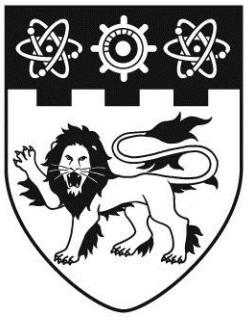

NANYANG TECHNOLOGICAL UNIVERSITY

IRON- AND COPPER-CATALYZED CHEMISTRY OF IMINOIODANES AS NOVEL SYNTHETIC STRATEGIES FOR C–N BOND FORMATION

THI MY UYEN TON

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

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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 2009 to August 2012 under the supervision of Asst. Prof. Philip Wai Hong Chan.

The work of this thesis has been directed toward the development of new iron- and copper-catalyzed chemistry of nitrogen atom transfer reactions from iminoiodanes to C=C and C−H bonds as efficient synthetic strategies to C−N bond formation. This thesis is divided into three parts:

- Part I consists of Chapter I, which gives an introduction to iron and copper catalysis and its application to aziridination and amination of C=C and C−H bonds with hypervalent iodine(III) reagents.
- Part II is aimed at exploring novel nitrogen atom transfer reactions employing the inexpensive, less-toxic and biocompatible nature of iron and copper catalysis. Chapter II details the efficient and practical iron-catalyzed synthetic route to acyl sulfonamides based on nitrene/imido insertion into the formylic C−H bond of aldehydes. The methodology is aimed to expand the reaction tolerance toward a structurally diverse set of starting aldehydes and compliment earlier works mediated by Ru(II) and Cu(I) catalysts. Detailed mechanistic studies to delineate this amination process will also be discussed. In chapter III, the intriguing conversion of 2-alkyl substituted 1,3-dicarbonyl compounds to α-acyl-β-amino

acid and 2,2-diacyl aziridine derivatives mediated by $Cu(OTf)_2$ and PhI=NTs are described. Complete control of product selectivity in the reaction is shown to be possible through slight modification of the reaction conditions. Chapter IV addresses a highly efficient copper-catalyzed amination of various 1,3-dicarbonyl compounds as a convenient and effective route to ketone-substituted α-amino acid derivatives. Chapter V presents the ligand-free iron-catalyzed α-amination of saturated *N*- and *O*-heterocyclic compounds *via* a nitrogen atom insertion into the α-C−H bond of the substrates. The synthetic utility of this methodology is exemplified by ring-opening of the α-aminated products by various nucleophiles to provide a range of substituted diamine and amino alcohol compounds.

- Part III contains experimental data (Chapter VI) and references (Chapter VII) pertaining to this thesis.

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1. "Copper(II) Triflate-Catalyzed Amination of 1,3-Dicarbonyl Compounds" Ton, T. M. U.; Himawan, F.; Chan, P. W. H. *Chem*. *Eur*. *J*. **2012**, *18*, 12020.

2. "Copper(II) Triflate-Catalyzed Amination and Aziridination of 2-Alkyl Substituted 1,3-Dicarbonyl Compounds" Ton, T. M. U.; Tejo, C.; Tiong, D. L. Y.; Chan, P. W. H. *J*. *Am*. *Chem*. *Soc*. **2012**, *134*, 7344.

3. "Transition-Metal-Catalyzed Aminations and Aziridinations of C–H and C=C Bonds with Iminoiodanes" Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem*. *Rec*. 2011, *11*, 331. (***Top 10 most accessed article in December 2011/June 2012, and most accessed in March 2012***).

4. "Iron(II)-Catalyzed Amidation of Aldehydes with Iminoiodinanes at Room Temperature and Under Microwave Assisted Conditions" Ton, T. M. U.; Tejo, C.; Tania, S.; Chang, J. W. W.; Chan, P. W. H. *J*. *Org*. *Chem*. **2011**, *76*, 4894. (***highlighted by Organic Chemistry Portal:*** *http://www.organic-chemistry.org/abstracts/lit3/306.shtm*)

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ABBREVIATIONS

Å	angström
acac	acetylacetonate
AnBOX	(*S,S*)-1,8-bis(4-(1-methylethyl)oxazolin-2-yl)anthracene
BHT	butylhydroxytoluene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
bipy	2,2′-bipyridine
Boc	*tert*-butyloxycarbonyl
Bu	butyl
cHBOX	(*S,S*)-1,2-bis((*S*)-(4-phenyl)oxazolin-2-yl)cyclohexane
^{c}Pr	cyclopropyl
Cl_3terpy	4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine
cyclam	1,4,8,11-tetraazacyclotetradecane
DBM	dibenzoylmethane
DCE	dichloroethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomer ratio
ee	enantiomer excess
eq	equivalent

esp	tetramethyl *m*-benzenedipropionic carboxylate
ESI	electrospray ionization
GC	gas chromatography
h	hour
Hoct	octanoic acid
HRMS	high-resolution mass spectrometry
H_2TDCPP	5,10,15,20-tetrakis-(2,6-dichlorophenyl) porphyrin
H_2TMP	5,10,15,20-tetramesitylporphyrin
H_2TPP	5,10,15,20-tetrakis-(phenyl)-21*H*,23*H*-porphyrin
H_2TTP	5,10,15,20-tetrakis-(4-methylphenyl)-21*H*,23*H*-porphyrin
HPLC	high performance liquid chromatography
^{i}Pr	isopropyl
IPr	1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene
^{i}Pr$_3$tacn	1,4,7-triisopropyl-1,4,7-triazacyclononane
IR	infrared
KIE	kinetic isotope effect
Mbs	methylbenzylsulfonyl
Me	methyl
min	minute
m.p.	melting point
MS	molecular sieves
MW	microwave
NHC	*N*-heterocyclic carbene

NMR	nuclear magnetic resonance
^{n}Pr	*n*-propyl
Ns	*p*-nitrobenzenesulfonyl
Nu	nucleophile
OAc	acetocy
OMe	methoxy
OTf	trifluoromethanesulfonate
PBN	*N*-tert-butyl-*α*-phenylnitrone
Ph	phenyl
phen	phenanthroline
Por	porphyrin
ppm	parts per million
py	pyridine
pyBOX	2,6-bis[4-phenyl-2-oxazolinyl]pyridine
r.t.	room temperature
Ses	trimethylethylsilylsulfonyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
tacn	triazacyclononane
^{t}Bu	*tert*-butyl
Tces	trichloroethylsulfonyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
terpy	2,2′:6′,2″-terpyridine
tfac	trifluoroacetylacetonate

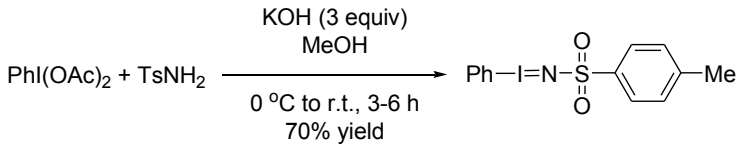
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tp′	hydrotris(3,5-dimethyl-1-pyrazolyl)borate
Tp^{Br3}	hydrotris(3,4,5-tribromo-1-pyrazolyl)borate
Ts	*p*-toluenesulfonyl
α	alpha
β	beta
γ	gamma
δ	delta
ε	epsilon
ζ	zeta
η	eta
μ	micro
π	pi
ρ	rho
σ	sigma

Chapter I. Iron- and Copper-Catalyzed Nitrogen Atom Addition and Insertion to C=C and C−H bonds with Iminoiodanes

1.1 Introduction

Carbon-nitrogen bond formation is a fundamental activity in organic chemistry because of the immense importance of nitrogen containing compounds in Nature, and the pharmaceutical, agrochemistry, fine chemical and material industries.[1] Added to this is the ability of nitrogen containing molecules to serve as building blocks in a broad spectrum of organic transformations and applications.[2] It is therefore not surprising to find a myriad of synthetic methods developed for the formation of the C−N bond and the field continues to be actively pursued. Conventionally, the introduction of the amino group has mostly relied upon the addition or substitution of a nitrogen nucleophile to a carbon electrophile.[3] Transition-metal catalysis has also contributed significantly to this field by mediating reactions such as the addition of a nitrogen nucleophile to the π bond of alkenes, alkynes and allenes and their coupling with aryl and vinyl halides.[4] However, the main drawback of these reactions is the required activation of the electrophile through pre-installation of reactive groups and, in some cases, the need for harsh reaction conditions that may lead to competitive by-product formation. While functional group protection chemistry has been found to be useful in addressing these shortcomings, a consequence is the increase in the number of synthetic steps, which is time consuming and leads to poor atom economy. Therefore, there remains a need to develop new methodologies that can install an amino group at strategic positions of a molecule in an efficient and selective manner under mild conditions.

One approach that has received an increasing amount of attention over the years is transition-metal-catalyzed nitrene/imido transfer reactions to C−H and C=C bonds. Until recently, this approach to C−N bond formation has been less well explored than the analogous transition-metal-catalyzed carbene and oxo transfer reactions. One reason for this lack of progress in this field was due to the scarcity of convenient nitrogen sources to facilitate such nitrogen transfer transformations. This situation changed in 1975 with a report by Yamada and co-workers showing a method for the straightforward and practical synthesis of (*p*-toluenesulfonyl)iminophenyliodinane (PhI=NTs) from (diacetoxyiodo)benzene ($PhI(OAc)_2$) and *p*-toluenesulfonamide ($TsNH_2$).[5] With the realization of this hypervalent iodine(III) compound as a useful and practical nitrogen source, the chemistry of transition-metal-catalyzed amination and aziridination of C−H and C=C bonds has witnessed an immense amount of progress.[6,7]



Scheme 1.1 Synthesis of PhI=NTs

The utility of these synthetic approaches to install the C−N bond has also been exemplified by its application in the construction of a number of complex natural products (Figure 1.1).[8] Despite these remarkable advances, much of the work within this area has been focused on using rhodium or ruthenium complexes as the catalyst. While

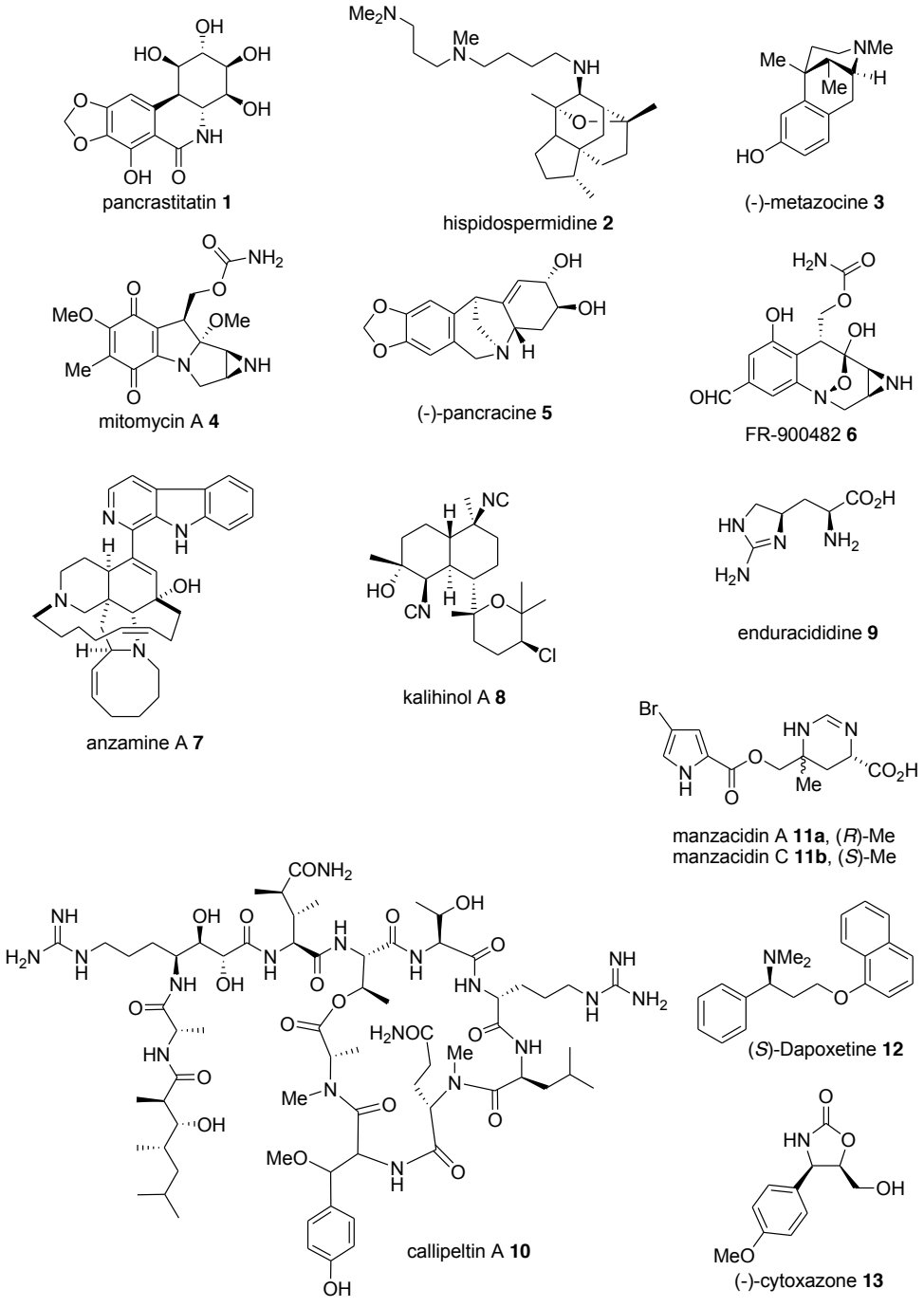
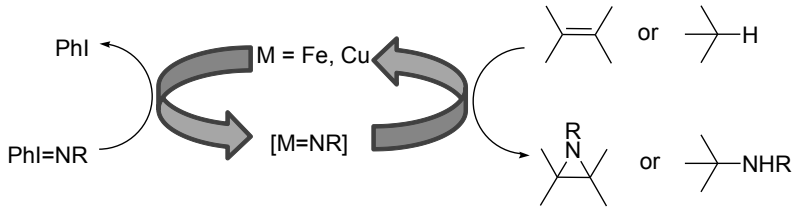


Figure 1.1 Application of transition-metal-catalyzed nitrene/imido transfer methodologies to the synthesis of natural products

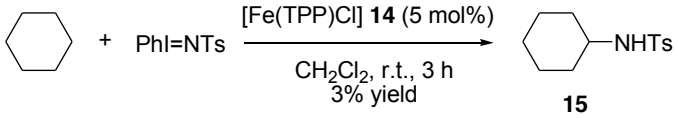
such catalytic systems were shown to be highly efficient, affording high product yields and applicable to a wide variety of substrates, their high cost and low natural abundance has lessened their potential to scale-up processes. A key challenge in this field has thus been to develop this type of reaction for C−N bond formation that can make use of inexpensive, readily available and more biocompatible metal catalysts such as iron and copper while maintaining comparable efficiency and selectivity. The focal point of this Introduction will be on the advances that have been made in the development of iron- and copper-catalyzed aziridination and amination of C=C and C−H bonds with iminoiodanes as nitrene/imido sources (Scheme 1.2).



Scheme 1.2 Iron- and copper-catalyzed nitrogen atom transfer to C=C and C−H bonds

1.2 Early Advances in Iron- and Copper-Catalyzed Nitrogen Atom Transfer Reactions

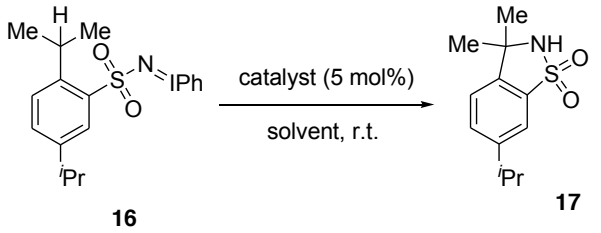
In 1982, Breslow and Gellman first explored the utility of PhI=NTs in transition-metal-catalyzed nitrene/imido insertion processes.[9] In this seminal work, the amination of cyclohexane mediated by [Fe(TPP)Cl] **14** (H_2TPP = 5,10,15,20-tetrakis-(phenyl)-21*H*,23*H*-porphyrin) in CH_2Cl_2 was reported to afford *N*-cyclohexyl-*p*-toluenesulfonamide **15** in a low yield of 3% (Scheme 1.3).



Scheme 1.3 [Fe(TPP)Cl] **14**-catalyzed amination of cyclohexane

Following this initial success, the analogous intramolecular nitrene/imido insertion of the 2,5-diisopropyl substituted iminoiodane **16** mediated by the iron complexes **14** or **18** or $FeCl_3$ as the catalyst was investigated and shown to be more efficient, furnishing the corresponding cyclic sulfonamide adduct **17** in 16-77% yield based on HPLC analysis (Table 1.1).[10] Both MeCN and CH_2Cl_2 were shown to be suitable solvents for the nitrene/imido insertion reaction.

Table 1.1 Iron-catalyzed intramolecular amination reaction of the 2,5-diisopropyl substituted iminoiodane **16**

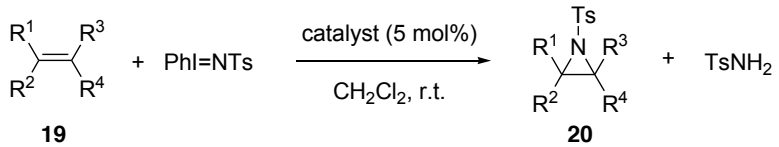


Entry	Catalyst	Solvent	Yield (%)
1	[Fe(TPP)Cl] **14**	MeCN	77
2	[Fe(TPP)Cl] **14**	CH_2Cl_2	35
3	[Fe(cyclam)Cl_2] **18**[a]	MeCN	42
4	$FeCl_3$	MeCN	16

[a]cyclam = 1,4,8,11- tetraazacyclotetradecane

At about the same time, Mansuy and co-workers communicated the first example of iron(III) porphyrin-catalyzed intermolecular nitrogen atom addition to C=C bonds with PhI=NTs (Table 1.2).[11,12] In this work, the aziridination process with a variety of aromatic alkenes **19** were shown to proceed smoothly and afford the corresponding products **20** in 21-90% yield.

Table 1.2 Iron(III) porphyrin-catalyzed aziridination reaction of alkenes **19** with PhI=NTs



19
R^1 - R^4 = H, Ph

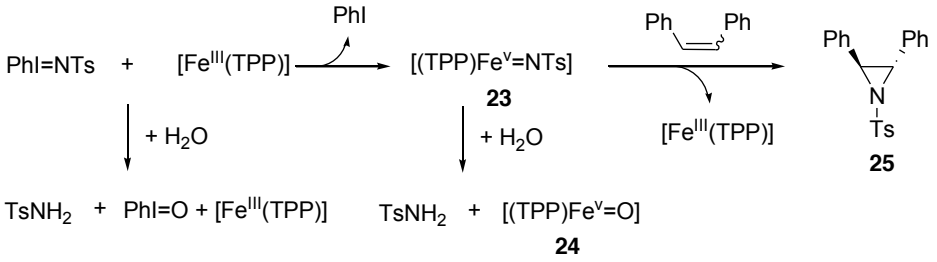
20

Entry	Catalyst	Yield (%)
1	[Fe(TPP)Cl] **14**	21-55
2	[Fe(TPP)(ClO_4)] **21**	24-57
3	[Fe(TDCPP)(ClO_4)] **22**[a]	36-90

[a] H_2TDCPP = 5,10,15,20-tetrakis-(2,6-dichlorophenyl)-21*H*,23*H*-porphyrin

An investigation into the reaction mechanism revealed that H_2O played a crucial role in the nitrene/imido transfer process (Scheme 1.4). In the presence of [Fe(TPP)(Cl)], it was thought that the role of H_2O was to hydrolyse PhI=NTs into PhI=O and $TsNH_2$ or facilitate the fast exchange of the oxygen atom with the NTs moiety of a possible [Fe^V=NTs] **23** intermediate complex to form $TsNH_2$ and the [(TPP)Fe^V=O] complex (Scheme 1.4). This led to the conclusion that the metal-catalyzed nitrene/imido transfer process required strict anhydrous conditions so as to achieve optimal product yields.

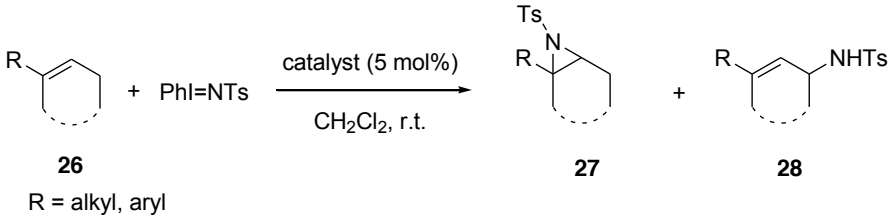
Additionally, it was noted that when the aziridination reaction was carried out with *cis*- and *trans*-stilbene as substrates, only the *trans*-*N*-tosyl-2,3-diphenylaziridine was obtained as the product.[11,12] The lack of stereospecificity observed in this reaction led to the suggestion of a radical stepwise mechanism occurred during the nitrogen atom transfer process.



Scheme 1.4 Catalytic cycle of Fe^{III}(TPP)-catalyzed aziridination of 1,2-diphenylethene

Iron(III) porphyrin complexes were also shown to convert aliphatic alkenes to their respective aziridines in moderate yields but with low to moderate chemoselectivity as shown in Table 1.3.[12,13] In both the aziridination and amination processes, the reactions were postulated to occur *via* formation of the high valent complexes [Fe^{V}=NTs] **29** (Scheme 1.5). This iron-nitrene complex was thought to have free radical like reactivity that could undergo a hydrogen abstraction/radical rebound process to give the intermediates **31** or **33**. The corresponding allylic amine **28** was believed to be obtained by rapid recombination of **31** with radical **32** whereas *N*-tosylaziridines **27** was formed *via* direct oxidative transfer of the NTs moiety to the intermediate carbon-centred radical (Scheme 1.5, route a) or *via* a four-membered Fe−C−C−N metallocycle (Scheme 1.5, route b).

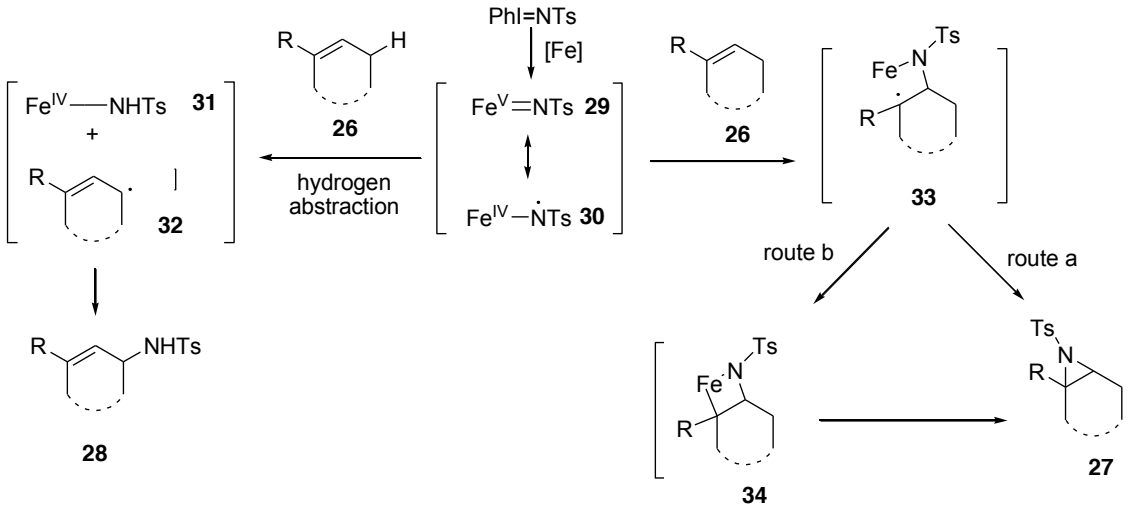
Table 1.3 Iron(III) porphyrin-catalyzed aziridination and amination reaction of alkenes **26** with PhI=NTs



26 **27** **28**

R = alkyl, aryl

Entry	Catalyst	Yield (%)	
		Aziridines **27**	Allylic amides **28**
1	[Fe(TPP)Cl] **14**	3-13	4-6
2	[Fe(TPP)(ClO_4)] **21**	13-28	2-30
3	[Fe(TDCPP)(ClO_4)] **22**	22-36	1-23

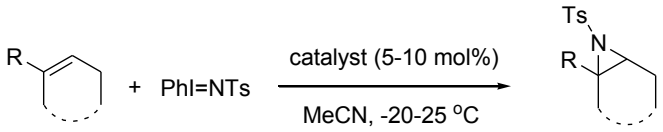


Scheme 1.5 Proposed mechanism for iron(III) porphyrin-catalyzed aziridination/amination reactions

It was not until the beginning of the 1990s when the first examples of Cu(I) and Cu(II)-catalyzed aziridination of alkenes using PhI=NTs as the nitrogen source was

reported by Evans and co-workers (Table 1.4).[14,15] In these works, the copper catalysts shown in Table 1.4 were found to mediate the reaction of a wide variety of substituted electron-rich as well as electron-deficient alkenes **26** with PhI=NTs to afford the corresponding aziridine products **27** in 23-95% yield. Notably, the catalytic copper systems were showed to be chemoselective as no allylic amination products were obtained for reactions with alkenes containing an aliphatic side chain. These studies also found that copper was superior to other metal complexes such as [Mn(TPP)Cl], [Fe(TPP)Cl], $Rh_2(OAc)_4$ and $Co(acac)_2$ with regard to the generality of the substrate scope. Futher investigations showed that reaction stereospecificity was both catalyst and substrate dependent for *cis*- and *trans*-disubstituted alkenes. On the other hand, the stereospecificity was found to be retained for alkyl substituted alkenes. These findings together with a radical clock experiment led to the suggestion that the aziridination

Table 1.4 Copper-catalyzed aziridination reaction of alkenes **26** with PhI=NTs



26

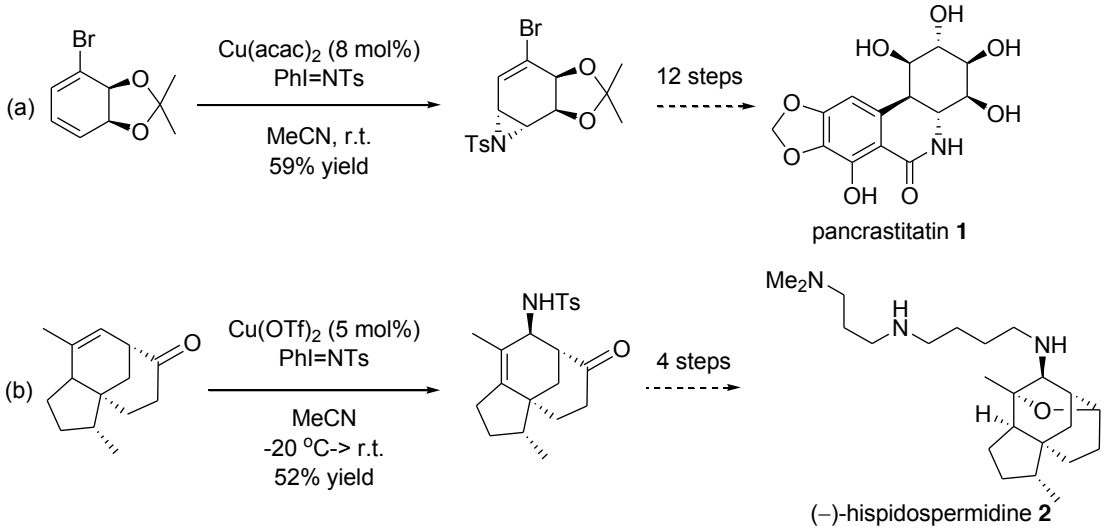
R = alkyl, aryl

27

Entry	Catalyst	Yield (%)
1	$Cu(MeCN)_4ClO_4$	23-89
2	$Cu(acac)_2$	30-95
3	$CuClO_4$	45-90
4	$Cu(OTf)_2$	40-92

reaction proceeded *via* a concerted mechanism for this class of alkene compounds.

In general, these early works by the groups of Breslow, Mansuy and Evans revealed that iron and copper could be utilized as efficient catalysts to mediate nitrogen atom transfer to C=C and C−H bonds with PhI=NTs as the nitrogen source. The mechanistic experiments conducted in these works provided many valuable insights on how processes occurred that enabled further advances in the field, particularly in terms of understanding and improving the efficiency and selectivity of new catalystic systems. Indeed, a reflection of this is the application of these early developed methodologies to the synthesis of natural products demonstrated by the groups of Hudlicky and Overman in their respective total synthesis of pancrastitatin **1** and (-)-hispidospermidine **2** (Scheme 1.6).[16]



Scheme 1.6 Synthesis of the natural products pancrastitatin **1** and (-)-hispidospermidine **2** using copper-catalyzed nitrene/imido transfer as the key step

1.3 Iron- and Copper-Catalyzed Aziridination of Alkenes

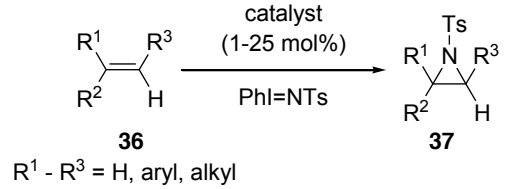
1.3.1 Iron- and Copper-Catalyzed Intermolecular Aziridination of Alkenes with PhI=NTs

Following the pioneering works of Evans and co-workers, the group of Pérez revealed that [Tp′Cu(C_2H_4)] **35a** (Tp′ = hydrotris(3,5-dimethyl-1-pyrazolyl)borate, Figure 1.2a) could effectively transfer the nitrene/imido moiety from PhI=NTs precursor into alkenes **36** to afford the corresponding *N*-tosylaziridine products **37** in 40-90% yield (Table 1.5, entry 1).[17] To gain an insight into the mechanism, the relative rates of aziridination of a series of para-substituted styrenes with [Tp′Cu(C_2H_4)] **35a** and PhI=NTs were measured.[18] This led to experimental data could fit into the two term equation $\log(k_X/k_H) = \rho^+\sigma^+ + \rho^\cdot\sigma^\cdot$ to provide values of $\rho^+ = -0.28 \pm 0.06$ (polar contribution) and $\rho^\cdot = +0.34 \pm 0.13$ (radical contribution). This led to the posited involvement of an electrophilic, nitrogen-centered radical copper nitrene/imido species.

In their efforts to develop the first heterogenous version of the reaction, Hutchings and co-workers described copper-exchanged zeolite [CuHY] **38** (Y = zeolite) to efficiently mediate alkene aziridination (Table 1.5, entry 2).[19] The reactions were shown to proceed smoothly to afford the desired aziridine products in 44-90% yield. In addition, the aziridination process was shown to occur within the intracrystalline spaces of CuHY **38** and such properties could be exploited to developed catalytic systems with high regioselectivity by constructing zeolites with a range of different pore sizes.

Consideration of the proposed electrophilic copper nitrene/imido species as the active intermediate in copper-catalyzed alkene aziridinations by Pérez and co-workers,[18] the group of Halfen envisioned that such an intermediate could be stabilized by electron-rich,

Table 1.5 Iron- and copper-catalyzed intermolecular aziridination of alkenes **36** with PhI=NTs



Entry	Catalyst	Yield (%)
1	[Tp′Cu(C_2H_4)] **35a**	40-90
2	[CuHY] **38**	44-90
3	[(^{i}Pr$_3$tacn)Cu(OTf)$_2$] **39**	25-96
4	copper(I) β-diketiminate **40**	14-98
5	copper(I) pyridinophane **41a**,**b**	59-96
6	[(η^5-C_5H_5)Fe(CO)$_2$(THF)(BF_4)] **42**	7-85
7	[Fe(Cl_3terpy)] **43**	68-97
8	Fe(OTf)$_2$	24-90

sterically hindered ancillary nitrogen-based ligands (Table 1.5, entry 3). The presence of other labile ligands or counterions was also thought to expedite the formation of the copper nitrene/imido species from a copper pre-catalyst and PhI=NTs.[20] In this seminal work, the nitrogen-based complex [(^{i}Pr$_3$tacn)Cu(OTf)$_2$] **39** (Figure 1.2b) was found to effectively mediate nitrogen atom transfer reactions to furnish the corresponding aziridine **37** in 25-96% yield. Subsequently, similar catalytic copper systems were also reported by the group of Vedernikov and Caulton,[21] and Warren[22]. In these respective works, the copper(I) pyridinophane **40**,[21] and copper(I) β-diketiminates **41a** and **41b**[22] were shown

to convert a range of alkenes to the corresponding products **37** in moderate to excellent yields (Figure 1.2c,d; Table 1.5 entries 4-5).

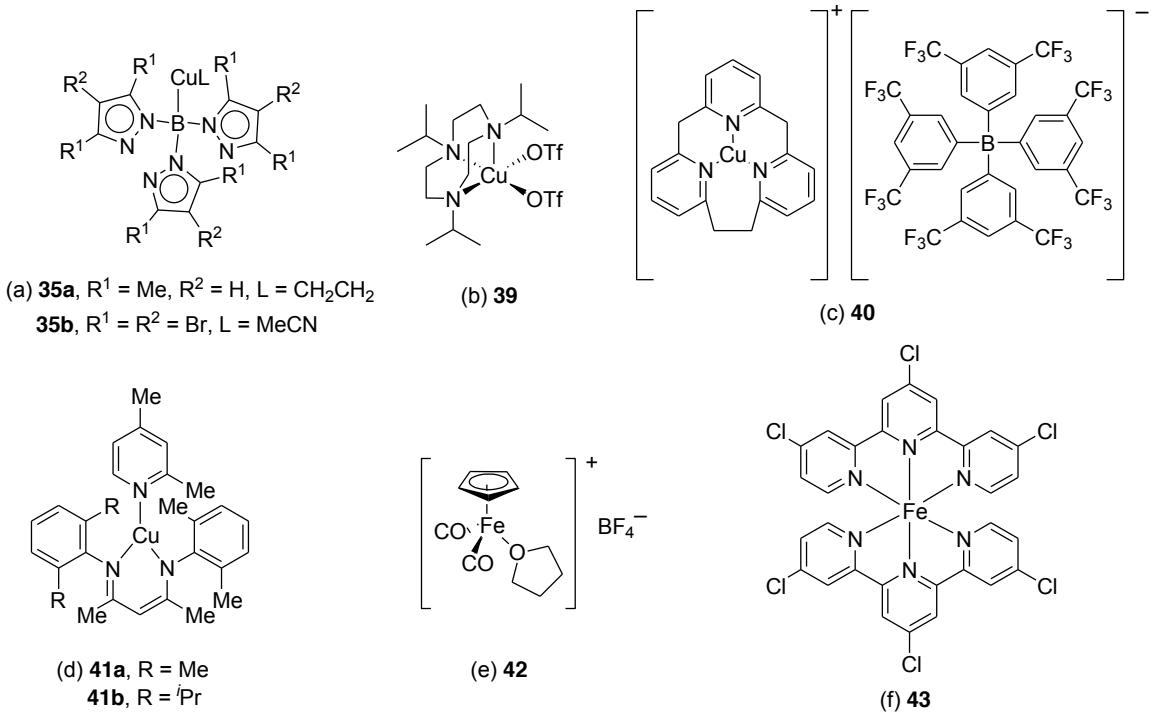


Figure 1.2 Iron- and copper catalysts used in aziridination of alkenes with PhI=NTs

Following these works, Hossain and co-workers reported that the Lewis acidic iron complex [(η^5-C_5H_5)Fe(CO)$_2$(THF)(BF_4)] **42** could mediate the aziridination of a variety of alkenes to furnish the corresponding products in 7-85% yield (Figure 1.2e and Table 1.5, entry 6).[23] However, a major disadvantage of this catalytic method was a substrate scope limited to only phenyl substituted alkenes. In view of this limitation, Che and co-workers subsequently developed a more efficient and robust protocol that made use of [Fe(Cl_3terpy)$_2$] **43** (Cl_3terpy = 4,4′,4″-tri-*tert*-butyl-2,2′:6′2″-terpyridine, Figure 1.2f) as the catalyst to perform the addition of the NTs moiety to C=C bonds (Table 1.5, entry 7).

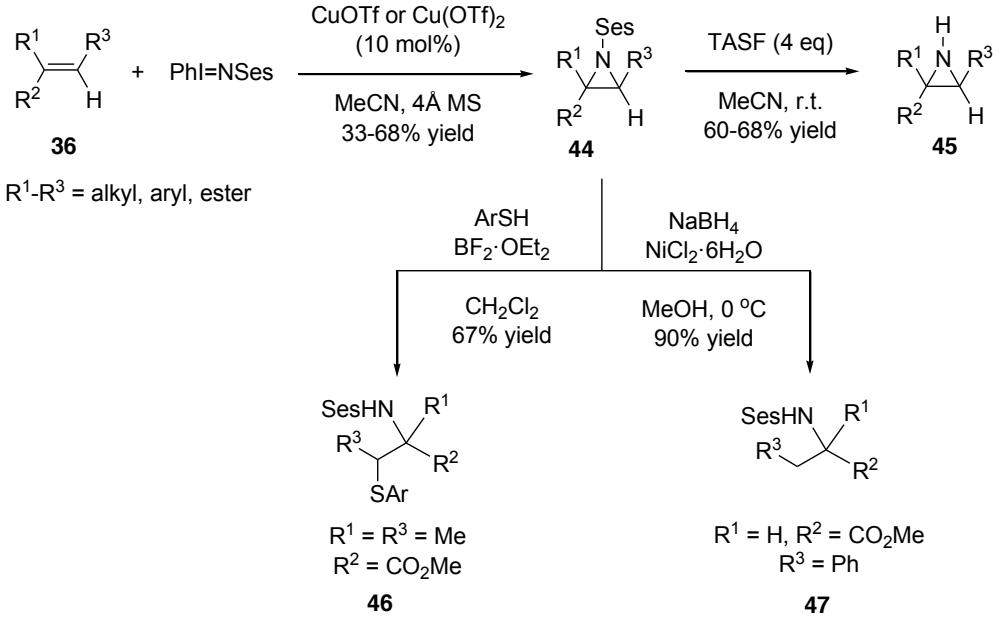
[24] The methodology was shown to be applicable to a wider range of alkenes and gave the corresponding products in 68-97% yield. During the course of this study, the ionic $[Fe(Cl_3terpy)_2(NTs)]^{2+}$ intermediate ion was detected by ESI-MS measurement.

At about the same time, Bolm and co-workers demonstrated an iron-catalyzed version of this reaction that gave the corresponding aziridine products in 24-90% yield (Table 1.5, entry 8).[25] The lack of stereospecificity observed in this $Fe(OTf)_2$-catalyzed reaction led to the suggestion that the nitrogen atom transfer process might occur *via* a radical intermediate.

1.3.2 Intermolecular Aziridination of Alkenes with Other Iminoiodanes

Until 1999, most of the transition-metal-catalyzed nitrogen transfer reactions had relied on [*N*-(arenesulfonyl)imino]phenyliodinanes ($PhI{=}NSO_2Ar$) as the nitrogen sources. Although several methods had been developed to deprotect the aryl sulfonamide groups,[26] their cleavage was sometimes shown to be troublesome.[27] In view of this shortcoming, the laboratory of Dodd and Dauban demonstrated the first non-aryl sulfonamide-based iminoiodane PhI=NSes ((trimethylsilylethanesulfonyl) iminophenyliodinane) as a new nitrogen precursor in alkene aziridination reactions (Scheme 1.7).[28] In the presence of CuOTf or $Cu(OTf)_2$ as the catalyst, the reaction was shown to be applicable to a series of alkenes **36** to afford the corresponding aziridines **44** in moderate to good yields of 33-68%. These product yields were found to be comparable to those afforded for the analogous copper-catalyzed aziridination reactions of alkenes with PhI=NTs as the nitrogen source. Subsequent deprotection of the Ses group with TASF (TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate) was shown to

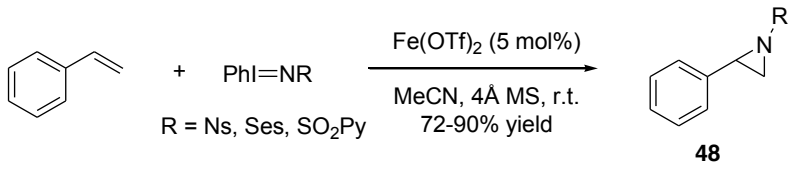
occur smoothly under mild conditions to give the aziridine products **45** in 60-68% yield. The synthetic utility of this methodology was further demonstrated by ring-opening of the aziridine **44** with nucleophiles such as sodium borohydride and arylthiophenols to give the corresponding 1,2-difunctionalized amines **46** and **47** in 67-90% yield.



Scheme 1.7 Copper-catalyzed aziridination with PhI=NSes followed by deprotection or ring-opening by nucleophiles

During the course of their studies on $Fe(OTf)_2$-catalyzed alkene aziridinations with PhI=NTs, Bolm and co-workers described that the methodology could be applied to other nitrogen carriers such as PhI=NNs ((*p*-nitrophenylsulfonyl)iminophenyliodinane), PhI=NSes and PhI=NSO_2Py (5-methyl-2-pyridinesulfonyliminoiodane) (Scheme 1.8). Reactions with styrene as the substrate were shown to proceed well with a variety of

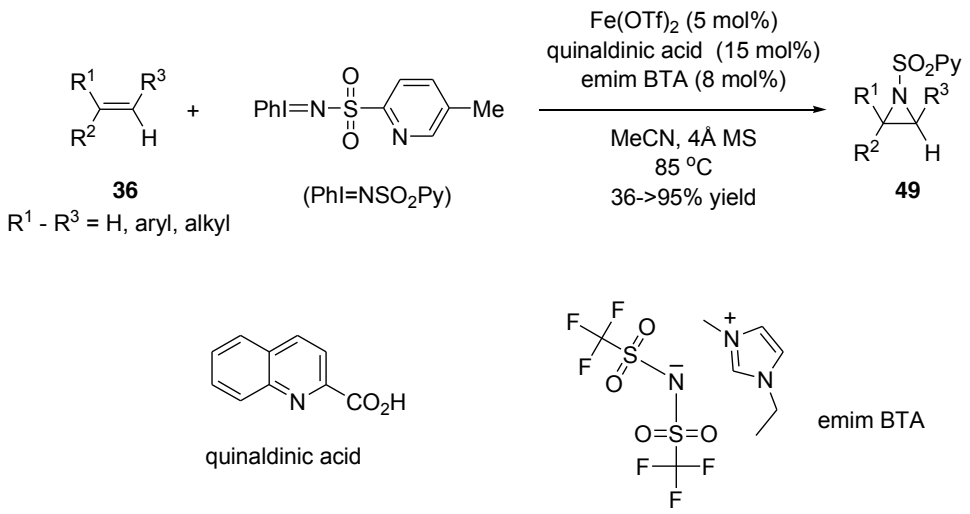
nitrogen sources and gave the corresponding aziridine products **48** in good to excellent yields of 72-90%.[25]



Scheme 1.8 $Fe(OTf)_2$-catalyzed aziridination with other iminoiodanes

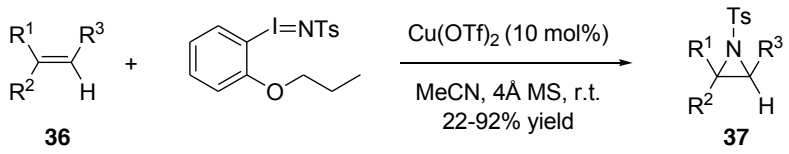
Following this work, a more practical and efficient version of this aziridination reaction was realized by the same group (Scheme 1.9).[29] It was found that addition of quinaldinic acid as a nitrogen-based ligand and ethylmethylimidazolium bis((trifluoromethyl)sulfonyl) amide) (emim BTA) as an additive would significantly enhance product yields. Furthermore, $PhI{=}NSO_2Py$ was shown to be the most effective nitrogen source as it was thought to coordinate to the metal catalyst to facilitate the nitrene/imido transfer process.[30] In this work, aziridination of a range of alkenes was shown to proceed smoothly and give the aziridine products **49** in 36->95% yield.

While iminoiodanes had been extensively used in nitrene/imido transfer processes, one of the major drawbacks of using such reagents was their insolubility in most of organic solvents. This is due to strong intermolecular I···O secondary bonding in these molecules that leads to the creation of a three-dimensional polymeric structure.[31] To overcome this hurdle, the groups of Zhdankin and Nemykin elegantly made use of an



Scheme 1.9 $Fe(OTf)_2$-catalyzed aziridination of alkenes with $PhI{=}NSO_2Py$ as nitrogen source

alkoxy group pendant at *ortho*-position of the phenyl ring of the iminoiodane to promote preferential intramolecular I···O bonding interaction (Scheme 1.10). The change in this structural motif was shown to significantly improve the solubility.[32,33] Application of this highly soluble iminoiodane to the aziridination reactions with $Cu(OTf)_2$ as the catalyst was shown to be efficient with moderate to excellent product yields of 22-92% obtained.



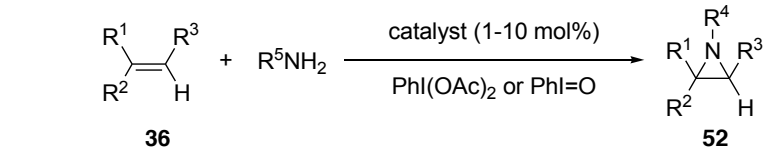
Scheme 1.10 $Cu(OTf)_2$-catalyzed aziridination of alkenes with *ortho*-alkoxy iminoiodane

1.3.3 Intermolecular Aziridination of Alkenes with Sulfonamides and an Hypervalent Iodine(III) Oxidant

Although demonstrated to be an efficient nitrogen source for transition-metal-catalyzed aziridination reactions, a major limitation of iminoiodanes has been the need to pre-form the reagent from a sulfonamide and a hypervalent iodine(III) oxidant, which can be time-consuming and arduous. Added to this, iminoiodanes have been shown to have a short shelf-life and can be explosive. In this regard, synthetic methodologies that made use of iminoiodanes generated *in situ* from stable and commercially available starting materials would be highly desirable.

The realization of this approach was first reported by Dodd, Dauban and co-workers who communicated that $Cu(MeCN)_4PF_6$ could act as a catalyst in the intermolecular aziridination with PhI=O as the oxidant and sulfonamides as nitrogen source (Table 1.6, entry 1). Using this method, the conversion of a range of alkenes to their corresponding aziridine products was obtained in 40-78% yield.[34] Importantly, the efficiency of this combination was found to be comparable to literature values obtained when PhI=NTs was employed as the nitrogen source. It was also found that the aziridination process tolerated the presence of H_2O and an excess amount of $TsNH_2$ was not necessary. These findings led to the hypothesis that the iminoiodane was formed *in situ* from $TsNH_2$ and PhI=O, and reacted rapidly with the catalyst to form a putative reactive copper-nitrene/imido species **51**. This active intermediate would then transfer the nirene/imido moiety to the C=C bond or degrade to release $TsNH_2$ as a by-product (Scheme 1.11).

