UNIVERSITY COLLEGE LONDON
DEPARTMENT OF CHEMISTRY

Synthesis of Nitrogen Heterocycles by Hypervalent Iodine Mediated Cyclization

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Declaration

I, Mohamed Raif Ibrahim, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

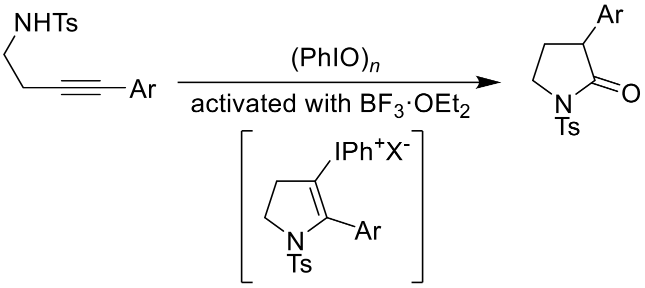
Date: 2 Dec 2022

Abstract

This thesis discusses the synthesis of 3-arylpyrrolidin-2-ones and the use of hypervalent iodine reagents in organic synthesis.

With that being the case, the first chapter provides a brief introduction to nitrogen heterocycles and discusses methods for the synthesis of 3-arylpyrrolidin-2-ones. The second chapter provides an introduction to the bonding and reactivity of hypervalent iodine reagents. The third chapter explores the prior applications of hypervalent iodine reagent in organic synthesis with a focus on areas relevant to this work. This includes the use of hypervalent iodine reagents in the functionalization of alkynes, in nitrogen heterocycle synthesis and in various migratory reactions.

The fourth chapter discusses the results of an investigation into the synthesis of pyrrolidinones. A novel synthesis of 3-arylpyrrolidin-2-ones by a hypervalent iodine induced cyclization-rearrangement cascade reaction is reported. Starting from *N*-(4-arylbut-3-yn-1-yl)tosylamides, the initial cyclization gives an intermediary *β*-arylvinyl(phenyl)iodonium salt which has been isolated and characterized by NMR spectroscopy. Hydration of this intermediate leads to the generation of 3-arylpyrrolidin-2-ones by a 1,2-aryl shift with expulsion of iodobenzene.



The fifth chapter summarizes the results and suggests some avenues for future research. The final chapter provides the experimental details and characterization data for compounds isolated during the course of this work.

Impact Statement

Nitrogen heterocycles are a commonly found structure in natural products, pharmaceuticals and other biologically active products. As a result the synthesis of nitrogen heterocycles is an important area of research in organic chemistry.

Another area which has garnered interest is the use of hypervalent iodine reagents in organic synthesis. In recent decades hypervalent iodine compounds have proven themselves to be valuable and versatile reagents, finding application in many different transformations from oxidations to carbon-carbon bond forming reactions. They have the ability to emulate some aspects of transition metal chemistry, but with the advantage of by-products that are more benign.

In this study we investigated the synthesis of pyrrolidines, a 5-membered nitrogen heterocycle, with hypervalent iodine reagents. A novel reaction that combines cyclization with rearrangement to give pyrrolidinones was found and investigated in detail.

Acknowledgements

First of all, I would like to thank Prof. Mike Porter for his valuable input and guidance throughout the project. I would also like to thank the other members of the Porter group, James and Diana, for their help with various things – mainly providing advice on laboratory procedures I was unfamiliar with. Additionally, I would like to thank Dr. Abil Aliev for providing assistance in the usage of UCL's NMR facilities and the staff of the UCL Mass Spectrometry Facility for recording the mass spectra used in this project. Lastly, I would like to thank UCL for granting me an Overseas Research Scholarship (ORS) and Graduate Research Scholarship (GRS) for my studies.

Table of Contents

Abbreviations

acac	acetylacetonate
aq.	aqueous
ATR	attenuated total reflectance
b.p.	boiling point
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
br	broad (peak)
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CI	chemical ionization
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Δ	used to represent addition of energy to a reaction as heat, or used to denote a difference
δ	chemical shift in ppm, or used to denote a small value
DABCO	1,4-diazabicyclo[2.2.2]octane
dan	1,8-diaminonaphthalene
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
dec.	decomposition
DEPT	distortionless enhancement by polarization transfer
DFA	difluoroacetic acid
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane

DMSO	dimethyl sulfoxide
E2	bimolecular elimination
EDG	electron donating group
ee	enantiomeric excess
EI	electron ionization
eq	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
EWG	electron withdrawing group
FDA	(United States) Food and Drug Administration
FTIR	Fourier-transform infrared spectroscopy
GB	Gaussian maximum position
$h\nu$	Planck constant × frequency, used as shorthand for electromagnetic radiation
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl)amide
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
HTIB	[hydroxy(tosyloxy)iodo]benzene
IBA	2-iodosobenzoic acid
IBX	2-iodoxybenzoic acid
J	coupling constant
LB	line broadening
LDA	lithium diisopropylamide
lit.	literature
LICA	lithium isopropylcyclohexylamide
LiTMP	lithium tetramethylpiperidide
m	multiplet (in NMR spectroscopy), or medium intensity (in IR spectroscopy)
m.p.	melting point
m/z	mass-to-charge ratio
*m*CBA	*meta*-chlorobenzoic acid
*m*CPBA	*meta*-chloroperoxybenzoic acid

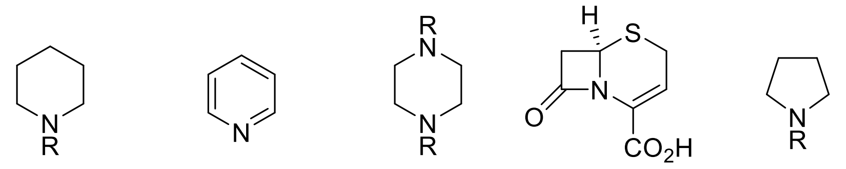
MIDA	*N*-methyliminodiacetic acid
MO	molecular orbital
MS	molecular sieves or mass spectrometry, depending on context
ν	frequency
ν_{max}	frequency at maximum intensity of peak
NMP	*N*-methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
phen	1,10-phenanthroline
PIDA	(diacetoxyiodo)benzene
PIFA	[bis(trifluoroacetoxy)iodo]benzene
pin	pinacol
Piv	pivaloyl
pmdba	4,4’-methoxydibenzylideneacetone
PMP	*para*-methoxyphenyl
ppm	parts per million
ppt	precipitate
Py	pyridine
q	quartet
QTOF	quadrupole time-of-flight
quint	quintet
rt	room temperature
σ	Hammett value
s	singlet (in NMR spectroscopy), or strong (in IR spectroscopy)
SET	single electron transfer
S_N2	bimolecular nucleophilic substitution
t	triplet
TEAB	tetraethylammonium bromide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPBSA	2,4,5-triisopropylbenzenesulfonic acid
TMS	trimethylsilyl
Tol	tolyl
UCL	University College London
UV	ultraviolet light
UV-vis	ultraviolet and visible light
vs	very strong
w	weak
Xantphos	(9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)

1. Nitrogen Heterocycles

1.1. Introduction

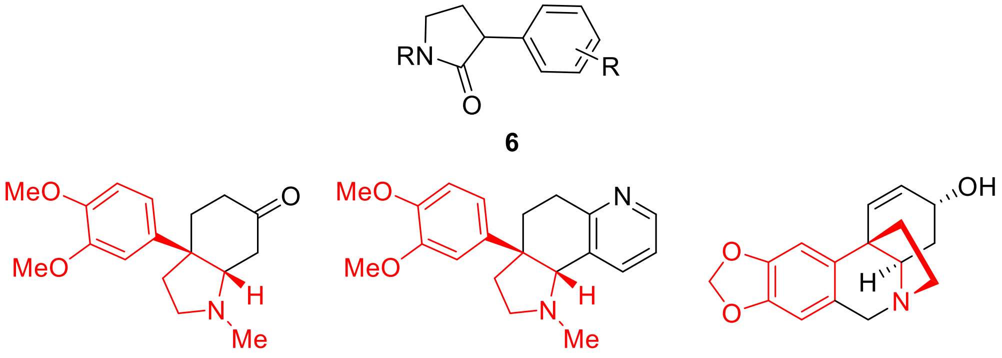
Nitrogen heterocycles are a class of compounds that are of crucial importance to many areas of organic chemistry. In addition to their common use in organic synthesis as reactants, catalysts or solvents, *N*-heterocycles are also present in many desirable compounds such as dyes,[1] pharmaceuticals[2] and pesticides.[3] A 2014 study found that 59% of small-molecule drugs approved by the United States FDA contained a nitrogen heterocycle.[2] The top five most frequent structural motifs in the drugs studied were found to be piperidines (**1**), pyridines (**2**), piperazines (**3**), cephems (**4**) and pyrrolidines (**5**) (Figure 1).



1 72/640 (11%)
2 62/640 (10%)
3 59/640 (9%)
4 41/640 (6%)
5 37/640 (6%)

Figure 1: Top five most frequent *N*-heterocycle motifs in FDA approved small molecule drugs.[2]

The research carried out in this thesis focuses on the synthesis of a structure relating to motif **5** – *α*-arylated pyrrolidinones **6**. This class of compounds is of interest in the synthesis of several natural products, including (−)-mesembrine (**7**), (+)-sceletium A-4 (**8**) and (−)-crinine (**9**) (Figure 2).[4]



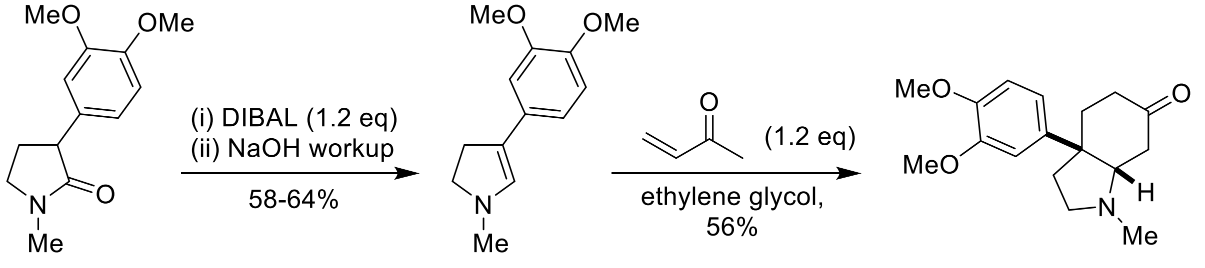
7
(−)-mesembrine

8
(+)-sceletium A-4

9
(−)-crinine

Figure 2: The 3-arylpyrrolidin-2-one motif **6** provides access to natural products such as (−)-mesembrine (**7**), (+)-sceletium A-4 (**8**) and (−)-crinine (**9**).[4]

For example, a short total synthesis of (±)-mesembrine reported in 1983 by Pinnick and Kochhar used pyrrolidinone **10** as a key intermediate (Scheme 1).[5] This pyrrolidinone was reduced with DIBAL and annulated[6] with methyl vinyl ketone giving (±)-**7**.



10 **11** (±)-**7**

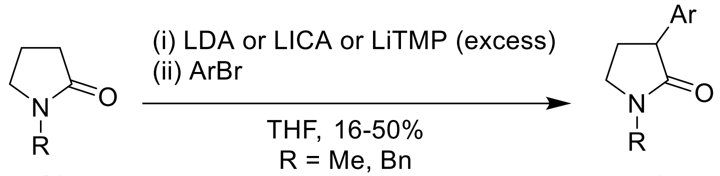
Scheme 1: *α*-Arylated pyrrolidinone **10** was used as an intermediate by Pinnick and Kochhar in their synthesis of (±)-mesembrine (**7**).[5]

1.2. Synthesis of 3-Arylpyrrolidin-2-ones

The methods of synthesising 3-arylpyrrolidin-2-ones reported in the literature can be classified into three categories: (i) *α*-arylation of pyrrolidinones, (ii) intramolecular amidation and (iii) ring expansion.

1.2.1. *α*-Arylation of Pyrrolidinones

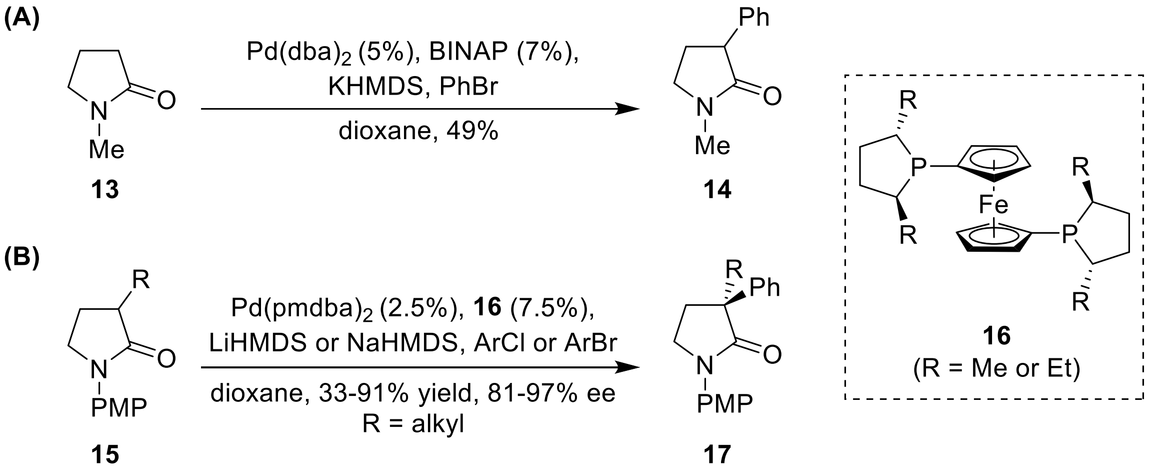
Early investigations into the *α*-arylation of pyrrolidinones were carried out by the group of Pinnick. These investigations were motivated by their interest in the total synthesis of mesembrine (discussed above, Scheme 1).[5] Pinnick and co-workers reported successful synthesis of 3-arylpyrrolidin-2-ones in low to moderate yields of 16–50% by the coupling of pyrrolidinone enolates with aryl bromides in the presence of an excess of strong base (Scheme 2).[7] The reaction is expected to be an elimination-addition reaction proceeding via a benzyne mechanism. Due to the involvement of a benzyne intermediate the reaction suffered from regioselectivity issues, with a 1:1 mixture of regioisomers reported for the reaction with *p*-bromoanisole.



