Transition metal-free iminoiodane-mediated amination of activated C-H bonds

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

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IMINOIODANE-MEDIATED AMINATION OF
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CIPUTRA TEJO

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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**TRANSITION METAL-FREE
IMINOIODANE-MEDIATED AMINATION OF
ACTIVATED C–H BONDS**

CIPUTRA TEJO

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School of Physical and Mathematical Sciences

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ABSTRACT

The work presented in this thesis was undertaken in Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences in Nanyang Technological University from August 2011 to July 2015 under the supervision of Assoc. Prof. Shunsuke Chiba and Prof. Philip Wai Hong Chan.

The work in this thesis is aimed towards establishing transition metal-free approaches for nitrogen atom transfer to activated C–H bonds with iminoiodanes. This thesis is divided into three parts:

- Part I consists of Chapter I, which gives an introduction to the early development of the use of iminoiodanes as nitrene precursors in transition metal catalysis and the recent use of these hypervalent iodine compounds for transition metal free transformations.
- Part II is targeted at exploring novel transformations by exploiting the ylide nature of iminoiodanes in the absence of transition metal catalyst to access various nitrogen containing compounds.
 - Chapter II disclosed the approach on synthesizing unnatural amino acids from 1,3-dicarbonyl compounds with iminoiodanes as nitrogen source in the presence of a Brønsted acid as the catalyst.
 - Chapter III discusses the development of the base-mediated version for the aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds.
 - Chapter IV describes the finding of the mild amination of cyclic ethers to their corresponding aminal products, which were functionalized with 1,3-dicarbonyl compounds in the presence of base to furnish coupling product of the cyclic ethers and 1,3-dicarbonyl compounds.

- Chapter V is an extension study of Chapter IV, employing a similar concept for the amination of cyclic ethers, and ring opening of the resulting aminal was studied. This chapter explores the synthesis of amino alcohols from a readily available starting material.
- Part III contains experimental data (Chapter VI) and references (Chapter VII) pertaining to this thesis.

PUBLICATIONS

1. “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.
2. “Brønsted Acid-Catalyzed Amination of 1,3-Dicarbonyl Compounds by Iminoiodanes” **Tejo, C.**; Yeo, H. Q.; Chan, P. W. H. *Synlett* **2014**, 25, 201.
3. “Iminoiodane- and Brønsted Base-Mediated Cross Dehydrogenative Coupling of Cyclic Ethers with 1,3-Dicarbonyl Compounds” **Tejo, C.**; Sim, X. R.; Lee, B. R.; Ayers, B. J.; Leung, C.-H.; Ma, D.-L.; Chan, P. W. C. *Molecules* **2015**, *20*, 13336.

ABBREVIATIONS

Ac	acetyl
aq	aqueous
Ar	aryl
B	base
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DIAD	diisopropylazodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	dimethylformamide
DMSO	dimethylsulfoxide
<i>n</i> -Bu	butyl
<i>i</i> -Bu	isobutyl
<i>t</i> -Bu	<i>tert</i> -butyl
dr	diastereomer ratio
ee	enantiomeric excess
Et	ethyl
equiv	equivalent
h	hour
Me	methyl
Mes	mesityl
min	minute

MS	molecular sieve
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MTBE	methyl <i>tert</i> -butylether
mp	melting point
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
<i>c</i> -Pent	cyclopentyl
Ph	phenyl
<i>i</i> -Pr	isopropyl
rt	room temperature
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TES	triethylsilyl
Tf	trifluoromethanesulfonyl or triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	<i>p</i> -toluenesulfonyl or tosyl
Xylyl	dimethylphenyl

Chapter I. Transition Metal-Free Iminoiodane-Mediated Amination of Activated C–H Bonds

1.1 Introduction

Carbon-nitrogen bond formation is a fundamental pursuit in organic synthesis owing to its vast importance to the pharmaceutical, agrochemistry, and material industries.¹ Nitrogen containing compounds serve as versatile building blocks in various organic transformations and applications.² For this reason, numerous synthetic methods have been developed and continue to be established for the formation of C–N bonds. Conventionally, the installation of the amino group has relied on nucleophilic substitution or addition of an amine nucleophile to a carbon electrophile.³ Transition metal catalysis has emerged as a powerful tool in this transformation by mediating the addition of nitrogen nucleophiles to π bonds of alkenes, alkynes and allenes as well as their coupling with aryl and vinyl halides.⁴ However, the activation of an electrophile through pre-installation of a reactive group and its associated harsh reaction conditions remain the main drawbacks of these transformations. While functional group protection chemistry has been shown to overcome these shortcomings, the increase in the number of synthetic steps results in poor overall atom economy, especially in large bioactive compound synthesis or material of current interest. Therefore, developing a synthetic method to introduce amino groups at strategic positions under mild conditions would have a great synthetic value to overcome such limitations posed by traditional methods.

Over the past few decades, transition metal-catalyzed nitrene/imido transfer reactions to C–H bonds and C=C bonds has gained a growing amount of attention as a direct and atom-economical synthetic strategy for C–N bond formation. Unlike the

analogous transition metal catalyzed carbene and oxo transfer reactions, initial studies on this approach were fragmented due to the scarcity of practical nitrogen sources to facilitate the transformation. This all changed in 1975, when Yamada and co-workers reported the straightforward and practical synthesis of (*p*-toluenesulfonyl) iminophenyl iodine (PhI=NTs) from iodosobenzenediacetate (PhI(OAc)₂) and *p*-toluenesulfonamide (TsNH₂).⁵ In this work, the putative nitrenoid species, which is electrophilic in nature, was proposed. The discovery of this hypervalent iodine(III) reagent as a nitrogen source led to the subsequent progress in the chemistry of transition metal-catalyzed C–N bond formation.⁶

Scheme 1.1 Synthesis of PhI=NTs

Since its discovery, the synthetic value of this approach has been demonstrated in the construction of a number of biologically active compounds (Figure 1.1).⁷ Typically, the transformations have been shown to require the use of a transition metal complex to facilitate the C–N bond formation process. Whilst the catalytic systems furnished high product yields, the use of expensive and, in some cases, less abundant transition metal catalysts has impeded the possibility for scale-up processes. In this context, recent efforts have focused on transition metal-free C–H bond functionalization for C–N bond formation. At the present time, the challenge in this emerging field is to develop synthetic methods as efficient as their transition metal-catalyzed counterparts. The focal point of this Introduction will be on the birth of transition metal-catalyzed nitrogen atom transfer reactions and the emergence of synthetic variants of these transformations in the absence of a transition metal.

Figure 1.1 Natural products synthesized via transition metal-catalyzed nitrogen atom transfer reaction step

1.2 Advancements in Transition Metal-Catalyzed Nitrogen Atom Transfer Reactions Mediated by Iminoiodanes

The seminal work demonstrating the utility of $\text{PhI}=\text{NTs}$ as a nitrogen source for transition metal-catalyzed nitrene/imido insertion to C–H bond was reported by Breslow and Gellman in 1982 (Scheme 1.2). In this study, the amination of cyclohexane with $\text{PhI}=\text{NTs}$ in the presence $[\text{Fe}(\text{TPP})\text{Cl}]$ **13** (H_2TPP = 5,10,15,20-tetrakis-(phenyl)-21*H*,23*H*-porphyrin) or $[\text{Mn}(\text{TPP})\text{Cl}]$ **14** in CH_2Cl_2 provided the *N*-tosylaminocyclohexane **15** in 3–7% yield.⁸

Scheme 1.2 Fe(III) and Mn(III)-catalyzed amination of cyclohexane with $\text{PhI}=\text{NTs}$

Following this work, the intramolecular nitrene/imido insertion of 2,5-diisopropylbenzenesulfonyliminoiodinane **16** was subsequently realized in the presence of a variety of transition metal salts and complexes to afford low to excellent product yields of 16–86% (Scheme 1.3).⁹ Notably, $[\text{Fe}(\text{TPP})\text{Cl}]$ **13** and $[\text{Mn}(\text{TPP})\text{Cl}]$ **14** showed a greater efficiency than the previous study. Furthermore, dirhodium(II,II) tetraacetate, one of the most efficient catalyst for carbene transfer reactions, was shown to exhibit the best efficiency among the catalysts examined.¹⁰

Scheme 1.3 Intramolecular C–H insertion of iminoiodanes with various transition metal catalyst (cyclam = 1,4,8,11-tetraazacyclotetradecane)

Subsequently, Mansuy and co-workers developed transition metal-catalyzed aziridine formation via nitrene/imido addition to C=C bonds (Scheme 1.4).¹¹ In the presence of iron(III) and manganese(III) porphyrin complexes **13** and **14**, the aziridination of several aryl substituted alkenes **19** with PhI=NTs was successfully demonstrated to give the aziridines **20** in 16–80% yields. The use of iron(III) porphyrin complex **22** gave better a outcome, furnishing the corresponding adducts in 36–90% yield.¹²

Scheme 1.4 Intermolecular aziridination of alkenes via nitrene transfer reaction

(H₂TDCPP = 5,10,15,20-tetrakis-(2,6-dichlorophenyl)-21*H*,23*H*-porphyrin)

The extension of this aziridination approach to aliphatic and alicyclic alkenes was then demonstrated, although the chemoselectivity and regioselectivity was found to be poor (Table 1.1).¹² Interestingly, iron(III) porphyrin complexes were shown to favor formation of aziridine product, while the use of manganese(III) porphyrin complexes shifted the chemoselective outcome toward allylic amination for the majority of examples.¹³

These initial studies on transition metal catalyzed nitrene/imido transfer reactions in general suffered from several drawbacks such as substrate dependency, the need for an excess amount of starting material, and moderate chemo- and regioselectivity. Added to these were the low product yields obtained by the synthetic strategy that limited its potential in organic synthesis.

Table 1.1 Reaction of *cis*-hex-2-ene **23** and *trans*-hex-2-ene **23** with PhI=NTs

		Yield (%)	
Entry	Catalyst	Aziridines 24	Allylic Amides 25+26
1	[Fe(TPP)ClO ₄] 21	12–27	20–30
2	[Fe(TDCPP)ClO ₄] 22	33–35	13–23
3	[Mn(TPP)ClO ₄] 14	2	37–41
4	[Mn(TDCPP)ClO ₄] 14	4–11	26–35

1.3 Transition Metal-Catalyzed Aziridination of Alkenes with Iminoiodanes

1.3.1 Intermolecular Aziridination of Alkenes with PhI=NTs

In the early 1990s, Evans and co-workers demonstrated aziridination of alkenes via nitrene/imido transfer using inexpensive copper(I) and copper(II) salts (Scheme 1.5).^{14,15} The reaction was shown to tolerate a wide range of substituted alkenes to give the aziridine products in moderate to excellent yields of 30–95% with high chemoselectivity over C–H bonds insertion adduct. These studies also showed the higher efficiency and broader substrate scope of copper catalysis to that of manganese, iron, cobalt, and rhodium systems.

Scheme 1.5 Copper-catalyzed aziridination of alkenes with PhI=NTs

Following Evans' studies, Perez and co-workers reported the synthesis of $[\text{Tp}^*\text{Cu}(\text{C}_2\text{H}_4)]$ **27a** to mediate the aziridination of alkenes in the presence of $\text{PhI}=\text{NTs}$ to afford the corresponding aziridines in 40–90% yields (Table 1.2, entry 1).¹⁶ Subsequently, Hutchings and co-workers described the use of copper-exchanged zeolite $[\text{CuHY}]$ **30** (Y = zeolite) as catalyst for the same reaction (Table 1.2, entry 2).¹⁷ The reaction was thought to proceed within the mesoporous material of the zeolite to furnish the aziridine products in moderate to good yields of 44–90%.

The above mentioned examples are generally limited by substrate scope as well as high catalyst loadings. It was later proposed that nitrogen-based ligands could increase both catalyst efficiency and substrate tolerance. The group of Halfen elucidated the utility of $[(i\text{-Pr}_3\text{tacn})\text{Cu}(\text{OTf})_2]$ **31** ($i\text{-Pr}_3\text{tacn}$ = 1,4,7-triisopropyl-1,4,7-triazanone) as a catalyst for the aziridination of alkenes with $\text{PhI}=\text{NTs}$ (Table 1.2, entry 3).¹⁸ In the presence of 0.5 mol % of **31** as catalyst, the aziridination of styrene was found to give the corresponding product in 96% yield. However, only a handful of substrates were demonstrated in this report, which remained a limitation to the synthetic utility of this method.

In their work toward the development of a cost effective catalyst for the aziridination of olefins, several groups pursued the fine-tuning of such catalysts by ligand design. In the early 2000s, two groups independently demonstrated the ability of copper(I) β -diketiminate **32**¹⁹ and copper(I) pyridinophane **33**²⁰ to mediate the aziridination reaction of alkenes (Table 1.2, entries 4 and 5). The former catalyst was shown to effect the aziridination process with good substrate to $\text{PhI}=\text{NTs}$ ratios to yield the products in 14–98% yield. The latter catalyst was found to be applicable to a broader substrate scope to afford various aziridines in 27–98% yield.

Table 1.2 Transition metal-catalyzed aziridination of alkenes with PhI=NTs

Entry	Catalyst	Yield (%)	Ref.
1	[Tp [*] Cu(C ₂ H ₄)] 27a	40–90	16
2	[CuHY] 30	44–90	17
3	[(<i>i</i> -Pr ₃ tacn)Cu(OTf) ₂] 31	25–96	18
4	copper(I) β-diketiminato 32	14–98	19
5	copper(I) pyridinophane 33	27–96	20
6	[Ru(TPP)(NTs) ₂] 34 or [Ru(OEP)(NTs) ₂] 35	66–85	21,22
7	AgNO ₃ + <i>t</i> -Bu ₃ terpy 36a	66–91	23
8	[(η ⁵ -C ₅ H ₅)Fe(CO) ₂ (THF)(BF ₄)] 38	7–85	24
9	Fe(ClO ₄) ₂ + Cl ₃ terpy 36b	68–97	25
10	Fe(OTf) ₂	24–82	26
11	[Tp ^{*,Br} Ag] 28	>99	27,28
12	[Tp [*] Fe(MeCN) ₃ (BF ₄) ₂] 29	46–94	29
13	Cu(TMGG ₃ trphen)PF ₆ 40	42–99	30

To gain a better mechanistic insight into the aziridination process, Che and co-workers reported the synthesis of bis(tosyl)imidoruthenium(VI) porphyrin complexes [Ru(TPP)(NTs)₂] **34** and [Ru(OEP)(NTs)₂] **35** (H₂OEP = 2,3,7,8,12,13,17,18-octaethyl-21*H*,23*H*-porphyrin) from PhI=NTs and the corresponding ruthenium(II)

Figure 1.2 Catalysts and ligands used for aziridination of alkenes

porphyrins which underwent the stoichiometric aziridinations with a variety of alkenes (Table 1.2, entry 6).²¹ The group subsequently revealed detailed mechanistic studies indicating that these ruthenium (VI) complexes were likely to be the active catalytic species involved in the nitrogen atom transfer step.²²

In 2003, the group of He and Hossain independently developed a method for the aziridination of alkenes mediated by silver(I) and iron(II) complexes, respectively (Table 1.2, entries 7 and 8). He demonstrated the combination of AgNO_3 and *t*-Bu₃terpy **36a** provided the *in situ* formation of the disilver(I),(I) complex $[\text{Ag}_2(\text{t-Bu}_3\text{terpy})_2\text{NO}_3]$ **37**, which was thought to be the active catalyst.²³ Hossain and co-workers found the iron(II) complex $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})(\text{BF}_4)]$ **38** to catalyze the aziridination of alkenes with PhI=NTs .²⁴ However, a drawback of this latter

approach was the substrate scope that was found to be limited to styrene and its derivatives that provided product yields of 7–85%.

Following this seminal work, Che and co-workers demonstrated the aziridination of alkenes in the presence of iron(II) perchlorate and Cl₃terpy **36b** as the catalyst (Table 1.2, entry 9).²⁵ The study showed that [Fe(Cl₃terpy)₂] **39** was formed *in situ* and this was the metal complex that catalyzed the reaction and was applicable to a broad substrate scope and good to excellent product yields of 68–97%. At about the same time, Bolm and co-workers showed Fe(OTf)₂ to effectively catalyze the aziridination of olefins (Table 1.2, entry 10).²⁶ The reaction was found to proceed well in the absence of ligands to furnish the corresponding product in 24–82% yield.

More recent work by Perez and co-workers demonstrated the selective aziridination of dienes in the presence of the silver-homoscorpionate complex **28** as the catalyst (Table 1.2, entry 11).²⁷ In this study, the aid of a neighboring directing group was delineated to be crucial to achieve high product selectivities. A subsequent study on the mechanism of this transformation revealed the involvement of an initial triplet metal-nitrenoid species and that the reaction proceeds via a radical pathway.²⁸ The catalytic system was also shown to be efficient at a catalyst loading of 0.5 mol % to achieve high conversion to the desired aziridines. The use of iron(III)-homoscorpionate complex **29** in the aziridination of alkenes was demonstrated by Jensen (Table 1.2, entry 12).²⁹ Unfortunately, only a handful of substrates were tested and the aziridine products were isolated in 46–94% yield.

In 2014, Stavropoulos described the synthesis of Cu(TMg₃trphen)PF₆ **40** and demonstrated its ability to mediate the nitrene transfer reaction (Table 1.2, entry 13).³⁰ In this work, the aziridination reaction was shown to proceed well for wide range of alkenes to afford the corresponding aziridines in 42–99% yield.

1.3.2 Intermolecular Aziridination of Alkenes with Other Iminoiodanes

As noted in Section 1.2, dirhodium(II,II) acetate was demonstrated to be a potentially versatile catalyst for nitrene/imido C–H bond insertion reactions. However, Evan and co-workers found the dirhodium(II,II) acetate-catalyzed aziridination of styrene with PhI=NTs afforded *N*-tosylphenylaziridine **20a** in moderate yield of 48%.¹⁵ Similarly Müller and co-workers showed the same reaction yielded 58% of the corresponding product (Scheme 1.6).³¹

Scheme 1.6 Rhodium-catalyzed aziridination of styrene with PhI=NTs

Notably, Müller had shown that by changing the protecting group of iminoiodane from *p*-toluenesulfonyl (Ts) to *p*-nitrobenzenesulfonyl (Ns), the rhodium-catalyzed aziridination of styrene and its derivatives proceeded to give the product in 18–85% yield (Scheme 1.7).^{31,32} Unfortunately, aliphatic alkenes were found to be less reactive in this catalytic system and gave the aziridine product in 27–54% yield.

Scheme 1.7 Rhodium-catalyzed aziridination of alkenes with PhI=NNs

Further exploration of this chemistry by Dodd and Dauban in 1999 illustrated the use of (trimethylsilylethanesulfonyl)iminophenyl iodane (PhI=NSes) as a nitrene precursor for the aziridination of a range of alkenes with CuOTf or $\text{Cu}(\text{OTf})_2$ as the

catalyst (Scheme 1.8).³³ Under these conditions, the corresponding aziridines were afforded in 33–68% yield. The use of the Ses group was found to be advantageous as it was easy to remove by using TASF (tris(dimethylamino)sulfonium difluorotrimethylsilicate) at room temperature. Additionally, the ring opening of aziridines was shown to proceed smoothly with various nucleophiles to furnish the corresponding functionalized amines **42** in good to excellent yields of 67–90% yield.

Scheme 1.8 Copper-catalyzed aziridination of alkenes with $\text{PhI}=\text{NSes}$

In 2008, Bolm and co-workers reported the aziridination of alkenes with the use of 5-methyl-2-pyridinesulfonyliminoiodane ($\text{PhI}=\text{NSO}_2\text{Py}$) in the presence of $\text{Fe}(\text{OTf})_2$ as the catalyst (Scheme 1.9).³⁴ The reaction worked well with various alkenes in the presence of quinaldic acid and ethylmethylimidazolium bis((trifluoromethyl)sulfonyl) amide (emim BTA) to yield the product in 36–95% yield.

Scheme 1.9 Iron-catalyzed aziridination of alkenes with $\text{PhI}=\text{NSO}_2\text{Py}$

Recently, Zhdankin reported the synthesis of *o*-propyloxyphenyliminoiodane **43** and its use as a nitrene precursor for the aziridination of alkenes (Scheme 1.10).³⁵ The structure of PhI=NTs was proposed to be polymeric in nature and exhibited an intermolecular I--N interaction which lessened its solubility in most organic solvents. Zhdankin proposed the *ortho*-alkoxy group would compete against the intermolecular interaction to promote its solubility and reactivity. The aziridination reaction of alkenes in the presence of the *o*-alkoxyphenyliminoiodane **43** and Cu(OTf)₂ afforded the corresponding product in 22–92% yield.

Scheme 1.10 Copper-catalyzed aziridination of alkenes with **40** as nitrene precursor

1.3.3 Asymmetric Intermolecular Aziridination of Alkenes with Iminoiodanes

Numerous research groups have been involved in the development of asymmetric aziridination of alkenes. Independently, the groups of Burrows,³⁶ Katsuki,³⁷ Jacobsen,³⁸ Evans,³⁹ Che,^{40,41} Müller,⁴² Hutchings,⁴³ Chan,⁴⁴ Scotts,⁴⁵ Xu,^{46,47} and Bolm²⁶ have reported the aziridination of alkenes in the presence of various chiral catalysts (Figure 1.3) and their results are summarized in Table 1.3. Notably, the combination of copper(I) and C₂-symmetry bisoxazoline type ligands were found to give better selectivities among those surveyed catalysts and ligands. This also applied to heterogeneous catalysis as described by Hutchings and co-workers.

Table 1.3 Enantioselective aziridination of alkenes with $\text{PhI=NSO}_2\text{Ar}$

Entry	Catalyst	Yield (%)	ee (%)	Ref.
1	44	60–86	33–53	36
2	45	9–13	36–61	37
3	CuOTf + 49	50–79	58–98	38
4	CuOTf + 50a	63–76	94–96	39
5	46	44–73	44–68	40
6	48	74–80	55–73	42
7	[CuHY] 28 + 49a	74–87	29–44	43
8	[Cu(MeCN) ₄ ClO ₄] + 51	25–92	11–90	44
9	47	72–91	<29	41
10	[Cu(MeCN) ₄ BF ₄] + 52	28–89	26–98	45
11	CuOTf + 53/54	21–92	19–99	46
12	Fe(OTf) ₂ + 55	40–75	<40	26

Figure 1.3 Chiral catalysts used in the asymmetric aziridination of alkenes

1.3.4 Intermolecular Aziridination of Enols with Iminoiodanes

In their work on the copper-catalyzed aziridination of alkenes, Evans and co-workers showed the use of silyl enol ethers as substrates for the aziridination/ring-opening reaction to afford the corresponding α -amino ketones in moderate to good yields of 53–75% (Scheme 1.11).¹⁵ The use of ketene acetals as substrates was shown to lead to the α -amino esters in 27–45% yield.

Scheme 1.11 Transition metal-catalyzed aziridination/ring-opening of silyl enol ethers and silyl ketene acetals.

Bolm and co-workers reported the iron-catalyzed version of this transformation. Using $\text{Fe}(\text{OTf})_2$ as catalyst led to the α -amino ketones being furnished in comparable yields of 46–72%.²⁶ In 2002, Che and co-workers described the first asymmetric aziridination of silyl enol ethers in the presence of $[\text{Ru}(\text{salen})(\text{PPh}_3)_2]$ **58**.⁴⁸ The reaction preceded well for the aziridination of various cyclic silyl enol ethers with $\text{PhI}=\text{NTs}$ to give the corresponding products in good yields of 68–85% and ee values up to 97%.

Further development on the enantioselective aziridination of silyl enol ethers was demonstrated by Hashimoto in 2007.^{7j} In this work, the synthetic utility of $[\text{Rh}_2((S)\text{-TFPPTL})_4]$ **59** as the catalyst for the aziridination of silyl enol ethers was demonstrated with product yields of 80–95% and with ee values of 47–95%. This method was also shown to be useful for the formal synthesis of (-)-metazocine **3** (Scheme 1.12). Subsequently, the same catalytic system was used for the aziridination of silyl ketene acetals.⁴⁹ While product yields of 48–98% and with ee values of up to 99% were obtained, the transformation was shown to have limited substrate scope.

Scheme 1.12 Application of rhodium-catalyzed aziridination of silyl enol ethers on the synthesis of (-)-metazocine **3**

In 2012, Chan and co-workers showed β -dicarbonyl compounds could undergo aziridination as the enolate with $\text{PhI}=\text{NTs}$.⁵⁰ In the presence of copper(II) triflate as Lewis acid as well as the nitrene transfer catalyst and 1,10-phenanthroline as the

ligand, the aziridination/ring opening reaction afforded the corresponding α -amino- β -dicarbonyl compounds in yields of 53–99% (Scheme 1.13).