Table 1.6 Iron- and copper-catalyzed aziridination of alkenes **36** with nitrogen sources in the presence of a hypervalent iodine(III) oxidant

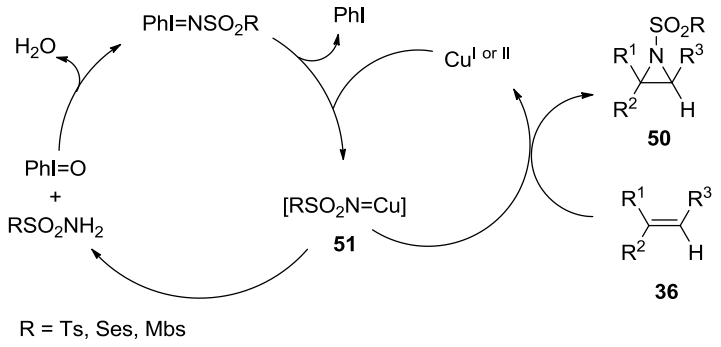


36 **52**

R^1 - R^3 = H, aryl, alkyl, ester

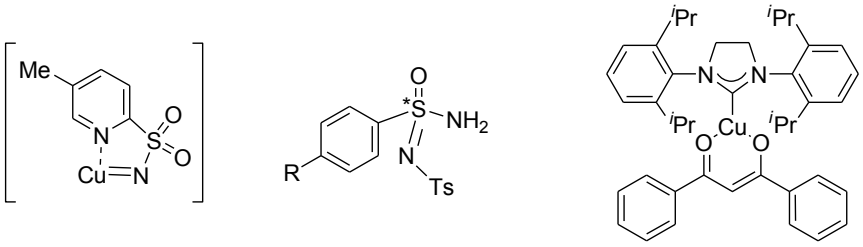
Entry	Catalyst	R^5NH_2	Oxidant	Yield (%)
1	$Cu(MeCN)_4PF_6$	$TsNH_2$, $SesNH_2$ or $MbsNH_2$[a]	PhI=O	40-78
2	[Cu(tfac)$_2$] **53**	$PySO_2NH_2$	$PhI(OAc)_2$	44-84
3	$Cu(MeCN)_4PF_6$	**55a**	PhI=O	35-96
4	CuOTf	**55b**	PhI=O	48-95
5	[IPrCu(DBM)] **56**	$TcesNH_2$	PhI=O	35-82
6	CuI	$TsNH_2$ or $TcesNH_2$	PhI=O	40-99
7	$Fe(OTf)_2$	$TsNH_2$, $NsNH_2$ or **55a**	$PhI(OAc)_2$ PhI=O	58-66

[a]Mbs = methylbenzylsulfonyl



Scheme 1.11 Proposed mechanism for copper-catalyzed aziridination of alkenes with sulfonamides and PhI=O

Prior to the work of Bolm and co-workers with $PhI{=}NSO_2Py$,[25,29] Chang and co-workers successfully demonstrated the use of $[Cu(tfac)_2]$ **53** (tfac = trifluoroacetylacetonate) to catalyze aziridination of alkenes with 5-methyl-2-pyridinesulfonamide ($PySO_2NH_2$) as the nitrogen source and $PhI(OAc)_2$ as the oxidant (Table 1.6, entry 2).[30b] In this work, coordination of copper catalyst to the pyridyl *N* atom of 2-pyridinesulfonamides was proposed to be the driving force for the transformation (Figure 1.3a). This chelation-assisted strategy was found to promote the conversion of alkenes to the corresponding aziridines in moderate to good yields of 44-84%. Kinetic studies revealed that the transfer of nitrogen atom from the copper nitrene/imido intermediate to the alkene was most probably the rate-limiting process and the final step was likely to take place *via* a stepwise sequence involving radical species. In addition, the reaction was found to be second order with regard to the concentration of the copper catalyst, which suggested that the C=C bond of the alkene was likely to be coordinated to a second copper species.[30a]



(a) **54** (b) **55a**, R = Me; **55b**, R = NO_2 (c) **56**

Figure 1.3 (a) Copper nitrene/imido species **54**, (b) sulfonimidamide **55** and (c) [IPrCu(DBM)] **56**

Dauban, Dodd and co-workers next demonstrated diastereoselective alkene aziridinations could be achieved through the use of a chiral iminoiodane generated *in situ* from reaction of the chiral sulfonimidamide **55a** with PhI=O (Table 1.6, entry 3).[35,36] By employing $Cu(MeCN)_4PF_6$ as a suitable catalyst, a variety of alkenes **36** were converted to the corresponding aziridine products in 35-96% yield and with diastereomeric excesses (d.e.) of up to 60%.[35] A more efficient version of this method was later realized with a combination of CuOTf, chiral sulfonimidamide **55b**, and PhI=O (Table 1.6, entry 4). Good levels of asymmetric induction were obtained in the case of electron-poor alkenes, with de values of up to 94% obtained.[36]

Apella and co-workers subsequently showed the *N*-heterocyclic carbene (NHC) copper complex [IPrCu(DBM)] **56** (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, DBM = dibenzoylmethane, Figure 1.3c) to be an effective catalyst for the aziridination of aliphatic alkenes with PhI=O and $TcesNH_2$ (trichloroethoxysulfonamide) (Table 1.6, entry 5).[37] In this work, the scope of the reaction was found to be broad with a variety of substrates found to provide the corresponding aziridine products in moderate to high yields. In examples where competitive allylic C−H insertion could be a potential problem such as in cyclopentene and cyclohexene, the reactions were demonstrated to work well and gave the aziridine products in 43-57% yield along with the allylic aminated by-products in 7 and 10% yield. Following this work, Chan and co-workers reported CuI-catalyzed alkene aziridination with $TsNH_2$ or $TcesNH_2$ as the nitrogen source and PhI=O as the oxidant (Table 1.6, entry 6).[38] This catalytic method was found to be influenced by both electronic and steric factors. However, a main limitation of this catalytic approach was that the substrate scope was limited to aryl substituted alkenes.

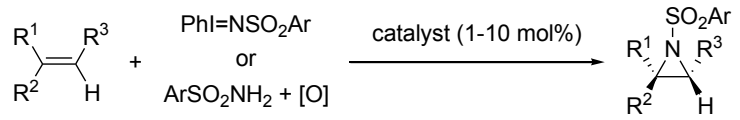
Recently, Bolm and co-workers demonstrated that the iron(II) salt $Fe(OTf)_2$ could be employed as a suitable catalyst to mediate alkene aziridinations with iminoiodanes formed *in situ* from $TsNH_2$, $NsNH_2$ or **55a** and $PhI(OAc)_2$ or PhI=O (Table 1.6, entry 7).[25] In this work, a variety of alkenes were mediated to give the aziridine products in moderate yields of 58-66%.

1.3.4 Intermolecular Asymmetric Aziridination of Alkenes

As a part of their ongoing studies, Evans and co-workers anticipated that chiral 4,4'-disubstituted bis(oxazoline) ligands **57a-c** shown in Figure 1.4a, which had been reported to be excellent ligands for copper-catalyzed alkene cyclopropanations,[39] might also be efficient chiral ligands for inducing enantioselective aziridinations (Table 1.7, entry 1). Initial studies toward this asymmetric process revealed that ligand architecture, solvent effects, and metal sources played important roles in the reaction enantioselectivity. In the presence of CuOTf and chiral bis(oxazoline) ligand **57a-c**, *trans*-aryl substituted alkenes were found to give the corresponding aziridine products **58** in up to 89% yield with enantioselectivities up to 97% ee.[40]

At about the same time, Jacobsen and co-workers demonstrated that the combination of CuOTf and Schiff base ligand **59** to selectively catalyze the aziridination reactions of various alkenes (Figure 1.4b, Table 1.7, entry 2).[41] The aziridine products were furnished in 50-79% yield and with ee values of 30->98%. In this work, the chiral catalytic system was found to be particularly efficient for *cis*-alkenes, and complimented the findings of Evans and co-workers for *trans*-substrates.[42] However, the reaction was shown to be nonstereospecific, and this was thought to be partially responsible for the diminished

Table 1.7 Iron- and copper-catalyzed asymmetric aziridination of alkenes **36**



36 **58**

R^1 - R^3 = H, aryl, alkyl, ester

Ar = *p*-NO_2Ph or *p*-MePh

Entry	Catalyst + Ligand	Yield (%)	Ee (%)
1	CuOTf + **57a-c**	16-89	19-97
2	CuOTf + **59**	50-79	30->98
3	[CuHY] **38** + **57a**	8-87	29-95
4	$Cu(MeCN)_4ClO_4$ + **60**	22-92	11-97
5	$Cu(MeCN)_4BF_4$ + **61**	32-89	88-98
6	$Cu(MeCN)_4ClO_4$ + **57b**	43-95	32-72
7	CuOTf + **62**/**63**	38-92	68->99
8	$Fe(OTf)_2$ + **64**	40-75	6-40

enantioselectivities obtained.[43] Subsequent works by the same group with $CuPF_6$ and ligand **59** as the catalytic system showed that the enantioselectivities observed were independent of the aryl substituents of the iminoiodanes.[44] The result led to the suggestion of a copper nitrene/imido intermediate in which ArI is fully dissociated from the active species. In addition, the enantioselectivity of the reaction with PhI=NTs was reported to match that obtained with TsN_3/hν, which provided evidence for a common discrete copper nitrene/imido species.

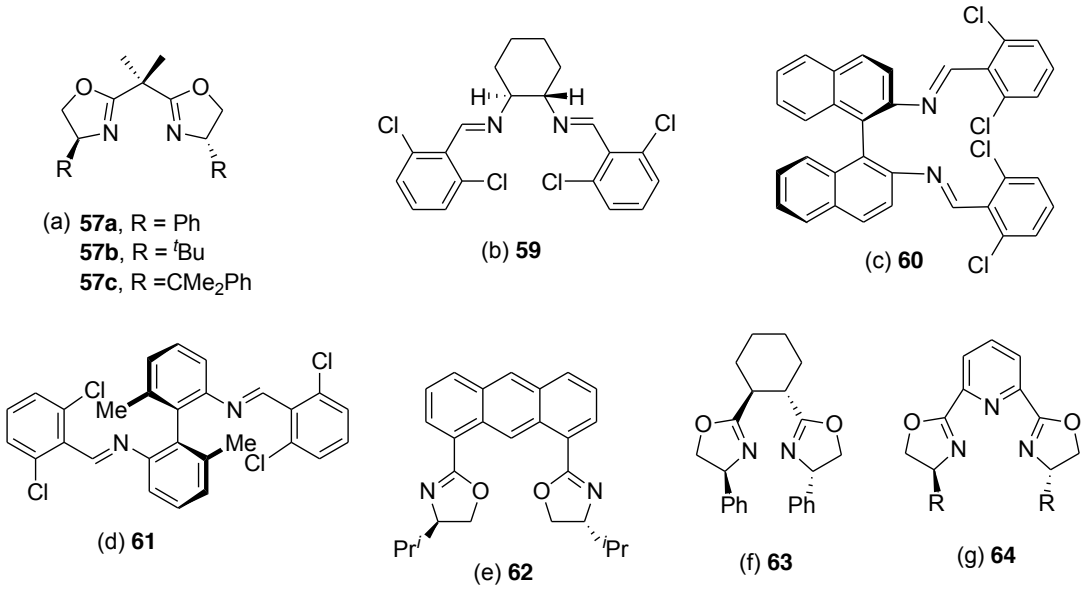


Figure 1.4 Chiral ligands in copper-catalyzed asymmetric aziridination reactions

Following initial works on heterogeneous copper-catalyzed aziridinations, Hutchings and co-workers realized that the enantioselectivities could be accomplished with CuHY **38** and the chiral bis(oxazoline) ligand **57a** (Table 1.7, entry 3).[45] The highest ee value of 61% was obtained when the reaction was carried out with PhI=NTs in the presence of this heterogenous catalytic system. Interestingly, switching from PhI=NTs to PhI=NNs was shown to enhance product ee value to 95%.[46] The ratio of the nitrogen source to alkene was also shown to be an important factor in controlling both product yields and enantiopurity of the aziridines furnished.

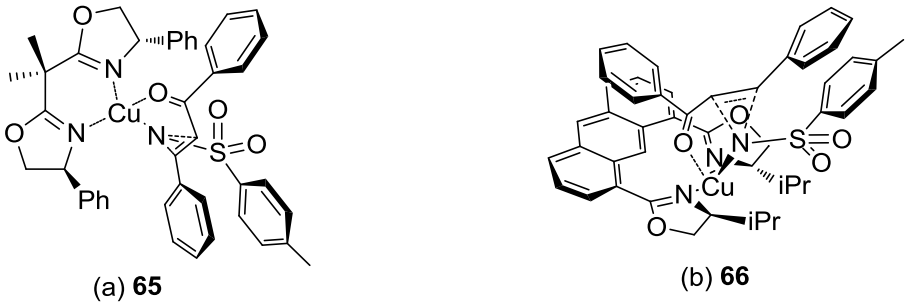
Chan and co-workers reported that the *C*2-symmetric salen-type ligand **60** employed with $Cu(MeCN)_4ClO_4$ as catalyst (Figure 1.4c) to give the chiral aziridine products in 22-92% yield and 19-97% ee (Table 1.7, entry 4).[47] A similar combination was described by Scott and co-workers, in which $Cu(MeCN)_4BF_4$ and chiral diimine **61** (Figure 1.4d) were found to be particularly effective with *trans*-cinnamate esters as the substrates (Table 1.7,

entry 5). With the reported conditions, this gave the corresponding aziridines in 32-89% yield and with ee values of 88-98%.[48] It was postulated that chiral induction was promoted by ancillary binding of the carbonyl group of the cinnamate ester to the metal center. In addition, the studies found that the performance of the catalysts was highly dependent on the substituents on the ligand and *ortho*-disubstitution was required to furnish the monometallic, active catalytic systems.

Following this work, Che and co-workers developed the first copper-catalyzed asymmetric alkene aziridination with *in situ* formed iminoiodanes (Table 1.7, entry 6).[49] By combining $Cu(MeCN)_4ClO_4$ with ligand **57b** (Figure 1.4a), the addition of a variety of sulfonamides to the C=C bond of alkenes were demonstrated to afford the corresponding aziridine products in good to excellent yields of up to 95% and with moderate ee values of up to 72%. However, the generality of this approach was found to be limited to aryl-substituted alkenes.

Xu and co-workers communicated the asymmetric aziridination of chalcones with CuOTf and 1,8-bisoxazolinylanthracene (AnBOX) **62** as the chiral ligand (Figure 1.4e).[50] The reaction was shown to be more efficient for electron-rich chalcones with product yields of up to 92% and with ee value of up to >99% obtained. Interestingly, the aziridine stereochemistry observed in this work was found to be opposite to that reported in earlier works by Evans and co-workers.[40] The proposed transition state for the asymmetric aziridination of *trans*-chalcones with copper-BOX and AnBOX complexes are shown in Figures 1.5a and 1.5b. The coordination of the oxy atom of the carbonyl group of the chalcones with the metal was noted to be crucial in furnishing the high enantioselectivities observed in this reaction. The limitation of electron-withdrawing

substrates was later overcome by switching to the chiral ligand cHBOX **63** (cHBOX = (*S*,*S*)-1,2-bis((*S*)-(4-phenyl)oxazolin-2-yl)cyclohexane, Figure 1.4f) (Table 1.7, entry 7).[51] Under these slightly modified conditions, the corresponding aziridine products were obtained in 38-92% yield and 68->99% ee. Subsequently, the developed methodology was shown to applicable to 1,3-dienes to afford vinyl aziridines in up to 73% yield and with up to >99% regio- and >99% diastereoselectivity, and ee values of up to 80%.[52]



(a) **65** (b) **66**

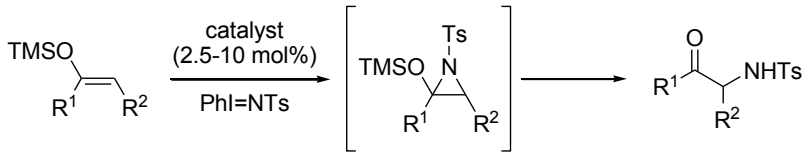
Figure 1.5 Transition states of copper-BOX and AnBOX complexes in asymmetric aziridination of *trans*-chalcones

More recently, Bolm and co-workers demonstrated an asymmetric version of this reaction by using $Fe(OTf)_2$ in combination with chiral pyridine bis(oxazoline) ligands **64** (Table 1.7, entry 8).[25] The aziridinations of styrene with various chiral ligands **64** were shown to give the 2-phenyl-1-tosylaziridine product in moderate yields and ee values of 40-75% and 6-40%, respectively.

1.3.5 Intermolecular Aziridination of Silyl Enol Ethers

In their seminal works, Evans and co-workers realized that $Cu(MeCN)_4ClO_4$ and $CuClO_4$ could be used as efficient catalysts in mediating aziridination reactions of silyl enol ethers **67**, which would subsequently undergo ring-opening step to afford α-amino ketones **70** in 53-75% yield (Table 1.8, entries 1 and 2).[14,15] A further application of this method to silyl ketene acetals **68** as a way to access α-amino esters and α-amino acids was also examined, but shown to be less efficient with product yields of 27-45% obtained.

Table 1.8 Iron- and copper-catalyzed aziridination of silyl enol ether **67** followed by ring-opening



67, R^1, R^2 = H, Ph, alkyl
68, R^1 = OR^3, R^2 = H, Ph, alkyl

69 **70**

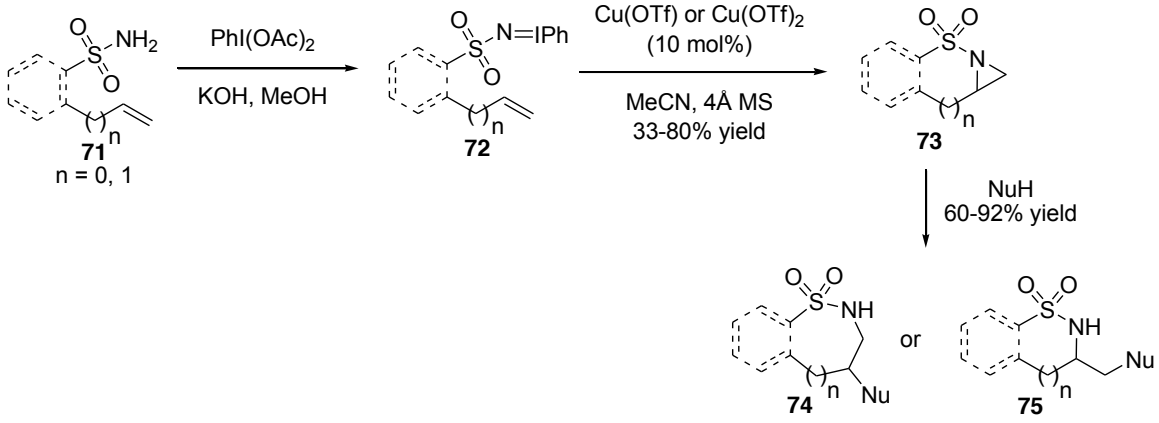
Entry	Catalyst	Yield (%)
1	$Cu(MeCN)_4ClO_4$	64-75
2	$CuClO_4$	27-75
3	$Fe(OTf)_2$	46-72

More recently, Bolm and co-workers demonstrated an iron-catalyzed version of this reaction (Table 1.8, entry 3).[25] By identifying $Fe(OTf)_2$ as the most suitable catalyst, the aziridination of a variety of silyl enol ethers **67** and silyl ketene acetals **68** was reported to

give the corresponding α-amino ketones and α-amino esters **70** in moderate to good yields of 46-72%.

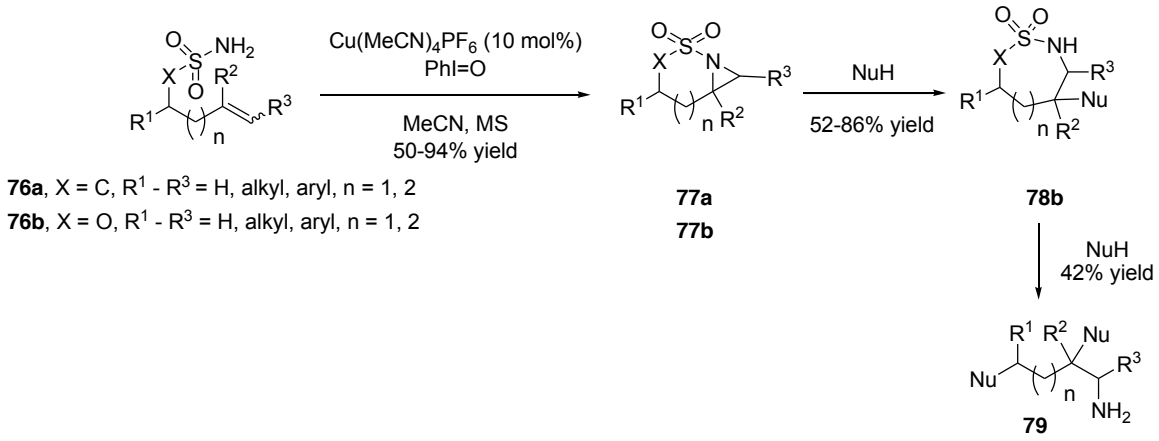
1.3.6 Intramolecular Aziridination of Alkenes

In 2000, the first example of intramolecular copper-catalyzed aziridinations as a route to substituted cyclic sulfonamides was reported by Dodd and Dauban (Scheme 1.12).[53] Iminoiodanes **72** were first synthesized by treatment of olefinic primary sulfonamides **71** with iodobenzene diacetate in the presence of potassium hydroxide in methanol. Copper(I) and copper(II) triflate were then employed to perform the transfer of nitrogen atom to the C=C bond of iminoiodane **72** and formed aziridine **73** in 33-80% yield. Ring-opening of the aziridine adduct by various nucleophiles was also noted to be readily achieved to afford the corresponding substituted cyclic sulfonamides **74** and **75** in 60-92% yield.



Scheme 1.12 Copper-catalyzed intramolecular aziridination of iminoiodanes **72** followed by ring-opening by nucleophiles

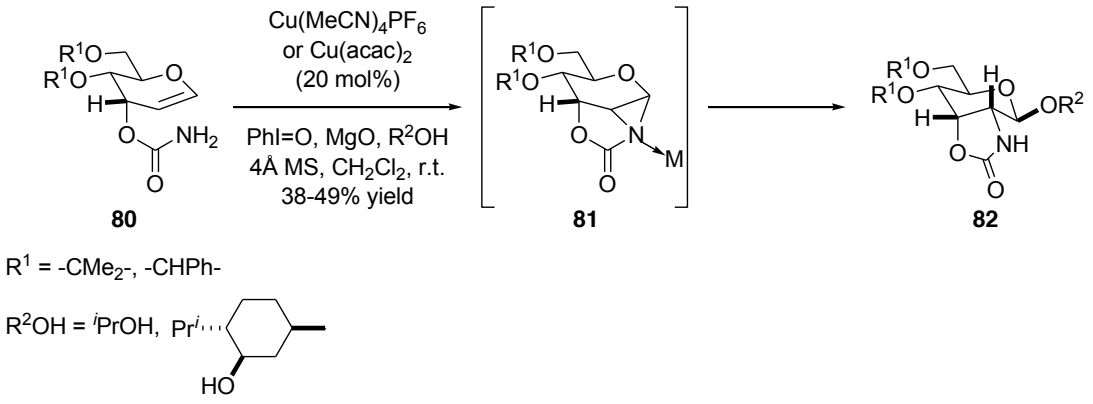
Following this seminal work, a one pot transformation of olefinic primary sulfonamides **76a** or sulfamate esters **76b** to aziridine **77a** and **77b** was realized by the same group (Scheme 1.13).[35,36,54] The methodology benefited from bypassing the synthetic step of preparing iminoiodanes **72**, making the approach more efficient. In this work, $Cu(MeCN)_4PF_6$ and PhI=O were found to be an efficient combination to convert olefinic primary sulfonamides **76a** or sulfamate esters **76b** to the corresponding bicyclic products **77a** and **77b** in 50-94% yield. Interestingly, different nucleophiles could be introduced to **77b** selectively and consecutively, while the sulfonyloxy moiety was shown to be readily removed to give the polysubstituted amine **79**. In more recent work, an enantioselective version of this reaction was described in which BOX **57b** was used as the chiral ligand to furnish the corresponding products in 24-86% yield and 34-84% ee.[55]



Scheme 1.13 $Cu(MeCN)_4PF_6$-catalyzed intramolecular aziridination of unsaturated sulfonamides **76a** and sulfamate esters **76b** followed by ring-opening by nucleophiles

Recently, the laboratory of Che and co-workers revealed that [Fe(Cl_3terpy)$_2$] **43** was also a suitable catalyst for mediating intramolecular aziridination of unsaturated sulfonamides **76a**. In this latter work, the corresponding products **77a** were furnished in 86-96% yield.[24]

A similar approach reported by Rojas and co-workers involving amidoglycosylation of allal 3-carbamates **80** was found to be feasible with $Cu(MeCN)_4PF_6$ or $Cu(acac)_2$ as catalyst (Scheme 1.14).[56] In this work, the tandem intramolecular aziridination/ring-opening reaction proceeded well to furnish the corresponding products **82** in moderate yields of 38-49% and with high regioselectivity of 95->99%.



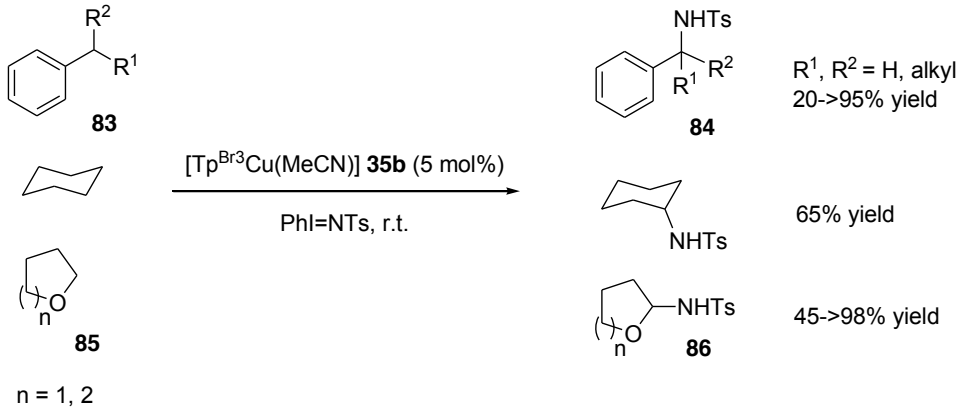
Scheme 1.14 Copper-catalyzed intramolecular aziridination of carbamate esters **80** followed by ring-opening by alcohols

1.4 Iron- and Copper-Catalyzed Nitrogen Atom Insertion into C–H Bonds

1.4.1 Amination of C(sp^3)–H Bonds

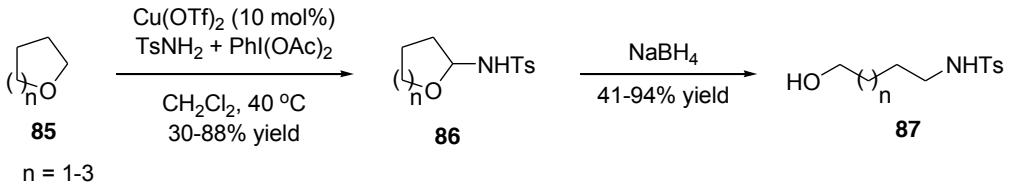
In 2003, Pérez and co-workers contributed one of the earliest advances in intermolecular amination C(sp^3)–H bonds with the groundbreaking copper(I)-

homoscorpionate complex [Tp^{Br3}Cu(MeCN)] **35b** (Tp^{Br3} = hydrotris(3,4,5-tribromo-1-pyrazolyl)borate) (Scheme 1.15).[57,58] In this seminal work, the nitrene/imido insertions to the saturated C−H bonds of a series of substrates such as alkyl benzenes, cyclohexane and cyclic ethers with PhI=NTs were found to proceed well and gave the corresponding aminated products in 20->98% yield.



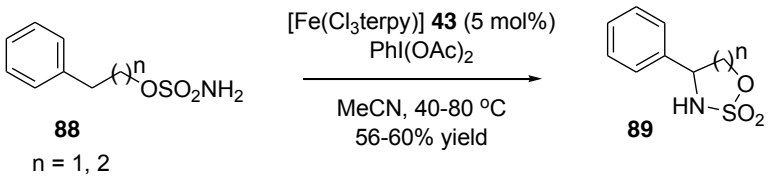
Scheme 1.15 [Tp^{Br3}Cu(MeCN)]-catalyzed intermolecular nitrogen atom insertion to different types of C(sp^3)−H bonds

Following this initial success, Yu and co-workers showed that intermolecular amination of the saturated C−H bond of cyclic ethers catalyzed by $Cu(OTf)_2$ using $TsNH_2$/$PhI(OAc)_2$ or PhI=NTs as the nitrogen source could be realized (Scheme 1.16).[59] Under mild conditions, α-amidated products **86** were generated in a highly selective manner with moderate to good yields of 30-88%. Subsequently, the *N*-tosylamidated products **86** were shown to undergo reductive ring-opening reaction by $NaBH_4$ to give the corresponding α,ω-amino alcohols **87** in 41-94% yield.



Scheme 1.16 $Cu(OTf)_2$-catalyzed intermolecular amination of cyclic esters **85** followed by ring-opening by $NaBH_4$

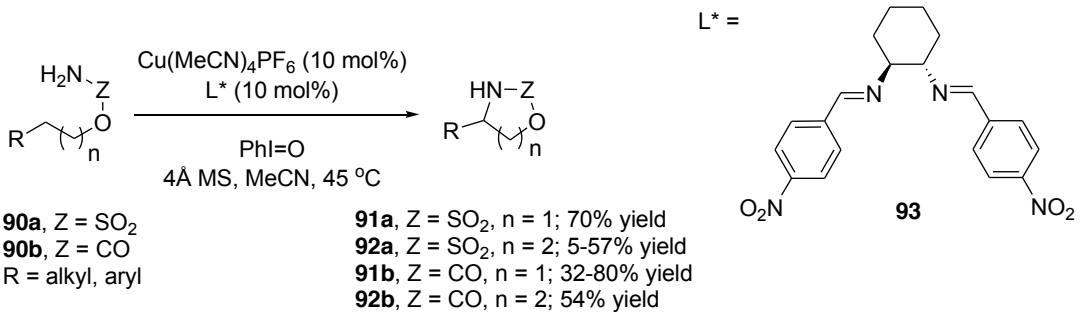
As part of a continued effort on establishing the chemistry of $[Fe(Cl_3terpy)_2]$ **43**, Che and co-workers found that the catalytic system could effectively mediate intramolecular amination of sulfamate esters **88** (Scheme 1.17). With $PhI(OAc)_2$ as the oxidant, this approach afforded the corresponding sulfamidates **89** in 56-60% yield.[24]



Scheme 1.17 $[Fe(Cl_3terpy)_2]$ **43**-catalyzed intramolecular amination of sulfamate esters **88**

More recently, Nicholas and co-workers further expanded this catalytic amination method to secondary, tertiary and benzylic C–H bonds of tethered sulfamates **90a** and carbamates **90b** (Scheme 1.18). By employing $Cu(MeCN)_4PF_6$ and Schiff bases ligand **93** as the catalytic system, amination was shown to proceed smoothly to afford the corresponding five- and six-membered *N,O*-heterocycles **91a**,**b** and **92a**,**b** in up to 80%

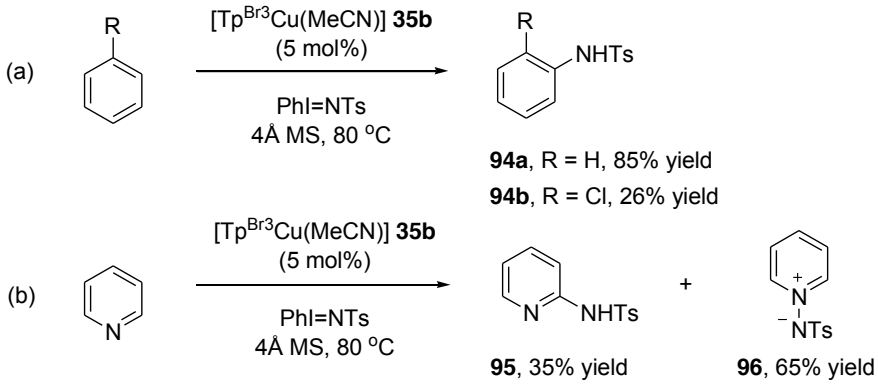
yield.[60] However, attempts to afford **91a** and **91b** in an asymmetric manner with other homochiral ligands were met with limited success (13-18% ee).



Scheme 1.18 $Cu(MeCN)_4PF_6$-catalyzed intramolecular amination of sulfamate esters **90a** and carbamate **90b**

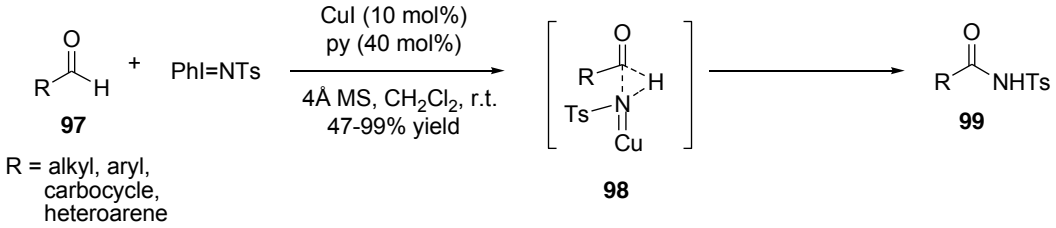
1.4.2 Amination of C(sp^2)–H Bonds

Despite the significant amount of works on transition-metal-mediated aziridination and amination reactions of alkenes and alkanes, studies on the analogous nitrene/imido transfer to C(sp^2)−H bonds has remained sparse in the literature. This is all the more so regarding methods that make use of either copper or iron catalysis and, to date, there are only two reported examples. The first is by the group of Pérez and co-workers who showed [Tp^{Br3}Cu(MeCN)] **35b** to efficiently catalyze the amination of benzene and chlorobenzene with PhI=NTs (Scheme 1.19a).[58] This gave the corresponding *ortho*-substituted *N*-tosylaniline **93a**,**b** as major products in 26 and 85% yield, respectively. On the other hand, the amination of pyridine was noted to result in the *ortho*-aminated product **95** as a minor product in 35% yield together with the zwitterionic compound **96** in 65% yield (Scheme 1.19b).



Scheme 1.19 [Tp^{Br3}Cu(MeCN)] **35b**-catalyzed nitrene/imido insertion to C(sp^2)–H bonds of aromatic compounds

The only other known example is that reported by Chan and co-workers (Scheme 1.20). In this latter work, tetrapyridyl complexes of copper(I) iodide was shown to mediate nitrogen atom insertion to the formylic C–H bond of aldehydes **97** to furnish the corresponding sulfonamide products **99** in 47-99% yield.[61] Mechanistic studies were shown to support the reaction proceeding by rate determing insertion of a putative copper-nitrene/imido species into the formylic C–H bond of the substrate *via* a concerted pathway.



Scheme 1.20 CuI-catalyzed amination of aldehydes **97**

1.5 Proposed Work

The work in this thesis has been directed toward developing novel and efficient synthetic methodologies that directly install C−N bonds at strategic positions from activated C−H bonds. These newly developed methods are envisioned to provide access to a range of unexplored nitrogen containing organic compounds of current biological and pharmaceutical interests. Importantly, the catalytic activities will be accomplished by the use of cheap, readily available and biocompatible metals in order to make these methodologies more applicable to the target synthesis of bioactive compounds, especially in scale-up process. Added on to this is the exploration of the scope of other functional groups that have received little or no attention previously.

Thus, the aim of this project has been involved in establishing new iron-catalyzed protocol for selective nitrogen atom insertion to the acyl C−H bond of aldehydes as an efficient approach to amide bond synthesis (Figure 1.6a). In addition, attention has also focused on the development of a convenient route to α-acyl-β-amino acid and 2,2-diacyl aziridine derivatives *via* a catalytic copper-catalyzed amination and aziridination of 2-alkyl substituted 1,3-dicarbonyl compounds (Figure 1.6b). The mechanism was thought to occur *via* a nitrene/imido insertion process to the allylic C−H bond of *in situ* formed enolate species from 2-alkyl substituted 1,3-dicarbonyl compounds with the copper catalyst. The finding led us to investigate the potential of applying this catalytic system to the α-amination of 1,3-dicarbonyl compounds (Figure 1.6c). We reasoned that a synthetic approach to ketone substituted α-amino acid derivatives would be possible *via* insertion of a putative copper nitrene/imido species to the α-C−H bond of the substrates. Finally, we surmised that the α-C−H bond of saturated heterocylic compounds would be feasible

to functionalize by nitrene/imido insertion and provided a straightforward approach to the classes of cylic aminals and hemiaminals (Figure 1.6d).

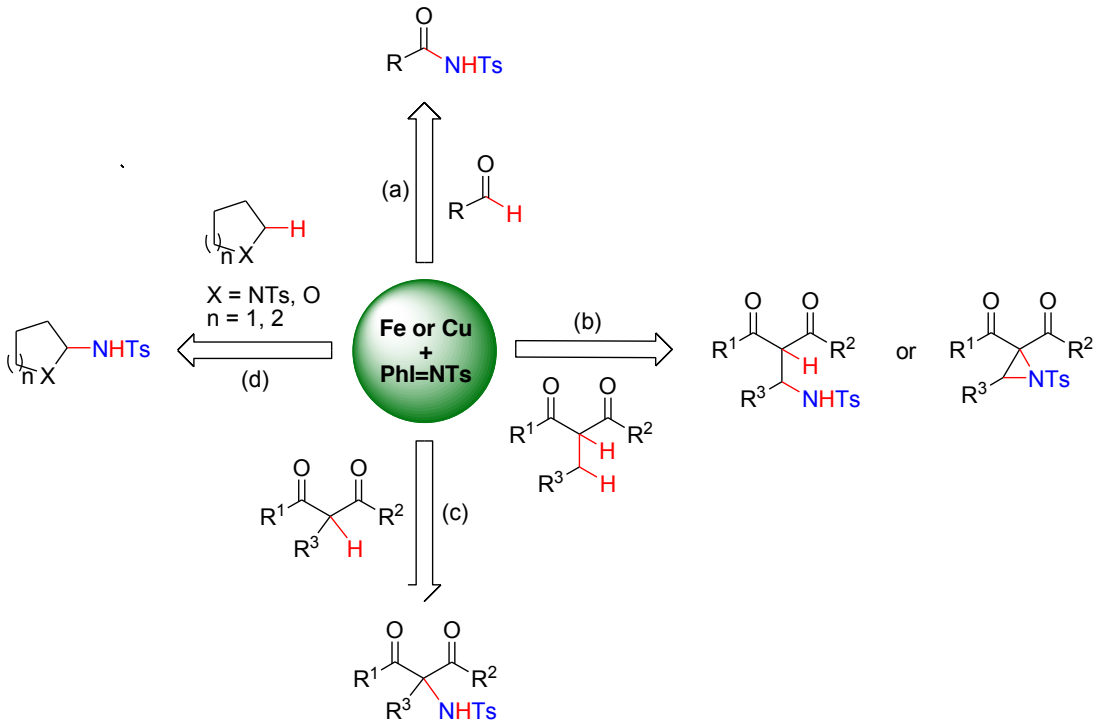


Figure 1.6 Iron- and copper-catalyzed nitrene/imido transfer reactions with PhI=NTs

Chapter II. Iron(II)-Catalyzed Amidation of Aldehydes with Iminoiodanes at Room Temperature and Under Microwave Assisted Conditions

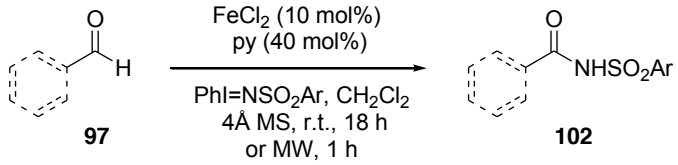
2.1 Introduction

Establishing methods to amides is an immensely important pursuit in organic synthesis due to the role of this functional group as a privileged pharmacophore and building block in a myriad of biomolecules as well as pharmaceutically interesting compounds.[62] Typically, amide bond synthesis has relied on the condensation of an amine with a carboxylic acid in the presence of a coupling reagent.[63] Although shown to be highly efficient, producing H_2O as potentially the only by-product, the utility of this approach has been lessened by the need for an extra step to convert the carboxylic acid to a more reactive derivative. This not only generates additional by-products but also, in some cases, synthetic complications in the activated intermediates. For this reason, the development of alternative synthetic strategies to this ubiquitously important functional group has received an immense amount of attention over the years.[61,64-73] This has hitherto included Staudinger ligation,[65] Beckmann rearrangement of oximes,[66] aminocarbonylation of haloarenes, alkenes and alkynes,[67] oxidative amidation of alcohols[68] and aldehydes,[69] hydrative amide synthesis with alkynes,[70] and amidation of ketones and thioacids with azides.[71]

As part of our efforts to develop new methods for amide bond synthesis, we recently reported one approach that relied on nitrene/imido insertion at the formyl C−H bond of aldehydes with PhI=NTs as the nitrogen source and [Ru(TTP)(CO)] **100** ((H_2(TTP) =

meso-tetrakis(*p*-tolyl)porphyrin) as the catalyst.[72] At about the same time, Chan and co-workers reported the same C−N bond forming process could be accomplished with $TsNH_2$ in the presence of $[Rh_2(esp)_2]$ **101** (esp = *α*,*α*,*α′*,*α′*-2-tetramethyl-1,3-benzenedipropionate) as the catalyst and $PhI(OC(O)^tBu)_2$ as the oxidant.[73] Thought to proceed *via* a highly reactive metal nitrene/imido species, in both synthetic strategies the corresponding acyl sulfonamides were afforded in good to excellent yields. We subsequently showed a more practical copper(I) halide catalyzed version of this reaction could be realized.[61] However, the main drawbacks of these approaches remained at the cost of $[Rh_2(esp)_2]$ **101** catalyst and $PhI(OC(O)^tBu)_2$ oxidant, the leakage of homogenous ruthenium complexes together with the aromatic sulfonamides during purification, and the need to develop two distinct catalytic Cu(I) systems to achieve a broad substrate scope that included aromatic compounds. Thus, it remains a challenge to develop a synthetic method that can effect such reactions for a wide range of substrates especially focusing on aromatic compounds in a manner that improves or at least maintains the practical and biocompatible nature of the catalytic system employed. In this regard, we envisioned that establishing an iron mediated approach to this important amide forming reaction could hold promise as the basis to readdressing this shortcoming.[74]

In this chapter, we report the use of the *in situ* formed complex $[FeCl_2(py)_4]$ (py = pyridine) for amidation of a wide variety of aldehydes with $PhI{=}NSO_2Ar$ at room temperature and under microwave assisted conditions (Scheme 2.1). The acyl sulfonamide products were afforded in moderate to excellent yields comparable to those reported for the analogous Ru(II) and Cu(I) promoted reactions.[61,72]



Scheme 2.1 Iron(II)-catalyzed amidation of aldehydes with PhI=NTs at room temperature or under microwave irradiation (MW)

2.2 Results and Discussion

In view of the challenges still posed by aromatic aldehydes in the analogous Cu(I) and Ru(II)-catalyzed reactions, we began by examining the amidation of benzaldehyde **97a** by a variety of Fe(II) and Fe(III) salts and the results are depicted in Table 2.1. This involved treating **97a** with 10 mol% of $FeCl_2$, pyridine (40 mol%) and PhI=NTs (2 eq) as the nitrogen source in CH_2Cl_2 at room temperature for 18 h gave the best result (Table 2.1, entry 1). Under these conditions, *N*-tosylbenzamide **102a** was afforded in 90% yield which was comparable to product yields of 83-93% obtained for the analogous amidations of **97a** with PhI=NTs mediated by Cu(I), Rh(II,II) and Ru(II).[61,72,73] Lower product yields of 74-78% were obtained when we employed a lower catalyst loading of 5 mol% or 1.5 eq of PhI=NTs (Table 2.1, entries 2 and 3). Likewise, conducting the reaction with benzene in place of CH_2Cl_2 as the solvent led to a comparable product yield of 73% (Table 2.1, entry 4). In marked contrast, the analogous reactions with $TsNH_2$ + $PhI(OAc)_2$ or chloramine-T trihydrate ($TsNClNa \cdot 3H_2O$) + PhI=O as the nitrogen source were also found to give low product yields along with **103a** in 8-35% yield (Table 2.1, entries 8 and 9). Similarly, low product yields along with recovery of **97a** and/or the imine **103a** were found when the reaction was performed with 1.5 eq of PhI=NTs in other

Table 2.1 Optimization of the reaction conditions[a]

97a **102a** **103a**

Entry	Catalyst	Ligand	Solvent	Yield (%)	
				102a	**103a**
1	$FeCl_2$	py	CH_2Cl_2	90	-
2[b]	$FeCl_2$	py	CH_2Cl_2	78	-
3[c]	$FeCl_2$	py	CH_2Cl_2	74	-
4[c]	$FeCl_2$	py	C_6H_6	73	-
5[c]	$FeCl_2$	py	PhMe	40	-
6[c]	$FeCl_2$	py	MeCN	27	-
7[c]	$FeCl_2$	py	1,4-dioxane	-[d,e]	-
8[f]	$FeCl_2$	py	CH_2Cl_2	25	35
9[g]	$FeCl_2$	py	CH_2Cl_2	59	8
10	$FeCl_2$	DMAP	CH_2Cl_2	88	-
11	$FeCl_2$	2-picolinic acid	CH_2Cl_2	36	10
12	$FeCl_2$	quinaldic acid	CH_2Cl_2	11	36
13	$FeCl_2$	2,6-pyridinedicarboxylic acid	CH_2Cl_2	-[d]	48
14	$FeCl_2$	quinoline	CH_2Cl_2	27[h]	33
15	$Fe(OTf)_2$	py	CH_2Cl_2	28	32
16	$FeCl_3$	py	CH_2Cl_2	49[h]	-
17	$FeCl_2$	-	CH_2Cl_2	35	42
18	$FeBr_2$	-	CH_2Cl_2	28	15
19	$Fe(OAc)_2$	-	CH_2Cl_2	26	51

Table 2.1 (*continued*)

Entry	Catalyst	Ligand	Solvent	Yield (%)	
				102a	**103a**
20	$Fe(OTf)_2$	-	CH_2Cl_2	50	49
21	$FeCl_3$	-	CH_2Cl_2	24	55

[a]All reactions were carried out for 18 h at room temperature in the presence of powdered 4 Å MS (400 mg) with [Fe]:py:**97a**:PhI=NTs molar ratio = 1:4:10:20. [b]Reaction conducted with 5 mol% of $FeCl_2$. [c]Reaction conducted with 1.5 eq of PhI=NTs. [d]No reaction based on TLC and ^{1}H NMR analysis of the crude mixture. [e]Near quantitative recovery of **97a**. [f]PhI=NTs was replaced by $PhI(OAc)_2$ and $TsNH_2$. [g]PhI=NTs was replaced by PhIO and $TsNClNa\cdot 3H_2O$. [h]Recovery of **97a** in 40-50% yield.

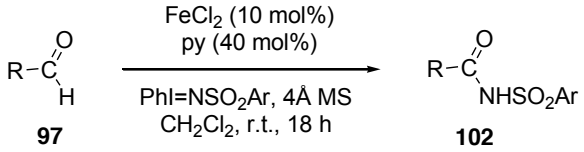
solvent systems or with other pyridyl-based ligands (Table 2.1, entries 5-7 and 11-14). In our hands, only the analogous reaction of **97a** with PhI=NTs mediated by $FeCl_2$ and DMAP afforded **102a** in a comparable yield of 88% (Table 2.1, entry 10).

