either PhI=NTs or TsNCINa·3H₂O were found to give no product formation (entries 15, 19 and 20). In these reactions, the starting materials were recovered in near quantitative yields.

In this work, we engaged in studies aimed at gaining an insight into the mechanism of this amidation of the aldehydic C–H. All the mechanistic studies reported here were carried out with $\text{PhI}=\text{NTs}$ as nitrogen source with 10 mol% of copper iodide and 40 mol% of pyridine as catalyst. One of the key aspects of this study is the identification of the various intermediates in this reaction.¹³⁶ During the course of our studies, formation of imine **144** was observed in several reactions (see Tables 3.5 and 3.6). While we postulated that these byproducts could have resulted from condensation of aldehydes and TsNH_2 furnished from hydrolysis of the iminoiodinane,¹⁵⁻¹⁸ they were also plausible intermediates (Scheme 3.4, route *a*). It would not be inconceivable that further oxidation of imines **144** could give *N*-acylsulfonamides **131**.

Scheme 3.4 Possible reaction mechanism.

To evaluate the possibility of an imine intermediate, *N*-benzylidene-*p*-toluenesulfonamide **144q** was independently prepared following literature procedures.¹³⁷ This involved reaction of 1 equiv of benzaldehyde with 1 equiv of *p*-toluenesulfonamide in the presence of trifluoroacetic anhydride in CH_2Cl_2 at reflux. Under these conditions, **144q** was furnished as a white solid in 47% yield. We found that when **144q** was subsequently subjected to either 2 equiv $\text{PhI}(\text{OAc})_2$ or $\text{PhI}=\text{O}$ as oxidant, formation of **131q** could not be detected by TLC and ^1H NMR analysis of the crude reaction mixture

(Scheme 3.5). With the recovery of **144q** in near quantitative yields, this suggested that it was not a reactive intermediate in the amidation reaction.

Scheme 3.5 Attempted amidation of **144q**.

Alternatively, amidation of aldehydes with $\text{PhI}=\text{NTs}$ could proceed via an oxaziridine intermediate **145** (Scheme 3.4, route *b*).¹³⁶ To support or rule out this possible pathway, we synthesized an authentic sample of the oxaziridine **145q** from the oxidation of **144q** with *meta*-chloroperoxybenzoic acid in the presence of powdered KOH in CH_2Cl_2 .¹³⁸ Subsequent reaction of **145q** under the standard reaction conditions was shown not to lead to formation of **131q**. This implied that an intermediate similar to that of **145q** did not participate in the amidation process (Scheme 3.6).

Scheme 3.6 Attempted amidation of **145q**.

A third possibility for the formation of acylsulfonamide **131** is *via* carbinolamine intermediate **146** (Scheme 3.4, route *c*).¹³⁶ However, as we were not able to prepare the carbinolamine, studies to prove or disprove this possible reaction pathway could not be conducted.

When benzaldehyde labeled with ^{13}C at the aldehyde position **130q**- ^{13}C was used as substrate, the progress of the reaction could be monitored by ^{13}C NMR spectroscopy (Figure 3.1).¹¹⁷ Two major signals were observed in aliquots taken from the reaction

mixture, namely the labeled benzaldehyde starting material **130q-¹³C** decreasing in intensity and labeled acylsulfonamide product **131q-¹³C** increasing in intensity. No formation of other intermediates was observed during the course of this reaction. All these data are consistent with direct conversion of aldehyde **130** to acylsulfonamide **131**.

Figure 3.1 Amidation of **130q-¹³C**.

The beneficial effect of pyridine in the reaction led us to consider the possibility that *N*-tosyliminopyridine **N-117** was an intermediate in this process (Scheme 3.7). The respective groups of Pérez,⁷⁴ Sain¹³⁹ and Shen¹⁴⁰ have reported the successful amidation at the nitrogen center of pyridine with PhI=NTs in the presence of either copper or ruthenium catalysts. An authentic sample of **N-117** was prepared from the reaction of pyridine with PhI=NTs (1.5 equiv) in the presence of 5 mol% of [Ru(TTP)(CO)] **47a** and

powdered 4 Å molecular sieves in CH_2Cl_2 at room temperature for 17 h.¹⁴⁰ In this study, reaction of compound **N-117** under our standard conditions did not give any amidation products, thereby demonstrating its inability to act as a nitrene source (Scheme 3.7a). This observation was consistent with that reported by Evans and co-workers who also showed that compound **N-117** could not mediate the CuOTf -catalyzed aziridination of styrene.¹⁹ Moreover, the formation of **N-117** was also not observed when pyridine, $\text{PhI}=\text{NTs}$ and copper iodide were combined in the absence of aldehyde (Scheme 3.7b). We therefore surmise that the role of pyridine in this reaction is as a ligand.

Scheme 3.7 (a) Attempted amidation of **130a** with **N-117** and (b) attempted *in situ* formation of **N-117**.

Given that direct reaction of an *in situ* formed copper nitrenoid species with the aldehyde appeared likely, we speculated that this occurred *via* rate determining insertion into the aldehyde C–H bond. This mechanism predicts deuterium incorporation into the amide product, that is formation of RCOND₂Ts (Scheme 3.8).^{69,76,78,93} Indeed, this was observed with the $[\text{Ru}(\text{TTP})(\text{CO})]$ -catalyzed version of the reaction described in the previous chapter. Reaction of benzaldehyde- α -d₁ **130q-d₁** with $\text{PhI}=\text{NTs}$ in the presence of copper iodide and pyridine under standard conditions led to 56% deuterium incorporation (*c.f.* 76% with $[\text{Ru}(\text{TTP})(\text{CO})]$).

Scheme 3.8 Amidation of benzaldehyde- α -d₁ **130q-d₁** under the standard reaction conditions.

We therefore proceeded to measure the deuterium kinetic isotope effect for this reaction with **130q** and benzaldehyde-*d*₆ **130q-d₆** as the test substrates (Scheme 3.9).¹¹⁷ In this study, an equimolar mixture of **130q** and **130q-d₆** were subjected to the standard conditions of CuI:pyridine: PhI=NTs:**130q**:**130q-d₆** molar ratio = 1:4:10:12:12. Analysis of the reaction mixture by LCMS gave a k_H/k_D value of 3.8 that was clearly indicative of a rate determining C–H bond cleavage. The value of 3.8 is similar to that reported by Taylor and co-workers in the copper-catalyzed nitrenoid insertion into dibenzyl ether, which was explained by an asynchronous concerted mechanism.¹³⁵

Scheme 3.9 Kinetic isotope studies with **130q** and **130q-d₆**.

In addition, competitive rate studies were conducted to assess the electronic nature of the transition state of this proposed pathway (Table 3.7). In these studies, equimolar amounts of benzaldehyde and benzaldehyde derivatives containing either electron donating or electron withdrawing groups at the *para*-position were subjected to reaction conditions. The results suggested that aldehydes with electron-donating substituents

promoted the amidation process whereas substrates containing electron withdrawing groups retarded reaction.

Table 3.7 Competitive rate studies^a

Entry	X	K_H/k_X^b	$\log (k_H/k_X)$
1	Me	0.671	-0.17
2	OMe	0.639	-0.19
3	F	2.092	0.32
4	Cl	1.934	0.19
5	Br	2.034	0.31

^a Reaction was carried out in the presence of powdered 4 Å molecular sieves in CH_2Cl_2 at room temperature for 2 h with $\text{CuI}:\text{pyridine}:\text{PhI=NTs}:\mathbf{130q}:\text{substituted benzaldehyde}$ at molar ratio = 1:4:10:15:15. ^b GC analysis.

Based on these results, we proposed that the transition state of this copper iodide-catalyzed amidation process could resemble that depicted in Scheme 3.10 where N–H bond formation is further advanced than C–N bond formation.^{69,76,78,93} The reaction of the copper catalyst with PhI=NTs is proposed to form the copper-nitrenoid species **147**. Introduction of aldehyde **130** to the reaction led to transfer of the imido/nitrene moiety by direct insertion at the aldehydic C–H bond to give the acylsulfonamide product **131**.

Scheme 3.10 Tentative mechanism for copper iodide-catalyzed amidation of aldehydes with PhI=NTs.

3.3 Conclusion

In conclusion, we have developed a highly practical and straightforward procedure for the amidation of a wide range of aldehydes. We have shown that this methodology employing copper(I) halides as catalyst were efficient in affording the corresponding *N*-acylsulfonamides in good to high yields. The catalytic activities exhibited by the present copper-mediated approach was shown to be comparable to that of the analogous [Ru(TTP(CO))]-catalyzed amidations. Reactions of aromatic aldehydes containing electron withdrawing groups on the benzene ring or heteroatoms were the only instances where ruthenium(II) catalysis was found to be superior. Nevertheless, the copper(I) catalysts employed in this process are commercially available and inexpensive. Our finding of copper iodide as the best copper catalyst for this amidation process is intriguing, as to date, copper iodide is not known to catalyze metal-imido/nitrene insertion reactions. Mechanistic studies suggested that the reaction proceeded by rate determining insertion of a copper-nitrenoid species into the carbon-hydrogen bond of the aldehyde.

Chapter IV. Copper-Catalyzed Amidation of 1,3-Dicarbonyl Compounds

4.1 Introduction

Chiral 2-amino-1,3-diols and β -hydroxy amino acids are prevalent moieties in many natural products and compounds of biological interests.^{1,141} Compounds containing these motifs have been reported to exhibit various bioactivities such as anticancer, antibacterial, antibiotic, antiviral and immunosuppressant properties. Moreover, their application as chiral auxiliaries, organocatalysts and ligands as well as key intermediates in the synthesis of natural products and bioactive materials have rendered these highly functionalized compounds as key building blocks in organic chemistry.^{2,142}

Accordingly, numerous methodologies have been developed toward the synthesis of optically pure derivatives of aminodiols and β -hydroxy amino acids.^{3,143} This has hitherto included the asymmetric aldol reaction,¹⁴⁴ alkylation of chiral enolates,¹⁴⁵ hydrolysis of aziridine carboxylates,¹⁴⁶ electrophilic amination,¹⁴⁷ Sharpless asymmetric aminohydroxylation, dihydroxylation and epoxidation,¹⁴⁸ asymmetric Strecker reaction,¹⁴⁹ asymmetric hydrogenation¹⁵⁰ and enzymatic transformation.¹⁵¹ While some of these methodologies have been shown to be highly selective, many have relied on the use of substrates from chiral pools or chiral auxiliaries to induce stereoselectivity. In instances where the chiral starting materials cannot be obtained from chiral sources, preparation of these compounds have been reported to often require multistep synthesis, which can be time consuming and tedious, and in some cases, involve non-trivial procedures.

In this context, we wondered whether an alternative entry into chiral 2-amino-1,3-diols and β -hydroxy amino acids could be developed *via* formal nitrene insertion into unsymmetrical 1,3-dicarbonyl compounds **147** in an enantioselective manner (Scheme

4.1). While transition metal complexes have been demonstrated to mediate the tandem aziridination/ring opening of silyl enol ethers with iminoiodinanes as nitrogen source to furnish the corresponding α -amino ketone derivatives as discussed in Section 1.4.5 of Chapter I, direct nitrogen atom transfer reactions to the α C-H bond of 1,3-dicarbonyl compounds **147** is not known. We envisaged that the amidation of these types of substrates under catalysis by copper salts and a chiral ligand would furnish the amido compound **148** and *in situ* reduction of either one or both carbonyl moieties by a reducing agent would afford **149** or **150** as the product. Herein, we describe our studies toward developing a method for copper-catalyzed amidation of dicarbonyl compounds with $\text{PhI}=\text{NTs}$.

Scheme 4.1 Copper-catalyzed amidation of 1,3-dicarbonyl compounds.

4.2 Results and Discussion

We began this study by examining the achiral amidation of ethyl benzoylacetate **147a** as the model substrate in the presence of various catalysts to establish reaction conditions (Table 4.1). This revealed that when 1 equiv of **147a** was subjected to 2 equiv of $\text{PhI}=\text{NTs}$ in the presence of 10 mol% of $[\text{Ru}(\text{TTP})(\text{CO})]$ **47a** and powdered 4 Å molecular sieves at room temperature in CH_2Cl_2 for 18 h, a yield of 68% of the desired mono-amidated product **148a** was obtained (entry 1). In addition to this was the formation of the diamidated 1,3-ketoester **151a** in 10% yield as determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. The structures of both **148a** and **151a** were confirmed by X-ray crystallography, as shown in Figure 4.1. On the other hand, the

Table 4.1 Catalyst screening^a

Entry	Catalyst	Yield (%) ^b	
		148a	151a
1	[Ru(TTP)(CO)] 47a	68 ^c	10
2	[Rh ₂ (oct) ₄] 86	34 ^c	- ^d
3	CuO	69 ^c	16
4	CuOTf	68 ^c	16
5	Cu(OTf) ₂	20	16
6	CuOAc	28	13
7	Cu ₂ O	12	8
8	CuBr	30	9
9	CuCl ₂	3	20
10	CuCl	- ^d	31
11	CuBr ₂	- ^d	10
12	CuCN	- ^d	23
13	CuI	- ^e	- ^e

^a Reactions were conducted in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with catalyst:**147a**:PhI=NTs molar ratio = 1:10:20. ^b ¹H NMR yield of crude mixture with CH₂Br₂ as internal standard. ^c Isolated yield.

^d Trace amounts observed based on ¹H NMR analysis of crude mixture. ^e No reaction.

(a) **148a**

(b) **151a**

Figure 4.1 ORTEP drawings of (a) **148a** and (b) **151a** with thermal ellipsoids at 50% probability levels.¹⁵²

reaction was shown to be less efficient when $[\text{Rh}_2(\text{oct})_4]$ **86** was employed as catalyst, furnishing **148a** in 34% yield and a trace amount of **151a** (entry 2).

When we switched to copper salts, the best product yield obtained was when 10 mol% of CuO was employed as catalyst (entry 3). In this instance, the desired product **148a** was furnished in 69% yield, comparable to that obtained with $[\text{Ru}(\text{TTP})(\text{CO})]$ **47a** as catalyst (*c.f.* entries 1 and 3). In this latter reaction, compound **151a** was also formed in 16% yield. CuOTf was also found to be a suitable catalyst for this reaction, affording **148a** and **151a** in 68% and 16% yields, respectively (entry 4). However, other copper catalysts such as $\text{Cu}(\text{OTf})_2$, CuOAc, Cu_2O and CuBr were shown to be less efficient for the amidation of **147a**, furnishing product **148a** in low yields of 20-30% (entries 5-8). These copper compounds were also shown to be poor catalysts for the formation of **151a** with the diamidated adduct **151a** afforded in low yields of 8-16%. In contrast, when CuCl_2 , CuCl, CuBr_2 or CuCN were employed as catalyst, the reaction was demonstrated to be more selective toward the formation of **151a** albeit in low product yields (entries 9-12). The use of copper iodide as catalyst was the only instance in which no reaction could be detected based on TLC and ^1H NMR analysis of the crude reaction mixture, and the starting materials were recovered in near quantitative amounts (entry 13).

We next sought to examine whether the introduction of a ligand would improve the reaction yields (Table 4.2). We found that the reaction of **147a** in the presence of a combination of $\text{Cu}(\text{OTf})_2$ and 1,10-phenanthroline **152a** as catalyst gave an improved yield of 85% for **148a** with trace amount of **151a** formed (entry 1). The introduction of 1,10-phenanthroline **152a** was demonstrated to have no significant effect on the product yield for the analogous reaction catalyzed by CuO (entry 2). In this reaction, both **148a** and **151a** were afforded in 76% and 11% yield, respectively. On the other hand, the presence

of 1,10-phenanthroline **152a** was shown to be detrimental to the activity of CuOTf and the amidated ketoester **148a** was formed in only 24% yield (entry 3).

Table 4.2 Effect of 1,10-phenanthroline **152a** on reaction yields^a

<div style="text-align: center;"> <p> <chem>CCOC(=O)CC(=O)c1ccccc1</chem> (147a) $\xrightarrow[\text{CH}_2\text{Cl}_2, 4 \text{ \AA MS, rt, 18 h}]{\text{Catalyst (10 mol\%)}, \text{1,10-phenanthroline 152a (10 mol\%)}, \text{PhI=NTs (2 equiv)}}$ <chem>CCOC(=O)C(=O)c1ccccc1Nc2ccccc2</chem> (148a) + <chem>CCOC(=O)C(=O)c1ccccc1C(=O)c2ccccc2Nc3ccccc3</chem> (151a) </p> </div>			
Entry	Catalyst	Yield (%) ^b	
		148a	151a
1	Cu(OTf) ₂	85 ^c	2
2	CuO	76	11
3	CuOTf	24	10

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with catalyst:**152a**:**147a**:PhI=NTs molar ratio = 1:1:10:20. ^b ¹H NMR yield of crude reaction mixture with CH₂Br₂ as internal standard. ^c Isolated yield.

The reaction of ethyl benzoylacetate **147a** with various nitrogen sources was also examined (Table 4.3). In this study, PhI=NTs was found to be the best nitrene precursor for the amidation of **147a**. The amidation of **147a** with TsNH₂ in the presence of hypervalent iodine(III) oxidants was found to be less effective. When PhI(OAc)₂ was employed as oxidant, a product yield of 51% was obtained (entry 1). The use of PhI=O or PhI(O₂C^{*i*}Bu)₂ as the oxidizing agent was shown to give **148a** in lower yields of 14–42% (entries 2–3). In all instances, the formation of **151a** was not observed based on TLC and

Table 4.3 Screening of nitrogen sources^a

$ \begin{array}{c} \text{Ph} \text{---} \text{C}(=\text{O}) \text{---} \text{CH}_2 \text{---} \text{C}(=\text{O}) \text{OEt} \\ \mathbf{147a} \end{array} + \begin{array}{c} \text{PhI=NNs} \\ \text{or} \\ \text{RNH}_2 + \text{oxidant} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, 4 \text{ \AA MS, rt. 18 h}]{\text{Cu(OTf)}_2 (10 \text{ mol\%}), 1,10 \text{ phenanthroline } \mathbf{152a} (10 \text{ mol\%})} \begin{array}{c} \text{Ph} \text{---} \text{C}(=\text{O}) \text{---} \text{CH}(\text{NHR}) \text{---} \text{C}(=\text{O}) \text{OEt} \\ \mathbf{148a, R = Ts} \\ \mathbf{148b, R = Ns} \end{array} + \begin{array}{c} \text{Ph} \text{---} \text{C}(=\text{O}) \text{---} \text{C}(\text{RHN})(\text{NHR}) \text{---} \text{C}(=\text{O}) \text{OEt} \\ \mathbf{151a, R = Ts} \\ \mathbf{151b, R = Ns} \end{array} $			
Entry	Nitrogen Source	Yield (%) ^b	
		2	3
1	TsNH ₂ + PhI(OAc) ₂	51	– ^c
2	TsNH ₂ + PhI=O	42	– ^c
3	TsNH ₂ + PhI(O ₂ C ^t Bu) ₂	14	– ^c
4 ^d	PhI=NNs	31	– ^c
5	NsNH ₂ + PhI(OAc) ₂	10	– ^c
6	NsNH ₂ + PhI=O	12	– ^c
7	NsNH ₂ + PhI(O ₂ C ^t Bu) ₂	– ^c	– ^c

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with Cu(OTf)₂:**152a**:**147a**:RNH₂:oxidant molar ratio = 1:1:10:20:20. ^b ¹H NMR yield of crude reaction mixture with CH₂Br₂ as internal standard. ^c Trace amounts of product observed based on ¹H NMR analysis of crude reaction mixture. ^d 2 equiv PhI=NNs was employed as nitrogen source.

¹H NMR analysis of crude reaction mixtures. Similarly, when PhI=NTs was replaced with PhI=NNs, the reaction was found to furnish **148b** in 31% yield (entry 4). In this reaction, formation of the diamidated product **151b** was not observed based on TLC and ¹H NMR analysis of crude reaction mixtures. The combination of NsNH₂ and a hypervalent iodine(III) oxidant was also shown to be poor nitrogen sources for the reaction of **147a** (entries 5–7). In these latter reactions, low product yields were observed.

We next turned our attention to introducing chirality at the newly formed C–N bond. Realizing that the product would exhibit similar epimerizable characteristics as that of its parent substrate, we rationalized an *in situ* reduction of either or both carbonyl carbon centers would also be required. With this in mind, the reduction of **148a** by NaBH₄ was carried out. In this reaction, **149a** was afforded as an inseparable mixture of products. Similarly, the reduction of **148a** with LiAlH₄ was demonstrated to give **150a** as an impure mixture.

Scheme 4.2 Reduction of **148a**.

We have thus far demonstrated that amidation of **147a** with PhI=NTs by the combination of Cu(OTf)₂ and 1,10-phenanthroline **152a** as catalyst in the presence of 4Å molecular sieves in CH₂Cl₂ at room temperature for 18 h gave the mono-amidated keto ester **148a** in good yields. The reduction of **148a** to the corresponding hydroxy amino ester **149a** or aminodiol **150a** has also been shown to be a facile process, although purification remained problematic.

Concurrent with this study, a variety of chiral nitrogen-based ligands in this amidation process were investigated (Figure 4.2). As the use of chiral bis(oxazoline) ligands in tandem with copper catalysts have been reported to work well for the asymmetric aziridination of alkenes as discussed earlier in Chapter I, we first applied these ligands to our reaction (Table 4.4). This showed treatment of **147a** with PhI=NTs in the presence of 10 mol% of Cu(OTf)₂ and 2,6-bis[(4*S*)-4-phenyl-2-oxazoliny]pyridine ((*S*)-PyBOX)

Figure 4.2 Chiral ligands employed in the enantioselective amidation of benzoyl acetate **147a**.

152b under the standard reaction conditions furnished the desired product **148a** after 18 h based on TLC analysis (entry 1). However, an aliquot of the crude reaction mixture that was subjected to HPLC analysis revealed that the reaction was not enantioselective as the **148a** found to be a racemate. Thus, the subsequent reduction of the crude was not conducted. Instead, work up of the reaction mixture followed by purification *via* silica gel column chromatography furnished (±)-**148a** in 98% yield. When we switched to (*S*)-tBuBOX **152c** as the ligand, the reaction was demonstrated to proceed smoothly to give **148a** in 92% yield but with no enantioselectivity (entry 2). It was also shown that *L*-proline **152d** was an efficient ligand for this reaction, affording **148a** in 99% yield but with 0% ee (entry 3). In contrast, (1*R*,2*R*)-(-)-1,2-cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene) **152e** was shown to be less efficient, affording a racemic mixture of **148a** in 71% yield (entry 4). Postulating that the lack of enantioselectivity in our reaction could be due to the relatively acidic reaction conditions, we opted to introduce bases such as Al₂O₃ and MgO as a counter measure (entries 5-7). We found that the reaction of **147a**

Table 4.4 Ligand screening^a

Reaction scheme showing the amidation of 147a with PhI=NTs catalyzed by Cu(OTf)₂ (10 mol%) and ligand 152 (10 mol%) in CH₂Cl₂ with 4A MS at rt for 18 h to yield 148a.

Entry	Ligand	Yield (%) ^b	Ee (%) ^c
1	152b	98 ^d	0
2	152c	92 ^d	0
3	152d	99	0
4	152e	71	0
5 ^e	152b	91 ^d	0
6 ^f	152b	47	0
7 ^e	152d	58	0
8 ^g	152b	95 ^d	0
9 ^{e,g}	152b	98	0
10 ^{e,h}	152b	— ⁱ	— ^j
11 ^h	152b	— ⁱ	— ^j
12	152f	68	0
13	152g	72	0
14	152h	79	40
15 ^k	152g	56	53

Table 4.4 (continued)

Entry	Ligand	Yield (%) ^b	Ee (%) ^c
16 ^{k,l}	152g	ⁱ	^j
17 ^{e,k}	152g	69	0
18	152h	48	0

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with Cu(OTf)₂:**152**:**147a**:PhI=NTs molar ratio = 1:1:10:20. ^b ¹H NMR yield of crude mixture with CH₂Br₂ as internal standard. ^c ee values obtained *via* HPLC with Chiralpak AS-H column. ^d Isolated yield. ^e Al₂O₃ (2 equiv) was added to the reaction. ^f MgO (2 equiv) was added to the reaction. ^g Reaction was conducted at 0 °C. ^h Reaction was conducted at -78 °C. ⁱ Trace amounts of product formed based on TLC and ¹H NMR analysis of crude reaction mixture. ^j HPLC analysis not carried out. ^k Cu(OTf)₂ was replaced by Cu(MeCN)₄PF₆ as catalyst. ^l Reaction carried out for 48 h.

in the presence of Cu(OTf)₂ and Al₂O₃ resulted in a slightly lower product yield of 91% (entry 5). When MgO was employed as base, the product yield decreased drastically to 47% (entry 6). Similarly, a combination of Al₂O₃ as base and **152d** as ligand gave a lower product yield of 58%. In all three cases, no improvement in product enantioselectivity was observed. Based on these results, we wondered whether lowering the reaction temperature would provide some degree of enantioselective control to the amidation process. However, reactions of **147a** employing **152b** as ligand conducted at 0 °C either in the absence or presence of Al₂O₃ furnished **148a** in 95-98% yield but with no

enantioselectivity (entries 8-9). Lowering the temperature to -78 °C resulted in formation of trace amount of product based on TLC and ^1H NMR analysis (entries 10-11).