12 **6**

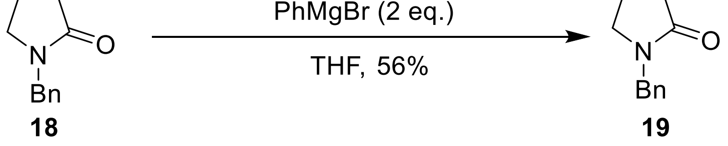
Scheme 2: *α*-Arylation of pyrrolidinones by an elimination-addition reaction was reported by Pinnick *et al.*[7]

In 1998, Hartwig *et al.* communicated a method for the *α*-arylation of amides via a palladium-catalysed coupling of pyrrolidinone enolates with aryl bromides.[8] They successfully applied their procedure to the *α*-arylation of *N*-methylpyrrolidin-2-one (NMP, **13**) giving the *α*-arylated product **14** in 49% yield (Scheme 3A). The reaction proceeds by oxidative addition of the aryl bromide to palladium, followed by ligand substitution of the bromide by the pyrrolidinone enolate. Subsequent reductive elimination gives the coupled product. Consequently, this reaction does not suffer from regioselectivity issues, making it advantageous compared to the earlier reaction by Pinnick. An enantioselective variation was reported by Stoltz and colleagues in 2019 (Scheme 3B).[4] This was achieved by using chiral ligand **16** which provided high enantioselectivities of up to 97% ee.



Scheme 3: Palladium-catalysed pyrrolidinone *α*-arylation methods were reported by Hartwig *et al.* (A) and Stoltz *et al.* (B).[4, 8]

A cobalt-catalysed *α*-arylation reaction has also been reported. Communicated by Cossy *et al.* in 2017, the reaction couples *α*-bromo amides with aryl Grignard reagents.[9] Application of the methodology to *α*-bromo pyrrolidinone **18** gave the corresponding arylated product in 56% yield (Scheme 4).

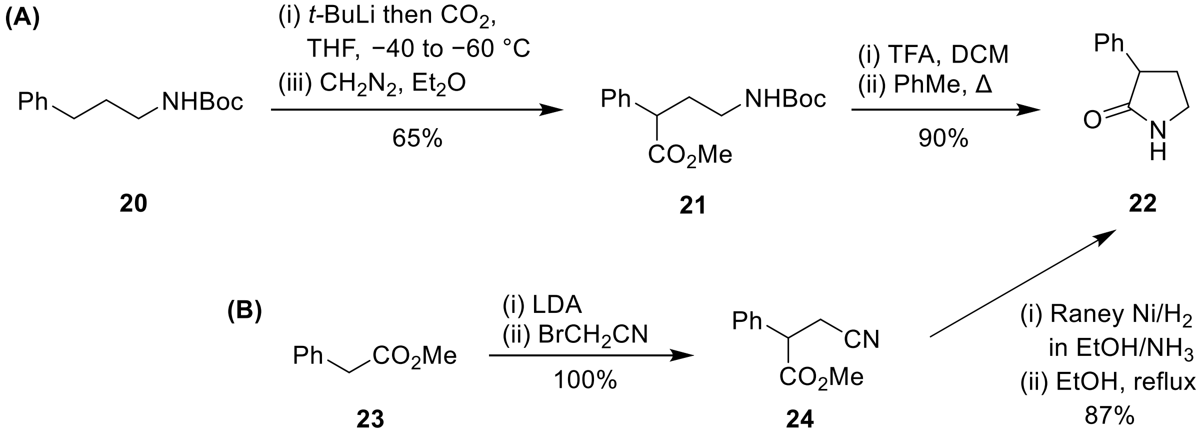


Scheme 4: A cobalt-catalysed pyrrolidinone *α*-arylation reaction was reported by Cossy *et al.*[9]

1.2.2. Intramolecular Amidation

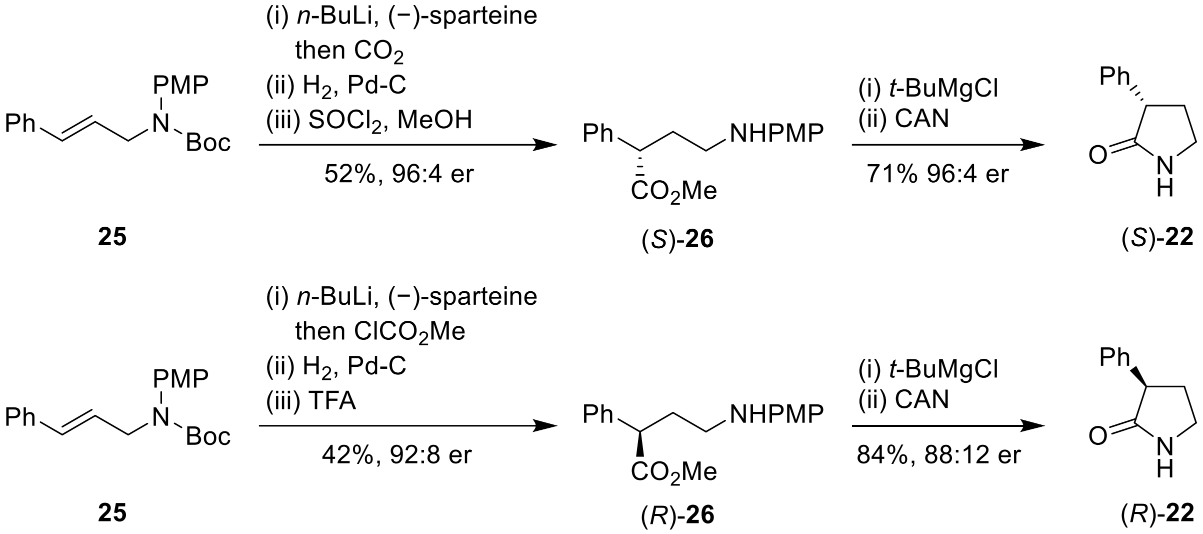
A multi-step procedure for synthesizing 3-phenylpyrrolidin-2-one (**22**) from Boc protected 3-phenyl-1-propylamine **20** was reported by Clark and Jahangir in 1992 (Scheme 5A).[10] In the first stage of the procedure, amine **20** is dilithiated and trapped by carbon dioxide. Methylation of the crude acid with diazomethane gives *γ*-amino acid ester **21**. Boc deprotection of **21** with TFA, followed by heating in toluene results in ring-closed product **22** with a high yield of 90%.

An alternate pathway utilising nitrile **24** has also been reported in the literature. First reported in a patent filing in 2001, this route utilised reductive cyclization of nitrile **24** by Raney Ni-catalysed hydrogenation.[11] The patent did not communicate yields for the reaction, therefore a similar reaction performed by a different group in 2015 is shown in Scheme 5B.[12] Nitrile **24** could be accessed in quantitative yield by the cyanomethylation of the enolate of methyl phenylacetate (**23**). Subsequent hydrogenation over a Raney Ni catalyst, followed by refluxing in EtOH gave pyrrolidinone **22** in a high yield of 87%.



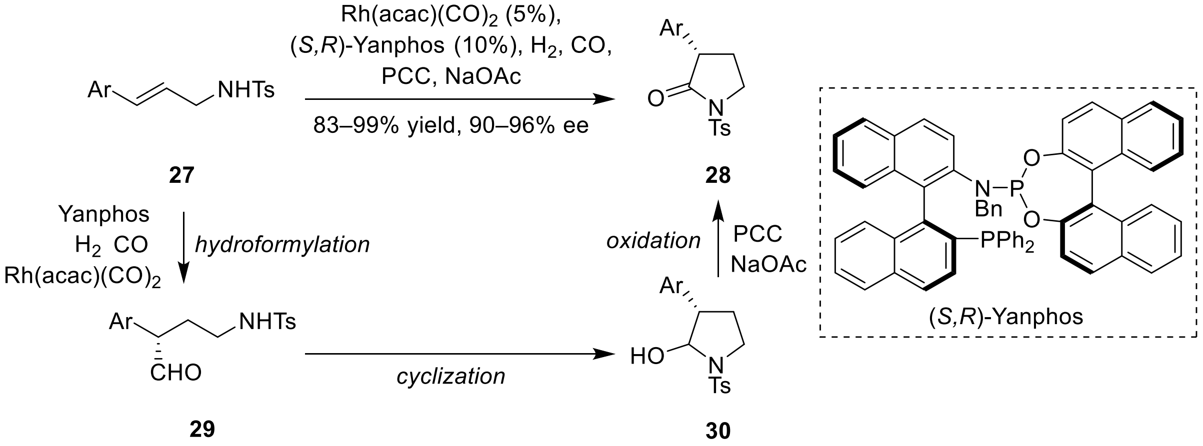
Scheme 5: Route for the synthesis of pyrrolidinone **22** by Clark and Jahangir (A).[10] Alternate routes via reductive cyclization of **24** have also been reported (B).[11, 12]

Beak and colleagues reported an enantioselective synthesis of 3-phenylpyrrolidin-2-one (**22**) from protected cinnamylamine **25** (Scheme 6).[13] The selectivity was obtained by using (−)-sparteine which forms a chiral complex with the deprotonated allyl species. Trapping this complex with carbon dioxide—a fast reacting electrophile under these conditions[14]—gives an (*S*)-*γ*-amino acid, which forms (*S*)-**26** upon subsequent hydrogen and esterification. The Boc group is also cleaved under the $SOCl_2$/MeOH esterification conditions. In contrast, utilising the slower reacting methyl chloroformate[14] to trap the allyllithium complex allows the synthesis of (*R)*-**26**. Subsequent cyclization using *t*-BuMgCl, followed by PMP deprotection by CAN allows access to both enantiomers of pyrrolidinone **22** with good yields and er.



Scheme 6: Beak *et al.* reported a route for the enantioselective synthesis of **22** via chiral *γ*-amino acids **26**.[13]

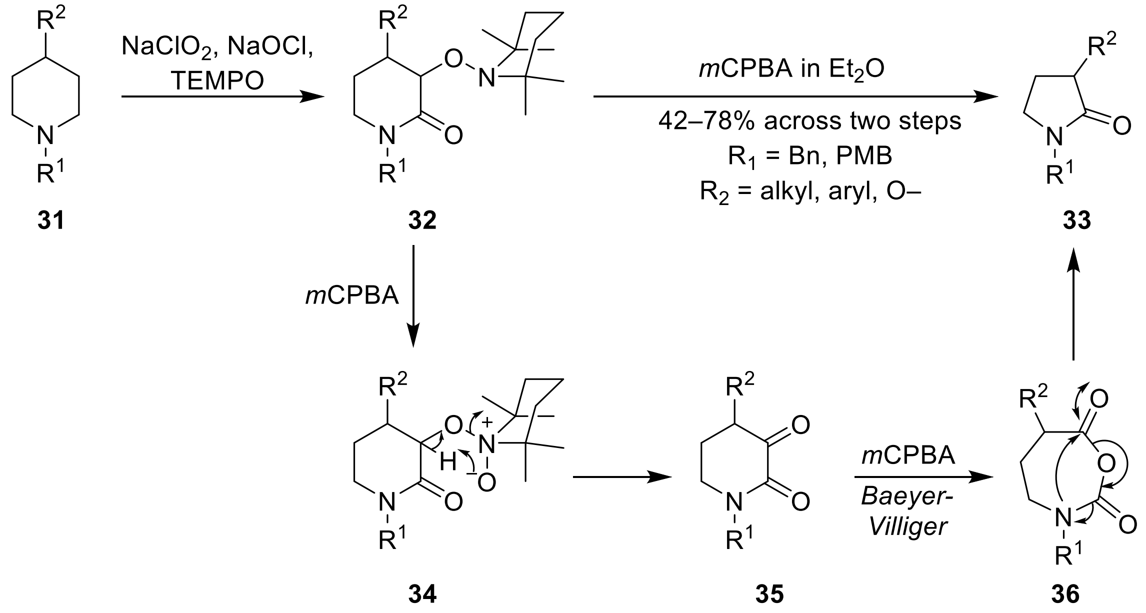
In 2016, Zhang *et al.* were able to achieve a similar transformation as a one-pot procedure. Their procedure converted tosylated cinnamylamines **27** to *N*-tosyl-3-arylpyrrolidin-2-ones **28** (Scheme 7).[15] The initial step in the reaction was the rhodium-catalysed hydroformylation of **27**. This step was asymmetric due to the use of a chiral phosphine ligand, Yanphos, and gave enantiomer **29**. Subsequent cyclization forms hemiaminal **30**, which is oxidized *in situ* by PCC giving pyrrolidinone **28**.