An inspection of entries 15-21 in Table 2.1 also revealed the reaction to proceed less effectively with other Fe(II) and Fe(III) salts in the presence or absence of a ligand. In these reactions, the imine by-product was additionally furnished in yields of 8-55%. More notably, the use of $Fe(OTf)_2$ was the only instance that was found to be superior than $FeCl_2$ in mediating the amidation process under ligand free conditions, furnishing **102a** in 50% yield (Table 2.1, entry 20). However, repeating this reaction with pyridine gave a lower product yield of 28% (Table 2.1, entry 15). Additionally, the contrasting activities

exhibited by $FeCl_2$ and $FeCl_3$ suggested it was unlikely that these latter reactions proceeded *via* a common catalytically active iron species (Table 2.1, entries 1 and 17 *vs.* 16 and 21).

To define the scope of the present procedure, we next turned our attentions to the reactions of a variety of aldehydes (Table 2.2). In general, these experiments showed that with the $FeCl_2$ and pyridine combination, reaction of **97a** with PhI=NNs gave **102b** and a variety of substituted aromatic aldehydes with PhI=NTs afforded the corresponding acyl sulfonamides **102c-o** in moderate to excellent yields (Table 2.2, entries 1-14). This hitherto included substrates with a pendant Br, Cl or MeO group at the *para* positon of the aromatic ring which were previously shown to give the corresponding amide products in moderate yields of 47-65% in the analogous Cu(I)-mediated reactions.[61] Under our conditions, the $FeCl_2$-mediated reaction of 1-naphthaldehyde was the only example of a sterically demanding substrate that was found to deliver the amidation product in a moderate yield of 46% (Table 2.2, entry 14). On the other hand, reactions of a variety of alkyl aldehydes examined were found to afford the corresponding acyl sulfonamide products **102p-z** in good to excellent yields (Table 2.2, entries 15-25). A similar outcome was found for reactions of aliphatic aldehydes containing an alkene functional group (Table 2.2, entries 26-29). More notably, in these reactions where either a competing aziridination or 3º C−H amidation process was a potential problem, the corresponding acyl sulfonamides **102e, 102q-r, 102u-w, 102**α**-**ε were furnished as the sole product in yields of 48-99%. The only substrates examined that failed or found to be less effective in our hands were **97m** and **97x** and the carbaldehydes of furan and thiophene **97**ζ and **97**η (Table 2.2, entries 12, 23, 31 and 32). Under the standard conditions, reaction of **97x** was

Table 2.2 Iron(II)-catalyzed amidation of aldehydes **97a-η**[a]



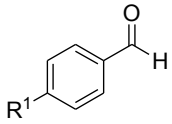
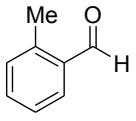
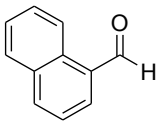
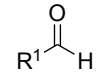
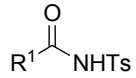
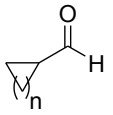
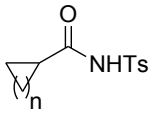
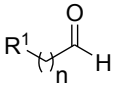
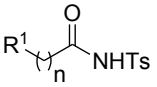
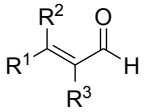
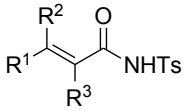
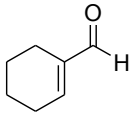
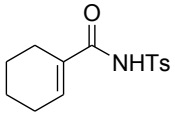
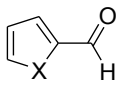
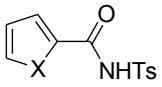
Entry	Substrate	Product	Yield (%)[b]
1[c]	 **97a**, **c-m**	**102b**, R^1 = H, Ar = *p*-$NO_2C_6H_4$	94
2		**102c**, R^1 = OMe, Ar = *p*-$CH_3C_6H_4$	77
3		**102d,** R^1 = ^{t}Bu, Ar = *p*-$CH_3C_6H_4$	95
4		**102e**, R^1 = ^{i}Pr, Ar = *p*-$CH_3C_6H_4$	92
5		**102f**, R^1 = Me, Ar = *p*-$CH_3C_6H_4$	94
6		**102g**, R^1 = Ph, Ar = *p*-$CH_3C_6H_4$	82
7		**102h**, R^1 = Br, Ar = *p*-$CH_3C_6H_4$	83
8		**102i**, R^1 = Cl, Ar = *p*-$CH_3C_6H_4$	82
9		**102j**, R^1 = F, Ar = *p*-$CH_3C_6H_4$	99
10		**102k**, R^1 = CF_3, Ar = *p*-$CH_3C_6H_4$	65
11		**102l**, R^1 = CO_2Me, Ar = *p*-$CH_3C_6H_4$	99
12		**102m**, R^1 = NO_2, Ar = *p*-$CH_3C_6H_4$	-[d]
13	 **97n**	**102n**	78
14	 **97o**	**102o**	46

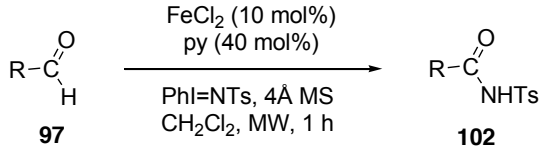
Table 2.2 (*continued*)

Entry	Substrate	Product	Yield (%)[b]
15	 **97p-t**	 **102p**, R^1 = Et	99
16		**102q**, R^1 = ^{i}Pr	99
17		**102r**, R^1 = ^{i}Bu	95
18		**102s**, R^1 = ^{t}Bu	70
19		**102t**, R^1 = ^{n}Hex	90
20	 **97u-w**	 **102u**, n = 1	96
21		**102v**, n = 3	99
22		**102w**, n = 4	90
23	 **97x-z**	 **102x**, n = 1, R^1 = Ph	-[e]
24		**102y**, n = 2, R^1 = Ph	61
25		**102z**, n = 2, R^1 = CO_2Me	50
26	 **97α-δ**	 **102α**, R^1 = R^2 = Me, R^3 = H	77
27		**102β**, R^1 = ^{n}Pr, R^2 = R^3 = H	83
28		**102γ**, R^1 = Ph, R^2 = R^3 = H	48
29		**102δ**, R^1 = Et, R^2 = H, R^3 = Ph	78
30	 **97ε**	 **102ε**	51
31	 **97ζ-η**	 **102ζ**, X = O	-[f]
32		**102η**, X = S	20

[a]All reactions were carried out for 18 h at rt in the presence of powdered 4Å MS with $FeCl_2$:py:**97**:PhI=NTs molar ratio = 1:4:10:20. [b]Isolated yield. [c]PhI=NTs was replaced by PhI=NNs. [d]Trace amount (< 1%) of product detected on the basis of ^{1}H NMR analysis of the crude mixture but not isolated. [e]Toluene detected on the basis of GC and 1H NMR analysis. [f]No reaction based on TLC and ^{1}H NMR analysis of the crude mixture.

found to lead to the formation of toluene on the basis of 1H NMR and ESI-MS measurements of the crude mixture, whereas **97m** and **97ζ** resulted in their recovery and **97η** afforded **102η** in 20% yield. The coordination between the heteroatom of furan- and thiophenecarbaldehyde with iron was thought to either de-activate the catalyst or hinder its release for the next step of the catalytic cycle.

Microwave irradiation has been extensively documented in recent years as a method to accelerate transition-metal-catalyzed reactions and their potential for scale-up applications.[75] With this in mind, we also investigated the iron-mediated transformation of aldehydes to amides under microwave assisted conditions with **97a**, **97o**, **97v**, **97β**, **97ε**, and **97η** chosen as representative examples, as shown in Scheme 2.2. In the presence of 10 mol% of $FeCl_2$, pyridine (40 mol%) and PhI=NTs (2 eq) in CH_2Cl_2 and microwave irradiation for 1 h, these subtrates provided the corresponding acyl sulfonamide products **102** in yields of 38-99%, comparable to those obtained at room temperature for 18 h.



102a, R = Ph, 93% yield
102o, R = 1-napth, 58% yield
102v, R = ^{c}Pr, 99% yield
102β, R = (*E*)-^{n}PrCH=CH, 82% yield
102ε, R = ^{c}hex-1-enyl, 60% yield
102η, R = 2-thiophenyl, 38% yield

Scheme 2.2 Iron(II)-catalyzed amidation of aldehydes with PhI=NTs under MW

The preferential formation of toluene for the amidation of **97x** mentioned earlier in entry 23 in Table 2.2 led us to speculate on the possible involvement of a radical species in the present iron (II)-catalyzed reactions. This would be not inconceivable in view of the fact that it has been previously reported that decarbonylation of a phenylacetyl radical has been measured in the order of k_d = 5.2 x 10^7 s^{-1} at 25 °C (Figure 2.1).[76]

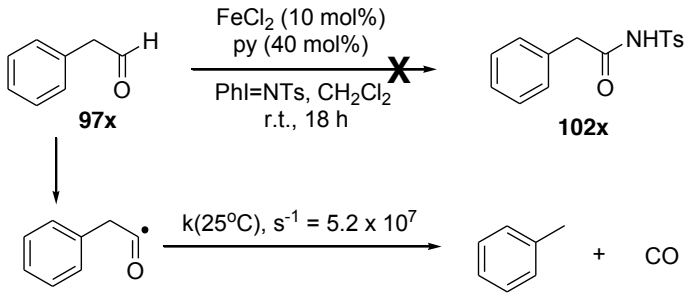
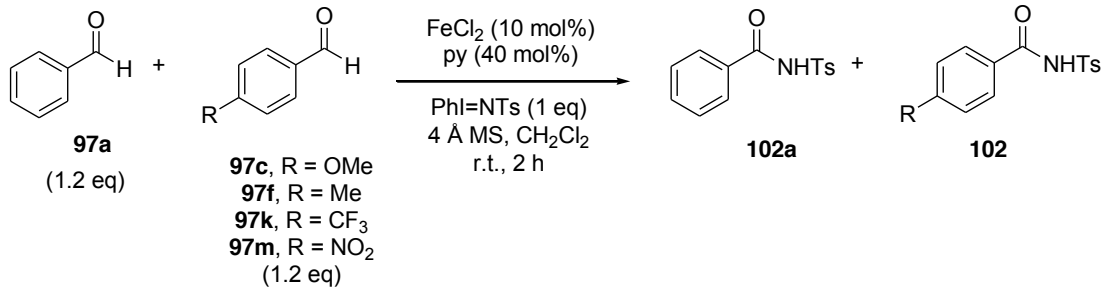


Figure 2.1 Radical clock experiment

The premise that the amidation proceeded *via* a radical intermediate would be consistent with our findings showing the detection of only the aldehyde based on TLC and ^{1}H NMR analysis of the crude reaction mixture of **97a** + PhI=NTs exposed to 10 mol% of $FeCl_2$, 40 mol% of pyridine and the radical scavenger butylhydroxytoluene (BHT) under the standard conditions. Indeed, this is further supported by competitive rate studies under the conditions shown in Table 2.3. This revealed a log(k_{rel}) value of –0.103 that suggested there were no significant electronic effects in the amidation process (Figure 2.2). With the exception of **97m**, the absence of such effects would also account for our earlier results showing aromatic aldehyde amidation to proceed well regardless of the presence of an electron-withdrawing or electon-donating group depicted in entries 2-11 in Table 2.2. Additionally, the near zero reaction constant is comparable to that found

Table 2.3 Competitive rate studies[a]



Entry	R	σ_p	$\log(k_X/k_H)^b$
1	OMe	-0.27	0.026
2	Me	-0.17	0.021
3	H	0	0
4	CF_3	0.54	-0.064
5	NO_2	0.78	-0.075

[a]Reaction was carried out in the presence of powdered 4Å MS in CH_2Cl_2 at room temperature for 2 h with $FeCl_2$:py:PhI=NTs:**97a**:substituted benzaldehyde molar ratio = 1:4:10:12:12. [b]Measurements based on GC analysis.

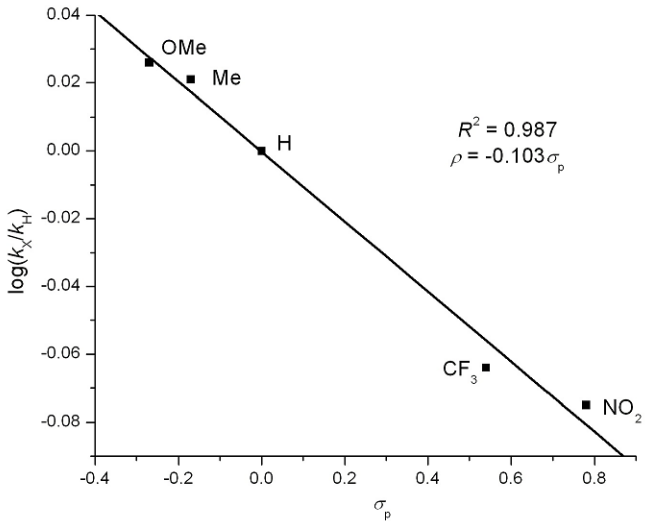
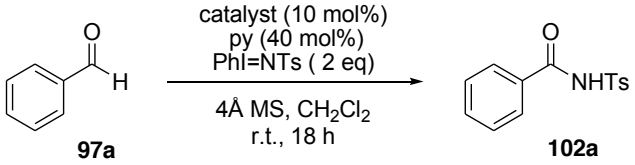


Figure 2.2 Linear free-energy correlation of log k_X/k_H vs σ_p plot for amidation of *para*-substituted aldehydes **97a**, **97c**, **97f**, **97k** and **97m**

for manganese corrole-catalyzed alkene aziridinations reported by Abu-Omar and co-workers in which a non-polar transition state and a radical-type mechanism was proposed.[77]

In view of recent works showing the true catalytic species in the reported cross-coupling reactions to be due to trace amounts of Cu and Pd in the iron salts,[78] we conducted a series of control reactions in order to determine the potential role of trace of amounts of other metals in $FeCl_2$ catalyst. In one set of experiments, different sources of iron catalyst were examined under standard reaction conditions with benzaldehyde **97a** as the model substrate (Table 2.4). Regardless of purity level of $FeCl_2$, *N*-tosylbenzamide

Table 2.4 Amindation of benzaldehyde **97a** with different sources of iron catalyst[a]



Entry	Catalyst	Yield (%)[b]
1	$FeCl_2$, 98% (Strem)	90
2	$FeCl_2$, 99.5% (Alfa Aesar)	93
3	$FeCl_2$, 99.99%, ultra dry, (Alfa Aesar)	92
4[c]	$FeCl_2$, 99.99%, ultra dry, (Alfa Aesar)	97
5[d]	$[Fe(py)_4Cl_2]$ **104** (synthesized from Fe, 99% Sigma Aldrich)	96

[a]All reactions were carried out for 18 h at room temperature in the presence of powdered 4Å MS with $FeCl_2$:py:**97a**:PhI=NTs molar ratio = 1:4:10:20. [b]Isolated yield. [c]Benzaldehyde was replaced by isovaleraldehyde. [d]Reaction conducted with 10 mol% of $[FeCl_2(py)_4]$ **104** and in the absence of py.

102a was obtained in comparable yields of 90-96%, which suggested that trace amounts of other metals were unlikely to be the active catalyst in this amidation reaction. To gain more insight into reaction mechanism, $[FeCl_2(py)_4]$ **104** complex was prepared from pure iron powder and HCl.[79] This complex was structurally determined by infrared spectrum and X-ray crystallography (Figure 2.3).[80] The reaction of **97a** with 10 mol% of $[FeCl_2(py)_4]$ **104**, was found to deliver **102a** in 96% yield (Table 2.4, entry 5). This finding supported complex **104** as the actual catalytic species in this reaction.

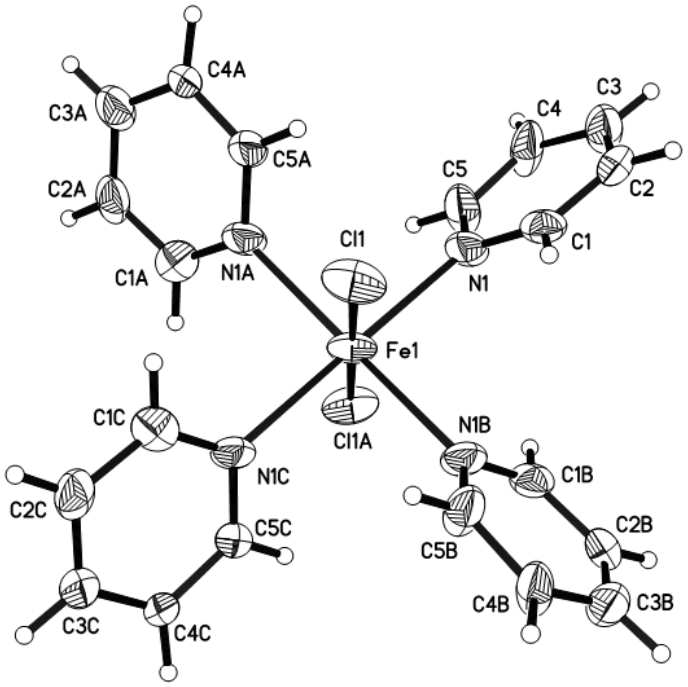
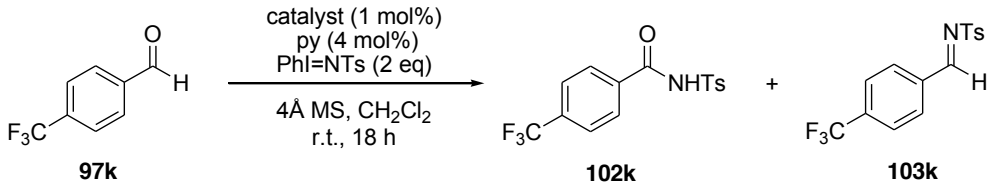


Figure 2.3 ORTEP drawing of $[Fe(py)_4Cl_2]$ **104** with thermal ellipsoids at 50% probability levels[80]

Next, we carried out another set of control experiments with **97k** in place of **97a** and 1 mol% of the metal oxide as well as chloride and triflate salts of Cu(I) and Cu(II) and found that the corresponding imine **103k** was preferentially afforded in near quantitative yields (Table 2.5, entries 2-6). The analogous reactions with 1 mol% of either $Pd(PPh_3)_4$ or $Pd(OAc)_2$ were also found to lead to the exclusive formation of the imine adduct in 58-61% yield and recovery of the substrate in 38-41% yield (Table 2.5, entries 7-8). In

Table 2.5 Determining the potential role of trace amounts of Cu and Pd in the aldehyde amidation process[a]



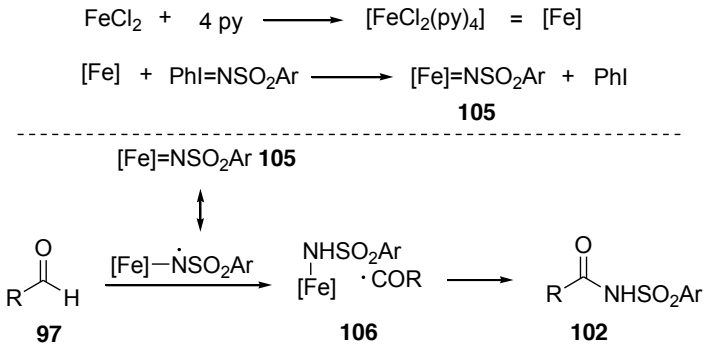
97k **102k** **103k**

Entry	Catalyst	Product	Yield (%)[b]
1[c]	$FeCl_2$	**102k**	70
2	Cu_2O	**103k**	99
3	CuCl	**103k**	99
4	CuOTf	**103k**	99
5	$Cu(OTf)_2$	**103k**	99
6	$CuCl_2$	**103k**	99
7	$Pd(PPh_3)_4$	**103k**	61[d]
8	$Pd(OAc)_2$	**103k**	58[d]

[a]All reactions were carried out for 18 h at room temperature in the presence of powdered 4Å MS with catalyst:py:**97k**:PhI=NTs molar ratio = 0.1:0.4:10:20. [b]Isolated yield. [c]Reaction conducted with 10 mol% of $FeCl_2$ of 99.99% purity and 40 mol% of py. [d]Recovery of aldehyde **97k** in 38-41% yield.

marked contrast, the acyl sulfonamide products **102k** were obtained in 70 % when we carried out the corresponding reactions **97k** with 10 mol% of $FeCl_2$ of 99.99% purity (Table 2.5, entry 1). The contrasting reactivities observed in Table 2.5 further provided evidence that trace amounts of Cu and Pd impurities present in $FeCl_2$ used in this work are not the catalytically active species.

On the basis of the above results, we tentatively propose the present iron(II)-catalyzed amidation of aldehydes with PhI=NTs to proceed by C–H bond functionalization as outlined in Scheme 2.3.[81] This could involve the initial formation of the pre-catalyst $[FeCl_2(py)_4]$ **104** from reaction of $FeCl_2$ with pyridine. Further reaction of this newly formed iron complex with $PhI{=}NSO_2Ar$ then generates the putative highly reactive $[Fe]{=}NSO_2Ar$ species **105**.[81] In contrast to the analogous CuI-catalyzed aldehyde amidation reactions,[61] subsequent insertion of the nitrene/imido group from this intermediate to the formylic C–H bond of the substrate *via* a H-atom abstraction/radical rebound pathway is then thought to deliver the amide product **102**.



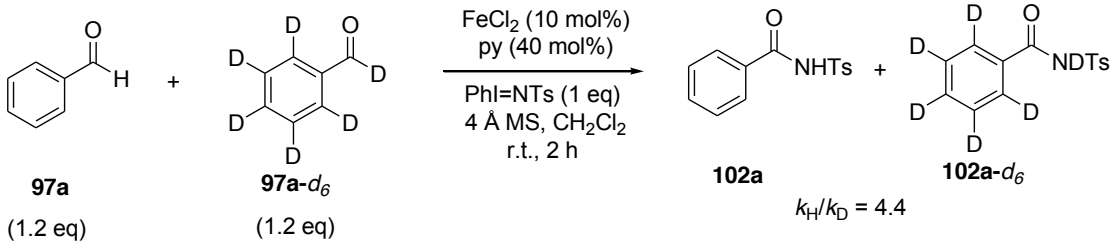
Scheme 2.3 Tentative reaction pathway for C–N bond formation

The obtained product chemoselectivities are in good agreement with recent DFT calculations by Bolm and Shaik showing amidation is favored over aziridination when the nitrogen substituent contains an electron-withdrawing group and steric effects having little influence in these reactions.[81b] The role of pyridine as a ligand in the catalytic system that tempers the Lewis acidity of $FeCl_2$ through coordination to the metal centre and *in situ* formation of $[FeCl_2(py)_4]$ **104** is evident in a number of experiments examined in this work. First is the formation of only the acyl sulfonamide product for reactions of **97** conducted in the presence of the iron(II) salt and pyridine or $[FeCl_2(py)_4]$ **104** under the various conditions described in Tables 2.1, 2.4 and 2.5. In contrast, both **102a** and **103a** were observed on either removing the nitrogen heterocycle from the reaction conditions or replacing it with less basic ligands when we examined the amidation of **97a** (Table 2.1, entries 11-14 and 17). We surmise the origin of the imine by-product could be due to iron-catalyzed hydrolysis of PhI=NTs to $TsNH_2$ by H_2O,[82] followed by condensation of this newly formed aryl sulfonamide with the aldehyde in the presence of the Lewis acidic metal salt.[83]

Given previous works demonstrating iron-catalyzed hydrolysis of the iminoiodane to the aryl sulfonamide by H_2O to occur *via* iron-nitrene/imido species of the type **105** and/or **106**,[82] the competitive formation of the imine by-product also implies the involvement of such intermediates in our reactions. Indeed, this speculation was supported by ^1H NMR measurements of an equimolar CD_2Cl_2 sample of $[FeCl_2(py)_4]$ and PhI=NTs. The resultant dark brown homogenous solution was found to be diamagnetic with well-resolved ^1H NMR signals at normal fields that showed the methyl and *ortho* and *meta* aromatic C–H resonances of the tosyl group shifted downfield by 0.10-0.35

ppm relative to the respective signals in PhI=NTs and $TsNH_2$. Subsequent addition of **97a** to this CD_2Cl_2 sample then led to the detection of **102a** by ^1H NMR and TLC analysis.

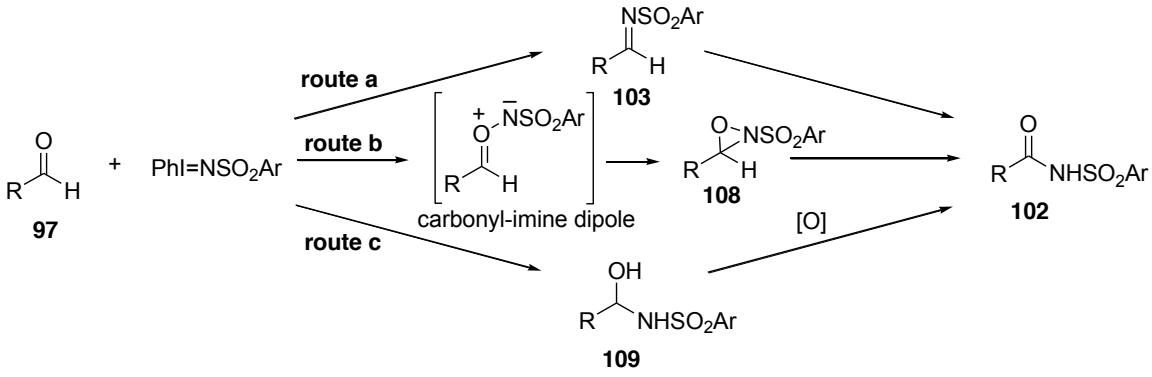
Although further NMR analysis and mass spectrometry was not able to elucidate the exact structure of **105**, measurement of the deuterium kinetic isotope effect with **97a** and benzaldehyde-d_6 as the test substrates revealed a k_H/k_D value of 4.4 based on LCMS analysis (Scheme 2.4). This suggested that C–H bond cleavage resulting in the formation of the proposed radical species **106** is most probably the rate determining step. This value is also comparable to k_H/k_D values reported for the analogous CuI-catalyzed benzaldehyde amidation reaction,[61] nitrene/imido insertion into the dibenzyl ether in the presence of CuCl as catalyst[84] and [Ru(TMP)$(NNs)_2$] **107** (H_2TMP = 5,10,15,20-tetramesitylporphyrin)-mediated amidation of ethyl benzene.[85]



Scheme 2.4 Deuterium kinetic isotope experiment with **97a** and **97a**-d_6

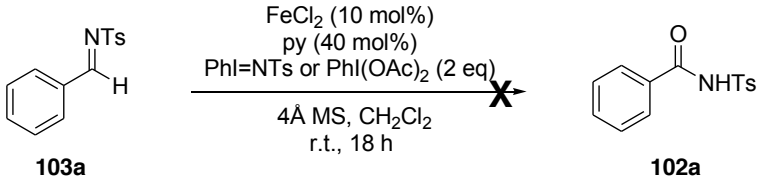
While the above results are consistent with a H-atom abstraction/radical rebound pathway depicted in Scheme 2.3, other possible pathways were also considered (Scheme 2.5).

During the course of our studies, formation of imine **103** was observed in several reactions (see Tables 2.1 and 2.5). While we postulated that these imines could be from condensation of aldehydes and $TsNH_2$, they were also plausible intermediates (Scheme 2.5, route a). To support or rule out this possible pathway, we independently synthesized *N*-benzylidine-*p*-toluenesulfonamide **103a** following procedures reported in literature.[86]



Scheme 2.5 Possible mechanistic pathway

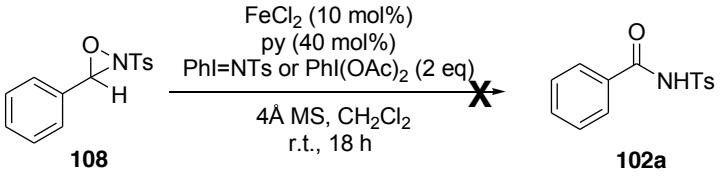
Compound **103a** was crystallized as a white solid in 51% yield by the reaction of 1 eq of benzaldehyde with 1 eq of *p*-toluenesulfonamide in the presence of trifluoroacetic anhydride in CH_2Cl_2 at reflux temperature. Subsequently, the reaction of compound **103a** with PhI=NTs was conducted under the standard conditions (Scheme 2.6). However, formation of amide **102a** could not be detected based on the basis of TLC and ^1H NMR crude analysis. This result led us to conclude the involvement of imine in this amidation reaction to be less likely.



103a **102a**

Scheme 2.6 Control experiment with **103a** under standard conditions

Similarly, the reaction pathway where amidation of aldehydes with PhI=NTs *via* an oxaziridine intermediate **108** was also tested. We synthesized oxaziridine **108** from the oxidation of imine **103a** with *meta*-chloroperoxybenzoic acid in the presence of powdered KOH in CH_2Cl_2.[87] However, our findings showing only the recovery of the starting material for the reactions of **108** exposed to 10 mol% of $FeCl_2$ and 40 mol% of pyridine under the standard conditions depicted in Scheme 2.7, which led us to also rule out the possibility of amide bond formation occurring *via* such intermediate.



108 **102a**

Scheme 2.7 Control experiment with **108** under standard conditions

The possibility for the formation of acylsulfonamide **102** *via* Scheme 2.5, route c is considered. However, as carbinolamine **109** is unable to prepare, we thus far are not able to prove or disprove this reaction pathway.

The direct conversion of the aldehyde to the amide functional group was further supported by our findings for the reaction of **97a** labeled with ^{13}C at the aldehyde

position in CD_2Cl_2 under the standard conditions (Figure 2.4). Monitoring the progress of the reaction by ^{13}C NMR spectroscopy revealed the presence of two major signals in aliquots taken from the reaction mixture. These were namely that of the labeled benzaldehyde substrate ^{13}C-**97a** decreasing in intensity and labeled amide product ^{13}C-**102a** increasing in intensity. There were no other intermediates observed during the course of this reaction. The results further supported a direct C−H bond amindation of aldehydes **97** to acylsulfonamide **102**.

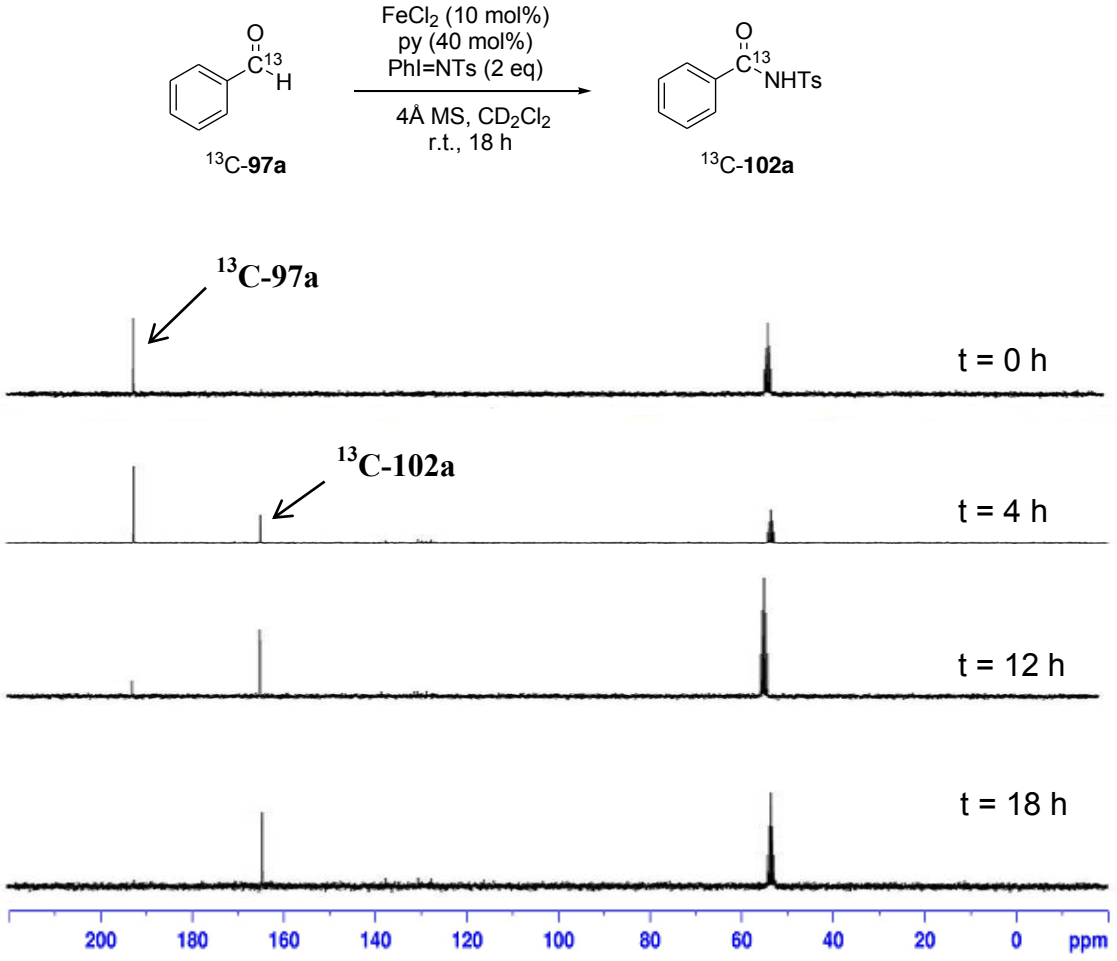
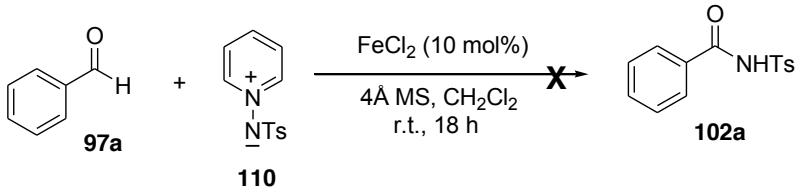


Figure 2.4 ^{13}C-Benzaldehyde *in situ* monitoring experiment at 0 h, 4 h, 12 h and 18 h

In addition to acting as a ligand to form the tetrapyridyliron(II) complex, we considered the possibility that pyridine could react with PhI=NTs and form the nitrogen transfer agent *N*-tosyliminopyridine **110**, which could be a possible intermediate in this process. An authentic sample of compound **110** was prepared from the reaction of pyridine with PhI=NTs (1.5 eq) in the presence of 5 mol% of [Ru(TTP)CO] **100** and powdered 4Å MS in CH_2Cl_2 at room temperature for 17 h.[88] Subsequent reaction of compound **110** under standard reaction conditions was shown not to lead to formation of product **102a** (Scheme 2.8). This suggested that *N*-tosyliminopyridine **110** is not a nitrogen transfer agent in this transformation.



Scheme 2.8 Attempted amidation of **97a** with *N*-tosyliminopyridine **110**

2.3 Conclusion

In summary, an efficient and practical iron-catalyzed synthetic route to acyl sulfonamides based on nitrene/imido insertion into the formylic C–H bond of aldehydes has been reported. These results show that the reaction tolerates a structurally diverse set of starting aldehydes and compliments earlier works mediated by Ru(II) and Cu(I) catalysts. While the product yields and chemoselectivities obtained are also comparable, the present method was shown to benefit from a low cost and extremely simple catalytic system generated *in situ* from iron(II) chloride and pyridine and withstand microwave

irradiation to achieve short reaction times. Similar to that for the analogous copper-catalyzed amidation reactions, our studies suggest the reaction to proceed by rate determining insertion of an iron nitrene/imido species into the acyl C–H bond. However, it differs in that the C–N bond forming process is more likely to follow a radical rather than a concerted mechanistic pathway.

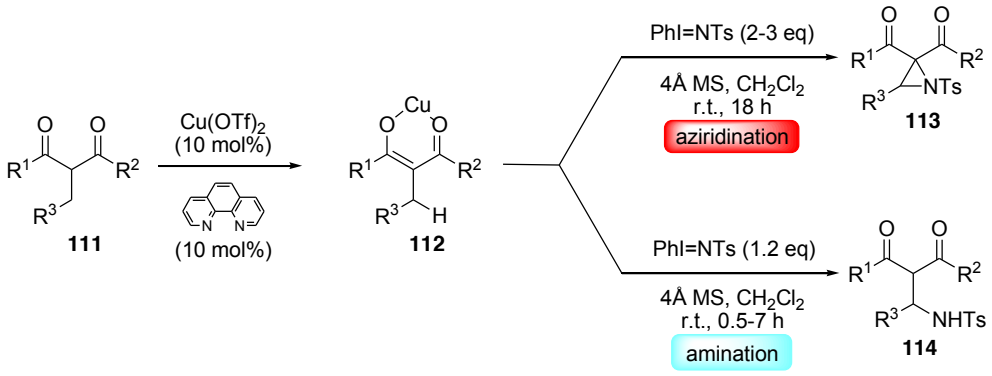
Chapter III. Copper(II) Triflate-Catalyzed Amination and Aziridination of 2-Alkyl Substituted 1,3-Dicarbonyl Compounds

3.1 Introduction

β-Amino acids and aziridines are immensely important targets in organic synthesis because of their ability to serve as building blocks in a wide variety of reactions.[89,90] They are also found as a substructure in numerous bioactive natural products and pharmaceutically interesting compounds. For this reason, establishing methods that can construct these two classes of nitrogen-containing compounds in an efficient manner and with control of substitution patterns from readily accessible substrates continues to be actively pursued. As part of our efforts on exploring the catalytic activities of copper salts for C−N bond formation,[38,61] we became interested in the potential chemical reactivity of readily available 2-alkyl substituted 1,3-dicarbonyl compounds. We reasoned that in the presence of Lewis acid, 2-alkyl substituted 1,3-dicarbonyls would undergo tautomerization to give the corresponding enolic form. Due to this conversion, *β*-C−H bond of the substrate then became allylic C−H bond *in situ*, which was more feasible for nitrene/imido insertion to occur and gave the corresponding *β*-aminated product.[91] The formation of aziridine **113** was unprecedented with a mechanistically intriguing formal aziridination of a C−C bond.

In this chapter, we report the synthesis of *α*-acyl-*β*-amino acid and 2,2-diacyl aziridine derivatives by copper(II)-catalyzed amination and azidirination of a common and readily available 2-alkyl substituted 1,3-dicarbonyl compounds with PhI=NTs (Scheme 3.1). This divergence in product selectivity was found to be possible through

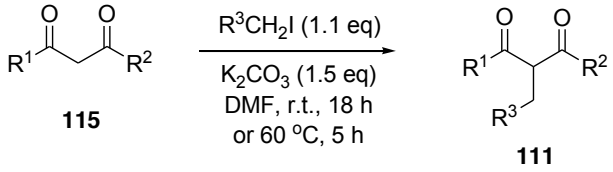
slight modification of the reaction conditions.



Scheme 3.1 Synthesis of 2,2-diacyl aziridines **113** and α-acyl-β-amino acids **114** from 2-alkyl substituted 1,3-dicarbonyl compounds **111**

3.2 Results and Discussion

All 2-alkyl substituted 1,3-dicarbonyl compounds **111** studied in this work were either purchased from commercial sources or prepared according to reported procedures.[92] This step involved alkylation of 1,3-dicarbonyl compounds **115** with iodoalkane and K_2CO_3 in *N*,*N*-dimethylformamide illustrated in Scheme 3.2.

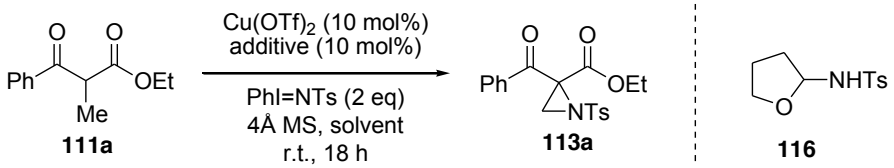


Scheme 3.2 Synthesis of 2-alkyl substituted 1,3-dicarbonyl compounds **111**

Our studies began with the copper-catalyzed reactions of ethyl 2-methyl-3-oxo-3 -phenylpropanoate **111a** and PhI=NTs (Table 3.1). While initial experiments with either CuI or CuCl gave <1 and 24% yield, respectively, when **111a** was treated with 10 mol%

of $Cu(OTf)_2$, PhI=NTs (2 eq) and 4Å MS in CH_2Cl_2 at room temperature for 18 h, ethyl 2-benzoyl-1-tosylaziridine-2-carboxylate **113a** was obtained in 80% yield (Table 3.1, entry 1). The structure of the nitrogen ring product was determined by ^1H NMR spectroscopy and X-ray crystallography of two closely related adducts (*vide infra*). Although geminal diacyl aziridines have been reported to exhibit a potent range of bioactivities of current interest, synthetic methods to prepare this *N*-heterocycle have remained sparse.[93] In this regard, the unprecedented formation of **113a** *via* a mechanistically intriguing formal aziridination of a C−C bond prompted us to examine this transformation more closely to establish the reaction conditions (Table 3.1, entries 2-17). This initially revealed that the addition of 10 mol% of a pyridyl-based additive, which could act as a ligand for the Cu(II) salt, to have a marked effect on the aziridination process (Table 3.1, entries 2-7). An increase of 3 and 10% in product yield, respectively, was obtained when either 3,4,7,8-tetramethyl-1,10-phenanthroline (TMP) or 1,10-phenthroline were employed (Table 3.1, entries 2 and 3). On the other hand, lower product yields were furnished on repeating the reaction with pyridine, bipyridine, terpyridine or picolinic acid (Table 3.1, entries 4-7). Lower product yields were also afforded on lowering either the catalyst loading from 10 to 5 mol% or amount of PhI=NTs from 2 to 1.5 eq (Table 3.1, entries 8 and 10). By removing 4Å MS from the reaction conditions, a similar outcome along with recovery of the *β*-ketoester substrate in 56% yield was found (Table 3.1, entry 11). In contrast, a further slight increase in product yield to 98% was obtained when both the catalyst and 1,10-phen loading was increased from 10 to 20 mol% (Table 3.1, entry 9). Changing the solvent from CH_2Cl_2 to MeCN, DMSO or toluene was found to give either no reaction or product **113a** in 10-27% yield

Table 3.1 Optimization of the reaction conditions[a]



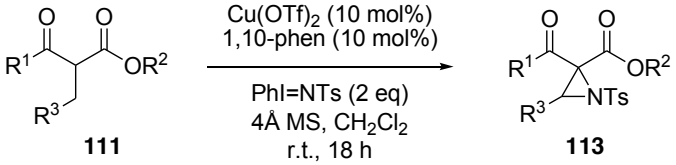
Entry	Additive	Solvent	Yield (%)[b]
1	-	CH_2Cl_2	80
2	1,10-phen	CH_2Cl_2	90
3	TMP	CH_2Cl_2	83
4	py[c]	CH_2Cl_2	12
5	bipy	CH_2Cl_2	70
6	terpy	CH_2Cl_2	45
7	picolinic acid	CH_2Cl_2	70
8[d]	1,10-phen	CH_2Cl_2	74
9[e]	1,10-phen	CH_2Cl_2	98
10[f]	1,10-phen	CH_2Cl_2	60
11[g]	1,10-phen	CH_2Cl_2	43[h]
12	1,10-phen	PhMe	10
13	1,10-phen	MeCN	27
14	1,10-phen	DMSO	-[i]
15	1,10-phen	THF	-[j]
16[k]	1,10-phen	CH_2Cl_2	50
17[l]	1,10-phen	CH_2Cl_2	-[i]

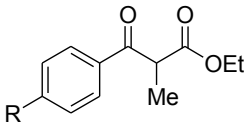
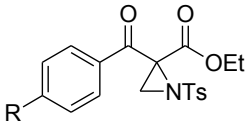
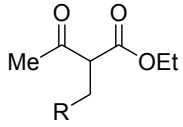
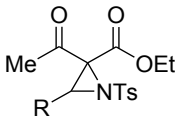
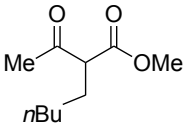
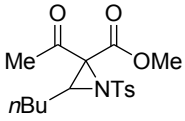
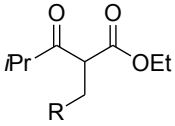
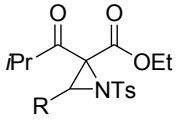
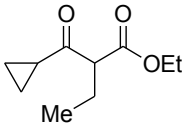
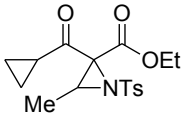
[a]All reactions were carried out at room temperature and 4Å MS (400 mg) in 2 mL of solvent for 18 h with catalyst:additive:**111a**:PhI=NTs molar ratio = 1:1:10:20. [b]Isolated yield. [c]Reaction conducted with 20 mol% of pyridine. [d]Reaction conducted with 5 mol% of $Cu(OTf)_2$ and 5 mol% of 1,10-phen. [e]Reaction conducted with 20 mol% of $Cu(OTf)_2$ and 20 mol% of 1,10-phen. [f]Reaction conducted with 1.5 eq of PhI=NTs. [g]Reaction conducted in the absence of 4Å MS. [h]Recovery of **111a** in 56% yield. [i]Trace amount of product detected on the basis of ^{1}H NMR analysis. [j]Compound **116** obtained in 47% yield. [k]Reaction conducted with $PhI(OAc)_2$ (2 eq) and $TsNH_2$ (2 eq) in place of PhI=NTs. [l]Reaction conducted with $TsNNaCl\cdot 3H_2O$ (2 eq) in place of PhI=NTs.

(Table 3.1, entries 12-14). The reaction with THF in place of CH_2Cl_2 as the solvent was the only exception, giving tetrahydo-*N*-tosylfuran-2-amine **116** as a by-product in 47% yield (Table 3.1, entry 15).[59] Likewise, a low product yield of 50% or no reaction was obtained on switching the nitrogen source from PhI=NTs to $PhI(OAc)_2$ + NH_2Ts or $TsNNaCl{\cdot}3H_2O$ (Table 3.1, entries 16 and 17). On the basis of the above results, reaction of **111a** in the presence of 10 mol% of $Cu(OTf)_2$, 1,10-phen (10 mol%), PhI=NTs (2 eq) and 4Å MS in CH_2Cl_2 at room temperature for 18 h provided the optimal conditions.

To define the generality of the present procedure, we next turned our attentions to the reactions of a series of 2-alkyl substituted *β*-ketoesters and the results are summarized in Table 3.2. Using the $Cu(OTf)_2$ + 1,10-phen system, these experiments showed the conditions to be broad, and a variety of 2-acyl-1-tosylaziridine-2-carboxylates **113b-m** could be obtained in 61-99% yield. This hitherto included 2-alkyl substituted *β*-ketoesters containing benzoyl groups bearing either an electron-donating (**111b**, Me) or electron-withdrawing (**111c-f**, F, Cl, Br, I) group, showing that such moieties were well tolerated under the reaction conditions. A similar outcome was found when we examined the reactivity of *β*-ketoesters with a pendant acyl and alkyl group (**111g-j**), including ones containing a carboxylic ester (**111h-i**) or cyclo-propane (**111m**) moiety. These reactions were found to proceed well and give the corresponding aziridine adducts **113g-m** in good to excellent yields. With the exception of **113i**, the trisubstituted products were also obtained as a mixture of diastereomers in ratios of up to 3.8:1 in reactions where $R^3 \neq H$.