Scheme 1.13 Copper-catalyzed aziridination of 1,3-dicarbonyl compounds

1.4 Transition Metal-Catalyzed Amination of C–H Bonds with Iminoiodanes

1.4.1 Intermolecular Amination of Saturated C–H Bonds with Iminoiodanes

In seminal works focused on the development of transition metal-catalyzed nitrene transfer reactions, amination of saturated C–H bonds were also investigated. However, these reactions suffered from the lack of chemoselectivity, as shown for the amination of *cis*- or *trans*-hexene **23** (Table 1.1). It was not until a decade later that this was improved, when Müller and co-workers reported the rhodium-catalyzed amination of cyclohexene **63** with PhI=NNs (Scheme 1.14).⁵¹ Interestingly, in this catalytic system, the allylic amine **64** was furnished in 70% yield while the corresponding aziridine **65** was obtained only in 5% yield.

Scheme 1.14 Rhodium-catalyzed amination of cyclohexene with PhI=NNs.

Further work in this field by Müller and co-workers led to a study on the amination on benzylic C–H and ethereal C–H bonds (Table 1.4, entry 1).⁵¹

Table 1.4 Transition metal-catalyzed nitrene insertion into saturated C–H bonds with iminoiodanes

Entry	Catalyst	Nitrogen Source	Yield (%)	Ref.
1	$Rh_2(OAc)_4$	$PhI=NNs$	13–84	51
2	$[Ru(Me_3tacn)(NHTs)_2(OH)]$ 66a	$PhI=NTs$	41–75	52
3	$[Ru(TPP)(NTs)_2]$ 33 or $[Ru(OEP)(NTs)_2]$ 34		10–88	21
4	$[Ru(F_{20}-TPP)CO]$ 67 or $[Mn(F_{20}-TPP)Cl]$ 68	$PhI=NTs$	56–90	53
5	$[Ru(Me_3tacn)(OTf)_3 \cdot H_2O]$ 66b	$PhI=NTs$	80–93	54
6	$[Ru(6,6'-Cl_2bpy)_2Cl_2]$ 69	$PhI=NTs$	81–92	54
7	$[Tp^{Br^3}Cu(MeCN)]$ 27b	$PhI=NTs$	45–98	55,56
8	$[Co(acacen)]$ 70	$PhI=NTs$	11–64	57
9	$[Ag_2(bp)_2]$ 71	$PhI=NNs$	25–71	58
10	$[Tp^{*,Br}Ag]$ 28	$PhI=NTs$	40–70	59
11	$[Fe(qpy)(MeCN)(ClO_4)_2]$ 72	$PhI=NTs$ or $PhI=NNs$	27–86	60
12	$[Cu(TMG_3trphen)PF_6]$ 40	$PhI=NTs$	13–84	30

By employing $Rh_2(OAc)_4$ as the catalyst, the reaction gave the corresponding amine products in 18–83% yields. Che and co-workers elucidated the structure of $[Ru(Me_3tacn)PF_6]$ **66a** and showed the complex to catalyze the amination of allylic,

benzylic, and saturated C–H bonds to afford the corresponding product in only moderate yields of 41–75% (Table 1.4, entry 2).⁵² In their work using [Ru(TPP)(NTs)₂] **33** or [Ru(OEP)(NTs)₂] **34** as stoichiometric nitrene transfer reagents in the aziridination reaction, Che and co-workers subsequently demonstrated this system for the amination of saturated alkanes to give the corresponding amino compounds in up to 88% yields (Table 1.4, entry 3).²¹ The mechanism of this reaction was postulated to involve a radical intermediate after the H-abstraction step based on kinetic isotope effect studies. In early 2000, Che and co-workers reported a further breakthrough in the amination of saturated C–H bonds (Table 1.4, entry 4).⁵³ By using the electron-deficient [Ru(F₂₀-TPP)CO] **67** or [Mn(F₂₀-TPP)Cl] **68** complexes (H₂F₂₀-TPP = 5,10,15,20-tetrakis-(pentafluorophenyl)-21*H*,23*H*-porphyrin), the amination reaction was shown to tolerate a broader substrate scope and provide higher product yields of 56–90%. In a subsequent study by the group, Che and co-workers demonstrated [Ru(Me₃tacn)(OTf)₃·H₂O] **66b** and [Ru(6,6'-Cl₂bpy)₂Cl₂] **69** to be efficient catalysts for the amination of saturated hydrocarbons.⁵⁴ These non-heme ruthenium(II) and ruthenium(III) catalysts were shown to give the products in 80–93% yields (Table 1.4, entries 5 and 6).

In 2003, Perez reported that the amination of C–H bonds by using copper-homoscrapioate complex [Tp^{Br3}Cu(MeCN)] **27b** could be achieved (Table 1.4, entry 7).⁵⁵ In this study, the amination of primary benzylic C–H bonds was found to provide product yields of >95%. The amination of cyclohexane was accomplished in 65% product yield, which compared favourably to all previous systems that were shown to be ineffective toward the substrate. The work also revealed the substrate scope to include cyclic ethers, with the corresponding adducts obtained in 45–98% yields.⁵⁶

Figure 1.4 Transition metal catalysts for C–H amination of alkanes

Subsequently, Cenini demonstrated the nitrene insertion reaction of C–H bonds using a cobalt(II) catalytic system (Table 1.4, entry 8).⁵⁷ A drawback of the [Co(acacen)] complex **70** was a limited substrate scope and yields of 11–64% of the allylic amines. A silver-based catalytic system was also reported by He and co-workers for the amination of saturated C–H bonds.⁵⁸ Employing the phenanthroline-type of ligand, [Ag₂(bp)₂] **71** was demonstrated to effect the amination of unsaturated C–H bonds with reactivity comparable to that previously reported for copper and ruthenium catalysis, giving the products in 25–71% yield (Table 1.4, entry 9). Following this work, Perez described the ability of silver-homoscorpionate complex **28** to access more challenging substrates (Table 1.4, entry 10).⁵⁹ Using this silver system, the amination of simple acyclic and cyclic alkanes was achieved in 40–70% yield, but with poor chemoselectivity. Recently, Che and co-workers reported the synthesis of the seven-coordinate non-heme iron(II) complex

[Fe(qpy)(MeCN)(ClO₄)₂] **72** and its ability to mediate the amination of benzylic and allylic C–H bonds, giving the corresponding products in 53–86% yield (Table 1.4, entry 11).⁶⁰ Remarkably, the amination of cyclic alkanes could be achieved to give the amine product in low to moderate yields of 27–63%. In the work by Stavropoulos, the amination reaction of hydrocarbons with copper(I) complex **40** was also shown to deliver the corresponding products in 13–84% yield (Table 1.4, entry 12).³⁰

1.4.2 Asymmetric Intermolecular Amination of Saturated C–H Bonds with Iminoiodanes

Che and co-workers reported the first enantioselective C–H amination of benzylic C–H bonds (Scheme 1.14).⁶¹ With the use of manganese porphyrin **46** or ruthenium porphyrin **47** as catalyst, the reaction provided the corresponding products in 16–85% yield and ee values up to 53%. The chiral manganese(III) salen complex **72** was demonstrated by Katsuki and co-workers to catalyze the amination of allylic and benzylic C–H bonds with PhI=NTs.⁶² While moderate to good product yields of 42–71% were obtained, the selectivity of this catalyst was found to be better with ee values of 41–89%.

Scheme 1.14 Transition metal-catalyzed asymmetric C–H amination with iminoiodanes

Following their previous works examining the use of dirhodium(II),(II) catalysis, Müller and co-workers reported a preliminary study that applied $[\text{Rh}_2((\text{R})(-)\text{-bnp})_4]$ **48** to mediate the asymmetric amination of indane which achieved a product yield of 71% and ee value of 31%.³² Subsequently in 2002, Hashimoto and co-workers reported the use of the dirhodium catalyst $[\text{Rh}_2((\text{S})\text{-TCPTTL})_4]$ **59b** to affect better product yields of 52–88% and higher selectivities up to 84% ee for the amination of activated C–H bonds of benzylic and allylic C–H bonds.⁶³

1.4.3 Intermolecular Amination of $\text{C}(\text{sp}^2)\text{-H}$ Bonds with Iminoiodanes

Owing to the immense importance of the amination of $\text{C}(\text{sp}^2)\text{-H}$ bonds in the organic chemistry, the nitrene transfer reaction on such transformations has provided numerous examples in the literature. Notably, there are several remarkable works that have been done on this functionalization in the presence of a transition metal complex as catalyst with iminoiodanes in the past decade. One of the first example was shown by Perez and co-workers who reported the copper-homoscorpionate complex **27b** to mediate amination of benzene and other aromatic compounds in product yields up to 40% (Scheme 1.15).^{55,56} The group of He also showed this transformation to be achievable in the presence of gold(III) chloride as the catalyst to give the aminated compounds in good to excellent yields of 61–90%.⁶⁴

Scheme 1.15 Copper-catalyzed $\text{C}(\text{sp}^2)\text{-H}$ amination of aromatic compounds iminoiodanes

Subsequently, Che reported the use of [Ru(TTP)CO] **76** (H₂TTP = 5,10,15,20-tetrakis-(tolyl)-21*H*,23*H*-porphyrin) as the catalyst for the amidation of heteroaromatic compounds **73** in the presence of iminoiodane (Scheme 1.16).⁶⁵ In this work, the reaction was found to proceed to give the mono- and di-*N,N*-disulfonimide products **74** and **75** in 33–91% and 50–87% yields, respectively.

Scheme 1.16 Ruthenium-catalyzed C–H amination of aromatic compounds with iminoiodanes

Recently, a number of groups reported the amidation of formyl C–H bonds via a transition metal-catalyzed nitrene insertion pathway (Scheme 1.17). Chan and co-workers described the first amidation of aldehydes with PhI=NTs in the presence of [Ru(TTP)CO] **76** as catalyst to give the corresponding amides **78** in 68–99% yield.⁶⁶ However, a drawback was catalyst leaching in the reaction of several substrates for this method. With this limitation, the copper-catalyzed version of the above method was developed.⁶⁷ With the use of copper(I) iodide as the catalyst and pyridine as the ligand, the reaction could afford the *N*-tosylamide **78** in excellent yields of 62–99% albeit with a slightly narrower substrate scope reported.

Scheme 1.17 Transition metal-catalyzed formyl C–H amidation with PhI=NTs

Following the previous works, the group of Che and Chan independently reported the iron-catalyzed nitrene insertion onto aldehydes. Che and co-workers described the use of iron(II) chloride and terpyridine as the ligand to give the amidation products in 40–89% yield.⁶⁸ Chan and co-workers showed the iron(II) chloride and pyridine combination to be a better catalytic system for the amidation reaction, giving a broader substrate scope and higher product yields of 19–99% yield.⁶⁹

1.5 Recent Developments in Transition Metal-Free Nitrogen Atom Transfer Reactions

In the past few years, the development of transition metal-free methods for the direct installation of the nitrogen atom to C=C and C–H bonds has progressively expanded. The aziridination of alkenes in the absence of a transition metal complex was studied by Sain and co-workers in 2004 (Scheme 1.18).⁷⁰ The simple combination of H₂O₂/HBr as the catalyst was reported to mediate the aziridination reaction of alkenes with chloramine-T, affording the corresponding products **20** in 45–92% yield. Subsequently, Sudalai and co-workers communicated the aziridination of olefins in the presence of NaIO₄ and LiBr to furnish the corresponding products in 40–81% yield.⁷¹ Recently, Chen and co-workers developed a synthetic method utilizing *N*-bromosuccinimide (NBS) as the oxidant for the aziridination of styrene with amides to provide the aziridines **20** in 36–86% yield.⁷²

Scheme 1.18 Transition metal-free aziridination of alkenes

In tandem with these studies, the C–H bond amination of alkanes was demonstrated to be feasible in the absence of a transition metal catalyst (Table 1.5). In 2009, Fan and co-workers reported the amination at the benzylic C–H bond in the presence of iodine as catalyst (Table 1.5, entry 1).⁷³ While this method only tolerated primary and secondary benzylic C–H bond, the reaction proceeded well in the presence of 3 equiv of $\text{PhI}(\text{OAc})_2$ to give the aminated product in 45–98% yield. Following this work, Minakata and co-workers demonstrated the iodine-mediated amination of benzylic C–H bonds with chloramine-T, furnishing the amine compound in low to excellent yields of 16–93% (Table 1.5, entry 2).⁷⁴ In this study, it was shown that the amination of an adamantane derivative gave the corresponding product in 55% yield. Subsequently, Chan and Li described the amination of allylic C–H bonds with the use of 2,3-dichloro-5,6-dicyano-4-benzoquinone (DDQ) under mild conditions (Table 1.5, entry 3).⁷⁵ Various allylic compounds and amines were revealed to give the desired products in 42–96% yield with complete chemoselectivity over aziridination.

Table 1.5 Transition metal-free amination of unsaturated C–H bonds

$\text{X} = \text{C}, \text{O}$

Entry	Catalyst	Oxidant	Yield (%)	Ref.
1	I_2	$\text{PhI}(\text{OAc})_2$	45–98	73
2	-	I_2	16–93	74
3	-	DDQ	42–96	75
4	-	Ph_2IPF_6	25–95	76
5	TBAI	<i>t</i> -BuO ₂ H	51–90	77

More recently, several groups independently reported a number of transition metal-free amination protocols for a variety of C–H bonds. In these studies, it was proposed that the C–N bond forming process might involve single electron transfer on to α -carbon of ethers, allylic or benzylic C–H bond. Subsequently, the group of Hu studied the α -C–H amination of ethers by utilizing the iodonium salt Ph_2IPF_6 (Table 1.5, entry 4).⁷⁶ This method afforded a wide range of products with yields of 25–95%. Following this work, He and co-workers described the use of tetrabutylammonium iodide (TBAI) and *tert*-butyl hydroperoxide for the amination of primary and secondary benzylic C–H and ether α -C–H bonds (Table 1.5, entry 5).⁷⁷ The method gave the aminated products in 51–90% yields. The scalability of this method was also demonstrated with comparable yields of the product obtained when the reaction was repeated at 10 mmol scale.

As shown in Table 1.6, the transition metal-free C–H bond amination of aromatic and hetero-aromatic compounds have also been realized in recent years. In a seminal work by Nachtsheim and co-workers, TBAI was found to be an effective catalyst for such transformation (Table 1.6, entry 1).⁷⁸ While a variety of amine substrates were well tolerated, the method was limited to benzoxazoles **79**, furnishing the coupling products **80** in 18–90% yield. About the same time, Bhanage and co-workers reported the analogous transformation in the presence of *N*-iodosuccinimide (NIS) (Table 1.6, entry 2).⁷⁹ The use of NIS as the catalyst and hydrogen peroxide as the oxidant afforded the corresponding products **80** in 81–98%. Subsequently, Wang and co-workers showed that the amination of heteroaromatic compounds using formamides as the nitrogen source could be achieved (Table 1.6, entry 3).⁸⁰ In this study, it was demonstrated that both benzoxazoles and benzothiazoles were tolerated to afford yields of 28–87% of the desired product.

Table 1.6 Transition metal-free amination of aromatic and heteroaromatic compounds

Entry	Catalyst	Oxidant	Yields (%)	Ref
1	TBAI	<i>t</i> -BuO ₂ H	18–90	78
2	NIS	H ₂ O ₂	81–98	79
3	TBAI	<i>t</i> -BuO ₂ H	28–87	80
4	-	NBS	82–93	81
5	-	-	53–96	82

Sun and co-workers studied the transition metal-free amination of benzoxazoles **79** under neat conditions at ambient temperature with NBS as the sole oxidant (Table 1.6, entry 4).⁸¹ The reaction proceeded well to furnish the corresponding product **80** in 82–93% yield. More recently, Yan and co-workers demonstrated the transition metal-free nitrene insertion of arenes **81** via thermal decomposition of arylsulfonyl azides (Table 1.6, entry 5).⁸² While the reaction gave the corresponding insertion product **81** in 53–96% yields, the regioselectivity was reported to be poor, giving 1:1 mixtures of the regioisomers of the products.

The amidation of aldehydes with primary amines by PhI(OAc)₂ was demonstrated by Bao and Qian (Scheme 1.19).⁸³ The reaction afforded the corresponding amide **77** in moderate to good yields of 46–85% at ambient temperature, albeit the scope of this transformation was limited to only aromatic aldehydes. Following this work, Zhang and co-workers described the amidation of

aldehydes by utilizing the tetrazoles as nitrogen source to give similar product yields of 38–82%.⁸⁴

Scheme 1.19 Transition metal-free amidation of formyl C–H bonds

The use of iminoiodanes as the nitrogen source for transition metal-free transformations was first reported in 1996 by Ahn and Lim (Scheme 1.20).⁸⁵ The functionalization of silyl enol ethers with PhI=NTs giving the α -amino ketones in good yields of 52–99% was demonstrated in the absence of a catalyst.

Scheme 1.20 Silyl enol ether aziridination/ring-opening with PhI=NTs

The first transition metal free aziridination using a hypervalent halogen reagent was reported by Ochiai and co-workers who developed the iminobromane **83** for this purpose (Scheme 1.21).⁸⁶ In this study, the aziridination of alkenes was shown to give the corresponding products in 53–97% yield and with high stereoselectivity. The mechanism of the olefin aziridination was suggested to proceed via the direct insertion of the iminobromane **83** onto the π bond of the alkene with small positive charge build-up in the transition state.⁸⁷

Scheme 1.21 Iminobromane-mediated aziridination of alkenes

Subsequently, the group reported the amination of alkanes with iminobromane **83** (Scheme 1.22).⁸⁸ The reaction furnished the corresponding *N*-triflylamide products in 42–96% yield with good to high regioselectivity. Furthermore, ethers were also shown to be aminated under ambient conditions to give the corresponding 2-triflylamino ethers in moderate to good yields of 46–92%.⁸⁹

Scheme 1.22 Iminobromane-mediated amination of alkanes and ethers

Recently, Muñiz and co-workers described the use of diiminoiodane $\text{PhI}(\text{NTs}_2)_2$ **85** as new reagent for the transition metal free amination reaction of alkenes, silyl enol ethers and ketones (Scheme 1.23).⁹⁰ In this work, it was demonstrated that the amination of such substrates proceeded with **85** in the absence of a catalyst or additive to furnish the corresponding products in 33–91% yield.

Scheme 1.23 Iminoiodane-mediated amination of alkenes, silyl enol ethers and ketones

Subsequently, Minakata and co-workers reported the aziridination of styrene derivatives by $\text{PhI}=\text{NTs}$ with TBAI and iodine as the catalyst combination

(Scheme 1.24).⁹¹ The reaction was shown to work well to afford the corresponding 2-aryl-aziridine products in 46–94% yield. Interestingly, this included [60]-fullerene, which gave the aziridine product in 37% yield.

Scheme 1.24 TBAI and iodine-catalyzed aziridination of styrenes

More recently, Zhdankin and coworkers developed the saccharin-based iminoiodane **87** as the reagent for the amination of silyl enol ethers.⁹² While the amination could proceed in the absence of a catalyst to furnish the α -amino ketones **88** in 22–68% yield, the isomeric product **89** was also obtained in 20–74% yield.

Scheme 1.25 Amination of silyl enol ether with **87**

1.6 Proposed Work

The work of this thesis was led by the growing interest to establish synthetic protocols for C–N bond formation in a transition metal-free manner. With the use of iminoiodanes as nitrogen source, these methods will provide protocols in the absence of transition metal catalysts to access synthetically useful building blocks and compounds of potential pharmaceutical interest (Figure 1.5). The use of cheap and readily available reagents and catalysts will also increase the potential for their scale-up.

Figure 1.5 Nitrogen containing compounds with pharmaceutical interests⁹³

The aim of this project has been to develop the methods for the functionalization of 1,3-dicarbonyl compounds with PhI=NTs as the nitrogen source under acid catalysis to give 2-amino-1,3-dicarbonyl compounds (Figure 1.6a). As the result, we found a method for the direct aziridination of 2-substituted-1,3-dicarbonyl compounds by using an organic or inorganic base (Figure 1.6b). This transformation was postulated to proceed via formal oxidation of the 2-substituted-1,3-dicarbonyl compound, which then deliver the desired aziridine.

Lastly, the α -amination of cyclic ethers with PhI=NTs leads us to hemiaminal intermediates. We then proposed that such aminated species would undergo ring opening and functionalization by 1,3-dicarbonyl compounds as the nucleophile to furnish the corresponding 2-functionalized cyclic ethers (Figure 1.6c). Finally, the addition of Grignard reagents instead of 1,3-dicarbonyl compounds would afford the *N*-tosylamino alcohols (Figure 1.6d).

Figure 1.6 Transition metal-free iminoiodane-mediated nitrogen atom transfer to activated C-H bonds

Chapter II. Brønsted Acid-Catalyzed Amination of 1,3-Dicarbonyl Compounds by Iminoiodanes

2.1 Introduction

Compounds containing an α -amino acid moiety outside the 20 used by Nature are important targets in medicinal chemistry owing to their potential to possess new bioactivities.^{94,95} A number of remarkable and elegant synthetic methods to install the C–N bond at the α -position of carbonyl groups have been demonstrated over the past decade.^{96,97} Recently, Chan and co-workers reported the synthesis of ketone-substituted α -amino acid derivatives that relied on Cu(OTf)₂-catalyzed amination of a 1,3-dicarbonyl compound with iminoiodanes (Chapter I, Scheme 1.13).⁵⁰ Zhang and co-workers also showed the analogous reactions of β -keto amides, esters, phosphonates and 1,3-diones with the combination of TsNH₂ and PhI=O mediated by Zn(ClO₄)₄·6H₂O could be achieved in good to excellent yields (Scheme 2.1).⁹⁸ The use of a transition metal complex in both instances was shown to be indispensable and developing methods for such transformation in the absence of transition metal is still posed as a challenge in organic synthesis.

Scheme 2.1 Zinc(II)-catalyzed amination of 1,3-dicarbonyl compounds by iminoiodanes

In view of these works and an ongoing program exploring the utility of iminoiodanes in organic synthesis, we became intrigued in the investigation of the

Brønsted acid-catalyzed amination of 1,3-dicarbonyl compounds. We disclose herein the details of this study involving TFA-mediated amination of β -keto esters and phosphonates and 1,3-diones by PhI=NTs (Scheme 2.1). This process provides a convenient and operationally straightforward route to the corresponding α,α -acyl amino acid derivatives in moderate to excellent yields.

Scheme 2.2 Brønsted acid-catalyzed amination of 1,3-dicarbonyl compounds by iminoiodanes

2.2 Results and Discussion

With ethyl benzoylacetate **61a** as the model substrate, we began by setting out the optimum reactions conditions of the present method (Table 2.1). This initial study showed that treating the β -keto ester with 2 equiv of PhI=NTs with 20 mol % of trifluoroacetic acid (TFA) in the presence of 240 mg of 4 Å molecular sieves (MS) in CH₂Cl₂ at room temperature for 15 min afforded the corresponding α -aminated product **62a** in 85% yield (Table 2.1, entry 1). Slightly lower yields of 75–79% were obtained on either lowering the catalyst loading from 20 to 10 mol % or the amount of the iminoiodane from 2 to 1.5 or 1.2 equiv (Table 2.1, entries 2–5). Lower product yields of 61–72% were also obtained when 5 mol % of TFA was employed and/or the reaction was conducted at 0 °C (Table 2.1, entries 6, 7 and 9). On the other hand, repeating the reaction with 10 mol % of the Brønsted acid at 0 °C for 90 min gave **62a** in 86% yield (Table 1, entry 8).

Table 2.1 Optimization of the reaction conditions^a

Entry	Catalyst (mol %)	PhI=NTs (eq)	Solvent	Temp (°C)	Time (min)	Yield (%) ^b
1	TFA (20)	2	CH ₂ Cl ₂	rt	15	85
2	TFA (20)	1.5	CH ₂ Cl ₂	rt	10	77
3	TFA (10)	1.5	CH ₂ Cl ₂	rt	10	79
4	TFA (20)	1.2	CH ₂ Cl ₂	rt	15	79
5	TFA (10)	1.2	CH ₂ Cl ₂	rt	10	75
6	TFA (5)	1.2	CH ₂ Cl ₂	rt	15	61
7	TFA (20)	1.2	CH ₂ Cl ₂	0	90	62
8	TFA (10)	1.2	CH₂Cl₂	0	90	86
9	TFA (5)	1.2	CH ₂ Cl ₂	0	90	72
10	TFA (10)	1.2	MeCN	0	90	68
11	TFA (10)	1.2	PhMe	0	90	51 ^c
12	TFA (10)	1.2	THF	0	90	11 ^c
13	HCl (20)	2	CH ₂ Cl ₂	rt	1080	52
14	H ₂ SO ₄ (20)	2	CH ₂ Cl ₂	rt	1080	78
15	H ₃ PO ₄ (20)	2	CH ₂ Cl ₂	rt	1080	66
16	AcOH (20)	2	CH ₂ Cl ₂	rt	1080	51

^aUnless otherwise stated, all reactions were performed in the presence of 4 Å MS under N₂ atmosphere at 0.5 mmol scale of **1a** in 2 mL of solvent at given temperature.