Scheme 7: Zhang *et al.* reported a one-pot procedure for the synthesis of 3-arylpyrrolidin-2-ones **28** from cinnamylamine analogues **27**.[15]

1.2.3. Ring Contraction

Sartillo-Piscil and co-workers reported a route to *α*-subsitituted pyrrolidinones **33** by the deconstructive lactamization of 4-substituted piperidines **31** (Scheme 8).[16] The reaction is carried out in two separate steps, with the first step being the oxidation of piperidine **31** to piperidinone **32** by $NaClO_2$, NaOCl and TEMPO. The second step is carried out with *m*CPBA and starts with the oxidation of **32** to *N*-oxide **34**. This *N*-oxide undergoes an oxidative deamination forming piperidine-2,3-dione **35**. A Baeyer-Villiger oxidation of **35** gives anhydride **36**. Finally, **36** undergoes a decarboxylative translactamization giving pyrrolidinone **33**.



Scheme 8: Sartillo-Piscil and colleagues synthesized *α*-subsitituted pyrrolidinones **33** by the deconstructive lactamization of 4-substituted piperidines **31**.[16]

2. Hypervalent Iodine Reagents

2.1. Introduction

In 1811, Bernard Courtois—a French chemist working in the manufacture of saltpetre—noticed that a violet vapour was liberated upon the reaction of sulfuric acid with seaweed ashes. This violet vapour condensed on the cooler parts of his reaction vessel forming dark, lustrous crystals.[17, 18] Investigations regarding this substance were carried out by Courtois and his friends, Charles Bernard Desormes and Nicolas Clément, with their findings being announced in November 1813. They provided the main properties of the newly isolated substance but did not make any claims regarding it's identity.[17, 18] A few months later this substance would be identified as a new element by the work of Sir Humphry Davy and Joseph Louis Gay-Lussac, with Davy giving the element the name *iodine*[18] and Gay-Lussac giving the element the name *iode*[17] – both derived from the Greek ἰοειδής (*ioeides*, violet-coloured).

$$2I^- + H_2SO_4 \rightarrow I_2 + SO_3^{2-} + H_2O$$

Scheme 9: Bernard Courtois isolated iodine by the oxidation of iodide to elemental iodine by action of sulfuric acid.[17]

In the two centuries since the isolation of iodine by Bernard Courtois, iodine and its compounds have been studied by countless chemists with applications in organic synthesis, material chemistry and medicine.[19] Today we know that iodine has five common oxidation states in its compounds: −1, +1, +3, +5 and +7. Compounds with iodine in the latter three oxidation states of +3, +5 and +7 are known as hypervalent iodine compounds or reagents.

Hypervalent iodine compounds were discovered soon after the discovery of iodine itself, with iodine trichloride and potassium iodate reported by Gay-Lussac in 1814.[20] Organic hypervalent iodine compounds took longer to be discovered, with the first example, (dichloroiodo)benzene isolated in 1885 by Conrad Willgerodt.[21] Willgerodt followed up his initial discovery with the isolation of more similar compounds, isolating (diacetoxyiodo)benzene (PIDA) and iodosylbenzene in 1892.[22] By 1914 more than 500 organic hypervalent iodine compounds had been described.[20]

Despite this plenitude of organic hypervalent iodine compounds, they only started seeing use as reagents in organic syntheses in the 1980s.[20] Since then the chemistry of hypervalent iodine reagents experienced a surge of interest, and today, both iodine(III) and iodine(V) compounds are regularly utilized in organic syntheses. Some common hypervalent iodine reagents, including those appearing in this work, are listed in the table below.

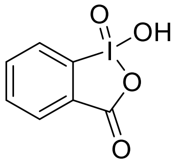
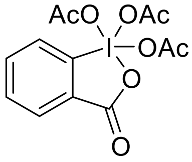
Compound	**Common names**	**Abbr.**
$(PhIO)_n$	iodosylbenzene iodosobenzene	-
$PhI(OAc)_2$	iodobenzene diacetate (diacetoxyiodo)benzene phenyliodine(III) diacetate	PIDA
$PhI(OCOCF_3)_2$	iodobenzene bis(trifluoroacetate) [bis(trifluoroacetoxy)iodo]benzene phenyliodine(III) bis(trifluoroacetate)	PIFA
PhI(OH)OTs	Koser's reagent [hydroxy(tosyloxy)iodo]benzene	HTIB
PhI(CN)OTf	Stang's reagent cyano(phenyl)iodonium triflate	-
	2-iodoxybenzoic acid	IBX
	Dess-Martin periodinane	DMP

Table 1: Some common hypervalent iodine reagents.

2.2. Bonding and Reactivity

2.2.1. Bonding

Hypervalent iodine compounds display an expanded shell of valence electrons, with I(III) compounds featuring ten electrons, and I(V) compounds twelve electrons. One potential way of accommodating the extra electrons is by hybridization involving the d-orbitals, forming sp^3d or sp^3d^2 hybrid orbitals. However, in the present literature it is generally accepted that the bonding in hypervalent Group 15–18 compounds is better explained by a 3-center 4-electron bond without the involvement of d-orbitals.[20]

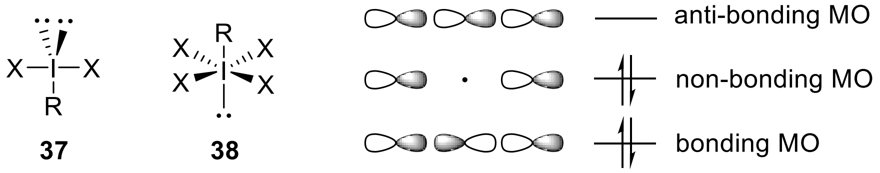


Figure 3: Structure of an I(III) compound (**37**) and an I(V) compound (**38**). Molecular orbitals of a hypervalent bond (right).

In this bonding system, iodine(III) compounds feature an sp^2 hybridized iodine with the hybrid orbitals making up one σ-bond and two lone pairs. The p_z orbital interacts with two axial ligand orbitals, giving rise to three molecular orbitals: a bonding, a non-bonding and an anti-bonding orbital (Figure 3). The bonding and the non-bonding orbitals are filled, forming a 3-center 4-electron bond. This type of bond is also known as a hypervalent bond, and is the origin of the term “hypervalent iodine reagent”. As a result of this bonding pattern, iodine(III) compounds adopt a “T” shape—as seen in molecule **37**—with the σ-bond perpendicular to the 3-center 4-electron bond.[20]

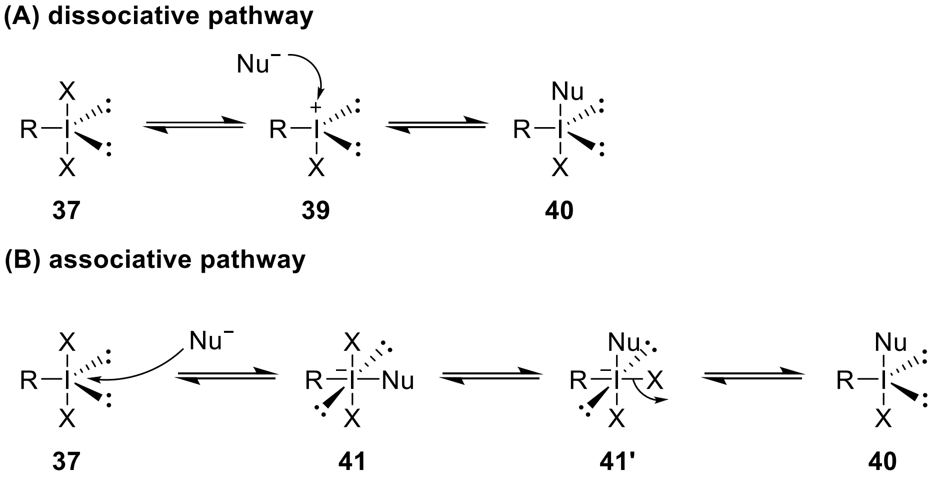
Iodine(V) compounds feature sp hybridized iodine with the hybrid orbitals making up one σ-bond and one lone pair. The p_x and p_y orbitals interact with four ligands in the equatorial plane forming two perpendicular 3-center 4-electron bonds. This gives the molecule a square pyramidal shape, as seen in molecule **38**.[20]

2.2.2. Ligand Exchange

Hypervalent iodine compounds are able to undergo ligand exchange. Ligand exchange is usually the first step in the reactions of hypervalent iodine reagents. The mechanism for ligand exchange in iodine(III) compounds is shown in Scheme 10. The exchange can proceed via two pathways, dissociative or associative.[20, 23]

In the dissociative pathway one of the ligands detaches from the iodine leaving positively charged iodonium cation **39** (Scheme 10A). This cation is quenched by a nucleophilic species completing the ligand exchange. The dissociative pathway is thought to be disfavoured due to the instability of the intermediate iodonium cation.[20] However, the presence of the solvated $[PhIOH]^+$ ion in aqueous solution has been confirmed by Richter and colleagues.[24]

The associative pathway starts with the attachment of a nucleophilic species to the hypervalent iodine reagent forming negatively charged, square planar species **41** (Scheme 10B). This square planar species undergoes *cis-trans* isomerisation to form **41'**, followed by detachment of a ligand molecule completing the ligand exchange. The successful isolation of stable iodate(III) species, such as ICl_4^-,[25] provides support for this pathway.[20]

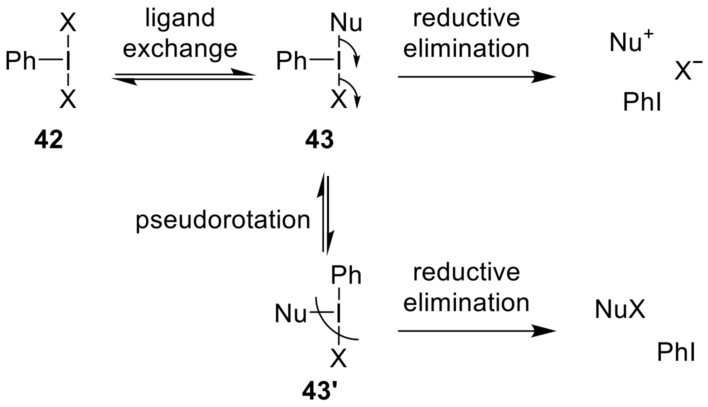


Scheme 10: Mechanism of dissociative and associative ligand exchange pathways in I(III) compounds.

2.2.3. Reductive Elimination

The final step in transformations mediated by hypervalent iodine reagents is generally the reductive elimination of iodobenzene or other aryl iodides.[20] Iodobenzene is an exceptional leaving group, superior to triflate by a factor of 10^6 in leaving group ability.[26] This makes the elimination of iodobenzene a very favourable process.

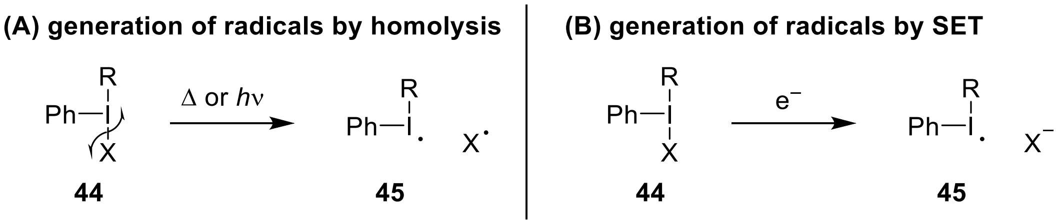
Usually, the reductive elimination of iodobenzene proceeds with the generation of two other species (Scheme 11). The reductive elimination generally leads to, or is triggered by, the substitution, fragmentation, elimination or rearrangement within the Nu group. Less commonly, the reductive elimination proceeds with coupling between the nucleophile and the ligand. In order for the coupling to occur, the hypervalent iodine species first needs to undergo pseudorotation placing the Nu and X groups to be coupled adjacent to each other (Scheme 11).[20]



Scheme 11: General pathway of many reactions involving I(III) reagents.

2.2.4. Radical Reactions

Hypervalent iodine reagents are also able to react via radical processes (Scheme 12).[27] The weak hypervalent bond can be homolysed by heating or irradiation generating an iodanyl radical and a heteroatom radical. Alternatively, a SET reducing agent could be used to reduce the hypervalent iodine reagent, generating an iodanyl radical and a ligand anion. The iodanyl radical can undergo further fragmentation generating iodobenzene and the radical R$^{\cdot}$. Radical hypervalent iodine reactions have been used to effect C─H functionalization, additions to alkenes and alkynes, and other transformations.[27]



Scheme 12: Iodanyl radicals can be generated by homolytic fission or SET.

3. Reactions of Hypervalent Iodine Reagents

Hypervalent iodine reagents find common use in many organic transformations, ranging from oxidations to C–C bond formations. Books covering the reactivity and detailed chemistry of hypervalent iodine have been published by Wirth *et al.*[28, 29] and Zhdankin[20] among others. In the following section a few areas of hypervalent iodine chemistry with relevance to our work are covered. This includes: (i) the functionalization of alkynes by hypervalent iodine mediated addition, (ii) synthesis of heterocycles by hypervalent iodine mediated intramolecular aminations and amidations, and (iii) hypervalent iodine mediated rearrangements.

3.1. Functionalization of Alkynes

The hypervalent-iodine mediated alkyne functionalization reactions that have been reported in the literature can be split into broadly four categories;

(i) reactions where the hypervalent iodine reagent is used to oxidize another species *in situ* which then activates the alkyne,
(ii) reactions where the alkyne is directly activated by the hypervalent iodine reagent,
(iii) reactions where *in situ* generated radical(s) react with the alkyne, and
(iv) reactions where the hypervalent reagent is used as a catalytic species.