Table 3.2 Copper(II)-catalyzed aziridination of 2-alkyl substituted *β*-ketoesters **111b-m**[a]

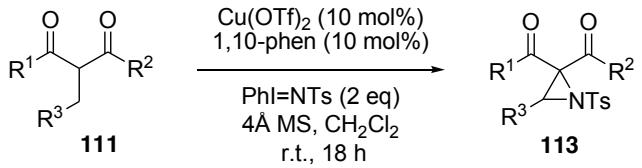


Entry	Substrate	Product	Yield (%)[b]
1	 **111b-f**	 **113b**, R = Me	64
2			**113c**, R = F	61
3			**113d,** R = Cl	73
4			**113e**, R = Br	83
5			**113f**, R = I	62
6[c,d]	 **111g-i**	 **113g**, R = Me	99
7[c,e]			**113h**, R = CO_2Et	99
8[c]			**113i**, R = CH_2CO_2Et	85
9[c,f]	 **111j**	 **113j**	95
10	 **111k-l**	 **113k**, R = H	70
11[c,g]			**113l**, R = Me	76
12[c,h]	 **111m**	 **113m**	96

[a]All reactions were carried out at room temperature and 4Å MS (400 mg) in 2 mL of CH_2Cl_2 for 18 h with $Cu(OTf)_2$:1,10-phen:**111**:PhI=NTs molar ratio = 1:1:10:20. [b]Isolated yield. [c]Reaction conducted with 3 eq of PhI=NTs. [d]Product obtained as a 1.8:1 mixture of diastereomers. [e]Product obtained as a 1:1 mixture of diastereomers. [f]Product obtained as a 3.8:1 mixture of diastereomers. [g]Product obtained as a 1.7:1 mixture of diastereomers. [h]Product obtained as a 1.3:1 mixture of diastereomers.

We next sought to evaluate the scope of this new methodology with respect to other types of 2-alkyl substituted 1,3-dicarbonyl compounds (Table 3.3). With this in mind, the reaction behavior of dimethyl 2-methylmalonate **111n** was first tested in the presence of 10 mol% of $Cu(OTf)_2$ and 10 mol% of 1,10-phen under the standard conditions and found that dimethyl 1-tosylaziridine-2,2-dicarboxylate **113n** could be afforded in 92% yield. Under similar conditions, repetition of the reaction with other 2-alkyl substituted malonates **111o-t** gave the corresponding dialkyl and dibenzyl 1-tosylaziridine-2,2-dicarboxylates **113o-t** in 60-90% yield. This included one example where the C−Cl bond remained intact when a chlorine substituent (**113t**) was introduced. Likewise, treating the

Table 3.3 Copper(II)-catalyzed aziridination of 2-alkyl substituted malonates and 1,3-diones **111n-v**[a]



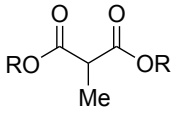
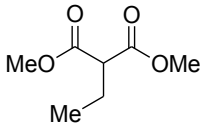
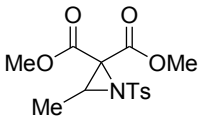
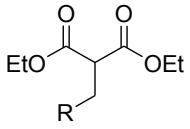
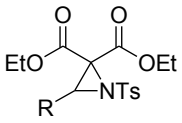
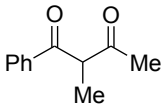
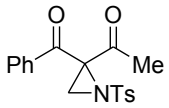
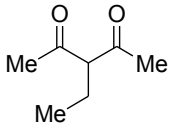
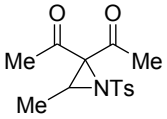
Entry	Substrate	Product	Yield (%)[b]
1	 **111n-p**	**113n**, R = Me	92
2		**113o**, R = Et	82
3		**113p**, R = Bn	60
4[c]	 **111q**	 **113q**	90

Table 3.3 (*continued*)

Entry	Substrate	Product	Yield (%)[b]
5[c]	 **111r-t**	 **113r**, R = Me	81
6[c]		**113s**, R = Et	89
7[c]		**113t**, R = $(CH_2)_2Cl$	90
8[c]	 **111u**	 **113u**	65
9[c]	 **111v**	 **113v**	99

[a]All reactions were carried out at room temperature and 4Å MS (400 mg) in 2 mL of CH_2Cl_2 for 18 h with $Cu(OTf)_2$:1,10-phen:**111**:PhI=NTs molar ratio = 1:1:10:20. [b]Isolated yield. [c]Reaction conducted with 3 eq of PhI=NTs.

2-alkyl substituted 1,3-diones **111u** and **111v** with the $Cu(OTf)_2$ + 1,10-phen catalyst system under the standard conditions afforded the corresponding 1,1'-(1-tosylaziridine-2,2 -diyl)-1,3-diones **113u** and **113v** in 65 and 99% yield, respectively. In these latter reactions, the structure of the aziridine products was determined on the basis of X-ray crystallographic analysis of **113o** and **113s** (Figure 3.1).[94] Additionally, no other side products were detected by TLC and ^{1}H NMR analysis of the crude mixtures.

Further exploration of the reaction conditions found that the α-acyl-β-amino acid derivatives **114** could be selectively formed in preference to the 2,2-diacyl aziridines **113** by simply reducing the amount of PhI=NTs from 2 to 1.2 eq (Table 3.4). Under these slightly modified conditions, reactions of 2-alkyl substituted β-ketoesters **111g**, **111l** and

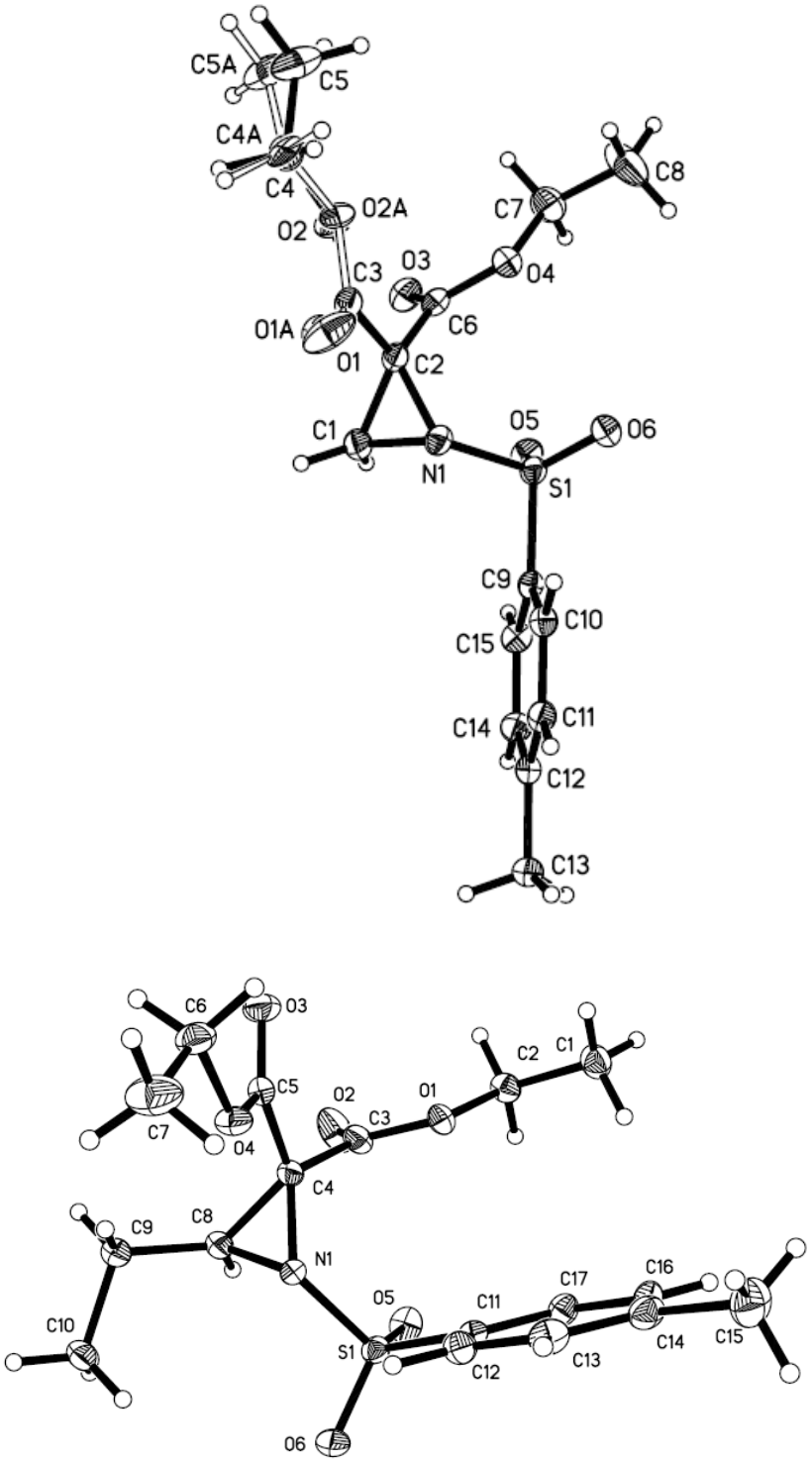
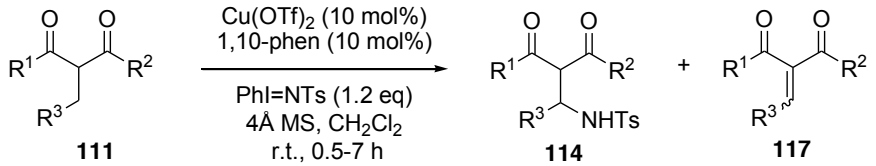


Figure 3.1 ORTEP drawings of **113o** and **113s** with thermal ellipsoids at 50% probability levels[94]

Table 3.4 Copper(II)-catalyzed amination of 2-alkyl substituted *β*-ketoesters **111g**, **111l**, and **111m**, and malonates **111q-t**[a]



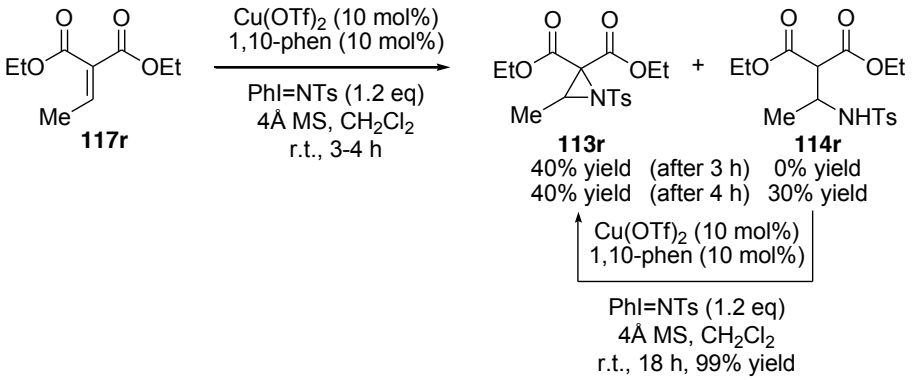
Entry	Substrate	Time (h)	Yield (%)[b]	
			114	**117**
1	**111g**, $R^1 = R^2 = Me$	3	70[c]	-[d]
2	**111l**, $R^1 = {}^iPr$, $R^2 = Me$	4	51[c]	40[e]
3	**111m**, $R^1 = {}^cPr$, $R^2 = Me$	0.5	40[c]	45[f]
4	**111q**, $R^1 = R^2 = Me$	4	90	-[d]
5	**111r**, $R^1 = Et$, $R^2 = Me$	4	95	2
6	**111s**, $R^1 = Et$, $R^2 = Et$	5	90	-[d]
7	**111t**, $R^1 = Et$, $R^2 = (CH_2)_2Cl$	7	82	16

[a]All reactions were carried out at room temperature and 4Å MS (400 mg) in 2 mL of CH_2Cl_2 with $Cu(OTf)_2$:1,10-phen:**111**:PhI=NTs molar ratio = 1:1:10:12 for 0.5-7 h. [b]Isolated yield. [c]Product obtained as a 1:1 mixture of diastereomers. [d]Trace amount of product detected on the basis of ^1H NMR analysis of the crude mixture. [e]Product obtained as a 4.4:1 mixture of geometric isomers. [f]Product obtained as a 1.6:1 mixture of geometric isomers and yield estimated on the basis of ^1H NMR analysis with CH_2Br_2 as the internal reference standard.

111m as representative examples with $Cu(OTf)_2$ (10 mol%) and 1,10-phen (10 mol%) gave the corresponding aminated products **114g**, **114l** and **114m** in 40-70% yield and as a 1:1 mixture of diastereomers. A similar outcome was observed with **114q-t** obtained in

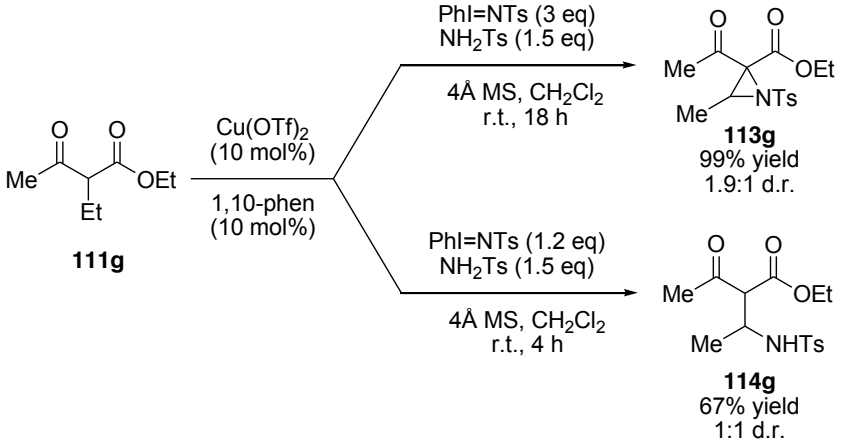
excellent yields of 82-95% from the corresponding selected 2-alkyl substituted malonates **111q-t** under these latter conditions. In the case of reactions with **111l**, **111m**, **111r** and **111t**, the corresponding alkene by-products **117l**, **117m**, **117r** and **117t** were also obtained in 2-45% yield.

In light of these latter results, we next performed a series of control experiments to gain a better understanding of the reaction mechanism (Schemes 3.3-3.7). In a first set of experiments, treating **117r** to the conditions depicted in Scheme 3.3 gave **113r** in 40% yield after 3 h. Repeating this transformation again for a longer reaction time of 4 h, on the other hand, gave the aziridine product along with compound **114r** in 40 and 30% yield, respectively. Conversion of the *β*-aminated adduct to **113r** in 99% yield was then accomplished by exposing **114r** once more to the same conditions for 18 h. This indicates that the aziridination process could proceed *via* a pathway involving either or both **114** and **117** as intermediates. It additionally suggests that the origin of the alkene could be due to the direct reaction of the enolate of **111** with PhI=NTs presumably *via* an addition-elimination process rather than from deamination of **114**.[93b] Formation of **117** in this manner would be consistent with our observations showing a marked increase in the amount of alkene obtained as the acidity of the substrate increased from 2-alkyl substituted malonates to *β*-ketoesters in Table 3.4. It would also explain the NH_2Ts and PhI detected by ^1H NMR analysis in the crude mixtures of these reactions.



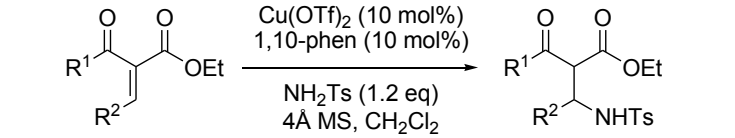
Scheme 3.3 $Cu(OTf)_2$-catalyzed reactions of **114r** and **117r** with PhI=NTs

The possibility that *in situ* formed NH_2Ts could then act as an inhibitor was also ruled out when we examined the reactions of **111g** with 1.2 or 3 eq of PhI=NTs and 1.5 eq of the aryl sulfonamide under the standard conditions (Scheme 3.4). In both instances, this revealed the production of the corresponding aziridine and *β*-aminated products **113g** and **114g** in 99 and 67% yield and diastereomeric ratio (d.r.) of 1.9:1 and 1:1, respectively, comparable to those furnished in the analogous reactions described in Tables 3.2 and 3.4.



Scheme 3.4 $Cu(OTf)_2$-catalyzed reactions of **111g** with PhI=NTs in the presence NH_2Ts

In another set of experiments, the interactions of compounds **117l**, **117r** and **117t** with 1.2 eq of NH_2Ts and 10 mol% of the Cu(II) + 1,10-phen catalyst system in CH_2Cl_2 at room temperature for 4-7 h was next investigated (Scheme 3.5). In our hands, subjecting **117r** to these conditions was found to give **114r** in 24% yield. In contrast, the analogous reactions with **117l** and **117t** led to recovery of only the starting alkene in both instances. Added to this are our findings that showed **117m** to rapidly decompose in CH_2Cl_2 over a 30 min period to give a variety of side products that could not be identified by NMR analysis. These marked differences in reactivity to those observed for **111r**, **111l**, **111m**, and **111t** with PhI=NTs shown in Table 3.4 suggest a pathway involving 1,4-conjugate addition of the aryl sulfonamide to an *in situ* formed alkene to be unlikely. While this amination path cannot be completely ruled out, if operative, we posit that it is most probably limited to sterically unhindered 2-alkyl substituted malonates and even then, at most provide a minor contribution to the overall yield.



117l, R^1 = ^{i}Pr, R^2 = Me
117r, R^1 = OEt, R^2 = Me
117t, R^1 = OEt, R^2 = $(CH_2)_2Cl$

114l, 0% yield (after 4 h)
114r, 24% yield (after 4 h)
114t, 0% yield (after 7 h)

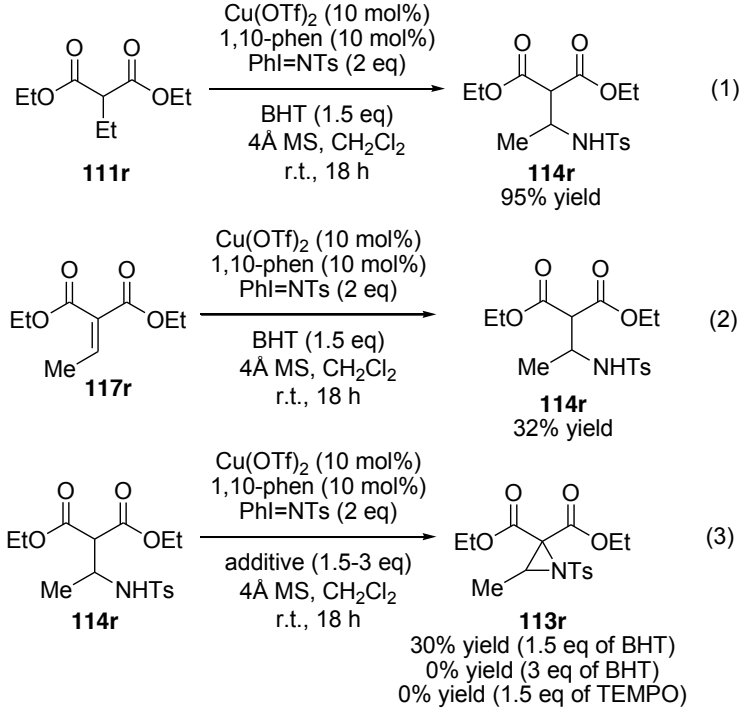
Scheme 3.5 $Cu(OTf)_2$-catalyzed reactions of **117l**, **117r** and **117t** with NH_2Ts as the nitrogen source

On the other hand, the premise that the present C−N bond forming processes occur *via* Cu(II)-mediated transfer of the nitrene/imido group from PhI=NTs to the substrate is

evident in two experiments examined in this work. First is the preferential amination of the α-C−H bond of THF to give compound **116** as a by-product for the reaction of **111a** with PhI=NTs and the oxygen heterocycle as the solvent under the conditions described in Table 3.1, entry 15.[59] Second is the markedly lower yield of **113a** and substantial recovery of the substrate observed when the analogous reaction was examined with CH_2Cl_2 as the solvent and in the absence of 4Å MS (Table 3.1, entry 11). This would be consistent with competitive hydrolysis of the nitrene/imido donor due to residual amounts of H_2O present in the reaction mixture.[95]

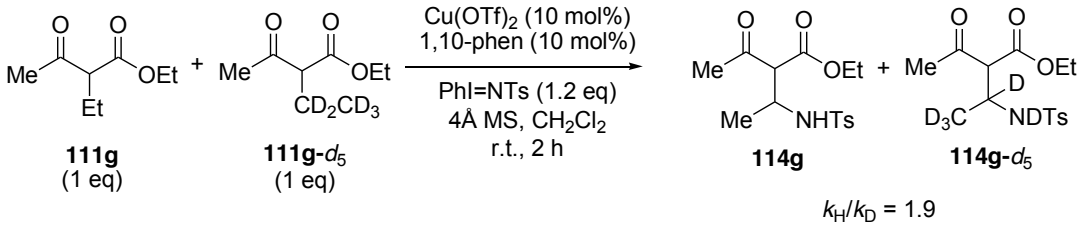
In a final set of control experiments, we turned our attentions to the nature of the nitrene/imido transfer in the present Cu(II)-catalyzed reactions. In an earlier work, the use of the radical inhibitor butylhydroxytoluene (BHT) was demonstrated to implicate the possible involvement of radical species in Ag(I)-catalyzed amination of the C–H bond of alkanes with PhI=NTs.[96] With this in mind, the reactivities of compounds **111r**, **114r** and **117r** in the presence of 1.5-3 eq of BHT or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and 2 eq of PhI=NTs were first compared (Scheme 3.6). This revealed a change in product selectivity in reactions with either **111r** or **117r** as the substrate, affording **114r** and not **113r** in 95 and 32% yield, respectively (Scheme 3.6, eq 1 and 2). In the latter case, this could be presumably due to decomposition of PhI=NTs to NH_2Ts by the metal catalyst,[6,95] followed by Cu(II)-mediated 1,4-conjugate addition of the aryl sulfonamide to the alkene, reflecting our earlier findings depicted in Scheme 3.5. In contrast, reactions with **114r** showed the yield of aziridine **113r** to decrease as the ratio of [BHT]:[PhI=NTs] increased while replacing the phenol additive with TEMPO led to only recovery of the β-aminated substrate in near quantitative yield (Scheme 3.6, eq 3). This

trend would account for **114r** obtained from **111r** shown in Scheme 3.6, eq 1 not proceeding on to the aziridine product as the amount of PhI=NTs decreases due to the gradual formation of the *β*-aminated adduct. It would also be in good agreement with that reported in works describing Ag(I)-catalyzed C–H bond aminations.[96] Overall, these observations suggest that C–H bond amination of **111** to give **114** occurs *via* a concerted asynchronous pathway whereas formal aziridination of **114** or **117** to afford **113** proceeds through a radical-based mechanism. This latter argument in which the aziridine formation process occurs *via* radical species is additionally corroborated by the lack of stereoselectivity found in a number of reactions of substrates examined in Table 3.2.



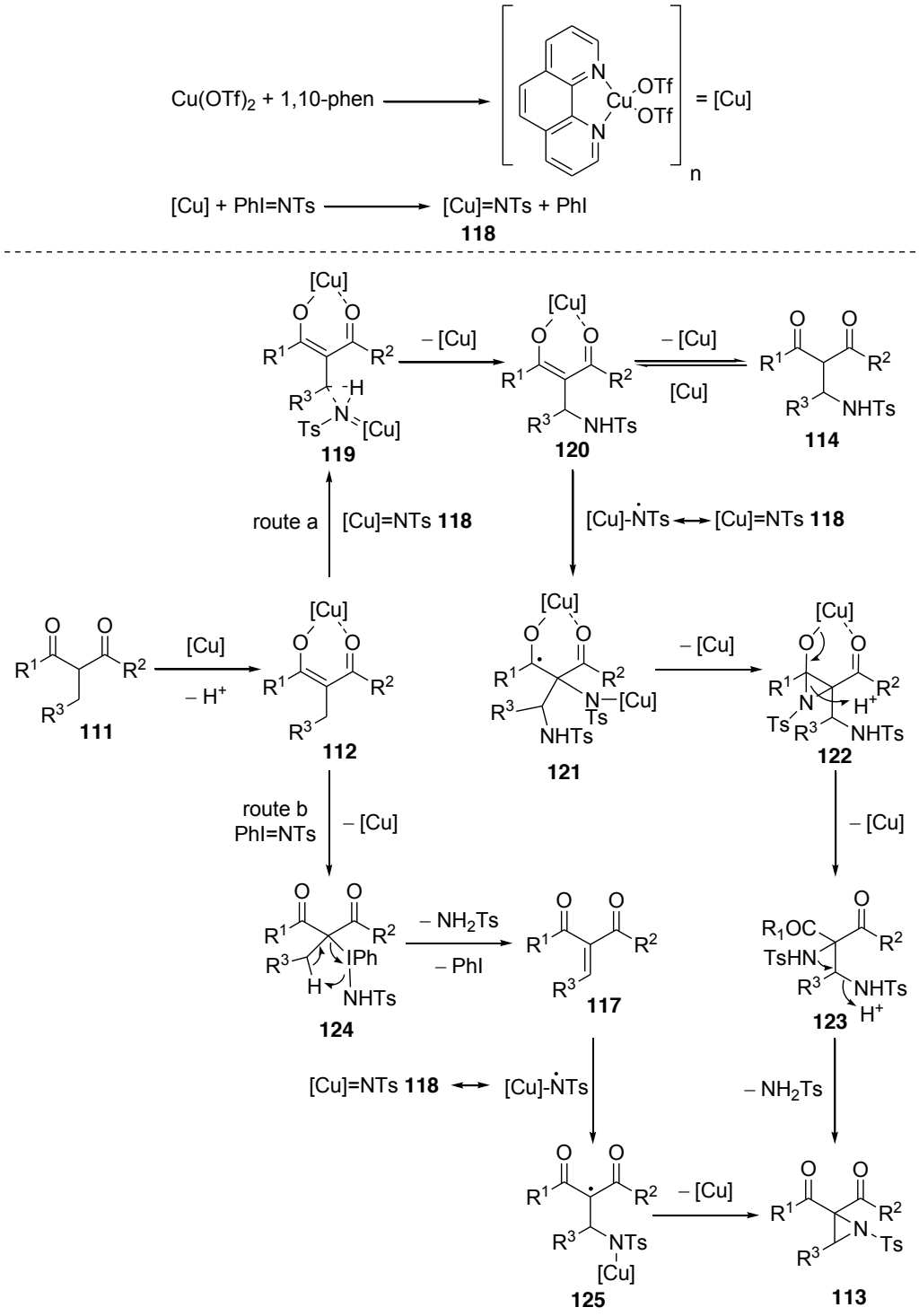
Scheme 3.6 $Cu(OTf)_2$-catalyzed reactions of **111r**, **114r** and **117r** in the presence of a radical scavenger

To provide further support for our hypothesis, we next turned to measuring the deuterium kinetic isotope effect (KIE) for the present Cu(II)-catalyzed reactions with **111g** and **111g**-d_5 as the test substrates under the conditions described in Scheme 3.7. Analysis by GC-MS gave a KIE value of 1.9 that suggested C−H bond cleavage might be the rate determining step. This value is in the same range to those previously reported for metal- and base-mediated concerted nitrene and carbene reactions, with KIE values of 1.2 to 2.1 depending on the catalyst and substrate employed.[97-99] By contrast, Fe(II)- and Ru(II)-based intermolecular C–H bond aminations, which are thought to occur by way of a H-atom abstraction/radical rebound pathway, afford KIE values of greater than 4.4.[100,101]



Scheme 3.7 Measurement of the deuterium kinetic isotope effect for the $Cu(OTf)_2$-catalyzed reactions of **111g** and **111g**-d_5

Although highly speculative, the above results led us to put forward the mechanism outlined in Scheme 3.8 for the present Cu(II)-catalyzed amination and aziridination of 2-alkyl substituted 1,3-dicarbonyl compounds **111** with PhI=NTs. This could involve the initial formation of a Cu-1,10-phen species **118**, in either the monomeric or polymeric form, from reaction of $Cu(OTf)_2$ and 1,10-phen additive.[102] Further reaction of this Cu-



Scheme 3.8 Proposed reaction pathway for the formation of *α*-acyl-*β*-amino acid and 2,2-diacyl aziridine derivatives

1,10-phen complex with PhI=NTs generates the putative highly reactive [Cu]=NTs nitrene/ imido group in [Cu]=NTs **118** into the allylic C–H bond of this newly formed species.[103] At the same time, coordination of the Cu-1,10-phen complex to **111** could occur and give the copper-enolate species **112**. Subsequent rate-limiting transfer of the enolic form of the substrate *via* a direct insertion pathway is then thought to deliver **114** (route a in Scheme 3.8).[91] Under conditions when the [Cu]=NTs species **118** can be rapidly reformed due to an excess amount of PhI=NTs, further transfer of the nitrene/ imido group to the C=C bond of the copper-enolate of **114** *via* the carboradical **121** would give the aziridine **122**.[104] Presumably, the acid labile nature of the aziridin-2-ol intermediate results in ring-opening to afford the diamine **123** that can undergo deaminative cyclization to provide **113**.[105] Alternatively, the copper-enolate species **118** could directly react with PhI=NTs to give the hypervalent iodine(III) adduct **124** (route b in Scheme 3.8).[93b] Deiodination of this newly formed intermediate would furnish **117**. Radical nitrene/ imido transfer of the [Cu]=NTs species to the alkene intermediate *via* the carboradical **125** would then complete the aziridination process to deliver **113**.

3.3 Conclusion

In summary, we have exploited the intriguing reactivities of 2-alkyl substituted 1,3-dicarbonyl compounds in the presence of a Cu(II) salt as catalyst and PhI=NTs to prepare α-acyl-β-amino acid and 2,2-diacyl aziridine derivatives. The reaction was shown to be applicable to a wide range of 2-alkyl substituted 1,3-dicarbonyl compounds containing electron-withdrawing, electron-donating and pendant functional groups. Complete control of product selectivity in the reaction was shown to be possible through slight

modification of the reaction conditions.

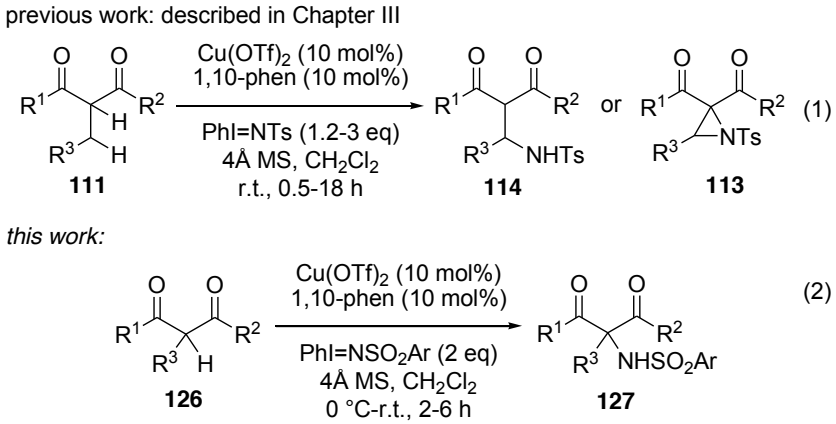
Chapter IV. Copper(II) Triflate-Catalyzed Amination of 1,3-Dicarbonyl Compounds

4.1 Introduction

An ongoing challenge in medicinal chemistry is the design of new compounds containing unnatural α-amino acids, those outside the set of 20 used by Nature, which can exhibit novel modes of therapeutic activity.[106] For this reason, the development of novel routes to new members of this immensely important class of biomolecules from readily available and inexpensive substrates and catalytic systems continues to be actively pursued in organic synthesis.[107]

In the previous chapter, we reported a method for the synthesis of α-acyl-β-amino acid derivatives **114** that relied on nitrene/imido insertion at the β-methylene C−H bond of 2-alkyl substituted 1,3-dicarbonyl compounds **111** with PhI=NTs as the nitrogen source and $Cu(OTf)_2$ + 1,10-phen catalyst system (Scheme 4.1, eq 1).[108] By increasing the amount of the iminoiodane employed, preferential formal aziridination of the C−C bond of the 2-alkyl substituent of the starting material to give 2,2-diacyl aziridines **113** could be realized. Further exploration of this field led us to investigate the potential chemical reactivity at the α-position of 1,3-dicarbonyl compounds **126** (Scheme 4.1, eq 2). We reasoned that insertion of a putative metal nitrene/imido species to the α-C−H bond of the substrate would represent an attractive synthetic approach to ketone substituted α-amino acid derivatives **127**, a new of class of these biomolecules that would be of interest in drug discovery.[106]

In this chapter, we disclose the details of this efficient synthetic method to this novel class of α-amino acid derivatives that relies upon copper(II)-catalyzed chemoselective amination of 1,3-dicarbonyl compounds with PhI=NSO_2Ar. The application of this catalytic C−N bond formation process to the enantioselective synthesis of a precursor of 3-styryl-2-benzoyl-L-alanine in two steps is also presented.



Scheme 4.1 Copper(II)-catalyzed reactivities of β-dicarbonyl compounds with PhI=NSO_2Ar

4.2 Results and Discussion

Following our success of using $Cu(OTf)_2$ + 1,10-phen to effect amination and aziridination of 2-alkyl substituted 1,3-dicarbonyl compounds **111** with PhI=NTs, we chose this catalytic system and ethyl 3-oxo-3-phenylpropanoate **126a** as the model substrate to test the feasibility of our hypothesis (Table 4.1). This revealed subjecting **126a** and 2 eq of PhI=NTs to 10 mol% of $Cu(OTf)_2$, 10 mol% of 1,10-phen and 4Å MS in CH_2Cl_2 at room temperature for 6 h gave the best result (Table 4.1, entry 1). Under these conditions, ethyl 3-oxo-3-phenyl-2-(tosylamino)propanoate **127a** was furnished in

near quantitative yield. On the other hand, lower product yields were found when the reaction was repeated with either terpyridine (terpy), pyridine or picolinic acid in place of 1,10-phen as the ligand (Table 4.1, entries 2-4). The reactions with pyridine or terpy as the ligand also afforded ethyl 3-oxo-3-phenyl-2,2-bis(tosylamino)propanoate **128a** in 8-42% yield (Table 4.1, entries 2 and 3).

The structure of both the α,α-acyl-amino acid derivative and diaminated by-product were determined by ^{1}H NMR measurements and X-ray crystallography (Figure 4.1).[109] A similar outcome was obtained on lowering the catalyst loading from 10 to 5 mol% or the amount of PhI=NTs from 2 to 1.5 eq, changing the nitrogen source from PhI=NTs to $TsNH_2$ and either $PhI(OAc)_2$ or PhI=O, or the solvent from CH_2Cl_2 to THF, MeCN or toluene (Table 4.1, entries 5-11). The reaction with THF in place of CH_2Cl_2 as the solvent was found to give tetrahydro-*N*-tosylfuran-2-amine **116** as an additional by-product in 26% yield (Table 4.1, entry 9).[58,59] Likewise, control experiments with $Cu(OTf)_2$ and other Cu(I) and Cu(II) salts in the absence of a ligand, $[Rh_2(oct)_4]$ **129** (Hoct = octanoic acid) or [Ru(TTP)CO] **100** as the catalyst did not lead to any improvements (Table 4.1, entries 12-21 and 24-25). A survey of all these latter metal catalysts showed that either or both the mono- and diaminated adducts were furnished in lower yields of 9-69% or no reaction was observed and the starting material was recovered in near quantitative yield. Interestingly, while reactions mediated by either CuO or CuOTf gave a slightly higher product yield than that with $Cu(OTf)_2$ as catalyst, their activity in analogous experiments in the presence of the 1,10-phen ligand were less effective (Table 4.1, entries 22 and 23).

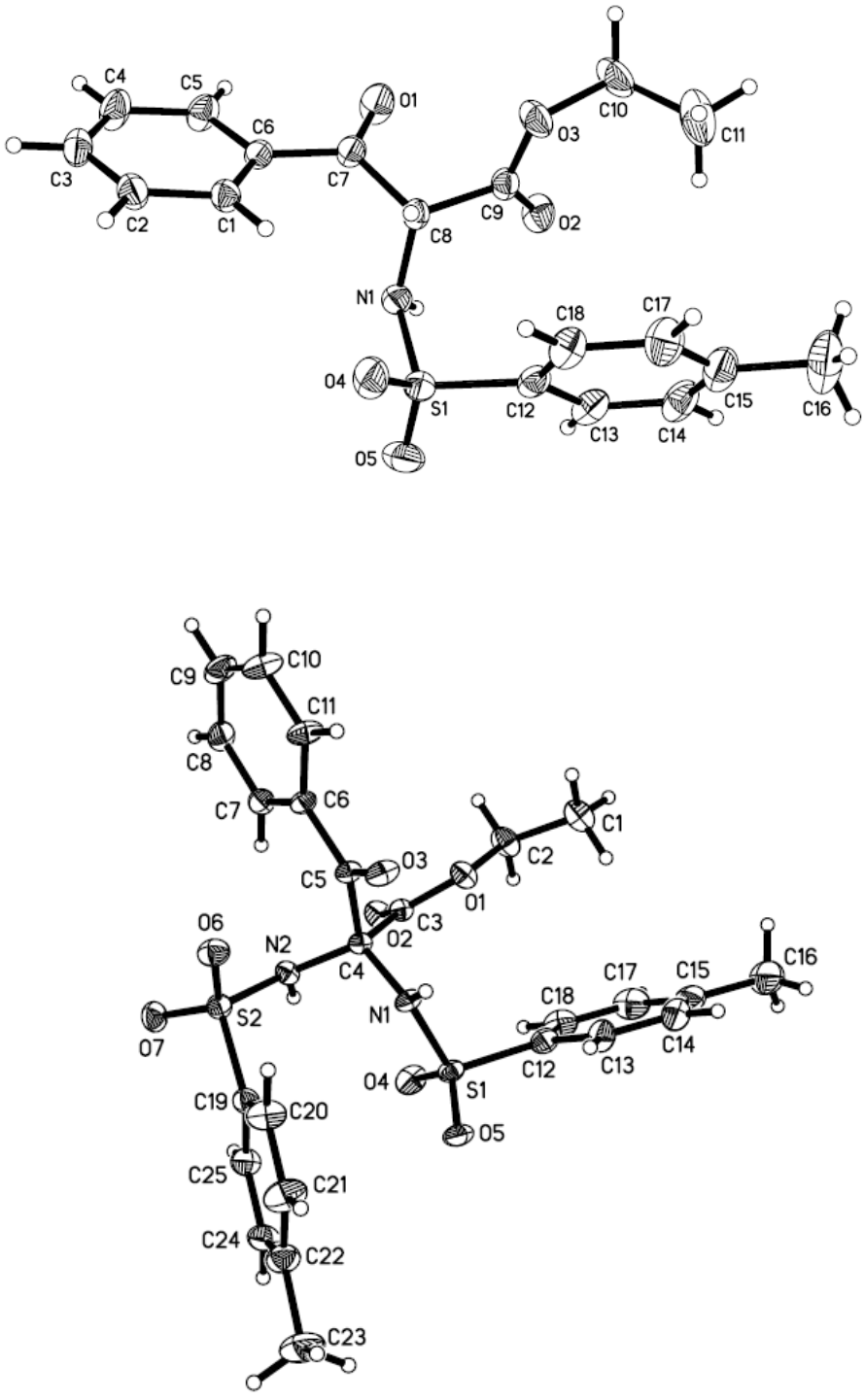
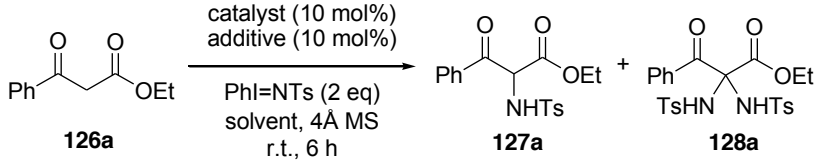


Figure 4.1 ORTEP drawings of **127a** and **128a** with thermal ellipsoids at 50% probability levels[109]

Table 4.1 Optimization of the reaction conditions[a]

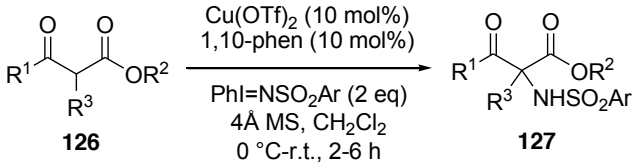


Entry	Catalyst	Additive	Solvent	Yield (%)[b]	
				127a	**128a**
1	$Cu(OTf)_2$	1,10-phen	CH_2Cl_2	99	-
2	$Cu(OTf)_2$	terpy	CH_2Cl_2	58	8
3	$Cu(OTf)_2$	py	CH_2Cl_2	12	42
4	$Cu(OTf)_2$	picolinic acid	CH_2Cl_2	76	-
5[c]	$Cu(OTf)_2$	1,10-phen	CH_2Cl_2	47	10
6[d]	$Cu(OTf)_2$	1,10-phen	CH_2Cl_2	74	-
7[e]	$Cu(OTf)_2$	1,10-phen	CH_2Cl_2	51	-
8[f]	$Cu(OTf)_2$	1,10-phen	CH_2Cl_2	42	-
9	$Cu(OTf)_2$	1,10-phen	THF	73[g]	-
10	$Cu(OTf)_2$	1,10-phen	MeCN	24	20
11	$Cu(OTf)_2$	1,10-phen	PhMe	37	-
12	$Cu(OTf)_2$	-	CH_2Cl_2	60	16
13	CuO	-	CH_2Cl_2	69	16
14	$CuCl_2$	-	CH_2Cl_2	3	20
15	$CuBr_2$	-	CH_2Cl_2	-	10
16	CuOTf	-	CH_2Cl_2	68	16
17	Cu_2O	-	CH_2Cl_2	12	8
18	CuCN	-	CH_2Cl_2	-	23
19	CuCl	-	CH_2Cl_2	-	31
20	CuBr	-	CH_2Cl_2	30	9
21	CuI	-	CH_2Cl_2	-	-
22	CuO	1,10-phen	CH_2Cl_2	76	11
23	CuOTf	1,10-phen	CH_2Cl_2	24	12
24	$[Rh_2(oct)_4]$	-	CH_2Cl_2	34	-
25	[Ru(TTP)(CO)]	-	CH_2Cl_2	68	10

[a]All reactions were carried out at room temperature in CH_2Cl_2 for 6 h in the presence of powdered 4Å MS with catalyst:ligand:**126a**:PhI=NTs molar ratio = 1:1:10:20. [b]Isolated yield. [c]Reaction conducted with 5 mol% of $Cu(OTf)_2$. [d]Reaction conducted with 1.5 eq of PhI=NTs. [e]PhI=NTs was replaced by $PhI(OAc)_2$ and $TsNH_2$. [f]PhI=NTs was replaced by PhI=O and $TsNH_2$. [g]Tetrahydro-*N*-tosylfuran-2-amine **116** was obtained in 26% yield.

The generality of our catalytic system was next challenged with a series of β-ketoesters and iminoiodane sources and the results are summarized in entries 1-17 in Table 4.2. In general, these reactions proceeded well and a variety of α,α-acyl amino acid derivatives could be afforded in good to excellent yields of 81-99%. With the exception of **126h**, which gave recovery of the substrate in near quantitative yield, β-ketoesters containing benzoyl groups bearing an electron-donating or electron-withdrawing group were found to be well tolerated, furnishing **127c-g** in 93-97% yield (Table 4.2, entries 2-6). A comparable outcome was found when we examined the reactivity of β-ketoesters

Table 4.2 $Cu(OTf)_2$-catalyzed amination of β-ketoesters **126a-r**[a]



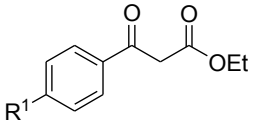
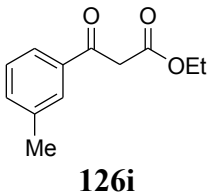
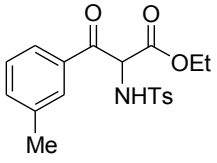
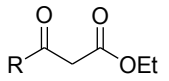
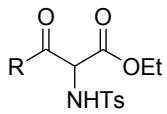
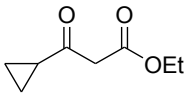
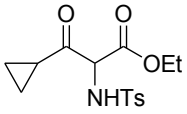
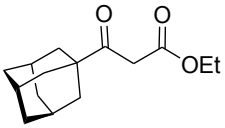
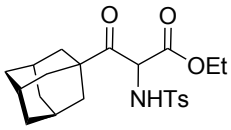
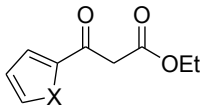
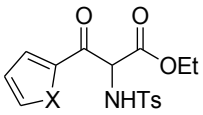
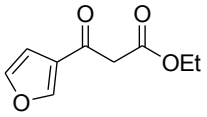
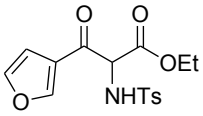
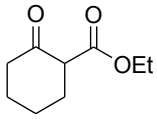
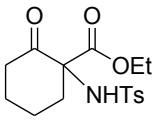
Entry	Substrate	Product	Yield (%)[b]
1	 **126a-h**	**127b**, R^1 = H, R^2 = Ns	94
2		**127c**, R^1 = OMe, R^2 = Ts	97
3		**127d**, R^1 = Me, R^2 = Ts	93
4[c]		**127e**, R^1 = F, R^2 = Ts	96
5[c]		**127f**, R^1 = Cl, R^2 = Ts	94
6[c]		**127g**, R^1 = Br, R^2 = Ts	95
7[c]		**127h**, R^1 = NO_2, R^2 = Ts	-[d]
8[c]	 **126i**	 **127i**	99

Table 4.2 (*continued*)

Entry	Substrate	Product		Yield (%)[b]
9	 **126j-k**		**127j**, R = ^{t}Bu	81
10[c]			**127k**, R = ^{i}Pr	83
11[c]	 **126l**		**127l**	93
12	 **126m**		**127m**	88
13	 **126n-p**		**127n**, X = O	93
14			**127o**, X = S	95
15			**127p**, X = NMe	92
16	 **126q**		**127q**	94
17	 **126r**		**127r**	-[e]

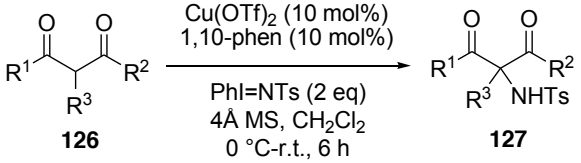
[a]All reactions were carried out at room temperature in CH_2Cl_2 in the presence of powdered 4Å MS with molar ratio $Cu(OTf)_2$:phen:**126**:PhI=NSO_2Ar molar ratio = 1:1:10:20 for 2-6 h; refer to experimental section for individual reaction time. [b]Isolated yield. [c]Reaction carried out at 0 °C. [d]Trace amount of product detected on the basis of ^{1}H NMR analysis of the crude mixture along with recovery of the starting material in near quantitative yield. [e]Mixture of unknown side-products afforded based on ^{1}H NMR analysis of the crude mixture.

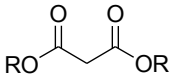
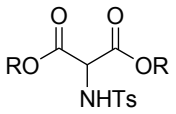
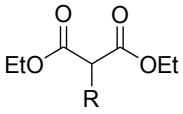
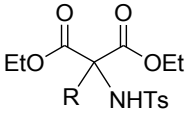
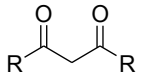
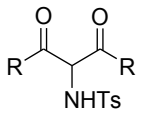
with a pendant alkane or cycloalkane moiety as in **126j-m** (Table 4.2, entries 9-12). These reactions were found to proceed well and gave the corresponding α-aminated adducts **127j-m** in excellent yields. Substrates containing a furan (**126n** and **126q**), thiophene (**126o**) or *N*-methyl substituted pyrrole (**126p**) moiety were well-tolerated under the reaction conditions, providing the corresponding α-aminated products **127n-q** in 92-95% yield (Table 4.2, entries 13-16). Changing the nitrogen source from PhI=NTs to PhI=NNs was also found to have no effect with the analogous reaction of **126a** with the latter nitrogen source giving **127b** in a comparable yield of 94% (Table 4.2, entry 1). In our hands, reaction of the cyclic β-ketoester **126r** was the only example that gave a mixture of decomposition products that could not be identified by ^{1}H NMR analysis of the crude mixture (Table 4.2, entry 17).