With the unsatisfactory results obtained from the utility of chiral nitrogen-based ligands, we next turned our attention to chiral phosphorus-based ligands. In general, chiral phosphine ligands **152f-h** were shown to be less efficient than the nitrogen-based ligands **152a-c**, affording the corresponding products in moderate yields (entries 12-14). The reaction of **147a** in the presence of $\text{Cu}(\text{OTf})_2$ and (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene ((*R*)-BINAP) **152f** was shown to give **148a** in 68% product yield while replacing **152f** with the more sterically bulky (*R*)-(+)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole ((*R*)-SEGPPOS) **152g** also furnished the product in 72% yield (entries 12-13). However, in both reactions, no enantioselectivity was obtained. In contrast, the combination of $\text{Cu}(\text{OTf})_2$ and (*R*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole ((*R*)-DTBM-SEGPPOS) **152h** afforded **148a** in a moderate yield of 77% and an improved product enantioselectivity of 40% was obtained (entry 14).

At this juncture, we wondered if the enantioselectivity of the amidation process could be further improved with the use of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ as catalyst. While the combination of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and **152g** was found to lead to an improved enantioselectivity of 53%, the product yield decreased to 56% (entry 15). We envisioned that prolonging the reaction time would enhance the reaction yield whilst maintaining the product enantioselectivity. However, it was shown that extending reaction time to 48 h led to a drastic decrease in product yield and loss of enantioselectivity (entry 16). We also found that conducting the reaction in the presence of Al_2O_3 as base was also detrimental to product yield and enantioselectivity (entry 17). Similarly, the amidation of **147a** in the presence of

$\text{Cu}(\text{MeCN})_4\text{PF}_6$ and **152h** was also demonstrated to furnish **148a** in a moderate yield of 48% and without any enantioselectivity (entry 18).

We surmised that the poor enantioselectivities in the amidation of **147a** with $\text{PhI}=\text{NTs}$ could be due to the presence of the two acidic α protons. Thus, we postulated that if one of these protons was replaced by an alkyl substituent, the corresponding product formed would be less susceptible to *in situ* racemization. Thus, we subjected ethyl cyclohexanone-2-carboxylate **147b** to the amidation process with 2 equiv of $\text{PhI}=\text{NTs}$ in the presence of either 10 mol% of $\text{Cu}(\text{OTf})_2$ or $\text{Cu}(\text{MeCN})_4\text{PF}_6$, 10 mol% of 1,10-phenanthroline and powdered 4 Å molecular sieves in CH_2Cl_2 at room temperature for 18 h (Scheme 4.3). In both instances, TLC analysis of the reaction mixture revealed formation of a mixture of adducts while no spot attributed to the starting material was observed. However, further analysis of the crude reaction mixture by ^1H NMR spectroscopy could not provide further information as to the identities of the adducts. On the other hand, treatment of **147b** with $\text{PhI}=\text{NNs}$ in the presence of 10 mol % $\text{Cu}(\text{OTf})_2$ and **152a** was found to give no reaction based on TLC and ^1H NMR analysis, and the starting materials were recovered in near quantitative yields.

Scheme 4.3 Attempted amidation of **147b**.

Our attempts to develop an enantioselective reaction for the amidation of 1,3-dicarbonyl compounds have met with limited success. Despite this setback, we decided to examine the scope of the achiral reaction using the $\text{Cu}(\text{OTf})_2$ and 1,10-phenanthroline **152a** catalyst and ligand combination since this was shown to work well for the achiral amidation of **147a** (*re* Table 6.2, entry 1). As shown in Table 4.5, amidation of 1,3-

dicarbonyl compounds **147c-f** containing different combinations of alkyl, aryl and alkoxy substituents were shown to proceed well and furnish the desired products in 40-98% yield. Notably, amidation of acetylacetone **147c** under the standard conditions gave the corresponding product **148d** in 98% yield (entry 1). Similarly, when benzoylacetone **147d** was subjected to the standard conditions, the corresponding amidated adduct **148e** was afforded in 92% yield (entry 2). In contrast, a moderate product yield of 40% was obtained for the reaction of **147e** with PhI=NTs (entry 3). In this reaction, no products attributed to diamidation was observed. Diethyl malonate **147f** was also demonstrated to be a suitable substrate for the amidation process, and the corresponding product **148g** was furnished in 82% yield (entry 4).

Table 4.5 Substrate scope^a

Entry	Substrate			Product	Yield (%) ^b
		R ¹	R ²		
1	147c	Me	Me	148d	98
2	147d	Me	Ph	148e	92
3	147e	Ph	Ph	148f	40
4	147f	OEt	OEt	148g	82

^a Reactions were carried out in the presence of powdered 4Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with Cu(OTf)₂:**152a**:**147**:PhI=NTs molar ratio = 1: 1: 10: 20. ^b Isolated yield.

Although no mechanistic studies on the current method have as yet been conducted, the present reaction is tentatively proposed to proceed in a manner similar to that reported for the aziridination/ring opening of silyl enol ethers, as shown in Scheme 4.4. This could involve formation of a putative copper nitrene species **146** from reaction of the copper catalyst with $\text{PhI}=\text{NTs}$. Subsequent transfer of the imido/nitrene moiety to the enol substrate **153** via either direct insertion (route *a*) or hydrogen atom abstraction/radical rebound (route *b*) could give the aziridine **154**. This unstable intermediate **154** would then undergo ring opening to give the corresponding amidated 1,3-dicarbonyl product **148**.

Scheme 4.4 Tentative mechanism for the amidation of copper-catalyzed 1,3-dicarbonyl compounds with $\text{PhI}=\text{NTs}$.

4.3 Conclusion

The achiral amidation of the model substrate with $\text{PhI}=\text{NTs}$ in the presence of 10 mol% of $\text{Cu}(\text{OTf})_2$ and 1,10-phenanthroline has been shown to proceed smoothly under mild conditions at room temperature to furnish the corresponding product in moderate to high yields. In contrast, our attempts to develop an enantioselective version of this reaction to access chiral 2-amino-1,3-diols and β -hydroxy amino acids was met with limited success. In general, the amidation of substrates in the presence of a combination

Chapter IV Copper-Catalyzed Amidation of 1,3-Dicarbonyl Compounds 96

of an achiral copper catalyst and chiral nitrogen-based ligands was shown to afford the desired product in good to excellent yields but with no enantioselectivity. On the other hand, when chiral phosphorus-based ligands were employed in the reaction, moderate enantioselectivities were obtained but with lower product yields.

Chapter V. Copper Iodide-Catalyzed Aziridination of Alkenes and Amidation of Alkanes

5.1 Introduction

The unexpected catalytic activity of copper iodide in mediating the amidation of aldehydes discussed in Chapter III led us to evaluate the reactivity of this metal halide in other known imido/nitrene transfer reactions, namely, aziridination of alkenes and amidation of alkanes. As mentioned earlier in Chapter I, catalytic systems that have been developed for such imido/nitrene transfer reactions have relied heavily on the use of metal catalysts such as complexes of iron(III), manganese(III), ruthenium(II), dirhodium(II,II), silver(I), and gold(I) with either preformed iminoiodinanes ($\text{PhI}=\text{NSO}_2\text{R}$, typically $\text{R} = \text{Ar}$) or sulfonamides and sulfamate esters in combination with hypervalent iodine(III) oxidants as the nitrogen source. However, a drawback of many of these methodologies has been the need to prepare the metal catalyst, which can be expensive, arduous and time-consuming. In addition, in many instances, a competitive C–H insertion process has been reported in the aziridination of alkenes containing aliphatic side chains. Similarly, in C–H amidations, competitive aziridination of C=C bonds have been demonstrated to occur in cases where the substrates contained a pendant alkene moiety. Moreover, the reactivities reported in many of these methodologies have been shown to be dependent on the need for an excess amount of the alkene or alkane starting material, which are often invaluable intermediates in natural product synthesis, to achieve high conversions and yields.

In this regard, attempts to overcome these limitations have led to a resurgence in interest toward exploring low cost and readily available catalysts such as copper complexes. As discussed earlier in Chapters I and III, this renewed interest in the use of

copper catalysis has led to a number of advances in reactivity and selectivity in works on aziridination of alkenes and C–H bond amidation of hydrocarbons. The latter is of particular note in view of earlier reports demonstrating the lower propensity of copper complexes as catalysts in C–H bond insertion reactions. Hence, based on the unexpected reactivity of copper iodide in mediating the amidation of the acyl C–H bond of aldehydes, we questioned whether this catalyst could find useful applications in known nitrogen atom transfer processes. Herein, we present a copper iodide-catalyzed method for the intermolecular aziridination of a wide variety of alkenes with sulfonamides and sulfamate esters and $\text{PhI}=\text{O}$ as oxidant (Scheme 5.1).¹⁵³ The reaction was shown to proceed under mild conditions at room temperature in good to excellent yields of up to 99%. A study that examines the applicability of this new catalytic method to intramolecular alkene aziridination and amidation of C–H bonds of alkanes is also presented.

Scheme 5.1 Copper iodide-catalyzed aziridination of alkenes and amidation of alkanes.

5.2 Results and Discussion

5.2.1 Copper Iodide-Catalyzed Intermolecular Aziridination of Alkenes

Initially, we examined the effect of various oxidizing agents and solvents on the aziridination of styrene **26a** in the presence of 10 mol % of copper iodide as catalyst and TsNH₂ **157a** as the nitrene source to establish the reaction conditions (Table 5.1). Our studies showed that the best yields were obtained when 1.5 equiv of PhI=O was employed as the oxidant in the presence of powdered 4 Å molecular sieves in MeCN at room temperature for 18 h. Under these conditions, aziridine **27a** was furnished in 99% yield (entry 1). Notably, no byproduct that could be attributed to the epoxidation of styrene by PhI=O was observed. Further investigations revealed that reducing the loading of PhI=O to 1.25 equiv gave the desired aziridine product in a lower yield of 79% (entry 4). A further reduction in oxidant loading to 1 equiv resulted in a respective decrease in product yield to 56% (entry 5). The use of 2 equiv of TsNH₂ was also found to be necessary for the aziridination to proceed smoothly; when 1.5 equiv TsNH₂ was employed in the reaction, a slightly lower product yield of 81% was afforded (entry 2). While a decrease of catalyst loading to 5 mol % in MeCN resulted in a drastic drop in product yield to 19%, the analogous reaction repeated at the same catalyst loading in CH₂Cl₂ afforded **27a** in 99% yield (entries 3 and 12). On the other hand, replacing PhI=O with other hypervalent iodine reagents, such as 2-iodobenzoic acid, hydroxyl-(tosyloxy)iodobenzene (HTIB), PhI(OAc)₂, PhI(OCOtBu)₂, and 2-iodoxybenzoic acid (IBX), resulted in no reaction and near quantitative recovery of the starting materials. Under similar conditions, the use of inorganic oxidants such as Oxone[®], K₃Fe(CN)₆, K₂Cr₂O₇, KIO₄, and K₂S₂O₈ in place of PhI=O was also found to give no reaction. With an oxidant loading of 2 equiv, an examination of solvent effects showed that reactions carried out in CH₂Cl₂ and 1,2-dichloroethane gave the desired aziridine **27a** in near quantitative yields (entries 10 and

11). In contrast, lower product yields of 21-66% were obtained when C₆H₆, MeNO₂, 1,4-dioxane, and CHCl₃ were employed as solvents (entries 6-9).

Table 5.1 Optimization of the reaction conditions^a

Entry	PhI=O (equiv)	Solvent	Yield (%) ^b
1	1.5	MeCN	99
2 ^c	1.5	MeCN	81
3 ^d	1.5	MeCN	19
4	1.25	MeCN	79
5	1	MeCN	56
6	2	C ₆ H ₆	21
7	2	CH ₃ NO ₂	66
8	2	1,4-dioxane	54
9	2	CHCl ₃	29
10	2	ClCH ₂ CH ₂ Cl	99
11	2	CH ₂ Cl ₂	99
12 ^d	1.5	CH ₂ Cl ₂	99

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves at room temperature for 18 h with CuI:**26a**:**157a** molar ratio = 1:10:20. ^b Isolated yield. ^c Reaction conducted with 1.5 equiv of **157a**. ^d Reaction conducted with 5 mol% of CuI.

To define the scope of the copper iodide-catalyzed alkene aziridination reaction, we applied this process to a variety of internal and terminal alkenes **26a-v** containing aromatic and aliphatic substituents (Table 5.2). In general, the reaction of alkenes with **157a** was shown to proceed smoothly and gave the corresponding aziridines in good to excellent yields of 40-99% (entries 1-13). In this work, the aziridination of a variety of styrene derivatives bearing electron-donating substituents at the *para*-position of the benzene ring such as **26b** and **26c** were shown to proceed smoothly to afford the corresponding products **27b** and **27c** in yields of 68% and 93%, respectively (entries 2-3). Similarly, when styrene derivatives containing electron-withdrawing functional groups **26d-f** were subjected to **157a** under our standard reaction conditions, the corresponding aziridine adducts **27d-27f** were furnished in excellent yields of 79-99% (entries 4-6). These results suggested that the electronic nature of the C=C bond of the starting styrene had no effect on the reaction yield. On the other hand, a competitive rate study on these *para*-substituted substrates carried out as shown in Table 5.3 suggested otherwise. These experiments implied that electron-deficient alkenes accelerated aziridination. In contrast, electron-rich alkenes were shown to retard the aziridination process.

In this work, we also found that steric effects of the alkene substrate may also play a role in determining reaction the outcome of the reaction. Increasingly bulky groups at the *ortho*-position of the benzene ring of styrene, such as an *o*-methyl in **26h** or *o*-bromo in **26i**, were shown to provide **27h** and **27i** in lower yields of 63% and 40%, respectively (entries 8-9). In contrast, the presence of a naphthyl moiety on the alkene **26j** was demonstrated to have no effect on the aziridination process. In this reaction, the aziridine **27j** was furnished in an excellent yield of 92% (entry 10).

Table 5.2 Copper iodide-catalyzed aziridination of alkenes **26a-v** with **157a**^d

Entry	Alkenes	Product	Yield (%) ^b
2	26b	27b , R = Me	68
3	26c	27c , R = ^t Bu	93
4	26d	27d , R = F	79
5	26e	27e , R = Cl	83
6	26f	27f , R = Br	99
7	26g	27g , R = OMe	- ^d
8	26h	27h , R = Me	63
9	26i	27i , R = Br	40
10	26j	27j	92
11	26k	27k , n = 1	25 (14) ^c
12	26l	27l , n = 2	25 (56) ^c
13	26m	27m , R ¹ =R ³ = H, R ² = Me	-(90) ^c
14	26n	27n , R ¹ = Me, R ² = R ³ = H	- ^d
15	26o	27o , R ¹ = R ² = H, R ³ = Ph	- ^d
16	26p	27p , R ¹ = R ³ = H, R ² = Ph	- ^d
17	26q	27q , R ¹ = R ³ = H, R ² = CH ₂ Br	- ^d
18	26r	27r	22

Table 5.2 (continued)

Entry	Alkene	Product	Yield (%) ^b
19	26s	27s	14
20	26t	27t	— ^d
21	26u	27u	— ^d
22	26v	27v	— ^d

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in MeCN at room temperature for 18 h with CuI:**26**:**157a**:PhI=O molar ratio = 1:10:20:15. ^b

Isolated yields. ^c Values in parentheses denote yields from reactions conducted in CH₂Cl₂. ^d

No reaction observed based on TLC and ¹H NMR analysis of the crude reaction mixture.

The aziridination of substrates containing an internal C=C bond with **157a** was also examined. In general, alkenes **26k–q** were shown to be poor substrates under the standard conditions (entries 11–17). In our hands, reaction of indene **26k** and 1,2-dihydronaphthalene **26l** was demonstrated to afford **27k** and **27l** in low product yields (entries 11–12). Interestingly, when *trans*-β-methylstyrene **26m** was examined under the standard reaction conditions, no reaction could be detected by TLC and ¹H NMR analysis of the crude reaction mixture and the starting materials were recovered in near quantitative yields (entry 13). However, in this case and for the reaction of **26l**, good to excellent product yields were obtained on changing the reaction medium from MeCN to CH₂Cl₂. In contrast, the use of CH₂Cl₂ as reaction solvent for the aziridination of **26k** did not lead to any improvement in product yield. Furthermore, no reaction could be detected by TLC and ¹H NMR analysis of the crude reaction mixture for the reactions of α-

Table 5.3 Competitive rate studies^a

Entry	R	K_X/K_H^b	$\log [K_X/K_H]$
1	Me	1.14	0.057
2	^t Bu	1.06	0.026
3	F	0.92	-0.034
4	Cl	0.83	-0.079
5	Br	0.87	-0.061

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in MeCN at room temperature for 2 h with CuI:**26a**:**26b-f**:**157a**:PhI=O molar ratio = 1:15:15:13:10. ^b Measured by GC analysis.

methylstyrene **26n**, *cis*-stilbene **26o**, *trans*-stilbene **26p** and cinnamyl bromide **26q** in either MeCN or CH₂Cl₂ (entries 14-17). In each of these reactions, the starting materials were recovered in near quantitative yields.

Our study on the copper iodide-catalyzed alkene aziridination also explored reactions with substrates bearing aliphatic substituents. Under the standard conditions, reaction of allyl benzene **26r** was shown to afford the corresponding products **27r** in a low yield of 22% but no byproducts attributed to amidation of the benzylic C–H bond was observed (entry 18). Similarly, amidation of cyclopentene **26s** was also demonstrated to be low yielding although competitive nitrogen insertion at the allylic C–H was not observed (entry 19). In contrast, no reaction was also observed for other aliphatic alkenes such as

norbornene **26t**, 1-hexene **26u** and dimethyl-2-methylene malonate **26v** based on TLC and ^1H NMR analysis of the crude reaction mixtures (entries 20-22).

In this work, reactions of styrene and styrene derivatives **26a-f** with other nitrogen sources **157b-h** were also carried out (Table 5.4). When aryl sulfonamide **157b** bearing an electron donating methoxy-substituent was subjected to **26a** under our standard reaction conditions, the corresponding aziridine **27w** was produced in an excellent yield of 99% (entry 1). Similarly, reaction of **26a** with the aryl sulfonamide **157c** containing an electron withdrawing *p*-chlorophenyl substituent was also found to furnish the corresponding product **27x** in 84% yield (entry 2). On the other hand, the presence of a nitro moiety on the *para*-position of the benzene ring of the aryl sulfonamide was shown to be detrimental to the aziridination process. In this instance, only 11% of the desired product was furnished (entry 3).

Recognizing that detosylation of **27a-m** to furnish the unprotected aziridines may not be trivial and could require harsh reaction conditions that could lead to the formation of ring-opened products or decomposition, we turned our attentions to the use of TcesNH_2 **157e** as an alternative nitrene source. The trichloroethoxy sulfonyl group of **157e** has been reported to be easily removed from the product under mild reductive conditions.^{37, 76} With this in mind, we examined the reaction of styrene **26a** with **157e** under standard reaction conditions and found it to furnish the desired aziridine **27w** in a good yield of 69% (entry 4). Similarly, when styrene derivatives containing electron donating substituents such as **26b** and **26c** were subjected to **157e**, the corresponding aziridines **27a** and **27b** were produced in good yields of 41 and 50%, respectively (entries 5-6). A similar outcome was found for aziridinations of styrene derivatives containing electron withdrawing groups as in **26d-26f** with **157e**, which were shown to proceed smoothly to afford **27g-e** in 60-68% yield (entries 7-9). In this study, we also attempted the

Table 5.4 Copper iodide-catalyzed aziridination of alkenes **26a-f** with other nitrogen sources^a

Entry	Substrates	Products	Yield (%) ^b
1	26a + 157b	27w , R = OMe	99
2	26a + 157c	27x , R = Cl	84
3	26a + 157d	27y , R = NO ₂	11
4	26a + 157e	27z , R = H	69
5	26b + 157e	27a , R = Me	41
6	26c + 157e	27β , R = ^t Bu	50
7	26d + 157e	27γ , R = F	67
8	26e + 157e	27δ , R = Cl	60
9	26f + 157e	27ε , R = Br	68
10	26a + 157f	27ζ , R = Bn	- ^c
11	26a + 157g	27η , R = ^t Bu	- ^c
12	26a + 157h	27a	30

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in MeCN at room temperature for 18 h with CuI:**26**:**157a**:PhI=O molar ratio = 1:10:20:15. ^b Isolated yields. ^c No reaction observed based on TLC and ¹H NMR analysis of reaction mixture.

aziridination of **26a** with carbamate esters **157f** and **157g** under our standard conditions (entries 10-11). In these latter instances, no reaction was observed based on TLC and ^1H NMR analysis of crude reaction mixture and the respective starting materials were recovered in near quantitative yields. Chloramine-T trihydrate **2h** was also shown to be a poor nitrogen source as the corresponding product was furnished in a low yield of 30% yield (entry 12).

5.2.2 Attempted Copper Iodide-Catalyzed Intramolecular Aziridination of Alkenes

In an effort to explore the scope of our copper iodide-catalyzed aziridination process, the intramolecular aziridination of alkenes **76a-e** under the standard reaction conditions was examined. These starting materials **76a-e** were prepared following literature procedures.^{86,87} In this work, *trans*-cinnamyl alcohol **158a** was obtained in quantitative yield from NaBH_4 -mediated reduction of *trans*-cinnamaldehyde (Scheme 5.2). Reaction of this allylic alcohol **158a** with chlorosulfonyl isocyanate was shown to proceed smoothly and afford the corresponding sulfamate ester **76a** in 80% yield.⁸⁷ Similarly, when commercially available 3-buten-1-ol **158b** was subjected to the same reaction conditions, the homoallylic sulfamate ester **76b** was furnished in 82% yield. Conversion of alcohols **158a** and **158b** to the corresponding carbamate esters **76c** and **76d** in 80% and

Scheme 5.2 Synthesis of alkenes **76a-d**.

85% yield, respectively, was achieved on treating with 1.2 equiv of trichloroacetyl isocyanate.⁸⁶

The *N*-tosyloxycarbamate ester **76e** was prepared from *trans*-cinnamyl alcohol **158a** (Scheme 5.3).¹⁵⁴ This involved conversion of **158a** to the *N*-hydroxycarbamate **159** via reaction with hydroxylamine hydrochloride in the presence of carbonyl diimide and imidazole at room temperature for 3 h. After an acidic work up, the crude mixture was purified *via* column chromatography to afford the desired *N*-hydroxycarbamate **159** in 70% yield. This intermediate was then treated with *p*-toluenesulfonyl chloride to furnish the *N*-tosyloxycarbamate **76e** in 85% yield after purification.

Scheme 5.3 Synthesis of *N*-tosyloxycarbamate **76e**.

With the starting materials in hand, we proceeded to examine the intramolecular cyclization of alkenes **76a-e** under our standard conditions (Scheme 5.4). However, in the presence of 10 mol% of copper iodide and 1.5 equiv of $\text{PhI}=\text{O}$, aziridinations of **76a-e** was shown to be unsuccessful. In all instances, no reaction could be detected by either TLC or ^1H NMR analysis and the starting materials were recovered quantitatively.

Scheme 5.5 Attempted intramolecular aziridinations of alkenes **76a-e**.