^bIsolated yield. ^cProduct yield was determined by ¹H NMR analysis of the crude mixture with CH₂Br₂ as the internal standard.

In our hands, amination of **61a** by PhI=NTs under these latter reaction conditions was found to give lower yields of 11–68% yields when THF, MeCN, or toluene was used as the reaction medium in place of dichloromethane (Table 2.1, entries 10–12). Similarly, reactions with other Brønsted acid such as HCl, H₂SO₄, H₃PO₄, and AcOH as the catalyst furnished lower yields of 51–78% even with extended reaction times to 18 h at room temperature (Table 2.1, entries 14–16). From the results stated above, the amination of **61a** by PhI=NTs (1.2 equiv) in the presence of 10 mol % of TFA and 4 Å MS (240 mg) in dichloromethane at 0 °C for 90 mins was deemed as the optimal reaction conditions.

To assess the scope of this method, we then explored the amination of a variety of 1,3-dicarbonyl compounds and the results are summarized in Table 2.2. The reactions of β -keto esters containing an electron-donating phenyl group with PhI=NTs were well tolerated to afford the corresponding α,α -acyl amino acid derivatives **62b–e** in 63–86% yield (Table 2.2, entries 2–5). When β -keto esters with the benzoyl group bearing electron-withdrawing substituent were used, the reaction gave the products **62f–i** in slightly lower yields of 53–65% (Table 2.2, entries 6–9). By changing the phenyl group of β -keto esters with a furan moiety or alkyl substituent, the reaction proceeded well, furnishing the corresponding product **62j**, **62l** and **62m** in 47–73% yield (Table 2.2, entries 10, 12 and 13). The only exception was the reaction of **61k** with PhI=NTs providing **62k** in a lower yield of 27% (Table 2.2, entry 11). Changing the β -keto ester to its phosphonate analogue **61n** was found to give the corresponding α -aminated product **62n** in 53% yield (Table 2.2, entry 14).

Table 2.2 Substrate scope for the amination of 1,3-dicarbonyl compounds **61** with PhI=NTs^a

61 + PhI=NTs $\xrightarrow[\text{4 Å MS, 0 °C}]{\text{TFA (10 mol \%), CH}_2\text{Cl}_2}$ **62**

Entry	Product	Time (h)	Yield (%) ^b
1	62a , R = H	1.5	86
2	62b , R = <i>o</i> -Me	3	65
3	62c , R = <i>m</i> -Me	3	84
4	62d , R = <i>p</i> -Me	1.5	84
5	62e , R = <i>p</i> -OMe	5	63
6	62f , R = <i>p</i> -I	1.5	53
7	62g , R = <i>p</i> -Cl	1	65
8	62h , R = <i>p</i> -Br	1.5	60
9	62i , R = <i>p</i> -F	1.5	58
10	62j	4	41
11	62k , R ¹ = R ² = Me	4.5	27
12	62l , R ¹ = Me, R ² = Et	6	73
13	62m , R ¹ = Me, R ² = <i>t</i> -Bu	18	47
14	62n	4	53
15	62o , R = Me	18	- ^c
16	62p , R = Et	18	- ^c

Table 2.1 (*continued*)

Entry	Product	Time (h)	Yield (%) ^b
17	62q , R ¹ = R ² = Ph	1	63
18	62r , R ¹ = Ph, R ² = Me	2	57
19	62s , R ¹ = R ² = Me	2	62
20	62t , R ¹ = R ² = <i>t</i> -Bu	18	- ^c

^aAll reactions were performed at 0.5 mmol scale of **61** with TFA:**61**:PhI=NTs ratio = 1:10:12 in the presence of 4 Å MS (240 mg) in CH₂Cl₂ (2 mL) at 0 °C. ^bIsolated yields. ^cNo reaction based on TLC and ¹H NMR analysis of the crude mixture.

Unfortunately, the analogous reactions with the alkyl malonates **61o** and **61p** led to the recovery of the 1,3-dicarbonyl compound in near quantitative yield, in both cases, based on TLC analysis and ¹H NMR analysis of the crude mixture (Table 2.2, entries 15 and 16). We then treated 1,3-diones **61q–61s** under the standard reaction conditions to give the corresponding 2-amino-1,3-dione products **62q–62s** in 57–63% yield (Table 2.2, entries 17–19). However, replacing the 1,3-dione with **61t** containing the bulky *tert*-butyl groups, was found to result in recovery of the substrate in near quantitative yield (Table 2.2, entry 20). As shown in Scheme 2.3, the amination of 1,3-cyclohexadione **61u** was also investigated but was found to afford the iodonium ylide **95u** in 83% yield.

Scheme 2.3 Amination of 1,3-cyclohexadione **61u**

A tentative mechanism for the Brønsted acid-catalyzed amination reaction is shown in Scheme 2.4. Under the acidic conditions, the tautomerization of **61** to **61'** followed by addition to PhI=NTs might occur to give the putative iodine(III) species **A** (path a in Scheme 2.4). This species has been proposed in the mechanism involving the use of other hypervalent iodine species.⁹⁹ Reductive elimination of the hypervalent iodine(III) moiety would lead to the removal of PhI and deliver the product **62**. The role of the Brønsted acid catalyst in facilitating the enolization of the 1,3-dicarbonyl compound would be consistent with the recovery of the substrate in reactions with the less acidic 1,3-dicarbonyl compounds as in malonates.¹⁰⁰ The formation of iodonium ylide **95u** could be due to preferential α -H elimination in intermediate **A** (path b in Scheme 2.4). This could be due to the more stable nature of the species provided by secondary bonding interactions between the carbonyl oxygen atoms and the iodine(III) centre on generating the cyclic form of the hypervalent iodine product.⁹⁹ The side-product additionally argues in favour of species **A** being the actual intermediate that undergoes reductive elimination to afford the product.

Scheme 2.4 Proposed mechanism for the Brønsted acid-catalyzed amination of 1,3-dicarbonyl compounds with iminoiodanes

A competition experiment investigation on the amination of β -keto esters **61d**, **61e** and **61g-i** revealed $\log(K_X/K_H)$ values of 0.02 (**61d**), 0.09 (**61e**), -0.09 (**61g**), -0.07 (**61h**), and -0.06 (**61i**). This implies that 1,3-dicarbonyl compounds substituted with an electron-donating group are more reactive than **61a**, whereas those with electron-withdrawing substituent impede the reaction. Fitting (by least squares method) the $\log(K_X/K_H)$ data to the σ_p scale gave rise to moderate linearity ($R^2 = 0.947$) with a ρ value of -0.306 (Figure 1.1).¹⁰¹ The small and negative ρ value indicates minimal positive-charge development on the aromatic ring of the intermediate **A** and implies its formation could be the rate-limiting step.¹⁰²

Figure 2.1 Linear free-energy correlation of $\log(K_X/K_H)$ against σ_p on the Brønsted acid-catalyzed amination of 1,3-dicarbonyl compounds **61d,e,g-i** with PhI=NTs

2.3 Conclusion

In summary, we have developed a Brønsted acid-catalyzed method to access unnatural α,α -acyl amino acid derivatives from 1,3-dicarbonyl compounds and PhI=NTs. Our studies show the reaction to be applicable to β -keto esters and phosphonates as well as 1,3-diones and complement earlier works that make use of Cu(II)⁵⁰ and Zn(II)⁹⁸ catalysis.

Chapter III. Base-Mediated Aziridination of 2-Alkyl Substituted-1,3-Dicarbonyl Compounds by Iminoiodanes

3.1 Introduction

Aziridines are one of the most versatile building blocks in organic synthesis.^{103,104} The moiety is also found in numerous natural products and pharmacologically active compounds.^{105,106} Owing to its importance, a myriad of methods for the synthesis of aziridines have been developed over the years such as the aza-Darzens, addition-elimination, and nitrene transfer reactions to alkenes.^{107,108} The construction of the moiety has also been achieved from readily available starting materials using the above methods. However, these transformations have targeted substrates containing an alkene, α,β -unsaturated carbonyl or imine functional group. Recently, our group demonstrated the copper(II)-catalyzed aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds with $\text{PhI}=\text{NTs}$ via double C–H bond activation to afford the corresponding α,α -diacylaziridines in moderate to good yields (Scheme 3.1).¹⁰⁶ⁱ

Scheme 3.1 Copper(II) triflate-catalyzed aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds

To date, there are no examples in the literature for the direct installation of the aziridine moiety to saturated C–H bonds without the aid of transition metal catalysis. As part of our efforts to investigate the use of iminoiodanes as an electrophilic

nitrogen source for transition metal-free organic transformations, we herein disclose a serendipitous finding on the base-mediated synthesis of α,α -diacylaziridines and α,α,β -triacylaziridines from 2-alkyl substituted-1,3-dicarbonyl compounds with iminoiodanes.

Scheme 3.2 Base-mediated aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds by iminoiodanes

3.2 Results and Discussion

We started our investigation on the present methodology by screening a variety of reaction conditions (Table 3.1). Treating the diethyl ethylmalonate **96a** and 2.2 equiv of NsN=IPh with 1.1 equiv of K₂CO₃ in acetonitrile at room temperature gave the 1,1-diacylaziridine **97a** and α,β -unsaturated-1,3-dicarbonyl compound **98a** in 70 and 23% yield, respectively (Table 3.1, entry 1). Changing the base to other inorganic bases such as KO^{*t*}-Bu, LiO^{*t*}-Bu, Na₂CO₃, or NaHCO₃ led to the recovery of the starting material (Table 3.1, entries 2–5). Turning our attention to the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, the reaction still proceeded to afford similar product yields with both 3.3 and 2.2 equiv of NsN=IPh (Table 3.1, entries 6 and 7). A lower product yield of 29% was observed when 20 mol % of DBU was used (Table 3.1, entry 8). An increase in the concentration of the reaction mixture from 0.1 M to 0.2 M was led to an increase in product yield from 29 to 71% (Table 3.1, entry 9). Decreasing the catalyst loading, or replacing the catalyst with other organic bases such as MTBD, TBD, and DABCO did not give any improvement in the

reaction outcome (Table 3.1, entries 10–13). A survey of the solvent effect on the transformation revealed that THF or toluene as solvent in place of MeCN resulted in no reaction based on TLC and ^1H NMR analysis of the crude mixtures (Table 3.1, entries 14 and 15). On the other hand, when dichloromethane was used as solvent, the product was delivered in 74% yield (Table 3.1, entry 16). Other arylsulfonyl-substituted iminoiodane were also investigated. Interestingly, replacing NsN=IPh to $o\text{-NsN=IPh}$ ($o\text{-Ns}$ = o -nitrobenzenesulfonyl) afforded the aziridine in 97% yield, but TsN=IPh gave a lower yield of 12% (Table 3.1, entries 17 and 18). From the results above, reacting 2-alkyl substituted-1,3-dicarbonyl compound **96** with 2.2 equiv of $o\text{-NsN=IPh}$ in the presence of 20 mol % of DBU at room temperature was determined to provide the optimal reaction conditions.

Table 3.1 Optimization studies for base-mediated aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds^a

Entry	Base (eq)	NsN=IPh loading (eq)	Solvent	Yield (%) ^b
1	K_2CO_3 (1.1)	3	MeCN	70 ^c
2	$\text{KO}t\text{-Bu}$ (1.1)	3	MeCN	-
3	$\text{LiO}t\text{-Bu}$ (1.1)	3	MeCN	-
4	Na_2CO_3 (1.1)	3	MeCN	-
5	NaHCO_3 (1.1)	3	MeCN	-
6	DBU (1.1)	3	MeCN	71
7	DBU (1.1)	2.2	MeCN	72

Table 3.1 (*continued*)

Entry	Base (eq)	NsN=IPh loading (eq)	Solvent	Yield (%) ^b
8	DBU (0.2)	2.2	MeCN	29
9^d	DBU (0.2)	2.2	MeCN	71
10 ^d	DBU (0.1)	2.2	MeCN	21
11 ^d	MTBD (0.2)	2.2	MeCN	58
12 ^d	TBD (0.2)	2.2	MeCN	52
13 ^d	DABCO (0.2)	2.2	MeCN	-
14 ^d	DBU (0.2)	2.2	THF	-
15 ^d	DBU (0.2)	2.2	PhMe	-
16 ^d	DBU (0.2)	2.2	CH ₂ Cl ₂	74
17^{d,e}	DBU (0.2)	2.2	MeCN	97^c
18 ^{d,f}	DBU (0.2)	2.2	MeCN	12

^aUnless otherwise specified, all reactions were performed with 0.1 M of 2-alkyl substituted 1,3-dicarbonyl compound. ^bYield was determined by the ¹H NMR analysis of the crude mixture with CH₂Br₂ as internal standard. ^cIsolated yield. ^dReactions were performed with 0.2 M of 2-alkyl substituted 1,3-dicarbonyl compound. ^e*o*-NsN=IPh was used instead. ^fTsN=IPh was used instead.

We then explored the generality of the present method by screening a number of 2-alkyl substituted-1,3-dicarbonyl compounds and the results are summarized in Table 3.2. An investigation on the effect of the substituent at R³ position found that extending the alkyl chain as in **96b** did not affect the reaction outcome, the product **97b** being obtained in 80% yield (Table 3.2, entry 2). However, changing the alkyl

Table 3.2 Substrate scope for base-mediated aziridination of 2-alkyl substituted 1,3-dicarbonyl compounds^a

Entry	Substrate	Product	Yield (%) ^b
1	 96a	 97a	97
2	 96b	 97b	80
3	 96c	 97c	- ^c
4	 96d	 97d	- ^c
5	 96e	 97e	- ^c
6	 96f	 97f	25

Table 3.2 (continued)

Entry	Substrate	Product	Yield (%)
7	96g	97g	- ^c
8	96h	97h	24 (46) ^d
9	96i	97i	- ^e

^aAll reactions were performed with 0.2 M of **96** in MeCN at room temperature with ratio of **96**:K₂CO₃:*o*-NsN=IPh = 1:1.1:2.2. ^bIsolated yield. ^cUnidentified decomposition of starting material. ^d3.3 equiv of *o*-NsN=IPh was used. ^eNo reaction based on TLC and ¹H NMR analysis of the crude mixture.

substituent to phenyl group in **96c** or hydrogen atom in **96d** gave no observable reaction based on TLC and ¹H NMR analysis of the respective crude mixture (Table 3.2, entries 3 and 4).

When 2-alkyl substituted- β -keto esters **96e** and **96f** were examined as the starting material, the desired aziridine products **97e** and **97f** were obtained in low yields of 0 and 25% yield, respectively (Table 3.2, entries 5 and 6). Decomposition of starting material was observed when ethyl 2-oxocyclopentane-carboxylate **96g** was

subjected to the optimum reaction conditions (Table 3.2, entry 7). Interestingly, when diethyl acetylsuccinate **96h** was treated to the optimum conditions, the reaction proceeded to give **97h** in 24% yield and by repeating it with 3.3 equiv of *o*-NsN=IPh, an increase in product yield to 46% was found (Table 3.2, entry 8). In both instances, only a single diastereomer was isolated. In contrast, extending the alkyl chain of the R³ group, as in diethyl acetylglutarate **96i**, no reaction was observed based on TLC and ¹H NMR analysis of the crude mixture (Table 3.2, entry 9). We postulated the presence of an acyl group at R³ position may be crucial for the reaction to take place.

Intrigued by the reactivity of diethyl acetylsuccinate **96h**, a further attempt to optimize the reaction conditions was undertaken (Table 3.3). We chose tricarbonyl compound **96h** as the model substrate and subjected it to a variety of reaction conditions. Repeating the reaction in the presence of 20 mol % of DBU with 2.2 equiv of *o*-NsN=IPh in dichloromethane in place of acetonitrile afforded the desired aziridine **97h** in a low yield of 31% (Table 3.3, entry 1). Interestingly, changing the base from DBU to K₂CO₃ and Cs₂CO₃ gave product yields of 52% and 34%, respectively (Table 3.3, entries 2 and 3). A screening of various solvents showed EtOAc, THF and toluene, gave low product yields of 18–31% (Table 3.3, entries 4–6). When hexane or methanol was employed as solvent, no reaction was observed for both instances (Table 3.3, entries 7 and 8). Increasing the iminoiodane loading to 3 equiv gave a product yield of 48% (Table 3.3, entry 9). Lastly, conducting the reaction at reflux temperature in dichloromethane furnished **97h** in a yield of 61% and this was deemed as providing the optimum reaction conditions for the aziridination of 2-acyl-1,4-dicarbonyl compounds (Table 3.3, entry 10).

Table 3.3 Optimization studies for base-mediated aziridination of 2-acyl-1,4-dicarbonyl compounds^a

Entry	<i>o</i> -NsN=IPh loading (eq)	Base (mol %)	Solvent	Temp (°C)	Yield (%) ^b
1	2.2	DBU (20)	CH ₂ Cl ₂	rt	31
2	2.2	K ₂ CO ₃ (110)	CH ₂ Cl ₂	rt	52
3	2.2	Cs ₂ CO ₃ (110)	CH ₂ Cl ₂	rt	34
4	2.2	K ₂ CO ₃ (110)	EtOAc	rt	31
5	2.2	K ₂ CO ₃ (110)	THF	rt	18
6	2.2	K ₂ CO ₃ (110)	Toluene	rt	25
7	2.2	K ₂ CO ₃ (110)	Hexane	rt	-
8	2.2	K ₂ CO ₃ (110)	MeOH	rt	-
9	3	K ₂ CO ₃ (110)	CH ₂ Cl ₂	rt	48
10	3	K₂CO₃ (110)	CH₂Cl₂	40	61^c

^aAll reactions were performed at 0.4 mmol of 2-acyl-1,4-dicarbonyl compounds in 2 mL of solvent. ^bYield was determined by ¹H NMR analysis of the crude mixture with CH₂Br₂ as internal standard. ^cIsolated yield.

We then continued our studies by screening several 2-acyl-1,4-dicarbonyl compounds and the results are presented in Table 3.4. Changing to substrate with benzoyl moiety at the R³ position, as in ethyl 2-acetyl-4-oxo-4-phenylbutanoate **96j**,

Table 3.4 Substrate scope for base-mediated aziridination of 2-acyl-1,4-dicarbonyl compounds^a

Entry	Substrate	Product	Yield (%) ^b
1	<p>96h</p>	<p>97h</p>	61
2	<p>96j</p>	<p>97j</p>	37
3	<p>96k</p>	<p>97k</p>	- ^c
4	<p>96l</p>	<p>97l</p>	58
5	<p>96m</p>	<p>97m</p>	56

Table 3.4 (continued)

Entry	Substrate	Product	Yield (%) ^b
6	96n	97n	50
7	96o	97o	41
8	96p	97p	45

^aAll reactions were performed at 0.4 mmol scale of with molar ratio of **1**:K₂CO₃:*o*-NsN=IPh = 1:1.1:3 in 2 mL of CH₂Cl₂ for 18 h at 40 °C. ^bIsolated yield.

^cUnidentified decomposition observed based on TLC and ¹H NMR analysis of the crude mixture.

gave aziridine **97j** in 37% yield as a single diastereomer (Table 3.4, entry 2). However, utilizing the tricarbonyl compound **96k** resulted in no product formation (Table 3.4, entry 3). The reaction proceeded well by changing to substrates with R¹ and R² group containing a carboxylate group **96l** and **96m**, furnishing the corresponding adducts **97l**

and **97m** in 58 and 56% yield (Table 3.4, entries 4–5). The steric effect of the alkyl chain of the malonate group in the substrate was found to have minimal effect on the reaction outcome. To further confirm the structure of the product, single X-Ray crystal analysis of compound **97m** was performed and the ORTEP drawing is illustrated in Figure 3.1. The new two C–N bonds were formed at α -carbon of 1,3-dicarbonyl group and the subsequent carbon atom.

Figure 3.1 ORTEP drawings of **97m** with thermal ellipsoids at 50% probability level

We then examined the effect of the electronic properties of the aryl group at R³ of the substrate. To our delight, the reactions with **96n**, having a benzoyl group containing electron donating group and **96o**, having a electron withdrawing group provided the aziridines **97n** and **97o** in yields of 41 and 50%, respectively (Table 3.4, entries 6 and 7). Lastly, triethyl 1,1,2-ethanetricarboxylate **96p** was used as starting material and demonstrated to afford the α,α,β -triacylaziridine product **97p** in 45% yield (Table 3.4, entry 8).

To gain an insight into the mechanism on this transformation, a number of control reactions were conducted. The α,β -unsaturated-1,3-dicarbonyl compound **98a** isolated during the optimization studies was tested under several different reaction conditions (Scheme 3.3). Initially, treatment of **98a** with 1.1 equiv *o*-NsN=IPh

afforded the aziridine **97a** in 20% yield (Scheme 3.3, eq 1.). It was believed that the *o*-NsN=IPh might decompose to *o*-NsNH₂ and PhI during the reaction and the former could promote the product formation along with *o*-NsN=IPh.

Scheme 3.3 Control reactions with α,β -unsaturated-1,3-dicarbonyl compound **98a**

To confirm the above hypothesis, we repeated the reaction with *o*-NsNH₂ instead of *o*-NsN=IPh and the reaction gave the α -acyl- β -aminoester **99a** in low yield of 27% (Scheme 3.3, eq 2). When the combination of both 1.1 equiv of the *o*-NsN=IPh and *o*-NsNH₂ was used, the reaction with **98a** furnished the corresponding aziridine in 79% yield (Scheme 3.3, eq 3). These results support that the formation of the product could occur via iminoiodane-mediated Michael-initiated ring closure

(MIRC). Lastly, conducting the reaction in the absence of base gave complete recovery of starting material (Scheme 3.3, eq 4).

On the basis of these results, the proposed mechanism for the base-mediated aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds is illustrated in Scheme 3.4. Firstly, the base-promoted tautomerization of 1,3-dicarbonyl compound **96** proceeds and the resulting enol might undergo nucleophilic attack onto the iodine centre of the iminoiodane to give the putative intermediate **B** species.⁹⁹ This would then undergo β -hydrogen abstraction to afford intermediate **98** along with the release of *o*-NsNH₂ and PhI. The iminoiodane-mediated MIRC proceeds subsequently. The addition of *o*-NsNH₂ onto the α,β -unsaturated moiety of **98** followed by a second nucleophilic addition step involving a molecule of *o*-NsN=IPh would lead to **C**. Reductive elimination would give the diamino intermediate **D**. This intermediate might be susceptible to ring closure to furnish the aziridine product **90** along with the elimination of one molecule of *o*-NsNH₂. From the results obtained during the

Scheme 3.4 Proposed mechanism of base-mediated aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds **96**

substrate scope studies, we proposed that the iminoiodane-mediated MIRC could be the rate determining step as additional acyl group at R³ position promotes the reaction by reducing the electron density of the alkene moiety of the α,β -unsaturated-1,3-dicarbonyl compound **98**.¹⁰⁹

3.3 Conclusion

The transition metal-free aziridination of 2-alkyl substituted-1,3-dicarbonyl compounds to access α,α -diacylaziridines and α,α,β -triacylaziridines was developed. This simple and straightforward protocol of the present methodology provides the ease of accessing such compounds without the need for inert reaction conditions. However, the scope of this method is limited to malonates and 2-acylsuccinate derivatives.

Chapter IV. Iminoiodane- and Brønsted Base-Mediated Cross Dehydrogenative Coupling of Cyclic Ethers with 1,3-Dicarbonyl Compounds

4.1 Introduction

In the recent years, the field of green and sustainable organic synthesis has gained immense amount of attention, owing to increased demands over the impact of present chemical methods and processes on the living environment.¹¹⁰ In this regard, the activation of the C–H bonds for the C–C bond forming transformations in the cross dehydrogenative coupling (CDC) reactions has emerged as one of the most powerful and atom-economical methods in modern organic chemistry.¹¹¹ A number of transition metal salts, such as Pd, Rh, Ru and Cu, in the presence of an oxidant, have often been utilized to effect these transformations at benzylic, aryl, and alkyl C(sp³)–H positions.^{112,113} In the case of the latter, the CDC reactions at the α -C–H bond of the heteroatom in ethers, amines and sulfides with carbon nucleophiles have been documented to be mediated by Fe or Cu salts as the catalyst.^{114,115} More recently, numerous developments of these reactions mediated by non-metal based catalysts has come under increasing scrutiny.^{116,117} In the presence of an oxidant such as a peroxide, DDQ, TEMPO, dioxygen or hypervalent iodide reagent, a variety of carbon nucleophiles were shown to functionalize the α -carbon position of the heteroatom in amines and ethers.^{118,119} As part of our work in the chemistry of iminoiodanes, we speculated that this class of iodine(III) compounds could mediate the α -functionalization of cyclic ethers by a carbon nucleophile under basic conditions. In doing so, we disclosed that THF, 2-methyl tetrahydrofuran and THP undergo α -C–H bond amination by PhI=NTs in Scheme 4.1.¹²⁰ This was followed by substitution at the amination carbon center by 1,3-dicarbonyl compounds under the basic conditions.