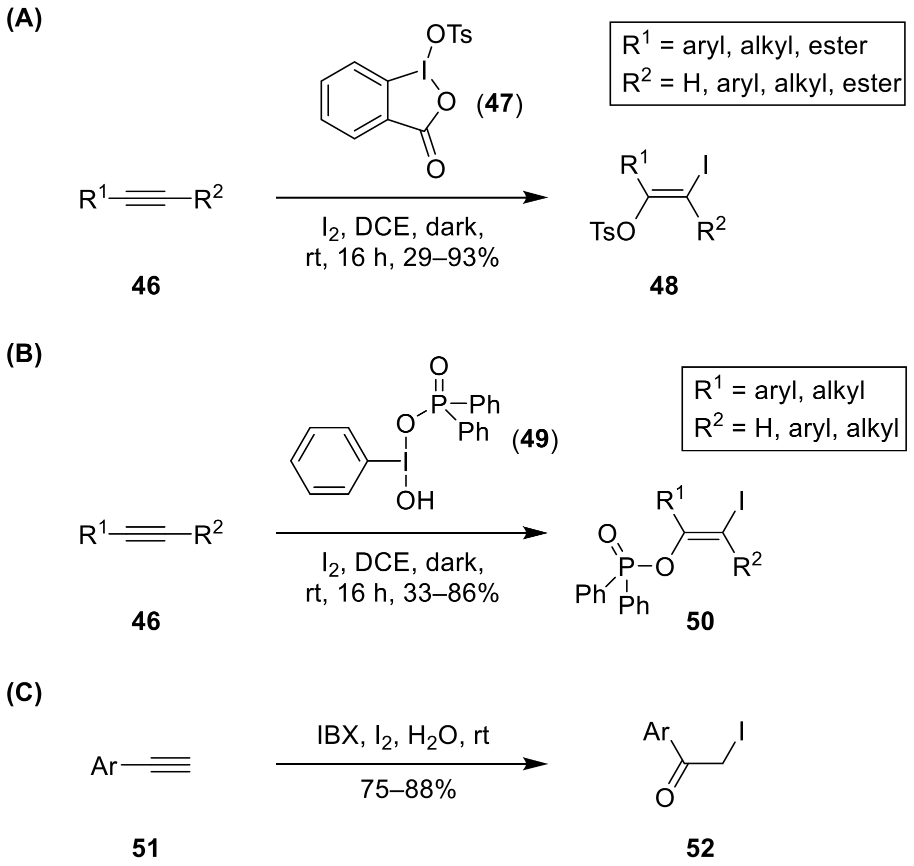
These categories are each covered separately below.

3.1.1. Activation of Alkynes With *in situ* Oxidized Species

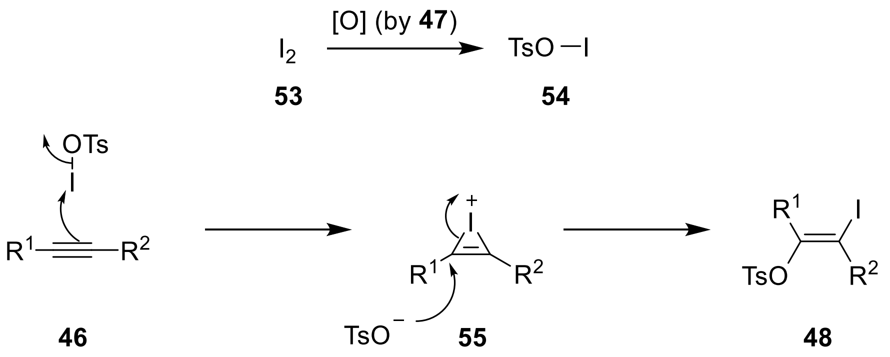
In 1999, Muraki and colleagues published a procedure for the iodotosyloxylation of alkynes using benziodoxolone **47** in the presence of iodine (Scheme 13A).[30] They quickly followed this up with a similar procedure for the iodophosphoryloxylation of alkynes using iodine(III) reagent **49** (Scheme 13B).[31] Yadav *et al.* published a strategy for converting terminal alkynes to α-iodoketones **52** using a similar IBX/I_2 reaction system (Scheme 13C).[32]

These reactions are all expected to be mechanistically similar. For example, the mechanism of Muraki's iodotosyloxylation reaction is shown in Scheme 14. First benziodoxolone **47** oxidizes iodine to tosyl hypoiodite (**54**).[30] Tosyl hypoiodite then undergoes electrophilic addition with the alkyne generating cyclic iodonium cation **55**.

Such intermediates had been previously proposed for similar reactions.[33] Finally cation **55** is ring-opened by the tosylate anion giving the observed *trans*-substituted alkene **48**.

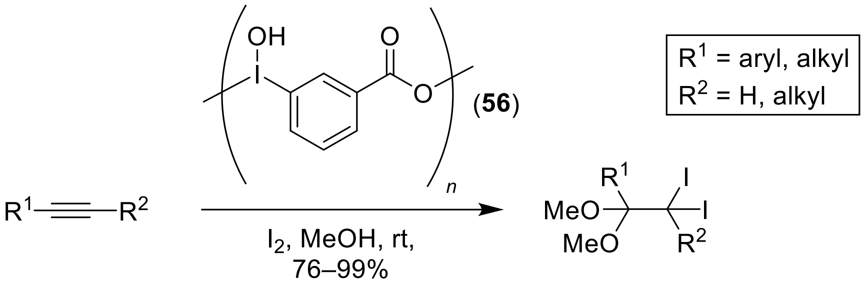


Scheme 13: Procedures for the iodotosyloxylation (A) and iodophosphoryloxylation (B) of alkynes by Muraki and coworkers.[30, 31] Yadav and colleagues described a similar procedure for the conversion of alkynes to *α*-iodoketones (C).[32]



Scheme 14: Mechanism for Muraki's iodotosyloxylation reaction.[30, 33]

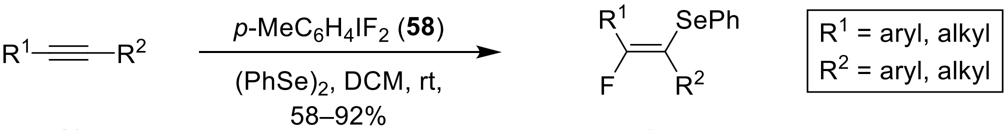
Yusubov *et al.* expanded this approach to a one-pot diiodomethoxylation reaction (Scheme 15).[34] They achieved this by reacting *m*-iodosylbenzoic acid (**56**) and iodine with the alkyne in methanol. The reactive species is expected to be methyl hypoiodite. Yusubov and colleagues also developed an efficient workup procedure for the reaction, using an anion exchange resin (IRA 900) to remove the reduced *m*-iodobenzoic acid by-product.



46 **57**

Scheme 15: Yusubov developed a procedure for the diiodomethoxylation of alkynes.[34]

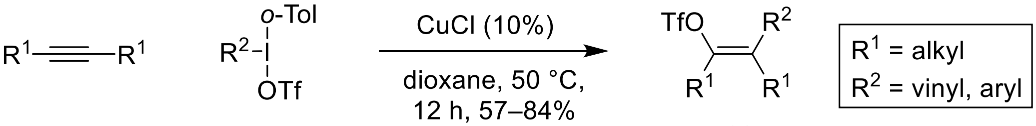
This approach of functionalizing alkynes has mainly focused on elemental iodine as the species to be oxidized. However, the group of Tingoli demonstrated that $(PhSe)_2$ can also be similarly utilized (Scheme 16).[35] In their paper they carried out the phenylselenofluorination of alkynes by using difluoroiodotoluene (**58**) and $(PhSe)_2$.



46 **59**

Scheme 16: Tingoli's method for the phenylselenofluorination of alkynes.[35]

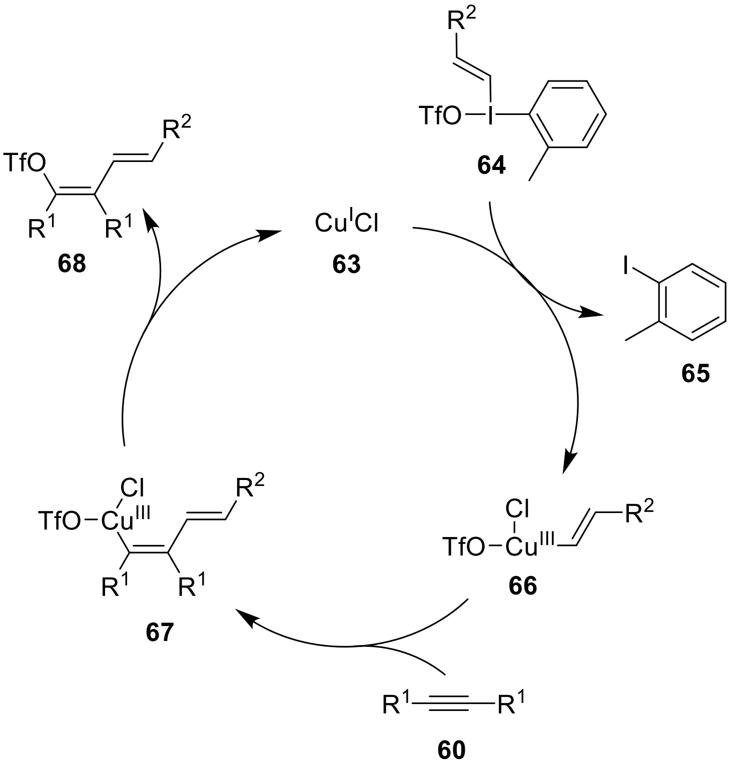
Additionally, Gaunt *et al.* reported a method for the vinyltriflation of alkynes via an aryl(vinyl)iodonium mediated oxidative addition to copper(I) (Scheme 17). Initially they focused on symmetrical alkynes but asymmetric examples were also reported.[36]



60 **61** **62**

Scheme 17: Gaunt *et al.* reported a method for the vinyltriflation of alkynes.[36]

The proposed catalytic cycle starts with the oxidative transfer of the triflyloxy and vinyl groups from iodine(III) to copper(I) (Scheme 18). This generates copper(III) species **66** and reduces aryl(vinyl)iodonium triflate **64** to *o*-iodotoluene (**65**). Addition of **66** across the alkyne triple bond generates copper(III) species **67**. Reductive elimination from **67** gives the observed product **68** while regenerating the copper(I) catalyst.

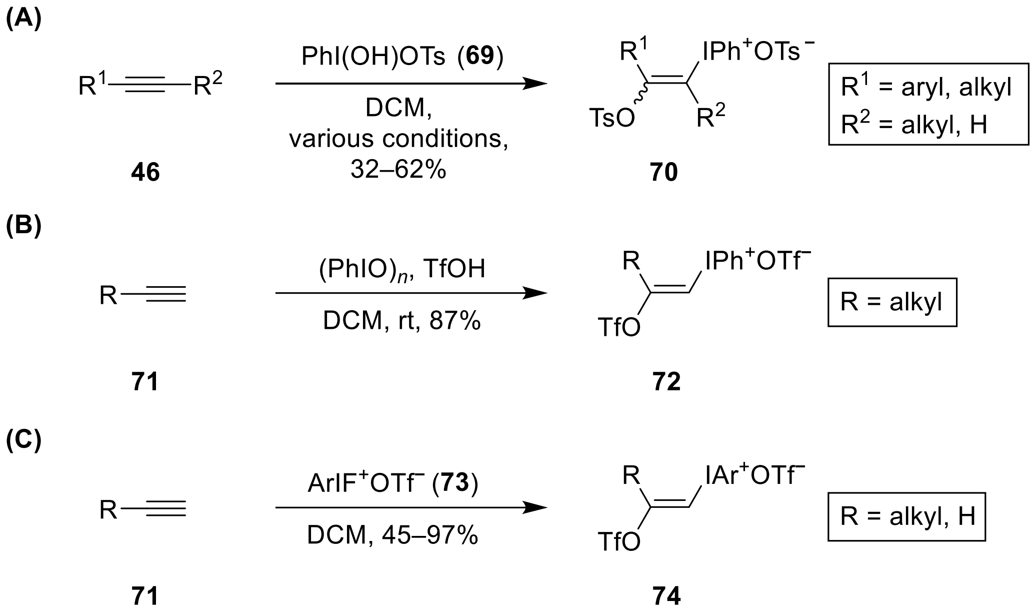


Scheme 18: Catalytic cycle for the vinyltriflation of alkynes.[36]

3.1.2. Direct Activation of Alkynes With Iodine(III) Species

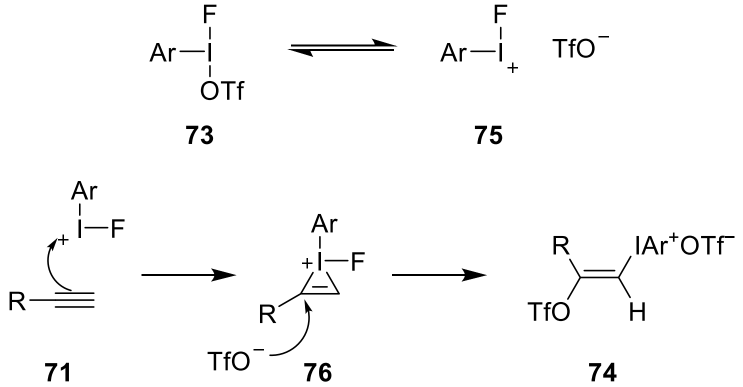
In these reactions the alkyne is activated by interaction with an iodine(III) species, usually an iodonium(III) cation. This approach has mainly been utilized for the synthesis of aryl(vinyl)iodonium salts.