5.2.3 Attempted Copper Iodide-Catalyzed Intermolecular Amidation of C-H Bonds of Alkanes

In this study, amidation of aryl alkanes **155a-f** bearing benzylic C-H bonds with TsNH₂ **157a** under standard reaction conditions were examined (Table 5.5). We found that treatment of indane **155a** with **157a** in the presence of 10 mol% of CuI and 1.5 equiv PhI=O in MeCN as solvent for 18 h furnished the desired product **156a** in a low yield of 10% (entry 1). However, when the reaction medium was switched from MeCN to CH₂Cl₂, the analogous reaction of indane **155a** with **157a** was found to be more efficient (entry 2). Under these latter conditions, the corresponding product **156a** was afforded in 70% yield. We then proceeded to examine the amidation of various ethyl benzene derivatives with CH₂Cl₂ as solvent (entries 3-7). Surprisingly, reaction of ethyl benzene **155b** with **157a** was shown to only afford the corresponding product **156b** in trace quantities (entry 3). In contrast, when the process was applied to ethyl benzene derivatives bearing either an electron withdrawing or electron donating substituent at the *para*-position of the benzene ring as in **155c** and **155d**, no reaction was observed (entries 4-5). Similarly, reactions of 2-ethylnaphthalene **155e** and tetrahydronaphthalene **155f** were also found to be unsuccessful (entries 6-7). In these latter reactions, no product formation could be detected by TLC and ¹H NMR analysis of crude reaction mixture and the starting materials were recovered in near quantitative yield.

Table 5.5 Copper iodide-catalyzed amidation of aryl alkanes **156a-f** with **157a**^a

Entry	Alkane	Product	Yield (%) ^b		
1 ^c			155a	156a	10
2			155b	156b , R = H	70
3			155c	156c , R = Br	- ^d
4			155d	156d , R = OMe	- ^d
5			155e	156e	- ^d
6			155f	156f	- ^d

^a All reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with CuI:**155**:PhI=O:TsNH₂ molar ratio = 1:10:15:20. ^b Isolated yield. ^c CH₂Cl₂ was replaced with MeCN as solvent. ^d No reaction observed based on TLC and ¹H NMR analysis of reaction mixture.

5.3 Conclusion

In summary, we have demonstrated a copper iodide-catalyzed process for the aziridination of a variety of alkenes in good to excellent yields. In some cases, near quantitative product yields could be obtained under the mild conditions employed at room temperature. The aziridination protocol was also shown to be applicable to a variety of aromatic alkenes and sulfonamide and sulfamate ester-based nitrogen sources. However,

Chapter V Copper Iodide-Catalyzed Aziridination and Amidation Reactions 111

the current method was shown to be limited to the aziridination of alkenes containing aromatic substituents; substrates containing aliphatic groups were shown to be unreactive under our reaction conditions. Similarly, carbamate esters were found to be unsuitable as the nitrogen source. A study directed toward evaluating the generality of this new copper iodide-catalyzed protocol also revealed that intramolecular aziridination of sulfamate and carbamate esters, as well as *N*-tosyloxycarbamates could not be accomplished using this catalytic approach. A similar outcome was found when the amidation of alkanes under these conditions was investigated. In this part of the study, only the amidation of indane with TsNH_2 was shown to be possible.

Chapter VI. Copper-Catalyzed Amidation of Aromatic Heterocycles

6.1 Introduction

Amino-substituted heteroarenes constitute an important class of compounds because of their utility to serve as building blocks for functional materials and as key components in a myriad of bioactive compounds.^{1,2,155} Despite this, examples to this class of synthetically useful compounds that makes use of transition metal-catalyzed C–H bond amidation in the literature has remained rare.¹⁵⁶ To our knowledge, amidation of aromatic heterocycles with $\text{PhI}=\text{NTs}$ mediated by $[\text{Ru}(\text{Ttp})(\text{CO})]$ **47a** reported by Che and co-workers is the only known reported example as mentioned earlier in Section 1.5.5 of Chapter I.

Drawn to this novel area of C–H bond amidation, we questioned whether a copper-catalyzed version of this transformation could be realized. In particular, we were attracted to the possibility of exploring the anticipated differences between a copper- and ruthenium-mediated approach and the implications of this on the regio- and chemoselective outcome of the reaction. Additionally, such an approach would benefit from the use of a copper catalyst that is ecologically benign, readily available and low costing, and provides the opportunity to establish a more practical and straightforward method for the amidation of heteroarenes. Herein, we present our studies in developing a methodology for copper-catalyzed diamidation of *N*-substituted nitrogen containing heteroaromatic compounds (Scheme 6.1).

Scheme 6.1 Copper-catalyzed amidation of aromatic heterocycles.

6.2 Results and Discussion

6.2.1 Copper-Catalyzed Amidation of Aromatic Heterocycles with PhI=NTs

N-Methylpyrrole **118a** and *N*-phenylpyrrole **118b** were chosen as the model substrates to establish the reaction conditions. *N*-Methylpyrrole is readily available while *N*-phenylpyrrole was prepared following a modified version of the Ullmann coupling reaction developed in our group.¹⁵⁷ This involved reaction of 1 equiv of pyrrole with iodobenzene (1equiv) in the presence of 10 mol% of copper iodide as catalyst, 10 mol% of ⁿBu₄NBr as additive and NaOH (2 equiv) as base in PhMe at reflux for 22 h. The details of this new approach that includes the generality and selectivity to the Ullmann reaction will be discussed in Section 6.2.2 of this chapter.

Previously, Che and co-workers demonstrated that the amidation of **118a** or **118b** by PhI=NTs (5 equiv) employing 10 mol% of [Ru(TTP)(CO)] as catalyst and powdered 4 Å molecular sieves in CH₂Cl₂ under sonication at 40 °C for 2 h gave the corresponding diamidated compounds **119a** and **119b** in 68 and 82% yield, respectively (Scheme 6.2).¹⁰⁰ In their work, amidation of **118a** and **118b** with PhI=NTs was noted to proceed in the absence of catalysts albeit in lower product yields that fell within the 18-54% range among the several substrates reported.

Scheme 6.2 [Ru(TTP)(CO)]-catalyzed amidation of **118a** and **118b**.

In our hands, we found that treatment of **118a** with 5 equiv PhI=NTs in CH₂Cl₂ at room temperature for 18 h furnished the corresponding product **119a** in a yield of 45% (Table 6.1, entry 1). Similarly, amidation of **118b** gave **119b** in 33% yield (entry 2). A

Table 6.1 Optimization studies on the diamidation of **118a** or **118b** with PhI=NTs^a

$\text{Pyrrole-N-R} + \text{PhI=NTs} \xrightarrow[\text{CH}_2\text{Cl}_2, 4 \text{ \AA MS}, 18 \text{ h, rt}]{\text{Cu catalyst (10 mol\%)}} \text{Pyrrole-N-R-2,5-bis(NHTs)}$

118a, R = Me **119a**, R = Me
118b, R = Ph **119b**, R = Ph

Entry	Substrate	Catalyst	Yield (%) ^b
1	118a	-	45 (48) ^c
2	118b	-	33 (35) ^c
3	118a	CuOAc	45
4	118a	Cu(OTf) ₂	42
5	118a	CuOTf	44
6	118a	CuI	40
7	118a	CuCl	37
8	118a	CuBr	36
9	118a	CuCl ₂	35
10	118a	CuBr ₂	30

^a Reactions were carried out in the presence of powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h with catalyst:**118**:PhI=NTs molar ratio 1:10:50. ^b

¹H NMR yield of crude reaction mixture with CH₂Br₂ as internal standard. ^c Values in parenthesis denote yield of reaction carried out under sonication at 40 °C for 2 h.

comparable yield for both **119a** and **119b** was also obtained when the analogous reactions were conducted under sonication at 40 °C for 2 h.

We next examined the amidation of **118a** with 5 equiv of PhI=NTs in the presence of a variety of copper catalysts and powdered 4 Å molecular sieves in CH₂Cl₂ at room temperature for 18 h. This revealed that reaction of **118a** with PhI=NTs in the presence of

10 mol% of CuOAc furnished **119a** as the sole product in 45% yield, comparable to that of the uncatalyzed amidation reaction (entry 3). Similarly, the use of CuOTf and Cu(OTf)₂ as catalysts were also shown to give the corresponding adduct **119a** in 42-44% yield (entries 4-5). The amidation of **118a** with other copper(I) halides such as CuI, CuCl and CuBr was shown to furnish the diamidated product **119a** in low yields of 36-40% (entry 6-8). In addition, the use of copper (II) halides was demonstrated to give **119a** in 30-35% product yields (entries 9-10). Based on these results, we surmised that the copper catalysts surveyed in this work did not play a part in mediating the diamidation of *N*-substituted pyrroles.

6.2.2 Copper Iodide-Catalyzed Ullmann Reaction of Azoles, Phenols and Thiols with Aryl Halides

Although a copper-catalyzed heteroarene amidation could not be realized, we were drawn to exploring the generality of our modified version of the Ullmann reaction. This was all the more so in view of the fact that *N*-arylated azoles, diaryl ethers and diaryl thioethers are common structural motifs in a myriad of natural products and bioactive compounds.^{1,2,158} They have also found wide applications in the fine chemicals and polymer industries. This class of compounds is commonly employed as key building blocks in organic synthesis, and ligands in metal-catalyzed organic transformations. Among the various strategies developed toward the formation of C(aryl)-heteroatom bond, the copper-catalyzed Ullmann coupling reaction has proven to be one of the most convenient synthetic routes for installing the aryl functionality.^{159,160} However, such reactions have traditionally suffered from high reaction temperatures (typically above 140 °C), the need for stoichiometric amounts of copper catalyst that make scale-up unfeasible and ecologically-unfriendly, the use of toxic and air-sensitive aryl coupling reagents that

can be difficult to access, and excess aryl halide starting materials to achieve reasonable product yields. In addition, low functional group tolerance and poor substrate generality have lessened the utility of these methods. In view of these shortcomings, the establishment of copper-mediated approaches under milder conditions has been actively pursued.

A recent notable achievement has been the use of “Cu + ligand” (ligand = diamine or amino acid) catalytic systems by Buchwald¹⁶¹ and Ma¹⁶² which showed the respective *N*-, *O*- and *S*-arylation of nitrogen heterocycles, phenols and thiols could be achieved in good yields. Following these pioneering works, a number of groups have reported similar approaches using a variety of phosphorus-, nitrogen- and oxygen-based ligands or additives such as Schiff bases, 1,10-phenanthroline, quinoline, aminoarenethiol, and oxime-phosphine oxide derivatives for these reactions.¹⁶³ Despite these advances, examples on analogous reactions that do not require a ligand or additive in tandem with aryl halides as starting materials have remained sparse.

Herein, we present our findings on a copper iodide catalyzed *N*-, *O*- and *S*-arylation of a variety of azoles, phenols and thiols respectively with equimolar amounts of aryl iodides in yields up to 95%, comparable to those reported using ligand and additive promoted strategies (Scheme 6.3).^{157,164,165}

Scheme 6.3 Copper iodide-catalyzed arylation of nucleophiles with aryl halides.

6.2.2.1 Copper Iodide-Catalyzed *N*-Arylation of Azoles

At the outset of this study, we examined the arylation of pyrrole **160a** with iodobenzene **161a** as our model substrates to establish reaction conditions (Table 6.2). We found that treatment of **160a** (1 equiv) with **161a** (1 equiv), 5 mol% of copper iodide as catalyst, 5 mol% of $n\text{Bu}_4\text{NBr}$ as phase transfer catalyst, and NaOH (2 equiv) in toluene at reflux for 22 h gave the best result, furnishing *N*-phenylpyrrole **118b** in 95% yield (entry 1). The use of other copper(I) and copper(II) catalysts in place of copper iodide under identical reaction conditions gave the desired product in lower yields of 57-84% (entries 2-6). High product yields were observed for reactions with catalyst loadings increasing to 10 or 20 mol% and at this latter catalyst loading with 3 equiv of NaOH (entries 8, 9 and 11). Slightly lower product yields (68-73%) were obtained upon lowering either catalyst loading of copper iodide to 1 mol% or NaOH to 1 equiv (entries 7 and 10). In contrast, when bromobenzene **161b** was employed as the aryl halide reagent, **118b** was afforded in a markedly lower yield of 25% (entry 12).

Inspection of entries 13-15 and 18-20 in Table 6.2 revealed that copper iodide-catalyzed coupling of **160a** with **161a** and other inorganic bases was significantly less effective. Under the conditions of 1 equiv of pyrrole, 1 equiv of iodobenzene, CuI (20 mol%), and $n\text{Bu}_4\text{NBr}$ (20 mol%) in PhMe at reflux for 22 h, *N*-arylation with 3 equiv of K_3PO_4 , K_2CO_3 , Al_2O_3 , MgO or $\text{LiOH}\cdot\text{H}_2\text{O}$ as base gave **118b** in markedly lower yields of 4-49%. Reactions of **160a** with **161a** with either MeCO_2Na or pyridine as the base are the only instances where no reaction was observed and both starting materials were recovered in quantitative yields (entries 21-22).

Table 6.2 Optimization of the reaction conditions^a

Entry	Catalyst (mol%)	<i>n</i> Bu ₄ NBr (mol%)	Base ^b	Yield (%) ^c
1	CuI (5)	5	NaOH (2)	95 ^d
2	CuCl (5)	5	NaOH (2)	84
3	CuCl ₂ (5)	5	NaOH (2)	67
4	CuBr (5)	5	NaOH (2)	76
5	CuBr ₂ (5)	5	NaOH (2)	78
6	Cu(OAc) ₂ (5)	5	NaOH (2)	57
7	CuI (1)	1	NaOH (2)	68
8	CuI (10)	10	NaOH (2)	88
9	CuI (20)	20	NaOH (2)	87
10	CuI (20)	20	NaOH (1)	73
11	CuI (20)	20	NaOH (3)	86 ^d
12 ^e	CuI (5)	5	NaOH (2)	25 ^d
13	CuI (5)	-	NaOH (2)	4
14	CuI (20)	20	K ₃ PO ₄ (3)	49
15	CuI (20)	20	K ₃ PO ₄ (3) ^f	14
16	CuI (20)	20	K ₂ CO ₃ (3)	16
17	CuI (20)	20	K ₂ CO ₃ (3) ^g	- ^h
18	CuI (20)	20	Al ₂ O ₃ (3)	11
19	CuI (20)	20	MgO (3)	6

Table 6.2 (continued)

Entry	Catalyst (mol%)	ⁿ Bu ₄ NBr (mol%)	Base ^b	Yield (%) ^c
20	CuI (20)	20	LiOH·H ₂ O (3)	4
21	CuI (20)	20	MeCO ₂ Na (3)	– ^h
22	CuI (20)	20	pyridine (3)	– ^h

^a All reactions were performed in PhMe at reflux for 22 h with CuI:ⁿBu₄NBr:base molar ratio as stated in the table. ^b Values in parentheses denote the equiv of base used. ^c ¹H NMR yield with CH₂Br₂ as internal standard. ^d Isolated yield. ^e Reaction carried out with **161b** in place of **161a**. ^f Reaction carried out with K₃PO₄ in 5 mL of water. ^g Reaction carried out with K₂CO₃ dried to a constant volume prior to use. ^h No reaction based on TLC and ¹H NMR analysis of crude reaction mixture.

At this juncture, we would like to highlight that employment of ⁿBu₄NBr as a phase transfer catalyst and the presence of a small amount of water intrinsically present in commercially available inorganic bases was essential for the *N*-arylation reaction. Under our experimental conditions, when ⁿBu₄NBr was removed from the reaction and 1 equiv of **160a** was treated with 1 equiv of **161a** in the presence of 5 mol% of copper iodide, and NaOH (2 equiv) in PhMe at reflux for 22 h, **118b** was afforded in 4% yield (entry 13). Conducting the reaction under the same conditions as that for entry 11 in Table 6.2 but with K₂CO₃ dried to a constant weight under reduced pressure at 200 °C prior to use, on the other hand, gave no reaction (entry 17) while the use of 5 mL of a saturated solution of K₃PO₄ in water was also found to be detrimental and a low product yield of 14% was obtained (entry 15).

To define the scope of copper iodide-catalyzed *N*-arylation reactions, we applied this process to a series of nitrogen heterocycles **160a-f** and aryl iodides **161a-l** (Table 6.3).

These reactions afforded the corresponding *N*-arylated adducts in good to excellent yields (up to 90%) and substrate conversion up to 99% (entries 2-15). Notably, we were able to exploit the difference in reactivity of aryl halides ($I > Br \gg Cl > F$) in the present method by coupling **160a** and the aryl iodide selectively in the presence of substrates containing aryl bromides, chlorides and fluorides (entries 2-4). The electron-rich and electron-deficient nature of the aryl iodide was also found to have no effect on reaction yield (*c.f.* entries 2-4 and 5-8). Furthermore, in instances where it was initially envisaged that the presence of a sterically demanding methyl group *ortho* to the iodine atom on the benzene ring of the aryl iodide would prevent coupling, the corresponding adduct was furnished albeit in slightly lower yields (entries 9-10). Similarly, the *N*-arylation of sterically hindered 2-acetylpyrrole **160b** was shown to proceed smoothly to furnish the corresponding *N*-phenyl-2-acetylpyrrole **118i** in 50% yield and 74% substrate conversion (entry 11).

The application of our catalytic system for the *N*-arylation of other classes of nitrogen heterocycles was also examined. Treatment of 1 equiv of indole **160c** with 1 equiv of either **161a** or **161h** and 5 mol% of copper iodide, 5 mol% of $t\text{Bu}_4\text{NBr}$ and NaOH (2 equiv) in toluene at reflux for 22 h, was shown to proceed to give the corresponding *N*-arylated products **118m** and **118n** in 80 and 64% yield with near quantitative and 73% substrate conversion, respectively (entries 12-13). Interestingly, when the reactions were repeated with DMSO as solvent, the arylation of **160c** with **161a** or **161h** under identical reaction conditions gave improved product yields, affording the corresponding product in 88% and 80% yields respectively. Under similar conditions, the coupling reactions of imidazole **160d** with electron withdrawing, electron donating and sterically bulky aryl iodides furnished the desired products **118p-r** in good yields of 68-84% (entries 15-18). In contrast, the *N*-arylation of indazole **160e**, 1,2,4-triazole **160f** and 1,2,4-triazole **160f**

with **161a**, **161h** and **161e** were less efficient, furnishing the corresponding products **118t-y** in markedly lower yields of 19-54% (entries 19-24).

Table 6.3 Copper iodide-catalyzed *N*-arylation of 1*H*-azoles **160** with aryl iodides **161**^a

Entry	Substrates	Product	Yield (%) ^{b, c}
1	160a + 161a	118b , R = H	95 (>99)
2	160a + 161c	118c , R = F	77 (>99)
3	160a + 161d	118d , R = Br	90 (>99)
4	160a + 161e	118e , R = Cl	80 (>99)
5	160a + 161f	118f , R = ^t Bu	86 (>99)
6	160a + 161g	118g , R = OMe	84 (>99)
7	160a + 161h	118h , R = Me	88 (>99)
8	160a + 161i	118i	83 (94)
9	160a + 161j	118j	62 (87)
10	160a + 161k	118k , R = Me	63 (88)
11	160b + 161a	118l	50 (74)

Table 6.3 (continued)

Entry	Substrates	Product	Yield (%) ^{b, c}
12	160c + 161a	118m , R = H	80 (>99)
13	160c + 161h	118n , R = Me	88(>99) ^d
14 ^d	160c + 161d	118o , R = Br	64 (73)
15 ^d	160d + 161a	118p , R = H	80 (>99) ^d
16 ^d	160d + 161h	118q , R = Me	33 (>99)
17 ^d	160d + 161e	118r , R = Cl	84 (88)
18 ^d	160d + 161l	118s , R = 1-naphthyl	69 (>99)
19 ^d	160e + 161a	118t , R = H	70 (>99)
20 ^d	160e + 161h	118u , R = Me	50 (80)
21 ^d	160e + 161e	118v , R = Cl	26
22 ^d	160f + 161a	118w , R = H	19
23 ^d	160f + 161h	118x , R = Me	45
24 ^d	160f + 161e	118y , R = Cl	47
			54

^a All reactions were performed in PhMe at reflux for 22 h with CuI:ⁿBu₄NBr:**160**:**161**:base molar ratio = 1:1:20:20:40. ^b Isolated yield. ^c Values in parentheses denote substrate conversion based on amount of aryl iodide consumed as determined by ¹H NMR analysis. ^d Reaction carried out with DMSO in place of PhMe as solvent.

6.2.2.2 Copper Iodide-Catalyzed *O*-Arylation of Phenols and Alcohols

In preliminary studies with the CuI/NaOH system, *O*-arylation of phenol **162a** with iodobenzene **161a** was found to give no reaction. Rationalizing that **162a** could be resistant to deprotonation, we conducted optimization studies with the same starting materials as the model substrates (Table 6.4). After screening a series of bases, 2 equiv of K₃PO₄ was determined to be the most effective base and gave diphenyl ether **163a** in 62% yield (entry 1). While replacing K₃PO₄ with K₂CO₃ afforded **163a** in a slightly lower yield of 51% (entry 2), the use of other inorganic bases such as NaOAc, Al₂O₃, and MgO, on the other hand, gave no reaction and the starting materials were recovered quantitatively. In addition, increasing the catalyst loading from 5 to 10 mol% was found to give an improved product yield of 82% (entry 3).

Finally, on turning our attention to examining solvent effects, we were pleased to find that DMF as solvent gave the best result, furnishing **163a** in 95% yield (entry 5). In contrast, the analogous *O*-arylation of **162a** with bromobenzene **161b** was shown to proceed in a lower product yield of 65% (entry 6). Similarly, a low product yield of 42% was obtained on conducting the reaction at 90 °C (entry 7). The presence of a trace amount of water intrinsically present in commercially available inorganic bases and ⁿBu₄NBr phase transfer catalyst was also shown to be essential. Under our conditions, no reaction occurred in the absence of ⁿBu₄NBr or when using K₃PO₄ dried to a constant weight under reduced pressure at 200 °C prior to use. This was consistent with our earlier findings for the analogous *N*-arylation reactions of nitrogen heteroarenes.

Table 6.4 Optimization of reaction conditions^a

Entry	Solvent	Yield (%) ^b
1 ^c	PhMe	62
2 ^{c,d}	PhMe	51
3	PhMe	82
4	DMSO	72
5	DMF	95
6 ^e	DMF	65
7 ^f	DMF	42

^a Unless otherwise stated, all reactions were performed at reflux for 22 h with CuI:

^b $n\text{Bu}_4\text{NBr}$:**162a**:**161a**: K_3PO_4 ratio of 1:1:10:10:20 in the solvent as stated in Table 6.4. ^b

Isolated yield. ^c Reaction carried out with 5 mol% of CuI and $n\text{Bu}_4\text{NBr}$. ^d K_2CO_3 used

in place of K_3PO_4 . ^e Reaction carried out with **161b** in place of **161a**. ^f Reaction carried

out at 90 °C.

To define the scope of the copper iodide-catalyzed *O*-arylation reaction, we applied this process to a variety of phenols **162a-e** and aryl iodides **161a-m**. As shown in Table 6.5, *O*-arylation of **162a** with aryl iodides bearing either electron-withdrawing or electron-donating substituents was shown to give the corresponding products in excellent yields of 80-95% (entries 1-5). Similarly, the coupling of phenols and aryl iodides containing various electron-withdrawing and electron-donating substrate combinations was found to proceed in good to excellent yields, comparable to those obtained for the analogous ligand or additive promoted reactions (entries 7-14). The present procedure

was also shown to work well for the *O*-arylation of phenols and aryl iodides in which either or both starting materials contained a sterically demanding *ortho*-substituent such as a methyl group with good to excellent product yields being obtained (entries 15-22). Only when both *ortho*-positions of the phenol were replaced with a sterically bulky methyl group as in **162e** was there a pronounced effect on product yield observed. In these latter reactions, the aryl ethers **163t-v** were isolated in moderate yields of 40-41% along with the aryl iodide starting material in yields up to 20% (entries 23-25).