We next turned our attention to define the scope of this methodology with respect to other types of 1,3-dicarbonyl compounds (Table 4.3). With this in mind, the amination of dimethyl malonate **126s** with PhI=NTs was first tested in the presence of 10 mol% of $Cu(OTf)_2$ and 10 mol% of 1,10-phen under the standard conditions and found that dimethyl 2-(tosylamino)malonate **127s** could be afforded in 87% yield (Table 4.3, entry 1). Under similar conditions, repetition of the reaction with other malonic esters **126t-y** gave the corresponding dialkyl and diphenyl 2-(tosylamino)malonates **127t-y** in 53-99% yield (Table 4.2, entries 2-7). This included one example that tolerated the introduction of a phenyl substituent (**127y**) at the α-position of the substrate (Table 4.3, entry 7). However, replacing the phenyl substituent at this position with a more bulky *tert*-butyl group (**127z**) was found to result in recovery of the substrate in near quantitative yield

(Table 4.3, entry 8). On the other hand, the reactions could be extended to the 1,3-diones **126**α-γ and give the corresponding 3-(tosylamino)pentane-2,4-diones **127**α-γ in 62-98% yield (Table 4.2, entries 9-11).

Table 4.3 $Cu(OTf)_2$-catalyzed amination of malonic esters and 1,3-diones **126s-**γ[a]

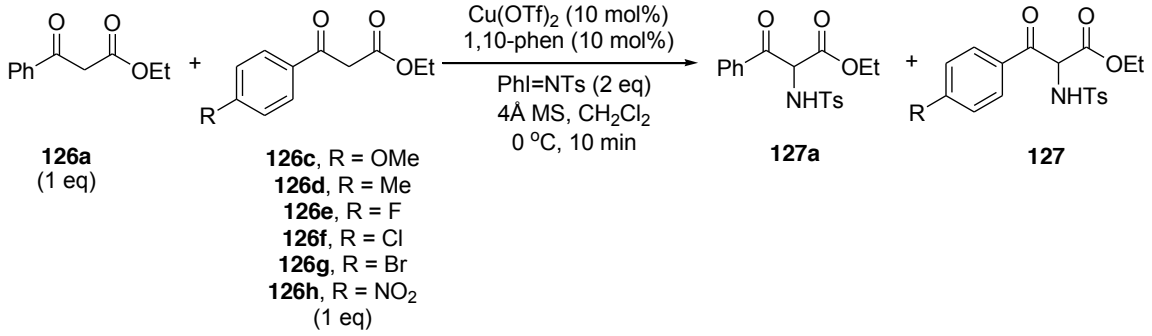


Entry	Substrate	Product	Yield (%)[b]
1		**127s**, R = Me	87
2		**127t**, R = Et	99
3[c]	 **126s-x**		**127u**, R = ^{i}Pr	99
4			**127v**, R = ^{t}Bu	98
5[c]			**127w**, R = Ph	53
6[c]			**127x**, R = allyl	88
7	 **126y-z**		**127y**, R = Ph	70
8			**127z**, R = ^{t}Bu	-[d]
9			**127**α, R = Me	98
10	 **126**α-γ		**127**β, R = ^{t}Bu	66
11			**127**γ, R = Ph	62

[a]All reactions were carried out at room temperature in CH_2Cl_2 in the presence of powdered 4Å MS with molar ratio $Cu(OTf)_2$:phen:**126**:PhI=NTs molar ratio = 1:1:10:20 for 6 h. [b]Isolated yield. [c]Reaction carried out at 0 °C. [d]Recovery of the starting material in near quantitative yield.

To gain an insight into the possible mechanism, we performed competition experiments on Cu(II)-catalyzed amination reactions of **126c-h** (Table 4.4). This gave $\log(k_X/k_H)$ values of 0.06 (**126c**), 0.01 (**126d**), −0.03 (**126e**), −0.11 (**126f**), −0.12 (**126g**) and −0.35 (**126h**), suggesting electron-donating substituents accelerate whereas electron-withdrawing substituents retard the amination process. Fitting (by least squares method) the $\log(k_X/k_H)$ data with the σ_p scale gave rise to good linearity (R^2 = 0.975) with a ρ value of −0.39 (Figure 4.2).[110] The small and negative ρ value indicates that only a

Table 4.4 Competitive rate studies[a]



Entry	R	σ_p	$\log(k_X/k_H)$[b]
1	OMe	-0.27	0.06
2	Me	-0.17	0.01
3	H	0	0
4	F	0.06	-0.03
5	Cl	0.23	-0.11
6	Br	0.23	-0.12
7	NO_2	0.78	-0.35

[a]Reaction was carried out in the presence of powdered 4Å MS in CH_2Cl_2 at 0 ºC for 10 min with $Cu(OTf)_2$:1,10-phen:PhI=NTs:**126a**:substituted ethyl 3-oxo-3-phenylpropanoate molar ratio = 1:1:20:10:10. [b]Measurements based on ^{1}H NMR analysis.

moderate positive charge is built-up in the transition state.[111] This value was found to be similar to that reported for Cu(II)-catalyzed alkene aziridinations (−0.6) in which an asynchronous transition state was proposed.[30a]

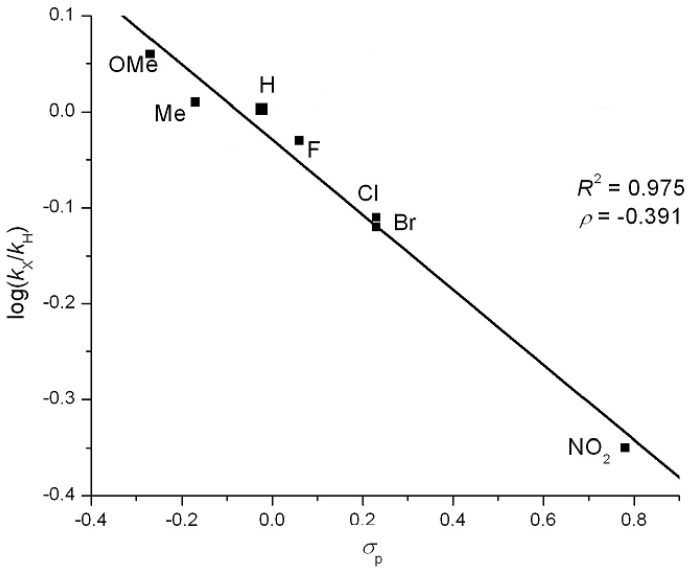
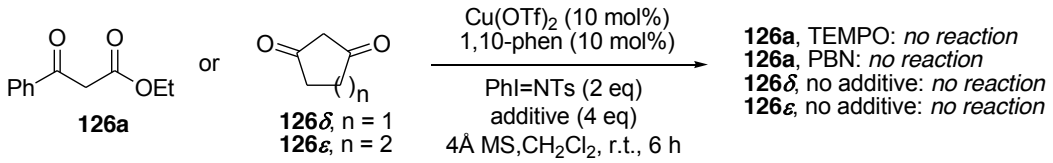


Figure 4.2 Linear free-energy correlation of log(k_X/k_H) versus σ_p for Cu(II)-catalyzed amination of 1,3-dicarbonyl compounds **126c-h** with PhI=NTs

While isolation of tetrahydro-*N*-tosylfuran-2-amine **115** furnished from reaction of **126a** by PhI=NTs in THF catalyzed by $Cu(OTf)_2$ + 1,10-phen outlined in entry 9 in Table 4.1 was fortuitous, the result argues in favour of a mechanistic pathway involving Cu(II)-mediated nitrene/imido transfer process.[59] The radical nature of this step was implied by our results showing decomposition of **126a** to a variety of unknown side-products when the substrate was treated with PhI=NTs and the Cu(II) catalyst in the presence of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or *N*-tert-butyl-*α*-phenylnitrone (PBN) under the conditions described in Scheme 4.2. This latter result would also be in good

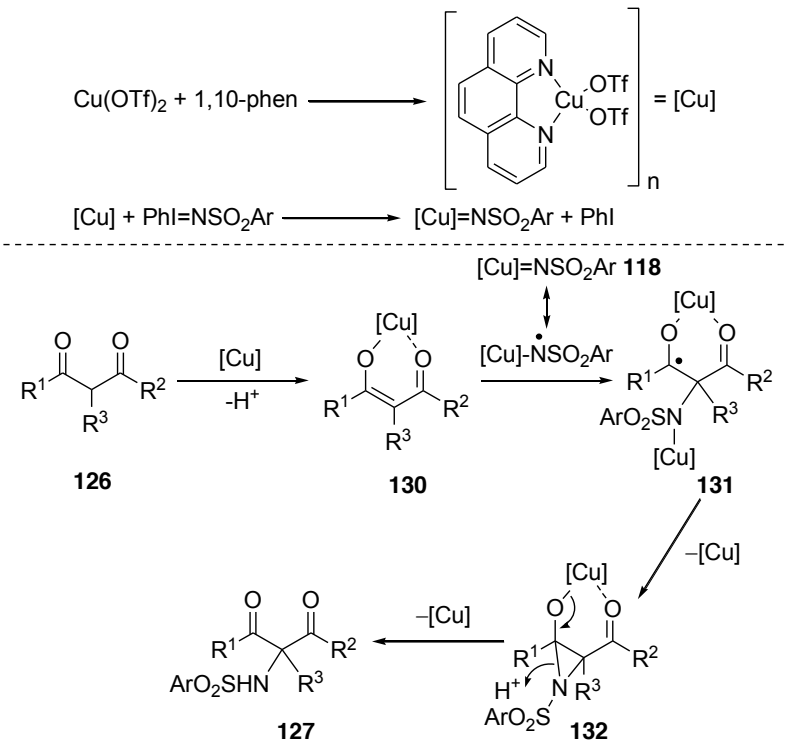
agreement with previous works using radical inhibitors to implicate the possible involvement of radical species in the respective Ag(I)- and Cu(II)-catalyzed amination of C−H bonds of alkanes and 2-alkyl substituted 1,3-dicarbonyl compounds with PhI=NTs.[96,108] Additionally, coordination of the metal catalyst to the substrate was shown to be important based on our observations for the Cu(II)-mediated control experiments of cyclopentane-1,3-dione **126*δ*** or cyclohexane-1,3-dione **126*ε*** with PhI=NTs (Scheme 4.2). These tests afforded only the recovery of the substrate in near quantitative yield and led us to surmise that the present Cu(II)-catalyzed amination process occurs *via* a copper-enolate species.



Scheme 4.2 Control experiments with **126a**, **126*δ*** and **126*ε*** catalyzed by $Cu(OTf)_2$ + 1,10-phen

A plausible mechanism for the present Cu(II)-catalyzed amination reaction is outlined in Scheme 4.3. This could involve the initial formation of a Cu-1,10-phen species from reaction of $Cu(OTf)_2$ and 1,10-phen additive in either the monomeric or polymeric form.[102] Further reaction of this Cu-1,10-phen complex with $PhI=NSO_2Ar$ generates the putative highly reactive [Cu]= NSO_2Ar species.[103] At the same time, coordination of the Cu-1,10-phen complex to **126** could occur and give the copper-enolate species **130**. In a manner similar to the analogous aminations of silyl enol ethers and *β*-enamino

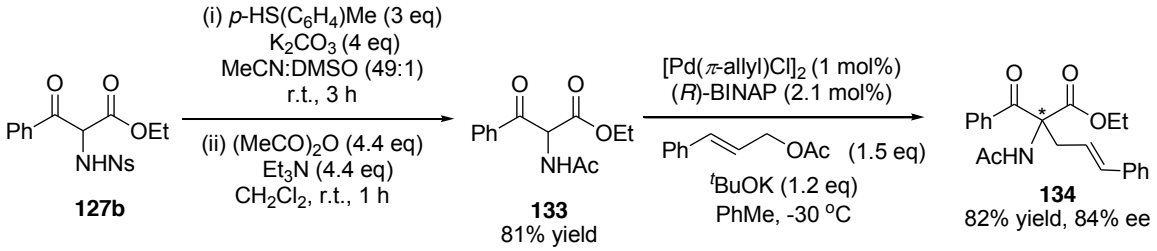
esters,[112,113] subsequent addition of the nitrene/ imido group in [Cu]= NSO_2Ar onto the C=C bond of this newly formed copper-enolate *via* the carboradical **131** would give intermediate **132**. Presumably, the acid labile nature of the aziridin-2-ol intermediate formed results in ring-opening of the cyclic moiety to provide the product **127**.



Scheme 4.3 Tentative proposed mechanism of copper(II)-catalyzed amination of 1,3-dicarbonyl compounds **126** with PhI=NSO_2Ar

Having established an efficient route to α,α-acyl-amino acid derivatives, we applied this new methodology to the synthesis of the chiral *N*-acyl-protected quaternary α-amino ethyl ester **134** (Scheme 4.4). At room temperature, nosyl deprotection of **127b** in MeCN:DMSO (49:1 v/v) was achieved with *p*-methoxyphenylthiol in the presence of K_2CO_3 . This was then followed by protection of the resultant free amine with acetic

anhydride and Et_3N in dicholoromethane to give the *N*-acyl-protected intermediate **133** in 81% yield over two steps. Subsequent treatment of this newly formed adduct with a toulene solution containing $[Pd(\pi\text{-allyl})Cl]_2$, (*R*)-BINAP and ^{t}BuOK afforded the allylated product **134** in 82% yield and 84% ee.[114]



Scheme 4.4 Synthesis of chiral 3-styryl-2-benzoyl-L-alanine derivative **134** from **127b**

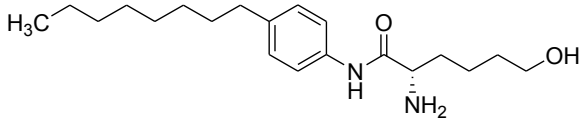
4.3 Conclusion

In summary, we have developed a mild and highly efficient copper(II)-catalyzed methodology for the amination of 1,3-dicarbonyl compounds with $PhI{=}NSO_2Ar$ as a nitrogen source. The catalytic system is inexpensive and extremely simple to form *in situ* from $Cu(OTf)_2$ and 1,10-phen. The reaction was shown to tolerate a wide variety of substrates and give the corresponding α-aminated products for applications in natural product synthesis and medicinal chemistry as exemplified by the preparation of a chiral quaternary α-amino acid derivative.

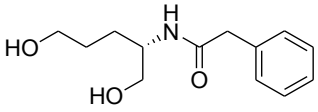
Chapter V. Iron(II) Triflate-Catalyzed Amination of Saturated *N*- and *O*-Heterocyclic Compounds

5.1 Introduction

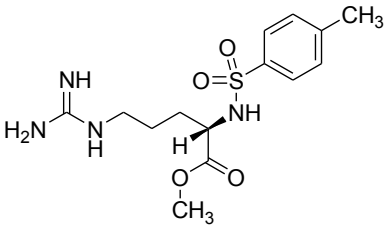
1,*n*-Diamines and 1,*n*-amino alcohols are important targets in organic synthesis because of their prominence in a myriad of biologically active compounds, use as ligands in metal catalysis and as organocatalysts.[115-117] For example, compounds **135-138** shown in Figure 5.1 have been reported to exhibit potent sphingosine kinase inhibitory,[117a] anti-inflammatory,[117b] thrombin inhibitory,[117c] anti-malarial,[117d] respectively. For this reason, developing methods that can construct these two classes of nitrogen-containing compounds from readily available, inexpensive and environmentally friendly catalytic systems would be highly desirable.



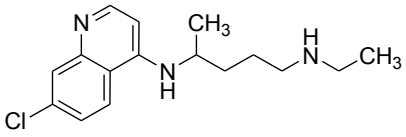
135



136



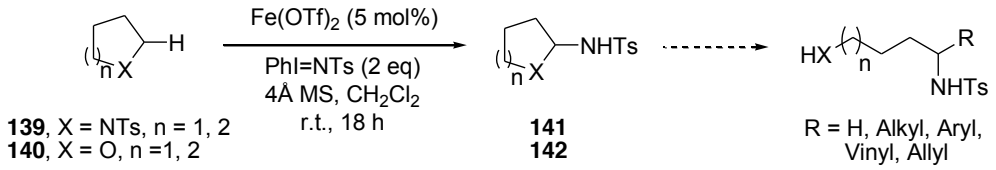
137



138

Figure 5.1 Bioactive compounds containing diamine and amino alcohol moiety

Following on from our initial success exploring the use of low cost iron- and copper-catalzyed nitrogen atom transfer reactions to C=C and C−H bonds to effect C−N bond formation,[118] we envisioned that a similar approach to functionalize the α-C−H bond of saturated *N*- and *O*-heterocylic compounds could be accomplished.[119] To our knowledge, the direct nitrene/imido insertion to α-C−H bond of saturated cyclic amines is not known. Herein, we disclose the study that led us to discover the amination of saturated nitrogen and oxygen heterocycles. The nirene/imido insertion could be achieved in the presence of $Fe(OTf)_2$ as the catalyst and PhI=NTs as the nitrogen source (Scheme 5.1). This provided the corresponding cyclic aminals and hemiaminals in good to excellent yields.

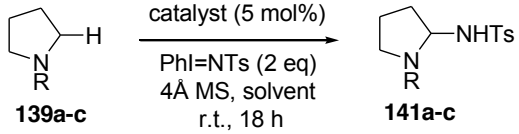


Scheme 5.1 $Fe(OTf)_2$-catalyzed amination of saturated *N*- and *O*-heterocyclic compounds

5.2 Results and Discussion

We began our studies by initially examining the $Fe(OTf)_2$-catalyzed amination of the Boc-protected pyrrolidine **139a** (Table 5.1, entry 1). The reaction was carried out with 5 mol% of the metal catalyst and PhI=NTs (2 eq) in CH_2Cl_2 at room temperature for 18 h but ^1H NMR analysis of the crude reaction mixture showed that no aminated product **141a** was obtained and the starting material **139a** was recovered in near quantitative yield. Recently, Murai and co-workers successfully demonstrated the carbonylation of $C(sp^3)$−H bonds adjacent to a nitrogen atom with $[RhCl(cod)]_2$ **143** (cod = cyclooctadiene) as the catalyst,[120] in which substrates containing a directing group

Table 5.1 Optimization of the reaction conditions[a]



Entry	**139**, R	Catalyst	Solvent	Yield (%)[b]
1	**139a**, Boc	$Fe(OTf)_2$	CH_2Cl_2	-[c]
2	**139b**, 2(5-Iodo-py)	$Fe(OTf)_2$	CH_2Cl_2	-[c]
3	**139c**, Ts	$Fe(OTf)_2$	CH_2Cl_2	80
4	**139c**, Ts	$Fe(OTf)_3$	CH_2Cl_2	78
5	**139c**, Ts	$FeCl_2$	CH_2Cl_2	70
6	**139c**, Ts	$FeBr_2$	CH_2Cl_2	72
7[d]	**139c**, Ts	$Fe(OTf)_2$	CH_2Cl_2	35
8[e]	**139c**, Ts	$Fe(OTf)_2$	CH_2Cl_2	65
9	**139c**, Ts	$Fe(OTf)_2$	DCE	67
10	**139c**, Ts	$Fe(OTf)_2$	MeCN	19
11	**139c**, Ts	$Fe(OTf)_2$	$C_6H_5CH_3$	-[c]
12	**139c**, Ts	$Fe(OTf)_2$	MeOH	-[c]
13[f]	**139c**, Ts	$Fe(OTf)_2$	CH_2Cl_2	-[c]
14[g]	**139c**, Ts	$Fe(OTf)_2$	CH_2Cl_2	-[c]
15	**139c**, Ts	$Rh_2(OAc)_4$	CH_2Cl_2	10
16	**139c**, Ts	$RuCl_3$	CH_2Cl_2	58
17	**139c**, Ts	$Cu(OTf)_2$	CH_2Cl_2	32

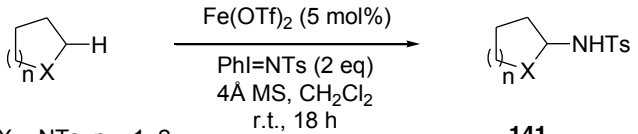
[a]All reactions were carried out at room temperature with catalyst:**139**:PhI=NTs molar ratio = 1:20:40. [b]Isolated yield. [c]Trace amount of product detected on the basis of ^1H NMR analysis of the crude mixture. [d]Reaction conducted with 2 mol% of $Fe(OTf)_2$. [e]Reaction conducted with 1.5 eq of PhI=NTs. [f]Reaction conducted with $PhI(OAc)_2$ (2 eq) and $TsNH_2$ (2 eq) in place of PhI=NTs. [g]Reaction conducted with $TsNNaCl{\cdot}3H_2O$ (2 eq) in place of PhI=NTs.

sufficiently close to the α-C−H bond was utilized as a driving force. Directed by this work, we next examined the analogous $Fe(OTf)_2$-catalyzed reaction of 5-iodo-2-(1-pyrrolidinyl)pyridine **139b** with 2 eq of PhI=NTs under similar conditions (Table 5.1, entry 2). However, no reaction was found and quantitative recovery of starting material **139b** was observed. On the other hand, switching from **139b** to 1-tosylpyrrolidine **139c** was found to give *N*,1-ditosylpyrrolidin-2-amine **141c** in 80% yield.

With this substrate in hand, the screening of a variety of iron catalysts such as $Fe(OTf)_3$, $FeCl_2$, $FeBr_2$ was found to give slightly lower product yields of 70-78% (Table 5.1, entries 4-6). Similarly, lower product yields were afforded on lowering either the catalyst loading from 5 to 2 mol% or the amount of PhI=NTs from 2 to 1.5 eq (Table 5.1, entries 7 and 8). Changing the solvent from dichloromethane to 1,2-dichloroethane, MeCN, toluene or MeOH or the nitrogen source from PhI=NTs to $PhI(OAc)_2$ + NH_2Ts or $TsNNaCl{\cdot}3H_2O$ was found to give either no reaction or **141c** in 19-67% yield (Table 5.1, entries 9-14). Analogous reactions with $Rh_2(OAc)_4$, $RuCl_3$ and $Cu(OTf)_2$ as the catalyst were also carried out and found that these catalysts were less efficient in mediating α-amination of 1-tosylpyrrolidine **139c** with product yields of 10-50% obtained (Table 5.1, entries 15-17). On the basis of the above results, reaction of **139c** in the presence of 5 mol% of $Fe(OTf)_2$, PhI=NTs (2 eq) and 4Å MS in CH_2Cl_2 at room temperature for 18 h provided the optimal conditions.

The scope and selectivity of the optimized reaction conditions were next investigated with a range of saturated *N*- and *O*-heterocyclic compounds and the results are summarized in Table 5.2. In general, the reaction conditions were found to be applicable to a variety of 5- and 6-membered cyclic amines **139** and cyclic ethers **140** with the

Table 5.2 $Fe(OTf)_2$-catalyzed amination of saturated *N*- and *O*-heterocyclic compounds[a]



139, X = NTs, n = 1, 2
140, X = O, n =1, 2

141
142

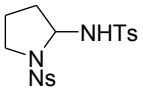
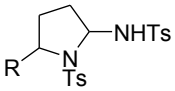
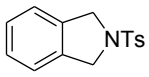
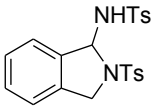
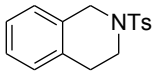
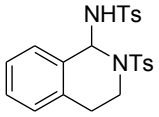
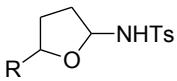
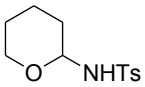
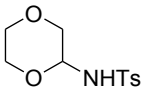
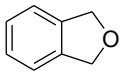
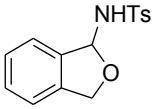
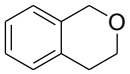
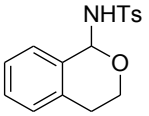
Entry	Substrate	Product		Yield (%)[b]
1[c]	 **139d**		**141d**	56
2[d]	 **139e-g**		**141e**, R = Me	40
3[e]			**141f**, R = Ph	42
4[f]			**141g**, R = *p*-FC_6H_4	38
5	 **139h**		**141h**	82
6	 **139i**		**141i**	86
7	 **140a-b**		**142a**, R = H	82
8[g]			**142b**, R = Me	56
9	 **140c**		**142c**	70
10	 **140d**		**142d**	55

Table 5.2 (*continued*)

Entry	Substrate	Product		Yield (%)[b]
11	 **140e**		**142e**	72
12	 **140f**		**142f**	90

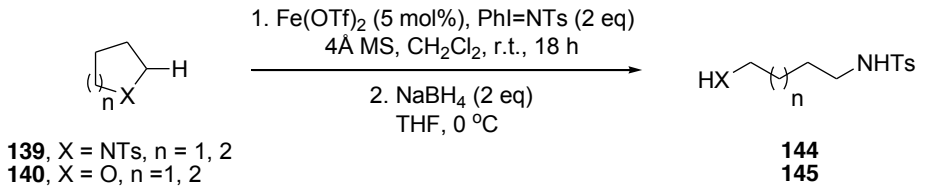
[a]All reactions were carried out at room temperature in CH_2Cl_2 for 18 h with $Fe(OTf)_2$:**139** or **140**:PhI=NTs molar ratio = 1:1:10:20. [b]Isolated yield. [c]Reaction conducted with 4 eq of PhI=NTs. [d]Product obtained as a 9.8:1 mixture of diastereomers. [e]Product obtained as a 3.6:1 mixture of diastereomers. [f]Product obtained as a 3.8:1 mixture of diastereomers. [g]Product obtained as a 1.7:1 mixture of diastereomers

corresponding aminated products **141** and **142** furnished in 38-90% yield. Steric effects may play a role as the amination of **139e-g** and **140b** gave **141e-g** and **142b** in lower yields of 38-56% (Table 5.2, entries 2-4 and 8). In addition, the diastereoselectivities obtained in **141e-g** were found to be controlled by the repulsion between the α-substituent and the -NHTs group. As the result, the bulkier α-substituent (R = Ph, *p*-FC_6H_4) was shown to give lower diastereomer ratios compared to the less bulky α-substituent (R = Me). In contrast, the saturated cyclic ether **140b** was shown to give low diastereomer ratio with α-methyl substituent as there was no significant steric difference between the upper- and lower-face of attack. On the other hand, the reaction was shown to be regioselective as the amination of substrates **139i** and **140f**, which contain three different

reactive C−H bonds at C1, C3 and C4 position, was found to proceed only at C1 and no other regioisomeric products were observed based on ^{1}H NMR analysis of the crude reaction mixtures (Table 5.3, entries 6 and 12). The C−H regioselectivities obtained herein could probably due to the double activations from benzylic position together with the inductive effect from the adjacent heteroatom. Switching the *N*-protecting group from tosyl to nosyl was found to lead to a lower product yield of 56% (Table 5.3, entry 1). Notably, one possibility for the lower product yields of 38-56% obtained from the reactions of **139d-g** and **140b** (Table 5.2, entries 1-4 and 8) could be due to the acid labile nature of the adducts during the purification process by flash column chromatography.

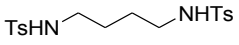
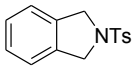
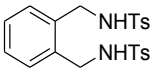
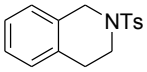
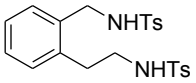
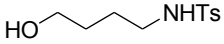
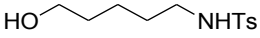
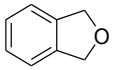
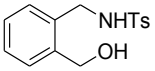
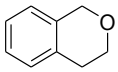
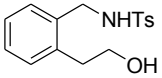
One of our interests when investigating on α-amination of saturated *N*- and O-heterocyclic compounds **139** and **140** is the ability of these cyclic aminals and hemiaminals products to undergo ring-opening to give a variety of diamines **144** and amino alcohols **145**. With this in mind, amination of a series of cyclic amines and ethers was carried out under optimized conditions followed by a reductive ring-opening with $NaBH_4$ at 0 ºC (Table 5.3). The reaction was found to proceed smoothly with 5- and 6-membered ring systems affording the corresponding diamines **144** and amino alcohols **145** in good to excellent yields of 60-87%. The synthesis benefits from by-passing the need to isolate the relatively unstable cyclic aminal **141** and hemiaminal **142**, which makes this approach less time-consuming and arduous.

Table 5.3 $Fe(OTf)_2$-catalyzed amination of saturated *N*- and *O*-heterocyclic compounds **139** and **140** followed by reductive ring-opening with $NaBH_4$[a]



139, X = NTs, n = 1, 2
140, X = O, n =1, 2

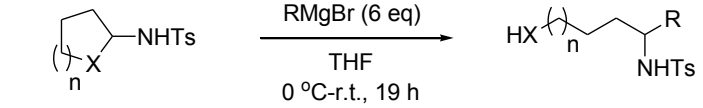
144
145

Entry	Substrate	Product		Yield (%)[b]
1	 **139c**		**144c**	68
2	 **139h**		**144h**	87
3	 **139i**		**144i**	83
4	 **140a**		**145a**	90
5	 **140c**		**145c**	63
6	 **140e**		**145e**	60
7	 **140f**		**145f**	80

[a]All reactions were carried out at room temperature in CH_2Cl_2 for 18 h with $Fe(OTf)_2$:**139** or **140**:PhI=NTs molar ratio = 1:20:40 followed by addition of $NaBH_4$ (2 eq) at 0 ºC in THF. [b]Isolated yield.

To further demonstrate the synthetic utility of this methodology, ring-opening reactions of cyclic aminals **141** and hemiaminals **142** with a variety of Grignard reagents were carried out and the results are summerized in Table 5.4. The reaction was shown to be well-tolerant to various nucleophiles ranging from alkyl, aryl, vinyl to allyl, furnishing the substituted diamines **146** and amino alcohols **147** in good to excellent yields of 66-95%. The reaction was also found to be efficient when the nucleophilic source was switched from the Grignard reagents to trimethylsilanes (Table 5.4, entries 7 and 9). In these latter reactions, the corresponding products **147b** and **147d** were afforded in 62 and 64% yield, respectively.

Table 5.4 Ring-opening of cyclic aminals **141** and hemiaminals **142** with different nucleophiles[a]



141, X = NTs, n = 1, 2
142, X = O, n =1, 2

146
147

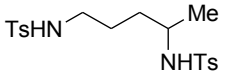
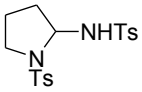
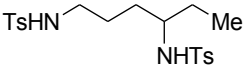
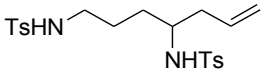
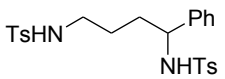
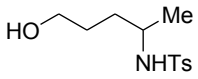
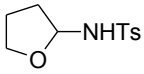
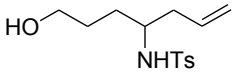
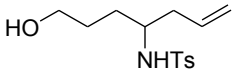
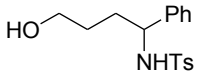
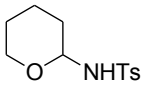
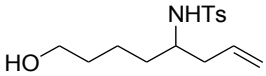
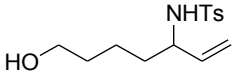
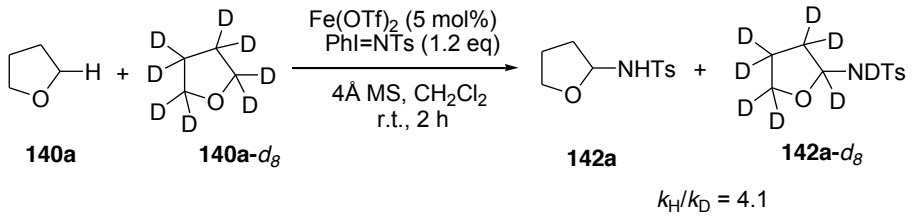
Entry	Substrate	Product		Yield (%)[b]
1			**146a**	75
2			**146b**	87
3	**141c**		**146c**	83
4			**146d**	86

Table 5.4 (*continued*)

Entry	Substrate	Product		Yield (%)[b]
5			**147a**	66
6			**147b**	95
7[c]	**142a**		**147b**	64
8			**147c**	90
9[c]			**147d**	62
10	**142c**		**147e**	75

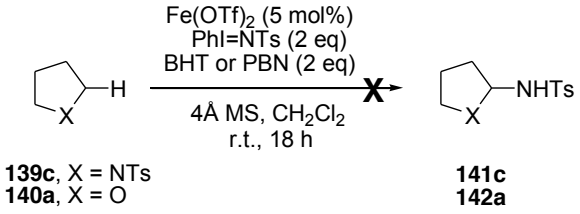
[a]All reactions were carried out in THF for 19 h with **141** or **142**:RMgBr molar ratio = 1:6. [b]Isolated yields. [c]Reaction was carried out in CH_2Cl_2 for 19 h with **142**:TMSOTf:$RSiMe_3$ molar ratio = 10:2:20.

In order to gain an insight into the reaction mechanism, we next proceeded to measure the deuterium kinetic isotope effect under our standard conditions with **140a** and **140a**-d_8 as the test substrates (Scheme 5.2). A k_H/k_D value of 4.1 was obtained on the basis of GC-MS analysis that indicated C−H bond cleavage to be rate determining step. This value was found to be comparable to that reported for ruthenium-catalyzed amination of ethylbenzene (4.8)[85] and iron-catalyzed amidation of aldehydes (4.4).[100]



Scheme 5.2 Deuterium kinetic isotope study with **140a** and **140a**-d_8

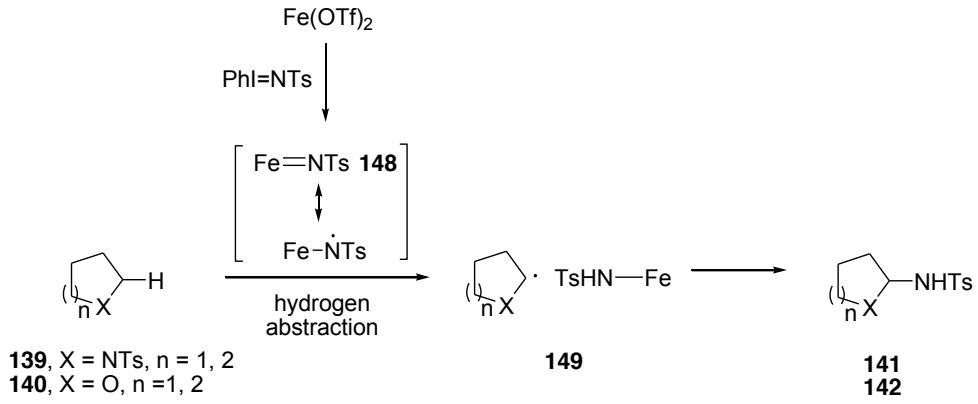
To delineate whether a concerted or radical reaction mechanism was in operation, the reactions of **139c** and **140a** under the optimal conditions and in the presence of 2 eq of the radical scavengers BHT or PBN were examined (Scheme 5.3).[96,108] Analysis of the crude reaction mixtures by ^{1}H NMR analysis revealed that neither of the desired products **141c** or **142a** were obtained and the starting material **139c** and **140a** were recovered in near quantitative yield. These results supported a nitrene/imido transfer mechanism that occurred *via* a stepwise process involving a radical intermediate.



Scheme 5.3 $Fe(OTf)_2$-catalyzed amidation of **139c**, **140a** in the presence of a radical scavenger

On the basis of the above results, a tentative mechanism for the present $Fe(OTf)_2$-catalyzed amination of saturated *N*- and *O*-heterocyclic compounds with PhI=NTs is outlined in Scheme 5.4. This could involve the initial formation of the putative [Fe=NTs]

species **148** from reaction of $Fe(OTf)_2$ and PhI=NTs.[81] Transfer of the nitrene/imido group from this putative highly reactive iron complex to the α-C−H bond of the substrate *via* a hydrogen abstraction/radical rebound pathway was then thought to give the the corresponding aminated products **141** and **142**.



Scheme 5.4 Proposed mechanism for $Fe(OTf)_2$-catalyzed amination of saturated *N*- and *O*-heterocyclic compounds **139** and **140**

5.3 Conclusion

In summary, we have developed a mild iron(II)-catalyzed methodology for the amination at the α-C−H bond of saturated *N*- and *O*-heterocyclic compounds with PhI=NTs as a nitrogen source. With only 5 mol% of catalyst loading, the reaction was shown to proceed smoothly and furnish the corresponding cyclic aminal and hemiaminal products in 38-90% yield with good regioselectivity. However, the current method was shown to be less efficient for the amination of α-substituted substrates or when switching the *N*-protecting group from tosyl to nosyl. Mechanistic studies suggested that the reaction proceeded by rate determining insertion of an iron nitrene/imido species into the

α-C–H bond of the starting material *via* a hydrogen abstraction/radical rebound pathway. The utility of this method to accessing 1,*n*-diamines and 1,*n*-amino alcohols was also demonstrated through ring-opening of the α-aminated products by different nucleophiles.

Chapter VI. Experimental Section

6.1 General Remarks

Unless specified, all reactions were performed in oven-dried glassware under a nitrogen atmosphere at ambient temperature. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received; CH_2Cl_2 and MeCN were purified prior to use by distilling 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 was distilled under reduced pressure. Molecular sieves were dried under vacuum at 200 ºC and stored under N_2.

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

Flash chromatography was performed using Merck silica gel 60 using a gradient solvent system (EtOAc/*n*-hexane as eluent).

^1H and ^{13}C NMR spectra were measured on Bruker Avance 300, 400 or 500 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). ^1H NMR product yields were estimated with CH_2Br_2 as the internal reference standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), quin (apparent quintet) or m (multiplet). The number of protons (*n*) for a given resonance is indicated by *n*H, and coupling constants are

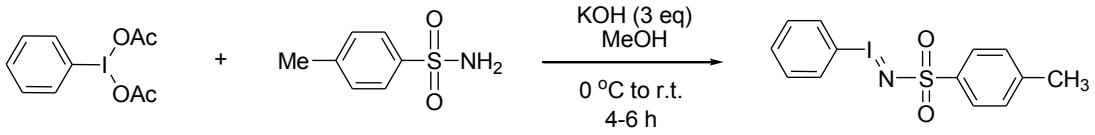
reported as a *J* value in Hz. Chemical shifts (ppm) for ^{13}C NMR were recorded relative to the signal of chloroform-*d* ($\delta = 77.0$)

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FTIR spectrometer. High performance liquid chromatography analysis was conducted on Shimadzu LC-20AD. Reactions conducted under microwave conditions were carried out with a CEM Discover Labmate microwave synthesizer with an internal IR sensor located at the bottom of the cavity, irradiation at 2450 MHz and temperature, power and pressure settings at 25 °C, 200 W and 17 bar, respectively.

Low resolution mass spectra (LCMS) were determined on a Finnigan LCQ XP MAX mass spectrometer. High resolution mass spectra (HRMS) were obtained using a 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 diffractionmeter. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensch polarimeter with a sodium vapor lamp at 589 nm and 1 cm cell (*c* given in g/100 mL).

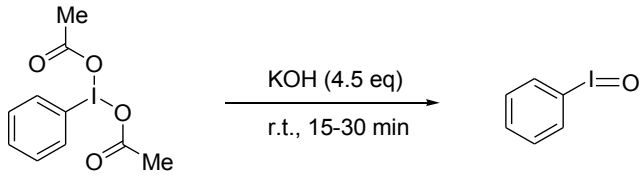
6.2 Iron(II)-Catalyzed Amidation of Aldehydes with Iminoiodanes at Room Temperature and Under Microwave Assisted Conditions

Procedure for the synthesis of (*p*-toluenesulfonyl)iminophenyliodiane[5]



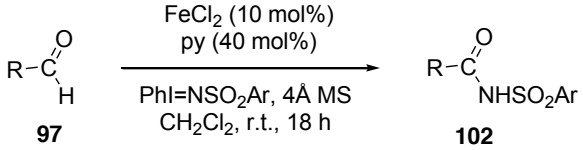
To a suspension of $TsNH_2$ (10.27 g, 60 mmol, 1 eq) and KOH (8.42 g, 150 mmol, 2.5 eq) in MeOH (100 mL) in an ice bath was added $PhI(OAc)_2$ (19.28 g, 60 mmol, 1 eq). The reaction mixture was left to stir at room temperature for 4-6 h. The resulting pale yellow suspension was filtered, washed with MeOH (25mL) and water (500 mL). The pale yellow solids were collected and dried under vacuum. Yield: 90%; ^{1}H NMR: (DMSO-*d6*, 300 MHz) δ 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).

Procedure for the synthesis of iodosylbenzene[34]



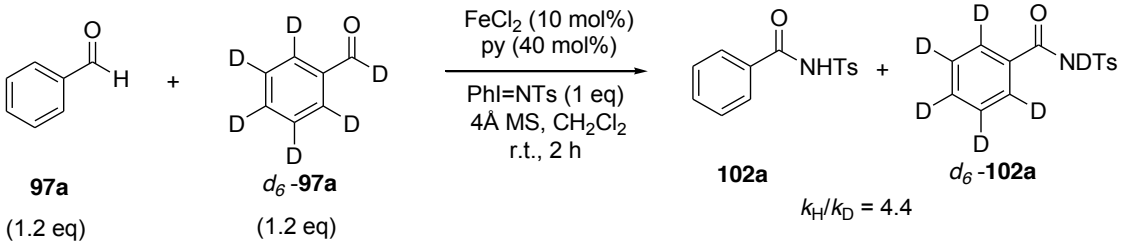
To a 500 mL conical flask containing $PhI(OAc)_2$ (77.1 g, 240 mmol, 1 eq) was added a solution of 3.5 M KOH (308 mL, 1.08 mol, 4.5 eq) dropwise over 15-30 min with vigorous stirring. The suspension was stirred at room temperature for 2 h. H_2O (200 mL) was added and reaction mixture was stirred vigorously for another 30 min. The crude mixture was filtered, washed repeatedly with H_2O and $CHCl_3$ and dried under vacuum.

General procedure for $FeCl_2$ + py-catalyzed amidation of aldehydes 97 with PhI=NTs or PhI=NNs



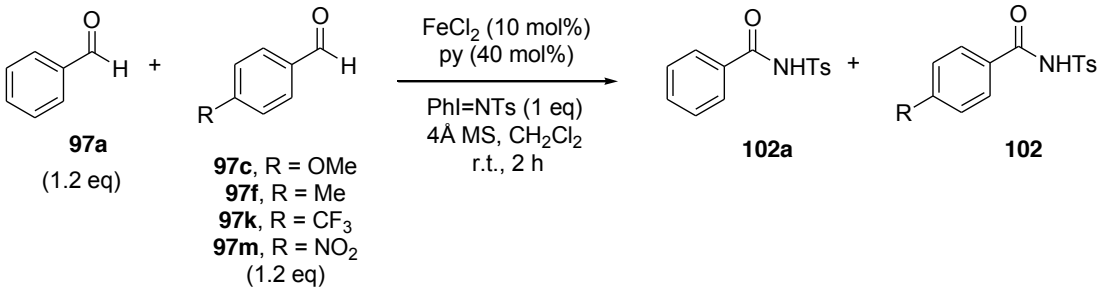
To a suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq) and powdered 4Å MS (400 mg) in CH_2Cl_2 (2 mL) was added pyridine (16.2 μL, 0.2 mmol, 0.4 eq). After stirring for 5 min, PhI=NTs or PhI=NNs (373 mg or 404 mg, 1 mmol, 2 eq) was added followed by addition of the aldehyde (0.5 mmol, 1 eq). The reaction was stirred at room temperature for 18 h (or 1h under microwave conditions), after which the crude mixture was filtered through Celite, washed with EtOAc, evaporated to dryness and purified by silica gel flash column chromatography (*n*-hexanes:EtOAc as eluant) to give the acyl sulfonamide product **102**.

Procedure for kinetic isotope study



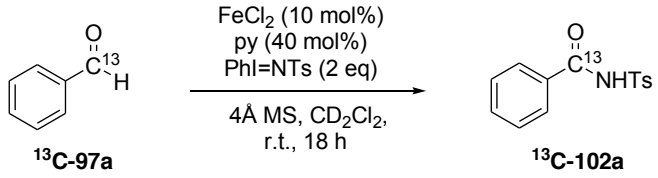
To a suspension of $FeCl_2$ (3.3 mg, 25 μmol, 0.1 eq) and powdered 4Å MS (200 mg) in CH_2Cl_2 (2 mL) was added pyridine (8.1 μL, 0.1 mmol, 0.4 eq). After stirring for 5 min, PhI=NTs (93.3 mg, 0.25 mmol, 1 eq) was added followed by a solution of benzaldehyde (30.2 μL, 0.3 mmol, 1.2 eq) and d_6-benzaldehyde (32.0 μL, 0.3 mmol, 1.2 eq) was added. After 2 h, the solution was assayed via LCMS analysis.

Procedure for competitive rates studies



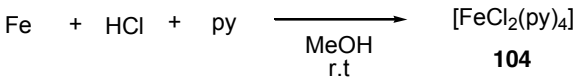
To a suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq) and powdered 4Å MS (400 mg) in CH_2Cl_2 (2 mL) was added pyridine (16.2 μL, 0.2 mmol, 0.4 eq). After stirring for 5 min, PhI=NTs (187 mg, 0.5 mmol, 1 eq) was added followed by a solution of benzaldehyde (60.4 μL, 0.6 mmol, 1.2 eq) and *p*-substituted benzaldehyde (0.6 mmol, 1.2 eq). After 2 h, the solution was assayed via GC analysis.

Procedure for ^{13}C-benzaldehyde *in situ* monitoring experiment



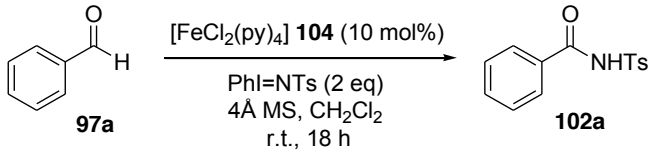
To a suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq) and 4Å powdered MS (400 mg) in CD_2Cl_2 (2 mL) was added py (16.2 μL, 0.2 mmol, 0.4 eq). After stirring for 5 min, PhI=NTs (373 mg, 1 mmol, 2 eq) and ^{13}C-benzaldehyde (50.3 μL, 0.5 mmol, 1 eq) was added. The crude reaction mixture was then filtered through Celite, diluted with CD_2Cl_2 and monitored by ^{13}C NMR spectroscopy. This process was repeated by taking subsequent aliquots at 4, 12 and 18 h and subjecting the resultant CD_2Cl_2 solutions of the crude reaction to ^{13}C NMR spectroscopic analysis.