The synthesis of such a salt by addition to alkynes was first reported by Koser and coworkers in 1981. They found that HTIB (**69**) reacted with alkynes giving phenyl-(*β*-tosyloxyvinyl)iodonium tosylates **70** as a mixture of stereoisomers (Scheme 19A).[37] Building upon this work, Stang *et al.* published two reports detailing methods for the stereoselective synthesis of aryl(*β*-triflyloxyvinyl)iodonium triflates.[38, 39] The first of their methods utilized triflic acid-activated iodosylbenzene (Scheme 19B) and the second utilized aryl(fluoro)iodonium triflates (Scheme 19C). Both methods were selective for the *trans*- isomer.



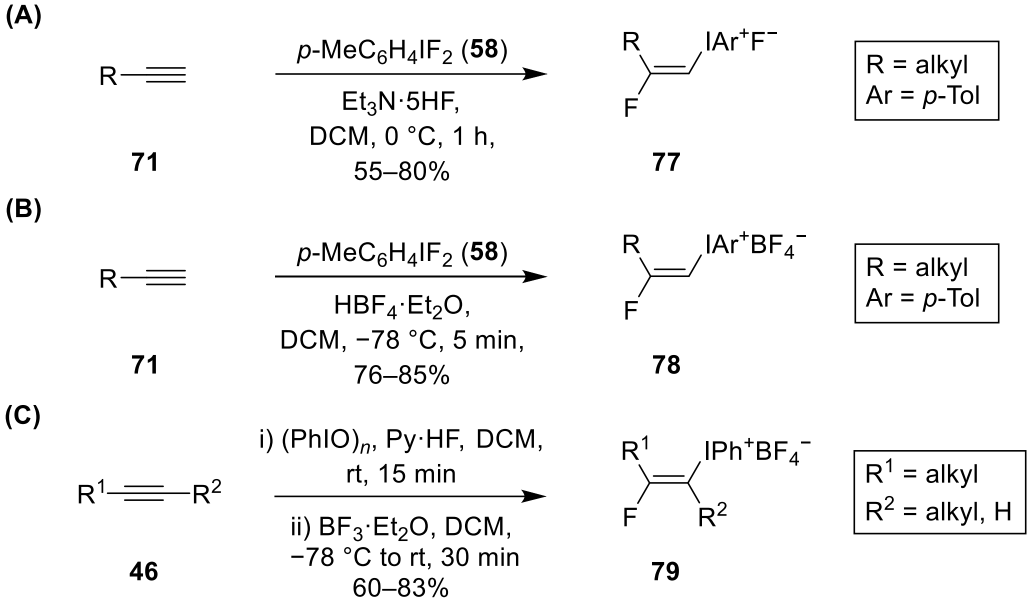
Scheme 19: Aryl(vinyl)iodonium salts were synthesized from alkynes by Koser and Stang *et al.*[37-39]

Stang and colleagues also proposed a mechanism for the reaction (Scheme 20).[39] First, the hypervalent iodine reagent **73** dissociates into iodonium cation **75** and triflate. This dissociation is facilitated by the excellent leaving group ability of the triflate anion. Iodonium ion **75** then undergoes electrophilic addition with the alkyne generating cyclic iodonium cation **76**. Ring-opening of this intermediate with triflate gives the observed *trans*- phenyl(vinyl)iodonium triflate **74**. The regioselectivity is determined by electronic considerations. The substituted end of alkene **76** carries a greater *δ*+ positive charge as it is able to stabilize this charge by hyperconjugation. Hence, the more substituted end is attacked by the triflate anion.



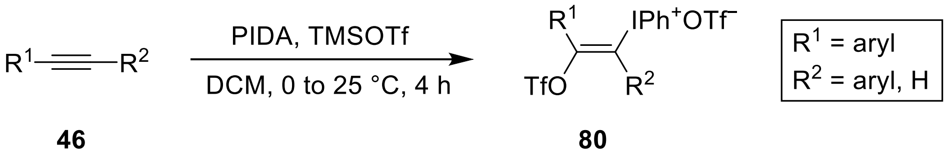
Scheme 20: A mechanism for the synthesis of aryl(vinyl)iodonium salts was proposed by Stang *et al.*[39]

Since the initial works by Koser and Stang, other similar syntheses have been reported in the literature. Hara *et al.* reported two methods for the conversion of alkynes to *β*-fluorovinyl(*p*-tolyl)iodonium salts (Schemes 21A and 21B).[40, 41] Both methods utilized difluoroiodotoluene (**58**) with different fluoric acids. The first method utilized $Et_3N{\cdot}5HF$ as the acid, while the second utilized $HBF_4{\cdot}Et_2O$. Kitamura and colleagues improved upon these syntheses with a method that uses the more easily accessible iodosylbenzene as a reagent (Scheme 21C).[42]



Scheme 21: Methods for the synthesis of aryl(*β*-fluorovinyl)iodonium salts.[40-42]

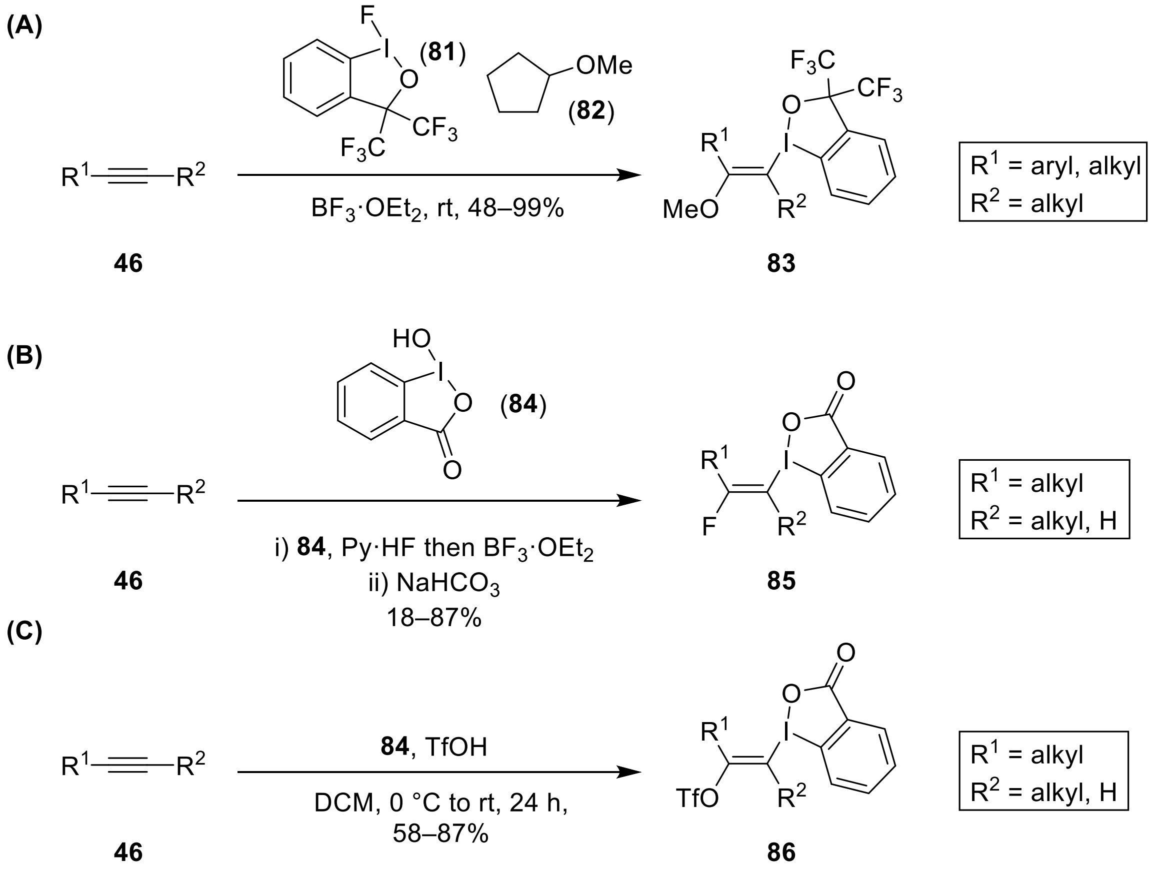
Building upon Stang's work, Tóth *et al.* recently published an improved procedure for the synthesis of phenyl(*β*-triflyloxyvinyl)iodonium triflates (Scheme 22).[43] Their method utilizes the bench-stable and commercially available reagent PIDA. This represents an improvement to Stang's method utilizing aryl(fluoro)iodonium triflates where the reagent was freshly generated by the exotic reagent FXeOTf.



Scheme 22: Method for the synthesis of phenyl(*β*-triflyloxyvinyl)iodonium triflates by Tóth *et al.*[43]

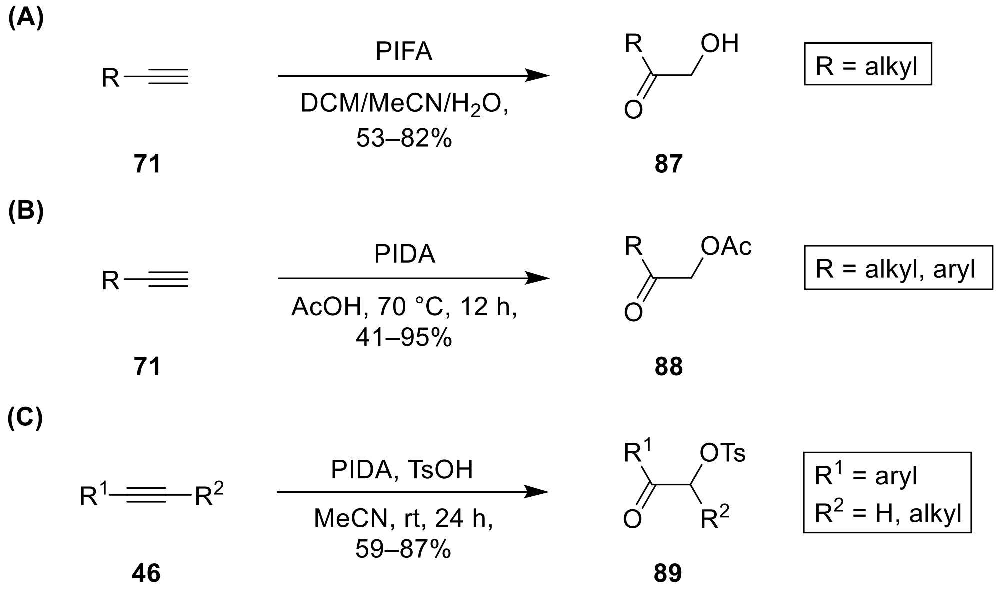
Benziodoxole and benziodoxolones have attracted interest as hypervalent iodine reagents due to their increased stability compared to their acyclic cousins.[44-46] Due to this interest, methods of synthesizing vinylbenziodoxol(on)es from alkynes have been developed.

Yoshikai and colleagues reported a method of synthesizing *β*-methoxyvinylbenziodoxoles **83**.[47] They utilized fluorobenziodoxole **81** activated with $BF_3 \cdot OEt_2$ as the hypervalent iodine reagent and cyclopentyl methyl ether (**82**) as the solvent and methoxy source (Scheme 23A). A report by Kitamura *et al*. described a method for forming *β*-fluorovinylbenziodoxolones **85** using *o*-iodosylbenzoic acid (**84**) and Py·HF (Scheme 23B).[48] A similar method utilizing **84** and TfOH was used by Yoshimura *et al.* to synthesize *β*-triflyloxyvinyl- derivatives **86** (Scheme 23C).[49]



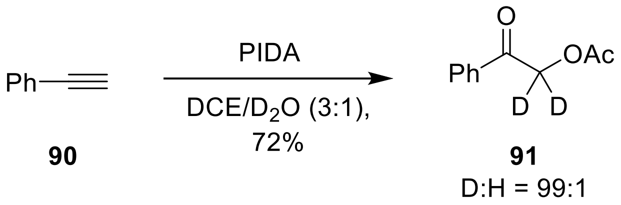
Scheme 23: Methods for the synthesis of vinylbenziodoxol(on)es from alkynes.[47-49]

Hypervalent iodine reagents have also been used to carry out the oxidation of alkynes to *α*-functionalized ketones. The initial reaction was reported by Tamura *et al.* in 1985.[50] They discovered that terminal alkynes could be oxidized to *α*-hydroxyketones **87** using PIFA (Scheme 24A).[50, 51] Similarly, Hou and colleagues reported a route to the preparation of *α*-acetoxyketones **88** using PIDA in acetic acid (Scheme 24B).[52] Deng *et al.* and Sreedhar *et al.* reported metal-catalysed versions of this reaction, utilizing silver(I) and iron(II) respectively.[53, 54] A method for synthesizing *α*-sulfonyloxyketones **89** in a PIDA/TsOH system was devised by Liu and coworkers (Scheme 24C).[55]



Scheme 24: Synthesis of *α*-functionalized ketones from alkynes.[50, 52, 55]