Table 6.5. Copper iodide-catalyzed *O*-arylation of phenols **162** with aryl iodides **161**^a

		162a: R = H	162d: R = H
		162b: R = Me	162e: R = Me
		162c: R = Cl	
Entry	Substrates	Product	Yield (%) ^b
1	162a + 161c	163b , R = F	90
2	162a + 161e	163c , R = Cl	90
3	162a + 161h	163d , R = Me	89
4	162a + 161m	163e , R = NO ₂	95
5	162a + 161g	163f , R = OMe	80
6	162b + 161a	163d , R = H	92
7	162b + 161e	163h , R = Cl	82
8	162b + 161h	163i , R = Me	87
9	162b + 161m	163j , R = NO ₂	89
10	162b + 161g	163k , R = OMe	48

Table 6.5 (continued)

Entry	Substrates	Product	Yield (%) ^b
11	162c + 161e	163m , R = Cl	80
12	162c + 161h	163h , R = Me	81
13	162c + 161m	163n , R = NO ₂	80
14	162c + 161g	163o , R = OMe	62
15	162a + 161j	163g , R = H	74
16	162b + 161j	163l , R = Me	81
17	162d + 161h		75
18	162c + 161j	163p , R = Cl	52
19	162d + 161e		80
20	162d + 161m	163q , R = NO ₂	77
21	162d + 161g	163r , R = OMe	60
22	162d + 161j	163s	87
23	162e + 161e	163t , R = Cl	40
24	162e + 161h	163u , R = Me	41
25	162e + 161j	163v	40

^a All reactions were performed in DMF at reflux for 22 h with CuI:ⁿBu₄NBr:**162**:**161**:K₃PO₄ molar ratio = 1:1:10:10:20. ^b Isolated yield.

The application of our catalytic system for the *O*-arylation of aliphatic alcohols was also examined and found to be somewhat intriguing (Table 6.6). As anticipated, our preliminary studies showed that reaction of butanol **162f** with **161d** and 10 mol% of

copper iodide, 10 mol% of $n\text{Bu}_4\text{NBr}$ and K_3PO_4 (2 equiv) in DMF at reflux for 22h gave 1-butoxy-4-chlorobenzene **166a** in 60% yield (entry 1). However, when the same conditions were applied to the reactions of **162g** with either aryl iodide **161d** or **161e**, the corresponding *O*-arylated products were obtained in low yields of 25 and 26%, respectively. On the other hand, by employing the conditions found suitable for the *N*-arylation of nitrogen heteroarenes by replacing the K_3PO_4 and DMF with NaOH and

Table 6.6 Copper iodide-catalyzed *O*-arylation of alcohols **162f-h** with aryl iodides **161**^a

Entry	Alcohol	Aryl iodide	Product	Yield (%) ^b
1	$n\text{Pr-OH}$ 162f	161e		166a 60
2 ^c	162g	161e		166b 55
3 ^c		161h		166c 54
4	162h	161a		166d 50
			166e 15
5 ^d				166f 55
			166f 20

^a Unless otherwise stated, all reactions were performed in DMF at reflux for 22 h with $\text{CuI} : n\text{Bu}_4\text{NBr} : \text{162} : \text{161} : \text{K}_3\text{PO}_4$ molar ratio = 1:1:10:10:20. ^b Isolated yield. ^c Reaction carried out with NaOH as base and PhMe as solvent. ^d Reaction carried out with PhMe as solvent.

toluene, respectively, these latter reactions were shown to proceed to give **166b** and **166c** in good yields (entries 2 and 3). In addition, when the present *O*-arylation method was applied to **162h**, which contains both an amino and an alcohol functionality, the chemoselective outcome was found to be dependent on the solvent employed. With 1 equiv of **161a** as the aryl iodide coupling partner, the reaction of **162h** in the presence of 10 mol % of Copper iodide, 10 mol % of $n\text{Bu}_4\text{NBr}$, K_3PO_4 (2 equiv) in DMF as solvent at reflux for 22 h proceeded to afford the *N*-arylated and *N,O*-diarylated products **166d** and **166e** in yields of 50% and 15%, respectively (entry 4). Conversely, repetition of the same reaction with toluene as the solvent gave a switch in selectivity with **166e** obtained as the major product in 55% yield and the *O*-arylated amine **166f** isolated as the minor product in 20% yield (entry 5).

6.2.2.3 Copper Iodide-Catalyzed *S*-Arylation of Thiols

Initially, we found that the conditions reported previously for the *N*-arylation of nitrogen heterocycles with aryl iodides also worked well for the coupling of a variety of substituted aryl thiols **164a-e** and aryl iodides **161a-m** (Table 6.7). In the presence of 10 mol% of copper iodide as catalyst, 10 mol% of $n\text{Bu}_4\text{NBr}$ as phase transfer catalyst, and NaOH (2 equiv) in toluene at reflux for 22 h, *S*-arylation of 4-methylbenzenethiol **164a** (1 equiv) with a variety of aryl iodides bearing either electron-withdrawing or electron-donating substituents (1 equiv) was shown to give the corresponding products in excellent yields of 80-96% (entries 1-6). Notably, this included the ability to exploit the difference in reactivity of aryl halides ($\text{I} \gg \text{Br} > \text{Cl} > \text{F}$) by coupling **164a** and the aryl iodide selectively in the presence of substrates containing aryl bromides, chlorides and fluorides. Similarly, the coupling of aryl thiols and aryl iodides containing various electron-withdrawing and electron-donating substrate combinations was found to proceed in good

to excellent yields (entries 7-13). The present procedure was also shown to work well for the *S*-arylation of aryl thiols and aryl iodides in which either or both starting materials contained sterically demanding *ortho*-substituents such as a methyl group or a fused benzene ring. In all instances, the present procedure was found to proceed in good to excellent yields (entries 14-24).

Table 6.7 Copper iodide-catalyzed *S*-arylation of aryl thiols **164** with aryl iodides **161**^a

		164a : R = Me	164d : R = H
		164b : R = OMe	164e : R = Me
		164c : R = Cl	
Entry	Substrates	Product	Yield (%) ^b
1	164a + 161a	165a , R = H	95
2	164a + 161e	165b , R = Cl	96
3	164a + 161d	165c , R = Br	96
4	164a + 161c	165d , R = F	96
5	164a + 161m	165e , R = NO ₂	80
6	164a + 161h	165f , R = Me	94
7	164b + 161e	165g , R = Cl	90
8	164b + 161m	165h , R = NO ₂	78
9	164b + 161g	165i , R = OMe	78
10	164c + 161e	165j , R = Cl	80
11	164c + 161m	165k , R = NO ₂	80
12	164c + 161h	165b , R = Me	81
13	164c + 161g	165g , R = OMe	62

Table 6.7 (continued)

Entry	Substrates	Product	Yield (%) ^b
14	164c + 161l		80
15	164a + 161j	165m , R = Me	96
16	164d + 161h		94
17	164d + 161e	165n , R = Cl	95
18	164d + 161m	165o , R = NO ₂	90
19	164d + 161h		95
20	164e + 161e	165q , R = Cl	96
21	164e + 161m	165r , R = NO ₂	81
22	164e + 161h		95
23	164e + 161g	165t , R = OMe	81
24	164e + 161j		96

^a All reactions were performed in PhMe at reflux for 22 h with CuI:ⁿBu₄NBr:**164**:**161**:NaOH molar ratio = 1:1:10:10:20. ^b Isolated yield.

To define the scope of the present reaction, the *S*-arylation of a representative aliphatic thiol, ethanethiol **164f**, with a variety of aryl iodides was also examined (Scheme 6.4). Analogous to our findings for the Cu-catalyzed *O*-arylation of alcohols, we found the reactivity of **164f** to be solvent and base dependent. When **164f** was treated with either 1 equiv of **161e** or **161h** in the presence of copper iodide (10 mol%) and ⁿBu₄NBr (10 mol%) in toluene at reflux for 22 h, the corresponding ethyl(aryl)sulfane

adducts **10a** and **10b** were obtained in only 50% yield in both cases. In contrast, repetition of these reactions but with DMF as solvent and K_3PO_4 as base was found to give **10a** and **10b** in yields of 86% and 82%, respectively. Under similar conditions, *S*-arylation of **164f** with **161n** was found to give **10c** in 86% yield.

Scheme 6.4 Copper iodide-catalyzed *S*-arylation of alkylthiols.

6.3 Conclusion

In summary, our studies on the copper-mediated reaction of *N*-methyl pyrrole with $\text{PhI}=\text{NTs}$ showed that the various copper salts employed in this study were unable to catalyze the diamidation process. Thus, further exploration of reaction conditions using this class of catalysts were not conducted. However, in the course of this study and as part of an initiative to develop a general and mild route to the starting *N*-arylated nitrogen heterocycles which are substrates for this diamidation process, we have demonstrated a practical and straightforward copper iodide-catalyzed method for their preparation. This modified ligand-free version of the Ullmann reaction was subsequently shown to be applicable to *O*-arylation of phenols and aliphatic alcohols as well as *S*-arylation of thiols with aryl iodides. In all of these reactions, the arylation process was shown to be highly efficient, giving the corresponding arylated products in good to excellent yields.

Chapter VII. Experimental Section

7.1 General Experimental Method

Unless specified, all reactions were performed using oven-dried glassware. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received; CH_2Cl_2 and MeCN was purified prior to use by distillation over CaH_2 ; MeOH was distilled over Mg/I_2 ; PhMe and THF were distilled over sodium and benzophenone; pyridine was distilled over KOH; benzaldehyde and pyrrole were distilled under reduced pressure. Molecular sieves were dried under vacuum at 200 °C and stored under N_2 .

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate and visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with ninhydrin or potassium permanganate solution, followed by heating.

Unless specified, flash chromatography was performed using Merck silica gel 60 using a gradient solvent system (EtOAc: *n*-hexane as eluant).

^1H and ^{13}C NMR spectra were measured on Bruker Avance 300 or 400 MHz or JEOL ECA 400 MHz spectrometer. Unless otherwise stated, chemical shifts (ppm) for ^1H NMR were recorded in CDCl_3 solution with tetramethylsilane (TMS) as the internal reference standard (δ 0.00). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); qt (quintet); dd (doublet of doublets); dt (doublet of triplets) and m (multiplets). The number of protons(n) were given as nH. Coupling constants are reported as a *J* value in Hz. Chemical shifts (ppm) for ^{13}C NMR were recorded relative to the signal of chloroform-*d* (δ = 77.0).

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FTIR spectrometer. High performance liquid chromatography analysis was conducted on Shimadzu LC-20AD.

Low resolution mass spectra were determined on a Finnigan LCQ XP MAX mass spectrometer. High resolution mass spectra (HRMS) were obtained using Finnigan MAT95XP LC/HRMS. Melting point analyses were carried out on Optimelt Automated Melting Point System. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer.

7.2 Ruthenium(II) Porphyrin-Catalyzed Amidation of Aldehydes

General procedure for the synthesis of symmetrical porphyrins 135a-b – Method

A¹¹⁹

To a 250 mL two-neck round bottom flask was added freshly distilled pyrrole (40 mmol, 1 equiv), the benzaldehyde (40 mmol, 1 equiv) and propionic acid (100 mL). The reaction mixture was refluxed for 30 min. After cooling to room temperature, cold MeOH (80 mL) was added to the reaction mixture. The flask was cooled in an ice bath for ~2 h, after which the purple crystals were filtered, washed with cold methanol (100 mL) and dried under vacuum.

General procedure for the synthesis of symmetrical porphyrin 135c – Method B¹²⁰

To a three-neck round bottom flask was added CHCl_3 (250 mL), freshly distilled pyrrole (10 mmol, 1 equiv) and the corresponding benzaldehyde (10 mmol, 1 equiv). BF_3OEt_2 (3.3 mmol, 0.33 equiv) was added. The reaction was left to stir for 1 h, after which, *p*-chloranil (7.5 mmol, 0.75 equiv) was added. After refluxing for 1 h, the reaction mixture was then cooled to room temperature. Et_3N (3.3 mmol, 0.33 equiv) was added and the solution evaporated to dryness. The crude product was resuspended in MeOH (50 mL), filtered and washed with copious amounts of MeOH (150 mL). The crystals were collected and dried under vacuum.

General procedure for the synthesis of asymmetrical porphyrin 135d – Method C¹¹⁹

To a 250 mL two-neck round bottom flask was added freshly distilled pyrrole (40 mmol, 4 equiv), *p*-tolualdehyde (30 mmol, 3 equiv), *p*-hydroxybenzaldehyde (10 mmol, 1 equiv) and propionic acid (100 mL). The reaction mixture was refluxed for 30 min. After cooling to room temperature, cold MeOH (80 mL) was added to the reaction mixture. The flask was cooled in an ice bath for ~2 h, after which the purple crystals were filtered, washed with cold methanol (100 mL) and dried under vacuum.

General procedure for the synthesis of ruthenium(II) porphyrin complexes¹¹⁹

To a 250 mL round bottom flask was added $\text{Ru}_3(\text{CO})_{12}$ (2 mmol, 1 equiv) and porphyrin (2 mmol, 1 equiv). The mixture was refluxed in decalin (100 mL) for 20 h. The reaction mixture was then cooled to room temperature and loaded directly onto a neutral alumina column. Decalin and other impurities were removed using *n*-hexane (500 mL) followed by CH_2Cl_2 (500 mL) as eluant. The ruthenium(II) porphyrin was eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$. The red solid was recrystallized in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give the title compound.

Procedure for the synthesis of (*p*-toluenesulfonyl)iminophenylidiane⁸

To a suspension of TsNH₂ (10.27 g, 60 mmol, 1 equiv) and KOH (8.42 g, 150 mmol, 2.5 equiv) in MeOH (100 mL) in an ice bath was added PhI(OAc)₂ (19.28 g, 60 mmol, 2.5 equiv). The reaction mixture was left to stir at room temperature for 4-6 h. The resulting pale yellow suspension was filtered, washed with MeOH (25 mL) and water (500 mL). The pale yellow solid was collected and dried under vacuum. Yield: 92%; ¹H NMR (DMSO-d₆) 7.68 (d, *J* = 7.6 Hz, 2H), 7.37-7.44 (m, 3H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 2.26 (s, 3H).

General procedure for the optimization of ruthenium(II) porphyrin-catalyzed amidation of isovaleraldehyde **130a to **131a** with PhI=NTs**

To a suspension of the catalyst and PhI=NTs (please refer to Table 2.1) in 2 mL of CH₂Cl₂, was added isovaleraldehyde **130a** (54 μL, 0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 30 min, after which the mixture was evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for [Ru(TTP)(CO)]-catalyzed amidation of aldehydes **130b-β with PhI=NTs**

To a suspension of [Ru(TTP)(CO)] (40.0 mg, 0.05 mmol, 0.1 equiv) and PhI=NTs (373 mg, 1 mmol, 2 equiv) in 2 mL of CH₂Cl₂, was added the aldehyde (0.5 mmol, 1 equiv) under N₂ atmosphere. The reaction was stirred at room temperature for 30 min, after which the mixture was evaporated to dryness under reduced pressure and purified by silica gel flash column chromatography.

Deuterium labeling experiment: [Ru(TTP)(CO)]-catalyzed amidation of benzaldehyde- α -d₁ **130q-d₁ to *N,N*-d₁-tosylbenzamide **131q-d₁** with PhI=NTs**

To a suspension of [Ru(TTP)(CO)] (20.0 mg, 0.025 mmol, 0.1 equiv) and PhI=NTs (1 mmol) in 1 mL CH₂Cl₂ or CD₂Cl₂ in a pre-dried NMR tube was added benzaldehyde- α -d₁ **130q-d₁** (51 μ L, 0.25 mmol, 1 equiv) under a N₂ atmosphere. The reaction was left at room temperature for 1 h, after which ¹H NMR and mass spectra of the reaction mixture was obtained. MS (ESI) *m/z* 277 [M+H]⁺.

Synthesis of Merrifield peptide resin-supported ruthenium(II) porphyrin **137**^{125b}

To a solution of ruthenium(II) porphyrin **136** at two different loadings, (2 and 50 μmol) in DMF (30 mL) was added Merrifield's peptide resin (1.0 g) and K_2CO_3 (0.5 g). The reaction mixture was stirred at 80 $^\circ\text{C}$ under N_2 atmosphere for 4 h. After cooling to room temperature, the red resin was filtered, washed with H_2O , EtOH and CHCl_3 , and dried under vacuum to give **137-1**. **137-2** was prepared in a similar manner with 40.0 mg (0.05 mmol) ruthenium porphyrin **136**. **137-1**: Deep red solid; Yield: 95%; IR $\nu(\text{CO})$ 1947 cm^{-1} . **137-2**: Deep red solid; Yield: 98%; IR $\nu(\text{CO})$ 1947 cm^{-1} .

Synthesis of Wang's resin-supported ruthenium(II) porphyrin¹²⁸

To a mixture of ruthenium porphyrin **136** (80.1 mg, 0.1 mmol, 1 equiv), PPh_3 (26.2 mg, 0.1 mmol, 1 equiv) and Wang's resin (1.0 g) in THF (10 mL) was added DEAD (15 μL , 0.1 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 20 h, after which the suspension was filtered, washed with THF and CH_2Cl_2 . The solids were collected and dried under vacuum. Deep red solid; Yield 85%; IR $\nu(\text{CO})$ 1946 cm^{-1} .

Synthesis of poly(ethyleneglycol)-supported ruthenium(II) porphyrin^{125a,129}

To a mixture of PEG (950 mg, 0.5 mmol, 1 equiv) and MsCl (85 μL , 0.55 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) was added trioctylamine (655 μL , 0.75 mmol, 1.5 equiv). The reaction was stirred at room temperature for 20 h, after which Et_2O was added to precipitate the polymer mesylate **139**. The suspension was filtered, washed with Et_2O and dried under vacuum.

To a solution of ruthenium porphyrin **139** (0.2 g, 0.25 mmol, 1 equiv) in DMF (7.5 mL) was added **136** (380 mg, 0.2 mmol, 0.8 equiv) and K_2CO_3 (500 mg, 0.36 mmol, 1.4 equiv). The reaction was stirred at 60 $^\circ\text{C}$ for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining residue was redissolved in CH_2Cl_2 (20 mL), washed with brine (3 x 20 mL) and water (20 mL), dried with anhydrous MgSO_4 and concentrated to 2 mL. To the residue was added Et_2O at 0 $^\circ\text{C}$. The red solid was washed with cold isopropanol and dried at 80 $^\circ\text{C}$ under vacuum for 18 h. Red solid; Yield: 83%; UV/Vis (CHCl_3): λ_{max} 412, 527 nm; ^1H NMR δ 8.46-8.53 (m, 8H), 8.01-8.09 (m, 4H), 7.92-7.96 (m, 4H), 7.45-7.50 (m, 6H), 6.89-6.95 (m, 2H), 4.06 (t, $J = 8.3$ Hz, 2H, $\text{PEGCH}_2\text{CH}_2\text{O-Por}$), 3.38-3.75 (PEG peak), 3.33 (s, MeO-PEG), 2.70 (s, 12H).

Meso-5,10,15,20-tetrakis-(4-tolyl)-21H,23H-porphyrin 135a¹¹⁹

Method A; purple crystal; Yield: 20%; ¹H NMR δ 8.85 (s, 8H) 8.09 (d, J = 7.9 Hz, 8H) 7.75 (d, J = 7.6 Hz, 8H), 2.70 (s, 12H), -2.78 (s, 2H); UV/Vis (CHCl₃): λ_{max} 417, 519 nm.

Meso-5,10,15,20-tetrakis(phenyl)-21H,23H-porphyrin 135b¹¹⁹

Method A; purple crystal; Yield : 16%; ¹H NMR 8.84 (s, 8H) 8.21 (dd, J = 6.0, 1.4 Hz, 8H) 7.75-7.77 (m, 12H) -2.77 (s, 2H); UV/Vis (CHCl₃): λ_{max} 416, 515 nm.

Meso-5,10,15,20-tetrakis (pentafluorophenyl)-21H,23H-porphyrin 135c¹²⁰

Method B; purple crystal; Yield: 13%; ¹H NMR 8.92 (s, 8H), -2.74 (2H); UV/Vis (CHCl₃): λ_{max} 414, 515nm.

Meso-5,10,15-tris(4-tolyl)-20-(4-hydroxyphenyl)porphyrin 135d^{125a}

Method C; purple crystal; Yield: 3%; ¹H NMR δ 9.72 (s, 2H), 8.89 (s, 2H), 8.66-8.69 (m, 2H), 8.55-8.59 (s, 2H), 7.96-8.07 (m, 8H), 7.68 (d, J = 8.1 Hz, 6H), 7.53 (d, J = 8.0 Hz, 4H), 7.24 (m, 2H), 2.71 (s, 9H), -2.65 (s, 2H) ; UV/Vis (CHCl₃): λ_{max} 417, 529 nm.

Carbonyl(5,10,15,20-tetratolylporphinato)ruthenium 47a¹¹⁹

Deep red solid, Yield: 91%; ¹H NMR 8.72 (s, 8H), 8.05 (d, J = 7.6 Hz, 8H). 7.52 (d, J = 6.64 Hz), 2.70 (s, 12H); UV/Vis (CHCl₃): λ_{max} 405, 525 nm.

Carbonyl(5,10,15,20-tetra(pentafluorophenyl)porphinato)ruthenium 88a¹¹⁹

Deep red solid, Yield: 61%; ¹H NMR δ 8.76 (s, 8H); UV/Vis (CHCl₃): λ_{max} 401, 551 nm.

Carbonyl (5,10,15-tris(4-tolyl)-20-(4-hydroxyphenyl)porphyrin) ruthenium 136^{125b}

Deep red solid, Yield: 83%; ¹H NMR 8.71 (s, 8H), 7.95-8.03 (m, 8H), 7.51-7.57 (m, 6H), 6.91-6.95 (m, 2H), 2.67 (s, 9H); UV/Vis (CHCl₃): λ_{max} 414, 529 nm.

3-Methyl-N-tosylbutanamide 131a¹⁶⁶

White solid; Yield: 94%; ¹H NMR δ 8.25 (bs, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.45 (s, 3H), 2.10 (d, *J* = 6.24 Hz, 2H), 2.00-2.09 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 2H); ¹³C NMR δ 170.7, 145.0, 139.0, 135.5, 129.5, 128.2, 45.1, 25.5, 22.0, 21.6, 21.4; MS (ESI) *m/z* 256 [M+H]⁺.

N-Tosylpropionamide 131b¹⁶⁷

White solid; Yield: 97 %; mp: 109-111 °C; ¹H NMR δ 8.66 (s, 1H), 7.95 (d, *J* = 8.2Hz, 2H), 7.35 (d, *J* = 8.1Hz, 2H), 2.45 (s, 3H), 2.29 (qt, *J* = 7.4 Hz, 2H) 1.07 (t, *J* = 7.4 Hz, 3H); ¹³C NMR δ 171.5, 145.2, 135.5, 129.6, 128.3, 29.5, 21.7, 8.2; IR (neat, cm⁻¹): 3427, 3081, 1639, 1436, 1338, 1265, 1157, 1089; MS (ESI) *m/z* 228 [M+H]⁺; HRMS calcd. for C₂₀H₂₆N₂NaO₆S₂: 477.1130, found: 477.1119.

N-Tosylheptanamide 131c

White solid; Yield: 97%; mp: 96-98 °C; Anal. calcd. for C₁₄H₂₁NO₃S: C 59.34; H 7.47; N 4.94; S 11.31; found: C 59.06; H 7.33; N 4.93; S 11.67; ¹H NMR δ 8.37 (bs, 1H), 7.95 (d,

$J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 2.45 (s, 3H), 2.24 (t, $J = 7.5$ Hz, 2H) 1.56 (t, $J = 6.8$ Hz, 2H) 1.26-1.21 (m, 6H), 0.84 (t, $J = 7.2$ Hz, 2H); ^{13}C δ 170.8, 145.1, 135.6, 129.6, 128.3, 36.3, 31.3, 28.5, 24.2, 22.3, 21.7, 13.9; IR (neat, cm^{-1}) 3431, 2954, 1643, 1352, 1172, 1083; MS (ESI) m/z 271 $[\text{M}+\text{H}]^+$; HRMS calcd. for $\text{C}_{28}\text{H}_{42}\text{N}_2\text{NaO}_6\text{S}_2$: 589.2382, found: 589.2368.

***N*-Tosylisobutyramide 131d¹⁶⁶**

White solid; Yield: 86%; ^1H NMR δ 9.03 (bs, 1H), 7.96 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 2.34-2.44 (m, 4H), 1.10 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR δ 174.8, 145.1, 135.4, 129.6, 128.2, 35.6, 21.6, 18.5; MS (ESI) m/z 242 $[\text{M}+\text{H}]^+$.

***N*-Tosylpivalamide 131e¹⁶⁸**

White solid; Yield: 60%; ^1H NMR δ 8.31 (bs, 1H), 7.94 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 2.44 (s, 3H), 1.15 (s, 9H); ^{13}C δ 174.8, 145.0, 135.4, 129.6, 128.2, 35.6, 21.6, 18.5; MS (ESI) m/z 257 $[\text{M}+\text{H}]^+$.