Procedure for the synthesis of $[FeCl_2(py)_4]$[79]



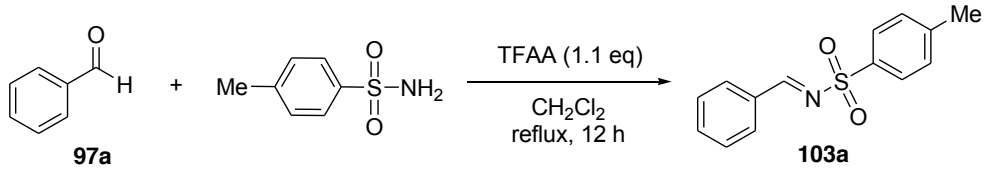
Pure iron powder (5.04 g, 0.09 mol, 1 eq) was slowly and carefully added to 15 mL of 5M HCl [**CAUTION**: a large volume of H_2(g) is evolved on addition to HCl and care should be exercised] over a period of 45 min. When all the H_2(g) was evolved, MeOH (20 mL, distilled) was added and under a dry nitrogen atmosphere, the solution was filtered into a flask containing 100 mL of pyridine (purified by distillation in a dry N_2 atmosphere prior to use). Intensely yellow crystals of tetrakis(pyridyl)iron(II) chloride **104** separated out immediately from the solution and allowed to stand overnight under a dry N_2 atmosphere. The crystals were then filtered off, recrystallized from distilled pyridine and dried in a vacuum desiccator. IR (NaCl, neat): 3420, 3312, 3198, 1605, 1487, 1223, 1042, 756, 694 cm^{-1}; MS (ESI): *m/z* 443 $[M+H]^+$.

Procedure for amidation reaction of 97a with $[FeCl_2(py)_4]$ 104



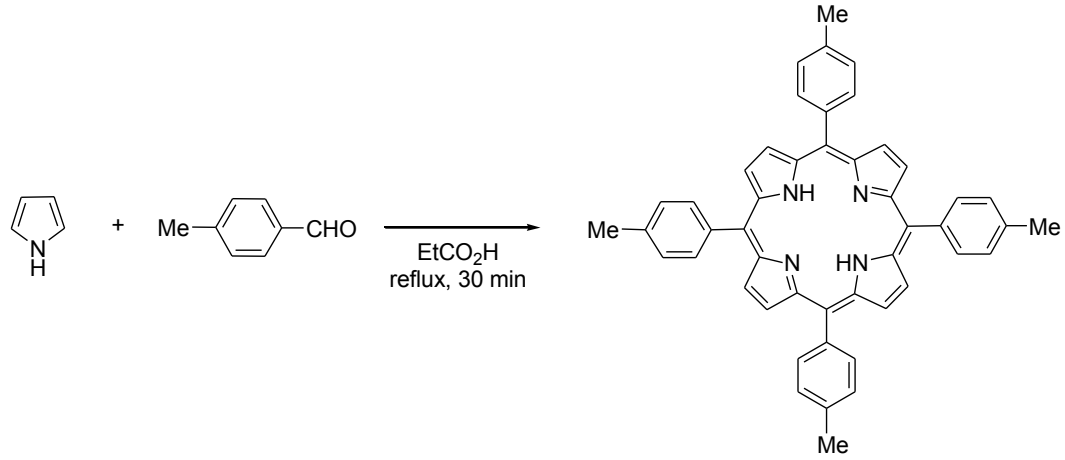
To a suspension of tetrakis(pyridyl)iron(II) chloride **104** (22.2 mg, 0.05 mmol, 0.1 eq), PhI=NTs (373 mg, 1 mmol, 2 eq) and 4Å powdered MS (400 mg) in 2 mL of CH_2Cl_2 was added **97a** (50.3 μL, 0.5 mmol, 1 eq). The reaction was stirred at room temperature for 18 h, after which the mixture was filtered through Celite, washed with EtOAc and evaporated to dryness and purified by silica gel flash column chromatography.

Procedure for the synthesis of 103[86]



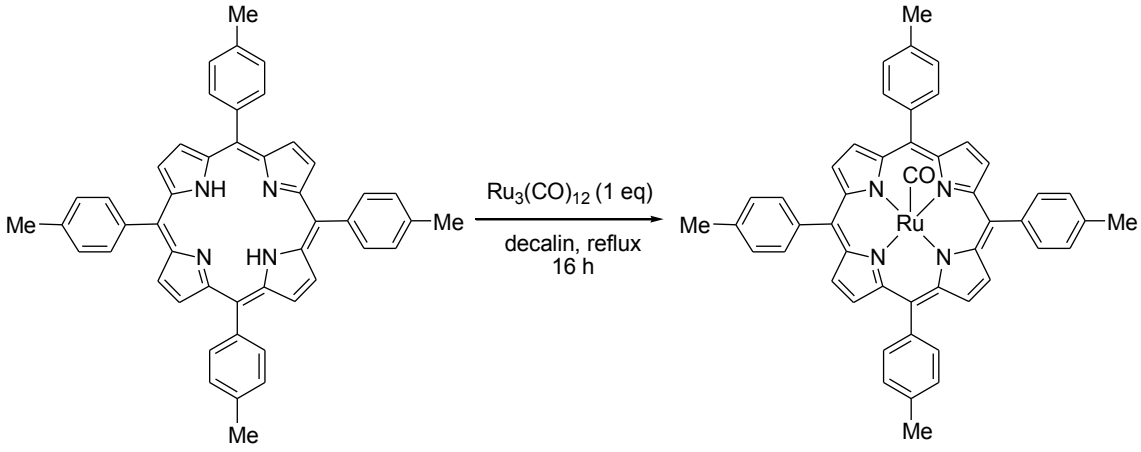
To a solution of benzaldehyde **97a** (1.0 mL, 10 mmol, 1 eq) and *p*-toluenesulfonamide (1.7 g, 10 mmol, 1 eq) in 50 mL of CH_2Cl_2 was added trifluoroacetic anhydride (1.5 mL, 11 mmol, 1.1 eq). The reaction was refluxed for 12 h after which the reaction mixture was poured into cold water, extracted with CH_2Cl_2, dried with $MgSO_4$, evaporated to dryness and recrystallized to give the title compound as a white solid in 81% yield. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 9.03 (s, 1H) 7.94-7.88 (m, 4H), 7.62 (t, J = 7.4 Hz, 1H) 7.49 (d, J = 7.7 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 170.1, 144.6, 135.2, 135.0, 132.4, 131.3, 129.8, 129.2, 128.1, 21.7; MS (ESI): m/z 260 $[M+H]^+$.

Procedure for the synthesis of symmetrical 5,10,15,20-tetrakis-(4-methylphenyl)-21*H*,23*H*-porphyrin[121]



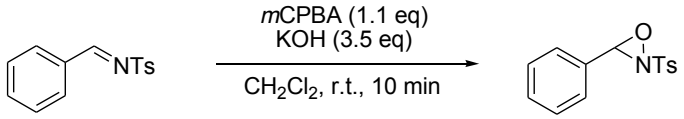
To a 250 mL two-neck round bottom flask was added freshly distilled pyrrole (2.8 mL, 40 mmol, 1 eq), 4-methylbenzaldehyde (4.7 mL, 40 mmol, 1 eq) and propionic acid (100 mL). The reaction mixture was refluxed for 30 min. After cooling to room temperature, cold MeOH (80 mL) was added to the reaction mixture. The flask was cooled in an ice bath for 2 h, after which the purple crystal were filtered, washed with cold MeOH (100 mL) and dried under vacuum.

Procedure for the synthesis of [Ru(TTP)CO] complex[121]



To a 250 mL round bottom flask was added $Ru_3(CO)_{12}$ (1.27 g, 2 mmol, 1 eq) and porphyrin (1.34 g, 2 mmol, 1 eq). The mixture was refluxed in decalin (100 mL) for 16 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). The ruthenium(II) porphyrin was eluted with CH_2Cl_2/MeOH. The red solid was recrystallized in CH_2Cl_2/MeOH to give [Ru(TTP)CO] complex.

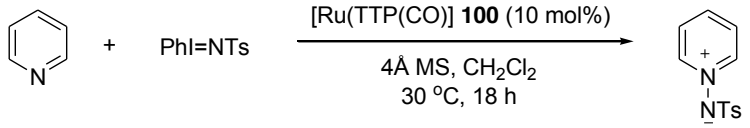
Procedure for the synthesis of 108[87]



103a **108**

To a suspension of powdered KOH (392 mg, 7 mmol, 3.5 eq) and *m*-chloroperoxybenzoic acid (380 mg, 2.2 mmol, 1.1 eq) in 1 mL of CH_2Cl_2 was added a solution of **103a** (519 mg, 2 mmol, 1 eq) in 3 mL of CH_2Cl_2. After 5 min, the suspension was filtered, evaporated to dryness and dried under vacuum to afford the product **108** as a white solid in 90% yield. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 8.4 Hz, 2H), 7.37-7.46 (m, 7H), 5.44 (s, 1H), 2.49 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 162.3, 146.4, 131.5, 131.4, 130.6, 130.1, 129.4, 128.7, 128.3, 76.3, 21.9; MS (ESI): m/z 276 $[M+H]^+$.

Procedure for the synthesis of 110[88]

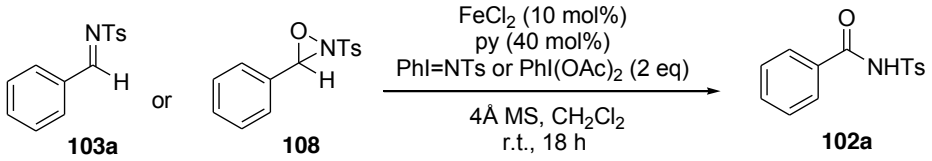


110

To a suspension of [Ru(TTP)CO] **100** (160.0 mg, 0.2 mmol, 0.1 eq) and PhI=NTs (1.1 g, 3 mmol, 1.5 eq) in 2 mL of CH_2Cl_2 in the presence of powdered 4Å molecular sieves (400 mg) was added pyridine (162 mL, 2 mmol, 1 eq). 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 (CH_2Cl_2: CH_3COCH_3 as eluant) to afford the product **110** in 63% yield. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.45 (d, J = 5.7 Hz, 2H), 7.96 (t, J = 7.8,

1H), 7.54-7.61 (m, 4H), 7.15 (d, J = 8.2 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 145.2, 141.7, 138.9, 138.6, 129.3, 127.1, 126.9, 21.4; MS (ESI) m/z 249 $[M+H]^+$.

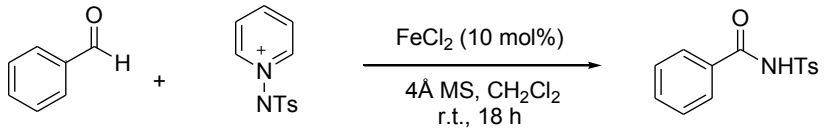
Procedure for $FeCl_2$ + py-catalyzed reaction of 103a or 108



103a **108** **102a**

A suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq), pyridine (16.2 μL, 0.2 mmol, 0.4 eq) and powdered 4Å MS (400 mg) were stirred for 5 min in 2 mL of CH_2Cl_2. On completion, PhI=NTs or $PhI(OAc)_2$ (373 mg or 322 mg, 1 mmol, 2 eq) and **103a** or **108** (130 mg or 138 mg, 0.5 mmol, 1 eq) 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 ^{1}H NMR spectroscopy.

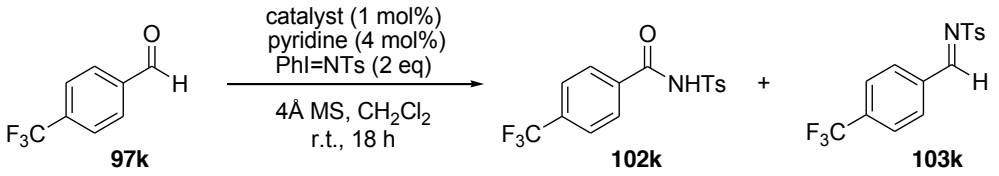
Procedure for $FeCl_2$-catalyzed reaction of 97a with 110



97a **110** **102a**

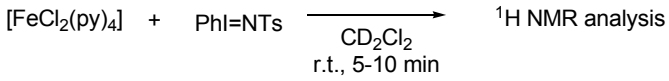
To a suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq), **110** (496 mg, 1 mmol, 2 eq) and 4Å powdered MS (400 mg) in 2 mL of CH_2Cl_2, was added **97a** (50.3 μL, 0.5 mmol, 1 eq). The reaction was stirred at room temperature for 18 h, after which the mixture was filtered through Celite, washed with EtOAc and evaporated to dryness. The reaction mixture was then analyzed by ^{1}H NMR spectroscopy.

Procedure for control reactions on traces impurities in $FeCl_2$ + py-catalyzed amidation of 97k with PhI=NTs



To a suspension of Cu_2O, CuCl, $CuCl_2$, Cu(OTf), $Cu(OTf)_2$, $Ph(OAc)_2$ or $Pd(PPh_3)_4$ (0.005 mmol, 0.01 eq) and powdered 4Å molecular sieves (400 mg) in CH_2Cl_2 (2 mL) was added pyridine (0.02 mmol, 0.04 eq). After stirring for 5 min, PhI=NTs (373 mg, 1 mmol, 2 eq) was added followed by **97k** (68.3 μL, 0.5 mmol, 1 eq). The reaction was stirred at room temperature for 18 h, after which the mixture was filtered through Celite, washed with EtOAc and evaporated to dryness. The reaction mixture was then analyzed by ^{1}H NMR spectroscopy. 4-Methyl-*N*-(4-(trifluoromethyl)-benzylidene)benzenesulfonamide **103k**[122] was detected as a sole product. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H); 2.45 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 168.5, 145.1, 137.5, 131.4, 130.3, 129.9, 128.2, 126.1, 21.7; MS (ESI): m/z 328 $[M+H]^+$.

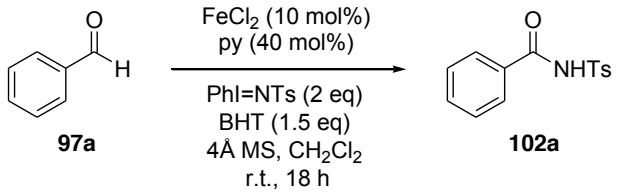
Procedure for ^{1}H NMR analysis of a product obtained from $[Fe(py)_4Cl_2]$ 104 + PhI=NTs



To a yellow suspension $[Fe(py)_4Cl_2]$ **104** (11.1 mg, 0.025 mol, 1 eq) in CD_2Cl_2 (1 mL) was added PhI=NTs (37.3 mg, 0.1 mmol, 4 eq). The mixture was stirred at room

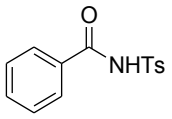
temperature and under N_2. After 5-10 min, a homogeneous brown solution was obtained and assayed via ^{1}H NMR spectroscopy.

Procedure for $FeCl_2$ + py-catalyzed amidation of 97a with PhI=NTs in the presence of radical scavenger



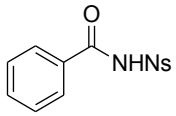
To a suspension of $FeCl_2$ (6.5 mg, 0.05 mmol, 0.1 eq) and powdered 4Å MS (400 mg) in CH_2Cl_2 (2 mL) was added pyridine (16.2 μL, 0.2 mmol, 0.4 eq). After stirring for 5 min, PhI=NTs (373 mg, 1 mmol, 2 eq) and BHT (165 mg, 0.75 mmol 1.5 eq) followed by **97a** (50.3 μL, 0.5 mmol, 1 eq) was added. The reaction was stirred at room temperature for 18 h, after which the crude mixture was filtered through Celite, washed with EtOAc, evaporated to dryness. The reaction mixture was then analyzed by ^{1}H NMR spectroscopy.

***N*-Tosylbenzamide 102a**[67c]



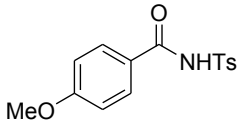
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.83 (bs, 1H), 8.03 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.6, 145.2, 135.5, 133.5, 131.1, 129.7, 128.9, 128.6, 128.0, 21.7; MS (ESI): *m/z* 276 $[M+H]^+$.

_N_-(4-Nitrophenyl sulfonyl)benzamide 102b[123]



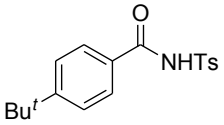
White solid; ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 8.45 (d, J = 8.8 Hz, 2H), 8.37 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H); ^{13}C NMR: (CD_3COCD_3, 100 MHz) δ 165.8, 150.7, 145.6, 133.2, 132.1, 129.8, 128.6, 128.4, 124.1; MS (ESI): m/z 307 $[M+H]^+$.

4-Methoxy-_N_-tosylbenzamide 102c[67c]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) 9.21 (bs, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 2.42 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.8, 145.1, 135.7, 130.0, 129.6, 128.6, 126.5, 123.3, 114.1, 55.5, 21.7; MS (ESI): m/z 306 $[M+H]^+$.

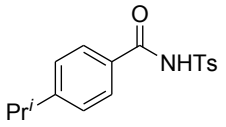
4-_tert_-Butyl-_N_-tosylbenzamide 102d[124]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.69 (bs, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 2.41 (s, 3H), 1.27

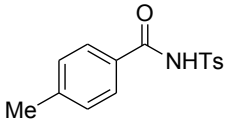
(s, 9H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.4, 157.3, 145.1, 135.7, 129.6, 128.6, 128.2, 127.9, 125.8, 35.1, 31.0, 21.7; MS (ESI): *m/z* 332 $[M+H]^+$.

4-Isopropyl-*N*-tosylbenzamide 102e



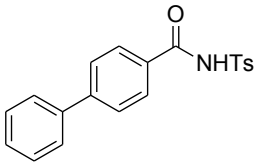
White solid; m.p. = 155-157 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.36 (bs, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.89 (quin, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.7, 155.0, 145.1, 135.7, 129.6, 128.7, 128.6, 128.3, 126.9, 34.2, 23.6, 21.7; IR (neat, cm^{-1}): 3273, 3020, 2964, 1697, 1608, 1427, 1215, 1166, 1070; MS (ESI): *m/z* 318 $[M+H]^+$; HRMS (ESI): calcd. for $C_{17}H_{20}NO_3S$: 318.1164, found: 318.1164.

4-Methyl-*N*-tosylbenzamide 102f[67c]



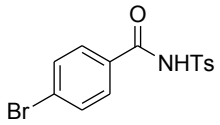
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.56 (bs, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.5, 145.1, 144.4, 135.6, 129.6, 129.5, 128.6, 128.3, 128.0, 21.7, 21.6; MS (ESI) *m/z* 290 $[M+H]^+$.

4-Phenyl-*N*-tosylbenzamide 102g



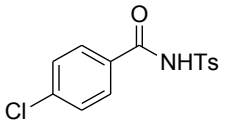
White solid; m.p. = 200-202 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.07 (bs, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.46-7.35 (m, 5H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.5, 145.5, 144.6, 139.4, 137.1, 130.7, 129.4, 129.0, 128.8, 128.4, 128.3, 127.1, 127.0, 20.6; IR (neat, cm-^{1}): 3286, 3018, 1697, 1606, 1425, 1334, 1215, 1165; MS (ESI): m/z 352 $[M+H]^+$; HRMS (ESI): calcd. for $C_{20}H_{18}NO_3S$: 352.1007, found: 352.0991.

4-Bromo-*N*-tosylbenzamide 102h[61]



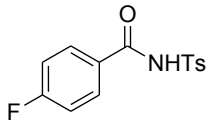
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.53 (bs, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.4, 145.0, 134.9, 131.8, 129.6, 129.3, 129.1, 128.2, 21.3; MS (ESI): m/z 354 $[M+H]^+$.

4-Chloro-*N*-tosylbenzamide 102i[61]



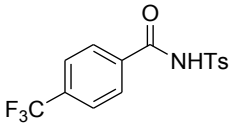
Pale yellow solid; ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 9.63 (bs, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.39-7.26 (m, 4H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 163.5, 145.4, 140.0, 135.1, 129.6, 129.4, 129.3, 129.1, 128.5, 21.6; MS (ESI): *m*/*z* 310 $[M+H]^+$.

4-Fluoro-*N*-tosylbenzamide 102j[125]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.70 (bs, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.87 (dd, J = 8.4, 5.1, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 8.4 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.6, 145.4, 135.3, 130.8, 130.6, 129.7, 128.6, 127.3, 116.2, 115.9, 21.7. MS (ESI): *m*/*z* 294 $[M+H]^+$.

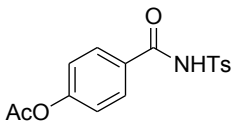
4-Trifluoromethyl-*N*-tosylbenzamide 102k[67c]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.78 (bs, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H); ^{13}C

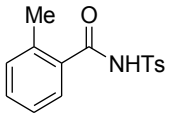
NMR: ($CDCl_3$, 75 MHz) δ 163.5, 145.7, 135.1, 134.6, 134.4, 129.8, 128.7, 128.5, 125.9, 125.8, 125.1, 21.7; MS (ESI): *m/z* 344 $[M+H]^+$.

4-Acetoxy-*N*-tosylbenzamide 102l



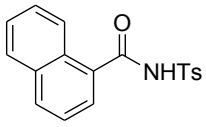
White solid; m.p. = 138-139 °C; ^1H NMR: ($CDCl_3$, 300 MHz) δ 9.39 (bs, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 168.5, 168.0, 163.4, 154.6, 145.3, 135.1, 129.7, 129.5, 128.7, 122.2, 21.7, 21.1; IR (neat, cm^{-1}): 3018, 2399, 1759, 1705, 1602, 1425, 1165, 1066; MS (ESI): *m/z* 318 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{16}NO_5S$: 334.0749, found: 334.0762.

2-Methyl-*N*-tosylbenzamide 102n[67c]



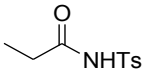
White solid; ^1H NMR: ($CDCl_3$, 300 MHz) δ 9.17 (bs, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.5, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.29-7.35 (m, 1H), 7.17 (d, *J* = 7.5, 1H), 7.13-7.18 (m, 1H), 2.44 (s, 3H), 2.33 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 166.5, 145.2, 138.0, 135.6, 132.1, 131.8, 131.6, 129.6, 128.5, 127.5, 125.9, 21.7, 20.1; MS (ESI): *m/z* 290 $[M+H]^+$.

_N_-Tosyl-1-napthamide 102o[67c]



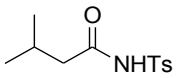
Yellow solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.81 (bs, 1H), 8.17 (m, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.1 Hz, 1H), 7.82 (m, 1H), 7.65 (dd, J = 7.2, 0.9 Hz, 1H), 7.47-7.52 (m, 2H), 7.33-7.42 (m, 3H), 2.45 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 165.9, 145.3, 135.5, 133.7, 132.9, 130.0, 129.9, 129.7, 128.6, 128.5, 127.9, 126.8, 126.6, 124.9, 124.4, 21.7; MS (ESI): m/z 326 $[M+H]^+$.

_N_-Tosylpropionamide 102p[126]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.85 (bs, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 2.43 (s, 3H), 2.29 (q, J = 7.5 Hz, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 171.8, 145.2, 135.6, 129.7, 128.3, 29.5, 21.7, 8.2; MS (ESI): m/z 228 $[M+H]^+$.

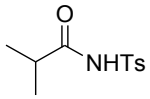
3-Methyl-_N_-tosylbutanamide 102q[127]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.99 (bs, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 2.41 (s, 3H), 2.10 (d, J = 6.3 Hz, 2H), 2.00-2.06 (m, 1H), 0.86 (d, J =

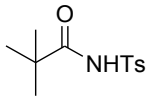
6.6 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 171.1, 145.2, 135.7, 129.7, 128.4, 45.3, 25.7, 22.3, 21.8; MS (ESI): *m*/*z* 256 $[M+H]^+$.

_N_-Tosylisobutyramide 102r[127]



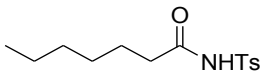
Pale yellow solid; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.86 (bs, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 2.39-2.46 (m, 4H), 1.09 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 175.0, 145.4, 135.7, 129.9, 128.6, 35.9, 22.0, 18.8; MS (ESI): *m*/*z* 344 $[M+H]^+$.

_N_-Tosylpivalamide 102s[128]



Pale yellow solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.68 (bs, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 2.43 (s, 3H), 1.14 (s, 9H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 176.0, 145.0, 135.6, 129.6, 128.4, 40.0, 26.7, 21.6; MS (ESI): *m*/*z* 256 $[M+H]^+$.

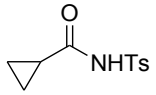
_N_-Tosylheptanamide 102t[72]



Pale yellow solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.19 (bs, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.56 (t, *J* = 6.9 Hz, 2H),

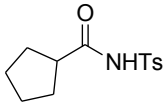
1.20-1.26 (m, 6H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 171.5, 145.1, 135.6, 129.6, 128.3, 36.3, 31.3, 28.5, 24.3, 22.4, 21.7, 13.9; MS (ESI): m/z 284 $[M+H]^+$.

_N_-Tosylcyclopropanecarboxamide 102u[72]



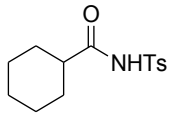
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.88 (bs, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 2.44 (s, 3H), 1.56-1.51 (m, 1H), 1.02 (m, 2H), 0.87-0.83 (m, 2H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 172.3, 145.1, 135.6, 129.6, 128.3, 21.7, 14.7, 9.7; MS (ESI): m/z 240 $[M+H]^+$.

_N_-Tosylcyclopentanecarboxamide 102v[72]



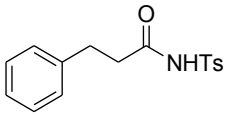
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.67 (bs, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 2.62 (m, 1H), 2.43 (s, 3H), 1.51-1.82 (m, 8H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 173.9, 145.0, 135.7, 129.6, 128.3, 45.5, 29.6, 25.9, 21.7; MS (ESI): m/z 268 $[M+H]^+$.

_N_-Tosylcyclohexanecarboxamide 102w[127]



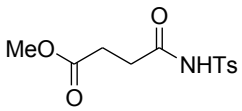
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.12 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H), 2.13 (tt, J = 11.6, 3.5 Hz, 1H), 1.76 (t, J = 13.8 Hz, 4H), 1.63 (bd, J = 9.9 Hz, 2H), 1.12-1.40 (m, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 173.7, 145.0, 135.6, 129.6, 128.3, 45.1, 28.7, 25.4, 25.2, 21.7; MS (ESI): m/z 282 $[M+H]^+$.

3-Phenyl-_N_-tosykpropanamide 102y[72]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.96 (bs, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.18-7.25 (m, 3H), 7.04 (d, J = 7.5 Hz, 2H), 2.86 (t, J = 7.7, 2H), 2.54 (t, J = 7.7, 2H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 170.2, 145.2, 139.6, 135.5, 129.6, 128.6, 128.4, 128.3, 126.5, 38.0, 30.3, 21.7; MS (ESI): m/z 304 $[M+H]^+$.

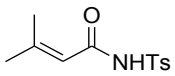
Methyl 4-(4-methylphenylsulfonamido) 4-oxobutanoate 102z[129]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.00 (bs, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 3.65 (s, 3H), 2.58-2.60 (m, 4H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75

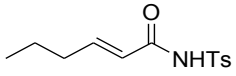
MHz) δ 173.0, 169.7, 145.1, 135.6, 129.6, 128.3, 52.1, 31.0, 28.2, 21.7; MS (ESI): *m/z* 286 $[M+H]^+$.

3-Methyl-*N*-tosylbut-2-enamide 102α[130]



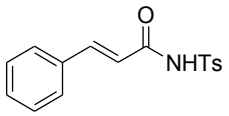
Pale yellow solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.87 (bs, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 2.43 (s, 3H), 2.10 (s, 3H), 1.84 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.4, 160.2, 144.7, 135.9, 129.6, 128.3, 115.5, 27.6, 21.6, 20.5; MS (ESI): *m/z* 254 $[M+H]^+$.

(*E*)-*N*-tosylhex-2-enamide 102β[131]



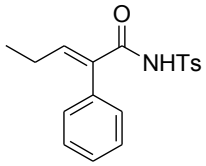
Yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 9.29 (bs, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.98 (dt, *J* = 15.4, 7.0 Hz, 1H), 5.85 (d, *J* = 15.4 Hz, 1H), 2.41 (s, 3H), 2.14 (q, *J* = 7.0 Hz, 2H), 1.37-1.44 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.5, 151.0, 145.1, 135.7, 129.6 128.4, 121.4, 34.3, 21.7, 21.1, 13.6; MS (ESI): *m/z* 268 $[M+H]^+$.

_N_-Tosylcinnamamide 102γ[132]



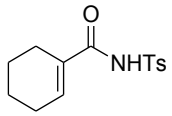
White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.00 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 15.6 Hz, 2H), 7.46 (m, 3H), 7.33-7.38 (m, 5H), 6.44 (d, J = 15.8, 1H), 2.43 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.2, 146.0, 145.2, 135.7, 133.7, 131.0, 129.7, 129.0, 128.5, 128.4, 117.3, 21.7; MS (ESI): m/z 302 $[M+H]^+$.

2-Phenyl-_N_-tosylpent-2-enamide 102δ



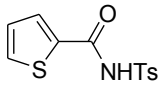
White solid, m.p. = 118-120 °C ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 8.3 Hz, 2H), 7.46-7.38 (m, 3H), 7.33 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 1.56 Hz, 2H), 7.03 Hz (t, J = 7.7 Hz, 1H), 2.43 (s, 3H), 1.96 (quin, J = 7.6 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.7, 147.9, 145.0, 135.6, 133.5, 133.3, 129.6, 129.5, 129.4, 128.9, 128.6, 23.0, 21.7, 13.0; IR (neat, cm^{-1}): 3365, 3284, 3022, 2970, 2933, 1701, 1627, 1597, 1492, 1406, 1342, 1215, 1176, 1145 cm^{-1}; MS (ESI): m/z 330 $[M+H]^+$; HRMS (ESI): calcd. for $C_{18}H_{20}NO_3S$: 330.1164, found: 330.1164.

_N_-Tosylcyclohex-1-enecarboamide 102ε



White solid, m.p. = 164-166 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.76 (bs, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.77 (s, 1H), 2.43 (s, 3H), 2.16 (m, 4H), 1.57 (m, 4H);^{13}C NMR: ($CDCl_3$, 75 MHz) δ 165.2, 144.9, 139.1, 135.8, 131.8, 129.5, 128.5, 25.8, 23.6, 21.72, 21.69, 21.1; IR (neat, cm^{-1}): 3275, 3018, 1693, 1417, 1215, 1161; MS (ESI): m/z 280 $[M+H]^+$; HRMS (ESI): calcd. for $C_{14}H_{18}NO_3S$: 280.1007, found: 280.1015.

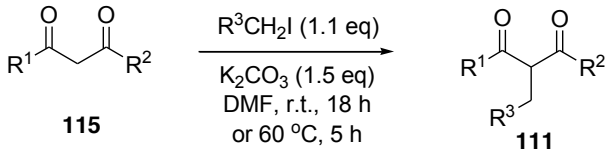
_N_-Tosylthiophene-2-carboxamide 102η[67c]



White solid; ^{1}H NMR: ($CDCl_3$, 300 MHz) 8.04 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 3.5 Hz, 1H), 7.59 (d, J = 4.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.07 (t, J = 4.39 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 158.7, 145.3, 135.9, 135.4, 133.7, 131.1, 129.6, 128.6, 128.2, 21.7; MS (ESI): m/z 282 $[M+H]^+$

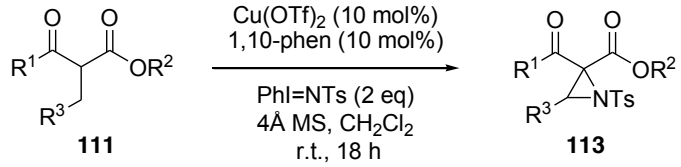
6.3 Copper(II) Triflate-Catalyzed Amination and Aziridination of 2-Alkyl Substituted 1,3-Dicarbonyl Compounds

General procedure for the synthesis of 2-alkyl-1,3-dicarbonyl compounds 111[92]



To a mixture of the 1,3-dicarbonyl compound (2.0 mmol, 1 eq) and iodoalkane (2.2 mmol, 1.1 eq) in *N*,*N*-dimethylformamide (5 mL) was added K_2CO_3 (415 mg, 3 mmol, 1.5 eq) at room temperature. The resulting reaction mixture was stirred at room temperature for 18 h or at 60 °C for 5 h. The reaction was then quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

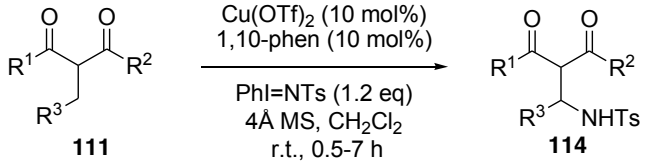
General procedure for Cu(II)-catalyzed aziridination of 2-alkyl 1,3-dicarbonyl compounds 111 to 2,2-diacyl aziridine derivatives 113



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (373 mg or 560 mg, 1.0 mmol or 1.5 mmol, 2 or 3 eq) and **111** (0.5 mmol, 1 eq) was added. The reaction mixture stirred for a further 18 h at room temperature, after which the mixture was filtered through Celite, washed with EtOAc (50

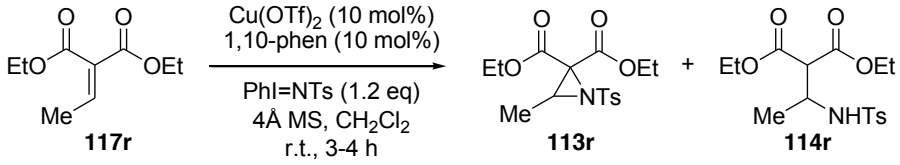
mL), evaporated to dryness, and purified by flash column chromatography (4:1 *n*-hexanes/EtOAc as eluent) to give the title compound.

General procedure for Cu(II)-catalyzed amination of 2-alkyl 1,3-dicarbonyl compounds 111 to *α*-acyl-*β*-amino acid derivatives 114



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (224 mg, 0.6 mmol, 1.2 eq) and **111** (0.5 mmol, 1 eq) was added. The reaction mixture stirred at room temperature and monitored by TLC analysis. Upon completion, the mixture was filtered through Celite, washed with EtOAc (50 mL), evaporated to dryness, and purified by flash column chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

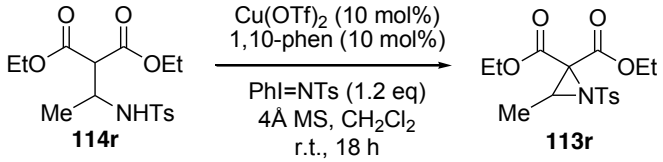
Control experiment procedure for Cu(II)-catalyzed aziridination of 117r to 113r and 114r



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (224 mg, 0.6 mmol, 1.2 eq), and **117r** (90 μL, 0.5 mmol, 1 eq) was

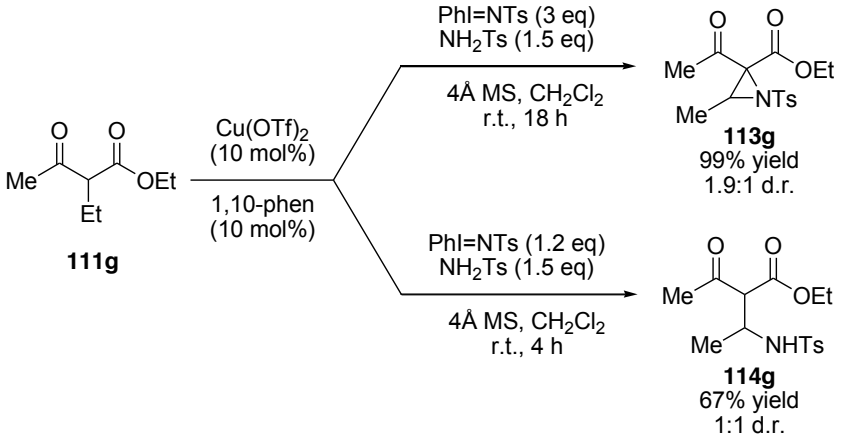
added. The reaction mixture was stirred for a further 3-4 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

Control experiment procedure for Cu(II)-catalyzed aziridination of 114r to 113r



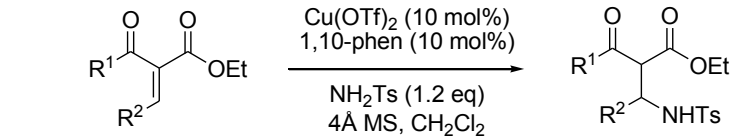
To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (224 mg, 0.6 mmol, 1.2 eq), and **114r** (179 mg, 0.5 mmol, 1 eq) was added. The reaction mixture stirred for a further 18 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

Control experiment procedure for Cu(II)-catalyzed aziridination and amination of 111g to 113g or 114g in the presence of NH_2Ts



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (560 mg or 224 mg, 1.5 mmol or 0.6 mmol, 3 eq or 1.2 eq), H_2NTs (128 mg, 0.75 mmol, 1.5 eq) was added followed by **111g** (81 μL, 0.5 mmol, 1 eq). The reaction mixture stirred for a further 4-18 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

Control experiment procedure for attempted Cu(II)-catalyzed amination of 117l, 117r, 117t

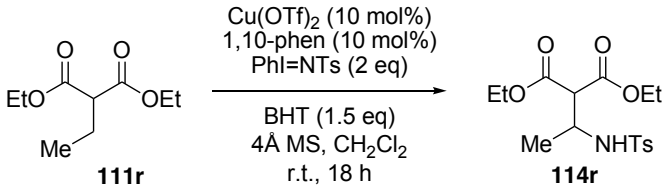


117l, R^1 = ^{i}Pr, R^2 = Me
117r, R^1 = OEt, R^2 = Me
117t, R^1 = OEt, R^2 = $(CH_2)_2Cl$

114l, t = 4 h
114r, t = 4 h
114t, t = 7 h

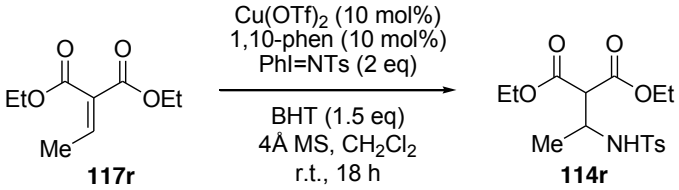
To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4 Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, $TsNH_2$ (103 mg, 0.6 mmol, 1.2 eq), and a solution of **117l**, **117r** or **117t** (92 mg, 90 μL or 117 mg, 0.5 mmol, 1 eq) in 0.5 mL of CH_2Cl_2 was added. The reaction mixture stirred for a further 4-7 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy.

Control experiment procedure for Cu(II)-catalyzed amination of 111r to 114r in the presence of BHT



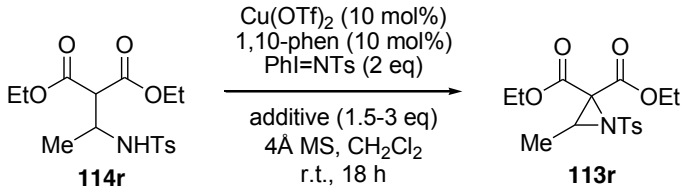
To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (373 mg, 1 mmol, 2 eq), BHT (165 mg, 0.75 mmol, 1.5 eq) was added followed by **111r** (94 μL, 0.5 mmol, 1 eq). The reaction mixture stirred for a further 18 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

Control experiment procedure for Cu(II)-catalyzed amination of 117r to 114r in the presence of BHT



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (373 mg, 1 mmol, 2 eq), BHT (165 mg, 0.75 mmol, 1.5 eq) was added followed by **117r** (90 μL, 0.5 mmol, 1 eq). The reaction mixture stirred for a further 18 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

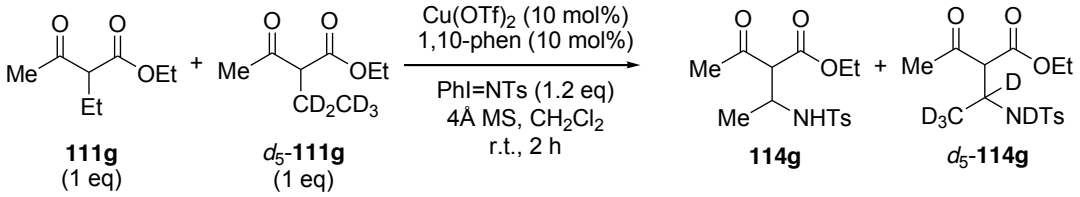
Control experiment procedure for Cu(II)-catalyzed aziridination of 114r to 113r in the presence of radical scavenger



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of, PhI=NTs (373 mg, 1 mmol, 2 eq), BHT (165 mg or 330 mg, 0.75 mmol or 1.5 mmol, 1.5 or 3 eq) or TEMPO (117 mg, 0.75 mmol, 1.5 eq) was added followed by **114r** (179 mg,

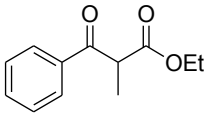
0.5 mmol, 1 eq). The reaction mixture stirred for a further 18 h at room temperature. After that, the reaction was filtered through Celite, washed with EtOAc (50 mL), and evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (*n*-hexanes/EtOAc as eluent) gave the title compound.

Control experiment procedure for measuring the deuterium kinetic isotope effect for Cu(II)-catalyzed amination of 111g and d_5-111g to 114g and d_5-114g



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2. After 1 h of stirring, PhI=NTs (224 mg, 0.6 mmol, 1.2 eq) was added followed by a solution of **111g** (81 μL, 0.5 mmol, 1 eq) and d_5-**111g** (83 μL, 0.5 mmol, 1 eq). After 2 h, the solution was assayed by GC-MS analysis.

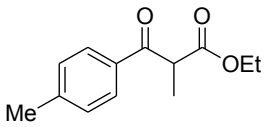
Ethyl 2-methyl-3-oxo-3-phenylpropanoate 111a[133]



Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.98 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (dd, J = 8.0, J = 7.2 Hz, 2H), 4.37 (q, J = 7.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.50 (d, J = 6.8 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ

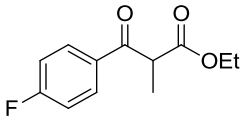
195.9, 170.9, 135.9, 133.4, 128.7, 128.6, 61.4, 48.4, 14.0, 13.8; MS (ESI): *m/z* 207 $[M+H]^+$.

Ethyl 2-methyl-3-oxo-3-(*p*-tolyl)propanoate 111b[134]



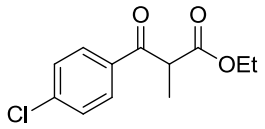
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.88 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 4.37 (q, J = 7.1 Hz, 1H), 4.21-4.10 (m, 2H), 2.40 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 195.4, 170.9, 144.3, 133.4, 129.4, 128.7, 61.2, 48.1, 21.5, 13.9, 13.7; MS (ESI): *m/z* 221 $[M+H]^+$.

Ethyl 3-(4-fluorophenyl)-2-methyl-3-oxopropanoate 111c



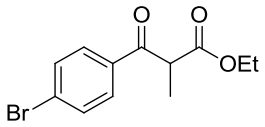
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.06-8.15 (m, 2H), 7.18-7.12 (m, 2H), 4.39 (q, J = 7.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.49 (d, J = 6.9 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 194.2, 170.6, 167.5, 164.1, 132.3, 132.3, 131.3, 131.2, 116.0, 115.9, 115.6, 115.5, 61.3, 48.2, 13.8, 13.5; IR (neat, cm^{-1}) *v*: 3078, 2986, 2940, 2909, 1728, 1682, 1597, 1504, 1226; HRMS (ESI): calcd. for $C_{12}H_{14}O_3F$ (M^++H): 225.0931, found: 225.0927.

Ethyl 3-(4-chlorophenyl)-2-methyl-3-oxopropanoate 111d[135]



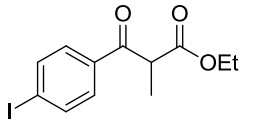
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.92 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 4.32 (q, J = 7.2 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 1.49 (d, J = 7.2 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 194.6, 170.5, 139.9, 134.2, 130.0, 129.0, 61.4, 48.3, 13.9, 13.6; MS (ESI): m/z 241 $[M+H]^+$.

Ethyl 3-(4-bromophenyl)-2-methyl-3-oxopropanoate 111e[136]



Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.85 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 4.33 (q, J = 7.2 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 1.48 (d, J = 7.2 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 194.7, 170.5, 134.6, 132.0, 130.1, 128.6, 61.4, 48.3, 14.0, 13.6; MS (ESI): m/z 285 $[M+H]^+$.

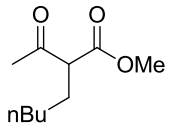
Ethyl 3-(4-iodophenyl)-2-methyl-3-oxopropanoate 111f



Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.79-7.52 (m, 2H), 7.64-7.60 (m, 2H), 4.21 (q, J = 7.1 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 1.41 (d, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 195.1, 170.5, 138.0, 135.2, 130.0, 129.9,

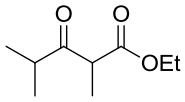
101.6, 61.4, 48.2, 14.0, 13.6; IR (neat, cm^{-1}) *v*: 3016, 2987, 2924, 2906, 1748, 1657, 1586; HRMS (ESI): calcd. for $C_{12}H_{14}O_3I$ (M^++H): 332.9988, found: 332.9998.

Methyl 2-acetylheptanoate 111j[137]



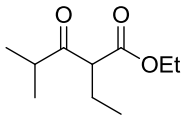
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 3.61 (s, 3H), 3.32 (t, *J* = 7.4 Hz, 1H), 2.10 (s, 3H), 1.73-1.70 (m, 2H), 1.18 (m, 6H), 0.76 (t, *J* = 3.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 203.0, 170.2, 59.5, 52.1, 31.4, 28.6, 28.1, 27.0, 22.2, 13.8; MS (ESI): *m*/*z* 187 $[M+H]^+$.

Ethyl 2,4-dimethyl-3-oxopentanoate 111k[138]



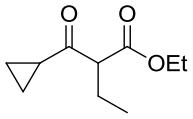
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 4.18 (q, *J* = 7.1 Hz, 2H), 3.69 (q, *J* = 7.1 Hz, 1H), 2.84 (m, *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 209.8, 170.5, 61.1, 50.7, 40.0, 18.4, 18.0, 14.0, 12.9; MS (ESI): *m*/*z* 173 $[M+H]^+$.

Ethyl 2-ethyl-4-methyl-3-oxopentanoate 111l[139]



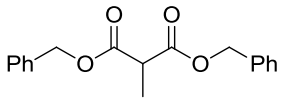
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 4.09 (q, J = 7.1 Hz, 2H), 3.48 (t, J = 7.2 Hz, 1H), 2.73 (m, J = 6.8 Hz, 1H), 1.81-1.77 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H), 1.04-1.01 (m, 6H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 208.8, 169.5, 60.9, 58.3, 40.4, 21.5, 18.1, 17.8, 13.9, 11.8; MS (ESI): m/z 187 $[M+H]^+$.

Ethyl 2-(cyclopropanecarbonyl)butanoate 111m



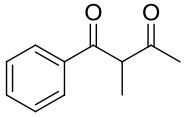
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 4.21 (q, J = 7.1 Hz, 2H), 3.47 (t, J = 7.4 Hz, 1H), 2.10-2.04 (m, 1H), 1.97-1.90 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H) 1.10-106 (m, 2H), 0.97-0.91 (m, 5H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 205.5, 170.0, 61.6, 61.2, 21.6, 19.6, 14.2, 12.0, 11.7, 11.4; IR (neat, cm^{-1}) v: 2972, 2937, 2877, 1737, 1699, 1458, 1384; HRMS (ESI): calcd. for $C_{10}H_{16}O_3$ (M^++H): 185.1178, found: 185.1180.

Dibenzyl 2-methylmalonate 111p[140]



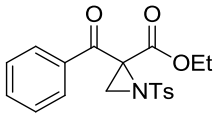
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.31-7.25 (m, 10H), 5.13 (s, 4 H), 3.53 (q, J = 7.2 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 169.7, 135.4, 128.5, 128.2, 128.0, 67.0, 46.1, 13.5; MS (ESI): m/z 299 $[M+H]^+$.