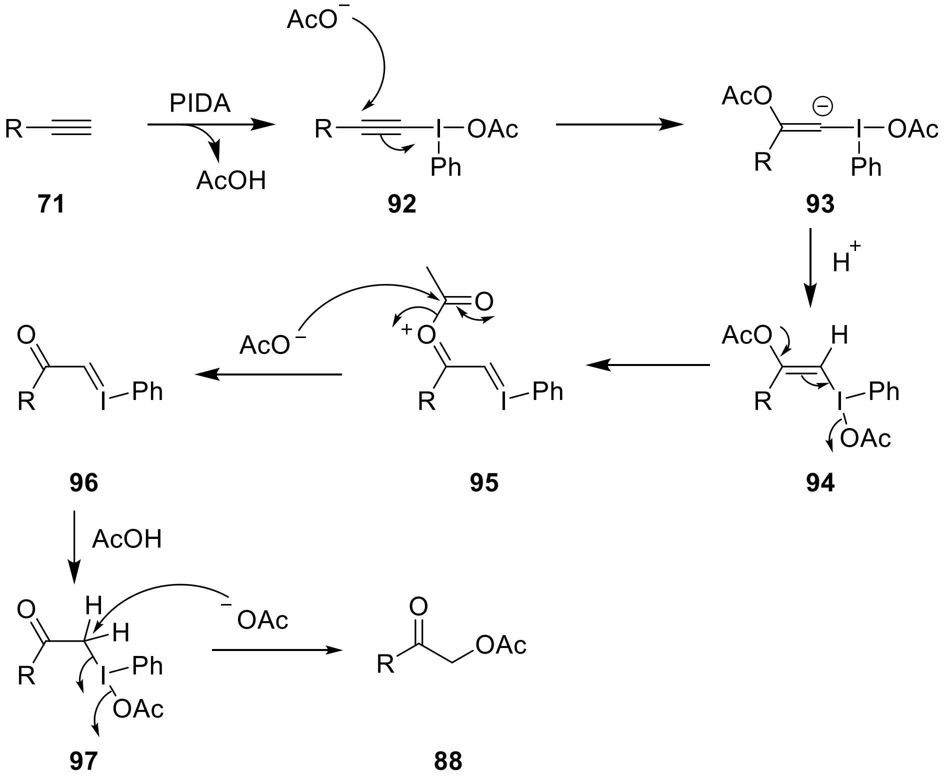
Mechanistic studies performed by Hou *et al.* showed that in the presence of D_2O the product is doubly deuterated at the *α* position (Scheme 25).[52]



Scheme 25: Hou *et al.* demonstrated that the acetoxylation of pheylacetylene (**90**) in the presence of D_2O gives the doubly deuterated product **91**.[52]

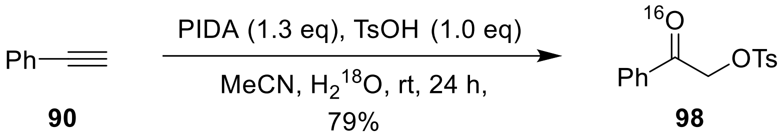
Based on this observation they postulate that the acetoxylation reaction of terminal alkynes proceeds via an alkynyl(phenyl)iodonium acetate intermediate—with loss of the terminal proton—rather than a phenyl(vinyl)iodonium acetate intermediate, which would preserve the terminal proton.

In their proposed mechanism, reaction of the alkyne with PIDA generates alkynyliodonium acetate **92** (Scheme 26). A Michael-type addition of acetic acid to this intermediate generates intermediate **93** which is then protonated to give vinyliodonium acetate **94**. Loss of acetate from **94** leads to the formation of oxonium ion **95**. Attack of acetate on **95** gives iodonium ylid **96**. Subsequent protonation of this ylid provides ketone **97**. Finally, nucleophilic attack of acetate on **97** gives the observed *α*-acetoxyketone **88**.



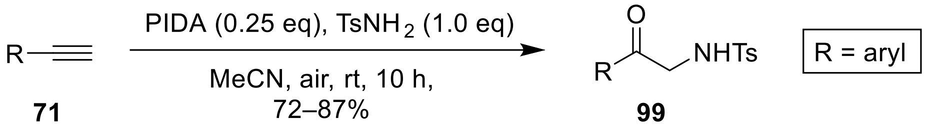
Scheme 26: Mechanism proposed by Hou *et al.* for the acetoxylation of terminal alkynes.[52]

Further supporting Hou's proposed mechanism, Liu *et al.* later performed mechanistic studies on a similar reaction – using $H_2{}^{18}O$ to elucidate the origin of carbonyl oxygen in **98** (Scheme 27).[55] They found that the product was obtained in 79% yield *without* any ^{18}O incorporated. The participation of atmospheric oxygen was excluded by performing the experiment under nitrogen. Based on these observations, they conclude that the carbonyl oxygen likely originated from the acetate group of PIDA.



Scheme 27: Mechanistic studies performed by Liu *et al.* showed that ^{18}O is *not* incorporated into product **98** in the presence of $H_2{}^{18}O$.[55]

Recently, the group of Majee reported the synthesis of *α*-sulfonamidoketones **99** from a PIDA/TsNH2 reaction system (Scheme 28).[56] Notably their method did not require a stoichiometric amount of the hypervalent iodine regent – only 0.25 eq of PIDA were utilized. The reactions were performed in air, so involvement of atmospheric oxygen seems plausible. However, mechanistic studies of the reaction have not yet been performed.

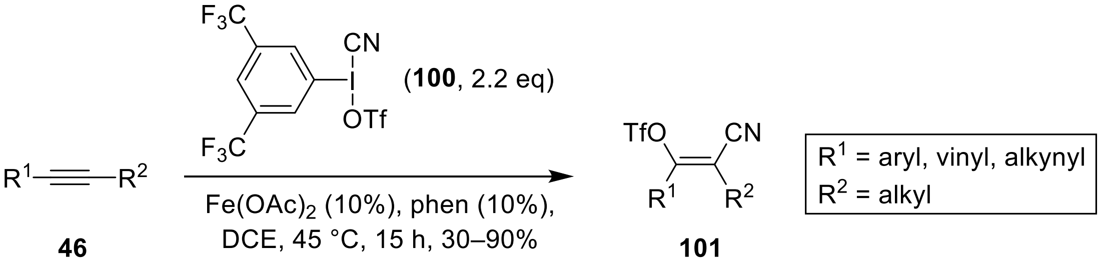


Scheme 28: A method for the synthesis of *α*-sulfonamidoketones requiring a less than stoichiometric amount of PIDA was reported by Majee *et al*.[56]

3.1.3. Functionalization of Alkynes by Hypervalent Iodine Mediated Radical Reactions

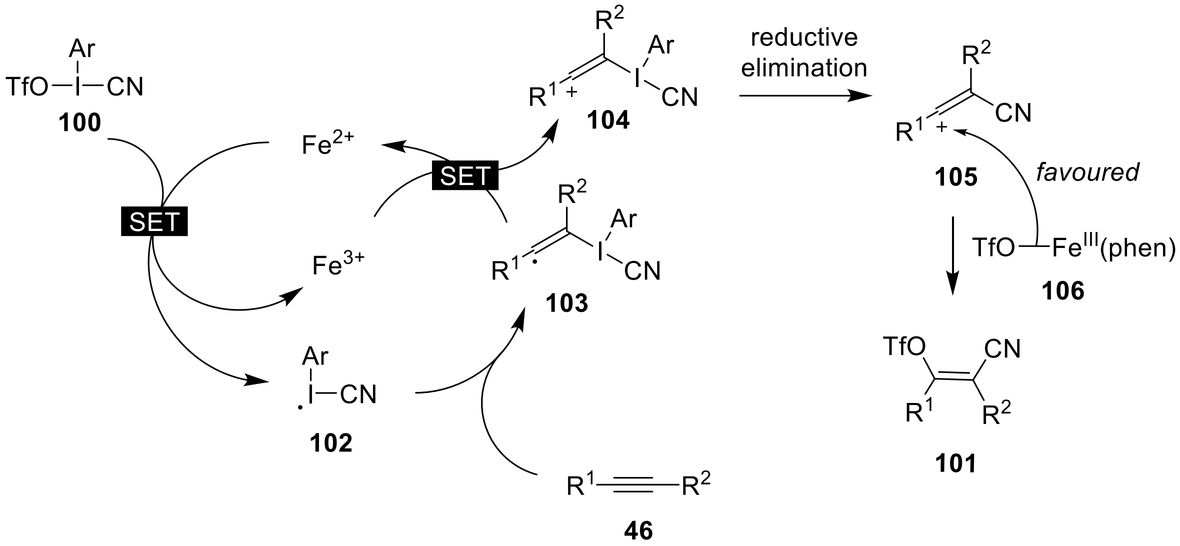
In these reactions the hypervalent iodine reagent is used to generate radical species which then reacts with the alkyne.

Studer and Wang reported a method for the radical *syn*-cyanotriflation of alkynes using aryl(cyano)iodonium triflates **100** (Scheme 29).[57] A catalytic Fe(II)/Fe(III) redox couple was utilized to generate the necessary radical.



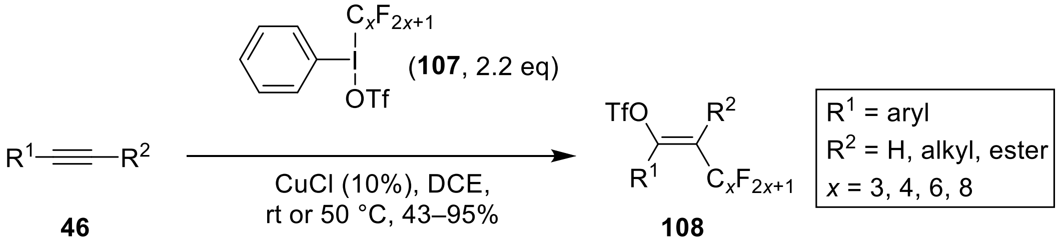
Scheme 29: Studer and Wang's method for the cyanotriflation of alkynes.[57]

A mechanism for the reaction was proposed by Studer and Wang (Scheme 30). Initially, SET reduction of aryl(cyano)iodonium triflate **100** by Fe(II) generates *λ*2-iodanyl radical **102**. The addition of radical **102** to alkyne **46** produces π-stabilized vinylic radical **103**. Oxidation of **103** by Fe(III) gives vinylic carbocation **104** regenerating the Fe(II) catalyst in the process. Reductive elimination of ArI from **104** produces carbocation **105**. The carbocation is then trapped by triflate from the less hindered side, giving *syn*- addition product **101**. The authors found that the selectivity of the addition is enhanced by using a large ligand such as 1,10-phenanthroline. This suggests that the triflate is transferred from Fe(III) complex **106**. The authors noted that the observed regioselectivity precludes electrophilic iodonium activation of the alkyne as a mechanism – such a mechanism would not give the *syn*- addition product as observed (*cf*. Stang's mechanism on page 16).



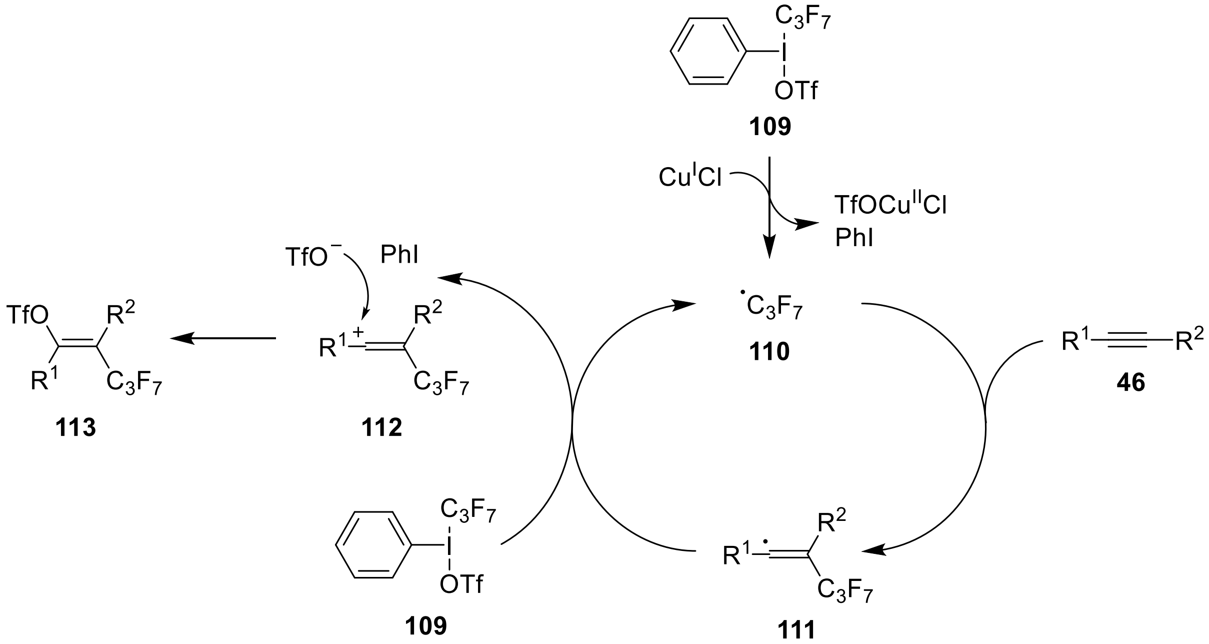
Scheme 30: Mechanism for the radical cyanotriflation of alkynes.[57]

Studer and Wang followed up their initial report with a procedure for the radical *anti*-perfluoroalkyltriflation of alkynes (Scheme 31).[58] This reaction used a different mechanistic approach to the reaction – utilizing Cu(I) to initiate a radical chain reaction.