***N*-Tosylcyclopropanecarboxamide 131f**

White solid; Yield: 91 %; mp: 154-156 °C; ^1H NMR δ 9.04 (bs, 1H), 7.95 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 2.45 (s, 3H), 1.57-1.51 (m, 1H), 1.02 (q, $J = 4.0$ Hz, 2H),

0.89-0.84 (m, 2H); ^{13}C NMR δ 171.9, 145.1, 135.5, 129.6, 128.3, 21.7, 14.7, 9.6; IR (neat, cm^{-1}) 3431, 1637, 1438, 1340, 1265, 1219, 1136, 1087, 1031; MS (ESI) m/z 240 $[\text{M}+\text{H}]^+$; HRMS calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{NaO}_6\text{S}_2$: 501.1130, found: 501.1143.

***N*-Tosylcyclopentanecarboxamide 131g**

White solid; Yield: 99 %; mp: 137-138 $^{\circ}\text{C}$; ^1H NMR δ 8.72 (bs, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 2.62 (q, J = 8.2 Hz, 1H), 2.66-2.57 (m, 1H), 2.45 (s, 3H), 1.83-1.51 (m, 8H); ^{13}C δ 173.9, 145.0, 135.5, 129.6, 128.3, 45.4, 29.5, 25.8, 21.7; IR (neat, cm^{-1}) 3412, 3055, 1629, 1419, 1265, 1183; MS (ESI) m/z 268 $[\text{M}+\text{H}]^+$; HRMS calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{NaO}_6\text{S}_2$: 557.1756, found: 557.1726.

***N*-Tosylcyclohexanecarboxamide 131h¹⁶⁶**

White solid; Yield: 97%; ^1H NMR δ 8.31 (bs, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H), 2.13 (tt, J = 11.6, 3.5 Hz, 1H), 1.77 (t, J = 14.2 Hz, 4H), 1.63 (bd, J = 7.8 Hz, 2H), 1.39-1.13 (m, 6H); ^{13}C δ 173.3, 145.1, 135.6, 129.6, 128.4, 45.1, 28.7, 25.4, 25.2, 21.7; MS (ESI) m/z 282 $[\text{M}+\text{H}]^+$.

2-Phenyl-*N*-tosylacetamide 131i¹⁶⁹

White solid; Yield: 86%; ¹H NMR δ 8.08 (bs, 1H), 7.88 (d, J = 8.4 Hz), 7.33-7.30 (m, 3H), 7.15 (t, J = 5.4 Hz, 2H), 3.58 (s, 2H), 2.44 (s, 3H); ¹³C NMR δ 168.4, 145.2, 135.2, 132.2, 129.6, 129.4, 129.3, 128.5, 128.1, 43.7, 21.7; MS (ESI) m/z 290 [M+H]⁺.

3-Phenyl-*N*-tosylpropanamide 131j

White solid; Yield: 68%; mp: 110-112 °C; Anal. Calcd. for C₁₆H₁₇NO₃S: C 63.34; H 5.65; N 4.62; S 10.57; found: C 63.00; H 5.575; N, 4.55; S, 10.99; ¹H NMR δ 8.95 (bs, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.22-7.16 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 2.85 (t, J = 7.5 Hz, 2H), 2.54 (t, J = 8.0 Hz, 2H), 2.44 (s, 3H); ¹³C NMR δ 170.3, 145.1, 139.6, 135.3, 129.6, 128.3, 128.2, 126.4, 37.8, 30.2, 21.7; IR (neat, cm⁻¹) 3427, 3059, 1718, 1629, 1598, 1438, 1340, 1265, 1168, 1122, 1087, 1041; MS (ESI) m/z 302 [M+H]⁺; HRMS calcd. for C₁₆H₁₇NO₃S: 629.1756, found: 629.1731.

5-Bromo-*N*-tosylpentanamide 131k¹⁷⁰

White solid; Yield: 96%; ¹H NMR δ 8.77 (bs, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.33 (t, J = 6.3 Hz, 2H), 2.43 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 1.82-1.68 (m, 4H); ¹³C NMR δ 170.8, 145.2, 135.3, 129.6, 128.2, 35.0, 32.8, 31.5, 22.7, 21.6; MS (ESI) m/z 335 [M+H]⁺.

(E)-N-tosylhex-2-enamide 131n¹⁷¹

Yellow oil; Yield: 99%; ¹H NMR δ 8.90 (bs, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.98 (dt, J = 15.4, 7.0 Hz, 1H), 5.84 (d, J = 15.4 Hz, 1H), 2.43 (s, 3H), 2.14 (qt, J = 7.0 Hz, 2H), 1.37-1.45 (m, 2H), 0.88 (t, J = 7.36 Hz, 3H); ¹³C NMR δ 163.3, 150.9, 145.0, 135.6, 129.6, 128.4, 121.2, 34.2, 21.6, 21.1, 13.6; MS (ESI) m/z 278 [M+H]⁺.

3-Methyl-N-tosylbut-2-enamide 131o¹⁷²

White solid; Yield: 91%; ¹H NMR δ 8.26 (bs, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.343 (d, J = 8.1 Hz, 2H), 5.57 (s, 1H), 2.44 (s, 3H), 2.11 (s, 3H), 1.86 (s, 3H); ¹³C NMR δ 163.0, 160.5, 144.8, 135.9, 129.6, 128.3, 115.4, 27.7, 21.7, 20.6; MS (ESI) m/z 253 [M+H]⁺.

N-Tosylpent-4-enamide 131p¹⁷³

White solid; Yield: 99%; ¹H NMR δ 8.72 (bs, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.78-5.68 (m, 1H), 4.97-4.92 (m, 2H), 2.44 (s, 3H), 2.40-2.32 (m, 4H); ¹³C NMR δ 170.8, 145.0, 135.8, 135.4, 129.5, 128.2, 115.9, 35.2, 28.0, 21.6; MS (ESI) m/z 253 [M+H]⁺.

***N*-Tosylbenzamide 131q**¹⁷⁴

White solid; Yield: 93%; ¹H NMR δ 8.75 (br s, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 4.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 2.44 (s, 3H); ¹³C NMR δ 164.4, 145.2, 135.4, 133.7, 133.4, 131.2, 130.1, 129.6, 128.8, 128.6, 128.5, 127.9, 21.7; MS (ESI) m/z 276 [M+H]⁺.

4-Methyl-*N*-tosylbenzamide 131r¹⁷⁴

White solid; Yield: 92%; ¹H NMR δ 9.32 (br s, 1H), 8.03 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H); ¹³C NMR δ 164.8, 145.1, 143.5, 139.1, 135.5, 133.3, 129.7, 129.5, 128.8, 128.5, 127.9, 21.6, 21.5; MS (ESI) m/z 290 [M+H]⁺.

4-Methoxy-*N*-tosylbenzamide 131s¹⁷⁴

White solid; Yield: 96%; ¹H NMR δ 8.04 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.43 (s, 3H); ¹³C NMR δ 164.0, 163.7, 145.0, 135.7, 130.1, 129.6, 129.5, 128.5, 126.3, 114.0, 55.7, 21.6; MS (ESI) m/z 306 [M+H]⁺.

N-Tosyl-1-naphthamide 131w¹⁷⁴

White solid; Yield: 68%; ¹H NMR δ 8.90 (bs, 1H), 8.18 (t, J = 3.4 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 7.83 (t, J = 3.3 Hz, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.51-7.50 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H); ¹³C NMR δ 165.9, 145.3, 135.5, 133.7, 132.9, 130.0, 129.9, 129.7, 128.6, 128.5, 127.9, 126.9, 126.6, 124.9, 124.4, 21.8; MS (ESI) m/z 326 [M+H]⁺.

N-tosyl-2-naphthamide 131x¹⁶⁷

White solid; Yield: 28%; ¹H NMR δ 9.51 (brs, 1H), 8.37 (s, 1H), 8.10 (d, J = 8.2 Hz, 2H), 7.82-7.88 (m, 4H), 7.58 (t, J = 6.9 Hz, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H); ¹³C NMR δ 164.5, 145.2, 135.5, 132.2, 129.6, 129.3, 129.2, 128.9, 128.8, 128.7, 128.3, 127.7, 127.1, 123.4, 21.7; MS (ESI) m/z 326 [M+H]⁺.

N-Tosylfuran-2-carboxamide 2y¹⁷⁵

White solid; Yield: 93%; ¹H NMR δ 7.99 (d, J = 11.2 Hz, 2H), 7.55 (d, J = 1.2 Hz, 1H), 7.27 (d, J = 10.8 Hz, 2H), 7.21 (d, J = 4.7 Hz, 1H), 6.54 (t, J = 2.4 Hz, 1H), 2.36 (s, 3H); ¹³C NMR δ 162.3, 154.3, 145.7, 145.3, 145.2, 135.5, 129.6, 128.6, 118.1, 113.1, 21.7; MS (ESI) m/z 266 [M+H]⁺.

N-Tosylthiophene-2-carboxamide 131z¹⁷⁴

White solid; Yield: 76%; ¹H NMR δ 8.03 (d, J = 11.0 Hz, 2H), 7.72 (d, J = 5.0 Hz, 1H), 7.57 (d, J = 6.6 Hz, 1H), 7.32 (d, J = 10.9 Hz, 2H), 7.04 (t, J = 6.4 Hz, 1H), 2.44 (s, 3H); ¹³C NMR δ 158.6, 145.4, 135.8, 135.4, 133.7, 131.0, 129.7, 128.7, 128.3, 21.7; MS (ESI) m/z 282 [M+H]⁺.

7.3 Copper-Catalyzed Amidation of Aldehydes**General procedure for the optimization of copper-catalyzed amidation of isovaleraldehyde 130a to 131a with PhI=NTs**

To a suspension of the catalyst (0.05 mmol, 0.1 equiv), PhI=NTs (373 mg, 1 mmol, 2 equiv) and powdered 4Å molecular sieves (400 mg) in 2 mL of CH₂Cl₂, was added isovaleraldehyde **130a** (54 μ L, 0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the CuI-catalyzed amidation of aliphatic aldehydes 130b-c and 130g-h with PhI=NTs

To a suspension of the CuI (9.5 mg, 0.05 mmol, 0.1 equiv), PhI=NTs (373 mg, 1 mmol, 2 equiv) and powdered 4Å molecular sieves (400 mg) in 2 mL of CH₂Cl₂, was added the aldehyde (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the amidation of aliphatic aldehydes 130b-c with PhI=NTs with stoichiometric CuI

To a suspension of the CuI (95.1 mg, 0.5 mmol, 1 equiv), PhI=NTs (373 mg, 1 mmol, 2 equiv) and powdered 4Å molecular sieves (400 mg) in 2 mL of CH₂Cl₂, was added the aldehyde (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the optimization of copper + ligand-catalyzed amidation of **130a to **131a** with PhI=NTs**

A suspension of the catalyst (0.05 mmol, 0.01 mmol), ligand **143** (refer to Table 3.3 and 3.4) and powdered 4Å molecular sieves was stirred for 1 h in 2 mL of CH₂Cl₂ under a N₂ atmosphere. On completion, PhI=NTs (373 mg, 1 mmol, 2 equiv) and isovaleraldehyde **130a** (54 µL, 0.5 mmol, 1 equiv) were added. The reaction was stirred at room temperature for a further 18 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the optimization of CuI + pyridine-catalyzed amidation of **130q to **131q** with PhI=NTs**

A suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), pyridine (16 µL, 0.2 mmol, 0.4 equiv) and powdered 4Å molecular sieves was stirred for 1 h in 2 mL of CH₂Cl₂ under a N₂ atmosphere. On completion, PhI=NTs (373 mg, 1 mmol, 2 equiv) was added. Benzaldehyde **130q** (51 µL, 0.5 mmol, 1 equiv) diluted in 1 mL CH₂Cl₂ was added into the reaction mixture *via* a syringe pump over a period of time as stated in Table 3.5. The reaction was stirred at room temperature for a further 14-18 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the optimization of copper-catalyzed amidation of benzaldehyde **130q to **131q** with TsNCINa·3H₂O**

To a suspension of copper catalyst (0.05 mmol, 0.1 equiv) and TsNCINa·3H₂O (1.3 mmol, 2.6 equiv) in 7.5 mL of MeCN was added benzaldehyde **130q** (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through a plug of silica gel, washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography.

General procedure for the CuI + pyridine-catalyzed amidation of aldehydes **130 with PhI=NTs**

A suspension of CuI (0.05 mmol, 10 mol %), pyridine (0.2 mmol, 40 mol %) and powdered 4 Å molecular sieves were stirred for 1 h in 2 mL of CH₂Cl₂ under a N₂ atmosphere. On completion, PhI=NTs (1 mmol, 2 equiv) was added and the aldehyde (0.5 mmol, 1 equiv) diluted in 1 mL of CH₂Cl₂ was added into the reaction mixture over 2 h via a syringe pump. The reaction was stirred at room temperature for 16 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography to give the acylsulfonamide product.

General procedure for the CuCl-catalyzed amidation of aldehydes 1j-v with TsNCINa·3H₂O

To a suspension of CuCl (0.05 mmol, 10 mol %) and TsNCINa·3H₂O (1.3 mmol, 2.6 equiv) in 7.5 mL of MeCN was added the aldehyde (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through a plug of silica gel, washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography to give the acylsulfonamide product.

Synthesis of PhI=O³⁶

To a 500 mL conical flask containing PhI(OAc)₂ (77.1 g, 240 mmol, equiv) was added 3.5 M KOH (308 mL, 1.08 mol, 4.5 equiv) dropwise over 15-30 min with vigorous stirring. The suspension was stirred at room temperature for 2 h. H₂O (200 mL) was added and reaction mixture was stirred vigorously for another 30 min. The crude product was filtered, washed repeatedly with H₂O and CHCl₃, and dried under vacuum.

Procedure for the synthesis of *N*-benzylidene-*p*-toluenesulfonamide 144q¹³⁷

To a solution of benzaldehyde (10 mmol, 1 equiv) and *p*-toluenesulfonamide (10 mmol, 1 equiv) in 50 mL of CH₂Cl₂ was added trifluoroacetic anhydride (11 mmol, 1.1

equiv). The reaction was refluxed for 12 h after which the reaction mixture was poured into cold H₂O (30 mL), extracted with CH₂Cl₂ (20 mL), dried with MgSO₄, evaporated to dryness and purified by silica gel flash column chromatography to give the title compound as a white solid in 76% yield. ¹H NMR δ 9.03 (s, 1H), 7.94-7.88 (m, 4H), 7.62 (t, *J* 6.18 Hz, 1H) 7.49 (d, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H); ¹³C NMR δ 170.1, 144.6, 134.9, 132.4, 131.3, 129.8, 129.1, 128.1, 126.4, 21.6; MS (ESI) *m/z* 260 [M+H]⁺.

Procedure for the synthesis of 2-(*p*-Toluenesulfonyl)-3-phenyloxaziridine 145b¹³⁸

To a suspension of powdered KOH (392 mg, 7 mmol, 3.5 equiv) and *m*-chloroperoxybenzoic acid (380 mg, 2.2 mmol, 1.1 equiv) in 1 mL of CH₂Cl₂ was added a solution of **3b** (519 mg, 2 mmol, 1 equiv) in 3 mL of CH₂Cl₂ with vigorous stirring. After 10 min, the suspension was filtered, evaporated to dryness and dried under vacuum to afford the product as a white solid in 95% yield. ¹H NMR δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.46-7.40 (m, 7H), 5.45 (s, 1H), 2.49 (s, 3H); ¹³C NMR δ 146.3, 131.5, 131.4, 130.5, 130.0, 129.4, 128.7, 128.2, 76.3, 21.8; MS (ESI) *m/z* 276 [M+H]⁺.

Procedure for the synthesis of [1-(*p*-Toluenesulfonyl)amino] pyridinium inner salt***N*-117**¹⁴⁰

To a suspension of [Ru(TTP)CO] (160 mg, 0.2 mmol, 0.1 equiv) and PhI=NTs (1.12 g, 3 mmol, 1.5 equiv) in 4 mL of CH₂Cl₂ in the presence of powdered 4Å molecular sieves was added pyridine (160 μL, 2 mmol, 1 equiv) under N₂ atmosphere. The reaction was stirred at 30 °C until completion based on TLC analysis, after which the reaction mixture was cooled to room temperature, filtered, evaporated to dryness and purified by silica gel flash column chromatography (CH₂Cl₂: acetone as eluant) to afford the product in 64% yield. ¹H NMR δ 8.46 (d, *J* = 3.8 Hz, 2H), 8.01 (dt, *J* = 7.75, 1.05 Hz, 2H), 7.63–7.59 (m, 4H), 7.17 (d, *J* = 6.54 Hz, 2H), 2.36 (s, 3H); ¹³C NMR δ 145.2, 141.6, 138.6, 129.2, 127.0, 126.7, 21.3; MS (ESI) *m/z* 249 [M+H]⁺.

General procedure for the CuI + pyridine-catalyzed reaction of 144q or 145q

A suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), pyridine (16 μL, 0.2 mmol, 0.4 equiv) and 4Å powdered molecular sieves was stirred for 1 h in 2 mL of CH₂Cl₂ under a N₂ atmosphere. On completion, PhI=O or PhI(OAc)₂ (1 mmol, 2 equiv) and **144q** or **145q** (0.5 mmol, 1 equiv) was added. The reaction was stirred at room temperature for a further 18 h, after which the mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The reaction mixture was then analyzed by ¹H NMR spectroscopy and mass spectrometry.

Procedure for the CuI + py-catalyzed reaction of 130a with N-117

To a suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), *N*-117 (496 mg, 1 mmol, 2 equiv) and 4Å powdered molecular sieves in 2 mL of CH₂Cl₂, was added **130a** (54 μL, 0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 hr, after which the mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The reaction mixture was then analyzed by ¹H NMR spectroscopy and mass spectrometry.

Procedure for the benzaldehyde- α -¹³C **130q-¹³C *in situ* monitoring experiment¹¹⁷**

A suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), pyridine (16 μL, 0.2 mmol, 0.4 equiv) and 4Å powdered molecular sieves in CD₂Cl₂ was stirred for 1 h. After completion, PhI=NTs (373 mg, 1 mmol, 2 equiv) was added. A solution of benzaldehyde- α -¹³C **130q**-¹³C (51 μL, 0.5 mmol, 1 equiv) in CD₂Cl₂ (1 mL) was added via syringe pump over 1 h. Upon completion of addition, an aliquot (100 μL) was filtered through Celite[®], diluted with CD₂Cl₂ and monitored by ¹³C NMR. Subsequent aliquots at 2, 6, 10 and 18 h were obtained and subjected to ¹³C NMR analysis.

Procedure for the deuterium labeling experiment: CuI + py-catalyzed amidation of benzaldehyde- α - d_1 130q-d₁ to *N,N*- d_7 -tosylbenzamide with PhI=NTs

A suspension of CuI (4.8 mg, 0.025 mmol, 0.1 equiv), pyridine (8 μ L, 0.1 mmol, 0.4 equiv) and 4Å powdered molecular sieves in CH₂Cl₂ or CD₂Cl₂ was stirred for 1 h. After completion, PhI=NTs (186.7 mg, 0.5 mmol, 2 equiv) in 1 mL CH₂Cl₂ or CD₂Cl₂ was added α -*d*₁-benzaldehyde **130q-d₁** (0.25 mmol, 1 equiv) under a N₂ atmosphere. The reaction was left at room temperature for 18 h, after which a ¹H NMR and mass spectra of the reaction mixture was obtained.

Procedure for the kinetic isotope study¹¹⁷

A suspension of CuI (4.8 mg, 0.025 mmol, 0.1 equiv), pyridine (8 μ L, 0.1 mmol, 0.4 equiv) and 4Å powdered molecular sieves in CH₂Cl₂ was stirred for 1 h. After completion, PhI=NTs (93.3 mg, 0.25 mmol, 1 equiv) was added. A solution of benzaldehyde **130q** (30 μ L, 0.3 mmol, 1.2 equiv) and *d*₆-benzaldehyde **130q-d₆** (30 μ L, 0.3 mmol, 1.2 equiv) in CH₂Cl₂ (1 mL) was added via syringe pump over 1 h. After 2 h, the solution filtered through Celite[®] and was assayed via LCMS.

Procedure for the competitive rates study

A suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), pyridine (16 μL , 0.2 mmol, 0.4 equiv) and 4Å powdered molecular sieves in CH_2Cl_2 was stirred for 1 h. After completion, PhI=NTs (186.7 mg, 0.5 mmol, 1 equiv) was added. A solution of benzaldehyde (76 μL , 0.75 mmol, 1.5 equiv) and *p*-substituted benzaldehyde (0.75 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) was added via syringe pump over 1 h. After 2 h, the solution was filtered through Celite[®] and assayed via GC.

4-Chloro-*N*-tosylbenzamide 131t¹⁷⁶

White solid; Yield: 47%; ¹H (300 MHz) NMR δ 9.43 (bs, 1H), 8.00 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.35-7.39 (m, 4H), 2.43 (s, 3H); ¹³C (75 MHz) NMR δ 163.5, 145.5, 140.0, 135.3, 129.7, 129.6, 129.3, 129.2, 128.7, 21.7; MS (ESI) m/z 310 $[\text{M}+\text{H}]^+$.

4-Bromo-*N*-tosylbenzamide 131u¹⁷⁷

White solid; Yield: 64%; ¹H (300 MHz) NMR δ 9.32 (bs, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H); ¹³C (75 MHz) NMR δ 163.8, 163.3, 145.5, 135.3, 132.2, 130.0, 129.7, 129.5, 128.6, 21.7; MS (ESI) m/z 354 $[\text{M}+\text{H}]^+$.

7.4 Copper-Catalyzed Amidation of 1,3-Dicarbonyl Compounds

Synthesis of $\text{PhI}=\text{NNs}$ ⁸

$\text{PhI}=\text{NNs}$ was prepared following the procedure $\text{PhI}=\text{NTs}$ synthesis (*re* Section 7.2).

Pale yellow solid; Yield: 85%; ^1H NMR δ 8.02 (d, J = 6.09 Hz, 2H), 7.70-7.74 (m, 3H), 7.41 (d, J = 7.5 Hz, 2H), 7.25 (t, 7.7 Hz, 2H).

General procedure for the optimization of copper-catalyzed amidation of ethyl benzoylacetate **147a** with $\text{PhI}=\text{NTs}$

To a suspension of the catalyst (0.05 mmol, 0.1 equiv), $\text{PhI}=\text{NTs}$ (1 mmol, 2 equiv) and powdered 4 Å molecular sieves in 2 mL of CH_2Cl_2 , was added ethyl benzoyl acetate **147a** (87 μL , 0.5 mmol, 1 equiv) under a N_2 atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness. The crude yields of products **148a** and **151a** were obtained by ^1H NMR analysis with CH_2Br_2 as internal standard.

General procedure for the optimization of copper + 1,10-phenanthroline-catalyzed amidation of 147a to 148a with PhI=NTs

A suspension of the catalyst (0.05 mmol, 0.1 equiv), 1,10-phenanthroline (18.0 mg, 0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves was stirred for 1 h in 2 mL of CH_2Cl_2 under a N_2 atmosphere. On completion, PhI=NTs (1 mmol, 2 equiv) and ethyl benzoyl acetate **147a** (87 μL , 0.5 mmol, 1 equiv) were added. The reaction was stirred at room temperature for a further 18 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The crude yields of products **148a** and **151a** were obtained by ^1H NMR analysis with CH_2Br_2 as internal standard.

General procedure for the optimization of $\text{Cu}(\text{OTf})_2$ + 1,10-phenanthroline - catalyzed amidation of 147a to 148a with various nitrogen sources

A suspension of the $\text{Cu}(\text{OTf})_2$ (18.1 mg, 0.05 mmol, 0.1 equiv), 1,10-phenanthroline (18.0 mg, 0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves were stirred for 1 h in 2 mL of CH_2Cl_2 under a N_2 atmosphere. On completion, PhI=NNs (404 mg, 1 mmol, 2 equiv) or TsNH_2 (171 mg, 1 mmol, 2 equiv) and oxidant (1 mmol, 2 equiv) was added, followed by ethyl benzoyl acetate **1a** (87 μL , 0.5 mmol, 1 equiv) were added. The reaction was stirred at room temperature for a further 18 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The crude

yields of products **148** and **151** were obtained by ^1H NMR analysis with CH_2Br_2 as internal standard.