Herein, we report the chemistry that provides access to 2-tetrahydrofuran and -pyran substituted 1,3-dicarbonyl compounds in up to 80% yield over two steps.

Scheme 4.1 Iminoiodane- and base-mediated cross dehydrogenative coupling of cyclic ethers with 1,3-dicarbonyl compounds.

4.2 Results and Discussion

Our investigations began with the *in situ* generation of 2-tosylaminotetrahydrofuran from THF **100a** and PhI=NTs, which was obtained in 90% yield, based on ^1H NMR measurements.⁸⁹ Subsequently, treatment with 3 equiv of ethyl benzoylacetate **61a** and 10 mol % of DBU as the catalyst in THF at room temperature for 18 h gave ethyl 3-oxo-3-phenyl-2-(tetrahydrofuran-2-yl)propanoate **102a** in 41% yield with 1.3:1 dr (Table 4.1, entry 1). Changing the solvent from THF to diethyl ether in the second step gave a comparable product yield of 54% (Table 4.1, entry 2). Our subsequent studies found that the use of dichloromethane and toluene in place of THF led to higher product yields of 79% and 78%, respectively (Table 4.1, entries 3 and 4). However, other bases such as triethylamine, DABCO and MTBD in place of DBU as the catalyst afforded lower product yields of 61% or no reaction (Table 4.1, entries 5–7). Proceeding with DBU as the base and toluene as the solvent, lowering the amount of **61a** from 3 to 2 or 1 equiv led to similar product yields of 80 and 73%, respectively (Table 4.1, entries 8 and 9). On the other hand, a lower yield of 67% was observed on decreasing the catalyst loading of DBU from 10 to 5 mol %

(Table 4.1, entry 10). From these results, the one-pot reaction of **100a** and PhI=NTs at room temperature for 50 min followed by treatment with 2 equiv of **61a** in the presence of 10 mol % of DBU catalyst in toluene at room temperature for 18 h was deemed to provide the optimal reaction conditions.

Table 4.1 Optimization of reaction conditions^a

Entry	Catalyst (mol %)	Solvent	Yield (%) ^b
1	DBU (10)	THF	41
2	DBU (10)	Et ₂ O	54 ^c
3	DBU (10)	CH ₂ Cl ₂	79
4	DBU (10)	PhMe	78
5	Et ₃ N (10)	PhMe	-
6	DABCO (10)	PhMe	-
7	MTBD (10)	PhMe	61
8^d	DBU (10)	PhMe	80
9 ^e	DBU (10)	PhMe	73 ^c
10 ^d	DBU (5)	PhMe	67

^aAll reactions were carried out under N₂ with 0.25 M of PhI=NTs in THF for 50 min followed by treatment with 3 equiv of **61a** at respective reaction conditions. ^bIsolated yield over two steps. ^cYield was determined by ¹H NMR analysis of crude mixture. ^d2 equiv of **61a** was used. ^e1 equiv of **61a** was used.

To define the generality of the present method, a variety of cyclic ethers **100** and 1,3-dicarbonyl compounds **61** were screened and the results are summarized in Table 4.2. These experiments revealed that reaction of **100a** with a range of aryl substituted β -ketoesters bearing electron-donating groups afforded the corresponding 2-substituted tetrahydrofuran **102b–d** in good yields of 40–72% (Table 4.2, entries 2–4). The β -ketoesters with a benzoyl group containing electron-withdrawing groups proceed well to afford a higher yield of the corresponding targets **102e–h** in 71–78% yield (Table 4.2, entries 5–8). Likewise, aliphatic substituted β -ketoesters were well tolerated, furnishing the corresponding adducts **102i–k** in yields of 32–63% (Table 4.2, entries 9–12). The present methodology was also applicable to dialkyl malonates to deliver the adducts **102l–o** in 42–71% yield (Table 4.2, entries 13–15). Interestingly, the adduct **102p** of THF **100a** with 2,4-pentadione was obtained in good yields of 65% (Table 4.2, entry 16). This is notable as existing transition metal-catalyzed CDC reactions of these malonates and β -diketones have been previously reported to be incompatible.^{115f}

The influence of the cyclic ether coupling partner on the outcome of the reaction was examined next. For 2-methyltetrahydrofuran **100b** and THP **100c**, the reaction of these cyclic ethers with **61a** gave the corresponding adducts **102q** and **102r** in 43% and 57% yield, respectively (Table 4.2, entries 17–18). However, no reaction was observed when either 2,3-dihydrobenzofuran **100d** or dibutyl ether **100e** was treated with **61a** under the standard conditions with PhI=NTs and DBU (Table 4.2, entries 19–20). In the case of **100e**, decomposition of the α -aminated ether intermediate was observed by both TLC and ¹H NMR analysis of the crude reaction mixture. Most of the products above are isolated in near 1:1 diastereomer ratio.

Table 4.2 Substrate scope for the iminoiodane- and base-mediated CDC of cyclic ethers **100** with 1,3-dicarbonyl compounds **61**^a

Entry	Product	Yield (%) ^b
1	102a , R = C ₆ H ₅	80
2	102b , R = <i>o</i> -MeC ₆ H ₄	59
3	102c , R = <i>p</i> -MeC ₆ H ₄	72
4	102d , R = <i>p</i> -MeOC ₆ H ₄	40
5	102e , R = <i>p</i> -IC ₆ H ₄	73
6	102f , R = <i>p</i> -BrC ₆ H ₄	78
7	102g , R = <i>p</i> -ClC ₆ H ₄	71
8	102h , R = <i>p</i> -FC ₆ H ₄	76
9	102i , R = Me	32
10	102j , R = Et	63
11	102k , R = <i>i</i> -Pr	61
12	102l , R = Me	51
13	102m , R = Et	42
14 ^c	102n , R = <i>i</i> -Pr	67
15 ^c	102o , R = Bn	71
16	102p	65

Table 4.2 (*continued*)

Entry	Product	Yield (%) ^b
17		43 ^{c,d}
18		57 ^{d,e}
19		^f
20		^g

^aAll reactions were carried out under N₂ with 0.25 M of PhI=NTs in ether **100** for 50 mins followed by treatment with 2 equiv of **61** and of 10 mol % DBU in toluene for 18 h. ^bIsolated yields over two steps. ^cReaction temperature = 40 °C. ^dIsolated yield is calculated based on the conversion of step one. ^eReaction temperature = 80 °C. ^fNo reaction observed based on TLC and ¹NMR analysis of the crude mixture. ^gDecomposition of starting material based on TLC and ¹NMR analysis of the crude mixture.

At room temperature, reaction of **100a** with diisopropyl malonate **61v** was found to give **103n** in 25% yield (Scheme 4.2). The structure of compound **103n** was

further elaborated by single crystal X-ray analysis, showing the formation C–C bond at the α -carbon of malonate **61v** with the putative ring opening intermediate as illustrated in Figure 4.1.

Scheme 4.2 Reaction of **100a** with diisopropyl malonate **61v** under optimum conditions at room temperature

Figure 4.1 ORTEP drawing for **103n** with thermal ellipsoids at 50% probability level¹²¹

The isolation of this acyclic adduct led us to suspect its possibility to be an intermediate in the α -functionalization reaction. This was further supported by re-subjecting **103n** to 10 mol % of DBU under the standard reaction conditions at 40 °C. This test gave **102n** along with a 1:1 mixture of **100a** and **61v** in 35% and 43%

yield, respectively (Scheme 4.3, eq. 1). The latter two adducts was obtained presumably due to a competitive retro-Mannich-type pathway.¹²² The role of DBU in the mediation of the cyclization of the 1,4-amino alcohol moiety was also supported by our findings showing the full recovery of the substrate on treating it to the standard conditions in the absence of the Schiff base (Scheme 4.3, eq 2).

Scheme 4.3 Control reactions using **103n**

A tentative mechanism for the present iminoidane-mediated transformation under basic conditions is illustrated in Scheme 4.4. This could initially involve formation of **101** on treating the cyclic ether **100** with the PhI=NTs. It is postulated that such conversion would proceed via direct insertion of nitrogen atom of the nitreneoid species or an oxonium intermediate described in the previous study.^{88,89} While the possible amination pathway of this step remains presently unclear, the basic conditions provided by DBU may promote ring-opening of the adduct to give the imino alcohol intermediate **E**. Nucleophilic attack at the imino carbon center of this substrate by the enolate of **61'** would deliver the amino alcohol **103**. The base-mediated deamination ensued to generate the 2-methylene β -keto ester **F**.

Subsequently, the 5-exo-trig cyclization occurred via Michael addition of the hydroxyl moiety onto the alkene bond of **F** to provide the product **102**.

Scheme 4.4 Proposed mechanism for iminoiodane- and Brønsted base-mediated cross dehydrogenative coupling of cyclic ethers with 1,3-dicarbonyl compounds

4.3 Conclusions

In summary, a mild transition metal-free cross dehydrogenative coupling (CDC) synthetic route to 2-tetrahydrofuran and -pyran substituted 1,3-carbonyl compounds from commercially available cyclic ethers and 1,3-dicarbonyl derivatives with iminoiodanes has been developed. The synthetic method was shown to tolerate β -ketoesters, dialkyl malonates and 1,3-diones and achieved in moderate to excellent yields of 32–80%. This present method complements and supplements the existing transition metal approaches and also shows the promising utility of other hypervalent iodine reagents other than diaryliodonium salts for transition metal-free CDC reactions.

Chapter V. Iminoiodane-Mediated Synthesis of 1,4-Amino Alcohols with Grignard Reagents

5.1 Introduction

The development of synthetic methodology to access valuable building blocks is a continuous pursuit in organic chemistry. A variety of nitrogen containing building blocks such as lactams, pyrrolidines, oxazoles, allylic amines and amino alcohols have been targeted due to their presence in numerous natural products and biologically active products.¹²³ In the case of the latter, amino alcohol derivatives have often been targeted as they are a privileged structure and can also serve as ligands for numerous types of catalysts.¹²⁴ The amino alcohols have typically been synthesized from epoxides or aziridines ring opening, aminohydroxylation of alkenes, as well as methods requiring one or more steps.¹²⁵ However, methods for the direct installation of amino group for the synthesis of 1,4-amino alcohols are sparse and only a handful of strategies are known.¹²⁶ Herein, we disclose our findings on the transition metal-free synthesis of *N*-tosylamino alcohols from the reaction of tetrahydrofuran with PhI=NTs followed by Grignard addition under mild reaction conditions in a one pot manner (Scheme 5.1, eq 1). In a number of examples, the formation of the detosylation product leading to the free amino alcohol was also observed. The synthetic utility of this class of compounds was demonstrated by the synthesis of γ -lactams and pyrrolidines in one step (Scheme 5.1, eq 2).

Scheme 5.1 Iminoiodane-mediated synthesis of 1,4-amino alcohols with Grignard reagents

5.2 Results and Discussion

An initial study shows the treatment of THF with PhI=NTs at room temperature for 50 min followed by the addition of 3 equiv of phenylmagnesium bromide, furnished the *N*-tosylamino alcohol product **104a** in 43% yield (Table 5.1, entry 1). Increasing the amount of the Grignard reagent to 5 equiv gave the desired product in a higher yield of 86% (Table 5.1, entry 2). Subsequently, the scope and limitation of the present method was established by screening various Grignard reagents. When *o*-tolylmagnesium bromide was used in place of phenylmagnesium bromide, the *N*-tosylamino alcohol **104b** was furnished in 72% yield (Table 5.1, entry 3).

Further exploration on the substrate scope revealed that alkyl Grignard reagents were well tolerated and afforded the corresponding products **104c–e** in good to excellent yields of 68–88% (Table 5.1, entries 4–6). The use of a bulky Grignard reagent bearing β -hydrogen on the alkyl group, such as isobutylmagnesium bromide, was found to give the *N*-tosylamino alcohol **104f** in 42% yield due to a possible competitive reduction of the imine intermediate based on TLC and ^1H NMR analysis

of the crude mixture (Table 5.1, entry 7). Repeating the reaction with 5 mol % of copper(I) or copper(II) triflate as the catalyst could overcome this shortcoming, increasing the desired ring opening product yield to 82% (Table 5.1, entry 8). Similarly, when *n*-pentyl and cyclopentylmagnesium bromide were used, the use of the copper catalyst was required to obtain good product yields of 71% and 72% for **104g** and **104h**, respectively (Table 5.1, entries 9 and 10). Several alkenyl and alkynyl Grignard reagents were also tested and found to give the corresponding *N*-tosylamino alcohol products **104i–k** in 66–72% yield (Table 5.1, entries 11–13). The use of Grignard reagents such as 2-methylprop-1-enylmagnesium bromide with the absence of β -hydrogen on the alkyl group led to the formation desired product **104j** in a high yield of 72% without the aid of copper(I) catalyst (Table 5.1, entry 12).

Table 5.1. Substrate Scope^a

Entry	Grignard reagent (equiv)	Product	Yield (%) ^b
1	R = Ph (3)	104a	43
2	R = Ph (5)	104a	86
3	R = <i>o</i> -Tol (5)	104b	72
4	R = Me (5)	104c	88
5	R = Et (5)	104d	68
6	R = Allyl (5)	104e	86
7	R = <i>i</i> -Bu (5)	104f	42 ^c
8 ^d	R = <i>i</i> -Bu (5)	104f	82

Table 5.1 (*continued*)

Entry	Grignard reagent (equiv)	Product	Yield (%) ^b
9 ^d	R = Pent (5)	104g	71
10 ^d	R = <i>c</i> -Pent (5)	104h	72
11	R = 2-Prop-1-enyl (5)	104i	66
12	R = 2-Methylprop-1-enyl (5)	104j	72
13	R = Propynyl (5)	104k	66
14	R = <i>c</i> -Pr (5)	104l + 105l	29 (33)
15	R = <i>p</i> -MeOC ₆ H ₄ (5)	104m + 105m	62 (33)
16	R = <i>p</i> -ClC ₆ H ₄ (5)	104n + 105n	28 (59)
17	R = <i>m</i> -CF ₃ C ₆ H ₄ (5)	105o	- (44)
18	R = 3,5-Xylyl (5)	105p	- (62)
19	R = 2,6-Xylyl (5)	104q	- ^e
20	R = Mes	104r	- ^e
21	R = 1-Naphthalyl (5)	105s	- (85)

^aAll reactions were carried out under N₂ atmosphere with 0.50 mmol scale of PhI=NTs. ^bIsolated yield, yield of **105** are shown in parentheses. ^cMeerwein-Ponndorf-Verley reduction product was observed based on TLC and ¹H NMR analysis of the crude mixture. ^dReaction was performed in the presence of 5 mol % of CuOTf/Cu(OTf)₂ as catalyst. ^eNo reaction based on TLC and ¹H NMR analysis of the crude mixture.

Surprisingly, the addition of cyclopropylmagnesium bromide furnished the *N*-tosylamino alcohol **104l** in a low yield of 29%, along with the amino alcohol **105l** in 33% yield (Table 5.1, entry 14). This detosylation was also observed with other aryl magnesium bromide reagents such as *p*-methoxyphenyl and

p-chlorophenylmagnesium bromide, which were found to give the corresponding *N*-tosylamino alcohols **104m** and **104n** in 62 and 28% yield and the amino alcohols **105m** and **105n** in 33 and 59% yield, respectively (Table 5.1, entries 15 and 16). Interestingly, when an electron-withdrawing group or electron-donating group was present at the meta-position of the aryl ring, the amino alcohols **105o** and **105p** were isolated as the sole product in 44 and 62% yields, respectively (Table 5.1, entries 17 and 18). The use of bulky 2,6-xylyl and mesitylmagnesium bromide failed to furnish the product, presumably due to the steric hindrance introduced by the two *ortho* methyl groups on the phenyl ring. Lastly, the addition of 1-naphthylmagnesium bromide gave the amino alcohol **105s** in 85% yield (Table 5.1, entries 19–21).

Next, the synthetic utility of the 1,4-amino alcohols obtained via the present protocol was examined. First, oxidative cyclization of *N*-tosylamino alcohol **104a** in the presence of 5 equiv of pyridinium dichromate in dimethylformamide at ambient temperature was demonstrated to give the γ -lactam **106a** in 75% yield (Scheme 5.2, eq 1). The synthesis of *N*-tosylpyrrolidine **107f** was also shown by treating *N*-tosylamino alcohol **104f** via Mitsunobu reaction conditions with 1.2 equiv of diisopropyl-azodicarboxylate and triphenylphosphine to furnish the desired product in 89% yield (Scheme 5.2, eq 2)

Scheme 5.2 Examples on further transformation of *N*-tosylamino alcohol

Due to the intriguing outcome of this reaction, we subsequently sought to investigate the mechanism of the detosylation of the product. Repeating the reaction with 7 equiv of phenylmagnesium bromide gave the desired *N*-tosylamino alcohol **104a** in 40% yield and the amino alcohol **105a** in the yield of 49% (Scheme 5.3).

Scheme 5.3 Mechanistic study on the equivalent of the Grignard reagent

A possible mechanism for the present 1,4-amino alcohol forming reaction is depicted in Scheme 5.4. The amination of THF could proceed in a related manner to that discussed in Chapter IV. The resulting 2-aminated tetrahydrofuran **101a** might subsequently undergo ring opening in the presence of the Grignard reagent to give the imine **E**. In the examples when copper(I) salt was added to the reaction mixture, transmetallation would occur to form the organocuprate reagent *in situ*. The nucleophilic addition by another molecule of the Grignard reagent or organocuprate species onto the imine would afford the *N*-tosylamino alcohol product **104**. The *N*-tosylamino alcohol could also undergo a radical detosylation furnishing the corresponding amino alcohol **105**, which governed by radical anion stability of the Grignard reagent. We proposed that the cleavage of the sulfonyl group could be due to the radical nature of Grignard reagent.¹²⁷ This is consistent with the results obtained on hand as shown in Table 5.1, entries 15–18 and 21. There are numerous publications on the discussion of cyclopropyl radical which was observed to be stabilized by the equilibration of its configuration.¹²⁸ On the other hand, the reaction conducted in the presence of substituted aryl Grignard reagent gave the amino alcohol

as major product in most of the examples. Due to the electronic effect on such arylmagnesium bromide reagents, the radical species might be responsible for the cleavage of the *p*-toluenesulfonyl moiety.

Scheme 5.4 Proposed mechanism for the iminoiodane-mediated synthesis of 1,4-amino alcohols with Grignard reagents

On the basis of the proposed mechanism illustrated on Scheme 5.4, it was rationalized that the addition of the Grignard reagent onto the imine could be performed asymmetrically with the aid of a chiral copper complex.¹²⁹ With this in mind, we then pursued the enantioselective version of this transformation in the presence of copper(I) salt and chiral ligand (Table 5.2). The reaction was initially conducted by treating the *in situ* generated 2-tosylamino substituted THF with 5 equiv of isobutyl magnesium bromide in the presence of 5 mol % of copper(I) triflate and 6 mol % of **PN-1**, **PN-2**, or **PN-3** as the ligand in diethyl ether as solvent, however only the reaction with ligand **PN-1** gave the product with an ee value of 3% (Table 5.2, entries 1–3). This suggested that the enantioselectivity of the product could be governed by the substituent of the bis(ethylphenyl) group at the nitrogen atom.

Table 5.2. Optimization study for the enantioselective ring opening with Grignard reagent^a

Entry	Catalyst (mol %)	Ligand (mol %)	<i>i</i> -BuMgBr (equiv)	Solvent	ee (%)
1	(CuOTf) ₂ .PhMe (5)	PN-1 (6)	5	Et ₂ O	3
2	(CuOTf) ₂ .PhMe (5)	PN-2 (6)	5	Et ₂ O	0
3	(CuOTf) ₂ .PhMe (5)	PN-3 (6)	5	Et ₂ O	0
4	Cu(OTf) ₂ (5)	PN-1 (6)	5	Et ₂ O	5
5	Cu(OTf) ₂ (5)	PN-1 (6)	5	PhMe	11
6	Cu(OTf) ₂ (5)	PN-1 (6)	5	MTBE	11
7 ^b	Cu(OTf) ₂ (5)	PN-1 (6)	5	PhMe	4
8	Cu(OTf) ₂ (5)	PN-1 (10)	5	PhMe	19
9	Cu(OTf) ₂ (5)	PN-1 (15)	5	PhMe	16
10	Cu(OTf) ₂ (10)	PN-1 (20)	5	PhMe	28
11	Cu(OTf) ₂ (5)	PN-1 (10)	3	PhMe	25

Table 5.2 (*continued*)

Entry	Catalyst (mol %)	Ligand (mol %)	<i>i</i> -BuMgBr (equiv)	Solvent	ee (%)
12	Cu(OTf) ₂ (5)	PN-1 (10)	3	MTBE	31
13	Cu(OTf) ₂ (5)	PN-4 (10)	3	MTBE	ND ^c
14	Cu(OTf) ₂ (5)	PN-5 (10)	3	MTBE	ND ^c
15	Cu(OTf) ₂ (2)	PN-1 (4)	5	MTBE	19
16	Cu(OTf) ₂ (10)	PN-1 (20)	3	MTBE	39

^aAll reactions were carried out under N₂ atmosphere for 18 h. ^bThe reaction was conducted at 0 °C. ^cNo reaction based on TLC analysis of the crude mixture.

Changing the copper catalyst to copper(II) triflate gave a slight improvement in product ee value of 5% (Table 5.2, entry 4). Using the copper(II) triflate and ligand **PN-1** combination, changing the solvent to toluene and MTBE furnished the product with an ee value of 11% for both instances (Table 5.2, entries 5 and 6). Previous studies have shown the Grignard reagent species in such solvents would be R₂Mg instead of RMgX based on the Schlenk equilibrium (Scheme 5.5).¹³⁰ We postulated that the R₂Mg species, which could be less reactive than RMgX for addition reaction, to be responsible in the transmetallation onto copper catalyst.

Scheme 5.5 Schlenk equilibrium of Grignard reagents

Decreasing the reaction temperature to 0 °C gave a low product conversion along with a reduced ee value to 4% (Table 5.2, entry 7). We then proceeded to examine the effect of catalyst and ligand loading with toluene as the solvent.

Increasing the ligand loading from 6 mol % to 10 mol % and 20 mol % gave an increase in product ee value to 19% and 16% (Table 5.2, entries 8 and 9). This result indicated that the active catalyst complex requires two molecules of the ligand to induce the best result. Similarly, increasing the catalyst loading to 10 mol % and the ligand to 20 mol % afforded the product with an ee value of 28% (Table 5.2, entries 10 and 11). Repeating the reaction with 3 equiv of isobutylmagnesium bromide in the presence of 5 mol % of the copper(II) triflate and 10 mol % of the ligand in toluene and MTBE gave the amino alcohol with ee values of 25% and 31%, respectively (Table 5.2, entries 12 and 13). Encouraged by these results, other ligands such as ligand **PN-4** and **PN-5** were screened, but no reaction was observed based on TLC analysis (Table 5.2, entries 14 and 15). The use of 2 mol % of copper(II) triflate and 4 mol % of the **PN-1** gave a product ee value of 19% (Table 5.2, entry 16). Increasing the catalyst and ligand loading to 10 mol % and 20 mol %, respectively, afforded the product with an ee value of 39% (Table 5.2, entry 17).

5.3 Conclusion

In conclusion, we have developed a protocol to synthesize *N*-tosylamino alcohols from tetrahydrofuran with PhI=NTs and Grignard reagents. Good to excellent product yields were realized under mild reaction conditions. Serendipitous findings on the removal of the sulfonyl group provided a convenient approach to obtain amino alcohols. Two transformations of the amino alcohol to their respective γ -lactam and 2-substituted pyrrolidine derivatives were achieved in good yields. Further explorations on the enantioselective study of the present method are currently ongoing.