2-Methyl-1-phenylbutane-1,3-dione 111u[141]



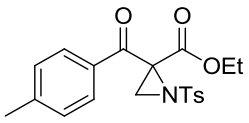
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.98 (d, J = 7.5 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.49-7.42 (m, 2H), 4.55 (q, J = 6.9 Hz, 1H), 2.16 (s, 3H), 1.43 (d, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 204.8, 197.4, 135.9, 133.6, 128.8, 128.6, 56.3, 28.1, 13.5; MS (ESI): m/z 177 $[M+H]^+$.

Ethyl 2-tosylaziridine-3-oxo-3-phenylpropanoate 113a



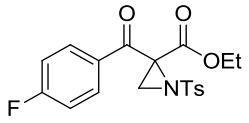
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.09 (d, J = 7.4 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 4.31-4.19 (m, 2H), 3.36 (s, 1H), 2.93 (s, 1H), 2.45 (s, 3H), 1.14 (t, J = 8.0 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 188.9, 164.9, 144.9, 136.3, 134.4, 134.0, 129.7, 129.6, 128.6, 127.9, 63.2, 53.7, 37.3, 21.7, 13.7; IR (neat, cm^{-1}) v: 3067, 3021, 2986, 1751, 1734, 1690, 1597, 1448, 1341, 1217, 1165; HRMS (ESI): calcd. for $C_{19}H_{19}NSO_5Na$ (M^++Na): 396.0882, found: 396.0892.

Ethyl 2-(4-methylbenzoyl)-1-tosylaziridine-2-carboxylate 113b



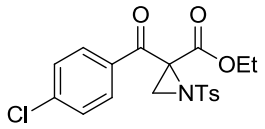
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.31-7.21 (m, 4H), 4.31-4.19 (m, 2H), 3.33 (s, 1H), 2.92 (s, 1H), 2.42 (s, 6H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 188.4, 165.1, 145.2, 144.9, 136.4, 132.0, 129.9, 129.8, 129.6, 129.4, 129.3, 128.0, 127.1, 63.2, 53.9, 37.3, 21.9, 21.8, 21.7, 13.8; IR (neat, cm^{-1}) v: 1734, 1684, 1607, 1341, 1215; HRMS (ESI): calcd. for $C_{20}H_{22}NSO_5$ (M^++H): 388.1219, found: 388.1223.

Ethyl 2-(4-fluorobenzoyl)-1-tosylaziridine-2-carboxylate 113c



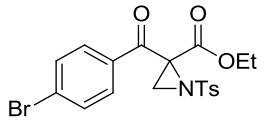
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.17-8.13 (m, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.16-7.10 (m, 2H), 4.32-4.19 (m, 2H), 3.34 (s, 1H), 2.91 (s, 1H), 2.40 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 187.5, 167.9, 164.8, 164.5, 145.0, 136.2, 132.6, 132.5, 130.9, 130.8, 129.8, 127.8, 115.9, 115.6, 63.3, 53.5, 37.4, 21.6, 13.7; IR (neat, cm^{-1}) v: 3071, 3024, 2986, 1751, 1697, 1597, 1335, 1227, 1088; HRMS (ESI): calcd. for $C_{19}H_{19}NSO_5F$ (M^++H): 392.0968, found: 392.0969.

Ethyl 2-(4-chlorobenzoyl)-1-tosylaziridine-2-carboxylate 113d



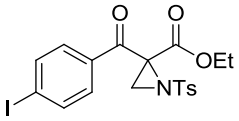
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.07 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.33-4.21 (m, 2H), 3.35 (s, 1H), 2.93 (s, 1H), 2.43 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 187.9, 164.8, 145.0, 140.6, 136.2, 132.8, 131.1, 129.8, 128.9, 127.8, 63.4, 53.4, 37.4, 21.6, 13.7. IR (neat, cm^{-1}) v: 2982, 1753, 1732, 1692, 1589, 1402, 1339, 760; HRMS (ESI): calcd. for $C_{19}H_{19}NSO_5SCl$ (M^++H): 408.0672, found: 408.0683.

Ethyl 2-(4-bromobenzoyl)-1-tosylaziridine-2-carboxylate 113e



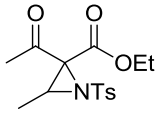
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.98 (d, J = 8.6 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.26 (q, J = 5.0 Hz, 2H), 3.34 (s, 1H), 2.92 (s, 1H), 2.42 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 188.2, 164.7, 145.0, 136.1, 133.2, 131.9, 131.1, 129.8, 129.5, 127.8, 63.4, 53.3, 37.4, 21.6, 13.7. IR (neat, cm^{-1}) v: 3019, 2399, 1748, 1694, 1339; HRMS (ESI): calcd. for $C_{19}H_{19}NSO_5Br$ (M^++H): 452.0167, found: 452.0167.

Ethyl 2-(4-iodobenzoyl)-1-tosylaziridine-2-carboxylate 113f



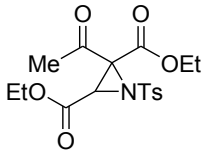
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.86-7.73 (m, 6H), 7.30 (d, J = 8.1 Hz, 2H), 4.31-4.20 (m, 2H), 3.33 (s, 1H), 2.92 (s, 1H), 2.41 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 188.5, 164.7, 145.0, 137.9, 136.1, 133.7, 130.9, 129.8, 127.8, 102.5, 63.4, 53.3, 37.3, 21.7, 13.7. IR (neat, cm^{-1}) v: 3019, 1734, 1684, 1935, 1395, 1213, 1165, 781; HRMS (ESI): calcd. for $C_{19}H_{19}NSO_5I$ (M^++H): 500.0029, found: 500.0047.

Ethyl 2-acetyl-3-methyl-1-tosylaziridine-2-carboxylate 113g



Pale yellow oil, obtained as two diastereomers in a ratio of 1.8:1; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 3H), 7.37 (d, J = 8.0 Hz, 3H), 4.34-4.26 (m, 3H), 3.79 (q, J = 5.7 Hz, 1H, major), 3.70 (q, J = 5.6 Hz, 0.5H, minor), 2.45, (s, 1.5H, minor), 2.46 (s, 3H, major), 2.23 (s, 3H), 1.35-1.27 (m, 4.5H), 1.21 (t, J = 6.6 Hz, 4.5); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 199.3, 196.0, 164.4, 164.0, 144.9, 144.8, 136.4, 136.0, 129.7, 129.6, 127.6, 63.1, 62.6, 59.9, 59.7, 45.1, 44.0, 29.6, 28.7, 21.6, 14.1, 13.9, 13.7, 13.0; IR (neat, cm^{-1}) v: 3024, 2986, 2940, 1720, 1636, 1597, 1334, 1211, 1165, 1088; HRMS (ESI): calcd. for $C_{15}H_{19}NSO_5$ (M^++H): 326.1062, found: 326.1058.

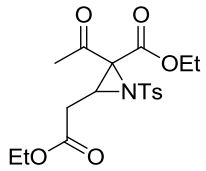
Diethyl 2-acetyl-1-tosylaziridine-2,3-dicarboxylate 113h



Diastereomer 1: Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.34 (q, J = 3.2 Hz, 2H), 4.26 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.29 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 198.3, 164.4, 162.6, 145.5, 129.9, 127.9, 63.7, 62.7, 58.3, 45.5, 28.3, 21.7, 13.8, 13.7; IR (neat, cm^{-1}) v: 3024, 2986, 2940, 1751, 1597, 1350, 1304, 1219, 1165, 1096; HRMS (ESI):calcd. for $C_{17}H_{22}NSO_7$ (M^++H): 384.1117, found: 384.1119.

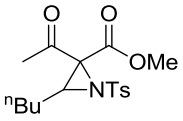
Diastereomer 2: Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.28 (dq, J = 7.2 Hz, J = 0.8 Hz, 2H), 4.24 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 2.44 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 193.9, 164.0, 163.4, 145.3, 129.8, 127.9, 63.0, 62.4, 58.9, 44.9, 29.4, 21.7, 13.9; IR (neat, cm^{-1}) v: 3024, 2986, 2940, 1751, 1597, 1350, 1304, 1219, 1165, 1096; HRMS (ESI):calcd. for $C_{17}H_{22}NSO_7$ (M^++H): 384.1117, found: 384.1119.

Ethyl 2-acetyl-3-(2-ethoxy-2-oxoethyl)-1-tosylaziridine-2-carboxylate 113i



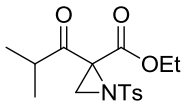
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.29, (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 2.88-2.84 (m, 2H), 2.42 (s, 3H), 2.54 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 204.4, 174.8, 170.2, 143.2, 138.9, 129.4, 126.6, 83.0, 64.8, 63.0, 31.0, 28.2, 24.6, 21.5, 14.0, 13.6; IR (neat, cm^{-1}) v: 3024, 2986, 2940, 1721, 1605, 1373, 1219, 1157, 1018; HRMS (ESI):calcd. for $C_{18}H_{24}NSO_7$ (M^++H): 398.1273, found: 398.1272.

Methyl 2-acetyl-3-butyl-1-tosylaziridine-2-carboxylate 113j



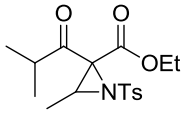
Colorless oil, obtained as two diastereomers in a ratio of 3.8:1; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.0 Hz, 2.5H), 7.37 (d, J = 8.0 Hz, 2.5H), 3.84 (s, 3H, major),), 3.81 (s, 0.8H, minor), 3.68 (dd, J = 8.4 Hz, J = 4.8 Hz, 1H), 3.60 (dd, J = 7.4 Hz, J = 5.4 Hz, 0.3H, minor), 2.48 (s, 0.8H), 2.45 (s, 3H), 2.23 (s, 3H), 1.57-1.50 (m, 1.3H), 1.28-1.11 (m, 6.4 H), 0.83-0.76 (m, 3.7H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 199.3, 195.9, 164.6, 165.2, 144.9, 136.0, 135.7, 129.7, 127.9, 127.8, 59.8, 59.6, 53.6, 53.2, 49.6, 48.5, 29.6, 28.8, 28.2, 27.3, 21.9, 21.6, 13.7; IR (neat, cm^{-1}) v: 3024, 2932, 2870, 1721, 1597, 1435, 1342, 1219, 1165; HRMS (ESI):calcd. for $C_{17}H_{24}NSO_5$ (M^++H): 354.1375, found: 354.1368.

Ethyl 2-isobutyryl-1-tosylaziridine-2-carboxylate 113k



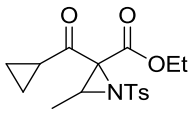
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 3.35 (s, 1H), 2.91-2.82 (m, 1H), 2.57 (s, 1H), 2.46 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.08-1.02 (m, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 204.9, 164.0, 145.1, 135.6, 129.7, 128.1, 63.0, 54.4, 36.3, 35.5, 21.7, 18.5, 17.5, 13.7; IR (neat, cm^{-1}) v: 3466, 2978, 2936, 2876, 1746, 1717, 1597, 1468, 1020; HRMS (ESI): calcd. for $C_{16}H_{22}NSO_5$ (M^++H): 340.1219, found: 340.1233.

Ethyl 2-isobutyryl-3-methyl-1-tosylaziridine-2-carboxylate 113l



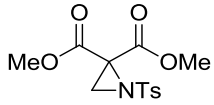
Brown oil, obtained as two diastereomers in a ratio of 1.7:1; major isomer: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 8.0 Hz, 3.4H), 7.36 (d, J = 7.6 Hz, 3.4H), 4.33-4.27 (m, 3.4 H), 3.78 (q, J = 5.7 Hz, 1H, major), 3.72 (m, 0.7H, minor), 3.05 (m, 0.7H, minor), 2.94 (m, J = 6.8 Hz, 1H, major), 2.46 (s, 3H, major), 2.43(m, 2.1H, minor), 1.39-1.30 (m, 12H), 1.18-1.09 (m, 12H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 205.6, 203.2, 164.7, 164.3, 144.8, 144.7, 136.6, 136.1, 129.8, 129.7, 129.6, 127.7, 127.1, 63.0, 62.4, 59.3, 45.0, 43.5, 38.3, 31.0, 21.7, 18.6, 18.0, 17.8, 14.0, 13.9, 13.7, 13.5; IR (neat, cm^{-1}) v: 2978, 2940, 2878, 1713, 1597, 1458, 1335, 1165; HRMS (ESI):calcd. for $C_{17}H_{24}NSO_5$ (M^++H): 354.1375, found: 354.1376.

Ethyl 2-(cyclopropanecarbonyl)-3-methyl-1-tosylaziridine-2-carboxylate 113m



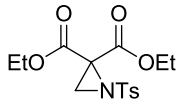
Pale yellow oil, obtained as two diastereomers in a ratio of 1.3:1; major isomer: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 4.34-4.26 (m, 2H), 3.78 (q, J = 5.6 Hz, 0.6H, major), 3.72 (m, 0.4H, minor), 2.45 (s, 3H), 2.28 (m, 0.6H, major), 2.18 (m, 0.4H, minor), 1.34-1.27 (m, 3H), 1.24-1.15 (m, 3H), 1.10-0.96 (m, 4H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 201.1, 198.6, 164.4, 164.2, 144.8, 136.3, 136.1, 129.7, 129.6, 127.7, 127.6, 62.9, 62.5, 60.6, 60.4, 44.7, 43.5, 21.9, 21.6, 19.1, 14.6, 14.1, 13.8, 13.7, 13.3, 12.9 ; IR (neat, cm^{-1}) v: 3095, 3067, 3026, 2988, 2938, 2874, 1694, 1597, 1447, 1385, 1337; HRMS (ESI): calcd. for $C_{17}H_{21}NSO_5$ (M^++H): 352.1219, found: 352.1223.

Dimethyl 1-tosylaziridine-2,2-dicarboxylate 113n



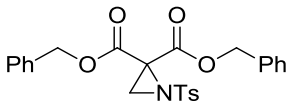
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 3.83 (s, 6H), 3.00 (s, 2H), 2.45 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 164.2, 145.2, 135.2, 129.7, 128.2, 53.7, 49.8, 35.9, 21.7; IR (neat, cm^{-1}) v: 3028, 2957, 1748, 1598; HRMS (ESI): calcd. for $C_{13}H_{16}NSO_6$ (M^++H): 314.0698, found: 314.0707.

Diethyl 1-tosylaziridine-2,2-dicarboxylate 113o



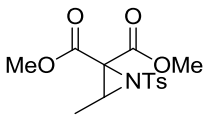
Pale yellow solid; m.p. = 85-88 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 4H), 2.99 (s, 2H), 2.46 (s, 3H), 1.32 (t, J = 7.0 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 163.8, 145.1, 135.4, 129.7, 128.1, 63.0, 50.1, 35.9, 21.7, 13.8; IR (neat, cm^{-1}) v: 3019, 1746, 1599; HRMS (ESI):calcd. for $C_{15}H_{20}NSO_6$ (M^++H): 342.1011, found: 342.1011.

Dibenzyl 1-tosylaziridine-2,2-dicarboxylate 113p



Colorless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.82 (d, J = 8.4 Hz, 2H), 7.33-7.23 (m, 12H), 5.20 (s, 4H), 3.02 (s, 2H), 2.41 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.6, 145.0, 135.3, 134.5, 129.7, 128.6, 128.5, 128.4, 128.2, 68.6, 50.1, 35.8, 21.7; IR (neat, cm^{-1}) v: 3017, 1751, 1636, 1605, 1342, 1219, 1165, 1088; HRMS (ESI): calcd. for $C_{25}H_{24}NSO_6$ (M^++H): 466.1324, found: 466.1322.

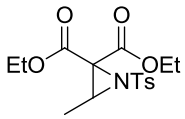
Dimethyl 3-methyl-1-tosylaziridine-2,2-dicarboxylate 113q



Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 3.78 (m, 4H), 2.44 (s, 3H), 1.26 (d, J = 5.6 Hz, 3H); ^{13}C NMR:

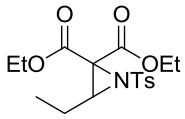
($CDCl_3$, 100 MHz) δ 164.0, 163.9, 144.7, 136.1, 129.7, 127.7, 55.2, 53.7, 53.3, 44.0, 21.6, 13.3; IR (neat, cm^{-1}) *v*: 3019, 2955, 2399, 1748, 1437, 1339, 1092; HRMS (ESI): calcd. for $C_{14}H_{18}NO_6S$ (M^++H): 328.0855, found: 328.0859.

Diethyl 3-methyl-1-tosylaziridine-2,2-dicarboxylate 113r



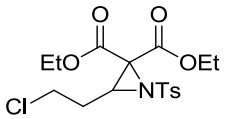
Pale yellow solid; m.p. = 101-105 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.4 Hz, 2H); 7.34 (d, *J* = 8.0 Hz, 2H), 4.36-4.21 (m, 4H), 3.78 (q, *J* = 5.7 Hz, 1H), 2.44 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 163.6, 163.4, 144.6, 136.4, 129.6, 127.7, 63.0, 62.5, 55.5, 43.9, 21.6, 14.0, 13.7, 13.3; IR (neat, cm^{-1}) *v*: 3420, 3021, 1746, 1636, 1339, 1092; HRMS (ESI): calcd. for $C_{16}H_{21}NO_6SNa$ (M^++Na): 378.0987, found: 378.0981.

Diethyl 3-ethyl-1-tosylaziridine-2,2-dicarboxylate 113s



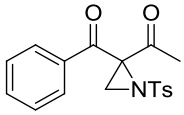
Pale yellow solid; m.p. = 64-66 ºC; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 4.32-4.16 (m, 4H), 3.60 (dd, *J* = 8.1, *J* = 5.4 Hz, 1H), 2.44 (s, 3H), 1.62-1.48 (m, 1H), 1.29-1.18 (m, 7 H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 163.6, 163.4, 144.6, 136.2, 129.6, 127.8, 63.0, 62.4, 55.6, 49.6, 21.6, 21.5, 14.0, 13.7, 10.9; IR (neat, cm^{-1}) *v*: 3011, 1645, 1339, 1094; HRMS (ESI): calcd. for $C_{17}H_{24}NO_6S$ (M^++H): 370.1324, found: 370.1328.

Diethyl 3-(2-chloroethyl)-1-tosylaziridine-2,2-dicarboxylate 113t



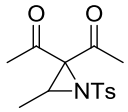
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.37-4.22 (m, 4H), 3.85 (dd, J = 6.2 Hz, J = 3.5 Hz, 1H), 3.55-3.50 (m, 1H), 3.42-3.37 (m, 1H), 2.45 (s, 3H), 2.11-2.06 (m, 1H), 1.79-1.73 (m, 1H), 1.35-1.25 (m, 6H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 163.4, 163.0, 145.0, 135.7, 129.7, 129.6, 128.0, 126.9, 63.2, 62.8, 55.1, 45.6, 41.1, 31.0, 21.7, 14.0, 13.7; IR (neat, cm^{-1}) v: 3024, 2983, 2940, 2907, 1748, 1597, 1445, 1369; HRMS (ESI): calcd. for $C_{17}H_{22}NO_6NaSCl$ (M^++Na): 426.0754, found: 426.0768.

1-(2-Benzoyl-1-tosylaziridin-2-yl)ethanone 113u



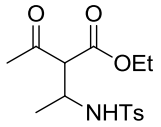
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.91 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.70 (t, J = 8.3 Hz, 1H), 7.58 (d, J = 7.4 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 3.16 (s, 1H), 2.92 (s, 1H), 2.45 (s, 3H), 2.31 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 199.7, 189.9, 145.2, 135.2, 134.7, 134.2, 129.8, 129.7, 128.7, 128.5, 128.2, 71.7, 71.1, 59.4, 35.4, 26.7, 21.7, 19.3, 13.9; IR (neat, cm^{-1}) v: 3019, 1715, 1690, 1215, 758; HRMS (ESI): calcd. for $C_{18}H_{17}NSO_4Na$ (M^++Na): 366.0776, found: 366.0779.

1,1'-(3-Methyl-1-tosylaziridine-2,2-diyl)diethanone 113v



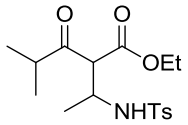
Pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.86 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.69 (q, J = 5.8, 1H), 2.46 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H), 1.17 (d, J = 5.7, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 202.0, 197.3, 145.1, 135.9, 129.8, 127.6, 64.8, 44.7, 30.1, 29.2, 21.6, 13.8; IR (neat, cm^{-1}) v: 3067, 3024, 2930, 1707, 1674, 1599, 1358, 1335, 1219, 1165, 1088; HRMS (ESI): calcd. for $C_{14}H_{17}NSO_4Na$ (M^++Na): 318.0776, found: 318.0786.

Ethyl 2-acetyl-3-(4-methylphenylsulfonamido)butanoate 114g



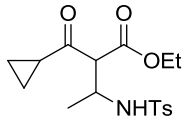
Reaction time = 3 h; white solid, obtained as two diastereomers in a ratio of 1:1; m.p. = 80-83 ºC; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 8.1 Hz, 4H), 7.30 (d, J = 7.2 Hz, 4H) 5.59 (d, J = 9.9 Hz, 1H), 5.47 (d, J = 9.6 Hz, 1H), 4.22-3.94 (m, 6H), 3.61 (d, J = 5.4 Hz, 1H), 3.58 (d, J = 4.8 Hz, 1H), 2.42 (s, 6H), 2.20 (s, 3H), 2.16 (s, 3H), 1.29-1.22 (m, 6H), 1.10 (t, J = 6.9 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 202.4, 201.7, 168.6, 167.8, 143.5, 143.4, 138.1, 129.7, 127.0, 63.8, 63,6, 61,8, 61.7, 49.1, 49.0, 30.1, 29.4, 21.5, 19.6, 19.3, 14.0; IR (neat, cm^{-1}) v: 3066, 3032, 3010, 2988, 2941, 1701, 1627, 1590, 1497, 1417; HRMS (ESI): calcd. for $C_{15}H_{22}NO_5S$ (M^++H): 328.1219, found: 328.1227.

Ethyl 4-methyl-2-(1-(4-methylphenylsulfonamido)ethyl)-3-oxopentanoate 114l



Reaction time = 4 h; white solid, obtained as two diastereomers in a ratio of 1:1; m.p. = 92-95 ºC; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 7.2 Hz, 4H), 7.29 (d, J = 6.9 Hz, 4H), 5.66 (d, J = 9.6 Hz, 1H), 5.44 (d, J = 9.3 Hz, 1H), 4.19-3.93 (m, 6H), 3.84 (d, J = 5.7 Hz, 1H), 3.80 (d, J = 4.2 Hz, 1H), 2.78-2.63 (m, 2H), 2.41 (s, 6H), 1.26-1.18 (m, 6H), 1.12-1.08 (m, 12H), 1.02 (t, J = 6.6 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 209.1, 207.6, 168.3, 167.8, 143.4, 143.3, 138.4, 138.1, 129.7, 129.6, 127.0, 127.0, 61.7, 61.7, 61.0, 59.9, 49.5, 49.1, 41.7, 40.6, 21.5, 19.6, 19.4, 18.0, 17.7, 17.4, 13.9; IR (neat, cm^{-1}) v: 3024, 2978, 2940, 1736, 1713, 1636, 1597, 1335, 1219, 1165, 1096; HRMS (ESI): calcd. for $C_{17}H_{26}NO_5S$ (M^++H): 356.1532, found: 356.1559.

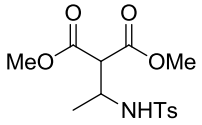
Ethyl 2-(cyclopropanecarbonyl)-3-(4-methylphenylsulfonamido)butanoate 114m



Reaction time = 0.5 h; white solid, obtained as two diastereomers in a ratio of 1:1; m.p. = 82-84 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 7.2 Hz, 4H), 7.29 (d, J = 9.6 Hz, 4H), 5.50-5.47 (m, 2H), 4.19-4.06 (m, 6H), 3.78 (d, J = 4.8 Hz, 1H), 3.73 (d, J = 5.2 Hz, 1H), 2.42 (s, 6H), 1.98-1.96 (m, 2H), 1.27-1.22 (m, 6H), 1.13 (t, J = 6.8 Hz, 6H), 1.05-0.88 (m, 8H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 204.7 203.8, 168.6, 167.9, 143.3, 143.3, 138.3, 138.3, 129.7, 127.0, 64.0, 63.3, 61.7, 61.7, 49.1, 49.1, 21.5, 21.4, 20.7, 19.9, 19.3, 14.0, 14.0, 12.4, 12.3, 12.2; IR (neat, cm^{-1}) v: 3067, 3026, 2984, 2940, 1686, 1599, 1447,

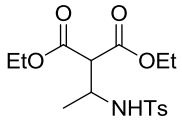
1420, 1387 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{24}NO_5S$ (M^++H): 354.1375, found: 354.1378.

Dimethyl 2-(1-(4-methylphenylsulfonamido)ethyl)malonate 114q



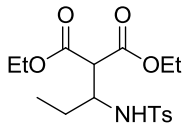
Reaction time = 4 h; white solid; m.p. = 125-128 ºC; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.58 (d, J = 9.8 Hz, 1H), 4.04-3.97 (m, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 3.54 (d, J = 4.8 Hz, 1H), 2.41 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 168.1, 167.5, 143.3, 138.2, 129.6, 127.0, 56.4, 52.6, 49.2, 21.5, 19.6; IR (neat, cm^{-1}) v: 3472, 3028, 2955, 1734, 1599, 1437, 1339, 1161, 1092; HRMS (ESI): calcd. for $C_{14}H_{19}NO_5SNa$ (M^++Na): 352.0831, found: 352.0848.

Diethyl 2-(1-(4-methylphenylsulfonamido)ethyl)malonate 114r



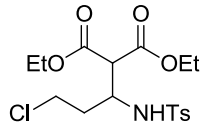
Reaction time = 4 h; colorless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.75 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.49 (d, J = 9.9 Hz, 1H), 4.25-3.93 (m, 5H), 3.47 (d, J = 4.7 Hz, 1H), 2.42 (s, 3H), 1.29-1.16 (m, 9H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 167.8, 167.2, 143.3, 138.4, 129.6, 127.0, 61.8, 61.7, 56.5, 49.2, 21.5, 19.6, 14.0, 13.9; IR (neat, cm^{-1}) v: 3442, 3028, 1722, 1636, 1418, 1341, 1094; HRMS (ESI): calcd. for $C_{16}H_{24}NO_6S$ (M^++H): 358.1342, found: 358.1313.

Diethyl 2-(1-(4-methylphenylsulfonamido)propyl)malonate 114s



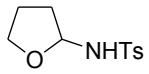
Reaction time = 5 h; colorless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.60 (d, J = 9.6 Hz, 1H), 4.22-4.13 (m, 2H), 4.07-3.91 (m, 2H), 3.84-3.78 (m, 1H), 3.56 (d, J = 4.2 Hz, 1H), 2.41 (s, 3H), 1.65-1.52 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 168.0, 167.4, 143.1, 138.6, 129.5, 126.9, 61.8, 61.6, 55.1, 54.4, 26.9, 21.4, 14.0, 13.9, 10.7; IR (neat, cm^{-1}) v: 3021, 2984, 1724, 1638, 1422, 1373, 1337, 1094; HRMS (ESI): calcd. for $C_{17}H_{25}NO_6SNa$ (M^++Na): 394.1300, found: 394.1303.

Diethyl 2-(3-chloro-1-(4-methylphenylsulfonamido)propyl)malonate 114t



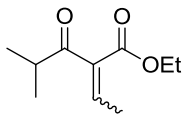
Reaction time = 7 h; white solid; m.p. = 75-79 ºC; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 5.72 (d, J = 9.9 Hz, 1H), 4.21-3.97 (m, 5H), 3.59 (d, J = 4.2 Hz, 1H), 3.63-3.43 (m, 1H), 3.39-3.33 (m, 1H), 2.38 (s, 3H), 2.18-2.10 (m, 1H), 1.99-1.93 (m, 1H), 1.28-1.19 (m, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 167.6, 167.1, 143.5, 138.1, 129.6, 126.9, 61.9, 61.8, 55.0, 50.9, 41.0, 36.1, 21.4, 14.1, 13.9, 13.8; IR (neat, cm^{-1}) v: 3345, 3030, 2984, 2940, 1716, 1634, 1599, 1495, 1094; HRMS (ESI): calcd. for $C_{17}H_{25}NO_6SCl$ (M^++H): 406.1091, found: 406.1103.

Tetrahydro-*N*-tosylfuran-2-amine 116[59]



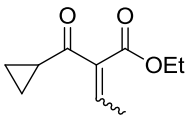
^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.63 (d, J = 8.7 Hz, 1H), 5.32-5.37 (m, 1H), 3.66-3.71 (m, 2H), 2.42 (s, 3H), 2.12-2.17 (m, 1H), 1.77-1.91 (m, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.3, 138.5, 129.5, 127.1, 85.0, 67.2, 32.7, 24.0, 21.6; MS (ESI) m/z 242 $[M+H]^+$.

Ethyl 2-ethylidene-4-methyl-3-oxopentanoate 117l[142]



Colorless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.04 (q, J = 7.3 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.95 (m, J = 7.0 Hz, 1H), 1.84 (d, J = 7.5 Hz, 3H), 1.29 (t, J = 7.2, 3H), 1.13 (d, J = 6.9 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 207.8, 164.5, 143.3, 136.3, 61.0, 40.6, 17.8, 15.4, 14.1; MS (ESI): m/z 185 $[M+H]^+$.

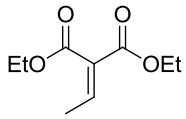
Ethyl 2-(cyclopropanecarbonyl)but-2-enoate 117m



The alkene was found to rapidly decompose in solution over a 30 min period after flash column chromatography. The ^{1}H and ^{13}C NMR spectra of **117m** containing these unknown decomposition products is provided as Figure S44 (*vide infra*). Colorless oil, IR

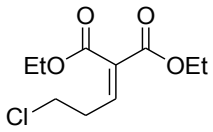
(neat, cm^{-1}) *v*: 2965, 2934, 2853, 1730, 1701, 1446, 1386, 1248; HRMS (ESI): calcd. for $C_{10}H_{15}O_3$ (M^++H): 183.1021, found: 183.1024.

Diethyl 2-ethylidenemalonate 117r[143]



Colorless oil; ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 6.92 (q, *J* = 7.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.86 (d, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 165.1, 163.7, 144.3, 129.6, 60.9, 15.2, 14.0, 13.9. MS (ESI): *m/z* 187 $[M+H]^+$.

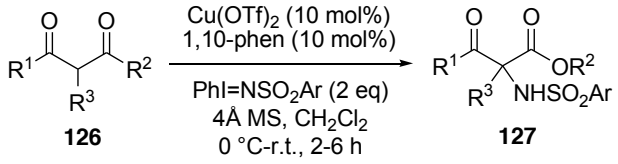
Diethyl 2-(3-chloropropylidene)malonate 117t



Colorless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.02 (t, *J* = 7.5 Hz, 1H), 4.36-4.17 (m, 4H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.81 (dt, *J* = 6.6 Hz, *J* = 7.2 Hz, 2H), 1.36-1.25 (m, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 164.8, 163.6, 144.4, 130.8, 61.4, 61.3, 42.2, 32.4, 14.1, 14.0; IR (neat, cm^{-1}) *v*: 3019, 2986, 2967, 2938, 2872, 2399, 1726, 1715, 1645, 1520, 1476, 1445, 1377, 1265; HRMS (ESI): calcd. for $C_{10}H_{15}O_4{}^{35}ClNa$ (M^++Na): 257.0557, found: 257.0549.

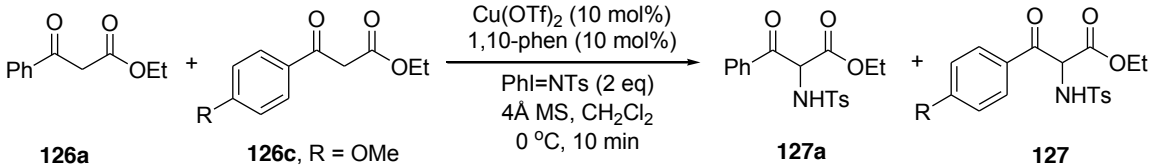
6.4 Copper(II) Triflate-Catalyzed Amination of 1,3-Dicarbonyl Compounds

General procedure for $Cu(OTf)_2$ + 1,10-phen-catalyzed amination of 1,3-dicarbonyls 126 with PhI=NTs or PhI=NNs



To a mixture of $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added CH_2Cl_2 (2 mL). After stirring for 1 h, PhI=NTs or PhI=NNs (337 mg or 404 mg, 1 mmol, 2 eq) was added followed by the 1,3-dicarbonyl compound **126** (0.5 mmol, 1 eq) at room temperature or 0 °C. The reaction was monitored by TLC. On complete consumption of the starting material **126**, the crude mixture was filtered through Celite, washed with EtOAc (50 mL), evaporated to dryness and purified by silica gel flash column chromatography (*n*-hexanes:EtOAc as eluant) to give the α-aminated product **127**.

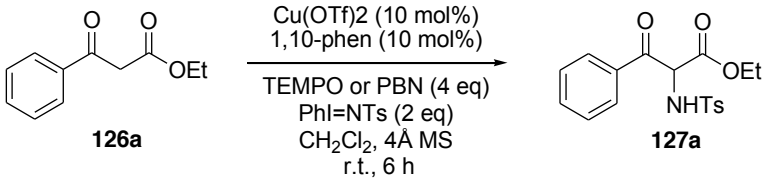
Procedure for competitive rates studies



To a mixture of $Cu(OTf)_2$ (9.1 mg, 0.025 mmol, 0.1 eq), 1,10-phen (4.9 mg, 0.025 mmol, 0.1 eq) and powdered 4Å MS (200 mg) was added CH_2Cl_2 (1 mL). After stirring

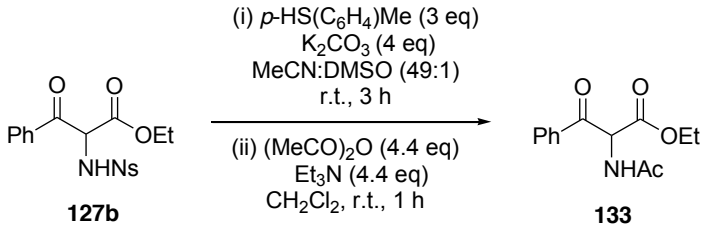
for 1 h, the reaction mixture was cooled down to 0 ºC, then PhI=NTs (187 mg, 0.5 mmol, 2 eq) was added followed by a solution of ethyl 3-oxo-3-phenylpropanoate **126a** (43 μL, 0.25 mmol, 1 eq) and *p*-substituted 3-oxo-3-phenylpropanoate (0.25 mmol, 1 eq) in CH_2Cl_2 (1 mL). After 10 min, the solution was assayed via ^{1}H NMR analysis.

Procedure for Cu(OTf)$_2$ + 1,10-phen-catalyzed amination of 126a with PhI=NTs in the presence of radical scavenger



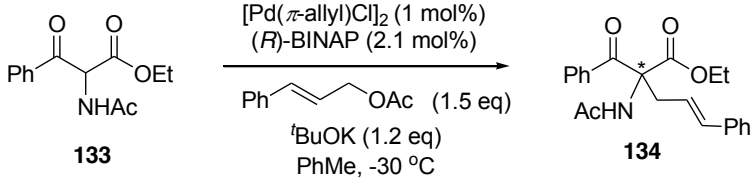
To a mixture of Cu(OTf)$_2$ (18.1 mg, 0.05 mmol, 0.1 eq), 1,10-phen (9.9 mg, 0.05 mmol, 0.1 eq), and powdered 4Å MS (400 mg) was added CH_2Cl_2 (2 mL). After stirring for 1 h, PhI=NTs (1 mmol, 373 mg) and TEMPO or PBN (312 mg or 355 mg, 2 mmol, 4 eq) was added in followed by **126a** (87 μL, 0.5 mmol, 1 eq). After 6 h, the crude mixture was filtered through Celite, washed with EtOAc (50 mL), evaporated to dryness. The reaction mixture was then analyzed by ^{1}H NMR spectroscopy.

Procedure for the synthesis of 133 from 127b



A mixture of sulfonamide **127b** (898 mg, 2.29 mmol, 1 eq) and *p*-methoxyphenylthiol (960 mg, 6.85 mmol, 3 eq) was dissolved in MeCN:DMSO (49:1, 15 mL). After which solid potassium carbonate (1.27 g, 9.2 mmol, 4 eq) was added and the heterogeneous mixture was stirred vigorously at room temperature for 3 h. The solvent was removed in vacuum and the residue was taken up in ethyl acetate (300 mL). The mixture was then diluted with H_2O (100 mL) and the layers were separated. The organic portion was washed with brine (100 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The mixture was dissolved in CH_2Cl_2 (10 mL) followed by addition of NEt_3 (1.4 mL, 10 mmol, 4.4 eq) and acetic anhydride (0.95 mL, 10 mmol, 4.4 eq). The mixture was stirred at room temperature for 1 h. The mixture was extracted with H_2O (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated to dryness and purified by silica gel flash column chromatography (*n*-hexanes:EtOAc as eluant) to give **133**.

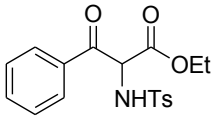
Procedure for asymmetric allylation of 133[114]



A mixture of [Pd(π-allyl)Cl]$_2$ (1.8 mg, 5.0 μmol, 0.01 eq) and (*R*)-BINAP (6.6 mg, 10.6 μmol, 0.02 eq) in toluene (0.5 mL) was stirred for 10 min at room temperature. Cinnamyl acetate (125 μL, 0.75 mmol, 1.5 eq) was added to the solution. After 10 min, the solution was added to a suspension of **133** (125 mg, 0.5 mmol, 1 eq) and ^{t}BuOK (67.3 mg, 0.6 mmol, 1.2 eq) in toluene (2 mL) at -30 ºC. The reaction was monitored by TLC until **133** was completely comsumed then quenched by 1N HCl aq. (3 mL). The mixture

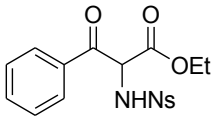
was extracted three times with EtOAc (50 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative TLC (*n*-hexanes:EtOAc) to give **134**.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-phenylpropanoate 127a



Reaction time = 6 h, white solid; m.p. = 109-110 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.98 (d, J = 7.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.97 (d, J = 9.2 Hz, 1H), 5.58 (d, J = 8.7 Hz, 1H), 3.97 (m, 2H), 2.38 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 190.3, 167.0, 144.0, 136.5, 134.6, 133.5, 130.2, 129.7, 129.4, 128.8, 128.4, 127.3, 62.6, 60.9, 21.5, 13.7; IR (neat, cm^{-1}) v: 3356, 1748, 1692, 1344, 1163, 1020; HRMS calcd. for $C_{18}H_{20}NSO_5$ (M^++H): 362.1062, found: 362.1057.

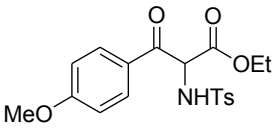
Ethyl 2-(4-nitrophenylsulfonamido)-3-oxo-3-phenylpropanoate 127b



Reaction time = 6 h, white solid; m.p. = 97-100 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.29 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 7.8 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 6.44 (d, J = 8.1 Hz, 1H), 5.73 (d, J = 8.7 Hz, 1H), 4.01 (q, J = 6.9 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 189.7, 165.5,

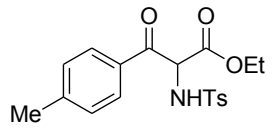
150.3, 145.6, 135.0, 133.3, 129.4, 129.0, 128.6, 124.3, 63.0, 60.8, 13.7; IR (neat, cm^{-1}) *v*: 1748, 1682, 1643, 1531, 1350, 1169, 1092; HRMS calcd. for $C_{17}H_{17}N_2SO_7$ (M^++H): 393.0756, found: 393.0771.

Ethyl 3-(4-methoxyphenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127c



Reaction time = 6 h, white solid; m.p. = 135-138 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 6.8 Hz, 2H), 7.24 (d, *J* = 6.8 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.10 (d, *J* = 8.4 Hz, 1H), 5.55 (d, *J* = 8.4 Hz, 1H), 3.96 (m, 2H), 3.88 (s, 3H), 2.38 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 188.3, 166.4, 164.9, 144.0, 136.7, 132.0, 129.8, 127.4, 126.4, 114.2, 62.7, 60.7, 55.8, 21.6, 13.8; IR (neat, cm^{-1}) *v*: 3385, 1748, 1682, 1344, 1163, 1094; HRMS calcd. for $C_{19}H_{22}NSO_6$ (M^++H): 392.1168, found: 392.1173.

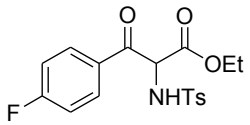
Ethyl 3-(4-methylphenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127d



Reaction time = 6 h, white solid; m.p. = 110-113 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.28-7.23 (m, 4H), 5.97 (d, *J* = 8.7 Hz, 1H), 5.55 (d, *J* = 8.7 Hz, 1H), 3.96 (m, 2H), 2.42 (s, 3H), 2.38 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 189.7, 166.2, 145.9, 143.9, 136.7, 132.0, 129.6, 129.5,

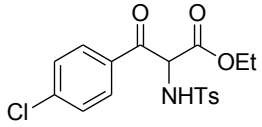
127.3, 62.6, 60.8, 21.8, 21.4, 13.5; IR (neat, cm^{-1}) *v*: 3325, 1751, 1690, 1344, 1163, 1092, 1070; HRMS calcd. for $C_{19}H_{22}NSO_5$ (M^++H): 376.1219, found: 376.1216.

Ethyl 3-(4-fluorophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127e



Reaction time = 6 h, white solid; m.p. = 115-118 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.05 (m, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.01 (d, *J* = 8.7 Hz, 1H), 5.55 (d, *J* = 8.7 Hz, 1H), 3.97 (m, 2H), 2.39 (s, 3H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 188.9, 166.1, 144.2, 136.5, 132.5, 132.4, 129.9, 127.5, 116.4, 116.2, 62.9, 61.0, 21.7, 13.7; IR (neat, cm^{-1}) *v*: 3356, 1747, 1681, 1337, 1234, 1161, 1090; HRMS calcd. for $C_{18}H_{19}NSO_5$ (M^++H): 380.0968, found: 380.0972.

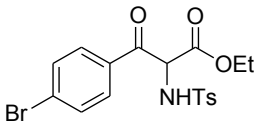
Ethyl 3-(4-chlorophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127f



Reaction time = 6 h, white solid; m.p. = 118-120 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.94 (d, *J* = 8.7, 1H), 5.53 (d, *J* = 8.5 Hz, 1H), 3.98 (m, 2H), 2.39 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 189.3, 166.4, 144.3, 144.2, 141.4, 136.5, 130.9, 129.8, 129.3, 127.4, 63.0, 61.0, 21.6, 13.8; IR (neat, cm^{-1}) *v*: 3300, 1734, 1687,

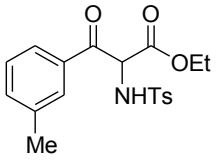
1342, 1165, 1109, 1088; HRMS calcd. for $C_{18}H_{19}NSO_5Cl$ (M^++H): 396.0672, found: 396.0671.

Ethyl 3-(4-bromophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127g



Reaction time = 6 h, white solid; m.p. = 130-133 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 5.91 (d, J = 9.2 Hz, 1H), 5.49 (d, J = 8.8 Hz, 1H), 3.94 (m, 2H), 2.37 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 189.5, 165.8, 144.1, 136.4, 132.2, 130.8, 130.1, 129.7, 129.3, 127.3, 62.8, 60.9, 21.5, 13.7; IR (neat, cm^{-1}) v: 3325, 1751, 1690, 1344, 1163, 1092, 1070; HRMS calcd. for $C_{18}H_{19}NSO_5Br$ (M^++H): 440.0167, found: 440.0146.

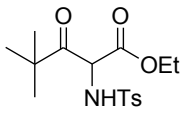
Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-m-tolylpropanoate 127i



Reaction time = 6 h, white solid; m.p. = 95-98 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80-7.77 (m, 2H), 7.73 (d, J = 8.3 Hz, 2H), 7.43-7.41 (m, 1H), 7.35 (dd, J = 7.7 Hz, J = 7.5 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 6.06 (d, J = 9.2 Hz, 1H), 5.58 (d, J = 8.8 Hz, 1H), 3.96 (m, 2H), 2.39 (s, 3H), 2.37 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 190.3, 166.1, 143.9, 138.8, 136.6, 135.4, 133.5, 129.8, 129.7, 128.7, 127.3, 126.6,

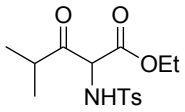
126.5, 62.6, 60.9, 21.5, 21.3, 13.7; IR (neat, cm^{-1}) *v*: 3328, 1755, 1682, 1598, 1454, 1337, 1164; HRMS calcd. for $C_{18}H_{19}NSO_5Cl$ (M^++H): 376.1219, found: 376.1215.

Ethyl 4, 4-dimethyl-2-(4-methylphenylsulfonamido)-3-oxopentanoate 127j



Reaction time = 3 h, pale yellow solid; m.p. = 85-87 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.84 (d, *J* = 9.6 Hz, 1H), 5.08 (d, *J* = 9.6 Hz, 1H), 3.98 (dq, *J* = 2.1, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.15 (s, 9H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 205.0, 166.2, 143.9, 136.5, 129.6, 127.3, 62.4, 58.6, 44.9, 26.1, 21.5, 13.7. IR (neat, cm^{-1}) *v*: 3340, 3019, 2960, 1749, 1715, 1599, 1344, 1163; HRMS calcd. for $C_{16}H_{24}NSO_5$ (M^++H): 342.1375, found: 342.1386.

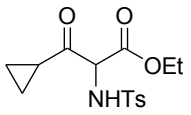
Ethyl 4-methyl-2-(4-methylphenylsulfonamido)-3-oxopentanoate 127k



Reaction time = 3 h, yellow oil; obtained as two ketone:enol tautomers in a ratio of 0.9:1; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 12.62 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 1.8H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.31-7.26 (m, 3.8H), 6.05 (d, *J* = 8.4 Hz, 0.9H), 5.92 (s, 1H), 4.82 (d, *J* = 8.4 Hz, 0.9H), 4.38-4.20 (m, 1.8H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.48-3.43 (m, 0.9H), 3.04-2.95 (m, 1H), 2.41 (s, 5.7H), 1.20-0.86 (m, 17.1H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 204.3, 186.1, 170.3, 166.1, 144.0, 143.4, 136.8, 136.4, 129.5, 129.4, 129.3, 127.6, 127.2, 97.8, 62.8, 62.6, 60.9, 38.2, 29.5, 21.44, 21.37, 19.2, 18.3, 17.6, 13.8, 13.5; IR (neat, cm^{-1}) *v*:

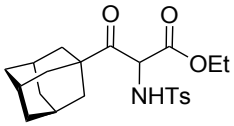
3280, 3024, 2984, 2940, 1732, 1599, 1339, 1215, 1094; HRMS calcd. for $C_{15}H_{22}NSO_5$ (M^++H): 328.1219, found: 328.1210.