Reduction of **148a** with NaBH_4

To a solution of **148a** (50 mg, 0.14 mmol, 1 equiv) in MeOH (5 mL) in an ice bath was added NaBH_4 (7.9 mg, 0.21 mmol, 1.5 equiv). The reaction mixture was left to stir to completion until **148a** was fully consumed based on TLC analysis. H_2O (2 mL) was added and the solvent was evaporated off. The residue was redissolved in CH_2Cl_2 (5 mL) and washed with H_2O (2 x 5 mL) and brine (5 mL). The organic solvent was dried with MgSO_4 , evaporated to dryness and purified *via* silica gel flash column chromatography to afford a pale yellow oil that was shown to be impure by NMR analysis. Presence of **149a** in the mixture was deduced based on LCMS data that gave m/z of 364.

Reduction **148a** with LiAlH_4

To a suspension of LiAlH_4 (8.0 mg, 0.21 mmol, 1.5 equiv) in THF (3 mL) in an ice bath was added a solution of **148a** (50 mg, 0.14 mmol, 1 equiv) in THF (2 mL). The reaction mixture was left to stir to completion until **148a** was fully consumed based on TLC analysis. H_2O (2 mL) was added slowly to the reaction mixture. The solution was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (2 x 5 mL) and brine (5 mL). The organic solvent was dried with MgSO_4 , evaporated to dryness and purified *via* silica gel

flash column chromatography to afford a mixture of unidentified products by NMR analysis.

General procedure for the optimization of $\text{Cu}(\text{OTf})_2$ + chiral ligand-catalyzed amidation of **147a to **148a** with $\text{PhI}=\text{NTs}$**

A suspension of the $\text{Cu}(\text{OTf})_2$ (18.1 mg, 0.05 mmol, 0.1 equiv), chiral ligand (0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves were stirred for 1 h in 2 mL of CH_2Cl_2 under a N_2 atmosphere. On completion, $\text{PhI}=\text{NTs}$ (373 mg, 1 mmol, 2 equiv) and ethyl benzoyl acetate **1a** (87 μL , 0.5 mmol, 1 equiv) were added. The reaction was stirred at room temperature for a further 18 h, after which an aliquot (100 μL) of the reaction mixture was drawn under N_2 , filtered through Celite[®], diluted with CH_2Cl_2 and assayed by HPLC with Chiralpak AS-H column. If the reaction was shown to be non-enantioselective, the remaining reaction mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The yield of the crude product was obtained with CH_2Br_2 as internal standard by NMR analysis.

If the reaction showed enantioselectivity, the reaction mixture was cooled in an ice bath. NaBH_4 (28.5 mg, 0.74 mmol, 1.5 equiv) was added and the reaction left to stir until TLC analysis indicated complete consumption of **148a**. H_2O (2 mL) was added and the reaction mixture was filtered, washed with EtOAc and extracted with EtOAc and brine.

General procedure for the optimization of copper + 1,10-phenanthroline-catalyzed amidation of **147b to **148c** with PhI=NTs or PhI=NNs**

A suspension of the catalyst (0.05 mmol, 0.1 equiv), 1,10-phenanthroline (18.0 mg, 0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves were stirred for 1 h in 2 mL of CH_2Cl_2 under a N_2 atmosphere. On completion, PhI=NR (1 mmol, 2 equiv) and ethyl 2-oxocyclohexanecarboxylate **147b** (80 μL , 0.5 mmol, 1 equiv) were added. The reaction was stirred at room temperature for a further 18 h, after which the crude mixture was filtered through Celite[®], washed with EtOAc and evaporated to dryness. The crude reaction mixture was assayed via ^1H NMR analysis with CH_2Br_2 as internal standard.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-phenylpropanoate **148a**^{152,178}

White solid; Yield: 85%; ^1H NMR δ 7.98 (d, $J = 7.3$ Hz, 2H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.63 (t, $J = 7.3$ Hz, 1H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.26 (d, $J = 3.2$ Hz, 2H), 5.94 (d, $J = 9.2$ Hz, 1H), 5.58 (d, $J = 9.2$ Hz, 1H), 3.97 (q, $J = 7.5$ Hz, 2H), 2.38 (s, 3H), 1.09 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ 190.1, 165.9, 143.9, 136.4, 133.7, 129.6, 129.3, 129.1, 128.9, 128.7, 127.3, 127.2, 62.5, 60.8, 21.4, 13.4; MS (ESI) m/z 362 $[\text{M}+\text{H}]^+$.

Ethyl 3-oxo-3-phenyl-2,2-bis(tosylamino)propanoate 151a¹⁵²

White solid; Yield: 20%; ¹H NMR δ 7.99 (d, J = 7.7 Hz, 4H), 7.73 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 4H), 7.23 (d, J = 3.2 Hz), 5.3 (brs, 2H), 4.13 (q, J = 7.0 Hz, 2H), 2.34 (s, 6H), 1.01 (t, J = 6.9 Hz, 3H); ¹³C NMR δ 192.1, 164.3, 143.5, 136.7, 133.5, 129.5, 129.0, 128.9, 128.8, 128.7, 127.0, 70.1, 60.9, 31.5, 13.1; MS (ESI) m/z 531 [M+H]⁺.

N-(2, 4-dioxopentan-3-yl)-4-methylbenzenesulfonamide 148c

White solid; Yield: 98%; ¹H NMR δ 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 5.98 (s, 1H), 2.44 (s, 3H), 1.88 (s, 6H); ¹³C NMR δ 194.0, 144.2, 36.5, 130.0, 127.3, 110.0, 22.1, 21.5; MS (ESI) m/z 270[M+H]⁺.

N-(1, 3-dioxo-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide 148d

White solid; Yield: 92%; ¹H NMR δ 7.88 (d, J = 7.3 Hz, 2H), 7.71-7.68 (m, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.31-7.29 (m, 2H), 6.25 (d, J = 6.4 Hz, 1H), 5.36 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.05 (s, 3H); ¹³C NMR δ 193.2, 190.0, 134.2, 133.9, 129.4, 129.2, 128.4, 128.1, 127.3, 127.1, 75.1, 22.3, 21.3; MS (ESI) m/z 332[M+H]⁺.

***N*-(1,3-dioxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide 148e**

White solid; Yield: 40%; ^1H NMR δ 7.88 (d, J = 7.3 Hz, 2H), 7.75-7.70 (m, 6H), 7.57-7.51 (m, 4H), 7.34-7.31 (m, 2H), 2.42 (s, 3H); ^{13}C NMR δ 191.8, 167.7, 143.2, 134.3, 134.0, 132.4, 129.7, 129.0, 128.8, 127.3, 68.1, 21.4; MS (ESI) m/z 394[M+H] $^+$.

Diethyl 2-(4-methylphenylsulfonamido)malonate 148f

Yellow oil, Yield: 82%; ^1H NMR δ 7.75 (d, J = 8.24 Hz, 2H), 7.30 (d, J = 8.24 Hz, 2H), 5.80 (d, J = 8.24 Hz, 1H), 4.66 (d, J = 8.72 Hz, 1H), 4.12 (qt, J = 2.75 Hz, 4H), 2.42 (s, 3H), 1.19 (t, J = 7.32 Hz, 6H); ^{13}C NMR δ 165.5, 144.0, 136.4, 134.0, 129.6, 57.3, 62.8, 58.7, 21.5, 13.8; MS (ESI) m/z 330[M+H] $^+$.

7.5 Copper Iodide-Catalyzed Aziridination of Alkenes and Amidation of Alkanes**General procedure for the optimization of copper(I) iodide-catalyzed aziridination of styrene 26a to 27a with TsNH₂ in the presence of an oxidant**

To a suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), TsNH₂ (171.2 mg, 1 mmol, 2 equiv) and PhI=O (refer Table 5.1) in the presence of powdered 4Å molecular sieves in the appropriate solvent was added styrene **26a** (57 μL , 0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 18 h. On

completion, the suspension was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified via silica gel flash column chromatography.

General procedure for copper(I) iodide-catalyzed aziridination of alkenes with RNH₂ in the presence of PhI=O as oxidant

To a suspension of PhI=O (165mg, 0.75 mmol, 1.5 equiv), RNH₂ **157** (1 mmol, 2 equiv), CuI (9.5 mg, 0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves in MeCN (2 mL) was added the alkene **26** (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 18 h. On completion, the suspension was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified via silica gel flash column chromatography.

General procedure for competitive rate studies

To a suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), TsNH₂ **157a** (111.3 mg, 0.65 mmol, 1.3 equiv) and PhI=O (110.0 mg, 0.5 mmol, 1 equiv) and powdered 4Å molecular sieves in MeCN (2 mL) was added the alkene **26a** (86 µL, 0.75 mmol, 1.5 equiv) and **26b-f** (0.25 mmol, 1.5 equiv) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 2 h. On completion, the suspension was filtered through Celite[®], diluted with CDCl₃, and subjected to GC analysis.

Procedure for the synthesis of *trans*-cinnamyl alcohol **158a**

To a solution of *trans*-cinnamylaldehyde (1.3 mL, 10 mmol, 1 equiv) in MeOH (20 mL) in an ice bath was added NaBH₄ (454 mg, 12 mmol, 1.2 equiv). The reaction mixture was left to stir to completion until the aldehyde was fully consumed, based on TLC analysis. H₂O (5 mL) was added and the solvent was evaporated off. The residue was redissolved in EtOAc (20 mL) and washed with H₂O (2 x 20 mL) and brine (20 mL). The organic solvent was dried with MgSO₄, evaporated to dryness and purified *via* silica gel flash column chromatography. Colorless oil; Yield: 99%; ¹H NMR δ 7.17-7.40 (m, 6H), 6.38 (dt, *J* = 15.8, 5.6 Hz, 1H), 4.34 (d, *J* = 4.9 Hz, 2H); MS (ESI) *m/z* 135[M+H]⁺.

General procedure for the preparation of sulfamate esters **76a-b**⁸⁷

Formic acid (290 μL, 7.5 mmol, 5 equiv) was added dropwise to neat chlorosulfonyl isocyanate (650 μL, 7.5 mmol, 5 equiv) with vigorous stirring at 0 °C. The resulting suspension was stirred at 0 °C for 5 min, after which CH₂Cl₂ (5 mL) was added. The reaction mixture was stirred for at 0 °C for 1 h and then at room temperature for 14 h. The reaction was then cooled to at 0 °C and a solution of the alcohol **158** (5 mmol, 1 equiv) and pyridine (600 μL, 7.5 mmol, 1.5 equiv) in 5 mL CH₂Cl₂ was added dropwise. The reaction mixture was warmed to room temperature and left to stir to completion. EtOAc (20 mL) and H₂O (10 mL) were added to the reaction, after which the reaction mixture was extracted with EtOAc/H₂O, washed with brine, dried with MgSO₄, evaporated to dryness and purified *via* silica gel flash column chromatography.

General procedure for the preparation of carbamate esters 76c-d⁸⁶

To a solution of alcohol **158** (5 mmol, 1 equiv) in 15 mL of CH_2Cl_2 at 0 °C was added trichloroacetyl isocyanate (710 μL , 6 mmol, 1.2 equiv) dropwise. The reaction was warmed to room temperature and stirred to completion. The reaction mixture was evaporated to dryness. The crude was redissolved in MeOH (15 mL), and K_2CO_3 (70 mg, 0.5 mmol, 0.1 equiv) was added. The solution was stirred for 4 h, after which the reaction mixture was extracted in CH_2Cl_2 /sat NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with brine (50 mL), dried with MgSO_4 , evaporated to dryness and purified via silica gel flash column chromatography.

Procedure for the synthesis of *N*-hydroxycarbamate 159¹⁵⁴

To a solution of trans-cinnamyl alcohol **158a** (71 mg, 5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added carbonyl diimidazole (892 mg, 5.5 mmol, 1.1 equiv). The reaction was left to stir at room temperature for 1 h. The resulting solution was washed with sat. NH_4Cl solution (3 x 10 mL), dried with MgSO_4 , and evaporated to dryness. The residue was dissolved in pyridine (15 mL), and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.04 g, 15 mmol, 3 equiv) was added. The solution was stirred at room temperature for 3 h. This was followed by addition of CH_2Cl_2 (20 mL) and 10% H_2SO_4 solution (25 mL). The biphasic layer was separated, and

the organic layer washed with 10% H₂SO₄ solution (3 x 25 mL), dried with MgSO₄, evaporated to dryness and purified via silica gel flash column chromatography to give **159** in 70% yield. ¹H NMR δ 7.26-7.39 (m, 5H), 7.15 (brs, 1H), 6.68 (d, J = 15.8 Hz, 1H), 6.28 (dt, J = 15.8, 6.5 Hz, 1H), 4.83 (d, J = 6.4 Hz, 2H); MS (ESI) m/z 216 [M+Na]⁺.

Procedure for the synthesis of *N*-tosyloxycarbamate **76e**¹⁵⁴

To a solution of *N*-hydroxycarbamate **159** (411 mg, 2.23 mmol, 1 equiv) in Et₂O (10 mL) at 0 °C, was added *p*-toluenesulfonyl chloride (425 mg, 2.23 mmol, 1 equiv). The solution was stirred at 0 °C for 15 min. A solution of Et₃N (280 μ L, 2.01 mmol, 0.9 equiv) in Et₂O (2 mL) was added slowly to the reaction mixture. The resulting suspension was filtered and washed with Et₂O. The combined filtrate was evaporated to dryness and purified via silica gel flash column chromatography to furnish the title compound in 85% yield. ¹H NMR δ 7.90 (d, J = 5.5 Hz, 2H), 7.80 (brs, 1H), 7.29-7.35 (m, 7H), 6.55 (d, J = 15.8 Hz, 1H), 6.07 (dt, J = 15.9, 6.6 Hz, 1H), 4.66 (d, J = 5.8, 2H), 2.34 (s, 3H); MS (ESI) m/z 370 [M+Na]⁺.

General procedure for copper(I) iodide-catalyzed intramolecular aziridination

To a suspension of CuI (9.5 mg, 0.05 mmol, 0.1 equiv), PhI=O (165mg, 0.75 mmol, 1.5 equiv) and powdered 4Å molecular sieves in MeCN (2 mL) was added the alkene **76** (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 18 h. On completion, the suspension was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified via silica gel flash column chromatography.

General procedure for CuI-catalyzed intermolecular amidation process

To a suspension of PhI=O (165mg, 0.75 mmol, 1.5 equiv), TsNH₂ (1 mmol, 2 equiv), CuI (9.5 mg, 0.05 mmol, 0.1 equiv) and powdered 4Å molecular sieves in CH₂Cl₂ (2 mL) was added the aryl alkane **155** (0.5 mmol, 1 equiv) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 18 h. On completion, the suspension was filtered through Celite[®], washed with EtOAc, evaporated to dryness and purified via silica gel flash column chromatography.

2-phenyl-1-tosylaziridine 27a¹⁷⁹

Off-white solid; Yield: 99%; ¹H NMR δ 7.86 (d, J = 8.2 Hz), 7.31-7.19 (m, 7H), 3.77 (dd, J = 7.2, 4.5 Hz, 1H), 2.98 (d, J = 7.2 Hz, 1H), 2.41 (s, 3H), 2.38 (d, J = 4.4 Hz, 1H). ¹³C NMR δ 144.6, 140.4, 135.1, 134.9, 128.5, 128.3, 127.9, 126.4, 41.0, 35.7, 21.7. MS (ESI) m/z 273 [M]⁺.

2-*p*-tolyl-1-tosylaziridine 27b¹⁷⁹

Off-white solid; Yield: 68%; ¹H NMR δ 7.89 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.12 (s, 4H), 3.77 (dd, J = 7.2, 4.5 Hz, 1H), 2.99 (d, J = 7.2 Hz, 1H), 2.45 (s, 3H), 2.40 (d, J = 4.5 Hz, 1H), 2.33 (s, 3H). ¹³C NMR δ 144.6, 138.2, 135.1, 132.0, 129.7, 129.3, 127.9, 126.5, 41.1, 35.8, 21.7, 21.2. MS (ESI) m/z 287 [M]⁺.

2-(4-*tert*-butylphenyl)-1-tosylaziridine 27c¹⁷⁹

Off-white solid; Yield: 93%; ¹H NMR δ 7.87-7.9 (d, J = 8.2 Hz, 2H), 7.35-7.28 (m, 4H), 7.12 (d, J = 8.1 Hz, 2H), 3.76 (dd, J = 7.2, 4.4 Hz, 1H), 2.98 (d, J = 7.2 Hz, 1H), 2.42 (s, 3H), 2.35 (d, J = 4.4 Hz, 1H), 1.30 (s, 9H). ¹³C NMR δ 144.4, 138.1, 135.0, 132.1, 129.6, 129.5, 127.8, 126.5, 41.1, 35.8, 34.2, 21.7, 21.2. MS (ESI) m/z 329 [M]⁺.

2-(4-fluorophenyl)-1-tosylaziridine 27d¹⁷⁹

Off-white solid; Yield: 79%; ¹H NMR δ 7.88 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.22-7.19 (m, 2H), 6.99 (t, J = 7.8 Hz, 2H), 3.77 (dd, J = 7.1, 4.5 Hz, 1H), 2.98 (d, J = 7.2 Hz, 1H), 2.45 (s, 3H), 2.37 (d, J = 4.4 Hz, 1H). ¹³C NMR δ 144.8, 134.9, 130.9, 130.8, 129.8, 128.4, 128.3, 128.0, 115.7, 115.5, 40.3, 36.0, 21.7. MS (ESI) m/z 291 [M]⁺.

2-(4-chlorophenyl)-1-tosylaziridine 27e¹⁷⁹

Off-white solid; Yield: 83%; ¹H NMR δ 7.88 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29-7.27 (m, 2H), 7.19 (d, J = 6.6 Hz, 2H), 3.75 (dd, J = 7.2, 4.4 Hz), 3.00 (d, J = 7.2 Hz, 1H), 2.46 (s, 3H), 2.37 (d, J = 4.4 Hz, 1H). ¹³C NMR δ 144.8, 134.8, 134.2, 133.7, 129.8, 128.8, 128.0, 127.9, 40.3, 36.1, 21.7; MS (ESI) m/z 307 [M]⁺.

2-(4-bromophenyl)-1-tosylaziridine 27f¹⁷⁹

Off-white solid; Yield: 99%; ¹H NMR δ 7.86 (d, J = 11.1 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 10.7 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 3.72 (dd, J = 9.5, 5.8 Hz, 1H), 2.98 (d, J = 9.6 Hz, 1H), 2.44 (s, 3H), 2.34 (d, J = 5.9 Hz, 1H). ¹³C NMR δ 144.6, 134.5, 134.1, 130.9, 129.6, 128.1, 127.8, 122.4, 40.1, 35.8, 21.7. MS (ESI) m/z 353 [M]⁺.

2-*o*-tolyl-1-tosylaziridine 27h

Yellow oil; Yield: 63%; ^1H NMR δ 7.93 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.1 Hz), 7.21-7.12 (m, 4H), 3.89 (dd, J = 7.2, 4.6 Hz, 1H), 3.01 (d, J = 7.2 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.34 (d, J = 4.6 Hz). ^{13}C NMR δ 144.7, 136.8, 135.0, 133.3, 130.0, 129.8, 128.1, 128.1, 126.1, 125.9, 39.5, 35.1, 21.7, 19.1. MS (ESI) m/z 287 $[\text{M}]^+$.

2-(2-bromophenyl)-1-tosylaziridine 27i²⁷

Pale yellow oil; Yield: 40%; ^1H NMR δ 7.92 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.24-7.13 (m, 3H), 4.01 (dd, J = 7.2, 4.4 Hz, 1H), 3.06 (d, J = 7.2 Hz, 1), 2.47 (s, 3H), 2.29 (d, J = 4.4 Hz, 1H). ^{13}C NMR δ 144.9, 134.8, 134.6, 132.4, 129.8, 129.6, 128.1, 127.8, 127.6, 123.3, 41.3, 35.9, 21.7. MS (ESI) m/z 353 $[\text{M}]^+$.

2-(naphthalen-3-yl)-1-tosylaziridine 27j¹⁸⁰

White solid; Yield: 92%; ^1H NMR δ 7.89 (d, J = 8.2 Hz, 2H), 7.78 (t, J = 8.7 Hz, 2H), 7.72 (s, 1H), 7.49-7.45 (m, 2H), 7.34-7.28 (m, 3H), 3.93 (dd, J = 7.1, 4.4 Hz, 1H), 3.07 (d, J = 7.2 Hz, 1H), 2.50 (d, J = 4.4 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR δ 144.7, 135.1, 133.2, 133.0, 132.5, 129.9, 128.5, 128.0, 127.8, 127.7, 126.5, 126.3, 126.2, 123.7, 41.3, 36.0, 21.7. MS (ESI) m/z 323 $[\text{M}]^+$.

***N*-Tosylindeno[1,2-*b*]aziridine 27k¹⁸¹**

White solid; Yield: 25%; ¹H NMR δ 7.85 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 6.6 Hz, 1H), 7.15-7.34 (m, 5H), 4.32 (d, J = 6.0 Hz, 1H), 3.89-3.94 (m, 1H), 3.14-3.17 (m, 1H), 2.45 (s, 3H); ¹³C NMR δ 144.3, 140.3, 139.5, 137.5, 129.4, 129.1, 127.9, 126.9, 124.3, 68.2, 52.0, 41.1m 21.4; MS (ESI) m/z 286 [M]⁺.

1a,2,3,7b-tetrahydro-1-tosyl-1H-naphtho[2,1-*b*]aziridine 27l¹⁷⁹

Yellow oil; Yield: 56%; ¹H NMR δ 7.82 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 7.8 Hz, 3H), 7.26-7.14 (m, 2H), 7.05 (d, J = 7.3 Hz, 1H), 3.82 (d, J = 7.0 Hz, 1H) 3.56 (d, J = 6.9 Hz, 1H) 2.76 (dt, J = 14.8, 6.2 Hz, 1H), 2.54 (dd, J = 15.6, 5.2 Hz, 1H), 2.42 (s, 3H), 2.26 (dd, J = 14.4, 4.4 Hz, 1H), 1.68 (dt, J = 13.2, 4.1 Hz, 1H). ¹³C NMR δ 144.3, 136.6, 135.6, 130.0, 129.7, 129.4, 128.6, 128.5, 127.6, 126.4, 42.1, 41.8, 24.7, 21.6, 20.0. MS (ESI) m/z 327 [M]⁺.

2-methyl-3-phenyl-1-tosylaziridine 27m¹⁷⁹

Yellow oil; Yield: 90%; ¹H NMR δ 7.82 (d, J = 11.1 Hz, 2H), 7.29-7.12 (m, 7H), 3.89 (d, J = 5.7 Hz, 1H), 2.94-2.86 (m, 1H), 2.37 (s, 3H), 1.83 (d, J = 8.0 Hz, 3H). ¹³C NMR δ 143.8, 137.7, 135.4, 129.4, 128.6, 128.1, 127.3, 126.3, 49.2, 49.0, 21.7, 14.2. MS (ESI) m/z 287 [M]⁺.

2-benzyl-1-tosylaziridine 27r¹⁸²

Pale yellow solid; Yield: 22%; ¹H NMR δ 7.64 (d, J = 7.9 Hz, 2H), 7.15-7.24 (m, 5H), 7.01-7.06 (m, 2H), 2.9402.99 (m, 1H), 2.77 (dd, J = 13.0 Hz, 4.8 Hz, 2H), 2.65 (dd, J = 13.4, 5.0 Hz, 1H), 2.43 (s, 3H), 2.15 (d, J = 4.7 Hz, 1H); ¹³C NMR δ 144.1, 137.0, 134.7, 129.7, 128.8, 128.2, 127.9, 126.2, 41.2, 37.6, 32.7, 21.5; MS (ESI) m/z 287 [M+H]⁺.

6-tosyl-6-aza-bicyclo[3.1.0]hexane¹⁷⁹

Yellow oil; Yield: 14%; ¹H NMR δ 7.75 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.33 (s, 2H), 2.41 (s, 3H), 1.88-1.95 (m, 4H), 1.53-1.63 (m, 2H); ¹³C NMR δ 143.3, 135.6, 129.8, 127.6, 46.8, 26.6, 21.5, 19.3 MS (ESI) m/z 237 [M+H]⁺.