Chapter VI. Experimental Section

6.1 General Consideration

All reactions were performed under a nitrogen atmosphere unless otherwise stated. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. PhI=NTs, PhI=NNs, and *o*-NsN=IPh were synthesized following literature procedure.⁵ Solvents are distilled prior to use according to literature procedure; CH₂Cl₂ and MeCN were distilled over CaH₂; PhMe, diethyl ether, and THF were distilled over Na/benzophenone. Molecular sieves were dried under vacuum at 200 °C and stored under N₂.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plates. Visualization was achieved by UV–vis light (254 nm) followed by staining with ninhydrin or KMnO₄ and heating. Flash chromatography was performed using silica gel and gradient solvent system (eluent: *n*-hexane:EtOAc).

¹H and ¹³C NMR spectra were measured on Bruker Avance 300 and 400 MHz spectrometers. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) 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.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FTIR spectrometer. All samples were examined as a thin film between NaCl salt plates. Solid samples were examined as a thin film between NaCl salt plates using dichloromethane as the solvent. Low resolution mass spectra (LCMS) were determined on a Finnigan LCQ XP MAX mass spectrometer. High resolution mass

spectra (HRMS) were obtained using a Q-Tof Premier LC/HRMS mass spectrometer using simultaneous electrospray (ESI). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter.

6.2 Brønsted Acid-Catalyzed Amination of 1,3-Dicarbonyl Compounds by Iminoiodanes

General Procedures for the Amination of 1,3-Dicarbonyl Compounds **61a–t**^{121a}

To a degassed mixture of PhI=NTs (0.6 mmol, 224 mg) and powdered 4 Å molecular sieves (240 mg) was added dichloromethane (1 mL). The reaction was then cooled to 0 °C and solution of trifluoroacetic acid (0.05 mmol, 3.83 μL) in dichloromethane (1 mL) was added. Successively, 1,3-dicarbonyl compounds **61** (0.5 mmol) was added and the reactions was monitored by TLC. Upon the full consumption of **61**, the reaction was filtered, washed with EtOAc and concentrated under reduced pressure to afford the crude mixture. The latter was then purified by flash chromatography (eluent: *n*-hexane/EtOAc, 4:1) to furnish the title compound.

General Procedures for the Competitive Studies on Amination of 1,3-Dicarbonyl Compounds **61d,e,g–i**^{121a}

A solution of trifluoroacetic acid (0.01 mmol, 0.766 μL) in CD_2Cl_2 (0.2 mL) was added to PhI=NTs (0.12 mmol, 44.8 mg) in NMR tube. The mixture was then cooled to 0 °C. A solution of ethyl 3-oxo-3-phenylpropanoate (0.1 mmol, 19 μL) and substituted ethyl 3-oxo-3-phenylpropanoate (0.1 mmol) in CD_2Cl_2 (0.2 mL) was added and shaken. The reaction mixture was then directly analysed by ^1H NMR spectroscopy.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-phenylpropanoate 62a^{50,98}

Yield 86%; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 7.4 Hz, Ar H, 2H), 7.73 (d, *J* = 8.3 Hz, Ar H, 2H), 7.62 (t, *J* = 7.4 Hz, Ar H, 1H), 7.47 (t, *J* = 7.7 Hz, Ar H, 2H), 7.24 (d, *J* = 8.1 Hz, Ar H, 2H), 6.00 (d, *J* = 8.9 Hz, -CHNHTs, 1H), 5.58 (d, *J* = 8.9 Hz, -CHNHTs, 1H), 3.97 (q, *J* = 7.1 Hz, -OCH₂CH₃, 2H), 2.38 (s, ArCH₃, 3H), 1.04 (t, *J* = 7.1 Hz, -OCH₂CH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 190.2, 165.9, 144.1, 144.0, 136.6, 134.7, 129.8, 129.5, 128.9, 127.4, 62.6, 60.9, 21.6, 13.8.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-*p*-tolylpropanoate 62b^{50,98}

Yield 84%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 8.3 Hz, Ar H, 2H), 7.72 (d, *J* = 8.3 Hz, Ar H, 2H), 7.28–7.23 (m, Ar H, 4H), 6.80 (d, *J* = 8.9 Hz, -CHNHTs, 1H), 5.52 (d, *J* = 8.9 Hz, -CHNHTs, 1H), 4.12–3.92 (m, -OCH₂CH₃, 2H), 2.42 (s, ArCH₃, 3H), 2.38 (s, ArCH₃, 3H), 1.05 (t, *J* = 7.1 Hz, -OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 189.0, 166.1, 145.9, 143.9, 137.0, 132.0, 129.7, 129.5, 127.3, 62.6, 60.8, 21.8, 21.5, 13.7.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxo-3-*m*-tolylpropanoate 62c^{50,98}

Yield 84%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 7.3 Hz, Ar H, 2H), 7.73 (d, J = 8.2 Hz, Ar H, 2H), 7.44–7.32 (m, Ar H, 2H), 7.23 (d, J = 8.1 Hz, Ar H, 2H), 6.05 (d, J = 8.9 Hz, –CHNHTs, 1H), 5.58 (d, J = 8.9 Hz, –CHNHTs, 1H), 4.00–3.93 (m, –OCH₂CH₃, 2H), 2.40 (s, ArCH₃, 3H), 2.38 (s, ArCH₃, 3H), 1.05 (t, J = 7.1 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 190.2, 166.1, 144.0, 138.8, 136.6, 135.4, 133.5, 129.8, 129.7, 128.7, 127.3, 126.6, 62.6, 60.9, 21.5, 21.3, 13.7.

Ethyl 2-(2-methylphenylsulfonamido)-3-oxo-3-*o*-tolylpropanoate 62d^{50,98}

Yield 65%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, J = 8.7 Hz, Ar H, 2H), 7.34 (m, Ar H, 2H), 7.27–7.22 (m, Ar H, 2H), 7.17–7.14 (m, Ar H, 2H), 6.10 (d, J = 8.5 Hz, –CHNHTs, 1H), 5.56 (d, J = 8.3 Hz, –CHNHTs, 1H), 4.00–3.90 (m, –OCH₂CH₃, 2H), 2.41 (m, ArCH₃, 3H), 2.37 (m, ArCH₃, 3H), 1.13 (t, J = 7.2 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 192.7, 176.2, 171.4, 166.0, 143.9, 142.9, 139.9, 137.2, 136.6, 133.7, 132.7, 132.1, 129.7, 129.6, 129.1, 127.3, 127.1, 125.8, 125.0, 100.9, 62.5, 61.6, 60.4, 21.4, 21.1, 19.8, 14.2, 13.8, 13.6.

Ethyl 3-(4-methoxyphenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate
62e^{50,98}

Yield 63%; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, *J* = 9.2 Hz, Ar H, 2H), 7.73 (d, *J* = 8.2 Hz, Ar H, 2H), 7.24 (d, *J* = 7.8 Hz, Ar H, 2H), 6.94 (d, *J* = 9.2 Hz, Ar H, 2H), 6.07 (d, *J* = 8.7 Hz, –CHNHTs, 1H), 5.55 (d, *J* = 8.7 Hz, –CHNHTs, 1H), 3.96 (q, *J* = 4.6 Hz, –OCH₂CH₃, 2H), 3.88 (s, ArOCH₃, 3H), 2.38 (s, ArCH₃, 3H), 1.05 (t, *J* = 7.1 Hz, –OCH₂CH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3, 166.4, 164.8, 144.0, 136.7, 132.0, 127.4, 126.4, 114.2, 62.6, 60.7, 55.7, 21.6, 13.8.

Ethyl 3-(4-iodophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate 62f^{50,98}

Yield 53%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, *J* = 8.6 Hz, Ar H, 2H), 7.72–7.67 (m, Ar H, 4H), 7.25 (d, *J* = 8.1 Hz, Ar H, 2H), 6.00 (d, *J* = 9.0 Hz, –CHNHTs, 1H), 5.52 (d, *J* = 9.0 Hz, –CHNHTs, 1H), 4.02–3.91 (m, –OCH₂CH₃, 2H), 2.39 (s, ArCH₃, 3H), 1.05 (t, *J* = 7.1 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 189.8, 165.8, 144.1, 138.2, 136.4, 132.7, 130.5, 129.7, 127.3, 103.2, 62.8, 60.8, 21.5, 13.7.

Ethyl 3-(4-chlorophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate**62g**^{50,98}

Yield 65%; white solid; keto:enol ratio = 8:2; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, J = 6.4 Hz, Ar H, 2H), 7.95 (d, J = 8.7 Hz, Ar H, 2H), 7.72 (d, J = 8.1 Hz, Ar H, 4H), 7.45 (d, J = 8.5 Hz, Ar H, 2H), 7.25 (d, J = 8.7 Hz, Ar H, 4H), 7.09 (d, J = 8.1 Hz, Ar H, 4H), 5.98 (d, J = 6.0 Hz, $-\text{CHNHTs}$, 1H), 5.53 (d, J = 9.0 Hz, $-\text{CHNHTs}$, 1H), 5.32, (s, $=\text{CNHTs}$, 1H), 4.22, (q, J = 7.2 Hz, $-\text{OCH}_2\text{CH}_3$, 2H), 4.03–3.91 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 2.39 (s, ArCH₃, 6H), 1.13–1.04 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 189.3, 165.9, 144.1, 141.3, 136.4, 131.8, 130.7, 129.7, 129.2, 127.3, 62.8, 60.9, 21.5, 13.7.

Ethyl 3-(4-bromophenyl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate**62h**^{50,98}

Yield 60%; white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, J = 7.2 Hz, Ar H, 2H), 7.72 (d, J = 8.3 Hz, Ar H, 2H), 7.62 (d, J = 8.7 Hz, Ar H, 2H), 7.25 (d, J = 8.2 Hz, Ar H, 2H), 5.96 (d, J = 8.7 Hz, $-\text{CHNHTs}$, 1H), 5.52 (d, J = 8.7 Hz, $-\text{CHNHTs}$, 1H), 4.02–3.93 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 2.39 (s, ArCH₃, 3H), 1.05 (t, J = 7.2 Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 189.6, 165.9, 144.2, 136.5, 132.3, 130.9, 130.2, 129.8, 127.4, 62.9, 60.9, 21.6, 13.8.

Ethyl 3-(4-fluorophenyl)-2-(4-methylphenylsulfonamido)-3-oxo-propanoate
62i^{50,98}

Yield 58%; white solid; ¹H NMR (400 MHz, CDCl₃) δ 8.08–8.03 (m, Ar H, 2H), 7.73 (d, *J* = 8.2 Hz, Ar H, 2H), 7.25 (d, *J* = 8.2 Hz, Ar H, 2H), 7.18–7.12 (m, Ar H, 2H), 6.02 (d, *J* = 8.7 Hz, –CHNHTs, 1H), 5.55 (d, *J* = 8.7 Hz, –CHNHTs, 1H), 4.01–3.93 (m, –OCH₂CH₃, 2H), 2.39 (s, ArCH₃, 3H), 1.05 (t, *J* = 7.3 Hz, –OCH₂CH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.8, 166.0, 144.2, 136.5, 132.4, 132.3, 129.8, 127.4, 116.3, 116.1, 62.8, 60.9, 21.6, 13.8.

Ethyl 3-(furan-3-yl)-2-(4-methylphenylsulfonamido)-3-oxopropanoate **62j**^{50,98}

Yield 41%; brown solid; keto:enol ratio = 6:4; ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, *J* = 8.4 Hz, Ar H, 2H), 7.82 (d, *J* = 8.4 Hz, Ar H, 2H), 7.74–7.69 (m, Ar H, 3H), 7.47–7.44 (m, Ar H, 2H), 7.36–7.24 (m, Ar H, 3H), 7.11 (t, *J* = 7.7 Hz, Ar H, 2H), 5.91 (m, –CHNHTs, 1H), 5.53 (d, *J* = 9.0 Hz, –CHNHTs, 1H), 4.93 (s, =CNHTs, 1H), 4.09–3.95 (m, –OCH₂CH₃, 2H), 2.43 (s, ArCH₃, 3H), 2.39 (s, ArCH₃, 3H), 1.06 (t, *J* = 7.2 Hz, –OCH₂CH₃, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 184.2, 166.0, 149.9, 147.6, 144.4, 144.1, 142.8, 136.3, 129.7, 129.4, 127.6, 127.3, 124.3, 110.2, 108.9, 62.8, 62.8, 61.2, 29.7, 21.5, 21.5, 13.7, 13.6.

(E)-methyl 3-hydroxy-2-(4-methylphenylsulfonamido)but-2-enoate 62k^{50,98}

Yield 27%; white solid; ^1H NMR (300 MHz, CDCl_3) δ 12.31 (s, =COH, 1H), 7.67 (d, J = 8.1 Hz, Ar H, 2H), 7.29 (d, J = 9.0 Hz, Ar H, 2H), 5.62 (s, =CNHTs, 1H), 3.19 (s, $-\text{OCH}_3$, 3H), 2.42 (s, ArCH_3 , 3H), 2.23 (s, $-\text{COCH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 179.7, 170.0, 143.6, 136.5, 129.8, 129.3, 127.6, 127.2, 99.9, 51.3, 21.5, 18.9.

Ethyl 2-(4-methylphenylsulfonamido)-3-oxobutanoate 62l^{50,98}

Yield 73%; colourless oil; keto:enol ratio = 3:7; ^1H NMR (300 MHz, CDCl_3) δ 12.5 (s, =COH, 1H), 7.74–7.66 (m, Ar H, 4H), 7.31–7.27 (m, Ar H, 4H), 6.00–5.86 (m, $-\text{NHTs}$, 2H), 4.68 (d, J = 7.8 Hz, $-\text{CHNHTs}$, 1H), 4.07 (q, J = 6.6 Hz, $-\text{OCH}_2\text{CH}_3$, 2H), 3.68 (q, J = 6.8 Hz, $-\text{OCH}_2\text{CH}_3$, 2H), 2.41 (s, ArCH_3 , 6H), 2.26 (s, $-\text{COCH}_3$, 3H), 2.23 (s, $-\text{COCH}_3$, 3H), 1.16 (t, J = 6.8 Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 0.87 (t, J = 6.7 Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 198.1, 179.3, 169.9, 165.8, 144.1, 143.6, 136.7, 129.7, 129.4, 127.5, 127.2, 100.0, 65.2, 62.8, 60.9, 27.1, 21.5, 19.0, 13.8, 13.5.

Tert-butyl 2-(4-methylphenylsulfonamido)-3-oxobutanoate 62m^{50,98}

Yield 47%; white solid; keto:enol ratio = 4:6; ^1H NMR (300 MHz, CDCl_3) δ 12.6 (s, =COH, 1H), 7.75–7.68 (m, Ar H, 4H), 7.30 (d, J = 8.3 Hz, Ar H, 4H), 5.77 (d, J =

7.5 Hz, $-\text{CHNHTs}$, 1H), 5.63 (s, $=\text{CNHTs}$, 1H), 4.54 (d, $J = 7.7$ Hz, $-\text{CHNHTs}$, 1H), 2.42 (s, ArCH_3 , 6H), 2.28 (s, $-\text{COCH}_3$, 3H), 2.25 (m, $-\text{COCH}_3$, 3H), 1.34 (s, $-\text{C}(\text{CH}_3)_3$, 9H), 1.12 (s, $-\text{C}(\text{CH}_3)_3$, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 198.5, 164.7, 144.0, 143.6, 136.8, 136.4, 129.7, 129.6, 127.7, 127.3, 100.7, 84.2, 82.8, 77.5, 76.6, 65.7, 27.6, 27.1, 21.5, 21.4, 19.2.

Diethyl (1-(4-methylphenylsulfonamido)-2-oxo-2-phenylethyl) phosphonate 62n^{50,98}

Yield 52%; white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 8.0$ Hz, Ar H, 2H), 7.61–7.55 (m, Ar H, 2H), 7.42–7.38 (m, Ar H, 2H), 7.05 (d, $J = 8.0$ Hz, Ar H, 2H), 6.12 (d, $J = 9.9$ Hz, $-\text{CHNHTs}$, 1H), 5.34 (dd, $J = 23.5$ Hz, 9.9 Hz, $-\text{CHNHTs}$, 1H), 4.20–3.99 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 2.25 (s, ArCH_3 , 3H), 1.25 (t, $J = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 1.15 (t, $J = 7.0$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.2, 144.0, 135.7, 134.6, 134.1, 129.6, 128.9, 128.3, 127.3, 64.3 (d, $J_{\text{C-P}} = 68$ Hz), 64.2 (d, $J_{\text{C-P}} = 68$ Hz), 56.5 (d, $J_{\text{C-P}} = 194$ Hz), 21.4, 16.3 (d, $J_{\text{C-P}} = 9$ Hz), 16.0 (d, $J_{\text{C-P}} = 9$ Hz).

N-(1,3-dioxo-1,3-diphenylpropan-2-yl)-4-methylbenzenesulfonamide 62q^{50,98}

Yield 63%; white solid; ^1H NMR (300 MHz, CDCl_3) δ 7.89 (d, $J = 9.6$ Hz, Ar H, 4H), 7.65 (d, $J = 8.2$ Hz, Ar H, 2H), 7.58 (t, $J = 6.8$ Hz, Ar H, 2H), 7.42 (t, $J = 7.7$ Hz, Ar H, 4H), 7.14 (d, $J = 8.3$ Hz, Ar H, 2H), 6.25 (s, 2H), 2.33 (s, ArCH_3 , 3H);

^{13}C NMR (75 MHz, CDCl_3) δ 213.1, 191.7, 136.0, 134.4, 134.0, 129.8, 129.2, 129.0, 127.4, 63.8, 21.5.

***N*-(1,3-dioxo-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide 62r**^{50,98}

Yield 57%; yellow oil; keto:enol ratio = 1:9; ^1H NMR (300 MHz, CDCl_3) δ 16.6 (s, =COH, 1H), 8.11 (d, J = 7.5 Hz, Ar H, 2H), 7.69 (d, J = 8.2 Hz, Ar H, 4H), 7.61–7.56 (m, Ar H, 4H), 7.45–7.40 (m, Ar H, 2H), 7.31–7.11 (m, Ar H, 4H), 6.90 (d, J = 9.0 Hz, Ar H, 2H), 6.72 (s, =CNHTs, 1H), 6.46 (d, J = 6.8 Hz, –CHNHTs, 1H), 5.43 (d, J = 6.9 Hz, –CHNHTs, 1H), 2.38 (s, ArCH₃, 6H), 2.32 (s, –COCH₃, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.5, 198.9, 191.6, 186.3, 144.2, 143.2, 135.6, 134.7, 133.6, 130.7, 129.9, 129.5, 128.8, 127.9, 127.8, 127.2, 127.0, 108.9, 68.5, 26.6, 23.8, 21.5, 21.4.

(E)-N-(2-hydroxy-4-oxopent-2-en-3-yl)-4-methylbenzenesulfonamide 62s^{50,98}

Yield 62%; yellow solid; ^1H NMR (300 MHz, CDCl_3) δ 16.3 (s, =COH, 1H), 7.71 (d, J = 8.1 Hz, Ar H, 2H), 7.32 (d, J = 8.1 Hz, Ar H, 2H), 6.16 (s, =CNHTs, 1H), 2.44 (s, ArCH₃, 3H), 1.87 (s, –COCH₃, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.1, 144.3, 136.6, 130.1, 127.4, 110.1, 22.1, 21.6.

Phenyl iodonium ylide 95u¹³¹

¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 7.7 Hz, Ar H, 2H), 7.52 (t, J = 7.4 Hz, Ar H, 1H), 7.36 (t, J = 7.8 Hz, Ar H, 2H), 2.61 (t, J = 6.3 Hz, $-\text{CH}_2\text{CO}-$, 4H), 1.94 (m, J = 6.3 Hz, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 189.3, 134.0, 131.6, 131.5, 111.5, 96.6, 37.1, 21.1.

6.3 Base-Mediated Aziridination of 2-Alkyl Substituted-1,3-Dicarbonyl Compounds by Iminoiodanes

General Synthetic Route for 2-Alkyl Substituted-1,3-Dicarbonyl Compounds

96¹⁰⁶ⁱ

To a 25 mL round-bottomed flask was added K_2CO_3 (7.5 mmol, 1.04 g), alkyl bromide (5.5 mmol), 1,3-dicarbonyl compound (5.0 mmol), and DMF (10 mL). The reaction was then stirred at 50 °C for 18 h. The reaction was then quenched with addition of H_2O (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layer was then washed with water (3×10 mL), dried over MgSO_4 , filtered, and concentrated to dryness. The crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 19:1 to 10:1) to give the title compound.

General Procedure for Aziridination 2-Alkyl Substituted-1,3-Dicarbonyl Compounds 97a–i

To a 4 mL screw-capped vial charged with magnetic stir bar, was added *o*-NsN=IPh (0.88 mmol, 356 mg) and MeCN (2 mL). Successively, 2-alkyl substituted-1,3-dicarbonyl compound **96** (0.4 mmol) and DBU (0.08 mmol, 12 μL) was added and the reaction was stirred at room temperature for 18 h. The reaction mixture was then

filtered and washed with EtOAc and concentrated to dryness. The crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 3:1) to give the aziridine product **97**.

General Procedure for Aziridination 2-Alkyl Substituted-1,3-Dicarbonyl Compounds **87h,j-q**

To a 4 mL screw-capped vial charged with magnetic stir bar, was added *o*-NsN=IPh (1.2 mmol, 484 mg), K_2CO_3 (0.44 mmol, 61 mg), CH_2Cl_2 (2 mL) and 2-alkyl substituted-1,3-dicarbonyl compound **96** (0.4 mmol). The reaction was stirred at 40 °C for 18 h. The reaction mixture was then purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 3:1) to give the aziridine product **97**.

Control Experiment Procedure for Base-Mediated Aziridination of **98a to **97a****

To a 4 mL screw-capped vial charged with magnetic stir bar, was added *o*-NsN=IPh (0.22 mmol, 89 mg) and MeCN (1 mL). Successively, diethyl ethylidenemalonate **98a** (0.2 mmol, 37 μ L) and DBU (0.04 mmol, 6 μ L) was added and the reaction was stirred at room temperature for 18 h. The reaction mixture was then filtered and washed with EtOAc and concentrated to dryness. The crude mixture was purified by

flash column chromatography (eluent: *n*-hexane/EtOAc, 3:1) to give the aziridine product **97a**.

Control Experiment Procedure for Base-Mediated Aziridination of **98a** to **99a**

To a 4 mL screw-capped vial charged with magnetic stir bar, was added *o*-NsNH₂ (0.22 mmol, 45 mg) and MeCN (1 mL). Successively, diethyl ethylidenemalonate **98a** (0.2 mmol, 37 μ L) and DBU (0.04 mmol, 6 μ L) was added and the reaction was stirred at room temperature for 18 h. The reaction mixture was then filtered and washed with EtOAc and concentrated to dryness. The crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 3:1) to give the title compound **99a**.

Control Experiment Procedure for Base-Mediated Aziridination of **98a** to **97a**

To a 4 mL screw-capped vial charged with magnetic stir bar, was added *o*-NsN=IPh (0.22 mmol, 89 mg), *o*-NsNH₂ (0.22 mmol, 45 mg) and MeCN (1 mL). Successively, diethyl ethylidenemalonate **98a** (0.2 mmol, 37 μ L) and DBU (0.04 mmol, 6 μ L) was added and the reaction was stirred at room temperature for 18 h. The reaction mixture was then filtered and washed with EtOAc and concentrated to dryness. The crude

mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 3:1) to give the title compound **97a**.

Ethyl 2-ethyl-3-oxo-3-phenylpropanoate 96e¹³²

Yield 80%; yellow oil; ¹H NMR (400MHz, CDCl₃) δ 8.00 (d, *J* = 7.6 Hz, Ar H, 2H), 7.59 (t, *J* = 7.2 Hz, Ar H, 1H), 7.48 (t, *J* = 7.6 Hz, Ar H, 2H), 4.23 (t, *J* = 7.2 Hz, –CHCH₂CH₃, 1H), 4.16 (q, *J* = 7.2 Hz, –OCH₂CH₃, 2H), 2.09–2.02 (m, –CHCH₂CH₃, 2H), 1.18 (t, *J* = 7.2 Hz, –OCH₂CH₃, 3H), 1.01 (t, *J* = 7.2 Hz, –CHCH₂CH₃, 3H); ¹³C NMR δ 195.7, 170.9, 135.8, 133.5, 128.6, 128.6, 61.2, 56.0, 22.5, 14.0, 12.3.