Ethyl 3-(cyclopropyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127l



Reaction time = 3 h, colorless oil; obtained as two ketone:enol tautomers in a ratio of 2:1; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 12.66 (s, 0.5H), 7.73 (d, J = 8.2 Hz, 3H), 7.30 (d, J = 8.2 Hz, 3H), 5.92 (d, J = 7.9 Hz, 1H), 5.75 (s, 0.5H), 4.87 (d, J = 7.9 Hz, 1H), 4.33 (q, J = 7.1, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.42 (s, 4.5H), 2.27-2.14 (m, 1.5H), 1.39-0.85 (m, 10.5H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 200.1, 166.0, 143.9, 136.5, 129.7, 129.3, 127.7, 127.3, 92.7, 65.3, 63.2, 62.6, 21.5, 18.6, 15.9, 13.9, 13.8, 13.3, 13.0, 12.8, 9.2 ; IR (neat, cm^{-1}) v: 3281, 2982, 2938, 1748, 1713, 1078; HRMS calcd. for $C_{15}H_{21}NSO_5$ (M^++H): 326.1062, found: 326.1069.

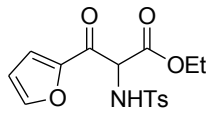
Ethyl 3-(1-adamantyl)-3-oxo-2-(tosylamino)propanoate 127m



Reaction time = 4 h, pale yellow solid; m.p. = 110-113 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.85 (d, J = 9.6 Hz, 1H), 5.08 (d, J = 9.6 Hz, 1H), 3.98 (m, 2H), 2.41 (s, 3H), 2.02 (m, 3H), 1.77-1.67 (m, 12H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 205.1, 166.3, 143.9, 136.6, 129.6, 127.4, 62.3, 58.0, 47.1, 38.6, 37.6, 36.4, 36.2, 27.8, 27.6, 21.5, 13.8; IR (neat, cm^{-1}) v: 3317, 3019,

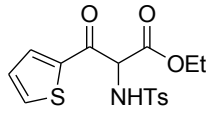
2911, 2853, 1748, 1707, 1599; HRMS calcd. for $C_{22}H_{30}NSO_5$ (M^++H): 420.1845, found: 420.1847.

Ethyl 3-(furan-2-yl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127n



Reaction time = 2 h, white solid; m.p. = 102-104 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 8.4 Hz, 2H), 7,66 (s, 1H), 7.41 (d, J = 3.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 6.60 (dd, J = 1.6 Hz, J = 2.0 Hz, 1H), 5.94 (d, J = 8.8 Hz, 1H), 5.35 (d, J = 8.8 Hz, 1H), 4.03 (q, J = 4.0 Hz, 2H), 2.39 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 178.4, 165.8, 149.8, 148.3, 144.0, 136.5, 129.7, 127.3, 121.1, 113.0, 62.8, 60.7, 21.5, 13.8; IR (neat, cm^{-1}) v: 3302, 3019, 1751, 1685, 1599, 1463, 1221, 1163; HRMS calcd. for $C_{16}H_{18}NSO_6$ (M^++H): 352.0855, found: 352.0852.

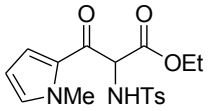
Ethyl 3-(thiophen-2-yl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127o



Reaction time = 2 h, pale yellow solid; m.p. = 118-121 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.98 (d, J = 4.0 Hz, 1H), 7.76 (d, J = 5.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.17 (dd, J = 5.2 Hz, J = 4.0 Hz, 1H), 5.93 (d, J = 8.8 Hz, 1H), 5.40 (d, J = 8.8 Hz, 1H), 3.97-4.06 (m, 2H), 2.39 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 182.7, 165.9, 144.1, 140.2, 136.5, 136.4, 135.3, 129.7, 128.7, 127.3, 62.8,

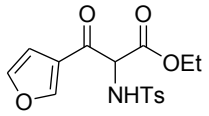
61.6, 21.5, 13.7; IR (neat, cm^{-1}) *v*: 3424, 3020, 1750, 1675, 1520, 1411, 1357, 1217, 1165; HRMS calcd. for $C_{16}H_{18}NS_2O_5$ (M^++H): 368.0626, found: 368.0635.

Ethyl 3-(1-methyl-1*H*-pyrrol-2-yl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 127p



Reaction time = 2 h, white solid; m.p. = 100-103 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.22-7.27 (m, 3H), 6.89 (s, 1H), 6.18 (dd, *J* = 2.4, *J* = 4.0 Hz, 1H), 6.02 (d, *J* = 8.8 Hz, 1H), 5.29 (d, *J* = 8.8 Hz, 1H), 3.95-4.04 (m, 2H), 3.79 (s, 3H), 2.38 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 178.5, 166.7, 143.7, 136.8, 133.5, 129.7, 127.8, 122.6, 109.4, 62.4, 60.8, 37.6, 21.5, 13.8; IR (neat, cm^{-1}) *v*: 3305, 2981, 1750, 1645, 1337, 1265; HRMS calcd. for $C_{17}H_{21}N_2SO_5$ (M^++H): 365.1171, found: 365.1166.

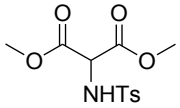
Ethyl 3-(furan-3-yl)-3-oxo-2-(tosylamino)propanoate 127q



Reaction time = 2 h, yellow solid; obtained as two ketone:enol tautomers in a ratio of 2:1; m.p. = 116-119 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 12.74 (s, 0.5H), 8.33 (s, 1H), 8.29 (s, 0.5H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.44 (s, 1H), 7.40 (s, 0.5H), 7.29-7.25 (m, 3H), 7.02 (d, *J* = 1.3 Hz, 0.5H), 6.77 (d, *J* = 1.3 Hz, 1H), 6.16 (d, *J* = 9.0 Hz, 1H), 6.06 (s, 0.5H), 5.17 (d, *J* = 9.0 Hz, 1H), 3.90-4.04 (m, 2H), 3.71-3.68 (m, 1H),

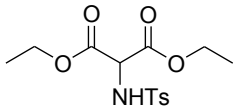
2.40 (s, 1.5H), 2.38 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.1 Hz, 1.5H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 184.4, 170.7, 168.2, 166.1, 149.9, 147.5, 144.4, 144.1, 143.6, 142.8, 137.1, 136.3, 129.7, 129.4, 127.5, 127.3, 124.4, 120.0, 110.2, 108.8, 98.4, 62.8, 62.7, 61.2, 21.5, 21.4, 13.7, 13.5; IR (neat, cm^{-1}) v: 3348, 3021, 1748, 1688, 1647, 1622, 1599, 1287, 1215, 1163; HRMS calcd. for $C_{16}H_{18}NSO_6$ (M^++H): 352.0855, found: 352.0850.

Dimethyl 2-(4-methylphenylsulfonamido)malonate 127s[144]



Reaction time = 6 h, pale yellow solid; obtained as a mixture with $TsNH_2$; m.p. = 117-118 °C; ^{1}H NMR: (CD_3COCD_3, 400 MHz) δ 7.80 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 9.2 Hz, 2H), 4.79 (d, J = 9.2 Hz, 1H), 3.61 (s, 6H), 2.43 (s, 3H); ^{13}C NMR: (CD_3COCD_3, 100 MHz) δ 166.0, 143.5, 141.5, 129.5, 126.1, 59.0, 52.6, 20.5; HRMS calcd. for $C_{12}H_{16}NSO_6$ (M^++H): 302.0698, found: 302.0706.

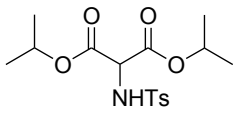
Diethyl 2-(4-methylphenylsulfonamido)malonate 127t



Reaction time = 6 h, yellow oil, ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.64 (d, J = 8.4 Hz, 1H), 4.66 (d, J = 8.7 Hz, 1H), 4.12 (q, J = 7.2, 4H), 2.41 (s, 3H), 1.19 (t, J = 6.9 Hz, 6H) ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 165.6, 144.0, 136.5, 129.7, 127.3, 62.8, 58.8, 21.5, 13.8; IR (neat, cm^{-1}) v: 3362, 3096, 1746,

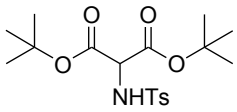
1645, 1344, 1302, 1288, 1163, 1094; HRMS calcd. for $C_{14}H_{20}NSO_6$ (M^++H): 330.1011, found: 330.1024.

Diisopropyl 2-(tosylamino)malonate 127u



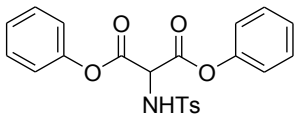
Reaction time = 6 h, pale yellow oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.68 (d, J = 8.4 Hz, 1H), 4.99-4.90 (m, 2H), 4.57 (d, J = 8.4 Hz, 1H), 2.41 (s, 3H), 1.12-1.06 (m, 12H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 165.2, 143.9, 136.6, 129.7, 127.3, 70.8, 59.0, 21.5, 21.4, 21.3; IR (neat, cm^{-1}) v: 3497, 3237, 1742, 1599, 1283, 1156, 1101; HRMS calcd. for $C_{16}H_{24}NSO_6$ (M^++H): 358.1324, found: 357.1323.

Di-*tert*-butyl 2-(tosylamino)malonate 127v



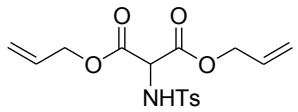
Reaction time = 6 h, pale yellow solid; m.p. = 113-115 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.72 (d, J = 8.8 Hz, 1H), 4.39 (d, J = 8.4 Hz, 1H), 2.36 (s, 3H), 1.33 (s, 18H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 164.7, 143.8, 136.7, 129.6, 127.3, 83.6, 60.0, 27.6, 21.4. IR (neat, cm^{-1}) v: 3362, 3020, 2982, 2934, 1738, 1599, 1371, 1348, 1163, 1144; HRMS calcd. for $C_{18}H_{28}NSO_6$ (M^++H): 386.1637, found: 386.1620.

Diphenyl 2-(4-methylphenylsulfonylamido)malonate 127w



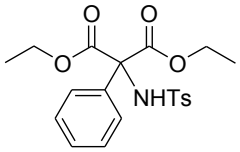
Reaction time = 6 h, white solid; m.p. = 166-169 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.69 (d, J = 8.20 Hz, 2H), 7.43-7.17 (m, 10H), 7.00 (d, J = 7.80 Hz, 2H), 6.70 (s, 1H), 2.36 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 162.9, 150.2, 144.2, 137.2, 129.8, 129.7, 129.6, 127.4, 126.9, 120.8, 120.5, 90.6, 72.7, 21.6; IR (neat, cm^{-1}) v: 3404, 3021, 1767, 1090; HRMS calcd. for $C_{22}H_{20}NSO_6$ (M^++H): 3426.1062, found: 426.1069.

Diallyl 2-(4-methylphenylsulfonamido)malonate 127x



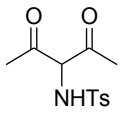
Reaction time = 6 h, white solid; m.p. = 84-86 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.82-5.73 (m, 2H) 5.67 (d, J = 8.5Hz, 1H), 5.30-5.22 (m, 4H), 4.73 (d, J = 8.60 Hz, 1H), 4.55 (dd, J = 5.70 Hz, J = 1.02 Hz, 4H), 2.42 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 165.2, 144.1, 136.4, 130.6, 129.7, 127.3, 119.5, 67.1, 58.7, 21.6; IR (neat, cm^{-1}) v: 3019, 1744, 1634, 1163, 1092, 988, 930; HRMS calcd. for $C_{16}H_{20}NSO_6$ (M^++H): 354.1011, found: 354.1000.

Diethyl 2-(4-methylphenylsulfonamido)-2-phenylmalonate 127y



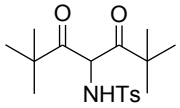
Reaction time = 6 h, white solid; m.p. = 110-115 °C ; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 7.4 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.21-7.14 (m, 3H), 7.07 (d, J = 8.1 Hz, 2H), 6.30 (s, 1H), 4.23-4.17 (m, 4H), 2.34 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 166.9, 142.9, 138.5, 133.6, 129.0, 128.7, 128.6, 128.4, 128.0, 127.8, 126.9, 63.1, 21.4, 13.8; IR (neat, cm^{-1}) v: 3435, 2957, 2926, 2853, 1740, 1456, 1094, 1016; HRMS calcd. for $C_{20}H_{24}SNO_6$ (M^++H): 406.1324, found: 406.1310.

N*-(2,4-dioxopentan-3-yl)-4-methylbenzenesulfonamide 127*α



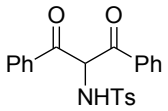
Reaction time = 6 h, white solid; m.p. = 166-169 °C; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.71 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H) 6.22 (s, 1H), 2.44 (s, 3H), 1.88 (s, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 194.2, 144.4, 136.7, 130.2, 127.5, 110.2, 22.3, 21.8; IR (neat, cm^{-1}) v: 3374, 1745, 1599, 1159, 1093; HRMS calcd. for $C_{12}H_{16}NO_4S$: (M^++H): 270.0800, found: 270.0808.

4-Methyl-*N*-(2,2,6,6-tetramethyl-3,5-dioxoheptan-4-yl)benzenesulfonamide 127*β*



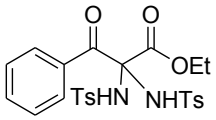
Reaction time = 6 h, white solid; m.p. = 146-148 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.81 (d, J = 10.0 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 2.39 (s, 3H), 1.08 (s, 18H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 208.0, 144.2, 135.5, 129.7, 127.8, 59.8, 44.3, 27.1, 21.5; IR (neat, cm^{-1}) v: 1719, 1697, 1643, 1342, 1165, 1092; HRMS calcd. for $C_{18}H_{28}NSO_4$ (M^++H): 354.1739, found: 354.1740.

N*-(1,3-dioxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide 127*γ



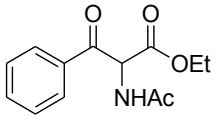
Reaction time = 6 h, white solid; m.p. = 166-169 °C; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.90 (d, J = 8.8 Hz, 4H), 7.65 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 7.2 Hz, 2H) 7.42 (t, J = 8.0 Hz, 4H), 7.14 (d, J = 8.0 Hz, 2H), 6.26 (s, 2H), 2.33 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 191.9, 144.0, 136.0, 134.4, 134.0, 129.7, 129.1, 128.9, 63.8, 21.5; IR (neat, cm^{-1}) v: 1697, 1674, 1639, 1597, 1335, 1161, 1090; HRMS calcd. for $C_{22}H_{20}NSO_4$ (M^++H): 394.1113, found: 394.1132.

Ethyl 3-oxo-3-phenyl-2,2-bis(tosylamino)propanoate 128a



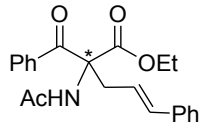
Reaction time = 6 h, white solid; m.p. = 155-159 °C ; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 4H), 7.53 (t, J = 7.6Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 4H), 6.83 (bs, 2H), 3.42 (m, 2H), 2.38 (s, 6H), 0.57 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 185.7, 164.0, 143.9, 137.2, 134.1, 132.4, 129.7, 129.4, 128.7, 127.6, 74.1, 63.6, 21.6, 12.8; IR (neat, cm^{-1}) v: 3018, 2954, 2922, 2852, 1751, 1691, 1452, 1377, 1167; HRMS calcd. for $C_{25}H_{26}S_2N_2O_7Na$ (M^++Na): 553.1079, found: 553.1077.

Ethyl 2-acetamido-3-oxo-3-phenylpropanoate 133[145]



Yellow solid; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.08 (d, J = 8.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 6.22 (d, J = 7.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.07 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 191.7, 170.0, 166.6, 134.2, 134.0, 129.4, 128.5, 62.2, 58.0, 22.6, 13.6; MS (ESI) m/z 250 $[M+H]^+$.

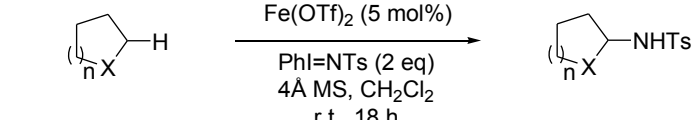
Ethyl 2-(*N*-acetylamino)-3-oxo-3-phenyl-2-{(*E*)-3-phenyl-2-propenyl}propionate 134



The enantiomeric excess of **134** was determined to be 84% ee by HPLC analysis (CHIRALCEL OJ-H, *n*-hexanes/2-propanol = 9:1). Pale yellow solid; m.p. = 124-127 °C; $[\alpha]^{21}_{D}$ = +31.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.28-7.20 (m, 5H), 7.16 (s, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.99-5.91 (m, 1H), 4.31-4.18 (m, 2H), 3.37 (d, *J* = 7.6 Hz, 2H), 1.89 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 191.4, 169.5, 168.6, 136.9, 135.0, 133.0, 128.5, 128.3, 127.6, 126.2, 122.6, 70.1, 63.2, 37.2, 22.9, 14.0; IR (neat, cm^{-1}) *v*: 3435, 1765, 1740, 1327, 1260, 1157, 1094, 1016; HRMS calcd. for $C_{22}H_{24}NO_4$ (M^++H): 366.1705, found: 366.1711.

6.5 Iron(II) Triflate-Catalyzed Amination of Saturated *N*- and *O*-Heterocyclic Compounds

General procedure for iron(II)-catalyzed amination of saturated *N*- and *O*-heterocylic compounds



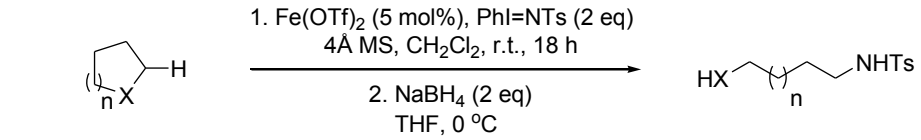
139, X = NTs, n = 1, 2
140, X = O, n =1, 2

141
142

To a mixture of $Fe(OTf)_2$ (9.1 mg, 0.025 mmol, 0.05 eq), PhI=NTs (373 mg, 1.0 mmol, 2 eq), powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2 followed by **139** or **140** (0.5 mmol, 1 eq) at room temperature under N_2 atmosphere. The reaction mixture

was stirred for a further 18 h at room temperature, after which the mixture was filtered through Celite, washed with EtOAc, evaporated to dryness, and purified by flash column chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

General procedure for iron(II)-catalyzed amination of saturated *N*- and *O*-heterocylic compounds followed by reductive ring-opening by $NaBH_4$

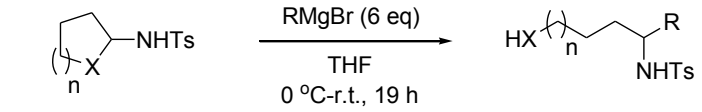


139, X = NTs, n = 1, 2
140, X = O, n =1, 2

144
145

To a mixture of $Fe(OTf)_2$ (9.1 mg, 0.025 mmol, 0.05 eq), PhI=NTs (373 mg, 1.0 mmol, 2 eq), powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2 followed by **139** or **140** (0.5 mmol, 1 eq) at room temperature under N_2 atmosphere. The reaction mixture was stirred for a further 18 h at room temperature, after which the mixture was evaporated to dryness. $NaBH_4$ (37.8 mg, 1 mmol, 2 eq) in 3 mL of THF was then added into the mixture dropwise at 0 ºC. After 15 min, the reaction was stirred at room temperature and monitored by TLC until completion. The resulting mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

General procedure for ring-opening of 141 and 142 with grignard reagent

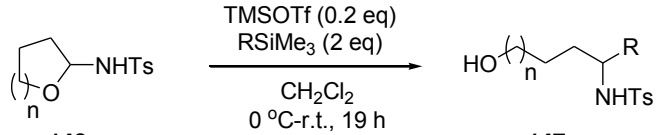


141, X = NTs, n = 1, 2
142, X = O, n =1, 2

146
147

A solution of RMgBr (1.5 mmol, 6 eq) in THF (1.5 mL) was added dropwise to a solution of **141** or **142** (0.25 mmol, 1 eq) in 2 mL of THF at 0 ºC. After 1 h, the reaction was stirred at room temperature for 18 h. The resulting mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

General procedure for ring-opening of 142 with $RSiMe_3$ in the presence of TMSOTf

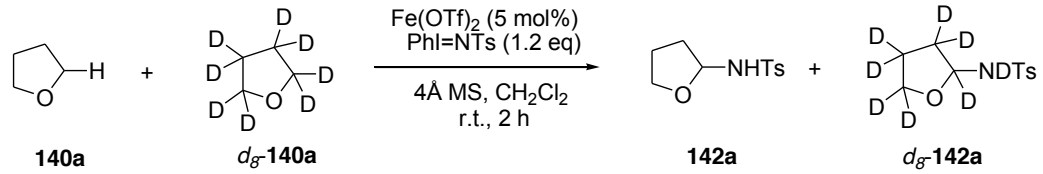


142
n = 1, 2

147

To a solution of **142** (0.25 mmol, 1 eq), $RSiMe_3$ (0.5 mmol, 2 eq) in CH_2Cl_2 was added TMSOTf (0.05 mmol, 0.02 eq) dropwise at 0 ºC. After 1 hour, the reaction was stirred at room temperature for 18 h. The resulting mixture was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate (2x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by flash chromatography (*n*-hexanes/EtOAc as eluent) to give the title compound.

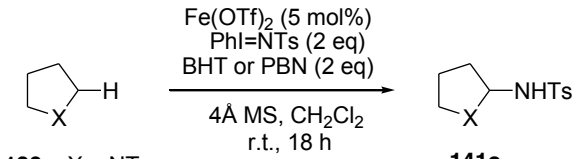
Procedure for the Kinetic Isotope Study



140a d_8-**140a** **142a** d_8-**142a**

To a mixture of $Fe(OTf)_2$ (9.1 mg, 0.025 mmol, 0.05 eq), PhI=NTs (224 mg, 0.6 mmol, 1.2 eq), powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2 at room temperature under N_2 atmosphere. A solution of **140a** (41 μL, 0.5 mmol, 1 eq) and d_8-tetrahydrofuran (41 μL, 0.5 mmol, 1 eq) was added. After 2 h, the solution was assayed via GC-MS.

Procedure for iron(II)-catalyzed amidation of 139c, 140a in the presence of a radical scavenger

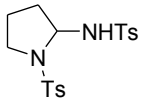


139c, X = NTs
140a, X = O

141c
142a

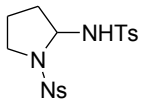
To a mixture of $Fe(OTf)_2$ (9.1 mg, 0.025 mmol, 0.05 eq), PhI=NTs (373 mg, 1 mmol, 2 eq), BHT or PBN (220 mg or 178 mg, 1 mmol, 2 eq), powdered 4Å MS (400 mg) was added 2 mL of CH_2Cl_2 followed by **139c** or **140a** (113 mg or 41 μL, 0.5 mmol, 1 eq) at room temperature under N_2 atmosphere. The reaction mixture stirred for a further 18 h at room temperature, after which the mixture was filtered through Celite, washed with EtOAc, evaporated to dryness. The crude mixture was then analyzed by ^{1}H NMR spectroscopy.

_N_,1-Ditosylpyrrolidin-2-amine 141c



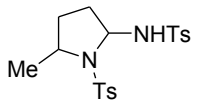
Pale yellow solid; m.p. = 148-151 ºC; ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.32 (bs, 1H), 4.65 (m, 1H), 3.50 (t, J = 8.0 Hz, 1H), 2.99 (m, 1H), 2.48 (s, 3H), 2.40 (s, 3H), 2.11-2.13 (m, 1H), 1.92-1.97 (m, 1H), 1.63-1.71 (m, 1H), 1.56-1.62 (m, 1H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 144.1, 143.8, 136.8, 133.9, 129.8, 129.7, 127.7, 127.3, 69.7, 48.6, 34.1, 22.6, 21.7, 21.6; IR (neat, cm^{-1}) v: 3649, 3269, 3030, 2984, 2926, 2876, 1599, 1350, 1161, 1090, 1032; HRMS (ESI): calcd. for $C_{18}H_{22}N_2S_2O_4Na$ (M^++Na): 417.0919, found: 417.0905.

1-Nosyl-_N_-tosylpyrrolidin-2-amine 141d



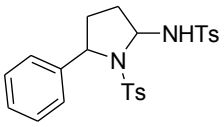
Pale yellow solid; m.p. = 165-168 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.13 (d, J = 5.2 Hz, 1H), 4.88 (m, 1H), 3.50 (m, 1H), 3.15 (m, 1H), 2.50 (s, 3H), 1.96-2.10 (m, 2H), 1.75-1.87 (m, 2H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 150.2, 144.2, 143.4, 136.1, 129.8, 128.9, 127.5, 124.3, 69.7, 48.4, 34.2, 22.7, 21.7; IR (neat, cm^{-1}) v: 3024, 2957, 2926, 1531, 1348, 1163, 1090, 1024; HRMS (ESI): calcd. for $C_{17}H_{19}N_3S_2O_6Na$ (M^++Na): 448.0613, found: 448.0619.

5-Methyl-*N*,1-ditosylpyrrolidin-2-amine 141e



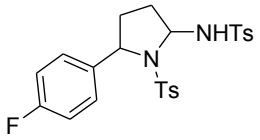
Pale yellow oil; isolated as 2 inseparable diastereomers with a ratio of 9.8:1; major isomer: ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 5.16 (d, J = 2.7 Hz, 1H), 4.62 (m, 1H), 3.57 (m, 1H), 2.49 (s, 3H), 2.40 (s, 3H), 2.07-2.13 (m, 1H), 1.40-1.79 (m, 3H), 1.3 (d, J = , 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 144.0, 143.8, 136.6, 134.3, 129.7, 129.6, 127.7, 127.3, 71.4, 58.0, 32.4, 31.3, 22.9, 21.6, 21.5; IR (neat, cm^{-1}) v: 3526, 3275, 3030, 2974, 2930, 2872, 1599, 1344, 1163, 1092, 1034; HRMS (ESI): calcd. for $C_{19}H_{24}N_2S_2O_4Na$ (M^++Na): 431.1075, found: 431.1056.

5-Phenyl-*N*,1-ditosylpyrrolidin-2-amine 141f



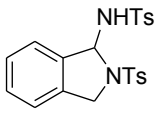
Pale yellow oil; isolated as 2 inseparable diastereomers with a ratio of 3.6:1; major isomer: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.26-7.33 (m, 5H), 7.19 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.31 (bs, 1H), 4.94 (d, J = 3.2 Hz, 1H), 4.59 (t, J = 7.6 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H), 1.91-2.11 (m, 3H), 1.71-1.80 (m, 1H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 141.1, 136.6, 134.6, 129.8, 129.6, 129.4, 128.5, 127.8, 127.6, 127.4, 126.5, 71.3, 65.3, 33.9, 32.8, 22.9, 21.7, 21.6; IR (neat, cm^{-1}) v: 3566, 3250, 2957, 2926, 2926, 1616, 1495, 1456, 1350, 1159, 1086; HRMS (ESI): calcd. for $C_{24}H_{26}N_2S_2O_4Na$ (M^++Na): 493.1232, found: 493.1227.

5-(4-Fluorophenyl)-*N*,1-ditosylpyrrolidin-2-amine 141g



Pale yellow solid; m.p. = 65-68 ºC; isolated as 2 inseparable diastereomers with a ratio of 3.8:1; major isomer: ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.12-7.26 (m, 4H), 7.13 (d, J = 8.0 Hz, 2H), 6.93 (dd, J = 8.8 Hz, 8.4 Hz, 2H), 5.32 (d, J = 3.2 Hz, 1H), 4.92 (dd, J = 3.2 Hz, 2.8 Hz, 1H), 4.55 (t, J = 7.2 Hz, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.02-2.14 (m, 2H), 1.89-1.98 (m, 1H), 1.74-1.79 (m, 1H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 162.0 (C−F, J = 245 Hz), 144.14, 144.06, 136.8, 136.5, 134.5, 129.8, 129.6, 128.3, 128.2, 127.7, 127.4, 115.3 (C−F, J = 22 Hz), 72.2, 64.6, 34.0, 32.6, 21.5, 21.4; IR (neat, cm^{-1}) v: 3248, 3038, 2955, 2926, 2872, 1599, 1510, 1352, 1161, 1094; HRMS (ESI): calcd. for $C_{24}H_{25}N_2S_2O_4FNa$ (M^++Na): 511.1137, found: 511.1122.

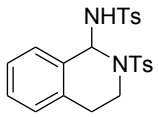
***N*,2-Ditosylisoindolin-1-amine 141h**



White solid; m.p. = 132-135 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.13-7.29 (m, 8H), 6.33 (d, J = 6.4 Hz, 1H), 5.40 (d, J = 6.8 Hz, 1H), 4.46 (s, 2H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 144.0, 143.6, 138.3, 136.0, 135.5, 135.0, 129.8, 129.5, 129.4, 128.1, 127.6, 127.4, 124.8, 122.3, 73.9, 52.5, 21.6, 21.5; IR (neat, cm^{-1}) v: 3447, 3264, 3030, 2926, 1636, 1346, 1215, 1163,

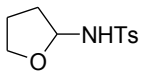
1096, 1030; HRMS (ESI): calcd. for $C_{22}H_{22}N_2S_2O_4Na$ (M^++Na): 465.0919, found: 465.0912.

1,2,3,4-Tetrahydro-*N*,2-ditosylisoquinolin-1-amine 141i



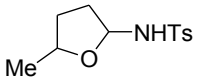
White solid; m.p. = 201-205 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.09-7.17 (m, 4H), 6.97 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.49 (s, 1H), 5.10 (bs, 1H), 3.60 (dd, J = 14.8 Hz, 6.4 Hz, 1H), 3.28 (m, 1H), 2.67 (m, 1H), 2.44-2.50 (m, 1H), 2.45 (s, 3H), 2.35 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.7, 143.5, 137.6, 137.1, 133.7, 132.2, 129.6, 129.4, 129.3, 128.7, 127.7, 127.5, 127.4, 127.0, 64.0, 37.9, 26.1, 21.6, 21.5; IR (neat, cm^{-1}) v: 3566, 3246, 3019, 2928, 2859, 1636, 1339, 1223, 1209, 1163; HRMS (ESI): calcd. for $C_{23}H_{24}N_2S_2O_4Na$ (M^++Na): 479.1075, found: 479.1072.

Tetrahydro-*N*-tosylfuran-2-amine 142a[59]



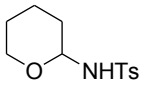
^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.69 (d, J = 8.7 Hz, 1H), 5.32-5.37 (m, 1H), 3.67-3.70 (m, 2H), 2.42 (s, 3H), 2.10-2.17 (m, 1H), 1.77-1.93 (m, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.3, 138.5, 129.5, 127.1, 85.0, 67.2, 32.6, 24.0, 21.6; ; MS (ESI) m/z 241 $[M+H]^+$.

Tetrahydro-5-methyl-*N*-tosylfuran-2-amine 142b



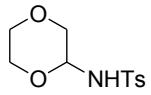
Pale yellow solid; m.p. = 86-89 ºC; isolated as two inseparable diastereomers with a ratio of 1.7:1; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 7.2 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.64 (d, J = 8.8 Hz, 0.6H), 5.50 (d, J = 8.8 Hz, 0.4H), 5.36-5.41 (m, 0.6H), 5.25-5.28 (m, 0.4H), 3.90-3.96 (m, 1H), 2.41 (s, 3H), 2.21-2.28 (m, 0.6H), 2.00-2.17 (m, 0.4H), 1.91-1.99 (m, 0.6H), 1.86-1.90 (m, 0.4H), 1.72-1.78 (m, 1H), 1.40-1.51 (m, 0.4H), 1.35-1.39 (m, 0.6H), 1.06 (d, J = 5.6 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.2, 143.1, 138.7, 138.6, 129.4, 129.3, 127.2, 127.1, 85.0, 84.9, 76.3, 74.2, 33.3, 33.0, 31.6, 31.3, 21.7, 21.5, 20.6; IR (neat, cm^{-1}) v: 3264, 3026, 2974, 2928, 2876, 1447, 1325, 1215, 1161, 1078, 1003; HRMS (ESI): calcd. for $C_{12}H_{17}NSO_3Na$ (M^++Na): 287.0827, found 287.0827.

Tetrahydro-*N*-tosyl-2*H*-pyran-2-amine 142c[146]



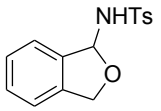
^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 5.00-5.07 (m, 1H), 4.73-4.80 (m, 1H), 3.70-3.74 (m, 1H), 3.34-3.43 (m, 1H), 2.41 (s, 3H), 1.79-1.87 (m, 2H), 1.44-1.60 (m, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 143.3, 138.8, 129.8, 127.2, 82.1, 66.3, 31.9, 24.7, 22.4, 21.5; MS (ESI): m/z $[M+H]^+$.

_N_-Tosyl-1,4-dioxan-2-amine 142d[59]



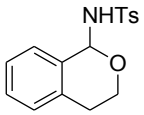
^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.00 (d, J = 9.6 Hz, 1H), 4.95-5.00 (m, 1H), 3.75-3.79 (m, 1H), 3.52-3.63 (m, 3H), 3.41-3.45 (m, 2H), 2.42 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.6, 138.4, 129.5, 127.1, 78.1, 68.5, 66.2, 62.4, 21.6; MS (ESI): m/z $[M+H]^+$.

1,3-Dihydro-_N_-tosylisobenzofuran-1-amine 142e[59]



^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 8.0 Hz, 2H), 7.18-7.34 (m, 5H), 7.19 (d, J = 7.2 Hz, 1H), 6.51 (d, J = 10.0 Hz, 1H), 5.33 (d, J = 10.0 Hz, 1H), 4.88-5.00 (m, 2H), 2.44 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.5, 139.3, 138.6, 136.6, 129.6, 129.5, 128.0, 127.2, 123.0, 121.2, 90.0, 72.0, 21.6; MS (ESI): m/z $[M+H]^+$.

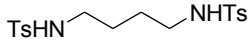
3,4-Dihydro-_N_-tosyl-1_H_-isochromen-1-amine 142f[84]



^{1}H NMR (DMSO, 400 MHz): δ 7.76 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.20-7.25 (m, 2H), 7.09-7.15 (m, 2H), 5.88 (m, 1H), 3.63-3.69 (m, 1H), 3.41-3.46 (m, 1H), 2.69-2.77 (m, 1H), 2.50-2.60 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (DMSO, 100 MHz): δ

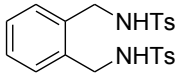
142.7, 140.5, 134.9, 133.6, 129.7, 129.1, 128.3, 127.2, 126.9, 126.6, 79.5, 58.1, 27.6, 21.5; MS (ESI): *m*/*z* $[M+H]^+$.

N^1,N^4-Ditosylbutane-1,4-diamine 144c[147]



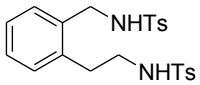
^{1}H NMR: ($CDCl_3$, 500 MHz) δ 7.75 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.0 Hz, 4H), 4.53 (t, J = 6.5 Hz, 2H), 2.93 (m, 4H), 2.46 (s, 6H), 1.53 (m, 4H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 143.6, 138.0, 129.8, 127.1, 42.6, 26.5, 21.5; MS (ESI): *m*/*z* $[M+H]^+$.

***N*-Tosyl(2-((tosylamino)methyl)phenyl)methanamine 144h**[148]



^{1}H NMR: ($CDCl_3$, 500 MHz) δ 7.66 (d, J = 8.0 Hz, 4H), 7.23 (d, J = 8.0 Hz, 4H), 5.35 (t, J = 6.0 Hz, 2H), 4.04 (d, J = 6.0 Hz, 4H), 2.40 (s, 6H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 143.5, 136.5, 134.7, 130.1, 129.8, 128.4, 127.2, 44.7, 21.6; MS (ESI): *m*/*z* $[M+H]^+$.

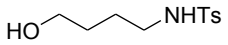
***N*-Tosyl-2-(2-((tosylamino)methyl)phenyl)ethanamine 144i**



Colourless oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.21-7.26 (m, 4H), 7.02-7.15 (m, 4H), 5.35 (t, J = 6.0 Hz, 1H), 5.19 (t, J = 6.0 Hz, 1H), 4.00 (d, J = 6.0 Hz, 2H), 3.07 (q, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.6, 143.4, 136.9, 136.8, 136.5,

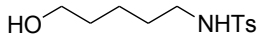
134.3, 130.1, 130.0, 129.8, 129.7, 128.5, 127.2, 127.1, 127.0, 45.0, 43.7, 32.3, 21.6, 21.5; IR (neat, cm^{-1}) *v*: 3445, 3285, 3028, 2928, 2878, 1645, 1599, 1408, 1327, 1159, 1094; HRMS (ESI): calcd. for $C_{23}H_{26}N_2S_2O_4Na$ (M^++Na): 481.1232, found: 481.1238.

4-(Tosylamino)butan-1-ol 145a[149]



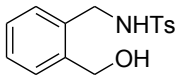
^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.55 (t, *J* = 6.0 Hz, 1H), 3.56 (t, *J* = 6.0 Hz, 2H), 2.90 (q, *J* = 6.0 Hz, 2H), 2.39 (s, 6H), 1.52 (m, 4H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 143.3, 136.9, 129.7, 127.0, 62.0, 43.0, 29.5, 26.1, 21.5; MS (ESI): *m*/*z* $[M+H]^+$.

5-(Tosylamino)pentan-1-ol 145c[150]



^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.63 (t, *J* = 6.0 Hz, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 2.91 (m, 2H), 2.43 (s, 3H), 1.40-1.58 (m, 4H), 1.32-1.39 (m, 2H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 143.3, 136.9, 129.7, 127.0, 62.3, 43.0, 31.9, 29.1, 22.7, 21.5; MS (ESI): *m*/*z* $[M+H]^+$.

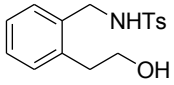
(2-((Tosylamino)methyl)phenyl)methanol 145e



White solid; m.p. = 114-116 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.16-7.29 (m, 6H), 5.63 (t, *J* = 6.0 Hz, 1H), 4.60 (s, 2H), 4.14 (d, *J* = 6.0 Hz, 2H), 2.42 (s,

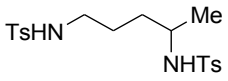
3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 142.4, 139.6, 136.7, 135.2, 130.4, 129.7, 129.6, 128.6, 128.4, 127.0, 63.5, 45.6, 21.6; IR (neat, cm^{-1}) *v*: 3447, 3293, 3030, 2963, 2930, 2874, 1636, 1325, 1159, 1094; HRMS (ESI): calcd. for $C_{15}H_{17}NSO_3Na$ (M^++Na): 314.0827, found: 314.0841

2-(2-((Tosylamino)methyl)phenyl)ethanol 145f[151]



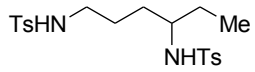
^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.07-7.28 (m, 6H), 6.40 (t, *J* = 5.4 Hz, 1H), 4.02 (d, *J* = 5.4 Hz, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 143.3, 138.3, 136.7, 134.7, 130.3, 129.9, 129.6, 128.6, 127.3, 126.7, 63.5, 45.2, 34.3, 21.5; MS (ESI): *m/z* $[M+H]^+$.

***N*^{1},*N*^{4}-ditosylpentane-1,4-diamine 146a**



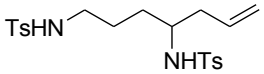
White solid; m.p. = 149-152 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.73 (dd, *J* = 8.0 Hz, 1.6 Hz, 4H), 7.29 (dd, *J* = 8.0 Hz, 1.6 Hz, 4H), 4.73 (t, *J* = 6.4 Hz, 1H), 4.55 (d, *J* = 8.4 Hz, 1H), 3.27 (m, 1H), 2.87 (q, *J* = 6.4 Hz, 2H), 2.43 (s, 6H), 1.37-1.51 (m, 4H), 0,90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.4, 138.0, 136.9, 129.7, 127.1, 127.0, 49.5, 42.8, 34.3, 25.4, 21.7, 21.6; IR (neat, cm^{-1}) *v*: 3476, 3402, 2974, 2932, 2872, 1628, 1321, 1161 1092; HRMS (ESI): calcd. for $C_{19}H_{26}N_2S_2O_4Na$ (M^++Na): 433.1232, found: 433.1233.

N^1,N^4-ditosylhexane-1,4-diamine 146b



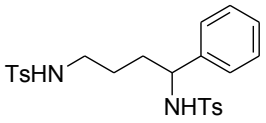
White solid; m.p. = 111-114 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 8.4 Hz, 4H), 7.27 (m, 4H), 5.04 (t, J = 6.0 Hz, 1H), 4.95 (d, J = 8.4 Hz, 1H), 3.07 (m, 1H), 2.81 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 1.21-1.43 (m, 6H), 0.66 (t, J = 7.4 Hz, 3H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.3, 143.2, 138.2, 136.9, 129.7, 129.6, 127.1, 126.9, 54.9, 42.9, 31.4, 27.8, 25.2, 21.5, 9.6; IR (neat, cm^{-1}) v: 3541, 3264, 3021, 2968, 2934, 2876, 1628, 1599, 1454, 1418, 1323, 1215, 1159, 1092; HRMS (ESI): calcd. for $C_{20}H_{28}N_2S_2O_4Na$ (M^++Na): 447.1388, found: 447.1405.

N^1,N^4-ditosylhept-6-ene-1,4-diamine 146c



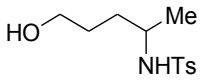
White solid; m.p. = 113-116 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.73 (dd, J = 8.0 Hz, 4.8 Hz, 4H), 7.29 (dd, J = 8.0 Hz, 6.0 Hz, 4H), 5.43(m, 1H), 5.08 (t, J = 6.0 Hz, 1H), 4.94 (dd, J = 8.0 Hz, 3.2 Hz, 1H), 4.87 (d, J = 17.2 Hz, 1H), 3.20 (m, 1H), 2.83 (m, 2H), 2.42 (s, 6H), 1.97 (m, 2H), 1.33-1.50 (m, 4H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.4, 143.3, 138.0, 136.9, 133.1, 129.7, 129.6, 127.1, 127.0, 118.9, 52.9, 42.8, 39.2, 31.4, 25.2, 21.5; IR (neat, cm^{-1}) v: 3456, 3296, 3028, 2928, 2870, 1639, 1599, 1418, 1325, 1159, 1094; HRMS (ESI): calcd. for $C_{21}H_{28}N_2S_2O_4Na$ (M^++Na): 459.1388, found: 459.1391.

1-Phenyl-N^1,N^4-ditosylbutane-1,4-diamine 146d



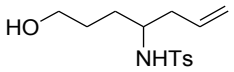
White solid; m.p. = 125-128 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.06-7.10 (m, 5H), 6.90-6.93(m, 2H), 5.38 (d, J = 8.0 Hz, 1H), 4.81 (t, J = 6.0 Hz, 1H), 4.22 (q, J = 7.6 Hz, 1H), 2.89 (q, J = 6.0 Hz, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 1.73-1.82 (m, 1H), 1.62-1.72 (m, 1H), 1.43-1.61 (m, 1H), 1.37-1.42 (m, 1H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.4, 143.0, 140.9, 137.5, 136.8, 129.7, 129.3, 128.4, 127.4, 127.1, 127.0, 126.3, 57.9, 42.4, 34.4, 25.9, 21.5, 21.4; IR (neat, cm^{-1}) v: 3507, 3281, 3028, 2953, 2928, 2872, 1645, 1599, 1495, 1454, 1418, 1323, 1159, 1094; HRMS (ESI): calcd. for $C_{24}H_{28}N_2S_2O_4Na$ (M^++Na): 495.1388, found: 459.1394.

4-(Tosylamino)pentan-1-ol 147a



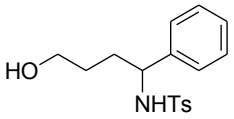
White solid; m.p. = 80-83 ºC; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.77 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H),), 5.15 (d, J = 8.0 Hz, 1H), 3.57 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.42 (s, 3H), 2.08 (bs, 1H), 1.46-1.54 (m, 4H), 1.00 (d, J = 6.4 Hz, 1H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.2, 138.6, 129.8, 127.8, 62.0, 49.9, 33.8, 28.3, 21.6, 21.5; IR (neat, cm^{-1}) v: 3262, 3017, 2934, 2878, 1433, 1321, 1043; HRMS (ESI): calcd. for $C_{12}H_{19}NSO_3Na$ (M^++Na): 280.0983, found: 280.0970.

4-(Tosylamino)hept-6-en-1-ol 147b



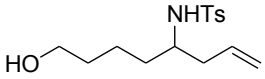
Colourless oil; ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 7.77 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H),), 5.15 (d, J = 8.0 Hz, 1H), 3.57 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.42 (s, 3H), 2.08 (bs, 1H), 1.46-1.54 (m, 4H), 1.00 (d, J = 6.4 Hz, 1H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 143.2, 138.6, 129.8, 127.8, 62.0, 49.9, 33.8, 28.3, 21.6, 21.5; IR (neat, cm^{-1}) v: 3539, 3350, 3030, 3011, 2947, 2882, 1643, 1418, 1323, 1157, 1094, 1022; HRMS (ESI): calcd. for $C_{12}H_{19}NSO_3Na$ (M^++Na): 280.0983, found: 280.0970.

4-Phenyl-4-(tosylamino)butan-1-ol 147c[152]



^{1}H NMR: ($CDCl_3$, 500 MHz) δ 7.51 (d, J = 8.0 Hz, 2H), 7.02-7.11 (m, 7H),), 6.06 (d, J = 7.5 Hz, 1H), 4.28 (q, J = 7.5 Hz, 1H), 3.52-3.60 (m, 2H), 2.41 (bs, 1H), 2.31 (s, 3H), 1.84-1.89 (m, 1H), 1.72-1.77 (m, 1H), 1.53-1.59 (m, 1H), 1.44-1.48 (m, 1H); ^{13}C NMR: ($CDCl_3$, 125 MHz) δ 142.9, 141.0, 137.7, 129.2, 128.3, 127.2, 127.0, 126.5, 62.1, 58.2, 34.2, 28.8, 21.4; MS (ESI): m/z $[M+H]^+$.

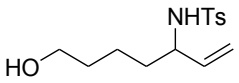
5-(Tosylamino)oct-7-en-1-ol 147d



Colourless oil; ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.76 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H),), 5.55 (m, 1H), 4.92-5.02 (m, 2H), 4.80 (d, J = 8.1 Hz, 1H), 3.56 (t, J = 6.3 Hz,

2H), 3.27 (m, 1H), 2.43 (s, 3H), 2.09 (t, J = 6.3 Hz, 2H), 1.86 (bs, 1H), 1.27-1.47 (m, 6H); ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 143.3, 138.2, 133.3, 129.6, 127.1, 118.8, 62.5, 53.3, 39.1, 34.2, 32.2, 21.5; IR (neat, cm^{-1}) v: 3447, 3285, 2941, 2864, 1628, 1437, 1412, 1323, 1157, 109; HRMS (ESI): calcd. for $C_{15}H_{23}NSO_3Na$ (M^++Na): 320.1296, found: 320.1287.

5-(Tosylamino)hept-6-en-1-ol 147e



Colourless oil; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H),), 5.52 (m, 1H), 5.11 (d, J = 8.0 Hz, 1H), 4.91-4.98 (m, 2H), 3.73-3.76 (m, 1H), 3.57 (t, J = 6.0 Hz, 2H), 2.41 (s, 3H), 1.93 (bs, 1H), 1.41-1.53 (m, 4H), 1.26-1.40 (m, 2H); ^{13}C NMR: ($CDCl_3$, 100 MHz) δ 143.2, 138.4, 137.8, 129.5, 127.1, 115.6, 62.4, 56.2, 35.2, 32.1, 21.5, 21.4; IR (neat, cm^{-1}) v: 3381, 3273, 3028, 3010, 2941, 2866, 1599, 1416, 1323, 1157, 1094, 1030; HRMS (ESI): calcd. for $C_{14}H_{21}NSO_3Na$ (M^++Na): 306.1140, found: 306.1146.

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