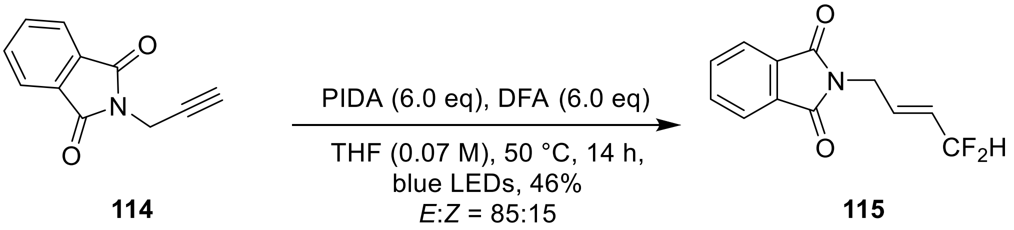
Scheme 31: Studer and Wang's method for the perfluoroalkyltriflation of alkynes.[58]

A possible mechanism for the reaction was proposed by Studer and Wang (Scheme 32). First, the radical chain is initiated by the SET reduction of iodonium triflate **109** by Cu(I). This generates TfOCu(II)Cl, iodobenzene and perfluoroalkyl radical **110**. Reaction of **110** with alkyne **46** produces the π-stabilized vinylic radical **111**. The next step is SET oxidation of **111** by iodonium triflate **109** generating iodobenzene, triflate and carbocation **112**. In addition, the oxidation also regenerates perfluoroalkyl radical **110** sustaining the chain. The trapping of carbocation **112** by triflate gives the final product **113**. Regioselectivity in the addition step is dictated by steric hindrance and electrostatic repulsion of the perfluoroalkyl group to the incoming triflate anion, leading to the formation of the *anti-* addition product.



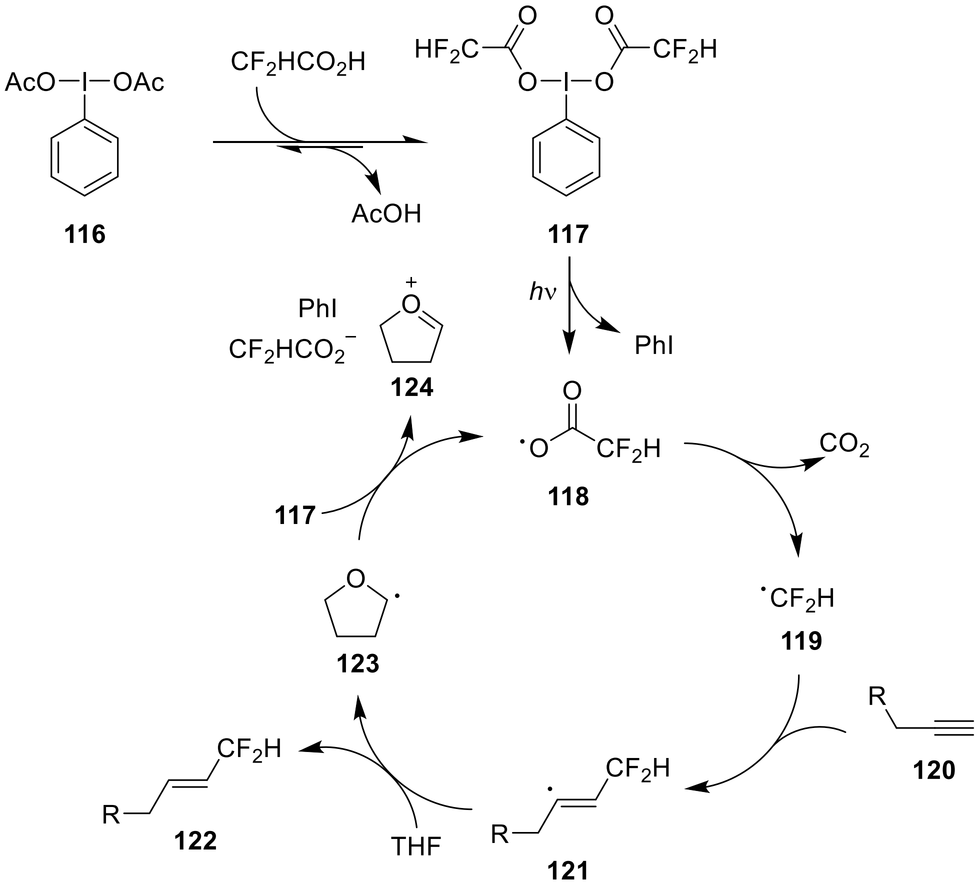
Scheme 32: Mechanism for the radical perfluoroalkyltriflation of alkynes.[58]

Gouverneur and colleagues detailed a method which can be used for the radical hydrodifluoromethylation of alkynes (Scheme 33).[59] They utilized PIDA and difluoroacetic acid under visible light irradiation.



Scheme 33: Gouverneur *et al*. reported a method for the hydrodifluoromethylation of alkyne **114**.[59]

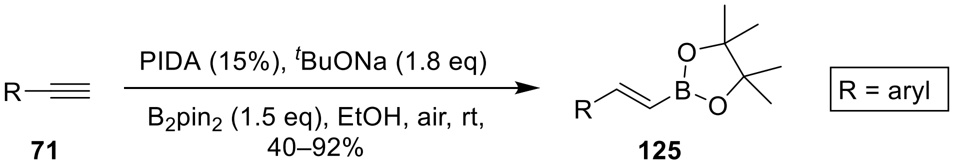
Gouverneur *et al.* elucidated the mechanism of the reaction by performing several radical quenching experiments. Initially, ligand exchange on PIDA (**116**) with difluoroacetic acid generates iodine(III) species **117** (Scheme 34). The photolysis of **117** leads to the formation of iodobenzene and two molecules of carboxyl radical **118**. The expulsion of carbon dioxide from **118** gives the difluoromethyl radical (**119**). The reaction of **119** with alkyne **120** gives vinylic radical **121**. At this stage the abstraction of a proton from the solvent gives the observed product **122** and the THF *α*-radical (**123**). SET oxidation of **123** by iodine(III) species **117** leads to the generation of iodobenzene, difluoroacetate and furanium ion **124**. In addition, the oxidation also regenerates carboxyl radical **118** sustaining the chain.



Scheme 34: Mechanism for the hydrodifluoromethylation of alkynes as proposed by Gouverneur *et al*. [59]

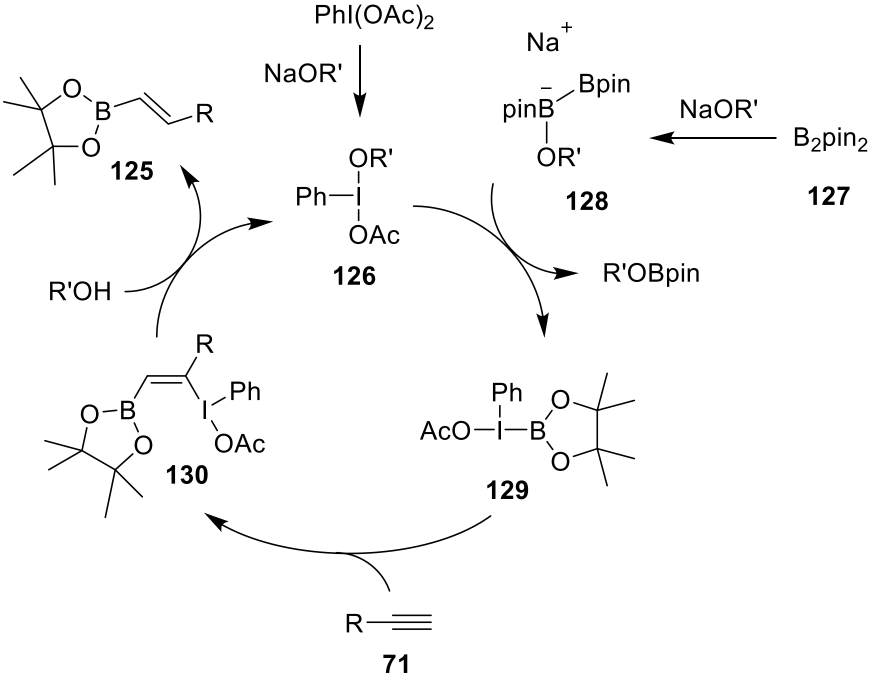
3.1.4. Functionalization of Alkynes by Hypervalent Iodine Catalysed Reactions

Wei *et al.* reported a PIDA catalysed method for the hydroboration of alkynes with B_2pin_2. Their reaction utilized 15 mol% of PIDA in ethanol under basic conditions (Scheme 35).[60]



Scheme 35: PIDA catalysed hydroboration of alkynes with B_2pin_2.[60]

Wei and co-workers identified possible reaction intermediates by LC-MS of the reaction mixture and postulated a possible mechanism for the reaction (Scheme 36). First, reaction of PIDA with alkoxide generates alkoxy(phenyl)iodonium acetate **126**. Reaction of iodonium acetate **126** with boronate complex **128**—obtained from the reaction of B_2pin_2 with alkoxide—gives borolanyl(phenyl)iodonium acetate **129**. The addition of **129** across the alkyne triple bond generates intermediate **130**. Protonolysis of **130** by the solvent gives the observed product **125** and regenerates iodonium acetate **126**, completing the catalytic cycle.



Scheme 36: Mechanism for the PIDA catalysed hydroboration of alkynes with B_2pin_2.[60]

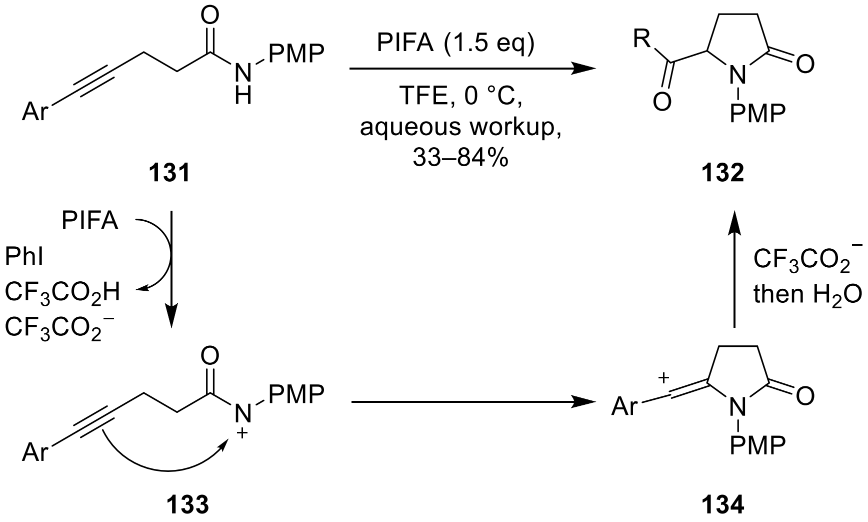
3.2. Intramolecular Amination in *N*-Heterocycle Synthesis

As discussed previously in Section 1, nitrogen heterocycles are a common structure in natural products and biologically active compounds. This makes techniques for synthesizing *N*-heterocyclic compounds an area of great interest to organic chemists. As such hypervalent iodine mediated amination strategies have been applied to *N*-heterocycle synthesis.

3.2.1. Intramolecular Addition to Alkynes

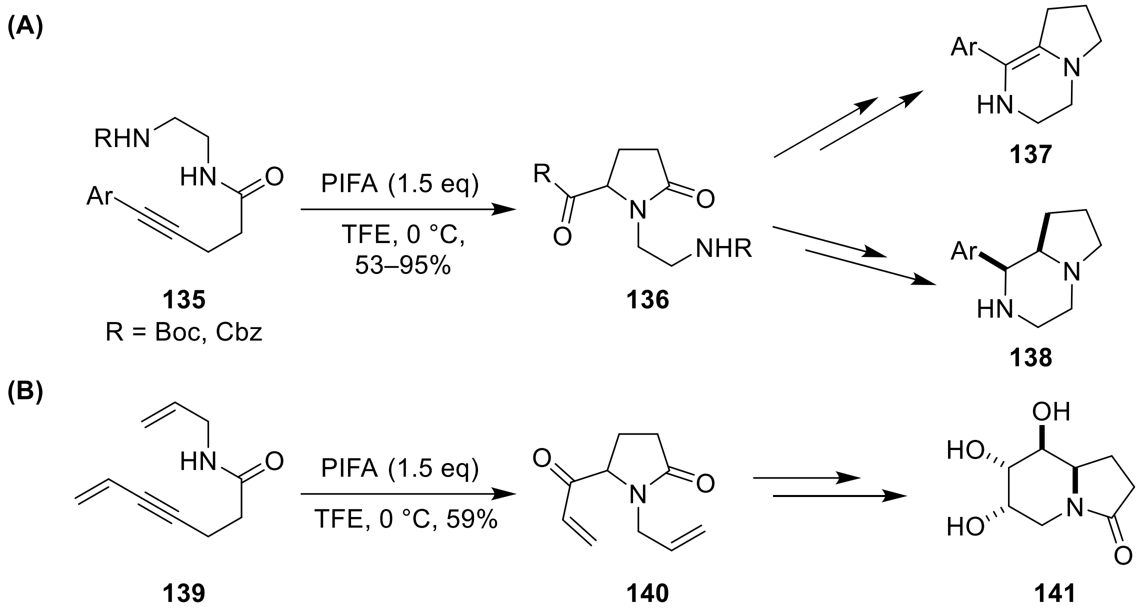
In 2005 Tellitu *et al.* reported a novel alkyne amidation reaction for the construction 5-aroylpyrrolidinones **132** (Scheme 37).[61] They were able to effect intramolecular cyclization of alkynes **131** using PIFA. The key intermediate in the reaction is expected to be nitrenium ion **133** formed by a PIFA mediated oxidation. This nitrenium ion is stabilized by the electron donating PMP group on the nitrogen. Electrophilic ring closure gives intermediate **134** which is quenched by trifluoroacetate and subsequently hydrolysed during workup to give the observed product **132**.