Ethyl 2-methyl-3-oxo-3-phenylpropanoate 96f¹⁰⁶ⁱ

Yield 95%; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 7.6 Hz, Ar H, 2H), 7.59 (t, *J* = 7.4 Hz, Ar H, 1H), 7.48 (t, *J* = 7.6 Hz, Ar H, 2H), 4.37 (q, *J* = 7.1 Hz, –CHCH₃, 1H), 4.15 (q, *J* = 7.2 Hz, –OCH₂CH₃, 2H), 1.50 (d, *J* = 6.8 Hz, –CHCH₃, 3H), 1.17 (t, *J* = 7.2 Hz, –OCH₂CH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.9, 170.9, 135.9, 133.4, 128.7, 128.6, 61.4, 48.4, 14.0, 13.8.

Ethyl 2-acetyl-4-oxo-4-phenylbutanoate 96k¹³³

Yield 50%; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.98–7.95 (m, Ar H, 2H), 7.59–7.54 (m, Ar H, 1H), 7.48–7.43 (m, Ar H, 2H), 4.26–4.18 (m, –OCH₂CH₃ and PhCOCH₂CH–, 3H), 3.75–3.48 (m, PhCOCH₂CH–, 2H), 2.43 (s, –COCH₃, 3H), 1.28 (t, *J* = 7.1 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 202.3, 197.1, 168.9, 136.1, 133.4, 128.6, 128.1, 61.7, 53.9, 37.4, 30.2, 14.0.

Ethyl 2-benzoyl-4-oxo-4-phenylbutanoate 96l¹³⁴

Yield 45%; pale yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 8.10–7.96 (m, Ar H, 4H), 7.60–7.40 (m, Ar H, 6H), 5.15–5.10 (m, PhCOCH₂CH–, 1H), 4.14 (q, *J* = 7.1 Hz, –OCH₂CH₃, 2H), 3.86–3.67 (m, PhCOCH₂CH–, 2H), 1.14 (t, *J* = 7.1 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 196.9, 194.8, 169.3, 136.1, 133.6, 133.5, 129.0, 128.8, 128.7, 128.2, 61.8, 48.9, 38.2, 13.9.

Diethyl 2-(2-oxo-2-phenylethyl)malonate 96m¹³⁵

Yield 25%; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 8.00–7.97 (m, Ar H, 2H), 7.58–7.55 (m, Ar H, 1H), 7.49–7.44 (m, Ar H, 2H), 4.28–4.20 (m, –OCH₂CH₃, 4H),

4.06 (t, $J = 7.1$ Hz, $\text{PhCOCH}_2\text{CH}-$, 1 H), 3.63 (d, $J = 7.1$ Hz, $\text{PhCOCH}_2\text{CH}-$, 2H), 1.29 (t, $J = 7.1$ Hz, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.5, 169.0, 136.1, 133.5, 128.7, 128.1, 61.7, 47.2, 37.8, 14.0.

Dimethyl 2-(2-oxo-2-phenylethyl)malonate 96n¹³⁶

Yield 50%; orange solid; ^1H NMR (300 MHz, CDCl_3) δ 7.98–7.96 (m, Ar H, 2H), 7.60–7.54 (m, Ar H, 1H), 7.48–7.43 (m, Ar H, 2H), 4.09 (t, $J = 7.1$ Hz, $\text{PhCOCH}_2\text{CH}-$, 1H), 3.77 (s, $-\text{OCH}_3$, 6H), 3.64 (d, $J = 7.1$ Hz, $\text{PhCOCH}_2\text{CH}-$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.4, 169.4, 136.0, 133.5, 128.7, 128.1, 52.8, 46.8, 37.9.

Dimethyl 2-(2-oxo-2-(p-tolyl)ethyl)malonate 96o¹³⁶

Yield 43%; orange oil; ^1H NMR (300 MHz, CDCl_3) δ 7.88 (d, $J = 8.2$ Hz, Ar H, 2H), 7.27 (d, $J = 7.9$ Hz, Ar H, 2H), 4.08 (t, $J = 7.1$ Hz, $\text{ArCOCH}_2\text{CH}-$, 1H), 3.78 (s, $-\text{OCH}_3$, 6H), 3.62 (d, $J = 7.1$ Hz, $\text{ArCOCH}_2\text{CH}-$, 2H), 2.42 (s, ArCH_3 , 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 196.0, 169.5, 144.4, 133.5, 129.4, 128.3, 52.8, 46.8, 37.8, 21.7.

Dimethyl 2-(2-(4-chlorophenyl)-2-oxoethyl)malonate 96p¹³⁶

Yield 52%; orange oil; ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, J = 8.6 Hz, Ar H, 2H), 7.45 (d, J = 8.6 Hz, Ar H, 2H), 4.08 (t, J = 7.1 Hz, ArCOCH₂CH-, 1H), 3.78 (s, -OCH₃, 6H), 3.60 (d, J = 7.1 Hz, ArCOCH₂CH-, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 195.3, 169.3, 140.1, 134.3, 129.6, 129.0, 52.9, 46.8, 37.8.

Diethyl 3-methyl-1-((4-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97a

Yield 70%; white solid; mp 101–102 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.39 (d, J = 8.8 Hz, Ar H, 2H), 8.21 (d, J = 8.8 Hz, Ar H, 2H), 4.36–4.34 (m, -OCH₂CH₃, 4H), 3.92 (q, J = 5.6 Hz, -CHNNs, 1H), 1.34–1.21 (m, -OCH₂CH₃ and -CHCH₃, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 163.2, 163.1, 150.6, 145.2, 128.9, 124.3, 63.5, 62.8, 56.0, 44.9, 14.1, 13.7, 13.6; IR (NaCl, neat) ν 3109, 2984, 1745, 1734, 1535 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₉N₂O₈S [M + H]⁺ 387.0862, found 387.0873.

Diethyl 3-methyl-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97a

Yield 97%; yellow oil, ^1H NMR (300 MHz, CDCl_3) δ 8.36–8.25 (m, Ar H, 1H), 7.95–7.93 (m, Ar H, 1H), 7.86–7.73 (m, Ar H, 2H), 4.38–4.26 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 4.08 (q, $J = 5.7$ Hz, $-\text{CHNNs}$, 1H), 1.40 (d, $J = 5.7$ Hz, $-\text{CHCH}_3$, 3H), 1.36–1.27 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.5, 163.7, 134.2, 132.9, 130.7, 124.9, 63.4, 62.5, 56.0, 48.0, 14.1, 14.0, 13.7; IR (NaCl, neat) ν 2985, 2983, 1745, 1734, 1546 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_8\text{S}$ $[\text{M} + \text{Na}]^+$ 409.0682, found 409.0691.

Diethyl 3-ethyl-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97b

Yield 80%; yellow oil, ^1H NMR (400 MHz, CDCl_3) δ 8.31–8.29 (m, Ar H, 1H), 7.86–7.84 (m, Ar H, 1H), 7.79–7.76 (m, Ar H, 2H), 4.35–4.27 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.92 (t, $J = 6.6$ Hz, $-\text{CHNNs}$, 1H), 1.94–1.84 (m, $-\text{CHCH}_2\text{CH}_3$, 1H), 1.44–1.36 (m, $-\text{CHCH}_2\text{CH}_3$, 1H), 1.34–1.30 (m, $-\text{OCH}_2\text{CH}_3$, 6H), 1.05 (t, $J = 7.2$ Hz, $-\text{CHCH}_2\text{CH}_3$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.5, 163.5, 147.9, 134.4, 133.7, 132.7, 130.8, 124.8, 63.4, 62.5, 56.2, 22.0, 14.0, 13.7, 10.3; IR (NaCl, neat) ν 3098, 2984, 2940, 1747, 1734, 1549 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_8\text{S}$ $[\text{M} + \text{H}]^+$ 401.1019, found 401.1014.

Ethyl 2-benzoyl-1-((4-nitrophenyl)sulfonyl)aziridine-2-carboxylate 97f

Yield 25%; pale yellow solid; mp 109–111 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.23–8.21 (m, Ar H, 1H), 8.12 (d, $J = 7.2$ Hz, Ar H, 2H), 7.82–7.80 (m, Ar H, 1H), 7.75–7.73 (m, Ar H, 2H), 7.61 (t, $J = 7.2$ Hz, Ar H, 2H), 7.50 (t, $J = 7.6$ Hz, Ar H, 2H), 4.35–4.23 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 3.77 (s, $-\text{CH}_2\text{NNs}$, 1H), 3.20 (s, $-\text{CH}_2\text{NNs}$, 1H), 1.20 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 188.8, 164.9, 147.9, 134.4, 134.2, 134.1, 132.7, 130.3, 129.5, 129.2, 128.6, 124.9, 63.5, 54.4, 13.7; IR (NaCl, neat) ν 3055, 2984, 1734, 1670, 1545 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_7\text{S}$ $[\text{M} + \text{H}]^+$ 405.0756, found 405.0740.

Diethyl 2-acetyl-1-((2-nitrophenyl)sulfonyl)aziridine-2,3-dicarboxylate 97h

Yield 61%; pale yellow solid; mp 83–85 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.29–8.27 (m, Ar H, 1H), 7.95–7.93 (m, Ar H, 1H), 7.85–7.82 (m, Ar H, 2H), 4.56 (s, $-\text{CHNNs}$, 1H), 4.42–4.32 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 4.28–4.19 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 2.41 (s, $-\text{COCH}_3$, 3H), 1.36 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 1.30 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR δ 197.4, 164.3, 162.8, 147.8, 134.9, 133.9, 133.2, 130.4, 125.6, 64.0, 62.8, 58.3, 49.4, 28.3, 13.9, 13.7; IR (NaCl, neat) ν 3055, 2986, 2926, 1734, 1549 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$ 415.0811, found 415.0820.

Ethyl 2-acetyl-3-benzoyl-1-((2-nitrophenyl)sulfonyl)aziridine-2-carboxylate 97k

Yield 37%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 8.33–8.31 (m, Ar H, 1H), 8.13–8.10 (m, Ar H, 3H), 7.90–7.80 (m, Ar H, 2H), 7.68–7.59 (m, Ar H, 1H), 7.55–7.45 (m, Ar H, 2H), 5.40 (s, $-\text{CHNNs}$, 1H), 4.48–4.36 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 2.63 (s, $-\text{COCH}_3$, 3H), 1.39 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 198.0, 188.8, 163.1, 135.4, 135.0, 134.7, 133.8, 133.7, 133.1, 130.6, 130.2, 129.0, 128.9, 128.5, 125.4, 64.1, 60.2, 51.5, 28.6, 13.7; IR (NaCl, neat) ν 3055, 2986, 2984, 2928, 1734, 1545 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{NaO}_8\text{S}$ $[\text{M} + \text{Na}]^+$ 469.0682, found 469.0695.

Diethyl 3-benzoyl-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97m

Yield 58%; Yellow solid; mp 89–90 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.38–8.36 (m, Ar H, 1H), 8.08 (d, $J = 7.2$ Hz, Ar H, 2H), 7.86–7.84 (m, Ar H, 1H), 7.80–7.77 (m, Ar H, 2H), 7.66 (t, $J = 7.6$ Hz, Ar H, 2H), 7.54 (t, $J = 7.6$ Hz, Ar H, 2H), 5.40 (s, $-\text{CHNNs}$, 1H), 4.47–4.41 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 4.25–4.14 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 1.39 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 1.14 (t, $J = 7.1$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.2, 162.6, 162.0, 147.7, 135.5, 134.8, 134.5, 133.7, 133.2, 131.0, 129.0, 128.8, 125.3, 64.3, 62.8, 56.3, 50.0, 29.7, 13.7; IR (NaCl, neat) ν 3055, 2986, 2984, 2926, 1749, 1700, 1545 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$ 477.0968, found 477.0960.

Dimethyl 3-benzoyl-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97n

Yield 56%; white solid; mp 54–56 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.38–8.36 (m, Ar H, 1H), 8.09–8.07 (m, Ar H, 2H), 7.89–7.87 (m, Ar H, 1H), 7.81–7.78 (m, Ar H, 2H), 7.69–7.67 (m, Ar H, 1H), 7.56–7.52 (m, Ar H, 2H), 5.42 (s, $-\text{CHNNs}$, 1H), 3.98 (s, $-\text{OCH}_3$, 3H), 3.77 (s, $-\text{OCH}_3$, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.3, 163.1, 162.7, 135.4, 134.8, 134.6, 133.7, 133.2, 131.1, 129.0, 128.9, 125.4, 56.0, 54.7, 53.6, 49.8; IR (NaCl, neat) ν 2986, 2984, 1734, 1454 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$ 449.0655, found 449.0646.

Dimethyl 3-(4-methylbenzoyl)-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97o

Yield 50%; pale yellow solid; mp 116–118 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.39–8.36 (m, Ar H, 1H), 7.90 (d, $J = 8.1$ Hz, Ar H, 2H), 7.88–7.85 (m, Ar H, 2H), 7.81–7.77 (m, Ar H, 2H), 7.33 (d, $J = 8.1$ Hz, Ar H, 2H), 5.39 (s, $-\text{CHNNs}$, 1H), 3.97 (s, $-\text{OCH}_3$, 3H), 3.76 (s, $-\text{OCH}_3$, 3H), 2.45 (s, ArCH_3 , 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 187.8, 163.2, 162.8, 147.7, 145.9, 134.8, 133.6, 133.2, 133.0, 131.0, 129.7, 129.1, 125.4, 55.9, 54.7, 53.6, 49.8, 29.7, 21.9; IR (NaCl, neat) ν 3055, 2984, 2926,

1755, 1690, 1545 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$ 463.0811, found 463.0803.

Dimethyl 3-(4-chlorobenzoyl)-1-((2-nitrophenyl)sulfonyl)aziridine-2,2-dicarboxylate 97p

Yield 41%, pale yellow solid; mp 146–148 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.36–8.34 (m, Ar H, 1H), 8.03 (d, $J = 8.1$ Hz, Ar H, 2H), 7.89–7.86 (m, Ar H, 1H), 7.81–7.78 (m, Ar H, 2H), 7.52 (d, $J = 8.1$ Hz, Ar H, 2H), 5.36 (s, $-\text{CHNNs}$, 1H), 3.98 (s, $-\text{OCH}_3$, 3H), 3.77 (s, $-\text{OCH}_3$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.4, 163.0, 162.7, 147.7, 141.4, 134.9, 133.7, 133.5, 133.3, 131.0, 130.3, 129.4, 125.5, 56.0, 54.8, 53.7, 49.6; IR (NaCl, neat) ν 3055, 2984, 2926, 1753, 1694, 1589, 1545 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{15}^{35}\text{ClN}_2\text{NaO}_9\text{S}$ $[\text{M} + \text{Na}]^+$ 505.0084, found 505.0080.

Triethyl 1-((2-nitrophenyl)sulfonyl)aziridine-2,2,3-tricarboxylate 97q

Yield 45%, pale yellow solid; mp 90–92 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.29–8.27 (m, Ar H, 1H), 7.91–7.88 (m, Ar H, 1H), 7.80–7.78 (m, Ar H, 2H), 4.57 (s, $-\text{CHNNs}$, 1H), 4.39 (q, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 2H), 4.32–4.21 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 1.36 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 1.31 (t, $J = 7.2$ Hz, $-\text{OCH}_2\text{CH}_3$, 3H), 1.28 (t, $J = 7.2$ Hz,

–OCH₂CH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 162.3, 161.9, 147.6, 71.7, 64.2, 62.8, 62.7, 54.9, 48.2, 14.0, 13.8, 13.7; IR (NaCl, neat) ν 3055, 2986, 2940, 1748, 1547 cm⁻¹; HRMS (ESI) calcd for C₁₇H₂₁N₂O₁₀S [M + H]⁺ 445.0917, found 445.0919.

Diethyl 2-ethylidenemalonate 98a¹⁰⁶ⁱ

Yield 23%; colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 6.92 (q, *J* = 7.2 Hz, =CHCH₃, 1H), 4.19–4.04 (m, –OCH₂CH₃, 4H), 1.80 (d, *J* = 7.2 Hz, =CHCH₃, 3H), 1.20–1.10 (m, –OCH₂CH₃ and =CHCH₃, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 165.1, 163.7, 61.0, 60.9, 15.2, 14.0, 13.9.

Diethyl 2-(1-((2-nitrophenyl)sulfonamido)ethyl)malonate 99a

Yield 27%; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.18–8.16 (m, Ar H, 1H), 7.88–7.86 (m, Ar H, 1H), 7.78–7.71 (m, Ar H, 2H), 6.44 (d, *J* = 8.8 Hz, –CHNHNs, 1H), 4.30–4.19 (m, –OCH₂CH₃ and –CHCHNHNs, 3H), 4.06 (q, *J* = 7.2 Hz, –OCH₂CH₃, 2H), 3.52 (d, *J* = 4.4 Hz, –CHCH(CH₃)NHNs, 1H), 1.29 (t, *J* = 7.2 Hz, –CHCH₃, 3H), 1.26–1.20 (m, –OCH₂CH₃, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 166.9, 147.7, 135.4, 133.4, 132.9, 130.4, 125.3, 62.0, 56.6, 50.0, 19.8, 14.0, 13.9; IR (NaCl, neat) ν 3354, 3098, 2984, 2940, 1734, 1732, 1537 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₀N₂NaO₈S [M + Na]⁺ 411.0838, found 411.0829.

6.4 Iminoiodane- and Brønsted Base-Mediated Cross Dehydrogenative Coupling of Cyclic Ethers with 1,3-Dicarbonyl Compounds

General Procedure for Iminoiodane- and Base-Mediated CDC of Tetrahydrofuran **100a** with 1,3-Dicarbonyl Compounds **61**¹³⁷

THF **100a** (1 mL) was added to PhI=NTs (0.25 mmol, 93 mg) in a 5 mL round-bottomed flask and stirred for 50 min under N₂ atmosphere at room temperature. The solvent was subsequently removed under reduced pressure and the flask was back filled with N₂. To the crude mixture, 1,3-dicarbonyl compound **61** (0.50 mmol), DBU (0.025 mmol, 4 μ L), and PhMe (1 mL) was subsequently added. The reaction was stirred for 18 h at room temperature or 40 °C. Upon completion of the reaction, based on TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 5:1 to 4:1) to give the corresponding adduct **102**.

General Procedure for Iminoiodane- and Base-Mediated CDC of 1-Methyltetrahydrofuran **100b** with 1,3-Dicarbonyl Compounds **61a**¹³⁷

2-Methyltetrahydrofuran **100b** (2 mL) was added to PhI=NTs (0.50 mmol, 186 mg) in a 5 mL round-bottomed flask and stirred for 50 min under N₂ atmosphere at room temperature (50% conversion based on ¹H NMR analysis). The solvent was removed

under reduced pressure and the flask back filled with N₂. To the crude mixture, ethyl benzoylacetate **61a** (0.50 mmol, 87 μ L) and DBU (0.05 mmol, 4 μ L) were subsequently added. In the absence of solvent, the reaction was stirred at 40 °C for 18 h. Upon completion of the reaction, based on TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 5:1) to give the corresponding product **102q**.

General Procedure for Iminoiodane- and Base-Mediated CDC of 1-Tetrahydropyran **100c with 1,3-Dicarbonyl Compounds **61a**¹³⁷**

Tetrahydropyran **100c** (2 mL) was added to PhI=NTs (0.50 mmol, 186 mg) in a 5 mL round-bottomed flask and stirred for 50 min under N₂ atmosphere at 65 °C (40% conversion based on ¹H NMR analysis). The solvent was removed under reduced pressure and the flask back filled with N₂. To the crude mixture, ethyl benzoylacetate **61a** (0.40 mmol, 69 μ L) and DBU (0.05 mmol, 3 μ L) were subsequently added. In the absence of solvent, the reaction was stirred at 80 °C for 18 h. Upon completion of the reaction, based on TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 5:1) to give the corresponding product **102r**.

Procedure for Iminoiodane- and Base-Mediated CDC of **100a with Diisopropyl malonate **61v** to **103n****¹³⁷

THF **100a** (2 mL) was added to $\text{PhI}=\text{NTs}$ (0.50 mmol, 186 mg) in a 5 mL round-bottomed flask and stirred for 50 min under N_2 atmosphere at room temperature. The solvent was then removed under reduced pressure and the flask back filled with N_2 . To the crude mixture, diisopropyl malonate **61v** (1.0 mmol, 190 μL) and DBU (0.05 mmol, 8 μL) and PhMe (2 mL) were subsequently added. The reaction was stirred at room temperature for 18 h. Upon completion of the reaction, based on TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 1:1) to give the corresponding product **103n**.

Control Experiment Procedure for the Iminoiodane- and Base-Mediated CDC from **102n to **102n****¹³⁷

To a 5 mL round-bottomed flask equipped with magnetic stir bar was charged **103n** (0.25 mmol, 107 mg), DBU (0.025 mmol, 4 μL) and PhMe (1 mL). The reaction was stirred under N_2 atmosphere at 40 °C for 18 h. Upon completion of the reaction, based on TLC analysis, the crude mixture was purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 5:1) to give the corresponding product **102n**.

Ethyl 3-oxo-3-phenyl-2-(tetrahydrofuran-2-yl)propanoate 102a¹³⁷

Yield 80%; obtained as two diastereomers with ratio of 1.3:1; yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.05–8.02 (m, Ar H, 4H), 7.61–7.56 (m, Ar H, 2H), 7.50–7.45 (m, Ar H, 4H), 4.73–4.65 (m, –OCHCH–, 2H), 4.46 (d, *J* = 8.8 Hz, –OCHCH–, 1H), 4.41 (d, *J* = 8.8 Hz, –OCHCH–, 1H), 4.20–4.11 (m, –OCH₂CH₃, 4H), 3.91–3.70 (m, –OCH₂CH₂–, 4H), 2.27–2.16 (m, –OCHCH₂–, 2H), 1.98–1.83 (m, –OCH₂CH₂–, 4H), 1.81–1.74 (m, –OCHCH₂–, 1H), 1.56–1.47 (m, –OCHCH₂–, 1H), 1.20–1.15 (m, –OCH₂CH₃, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 193.6, 193.3, 167.9, 167.5, 136.8, 136.4, 133.4, 133.7, 128.7, 128.7, 128.6, 78.1, 77.7, 68.2, 68.1, 61.6, 61.4, 60.2, 59.3, 30.2, 30.0, 29.7, 25.5, 25.4, 14.0, 13.9.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)-3-(*o*-tolyl)propanoate 102b¹³⁷

Yield 59%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.89–7.74 (m, Ar H, 2H), 7.42–7.35 (m, Ar H, 2H), 7.30–7.24 (m, Ar H, 4H), 4.66–4.58 (m, –OCHCH–, 2H), 4.34 (d, *J* = 3.0 Hz, –OCHCH–, 1H), 4.31 (d, *J* = 2.7 Hz, –OCHCH–, 1H), 4.21–4.09 (m, –OCH₂CH₃, 4H), 3.91–3.69 (m, –OCH₂CH₂–, 4H), 2.50 (s, ArCH₃, 3H), 2.49 (s, ArCH₃, 3H), 2.27–2.17 (m, –OCHCH₂–, 2H), 1.97–1.86 (m, –OCH₂CH₂–, 4H), 1.80–1.68 (m, –OCHCH₂–, 1H), 1.64–1.52 (m, –OCHCH₂–, 1H), 1.93 (t, *J* = 5.6 Hz, –OCH₂CH₃, 3H), 1.14 (t, *J* = 5.6 Hz, –OCH₂CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 197.2, 196.7, 167.9, 167.6,

138.9, 138.8, 132.0, 131.9, 131.8, 131.5, 129.0, 128.7, 125.7, 125.5, 78.1, 78.1, 68.1, 68.0, 62.3, 61.8, 61.4, 61.3, 30.2, 30.1, 25.5, 21.1, 20.9, 14.0, 13.9; IR (NaCl, neat) ν 2979, 2930, 1740, 1688, 1456 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 299.1259, found 299.1268.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)-3-(*p*-tolyl)propanoate 102c¹³⁷

Yield 72%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.95–7.91 (m, Ar H, 4H), 7.28–7.25 (m, Ar H, 4H), 4.73–4.62 (m, $-\text{OCHCH}-$, 2H), 4.42 (d, $J = 9$ Hz, $-\text{OCHCH}-$, 1H), 4.38 (d, $J = 9$ Hz, $-\text{OCHCH}-$, 1H), 4.20–4.10 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.91–3.68 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 2.41 (s, ArCH_3 , 3H), 2.40 (s, ArCH_3 , 3H), 2.27–2.13 (m, $-\text{OCHCH}_2-$, 2H), 1.98–1.83 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.81–1.71 (m, $-\text{OCHCH}_2-$, 1H), 1.56–1.44 (m, $-\text{OCHCH}_2-$, 1H), 1.20–1.15 (m, $-\text{OCH}_2\text{CH}_3$, 6H), ^{13}C NMR (75 MHz, CDCl_3) δ 193.1, 192.8, 168.0, 167.7, 144.7, 144.4, 134.4, 134.0, 129.4, 129.3, 129.0, 128.9, 78.1, 77.7, 68.1, 68.1, 61.5, 61.4, 60.1, 59.2, 30.2, 30.0, 25.5, 25.4, 21.7, 14.0; IR (NaCl, neat) ν 2980, 1732, 1682, 1607 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$ 277.1440, found 277.1439.