1-[(4-methoxyphenyl)sulfonyl]-2-phenyl-aziridine 27w¹²³

Off-white solid; Yield: 99%; ¹H NMR δ 7.91 (d, J = 8.8 Hz, 2H), 7.28-7.19 (m, 5H), 6.98 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H), 3.74 (dd, J = 7.1, 4.4 Hz, 1H), 2.95 (d, J = 7.2 Hz, 1H), 2.37 (d, J = 4.4, 1H). ¹³C NMR δ 163.9, 135.1, 130.5, 129.4, 128.3, 128.0, 126.9, 114.8, 55.9, 41.1, 35.9. MS (ESI) m/z 289 [M]⁺.

1-[(4-chlorophenyl)sulfonyl]-2-phenyl-aziridine 27x¹²³

Off-white solid; Yield: 84%; ¹H NMR δ 7.91 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.28-7.19 (m, 5H), 3.81 (dd, J = 7.1, 4.6 Hz, 1H), 3.00 (d, J = 7.2 Hz, 1H), 2.41 (d, J = 4.5 Hz, 1H). ¹³C NMR δ 140.2, 136.5, 134.5, 129.6, 129.2, 128.5, 128.4, 126.4, 41.2, 36.1. MS (ESI) m/z 293 [M]⁺.

1-[(4-nitrophenyl)sulfonyl]-2-phenyl-aziridine 27y⁴³

Off white solid; Yield: 11%; ¹H NMR δ 8.30 (d, J = 9.3 Hz, 2H), 8.15 (d, J = 9.1 Hz, 2H), 7.31-7.35 (m, 3H), 7.20-7.24 (m, 2H), 3.94 (dd, J = 7.2, 3.8 Hz, 1H), 3.11 (d, J = 7.1 Hz, 1H), 2.55 (d, J = 4.5 Hz, 1H); ¹³C NMR δ 151.2, 144.3, 134.5, 129.6, 129.0, 126.8, 124.6, 42.5, 36.6; MS (ESI) m/z 304 [M]⁺.

2,2,2-trichloroethyl 2-phenylaziridine-1-sulfonate 27z¹⁸³

Yellow oil; Yield: 69%; ¹H NMR δ 7.40-7.32 9m, 5H), 4.87 (q, J = 10.9 Hz, 2H), 3.90 (dd, J = 7.2, 4.8 Hz, 1H), 3.11 (d, J = 7.2 Hz, 1H), 2.65 (d, J = 4.6 Hz, 1H). ¹³C NMR δ 133.8, 128.9, 128.7, 126.5, 92.8, 79.6, 42.7, 37.5; MS (ESI) m/z 331 [M]⁺.

2,2,2-trichloroethyl 2-p-tolylaziridine-1-sulfonate 27 α ¹⁸³

Yellow oil; Yield: 41%; ¹H NMR δ 7.17 (s, 4H), 4.85 (q, J = 10.6 Hz, 2H), 4.77 (d, J = 10.9 Hz, 1H), 3.84 (dd, J = 7.5, 4.3 Hz, 1H), 3.06 (d, J = 6.7 Hz, 1H), 2.62 (d, J = 5.0 Hz, 1H) ¹³C NMR δ 152.1, 130.7, 126.3, 125.7, 92.8, 79.6, 42.6, 37.1, 34.6, 31.2; MS (ESI) m/z 343 [M]⁺.

2,2,2-trichloroethyl 2-(4-*tert*-butylphenyl)aziridine-1-sulfonate 27 β ¹⁸³

Pale yellow oil; Yield: 50%. ¹H NMR δ 7.39 (d, J = 8.92 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 4.83 (q, J = 10.9 Hz, 2H), 3.85 (dd, J = 7.0, 4.8 Hz, 1H), 3.05 (d, J = 7.2 Hz, 1H), 2.61 (d, J = 3.4 Hz, 1H), 1.34 (s, 9H); ¹³C NMR δ 152.1, 130.7, 129.3, 126.3, 125.9, 125.7, 92.9, 79.6, 42.6, 37.3, 34.6, 31.2; MS (ESI) m/z 385 [M]⁺.

2,2,2-trichloroethyl 2-(4-fluorophenyl)aziridine-1-sulfonate 27 γ ¹⁸³

Pale yellow oil; Yield: 67%; ¹H NMR δ 7.28 (dd J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 4.84 (q, J = 13.6 Hz, 2H), 3.85 (dd, J = 7.1, 4.7 Hz, 1H), 3.07 (d, J = 7.2 Hz, 1H), 2.59 (d, J = 4.6 Hz, 1H) ¹³C NMR δ 164.1, 161.6, 129.6, 129.6, 128.3, 128.2, 115.9, 115.6, 92.7, 79.6, 42.0, 37.5; MS (ESI) m/z 347 [M]⁺.

2,2,2-trichloroethyl 2-(4-chlorophenyl)aziridine-1-sulfonate 27d¹⁸³

Colorless oil; Yield: 60%; ¹H NMR δ 7.36 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 4.85 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 10.8 Hz, 1H), 3.82 (dd, J = 7.2, 4.5 Hz, 1H), 3.08 (d, J = 7.0 Hz, 1H), 2.55 (d, J = 4.8 Hz, 1H). ¹³C NMR δ 135.4, 132.7, 129.6, 128.4, 92.3, 79.8, 42.2, 37.9; MS (ESI) m/z 363 [M]⁺.

2,2,2-trichloroethyl 2-(4-bromophenyl)aziridine-1-sulfonate 27e¹⁸³

Colorless oil; Yield: 68%; ¹H NMR δ 7.48 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.84 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 3.84 (dd, J = 7.0, 4.9 Hz, 1H), 3.06 (d, J = 7.0 Hz, 1H), 2.59 (d, J = 4.2 Hz, 1H); ¹³C NMR δ 133.4, 132.4, 128.5, 123.3, 93.0, 79.9, 42.2, 37.8; MS (ESI) m/z 407 [M]⁺.

N-(2,3-dihydro-1H-inden-1-yl)-4-methyl-benzenesulfonamide 156a¹⁸⁴

Off white solid; Yield: 70%; ¹H NMR δ 7.88 (d, J = 7.9 Hz, 2H), 7.12-7.35 (m, 6H), 4.65-4.81 (m, 2H), 2.72-3.01 (m, 2H), 2.47 (s, 3H), 2.27-2.42 (m, 1H), 1.68-1.85 (m, 1H); ¹³C NMR δ 143.5, 142.5, 141.8, 139.1, 129.7, 128.0, 127.1, 126.6, 124.5, 124.0, 58.5, 34.3, 29.8, 21.4; MS (ESI) m/z 287 [M]⁺.

7.6 Copper-Catalyzed Amidation of Aromatic Heterocycles

General procedure for the uncatalyzed diamidation of *N*-substituted pyrrole

To a suspension of PhI=NTs (1.25 mmol, 5 equiv) and powdered 4Å molecular sieves in 2 mL of CH₂Cl₂, was added the pyrrole **118** (0.25 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h or sonicated for at 40 °C for 2 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness. The crude yield was obtained by ¹H NMR analysis with CH₂Br₂ as internal standard.

General procedure for the optimization of copper-catalyzed diamidation of *N*-methylpyrrole **118a**

To a suspension of catalyst (0.025 mmol, 0.1 equiv), PhI=NTs (1.25 mmol, 5 equiv) and powdered 4Å molecular sieves in 2 mL of CH₂Cl₂, was added the pyrrole **118a** (0.25 mmol, 1 equiv) under a N₂ atmosphere. The reaction was stirred at room temperature for 18 h. On completion, the crude mixture was filtered through Celite[®], washed with EtOAc, evaporated to dryness. The crude yield was obtained by ¹H NMR analysis with CH₂Br₂ as internal standard.

General procedure for the optimization of copper(I) iodide-catalyzed *N*-arylation of pyrrole **160a with iodobenzene **161a****

To a mixture of CuI, $t\text{Bu}_4\text{NBr}$ and base (refer Table 6.2) for in PhMe (1.3 mL) was added pyrrole **160a** (140 μL , 2 mmol, 1 equiv) and iodobenzene **161b** (220 μL , 2 mmol, 1 equiv). The reaction mixture was stirred at reflux for 22 h. On cooling to room temperature, saturated NH_4Cl solution (20 mL) was added and the organic layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , and evaporated to dryness. The crude product was purified via silica gel flash column chromatography.

General procedure for the copper(I) iodide-catalyzed *N*-arylation of azoles **160 with aryl iodides **161****

To a mixture of CuI (142.8 mg, 0.75 mmol, 0.05 equiv), $t\text{Bu}_4\text{NBr}$ (241.8 mg, 0.75 mmol, 0.05 equiv) and NaOH (1.2 g, 30 mmol, 2 equiv) for in PhMe (10 mL) was added azole **160** (15 mmol, 1 equiv) and aryl iodide **161** (15 mmol, 1 equiv). The reaction mixture was stirred at reflux for 22 h. On cooling to room temperature, saturated NH_4Cl solution (50 mL) was added and the organic layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , and

evaporated to dryness. The crude product was purified via silica gel flash column chromatography.

General procedure for the optimization of copper(I) iodide-catalyzed *O*-arylation of phenol **162a with iodobenzene **161a****

To a mixture of CuI (38.0 mg, 0.2 mmol, 0.1 equiv), *t*Bu₄NBr (64.5 mg, 0.2 mmol, 0.1 equiv) and K₃PO₄ (849 mg, 4 mmol, 2 equiv) in the solvents as given in Table 6.4 (1.3 mL) was added phenol **162a** (188.2 mg, 2 mmol, 1 equiv) and iodobenzene **161a** (220 μ L, 2 mmol, 1 equiv). The reaction mixture was stirred at reflux for 22 h. On cooling to room temperature, saturated NH₄Cl solution (20 mL) was added and the organic layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and evaporated to dryness. The crude product was purified via silica gel flash column chromatography.

General procedure for the copper(I) iodide-catalyzed *O*-arylation of phenols and alcohols **162 with aryl iodides **161****

To a mixture of CuI (38.0 mg, 0.2 mmol, 0.1 equiv), *t*Bu₄NBr (64.5 mg, 0.2 mmol, 0.1 equiv) and K₃PO₄ (849 mg, 4 mmol, 2 equiv) in DMF (1.3 mL) was added phenol or alcohol **162** (2 mmol, 1 equiv) and aryl halide **161** (2 mmol, 1 equiv). The reaction mixture was stirred at reflux for 22 h. On cooling to room temperature, saturated NH₄Cl

solution (20 mL) was added and the organic layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and evaporated to dryness. The crude product was purified via silica gel flash column chromatography.

General procedure for the copper(I) iodide-catalyzed *S*-arylation of thiols **164 with aryl iodides **161****

To a mixture of CuI (38.0 mg, 0.2 mmol, 0.1 equiv), ^tBu₄NBr (64.5 mg, 0.2 mmol, 0.1 equiv) and NaOH (160 mg, 4 mmol, 2 equiv) in PhMe (1.3 mL) was added thiol **164** (2 mmol, 1 equiv) and aryl iodide **161** (2 mmol, 1 equiv). The reaction mixture was stirred at reflux for 22 h. On cooling to room temperature, saturated NH₄Cl (20 mL) was added and the organic layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

N,N'*-(1-methyl-1*H*-pyrrole-3,4-diyl)bis(4-methyl-benzenesulfonamide) **119a*¹⁰⁰

White solid; Yield: 45%; ¹H NMR δ 7.87 (s, 2H), 7.84 (d, *J* = 8.1 Hz, 4H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.07 (s, 3H), 2.44 (s, 6H); ¹³C NMR δ 144.2, 137.2, 129.8, 127.1, 126.2, 26.8, 21.5; MS (ESI) *m/z* 419 [M]⁺.

***N,N'*-(1-phenyl-1*H*-pyrrole-3,4-diyl)bis[4-methyl-benzenesulfonamide) 119b**¹⁰⁰

White solid; Yield: 35%; ¹H NMR δ 8.06 (s, 2H), 7.78 (d, J = 8.2 Hz, 4H), 7.42-7.46 (m, 3H), 7.32 (d, J = 8.0 Hz, 4H), 7.13-7.18 (m, 2H), 2.44 (s, 6H); ¹³C NMR δ 130.2, 129.8, 129.6, 128.9, 128.5, 128.3, 127.4, 21.7; MS (ESI) m/z 481 [M]⁺.

***N*-phenylpyrrole 118b**¹⁸⁵

White solid; Yield: 95% ¹H NMR δ 7.38-7.42 (m, 3H), 7.22-7.26 (m, 2H), 7.10 (t, J = 2.2 Hz, 2H), 6.35 (d, J = 2.2 Hz, 2H); ¹³C NMR δ 140.8, 129.5, 125.4, 120.6, 119.3, 110.4; MS (ESI) m/z 144 [M]⁺.

1-*p*-fluoro-1*H*-pyrrole 118c¹⁰⁰

Off-white solid; Yield: 77%; ¹H NMR δ 7.54 (d, J = 8.8, 2H), 7.08 (d, J = 9.0 Hz, 2H), 7.05 (t, J = 2.2 Hz, 2H), 6.36 (t, J = 2.2 Hz, 2H); ¹³C NMR δ 144.2, 136.9, 122.3, 119.4, 119.2, 110.9; MS (ESI) m/z 161 [M]⁺.

1-*p*-bromo-1*H*-pyrrole 118d¹⁸⁶

Off-white solid; Yield: 77%; ¹H NMR δ 7.30-7.35 (m, 2H), 7.08 (t, J = 8.1 Hz, 2H), 7.00 (t, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 2H); ¹³C NMR δ 140.2, 132.9, 122.4, 119.6, 119.2, 111.3; MS (ESI) m/z 221 [M]⁺.

1-*p*-chloro-1*H*-pyrrole 118e¹⁸⁵

Off-white solid; Yield: 80%; ¹H NMR δ 7.39 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 8.9 Hz, 2H), 7.05 (t, J = 2.2 Hz, 2H), 6.36 (t, J = 2.2 Hz, 2H); ¹³C NMR δ 139.7, 131.5, 129.9, 121.9, 119.6, 111.2; MS (ESI) m/z 177 [M]⁺.

1-*p*-tert-butyl-1*H*-pyrrole 118f¹⁸⁷

Off-white solid; Yield: 88%; ¹H NMR δ 7.44 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.07 (t, J = 2.2 Hz, 2H), 6.33 (d, J = 2.2 Hz, 2H), 1.35 (s, 9H); ¹³C NMR δ 148.0, 138.0, 125.9, 119.8, 118.9, 109.9, 34.1, 31.0; MS (ESI) m/z 199 [M]⁺.

1-*p*-methoxy-1*H*-pyrrole 118g¹⁸⁸

Off white solid; Yield: 84%; ¹H NMR δ 7.31 (d, J = 10.2 Hz, 2H), 7.00 (t, J = 2.2 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.32 (t, J = 2.2 Hz, 2H), 3.83 (s, 3H); ¹³C NMR δ 157.7, 134.5, 122.4, 119.8, 114.7, 110.5, 55.6; MS (ESI) m/z 173 [M]⁺.

1-*p*-tolyl-1*H*-pyrrole 118h¹⁸⁵

Off-white solid; Yield: 88%; ¹H NMR δ 7.34 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.11 (t, J = 2.2 Hz, 2H), 6.39 (d, J = 2.2 Hz, 2H), 2.45 (s, 3H); ¹³C NMR δ 138.8, 135.4, 130.4, 120.7, 119.8, 110.3, 20.9; MS (ESI) m/z 157 [M]⁺.

1-*m*-tolyl-1*H*-pyrrole 118i¹⁸⁹

Pale yellow oil; Yield: 83%; ¹H NMR δ 7.27 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 9.7 Hz, 2H), 7.06 (t, J = 2.0 Hz, 2H), 6.96 (d, J = 7.8 Hz, 2H), 6.32 (t, J = 2.2 Hz, 2H), 2.38 (s, 3H) ¹³C NMR δ 139.7, 130.3, 125.7, 121.4, 120.7, 119.4, 117.1, 110.4, 21.6; MS (ESI) m/z 157 [M]⁺.

1-*o*-tolyl-1*H*-pyrrole 118j¹⁹⁰

Pale yellow oil; Yield: 62%; ¹H NMR δ 7.24-7.27 (m, 4H), 6.78 (t, J = 2.2 Hz, 2H), 6.31 (t, J = 2.2 Hz, 2H), 2.20 (s, 3H); ¹³C NMR δ 139.2, 129.1, 127.4, 125.9, 125.3, 121.9, 121.4, 110.5, 19.8; MS (ESI) m/z 157 [M]⁺.

1-(2,4-dimethylphenyl)-1*H*-pyrrole 118k¹⁹¹

Pale yellow oil; Yield: 63%; ¹H NMR δ 7.13 (d, J = 7.9 Hz, 2H), 7.10 (s, 1H), 7.05 (d, J = 7.9 Hz, 1H), 6.76 (t, J = 2.1 Hz, 2H), 6.29 (t, J = 2.1 Hz, 2H), 2.36 (s, 1H), 2.15 (s, 3H); ¹³C NMR δ 138.5, 135.4, 130.4, 126.7, 125.4, 121.7, 119.8, 110.3, 20.9, 19.1; MS (ESI) m/z 171 [M]⁺.

1-(1-phenyl-1*H*-pyrrol-2-yl)ethanone 118l¹⁹²

Colorless oil; Yield: 50%; ¹H NMR δ 7.40 (d, J = 7.2, 2H), 7.26 (t, J = 5.4 Hz, 2H), 7.11 (dd, J = 4.0, 1.8 Hz, 1H), 6.96 (dd, J = 4.0, 1.8 Hz, 1H), 6.30 (dd, J = 4.0, 2.6 Hz, 1H), 2.43 (s, 3H); ¹³C NMR δ 189.9, 140.5, 133.2, 129.3, 127.3, 122.3, 120.2, 110.4, 29.4; MS (ESI) m/z 185 [M]⁺.

1-phenyl-1*H*-indole 118m¹⁸⁶

White solid; Yield: 80%; ¹H NMR δ 7.67 (d, J = 6.6 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 4.3 Hz, 4H), 7.26-7.31 (m, 2H), 7.11-7.22 (m, 2H), 6.66 (d, J = 3.2 Hz, 1H); ¹³C NMR δ 140.0, 136.0, 129.7, 129.5, 128.1, 126.5, 124.5, 122.5, 121.3, 120.5, 110.6, 110.6, 103.7; MS (ESI) m/z 194 [M]⁺.

1-*p*-tolyl-1*H*-indole 118n¹⁸⁸

White solid; Yield: 80%; ¹H NMR δ 7.75 (d, J = 7.1 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.32-7.36 (m, 3H), 7.22-7.28 (m, 2H), 6.71 (d, J = 2.3 Hz, 1H), 2.49 (s, 3H); ¹³C NMR δ 137.3, 136.1, 135.7, 130.0, 129.2, 127.6, 124.5, 122.0, 120.8, 120.0, 110.5, 103.2, 21.3; MS (ESI) m/z 207 [M]⁺.

1-*p*-bromo-1*H*-indole 118o¹⁸⁸

White solid; Yield: 33%; ¹H NMR δ 7.68 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 7.95, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 3.2 Hz, 1H), 7.13-7.32 (m, 2H), 6.67 (d, J = 3.1 Hz, 1H); ¹³C NMR δ 138.9, 135.7, 132.8, 129.5, 129.7, 125.8, 122.7, 121.3, 120.7, 119.8, 110.3, 104.2; MS (ESI) m/z 271 [M]⁺.

1-phenyl-1*H*-imidazole 118p¹⁸⁶

Colorless liquid; Yield 84%; ¹H NMR δ 7.86 (s, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.35-7.40 (m, 3H), 7.29 (s, 1H), 7.21 (s, 1H) ¹³C NMR δ 135.7, 131.2, 130.1, 137.8, 122.4, 118.1; MS (ESI) m/z 144 [M]⁺.

1-*p*-tolyl-1*H*-imidazole 118q¹⁸⁶

White solid; Yield: 69% ¹H NMR δ 7.80(s, 1H), 7.18-7.24 (m, 6H), 2.29 (s, 3H) ¹³C NMR δ 137.4, 135.5, 130.3, 130.2, 121.3, 118.3, 20.9; MS (ESI) m/z 158 [M]⁺.

1-*p*-chloro-1*H*-imidazole 118r¹⁸⁶

White solid; Yield: 68%; ¹H NMR δ 7.83 (s, 1H), 7.45 (dt, J = 9.5, 2.3 Hz, 2H), 7.33 (dt, J = 9.5, 2.7 Hz, 2H), 7.25 (s, 1H), 7.21 (s, 1H); ¹³C NMR δ 135.9, 135.5, 133.1, 130.7, 130.0, 122.7, 118.2; MS (ESI) m/z 178 [M]⁺.

1-(naphthalen-1-yl)-1*H*-imidazole 118s¹⁹³

White solid; Yield: 70% ¹H NMR δ 7.97 (d, J = 5.7, 2H), 7.79 (s, 1H), 7.57-7.63 (m, 4H), 7.47 (dd, J = 9.7, 1,1, 1H), 7.32 (s, 1H), 7.28 (s, 1H) ¹³C NMR δ 162.3, 138.4, 134.2, 130.2, 129.5, 129.2, 128.3, 127.8, 127.6, 127.0, 125.2, 123.7, 122.3, 121.7; MS (ESI) m/z 194 [M]⁺.

1-phenyl-1*H*-indazole 118t¹⁹³

White solid.; Yield: 50%; ¹H NMR δ 8.29 (s, 1H), 7.81-7.90 (m, 4H), 7.63 (t, J = 5.5 Hz, 2H), 7.50 (t, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H); ¹³C NMR δ 140.2, 138.8, 135.4, 129.5, 127.2, 126.6, 125.4, 122.8, 121.5, 121.4, 110.4; MS (ESI) m/z 194 [M]⁺.

1-*p*-tolyl-1*H*-indazole 118u^{161g}

White solid.; Yield: 50%; ¹H NMR δ 8.18 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.37-7.43 (m, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.17-7.24 (m, 1H), 2.42 (s, 3H); ¹³C NMR δ 138.8, 137.8, 136.5, 135.0, 130.0, 126.8, 125.2, 122.7, 121.4, 121.3, 110.4, 21.1; MS (ESI) m/z 208 [M]⁺.

1-*p*-chloro-1*H*-indazole 118v¹⁹⁴

White solid; Yield: 19%; ¹H NMR δ 8.20 (s, 1H), 7.79-7.81 (m, 1H), 7.66-7.70 (m, 3H), 7.31-7.53 (m, 3H), 7.20-7.25 (m, 1H); ¹³C NMR δ 138.8, 138.7, 135.8, 132.0, 138.6, 127.4, 125.5, 123.7, 122.0, 121.8, 121.5, 110.2; MS (ESI) m/z 228 [M]⁺.

1-phenyl-1*H*-1,2,4-triazole 118w¹⁹³

White solid, Yield: 45%; ¹H NMR δ 8.57 (s, 1H), 8.11 (s, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.50 (t, J = 8.8, 2H), 7.40 (t, J = 7.41, 1H); ¹³C NMR δ 152.6, 140.9, 170.0, 129.8, 128.2, 120.1; MS (ESI) m/z 145 [M]⁺.

1-*p*-tolyl-1*H*-1,2,4-triazole 118x¹⁹⁵

White solid, Yield: 47% ¹H NMR δ 8.51 (s, 1H), 8.09 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H); ¹³C NMR δ 152.4, 140.8, 138.3, 134.7, 130.3, 120.0, 21.0; MS (ESI) m/z 159 [M]⁺.

1-*p*-chloro-1*H*-1,2,4-triazole 118y¹⁹⁶

White solid, Yield: 54% ¹H NMR δ 8.55 (s, 1H), 8.10 (s, 1H), 7.64 (d, J = 9.6 Hz, 2H), 7.48 (d, J = 9.5 Hz, 2H); ¹³C NMR δ 152.8, 140.8, 135.5, 133.9, 129.9, 121.2; MS (ESI) m/z 179 [M]⁺.

Diphenyl ether 163a¹⁹⁷

Colorless liquid; Yield: 95%; ¹H NMR δ 7.35 (t, J = 8.3 Hz, 4H), 7.12 (t, J = 7.12 Hz, 4H), 7.04 (d, J = 8.3 Hz, 2H); ¹³C NMR δ 157.2, 129.7, 123.2, 118.9; MS (ESI) m/z 170 [M]⁺.

1-fluoro-4-phenoxybenzene 163b¹⁹⁸

Colorless oil; Yield: 90% ¹H NMR δ 7.33 (t, J = 7.6 Hz, 2H), 7.06 (t, J = 8.2 Hz, 2H), 6.95-7.04 (m, 5H); ¹³C NMR δ 160.0, 157.7, 157.6, 152.8, 129.8, 123.1, 120.6, 120.5, 118.3, 116.4, 116.2; MS (ESI) m/z 188 [M]⁺.