Ethyl 3-(4-methoxyphenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate 102d¹³⁷

Yield 40%; obtained as two diastereomers with ratio of 1.4:1; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.04–8.01 (m, Ar H, 4H), 6.96–6.93 (m, Ar H, 4H), 4.73–4.64

(m, $-\text{OCHCH}-$, 2H), 4.40 (d, $J = 9.2$ Hz, $-\text{OCHCH}-$, 1H), 4.36 (d, $J = 9.2$ Hz, $-\text{OCHCH}-$, 1H), 4.20–4.11 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.88–3.70 (m, $-\text{OCH}_2\text{CH}_2-$ and $-\text{OCH}_3$, 10H), 2.24–2.14 (m, $-\text{OCHCH}_2-$, 2H), 2.00–1.85 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.81–1.74 (m, $-\text{OCHCH}_2-$, 1H) 1.54–1.47 (m, $-\text{OCHCH}_2-$, 1H), 1.21–1.16 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.9, 191.6, 168.2, 167.8, 164.1, 163.9, 131.3, 131.2, 129.5, 129.8, 113.9, 113.8, 78.2, 77.7, 68.2, 68.1, 61.5, 61.4, 60.0, 59.0, 55.5, 55.5, 30.2, 30.0, 25.5, 25.4, 14.0, 14.0; IR (NaCl, neat) ν 2978, 2938, 1736, 1674, 1601, 1574, 1512 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_5$ $[\text{M} + \text{H}]^+$ 293.1389, found 293.1400.

Ethyl 3-(4-iodophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate 102e¹³⁷

Yield 73%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.86–7.82 (m, Ar H, 4H), 7.75–7.71 (m, Ar H, 4H), 4.71–4.60 (m, $-\text{OCHCH}-$, 2H), 4.36 (d, $J = 9.0$ Hz, $-\text{OCHCH}-$, 1H), 4.34 (d, $J = 8.7$ Hz, $-\text{OCHCH}-$, 1H), 4.25–4.05 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.90–3.68 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 2.27–2.14 (m, $-\text{OCHCH}_2-$, 2H), 1.98–1.84 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.80–1.69 (m, $-\text{OCHCH}_2-$, 1H), 1.57–1.45 (m, $-\text{OCHCH}_2-$, 1H), 1.21–1.16 (m, $-\text{OCH}_2\text{CH}_3$, 6H), ^{13}C NMR (75 MHz, CDCl_3) δ 193.1, 192.7, 167.6, 167.3, 138.1, 138.0, 136.1, 135.6, 130.2, 130.1, 102.1, 101.7, 77.9, 77.7, 68.2, 68.1, 61.7, 61.6, 60.0, 59.4, 30.2, 30.1, 25.4, 14.0; IR (NaCl, neat) ν 2978, 1732, 1682, 1582 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{INaO}_4$ $[\text{M} + \text{Na}]^+$ 411.0069, found 411.0086.

Ethyl 3-(4-bromophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate 102f¹³⁷

Yield 78%; obtained as two diastereomers with ratio of 1.2:1; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.92–7.87 (m, Ar H, 4H), 7.64–7.60 (m, Ar H, 4H), 4.71–4.61 (m, –OCHCH–, 2H), 4.37 (d, *J* = 9.3 Hz, –OCHCH–, 1H), 4.36 (d, *J* = 8.7 Hz, –OCHCH–, 1H), 4.21–4.10 (m, –OCH₂CH₃, 4H), 3.90–3.68 (m, –OCH₂CH₂–, 4H), 2.27–2.15 (m, –OCHCH₂–, 2H), 1.99–1.81 (m, –OCH₂CH₂–, 4H), 1.79–1.69 (m, –OCH₂CH₂–, 1H), 1.58–1.46 (m, –OCH₂CH₂–, 1H), 1.21–1.16 (m, –OCH₂CH₃, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 192.8, 192.4, 167.7, 167.3, 135.6, 135.1, 132.1, 131.9, 130.3, 130.2, 129.1, 128.8, 77.9, 77.7, 68.2, 68.1, 61.7, 61.6, 60.1, 59.4, 30.2, 30.1, 25.4, 14.0; IR (NaCl, neat) ν 2980, 1738, 1682 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₇⁷⁹BrNaO₄ [M + Na]⁺ 363.0208, found 363.0222.

Ethyl 3-(4-chlorophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate 102g¹³⁷

Yield 71%; obtained as two diastereomers with ratio of 1:1; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 8.00–7.95 (m, Ar H, 4H), 7.47–7.43 (m, Ar H, 4H), 4.72–4.61 (m, –OCHCH–, 2H), 4.38 (d, *J* = 9.3 Hz, –OCHCH–, 1H), 4.36 (d, *J* = 8.7 Hz, –OCHCH–, 1H), 4.21–4.11 (m, –OCH₂CH₃, 4H), 3.90–3.69 (m, –OCH₂CH₂–, 4H), 2.27–2.15 (m, –OCHCH₂–, 2H), 1.99–1.80 (m, –OCH₂CH₂–, 4H), 1.79–1.69 (m, –OCH₂CH₂–, 1H), 1.58–1.46 (m, –OCHCH₂–, 1H), 1.21–1.16 (m, –OCH₂CH₃, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 192.5, 192.2, 167.7, 167.3, 140.3, 140.0, 135.2, 134.7,

130.2, 130.2, 129.1, 128.9, 77.9, 77.7, 68.2, 68.1, 61.7, 61.6, 60.2, 59.4, 30.2, 30.1, 25.4, 14.0; IR (NaCl, neat) ν 2980, 1736, 1684, 1589 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}^{35}\text{ClNaO}_4$ $[\text{M} + \text{Na}]^+$ 319.0713, found 319.0723.

Ethyl 3-(4-fluorophenyl)-3-oxo-2-(tetrahydrofuran-2-yl)propanoate 102h¹³⁷

Yield 76%; obtained as two diastereomers with ratio of 1.1:1; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 8.10–8.04 (m, Ar H, 4H), 7.18–7.11 (m, Ar H, 4H), 4.72–4.62 (m, $-\text{OCHCH}-$, 2H), 4.39 (d, $J = 9.0$ Hz, $-\text{OCHCH}-$, 1H), 4.37 (d, $J = 8.7$ Hz, $-\text{OCHCH}-$, 1H), 4.21–4.12 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.91–3.69 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 2.27–2.17 (m, $-\text{OCHCH}_2-$, 2H), 1.99–1.84 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.82–1.72 (m, $-\text{OCHCH}_2-$, 1H), 1.58–1.46 (m, $-\text{OCHCH}_2-$, 1H), 1.22–1.16 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 192.1, 191.8, 167.8, 167.4, 131.6, 131.6, 131.5, 131.4, 116.0, 115.9, 115.8, 115.6, 78.0, 77.7, 68.2, 68.1, 61.7, 61.5, 60.2, 59.4, 30.2, 30.1, 25.4, 13.9; IR (NaCl, neat) ν 2980, 1735, 1684, 1597 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{FNaO}_4$ $[\text{M} + \text{Na}]^+$ 303.1009, found 303.0999.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)butanoate 102i¹³⁷

Yield 32%; obtained as two diastereomers with ratio of 1.7:1; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 4.48–4.41 (m, $-\text{OCHCH}-$, 2H), 4.26–4.16 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.86–3.72 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 3.58 (d, $J = 8.4$ Hz, $-\text{OCHCH}-$, 1H), 3.51 (d, $J =$

9.2 Hz, $-\text{OCHCH}-$, 1H), 2.31 (s, $-\text{COCH}_3$, 3H), 2.25 (s, $-\text{COCH}_3$, 3H), 2.22–2.11 (m, $-\text{OCHCH}_2-$, 2H), 1.95–1.88 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.69–1.55 (m, $-\text{OCHCH}_2-$, 2H), 1.31–1.25 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.1, 201.5, 167.9, 167.5, 77.2, 68.2, 68.0, 65.4, 65.0, 61.5, 61.4, 30.4, 29.9, 29.8, 29.7, 25.5, 25.3, 14.0.

Ethyl 3-oxo-2-(tetrahydrofuran-2-yl)pentanoate 102j¹³⁷

Yield 63%; obtained as two diastereomers with ratio of 1.7:1; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 4.48–4.40 (m, $-\text{OCHCH}-$, 2H), 4.26–4.13 (m, $-\text{OCH}_2\text{CH}_3$, 4H), 3.87–3.72 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 3.61 (d, $J = 8.7$ Hz, $-\text{OCHCH}-$, 1H), 3.55 (d, $J = 9.6$ Hz, $-\text{OCHCH}-$, 1H), 2.68–2.52 (m, $-\text{COCH}_2\text{CH}_3$, 4H), 2.24–2.08 (m, $-\text{OCHCH}_2-$, 2H), 1.95–1.85 (m, $-\text{OCH}_2\text{CH}_2-$, 4H), 1.67–1.52 (m, $-\text{OCHCH}_2-$, 2H), 1.30–1.23 (m, $-\text{OCH}_2\text{CH}_3$, 6H), 1.10–1.03 (m, $-\text{COCH}_2\text{CH}_3$, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.6, 204.1, 168.0, 167.6, 77.4, 77.2, 68.1, 68.0, 64.3, 64.0, 61.4, 61.3, 36.3, 36.2, 30.4, 29.8, 25.5, 25.3, 14.0, 7.46, 7.37.

Ethyl 4-methyl-3-oxo-2-(tetrahydrofuran-2-yl)pentanoate 102k¹³⁷

Yield 61%; diastereomer ratio could not be determined; ^1H NMR (300 MHz, CDCl_3) δ 4.49–4.40 (m, $-\text{OCHCH}-$, 1H), 4.24–4.10 (m, $-\text{OCH}_2\text{CH}_3$, 2H), 3.87–3.69 (m,

–OCHCH– and –OCH₂CH₂–, 3H), 2.87–2.75 (m, –COCH(CH₃)₂, 1H), 2.23–2.09 (m, –OCHCH₂–, 1H), 1.94–1.85 (m, –OCH₂CH₂–, 2H), 1.66–1.47 (m, –OCHCH₂–, 1H), 1.29–1.23 (m, –OCH₂CH₃, 3H), 1.16–1.10 (m, –COCH(CH₃)₂, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 207.7, 207.4, 167.7, 167.4, 77.8, 77.5, 68.0, 68.0, 62.5, 62.0, 61.4, 61.2, 41.7, 41.2, 30.3, 29.9, 25.5, 25.3, 18.2, 17.8, 17.8, 17.7, 14.0, 14.0; IR (NaCl, neat) ν 2976, 2938, 1744, 1713, 1636 cm^{–1}; HRMS (ESI) calcd for C₁₂H₂₀NaO₄ [M + Na]⁺ 251.1259, found 251.1262.

Dimethyl 2-(tetrahydrofuran-2-yl)malonate 102l¹³⁷

Yield 51%; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 4.46 (dt, *J* = 8.7, 6.9 Hz, –OCHCH–, 1H), 3.88–3.79 (m, –OCH₂CH₂–, 2H), 3.77 (s, –OCH₃, 3H), 3.74 (s, –OCH₃, 3H), 3.49 (d, *J* = 9 Hz, –OCHCH–, 1H), 2.22–2.11 (m, –OCHCH₂–, 1H), 1.97–1.88 (m, –OCH₂CH₂–, 2H), 1.78–1.66 (m, –OCHCH₂–, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 167.6, 77.0, 68.3, 57.1, 52.6, 52.5, 29.9, 25.4.

Diethyl 2-(tetrahydrofuran-2-yl)malonate 102m¹³⁷

Yield 42%; colourless oil; ¹H NMR (300 MHz, CDCl₃) δ 4.54 (dt, *J* = 9.0, 6.9 Hz, –OCHCH–, 1H), 4.16–4.27 (m, –OCH₂CH₃, 4H), 3.90–3.74 (m, –OCH₂CH₂–, 2H), 3.44 (d, *J* = 9.3 Hz, –OCHCH–, 1H), 2.22–2.11 (m, –OCHCH₂–, 1H), 1.97–1.88 (m, –OCH₂CH₂–, 2H), 1.79–1.68 (m, –OCHCH₂–, 1H), 1.30–1.24 (m, –OCH₂CH₃, 6H);

^{13}C NMR (75 MHz, CDCl_3) δ 167.6, 167.2, 77.0, 68.2, 61.4, 61.4, 57.5, 29.9, 25.4, 14.0.

Diisopropyl 2-(tetrahydrofuran-2-yl)malonate 102n¹³⁷

Yield 67%; colourless oil; ^1H NMR (300 MHz, CDCl_3) δ 5.16–4.99 (m, $-\text{OCH}(\text{CH}_3)_2$, 2H), 4.47–4.39 (dt, $J = 9.0, 6.9$ Hz, $-\text{OCHCH}-$, 1H), 3.89–3.74 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 3.37 (d, $J = 9.0$ Hz, $-\text{OCHCH}-$, 1H), 2.20–2.09 (m, $-\text{OCHCH}_2-$, 1H), 1.96–1.87 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 1.79–1.68 (m, $-\text{OCHCH}_2-$, 1H), 1.27–1.23 (m, $-\text{OCH}(\text{CH}_3)_2$, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.1, 166.8, 76.9, 68.9, 68.8, 68.1, 57.8, 29.8, 25.4, 21.6, 21.6, 21.5; IR (NaCl, neat) ν 2982, 2878, 1748, 1732, 1636 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{22}\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 281.1365, found 281.1365.

Dibenzyl 2-(tetrahydrofuran-2-yl)malonate 102o¹³⁷

Yield 71%; colourless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.28 (m, Ar H, 10H), 5.18 (s, $\text{PhCH}_2\text{O}-$, 2H), 5.13 (s, $\text{PhCH}_2\text{O}-$, 2H), 4.50 (dt, $J = 9.2, 6.8$ Hz, $-\text{OCHCH}-$, 1H), 3.85–3.72 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 3.57 (d, $J = 9.2$ Hz, $-\text{OCHCH}-$, 1H), 2.15–2.07 (m, $-\text{OCHCH}_2-$, 1H), 1.90–1.84 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 1.76–1.67 (m, $-\text{OCHCH}_2-$, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 166.9, 135.5, 135.2, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 77.0, 68.3, 67.1, 57.4, 29.9, 25.5; IR (NaCl, neat) ν

3065, 3034, 2955, 2876, 1732, 1636 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{NaO}_5$ [$\text{M} + \text{Na}$] $^{+}$ 377.1365, found 377.1375.

3-(Tetrahydrofuran-2-yl)pentane-2,4-dione 102p¹³⁷

Yield 65%; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 4.50 (dt, $J = 9.2, 6.8$ Hz, $-\text{OCHCH}-$, 1H), 3.86–3.81 (m, $-\text{OCHCH}-$, 1H), 3.74–3.70 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 2.26 (s, $-\text{COCH}_3$, 3H), 2.21 (s, $-\text{COCH}_3$, 3H), 2.20–2.10 (m, $-\text{OCHCH}_2-$, 1H), 1.94–1.87 (m, $-\text{OCH}_2\text{CH}_2-$, 2H), 1.49–1.40 (m, $-\text{OCHCH}_2-$, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.8, 202.2, 77.5, 74.3, 67.9, 30.4, 30.2, 29.5, 25.3.

Ethyl 2-(5-methyltetrahydrofuran-2-yl)-3-oxo-3-phenylpropanoate 102q¹³⁷

Yield 41%; obtained as four diastereomers with ratio of 1.4:1.3:1.2:1; yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.05–8.01 (m, Ar H, 8H), 7.61–7.56 (m, Ar H, 4H), 7.49–7.45 (m, Ar H, 8H), 4.88–4.82 (m, $-\text{OCHCH}-$, 2H), 4.72–4.63 (m, $-\text{OCHCH}-$, 2H), 4.48 (d, $J = 2.8$ Hz, $-\text{OCHCH}-$, 1H), 4.45 (d, $J = 2.8$ Hz, $-\text{OCHCH}-$, 1H), 4.44 (d, $J = 4.4$ Hz, $-\text{OCHCH}-$, 1H), 4.41 (d, $J = 4.4$ Hz, $-\text{OCHCH}-$, 1H), 4.23–3.96 (m, $-\text{OCH}_2\text{CH}_3$ and $-\text{OCH}_2\text{CH}_2-$, 16H), 2.30–1.95 (m, 6H), 1.91–1.81 (m, 2H), 1.65–1.30 (m, 8H), 1.28–1.13 (m, $-\text{OCH}_2\text{CH}_3$ and $-\text{OCHCH}_3$, 24H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.7, 193.6, 168.0, 167.9, 167.6, 136.9, 136.5, 133.7, 133.4, 128.9, 128.8,

128.8, 128.7, 128.7, 128.6, 128.6, 78.0, 77.7, 77.7, 77.2, 75.8, 75.4, 75.2, 61.5, 61.4, 60.6, 60.2, 59.9, 59.6, 33.4, 33.3, 32.6, 32.6, 30.9, 30.5, 30.1, 29.8, 21.2, 21.1, 21.0, 14.0, 14.0; IR (NaCl, neat) ν 2976, 2872, 1734, 1684 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 299.1259, found 299.1263.

Ethyl 3-oxo-3-phenyl-2-(tetrahydro-2H-pyran-2-yl)propanoate 102r¹³⁷

Yield 57%; obtained as two diastereomers with ratio of 1.7:1; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 8.05–8.01 (m, Ar H, 4H), 7.61–7.54 (m, Ar H, 2H), 7.50–7.44 (m, Ar H, 4H), 4.47 (d, $J = 9.2$ Hz, $-\text{OCHCH}-$, 1H), 4.46 (d, $J = 9.2$ Hz, $-\text{OCHCH}-$, 1H), 4.23–4.09 (m, $-\text{OCH}_2\text{CH}_3$ and $-\text{OCH}_2\text{CH}_2-$, 6H), 4.02–3.99 (m, $-\text{OCHCH}-$, 1H), 3.86–3.83 (m, $-\text{OCHCH}-$, 1H), 3.54–3.48 (m, $-\text{OCH}_2\text{CH}_2-$, 1H), 3.46–3.40 (m, $-\text{OCH}_2\text{CH}_2-$, 1H), 1.89–1.73 (m, $-\text{OCHCH}_2-$, 4H), 1.70–1.40 (m, $-\text{OCH}_2\text{CH}_2-$ and $-\text{OCH}_2\text{CH}_2\text{CH}_2-$, 8H), 1.20–1.16 (m, $-\text{OCH}_2\text{CH}_3$, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.7, 192.7, 167.8, 167.2, 137.2, 136.6, 136.4, 133.8, 133.3, 128.8, 128.6, 77.1, 76.9, 68.9, 68.8, 61.5, 61.4, 60.7, 59.9, 29.9, 29.7, 25.8, 25.8, 23.2, 23.1, 14.0.

Diisopropyl 2-(4-hydroxy-1-(4-methylphenylsulfonamido)butyl)malonate 102n¹³⁷

Yield 25%; white solid; mp 108–114 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 8.0$ Hz, Ar H, 2H), 7.28 (d, $J = 8.0$ Hz, Ar H, 2H), 5.71 (d, $J = 9.6$ Hz, $-\text{CHNHTs}$, 1H), 5.03 (m, $J = 6.0$ Hz, $-\text{OCH}(\text{CH}_3)_2$, 1H), 4.99 (m, $J = 6.0$ Hz, $-\text{OCH}(\text{CH}_3)_2$, 1H),

3.94–3.87 (m, $-\text{CHNHTs}$, 1H), 3.54–3.51 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.48 (d, $J = 4.0$ Hz, $-\text{CHCHNHTs}$, 1H), 2.41 (s, ArCH_3 , 3H), 1.65 (q, $J = 7.6$ Hz, $-\text{CH}_2\text{CHNHTs}$, 2H), 1.56–1.37 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 1.23 (d, $J = 6.0$ Hz, $-\text{OCH}(\text{CH}_3)_2$, 6H), 1.18 (t, $J = 6.0$ Hz, $-\text{OCH}(\text{CH}_3)_2$, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 167.0, 143.3, 138.4, 127.0, 129.6, 69.7, 69.4, 61.8, 55.2, 53.1, 29.6, 28.7, 21.6, 21.6, 21.5, 21.5, 21.4; IR (NaCl, neat) ν 3362, 3310, 2983, 2936, 1732, 1722, 1599 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{NO}_7\text{S}$ $[\text{M} + \text{H}]^+$ 430.1899, found 430.1892.

6.5 Iminoiodane-Mediated Synthesis of 1,4-Amino Alcohol with Grignard Reagents

General Procedure for the Preparation of Grignard Reagents

To a 25 mL two-necked round-bottomed flask fitted with condenser and magnetic stir bar, was charged with Mg turnings (4.4 mmol, 106 mg) and ethereal solvent (4 mL). Catalytic amount of iodine was added and the suspension was brought to reflux. Alkyl or aryl bromide solution (4 mmol) in ethereal solvent (2 mL) was added dropwise over 30 minutes. The reaction was then stirred at reflux for 4 hours. The reaction was cooled down to ambient temperature. The solution was subsequently titrated and used immediately.

General Procedure for the Iminoiodane-Mediated Synthesis of 1,4-Amino Alcohol with Grignard Reagents

Tetrahydrofuran **100a** (2 mL) was added to PhI=NTs (0.5 mmol, 197 mg) in a 25 mL round-bottomed flask and stirred for 50 min under N₂ atmosphere at room temperature. After the full consumption of the PhI=NTs, (CuOTf)₂·PhMe (0.025 mol, 6.5 mg) was added to the reaction mixture when required. The Grignard reagent (2.5 mmol) was slowly added over 5 minutes. The reaction was stirred at room temperature for 18 h. The reaction mixture was quenched with the addition of saturated solution of NH₄Cl (5 mL), the two layers were then separated. The aqueous

layer was then extracted with EtOAc (3×10 mL) and the combined organic layer was dried over MgSO_4 , filtered and concentrated under vacuum to give the crude mixture. The latter was subsequently purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 2:1 to 1:3) to give the corresponding *N*-tosylamino alcohol **104** or amino alcohol **105**.

General Procedure for the Iminoiodane-Mediated Synthesis of 1,4-Amino Alcohol with Grignard Reagents

Tetrahydrofuran **100a** (2 mL) was added to PhI=NTs (0.5 mmol, 197 mg) in a 25 mL round-bottomed flask and stirred for 50 min under N_2 atmosphere at room temperature. After the full consumption of the PhI=NTs , the phenyl magnesiumbromide (3.5 mmol, 1.0 M in THF, 3.5 mL) was slowly added over 5 minutes. The reaction was stirred at room temperature for 18 h. The reaction mixture was quenched with the addition of saturated solution of NH_4Cl (5 mL), the two layers were then separated. The aqueous layer was then extracted with EtOAc (3×10 mL) and the combined organic layer was dried over MgSO_4 , filtered and concentrated under vacuum to give the crude mixture. The latter was subsequently purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 2:1 to 1:3) to give the corresponding *N*-tosylamino alcohol **104a** and amino alcohol **105a**.

General Procedure for the Synthesis of **106a**

To a degassed round-bottomed flask equipped with magnetic stir bar was added **104a** (0.1 mmol, 31.9mg) and pyridinium dichromate (0.5 mmol, 200 mg). DMF was then added subsequently and the reaction was stirred at ambient temperature for 18 h. The reaction was then quenched with the addition of water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with water (3 × 20 mL). The organic layer was then dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 4:1) to furnish the lactam **106a**.

General Procedure for the Synthesis of **107f**

To a degassed round-bottomed flask was added **104f** (0.1 mmol, 29.9mg), triphenylphosphine (0.12 mmol, 31 mg) and THF (3 mL). The reaction was cooled to 0 °C and diisopropylazodicarboxylate (0.12 mmol, 24 μL) was subsequently added in one portion and the reaction mixture was stirred at ambient temperature for 18 h. Upon completion, based on TLC analysis, the reaction mixture was concentrated under reduced pressure. The latter was then purified by flash column chromatography (eluent: *n*-hexane/EtOAc, 4:1) to furnish the corresponding pyrrolidine **107f**.