1-chloro-4-phenoxybenzene 163c¹⁹⁹

Colorless oil; Yield: 90%; ¹H NMR δ 7.37 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 6.8 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 7.7 Hz, 2H), 6.97 (d, J = 9.8 Hz, 2H); ¹³C NMR δ 156.8, 155.9, 129.8, 129.7, 128.2, 123.6, 120.0, 118.9; MS (ESI) m/z 204 [M]⁺.

1-methyl-4-phenoxybenzene 163d¹⁹⁷

Colorless oil; Yield: 89%; ¹H NMR δ 7.31 (t, J = 7.4 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 7.8 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 2.33 (s, 3H);

^{13}C NMR δ 157.9, 154.8, 132.9, 130.3, 129.7, 122.8, 119.2, 118.4; MS (ESI) m/z 184 $[\text{M}]^+$.

1-nitro-4-phenoxybenzene 163e¹⁹⁹

Yellow solid; Yield: 95%; ^1H NMR δ 8.20 (dd, $J = 10.4, 2.4$ Hz, 2H), 7.41 (t, $J = 9.1$ Hz, 2H), 7.26 (t, $J = 7.8$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 2H), 7.01 (dd, $J = 10.4, 5.4$ Hz, 2H); ^{13}C NMR δ 163.4, 154.7, 142.6, 130.3, 125.9, 125.4, 120.5, 17.1; MS (ESI) m/z 215 $[\text{M}]^+$.

1-(4-methoxyphenoxy)benzene 163f¹⁹⁷

Colorless oil; Yield: 80%; ^1H NMR δ 7.28 (t, $J = 7.4$ Hz, 2H), 6.86-7.05 (m, 7H), 3.79 (s, 3H); ^{13}C NMR δ 158.5, 155.8, 150.0, 129.6, 122.4, 120.8, 117.5, 114.8, 55.6; MS (ESI) m/z 200 $[\text{M}]^+$.

1-methyl-2-phenoxybenzene 163g¹⁹⁷

Colorless oil; Yield: 74%; ^1H NMR δ 7.22-7.29 (m, 4H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.01-7.08 (m, 2H), 6.88-6.92 (m, 3H), 2.34 (s, 3H); ^{13}C NMR δ 157.9, 154.4, 138.9, 131.4, 129.6, 127.1, 124.0, 122.3, 119.8, 117.3, 16.2; MS (ESI) m/z 184 $[\text{M}]^+$.

1-chloro-4-(*p*-tolylloxy)benzene 163h²⁰⁰

White solid; 82%; ^1H NMR δ 7.25 (d, $J = 9.0$ Hz, 2H), 7.15 (d, $J = 8.13$ Hz, 2H), 6.88-6.92 (m 4H), 2.32 (s, 3H); ^{13}C NMR δ 156.5, 154.3, 133.3, 130.3, 129.6, 127.7, 119.4, 119.1, 20.7; MS (ESI) m/z 218 $[\text{M}]^+$.

4,4'-oxybis(methylbenzene) 163i¹⁹⁸

Colorless oil; Yield: 87%; ^1H NMR δ 7.11 (d, $J = 8.2$ Hz, 4H), 6.89 (d, $J = 8.5$ Hz, 4H), 2.32 (s, 6H); ^{13}C NMR δ 154.3, 132.4, 130.1, 118.6, 20.6; MS (ESI) m/z 198 $[\text{M}]^+$.

1-methyl-4-(4-nitrophenoxy)benzene 163j²⁰¹

Pale yellow solid; Yield: 89%; ^1H NMR δ 8.18 (d, $J = 7.1$ Hz, 2H), 6.98 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 7.2$, 4H), 2.38 (s, 3H); ^{13}C NMR δ 163.7, 152.2, 142.3, 135.2, 130.7, 125.8, 120.4, 116.7, 20.8; MS (ESI) m/z 229 $[\text{M}]^+$.

1-methoxy-4-(*p*-tolylloxy)benzene 163k¹⁹⁸

White solid; Yield: 48%; ^1H NMR δ 7.10 (d, $J = 8.2$ Hz, 2H), 6.94 (d, $J = 10.1$ Hz, 2H), 6.83-6.88 (m 4H), 3.80 (s, 3H), 2.32 (s, 3H); ^{13}C NMR δ 156.1, 155.6, 150.7, 138.2, 132.0, 130.1, 120.4, 117.8, 116.4, 114.8, 55.8, 20.6; MS (ESI) m/z 214 $[\text{M}]^+$.

2,4'-oxybis(methylbenzene) 163l²⁰²

Colorless oil; Yield: 81%; ¹H NMR δ 7.23 (d, J = 5.2 Hz, 1H), 7.03-7.16 (m, 4H), 6.86 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.5 Hz, 2H), 2.32 (s, 3H), 2.25 (s, 3H); ¹³C NMR δ 155.6, 155.0, 140.0, 131.4, 130.2, 127.1, 123.6, 119.2, 117.6, 20.7, 16.3; MS (ESI) m/z 198 [M]⁺.

4,4'-oxybis(chlorobenzene) 163m²⁰³

Colorless oil; Yield: 80%; ¹H NMR δ 7.27 (dd, J = 6.8, 2.0 Hz, 4H), 6.89 (dd, J = 6.6, 2.0 Hz, 4H); ¹³C NMR δ 155.9, 130.1, 128.9, 120.4; MS (ESI) m/z 238 [M]⁺.

1-chloro-4-(4-nitrophenoxy)benzene 163n²⁰³

Yellow oil; Yield: 80%; ¹H NMR δ 8.05 (dd, J = 6.8, 2.5 Hz, 2H), 7.28 (dd, J = 6.6, 2.0 Hz, 2H), 6.80 – 6.96 (m, 4H); ¹³C NMR δ 163.1, 153.4, 143.2, 130.8, 130.5, 126.3, 121.9, 117.4; MS (ESI) m/z 249 [M]⁺.

1-chloro-4-(4-methoxyphenoxy)benzene 163o²⁰⁴

Colorless oil; Yield: 62%; ¹H NMR δ 7.24(d, J = 8.9 Hz, 2H), 6.94-6.98 (m, 2H), 6.84-6.87(m, 4H), 3.81 (s, 3H); ¹³C NMR δ 157.1, 156.0, 149.7, 129.3, 127.1, 120.5, 118.4, 114.9, 55.5; MS (ESI) m/z 234 [M]⁺.

1-(4-chlorophenoxy)-2-methylbenzene 163p²⁰³

Colorless oil; Yield: 80%; ¹H NMR δ 7.20 – 7.24 (m, 3H), 7.03 – 7.18 (m, 2H), 6.87 (d, J = 9.1 Hz, 1H), 6.79 (m, 2H), 2.22 (s, 3H); ¹³C NMR δ 156.5, 154.0, 131.4, 130.0, 129.6, 127.2, 124.4, 120.0, 118.4, 16.3; MS (ESI) m/z 218 [M]⁺.

1-methyl-2-(4-nitrophenoxy)benzene 163q²⁰³

Red solid; Yield: 77%; ¹H NMR δ 8.18 (dt, J = 9.3, 2.2 Hz, 2H), 7.16-7.29 (m, 3H), 7.01 (d, J = 6.5 Hz, 1H), 6.92 (dt, J = 9.3, 2.2 Hz, 2H), 2.18 (s, 3H); ¹³C NMR δ 162.5, 148.3, 145.1, 142.7, 136.5, 131.4, 130.5, 129.0, 127.5, 125.8, 124.1, 20.7; MS (ESI) m/z 229 [M]⁺.

1-(4-methoxyphenoxy)-2-methylbenzene 163r²⁰⁵

Colorless oil; Yield: 60% ¹H NMR δ 7.11 (t, J = 6.7 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.83-6.89 (m, 5H), 6.79 (d, J = 8.0 Hz, 1H), 3.79 (s, 3H), 2.28 (s, 3H); ¹³C NMR δ 155.8,

155.3, 151.0, 131.2, 139.0, 126.9, 123.0, 119.3, 117.9, 114.7, 55.6, 16.2; MS (ESI) m/z 214 $[M]^+$.

2,2'-oxybis(methylbenzene) 163s^{163r}

Colorless oil; Yield: 87%; ^1H NMR δ 7.24 (d, J = 6.8 Hz, 2H), 7.11 (t, J = 9.1 Hz, 2H), 7.00 (t, J = 7.4 Hz, 2H), 6.71 (d, J = 8.0 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR δ 155.2, 131.3, 128.8, 127.0, 123.0, 117.6, 16.1; MS (ESI) m/z 198 $[M]^+$.

2-(4-chlorophenoxy)-1,3-dimethylbenzene 163t²⁰⁶

Colorless liquid; Yield: 40%; ^1H NMR δ 7.20 (d, J = 9.0 Hz, 2H), 7.06-7.08 (m, 3H), 6.69 (d, J = 9.0 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR δ 156.4, 150.8, 131.3, 129.5, 129.1, 126.1, 125.3, 115.8, 16.2; MS (ESI) m/z 232 $[M]^+$.

1,3-dimethyl-2-(*p*-tolylloxy)benzene 163u²⁰⁴

Colorless oil; Yield: 41%; ^1H NMR δ 7.01-7.10 (m, 5H), 6.64 (d, J = 8.6 Hz, 2H), 2.28 (s, 3H), 2.12 (s, 3H); ^{13}C NMR δ 155.7, 151.2, 131.5, 130.4, 130.0, 128.9, 124.9, 114.3, 20.5, 16.3; MS (ESI) m/z 212 $[M]^+$.

1,3-dimethyl-2-(o-tolyloxy)benzene 163v²⁰⁴

Colorless oil; Yield: 40%; ^1H NMR δ 7.20-7.25 (m, 2H), 6.95-7.11 (m, 4H), 2.42 (s, 3H), 2.11 (s, 3H); ^{13}C NMR δ 155.9, 151.6, 131.6, 131.0, 128.9, 126.9, 126.0, 124.9, 120.9, 111.9, 16.3, 16.2; MS (ESI) m/z 212 $[\text{M}]^+$.

1-butoxy-4-chlorobenzene 166a²⁰⁷

Colorless oil; Yield: 60%; ^1H NMR δ 7.17 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.93 (t, J = 6.5 Hz, 3H), 1.73 (qt, J = 8.0 Hz, 2H), 1.52 (qt, J = 7.6 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 157.5, 129.1, 125.1, 115.5, 67.7, 31.1, 19.1, 13.6; MS (ESI) m/z 184 $[\text{M}]^+$.

1-chloro-4-phenethoxybenzene 166b²⁰⁸

Colorless oil; Yield: 55%; ^1H NMR δ 7.19-7.34 (m, 7H), 6.82 (d, J = 8.9 Hz, 2H), 4.14 (t, J = 7.1 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H); ^{13}C NMR δ 157.4, 138.0, 129.3, 128.9, 128.5, 126.5, 125.5, 115.8, 68.9, 35.6; MS (ESI) m/z 232 $[\text{M}]^+$.

1-methyl-4-phenethoxybenzene 166c²⁰⁹

Colorless oil; Yield: 54%; ^1H NMR δ 7.22-7.34 (m, 5H), 7.06 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.14 (t, J = 7.1 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR δ 156.6, 138.3, 129.9, 129.0, 128.4, 126.4, 114.4, 68.7, 35.8, 20.4; MS (ESI) m/z 212 $[\text{M}]^+$.

3-(phenylamino)propan-1-ol 166d²¹⁰

Colorless oil; Yield: 50%; ^1H NMR δ 7.18 (t, J = 7.4 Hz, 2H), 6.71 (t, J = 7.32, 1H), 6.64 (d, J = 7.6 Hz, 2H), 3.81 (t, J = 5.9 Hz, 2H), 3.28 (t, J = 6.48 Hz, 2H), 1.88 (qt, J = 6.3 Hz, 2H); ^{13}C NMR δ 129.3, 129.3, 117.7, 113.1, 61.7, 42.0, 31.9; MS (ESI) m/z 174 $[\text{M}+\text{Na}]^+$.

***N*-(3-phenoxypropyl)benzenamine 166e**²¹¹

Pale yellow oil; Yield: 55%; ^1H NMR δ 7.29 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.4 Hz, 2H), 6.90-6.98 (m, 3H), 6.70 (t, J = 7.32 Hz, 1H), 6.63 (d, J = 7.6 Hz, 2H), 4.09 (t, J = 5.9 Hz, 2H), 3.36 (t, J = 6.6 Hz, 2H), 2.10 (qt, J = 6.5 Hz, 2H); MS (ESI) m/z 250 $[\text{M}+\text{Na}]^+$.

3-phenoxypropan-1-amine 166f²¹²

Colorless oil; 20%; ^1H NMR δ 7.18 (t, J = 8.5 Hz, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 8.5 Hz, 2H), 4.20 (t, J = 6.2 Hz, 2H), 3.74 (brs, 2H), 3.23 (t, J = 6.8 Hz, 2H), 1.94 (qt,

$J = 6.39$ Hz, 2H); ^{13}C NMR δ 129.5, 129.3, 120.8, 117.3, 114.5, 112.8, 65.9, 41.3, 29.1; MS (ESI) m/z 174 $[\text{M}+\text{Na}]^+$.

Phenyl(*p*-tolyl)sulfane 165a²¹³

Colorless oil; Yield: 95%; ^1H NMR δ 7.07-7.11 (m, 4H), 7.17-7.23 (m, 5H), 2.34 (s, 3H); ^{13}C NMR δ 137.5, 137.1, 132.2, 131.2, 130.2, 130.0, 129.7, 129.0, 126.3, 21.1; MS (ESI) m/z 200 $[\text{M}]^+$.

(4-chlorophenyl)(*p*-tolyl)sulfane 165b²¹⁴

Pale yellow solid; Yield: 96%; ^1H NMR δ 7.13-7.31 (m, 8H), 2.35 (s, 3H); ^{13}C NMR δ 138.0, 135.9, 132.5, 132.2, 130.7, 130.2, 129.6, 129.1, 21.1; MS (ESI) m/z 234 $[\text{M}]^+$.

(4-bromophenyl)(*p*-tolyl)sulfane 165c²¹⁵

Pale yellow solid; Yield: 96%; ^1H NMR δ 7.37 (d, $J = 6.6$ Hz, 2H), 7.30 (d, $J = 6.3$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 6.8$ Hz, 2H), 2.35 (s, 3H); ^{13}C NMR δ 139.1, 138.2, 137.9, 136.8, 132.7, 132.1, 130.9, 130.4, 130.3, 120.1, 21.2; MS (ESI) m/z 278 $[\text{M}]^+$.

(4-fluorophenyl)(*p*-tolyl)sulfane 165d²¹⁶

Colorless oil; Yield: 96%; ¹H NMR δ 7.21-7.32 (m, 4H), 7.11 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 6.5 Hz, 2H), 2.33 (s, 3H) ¹³C NMR δ 160.8, 137.3, 132.9, 132.8, 132.3, 131.3, 130.1, 116.4, 116.2, 21.1; MS (ESI) m/z 218 [M]⁺.

(4-nitrophenyl)(*p*-tolyl)sulfane 165e²¹⁴

Yellow solid, Yield: 80%; ¹H NMR δ 8.05 (d, J = 7.02 Hz, 2H), 7.44-7.49 (d, J = 6.26 Hz, 2H), 7.27 (d, J = 7.0 Hz, 2H), 7.14 (d, J = 7.0 Hz, 2H), 2.42 (s, 3H); ¹³C NMR δ 149.3, 145.1, 140.2, 135.1, 130.8, 126.4, 126.1, 123.9, 21.3; MS (ESI) m/z 235 [M]⁺.

Di(*p*-tolyl)sulfane 165f²¹⁴

Colorless oil; Yield: 94%; ¹H NMR δ 7.23 (d, J = 6.2 Hz, 4H), 7.10 (d, J = 8.0 Hz, 4H), 2.32 (6H); ¹³C NMR δ 136.8, 132.6, 131.0, 129.9, 21.0; MS (ESI) m/z 214 [M]⁺.

(4-chlorophenyl)(4-methoxyphenyl)sulfane 165g²¹⁴

Colorless solid; Yield: 90%; ¹H NMR δ 7.40 (d, J = 6.8 Hz, 2H), 7.19 (d, J = 6.7 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.83 (s, 3H); ¹³C NMR δ 160.0, 137.4, 135.5, 131.6, 129.3, 129.0, 123.7, 115.1, 55.4; MS (ESI) m/z 250 [M]⁺.

(4-methoxyphenyl)(4-nitrophenyl)sulfane 165h^{163w}

Pale yellow oil; Yield: 78%; ¹H NMR δ 8.05 (d, J = 7.0 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 7.0 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ¹³C NMR δ 161.1, 150.1, 145.0, 137.1, 125.3, 123.9, 120.1, 115.6, 55.5; MS (ESI) m/z 261 [M]⁺.

Bis(4-methoxyphenyl)sulfane 165i²¹³

Pale yellow oil; Yield: 78%; ¹H NMR δ 7.30 (d, J = 9.0 Hz, 4H), 6.86 (d, J = 8.8 Hz, 4H), 3.81 (s, 6H); ¹³C NMR δ 160.1, 132.9, 127.6, 114.9, 55.5; MS (ESI) m/z 246 [M]⁺.

Bis(4-chlorophenyl)sulfane 165j²¹⁷

Colorless oil; Yield: 80%; ¹H NMR δ 7.22-7.29 (m, 8H); ¹³C NMR δ 133.9, 133.5, 132.3, 129.5; MS (ESI) m/z 254 [M]⁺.

(4-chlorophenyl)(4-nitrophenyl)sulfane 165k²¹⁴

Yellow solid; Yield: 80%; ¹H NMR δ 8.09 (d, J = 9.0 Hz, 2H), 7.40-7.48 (m, 4H), 7.20 (d, J = 9.0 Hz, 2H); ¹³C NMR δ 147.6, 136.0, 135.8, 130.3, 129.1, 126.9, 124.1; MS (ESI) m/z 265 [M]⁺.

(4-chlorophenyl)(naphthalen-1-yl)sulfane 165l²¹⁸

Colorless oil. Yield: 80%; ¹H NMR δ 8.29 (d, J = 2.5 Hz, 1H), 7.82-7.88 (m, 2H), 7.64-7.67 (m, 1H), 7.43-7.45 (m, 2H), 7.40 (t, J = 8.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 9.1 Hz, 2H); ¹³C NMR δ 135.6, 134.0, 133.3, 132.8, 131.6, 130.1, 129.5, 129.4, 129.0, 128.5, 127.0, 126.4, 125.6, 125.3; MS (ESI) m/z 270 [M]⁺.

***o*-tolyl(*p*-tolyl)sulfane 165m**²¹⁹

Colorless oil; Yield: 96%; ¹H NMR δ 7.09-7.23 (m, 8H), 2.37 (s, 3H), 2.32 (s, 3H); ¹³C NMR δ 138.8, 137.0, 135.2, 131.7, 131.4, 131.2, 130.5, 130.1, 127.2, 126.7, 21.2, 20.6; MS (ESI) m/z 214 [M]⁺.

(4-chlorophenyl)(*o*-tolyl)sulfane 165n²²⁰

Colorless oil; Yield: 95%; ¹H NMR δ 7.07-7.32 (m, 8H), 2.34 (s, 3H); ¹³C NMR δ 140.3, 135.1, 133.4, 133.1, 132.3, 130.8, 130.6, 129.3, 128.4, 126.9, 20.7; MS (ESI) m/z 234 [M]⁺.

(4-nitrophenyl)(*o*-tolyl)sulfane 165o²²¹

Colorless oil; Yield: 90%; ¹H NMR δ 8.05 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 7.53 Hz, 1H), 7.36-7.41 (m, 2H), 7.29 (d, J = 7.6, 1H), 7.06 (d, J = 9.0 Hz, 2H), 2.38 (s, 3H); ¹³C NMR δ 148.3, 145.2, 142.7, 126.5, 131.4, 130.5, 129.0, 127.5, 125.8, 124.1, 20.7; MS (ESI) m/z 245 [M]⁺.

Di(*o*-tolyl)sulfane 165p²²²

Colorless oil; Yield: 95%; ¹H NMR δ 7.04-7.22 (m, 8H), 2.38 (s, 6H); ¹³C NMR δ 138.9, 134.3, 131.1, 130.4, 127.1, 126.7, 20.4; MS (ESI) m/z 214 [M]⁺.

(4-chlorophenyl)(2,6-dimethylphenyl)sulfane 165q²²⁰

Colorless oil; Yield: 96%; ¹H NMR δ 7.09-7.27 (m, 6H), 6.84 (d, J = 8.64 Hz, 2H), 2.41 (s, 6H); ¹³C NMR δ 143.8, 136.6, 130.4, 130.1, 129.5, 129.0, 128.6, 127.9, 126.8, 21.8; MS (ESI) m/z 248 [M]⁺.

(4-nitrophenyl)(2,6-dimethylphenyl)sulfane 165r²²³

Pale yellow oil; Yield: 81%; ¹H NMR δ 8.03 (d, J = 9.0 Hz, 2H), 7.25-7.32 (m, 4H), 6.98 (d, J = 9.0 Hz, 2H), 2.41 (s, 6H); ¹³C NMR δ 148.2, 144.9, 143.9, 130.3, 128.9, 128.1, 124.8, 124.2, 21.6; MS (ESI) m/z 259 [M]⁺.

(2,6-dimethylphenyl)(p-tolyl)sulfane 165s²¹⁵

Colorless oil; Yield: 95%; ¹H NMR δ 7.14-7.24 (m, 3H), 6.99 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 2.42 (s, 6H), 2.26 (s, 3H); ¹³C NMR δ 143.8, 134.7, 131.0, 129.7, 129.1, 128.4, 128.0, 125.9, 21.9, 20.8; MS (ESI) m/z 228 [M]⁺.

(2,4-dimethylphenyl)(4-methoxyphenyl)sulfane 165t²²³

Colorless oil; Yield: 96%; ¹H NMR δ 7.12-7.25 (m, 3H), 6.90 (d, J = 6.7 Hz, 2H), 6.75 (d, J = 6.8 Hz, 2H), 3.74 (s, 3H), 2.43 (s, 6H); ¹³C NMR δ 157.5, 143.6, 131.9, 128.9, 128.6, 128.4, 127.9, 114.7, 55.3, 22.0; MS (ESI) m/z 244 [M]⁺.

(2,6-dimethylphenyl)(o-tolyl)sulfane 165u²²⁴

Colorless oil; Yield: 96%; ¹H NMR δ 7.00-7.26 (m, 4H), 6.98 (d, J = 7.2 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H), 2.44 (s, 3H), 2.39 (s, 6H); ¹³C NMR δ 144.0, 137.0, 134.8, 130.5, 129.9, 129.1, 128.4, 126.4, 124.3, 124.1, 21.7, 20.0; MS (ESI) m/z 228 [M]⁺.

(4-chlorophenyl)(ethyl)sulfane²²⁵

Colorless oil; Yield: 86%; ¹H NMR δ 7.25 (s, 4H), 2.9 (q, J = 5.5 Hz, 2H), 1.30 (t, J = 5.5 Hz, 3H); ¹³C NMR δ 135.11, 131.7, 130.3, 128.9, 27.9, 14.2; MS (ESI) m/z 172 [M]⁺.

(4-methylphenyl)(ethyl)sulfane²²⁶

Colorless oil; Yield: 82%; ¹H NMR δ 7.56 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 7.9 Hz, 2H), 2.90 (q, J = 7.2 Hz, 2H), 2.31 (s, 3H), 1.28 (t, J = 7.4 Hz, 3H); ¹³C NMR δ 135.9, 132.7, 129.9, 129.6, 28.3, 21.0, 14.5; MS (ESI) m/z 152 [M]⁺.

Ethyl(*o*-tolyl)sulfane²²⁷

Colorless oil; Yield: 86%; ¹H NMR δ 7.23 (t, J = 6.9 Hz, 1H), 7.13-7.16 (m, 2H), 7.08 (d, J = 6.1 Hz, 1H), 2.92 (q, J = 5.5 Hz, 2H), 2.36 (s, 3H), 1.33 (t, J = 5.6 Hz, 3H); ¹³C NMR δ 137.2, 136.0, 130.0, 127.3, 126.3, 125.3, 26.7, 20.2, 14.1; MS (ESI) m/z 152 [M]⁺.

Chapter VII. References

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