Representative Procedure for the Enantioselective Study for the Synthesis of 1,4-Amino Alcohol 104f

Tetrahydrofuran **100a** (1 mL) was added to PhI=NTs (0.25 mmol, 93 mg) in a 5 mL round-bottomed flask and stirred for 50 min under N₂ atmosphere at room temperature. After the full consumption of the PhI=NTs, the reaction mixture was concentrated under reduced pressure and back filled with N₂ and MTBE (1 mL). To a mixture of Cu(OTf)₂ (0.025 mmol, 9 mg) and ligand **PN-1** (0.05 mmol, 27 mg) in another 5 mL round-bottomed flask was added MTBE (2 mL) under N₂ atmosphere. To the copper and ligand solution was added isobutyl magnesiumbromide (0.75 mmol, 1.0 M in Et₂O + MTBE, 750 μ L) dropwise over 10 minutes. The 2-aminotetrahydrofuran solution in MTBE was then added slowly and the reaction mixture was stirred for 18 h. Upon completion, the reaction was quenched with the addition of saturated solution of NH₄Cl (5 mL). A portion of the organic layer was subsequently purified by preparative TLC (eluent: *n*-hexane/EtOAc, 1:1) to give the corresponding *N*-tosylamino alcohol **104f**.

***N*-(4-hydroxy-1-phenylbutyl)-4-methylbenzenesulfonamide 104a**¹³⁸

Yield 86%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, *J* = 8.3 Hz, Ar H, 2H), 7.11–7.00 (m, Ar H, 7H), 6.05 (d, *J* = 7.6 Hz, –CHNHTs, 1H), 4.29 (q, *J* = 7.3 Hz, –CHNHTs, 1H), 3.59–3.54 (dt, *J* = 6.2 Hz, 2.6 Hz, –CH₂CH₂OH, 2H), 2.40 (brs, –CH₂CH₂OH, 1H), 2.33 (s, ArCH₃, 3H), 1.94–1.71 (m, –CH₂CHNHTs, 2H),

1.69–1.39 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.8, 141.0, 137.7, 129.2, 128.3, 127.1, 127.0, 126.5, 62.1, 58.2, 34.2, 28.8, 21.4.

***N*-(4-hydroxy-1-(*o*-tolyl)butyl)-4-methylbenzenesulfonamide 104b**

Yield 72%; white solid; mp 88–90 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.49 (d, J = 8.0 Hz, Ar H, 2H), 7.06–7.01 (m, Ar H, 3H), 6.99–6.93 (m, Ar H, 3H), 5.91 (d, J = 7.6 Hz, $-\text{CHNHTs}$, 1H), 4.59 (q, J = 7.2 Hz, $-\text{CHNHTs}$, 1H), 3.63–3.53 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.31 (s, ArCH_3 , 3H), 2.17 (s, $-\text{CH}_2\text{CH}_2\text{OH}$ and ArCH_3 , 4H), 1.88–1.84 (m, $-\text{CH}_2\text{CHNHTs}$, 1H), 1.82–1.66 (m, $-\text{CH}_2\text{CHNHTs}$, 1H), 1.64–1.52 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 1.50–1.44 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.8, 139.5, 137.6, 134.5, 130.1, 129.1, 126.8, 126.8, 126.2, 125.9, 62.1, 53.8, 33.7, 28.9, 21.4, 19.1; IR (NaCl, neat) ν 3491, 3280, 3055, 2926, 2874, 1449 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{23}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 356.1296, found 356.1302.

***N*-(5-hydroxypentan-2-yl)-4-methylbenzenesulfonamide 104c**

Yield 88%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, J = 8.0 Hz, Ar H, 2H), 7.29 (d, J = 8.0 Hz, Ar H, 2H), 5.26 (d, J = 8.0 Hz, $-\text{CHNHTs}$, 1H), 3.57 (t, J = 8.0 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.33 (m, $-\text{CHNHTs}$, 1H), 2.42 (s, ArCH_3 , 3H), 1.54–1.45 (m, $-\text{CH}_2\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{CHNHTs}$, 4H), 1.01 (d, J = 4.0 Hz, $-\text{CH}(\text{CH}_3)\text{NHTs}$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.1, 138.2, 129.6, 127.0, 62.2, 49.8, 33.7, 28.4, 21.4;

IR (NaCl, neat) ν 3500, 3280, 2933, 2873, 1449, 1433 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{19}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 280.0983, found 280.0984.

***N*-(6-hydroxyhexan-3-yl)-4-methylbenzenesulfonamide 104d**

Yield 68%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.77 (d, J = 8.2 Hz, Ar H, 2H), 7.29 (d, J = 6.5 Hz, Ar H, 2H), 5.24 (d, J = 8.2 Hz, $-\text{CHNHTs}$, 1H), 3.54 (t, J = 5.4 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.18 (t, J = 6.1 Hz, $-\text{CHNHTs}$, 1H), 2.19 (s, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 2.42 (s, ArCH_3 , 3H), 1.50–1.46 (m, $-\text{CH}_2\text{CHNHTs}$, 2H), 1.45–1.37 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 1.37–1.30 (m, $-\text{CH}_2\text{CH}_3$, 2H), 0.73 (t, J = 7.4 Hz, $-\text{CH}_2\text{CH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.1, 138.4, 129.6, 127.0, 62.5, 55.2, 30.8, 28.1, 27.8, 21.5, 9.7; IR (NaCl, neat) ν 3491, 3286, 2963, 2936, 2876, 1449 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{21}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 294.1140, found 294.1145.

***N*-(7-hydroxyhept-1-en-4-yl)-4-methylbenzenesulfonamide 104e**

Yield 86%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, J = 8.3 Hz, Ar H, 2H), 7.30 (d, J = 8.2 Hz, Ar H, 2H), 5.61–5.47 (m, $-\text{CH}_2\text{CH}=\text{CH}_2$, 1H), 5.14 (d, J = 8.0 Hz, $-\text{CHNHTs}$, 1H), 4.98 (d, J = 10.4 Hz, $-\text{CH}_2\text{CH}=\text{CH}_2$, 1H), 4.94 (d, J = 17.1 Hz, $-\text{CH}_2\text{CH}=\text{CH}_2$, 1H), 3.56 (t, J = 5.5 Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.30 (t, J = 5.8 Hz, $-\text{CHNHTs}$, 1H), 2.42 (s, ArCH_3 , 3H), 2.27–2.07 (m, $-\text{CH}_2\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{CH}=\text{CH}_2$, 3H), 1.57–1.50 (m, $-\text{CH}_2\text{CHNHTs}$, 2H), 1.49–1.41 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.3, 138.1, 133.4, 129.6, 127.1, 118.7, 62.4, 53.2, 39.3, 30.9,

28.2, 21.5; IR (NaCl, neat) ν 3491, 3283, 2926, 2874, 1449, 1321 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 306.1140, found 306.1145.

***N*-(1-hydroxy-6-methylheptan-4-yl)-4-methylbenzenesulfonamide 104f**

Yield 82%; white solid; mp 76–77 °C ^1H NMR (300 MHz, CDCl_3) δ 7.77 (d, J = 8.2 Hz, Ar H, 2H), 7.29 (d, J = 8.0 Hz, Ar H, 2H), 5.37 (s, $-\text{CHNHTs}$, 1H), 3.54–3.51 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.28–3.26 (m, $-\text{CHNHTs}$, 1H), 2.49 (brs, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 2.41 (s, ArCH_3 , 3H), 1.54–1.36 (m, $-\text{CH}_2\text{CHNHTs}$, $-\text{CH}_2\text{CH}_2\text{OH}$ and $-\text{CH}(\text{CH}_3)_2$ 5H), 1.18 (t, J = 7.0 Hz, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, 2H), 0.75 (d, J = 6.6 Hz, $-\text{CH}(\text{CH}_3)_2$, 3H), 0.68 (d, J = 6.6 Hz, $-\text{CH}(\text{CH}_3)_2$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.1, 138.4, 129.5, 127.1, 62.5, 52.0, 44.5, 31.7, 27.9, 24.5, 22.5, 22.3, 21.5; IR (NaCl, neat) ν 3493, 3283, 2954, 2931, 2868, 1449, 1319 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{25}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 322.1453, found 322.1465.

***N*-(1-hydroxynonan-4-yl)-4-methylbenzenesulfonamide 104g**

Yield 71%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, J = 8.4 Hz, Ar H, 2H), 7.29 (d, J = 8.1 Hz, Ar H, 2H), 5.12 (d, J = 8.4 Hz, $-\text{CHNHTs}$, 1H), 3.58–3.53 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.25–3.20 (m, $-\text{CHNHTs}$, 1H), 2.86 (brs, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 2.42 (s, ArCH_3 , 3H), 1.60–1.45 (m, $-\text{CH}_2\text{CHNHTs}$ and $-\text{CH}_2\text{CH}_2\text{OH}$, 4H), 1.40–1.28 (m,

4H), 1.21–1.14 (m, 4H), 0.79 (t, $J = 10.4$ Hz, $-\text{CH}_2\text{CH}_3$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.1, 138.4, 129.5, 127.0, 62.5, 53.9, 35.0, 31.5, 28.1, 25.0, 22.4, 21.5, 13.9; IR (NaCl, neat) ν 3501, 3283, 2953, 2930, 1717, 1354, 1449, 1429, 1321 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{27}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 336.1609, found 336.1612.

***N*-(1-cyclopentyl-4-hydroxybutyl)-4-methylbenzenesulfonamide 104h**

Yield 72%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, $J = 8.2$ Hz, Ar H, 2H), 7.28 (d, $J = 8.2$ Hz, Ar H, 2H), 5.28 (d, $J = 8.5$ Hz, $-\text{CHNHTs}$, 1H), 3.56–3.46 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.17–3.13 (m, $-\text{CHNHTs}$, 1H), 2.41 (s, ArCH_3 , 3H), 2.34 (brs, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 1.91–1.80 (m, 1H), 1.61–1.40 (m, 10H), 1.15–1.05 (m, 1H), 1.06–0.97 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.0, 138.6, 129.5, 127.0, 62.6, 57.9, 44.1, 30.3, 29.2, 29.1, 27.9, 25.3, 25.0, 21.5; IR (NaCl, neat) ν 3374, 3055, 3026, 2926, 2598, 1495, 1452, 1331 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$ 312.1633, found 312.1631.

***N*-(6-hydroxy-2-methylhex-1-en-3-yl)-4-methylbenzenesulfonamide 104i**

Yield 66%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.73 (d, $J = 8.3$ Hz, Ar H, 2H), 7.26 (d, $J = 8.5$ Hz, Ar H, 2H), 5.46 (d, $J = 4.5$ Hz, $-\text{CHNHTs}$, 1H), 4.71 (d, $J = 1.4$ Hz, $-\text{C}(\text{CH}_3)=\text{CH}_2$, 1H), 4.68 (d, $J = 1.4$ Hz, $-\text{C}(\text{CH}_3)=\text{CH}_2$, 1H), 3.73 (q, $J = 6.9$ Hz, $-\text{CHNHTs}$, 1H), 3.59 (t, $J = 5.9$ Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.41 (s, ArCH_3 , 3H), 1.68–1.54 (m, $-\text{CH}_2\text{CHNHTs}$ and $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, 7H); ^{13}C NMR

(75 MHz, CDCl_3) δ 143.4, 143.1, 137.9, 129.4, 127.2, 113.3, 76.6, 62.2, 59.5, 30.4, 28.6, 21.5, 17.5; IR (NaCl, neat) ν 3485, 3285, 2954, 2874, 1651, 1599, 1454, 1319 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 306.1140, found 306.1146.

***N*-(7-hydroxy-2-methylhept-2-en-4-yl)-4-methylbenzenesulfonamide 104j**

Yield 72%; yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, $J = 8.2$ Hz, Ar H, 2H), 7.23 (d, $J = 8.1$ Hz, Ar H, 2H), 5.57 (d, $J = 7.5$ Hz, $-\text{CHNHTs}$, 1H), 4.68 (d, $J = 9.3$ Hz, $-\text{CH}=\text{C}(\text{CH}_3)_2$, 1H), 3.97–3.90 (m, $-\text{CHNHTs}$, 1H), 3.57 (t, $J = 6.1$ Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.73 (brs, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 2.38 (s, Ar CH_3 , 3H), 1.64–1.51 (m, $-\text{CH}_2\text{CHNHTs}$ and $-\text{CH}_2\text{CH}_2\text{OH}$, 4H), 1.40 (s, $-\text{CH}=\text{C}(\text{CH}_3)_2$, 3H), 1.37 (s, $-\text{CH}=\text{C}(\text{CH}_3)_2$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.8, 138.4, 134.3, 129.2, 127.2, 125.0, 62.2, 52.2, 32.7, 28.5, 25.3, 21.4, 17.9; IR (NaCl, neat) ν 3491, 3281, 2930, 2872, 1599, 1449, 1321 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{23}\text{NNaO}_3\text{S}$ $[\text{M} + \text{Na}]^+$ 320.1296, found 320.1299.

***N*-(7-hydroxyhept-2-yn-4-yl)-4-methylbenzenesulfonamide 104k**

Yield 66%; pale yellow solid; mp 119–121 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 7.78 (d, $J = 8.3$ Hz, Ar H, 2H), 7.30 (d, $J = 8.2$ Hz, Ar H, 2H), 5.22 (d, $J = 8.9$ Hz, $-\text{CHNHTs}$, 1H), 4.05 (d, $J = 6.1$ Hz, $-\text{CHNHTs}$, 1H), 3.74–3.60 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.42 (s, Ar CH_3 , 3H), 2.05 (brs, $-\text{CH}_2\text{CH}_2\text{OH}$, 1H), 1.75–1.63 (m, $-\text{CH}_2\text{CHNHTs}$ and

–CH₂CH₂OH, 4H), 1.50 (s, –C≡C–CH₃, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.2, 137.5, 129.3, 127.5, 80.7, 62.1, 45.7, 33.3, 28.3, 21.5, 3.2; HRMS (ESI) calcd for C₁₄H₁₉NNaO₃S [M + Na]⁺ 304.0983, found 304.0995.

***N*-(1-cyclopropyl-4-hydroxybutyl)-4-methylbenzenesulfonamide 104l**

Yield 29%; yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, Ar H, 2H), 7.29 (d, *J* = 7.4 Hz, Ar H, 2H), 5.25 (d, *J* = 7.1 Hz, –CHNHTs, 1H), 3.59 (m, –CH₂CH₂OH, 2H), 2.57 (t, *J* = 7.8 Hz, –CH₂CH₂OH, 1H), ArCH₃, 2.42 (s, ArCH₃, 3H), 2.02 (brs, –CH₂CH₂OH, 1H), 1.69–1.53 (m, –CH₂CHNHTs and –CH₂CH₂OH, 4H), 0.78–0.68 (m, 1H), 0.48–0.39 (m, 1H), 0.27–0.18 (m, 1H), 0.16–0.07 (m, 1H), –0.08–0.16 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 138.4, 129.5, 127.1, 62.6, 58.7, 32.2, 28.2, 21.5, 16.3, 3.8, 3.5; IR (NaCl, neat) ν 3491, 3287, 2926, 2874, 1449 cm^{–1}; HRMS (ESI) calcd for C₁₄H₂₁NNaO₃S [M + Na]⁺ 306.1140, found 306.1143.

***N*-(4-hydroxy-1-(4-methoxyphenyl)butyl)-4-methylbenzenesulfonamide 104m**

Yield 62%; white solid; mp 116–118 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, *J* = 8.3 Hz, Ar H, 2H), 7.09 (d, *J* = 8.1 Hz, Ar H, 2H), 6.93 (d, *J* = 8.4 Hz, Ar H, 2H), 6.64 (d, *J* = 8.7 Hz, Ar H, 2H), 5.85 (d, *J* = 7.4 Hz, –CHNHTs, 1H), 4.24 (q, *J* = 7.2 Hz, –CHNHTs, 1H), 3.72 (s, –OCH₃, 3H), 3.56 (dt, *J* = 6.2 Hz, 1.7 Hz,

–CH₂CH₂OH, 2H), 2.34 (s, ArCH₃, 3H), 2.24 (brs, –CH₂CH₂OH, 1H), 1.92–1.81 (m, –CH₂CHNHTs, 1H), 1.81–1.67 (m, –CH₂CHNHTs, 1H), 1.59–1.41 (m, –CH₂CH₂OH, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 158.7, 142.7, 137.8, 133.2, 129.2, 127.7, 127.0, 113.7, 62.1, 57.7, 55.2, 34.1, 28.9, 21.4; IR (NaCl, neat) ν 3491, 3225, 2952, 2936, 1750, 1449, 1319 cm⁻¹; HRMS (ESI) calcd for C₁₈H₂₄NO₃S [M + H]⁺ 334.1477, found 334.1461.

***N*-(1-(4-chlorophenyl)-4-hydroxybutyl)-4-methylbenzenesulfonamide 104n**

Yield 28%; white solid; mp 105–106 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, *J* = 8.3 Hz, Ar H, 2H), 7.11–7.05 (m, Ar H, 4H), 6.95 (d, *J* = 6.6 Hz, Ar H, 2H), 6.08 (d, *J* = 7.4 Hz, –CHNHTs, 1H), 4.28 (q, *J* = 7.2 Hz, –CHNHTs, 1H), 3.58 (td, *J*₁ = 8.1 Hz, *J*₂ = 3.9 Hz, –CH₂CH₂OH, 2H), 2.36 (s, ArCH₃, 3H), 2.23 (brs, –CH₂CH₂OH, 1H), 1.90–1.81 (m, –CH₂CHNHTs, 1H), 1.80–1.69 (m, –CH₂CHNHTs, 1H), 1.67–1.40 (m, –CH₂CH₂OH, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 143.2, 139.5, 137.5, 133.0, 129.3, 128.4, 128.0, 127.0, 62.1, 57.6, 34.1, 28.6, 21.4; IR (NaCl, neat) ν 3503, 3275, 3156, 3055, 2926, 1609, 1494, 1319 cm⁻¹; HRMS (ESI) calcd for C₁₇H₂₁³⁵ClNO₃S [M + H]⁺ 354.0931, found 354.0945.

4-Amino-4-phenylbutan-1-ol 105a¹³⁹

Yield 49%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.33–7.23 (m, Ar H, 5H), 4.68 (t, J = 6.3 Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 3.69–3.56 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.00 (brs, 2H), 1.86–1.79 (m, $-\text{CH}_2\text{CHNH}_2$, 2H), 1.71–1.56 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 144.7, 128.4, 127.4, 125.8, 74.3, 62.7, 36.3, 29.2.

4-Amino-4-cyclopropylbutan-1-ol 105l

Yield 33%; pale-yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 3.70–3.64 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.94–2.87 (m, $-\text{CH}_2\text{CHNH}_2$, 1H), 2.25 (brs, 2H), 1.87–1.58 (m, $-\text{CH}_2\text{CHNH}_2$ and $-\text{CH}_2\text{CH}_2\text{OH}$, 4H), 1.02–0.90 (m, 1H), 0.55–0.48 (m, 2H), 0.32–0.18 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 76.6, 63.1, 34.0, 29.3, 18.0, 2.8, 2.7; IR (NaCl, neat) ν 3375, 2928, 2874, 1265 cm⁻¹; HRMS (ESI) calcd for C₇H₁₅NNaO [M + H]⁺ 152.1051, found 152.1052.

4-Amino-4-(4-methoxyphenyl)butan-1-ol 105m¹³⁹

Yield 37%; white solid; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, J = 8.7 Hz, Ar H, 2H), 6.88–6.84 (m, Ar H, 2H), 4.63 (t, J = 6.3 Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 3.79 (s, $-\text{OCH}_3$, 3H), 3.68–3.60 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.92 (brs, 2H), 1.85–1.78 (m, $-\text{CH}_2\text{CHNH}_2$, 2H),

1.68–1.57 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.9, 136.9, 127.0, 113.8, 73.9, 62.8, 55.3, 36.2, 29.3.

4-Amino-4-(4-chlorophenyl)butan-1-ol, 105n^{123a}

Yield 59%; white solid; ^1H NMR (300 MHz, CDCl_3) δ 7.31–7.23 (m, Ar H, 4H), 4.65 (t, $J = 6.2$ Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 3.69–3.56 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.25 (brs, 2H), 1.83–1.76 (m, $-\text{CH}_2\text{CHNH}_2$, 2H), 1.67–1.60 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.2, 133.0, 128.5, 127.2, 73.5, 62.6, 36.5, 28.9.

4-Amino-4-(3-(trifluoromethyl)phenyl)butan-1-ol 105o

Yield 44%; brown oil; ^1H NMR (400 MHz, CDCl_3) δ 6.93 (s, Ar H, 3H), 6.88 (s, Ar H, 1H), 4.59 (t, $J = 6.2$ Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 3.69–3.58 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.01 (brs, 2H), 1.80 (q, $J = 6.6$ Hz, $-\text{CH}_2\text{CHNH}_2$, 2H), 1.69–1.51 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.8, 130.6 (q, $J_{\text{C-F}} = 32.0$ Hz), 129.1, 128.8, 124.2 (q, $J_{\text{C-F}} = 270.6$ Hz), 124.1 (d, $J_{\text{C-F}} = 3.6$ Hz), 122.5 (d, $J_{\text{C-F}} = 3.7$ Hz), 73.5, 62.5, 36.6, 28.8; ^{19}F NMR (225 MHz, CDCl_3) δ -62.5.

4-Amino-4-(3,5-dimethylphenyl)butan-1-ol 105p

Yield 62%; white solid; ^1H NMR (300 MHz, CDCl_3) δ 6.92 (s, Ar H, 2H), 6.88 (s, Ar H, 1H), 4.58 (t, $J = 6.2$ Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 3.65–3.58 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 3.16 (brs, 2H), 2.29 (s, ArCH_3 , 6H), 1.82–1.75 (m, $-\text{CH}_2\text{CHNH}_2$, 2H), 1.65–1.60 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.8, 137.9, 129.0, 123.6, 74.3, 62.7, 36.3, 29.3, 21.3.

4-Amino-4-(naphthalen-1-yl)butan-1-ol 105s

Yield 85%; white solid; ^1H NMR (300 MHz, CDCl_3) δ 8.11 (d, $J = 8.0$ Hz, Ar H, 1H), 7.82 (dd, $J = 7.4$ Hz, 2.1 Hz, Ar H, 1H), 7.72 (d, $J = 8.2$ Hz, Ar H, 1H), 7.65 (d, $J = 7.0$ Hz, Ar H, 1H), 7.50–7.40 (m, Ar H, 3H), 5.46 (q, $J = 4.1$ Hz, $-\text{CH}_2\text{CHNH}_2$, 1H), 4.79 (brs, 2H), 3.58 (t, $J = 6.5$ Hz, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H), 2.10–1.98 (m, $-\text{CH}_2\text{CHNH}_2$, 1H), 1.94–1.85 (m, $-\text{CH}_2\text{CHNH}_2$, 1H), 1.82–1.60 (m, $-\text{CH}_2\text{CH}_2\text{OH}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.6, 133.9, 130.5, 128.6, 127.3, 125.6, 125.1, 123.0, 122.7, 70.1, 61.8, 34.9, 29.0.

5-Phenyl-1-tosylpyrrolidin-2-one 106a¹⁴⁰

Yield 75%; light-yellow solid; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (d, J = 6.7 Hz, Ar H, 2H), 7.31–7.24 (m, Ar H, 3H), 7.18–7.11 (m, Ar H, 4H), 5.46–5.43 (m, –CH(Ph)NHTs, 1H), 2.75–2.46 (m, –COCH₂CH₂– and –COCH₂CH₂–, 3H), 2.39 (s, ArCH₃, 3H), 2.01–1.94 (m, –COCH₂CH₂– 1H); ¹³C NMR δ 173.5, 144.9, 140.7, 135.5, 129.1, 128.8, 128.5, 128.1, 126.1, 63.0, 30.6, 28.3, 21.6.

2-Isobutyl-1-tosylpyrrolidine 107f

Yield 89%; white solid; mp 69–70 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 8.0 Hz, Ar H, 2H), 7.31 (d, J = 8.0 Hz, Ar H, 2H), 3.69–3.63 (m, –CHNTs–, 1H), 3.40–3.35 (m, –CH₂NTs–, 1H), 3.23–3.17 (m, –CH₂NTs–, 1H), 2.43 (s, ArCH₃, 3H), 1.80–1.70 (m, –CH₂CH(CH₃)₂, 2H), 1.65–1.45 (m, –CH₂CH₂CH₂NTs– and –CH₂CH₂CH₂NTs–, 4H), 1.36–1.28 (m, –CH(CH₃)₂, 1H), 0.94 (d, J = 6.4 Hz, –CH(CH₃)₂, 6H); ¹³C NMR δ 143.2, 135.0, 129.6, 127.5, 58.9, 48.7, 45.6, 31.0, 29.7, 25.5, 24.0, 23.5, 21.9, 21.5; IR (NaCl, neat) ν 3491, 3055, 2957, 2926, 2853, 1473, 1339 cm^{–1}; HRMS (ESI) calcd for C₁₅H₂₄NO₂S [M + H]⁺ 282.1528, found 282.1529.

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