Tellitu and colleagues found that the reaction gave best performance with electron-rich aryl substituents on the alkyne. Tellitu and co-workers were subsequently able to extend this methodology to other substituents on the nitrogen including allyl, alkyl and benzyl groups.[62] Without significant stabilization for the nitrenium intermediate, these reactions are expected to proceed by nucleophilic cyclization of the amide on to a PIFA-activated alkyne.



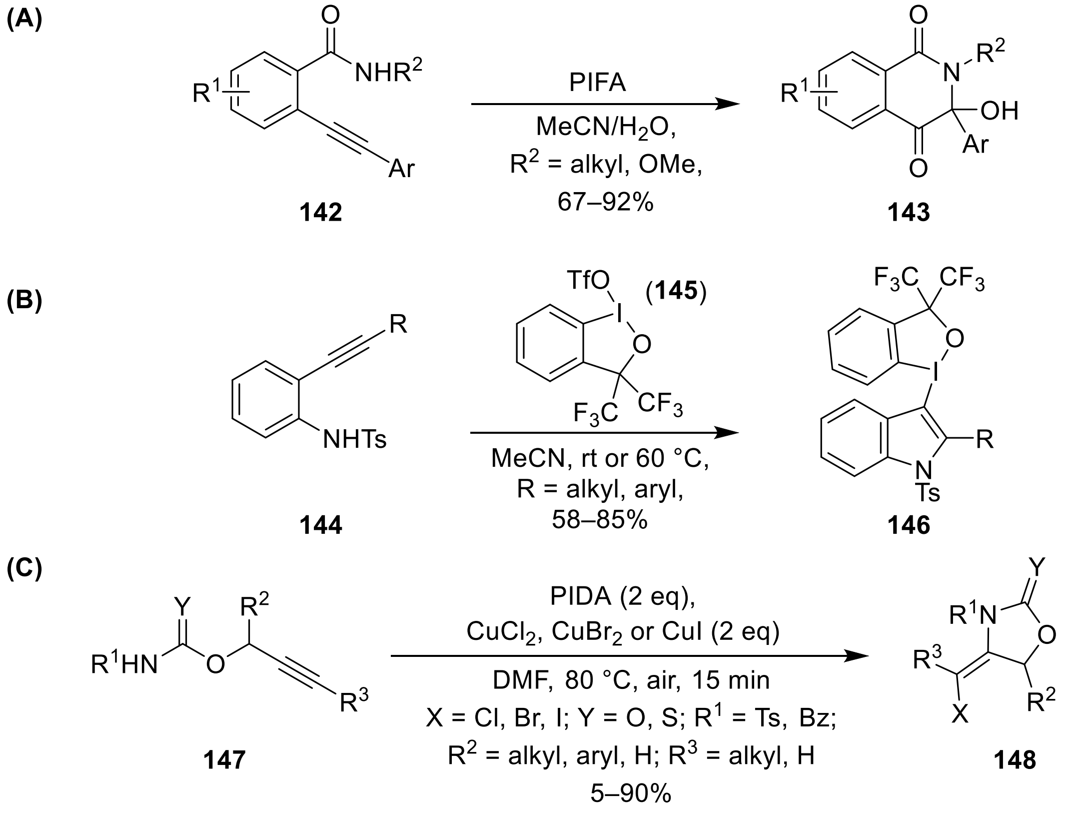
Scheme 37: Synthesis of 5-aroylpyrrolidinones by alkyne amidation.[61]

The same group found that the 1,2-diamine derivatives **135** also reacted successfully in the reaction giving pyrrolidinones **136** (Scheme 38A).[63] These pyrrolidinones could be further modified in order to form pyrrolopyrazinones **137** and **138**. Tellitu and co-workers also successfully extended the methodology to compound **139** with a vinyl substituent on the alkyne and an allyl substituent on the nitrogen (Scheme 38B).[64] Subsequent ring-closing metathesis and dihydroxylation could be use to fashion indolizidinone **141**.



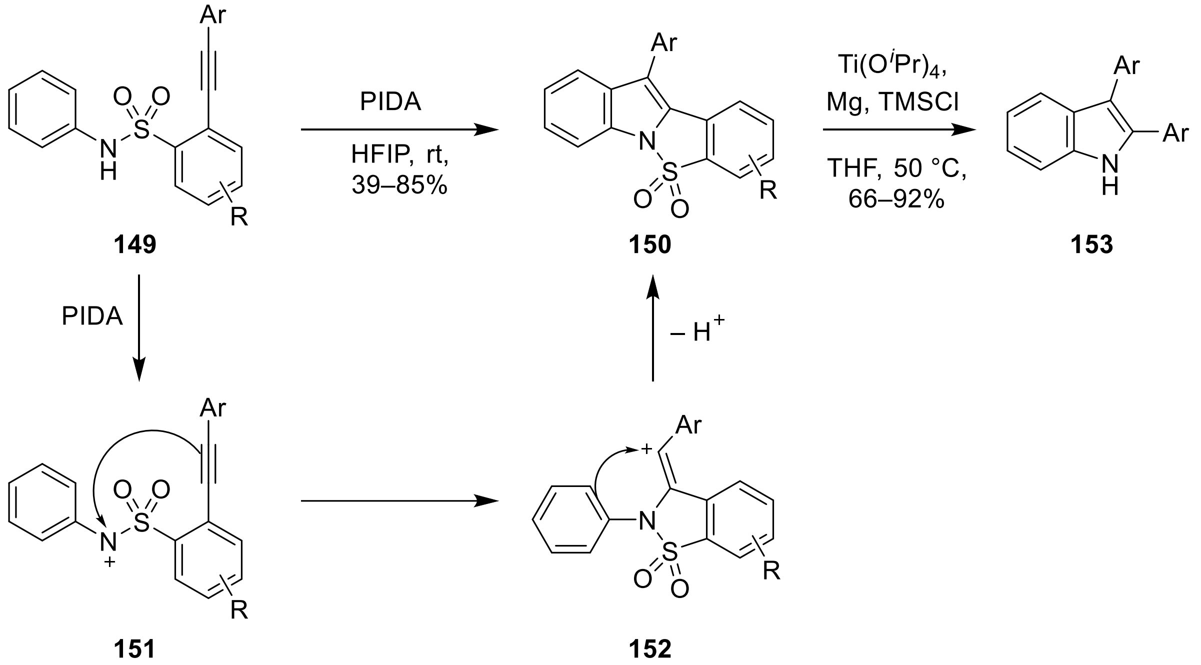
Scheme 38: Synthesis of pyrrolidinone derivatives by Tellitu and co-workers.[63, 64]

Zhao and Du *et al.* used similar methodology for the synthesis of isoquinoline-1,4-diones **143** (Scheme 39A),[65] while Yoshikai *et al.* prepared 3-indolylbenziodoxoles **146** (Scheme 39B).[66] Xiang, Deng and co-workers described a method for the preparation of oxazolidin-2-ones **148** (Scheme 39C).[67]



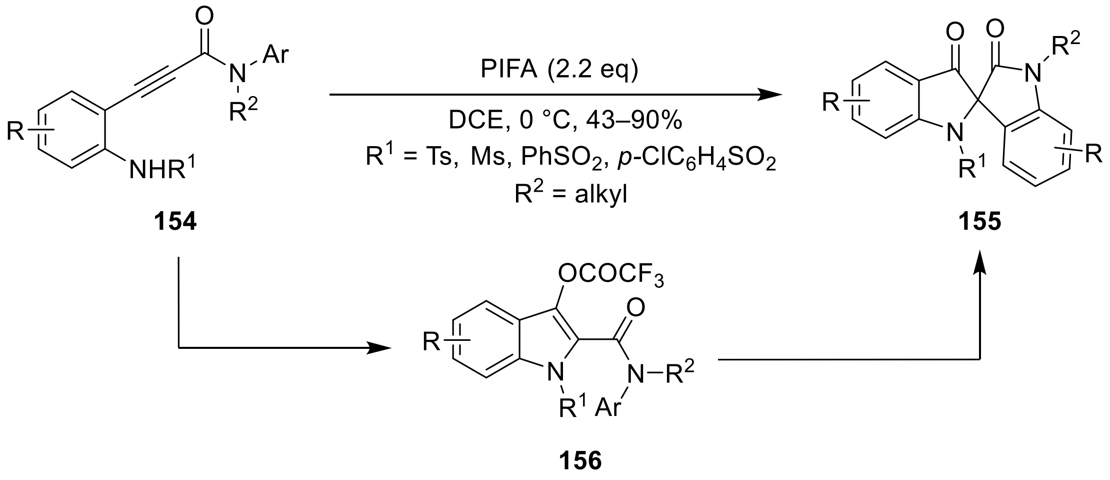
Scheme 39: Synthesis of various *N*-heterocycles by intramolecular cyclization onto alkynes.[65-67]

Muñiz and Fra reported a method for the synthesis of 2,3-diarylindoles using a sulfonyl tether (Scheme 40).[68] In the proposed reaction pathway, oxidation of sulfonamide **149** with PIDA leads to the formation of nitrenium ion **151**. Cyclization of the alkyne onto the nitrenium ion gives vinylic cation **152** which undergoes nucleophilic attack by the adjacent arene. Subsequent rearomatization forms sulfonyl tethered indole **150**. This tether can be removed in a separate reaction with magnesium, titanium isopropoxide and TMSCl to form 2,3-diarylindoles **153**.



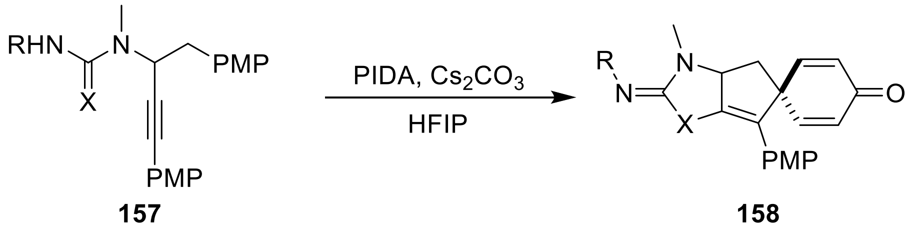
Scheme 40: Synthesis of 2,3-diarylindoles using a sulfonyl tether.[68]

Another use of intramolecular alkyne amidation is for the construction of spiro *N*-heterocycles. In a reaction reported by Du *et al*. in 2017 alkynes **154** were transformed into spiro compounds **155** by a PIFA induced cyclization (Scheme 41).[69] The first cyclization forms indoles **156** which is reactivated by a second molecule of PIFA and undergoes nucleophilic attack by the adjacent arene. This leads to the formation of the spiro product **155**. The full mechanism has not been determined conclusively.



Scheme 41: Synthesis of spiropseudoindoxyl compounds **155**.[69]

Similarly, Lovely *et al.* described a PIDA-induced spirocyclization to directly form the framework of spirocalcaridines A and B (Scheme 42).[70]

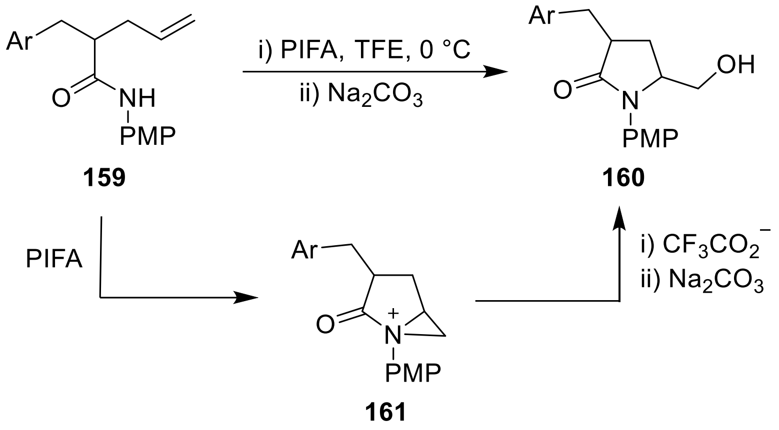


Scheme 42: Spirocyclization to form the framework of spirocalcaridines A and B.[70]

3.2.2. Intramolecular Addition to Alkenes

In 2004 Tellitu *et al.* reported the synthesis of pyrrolidines by a PIFA-mediated intramolecular addition to alkenes (Scheme 43).[71] The key intermediate in their reaction is expected to be aziridinium ion **161** which is formed by reaction of the alkene with the nitrenium ion formed by PIFA oxidation. The aziridinium ion is originally ring-opened by the trifluoroacetate ion during the reaction and then hydrolysed by a bicarbonate work-up giving the product **160**.

Tellitu's approach was used by Wardrop and co-workers to synthesize various bi- and tricyclic systems (Figure 4).[72]



Scheme 43: Synthesis of pyrrolidinones by intramolecular alkene hydroxyamination. The authors did not report the yield for the cyclization step, only combined yields with a subsequent step were included.[71]

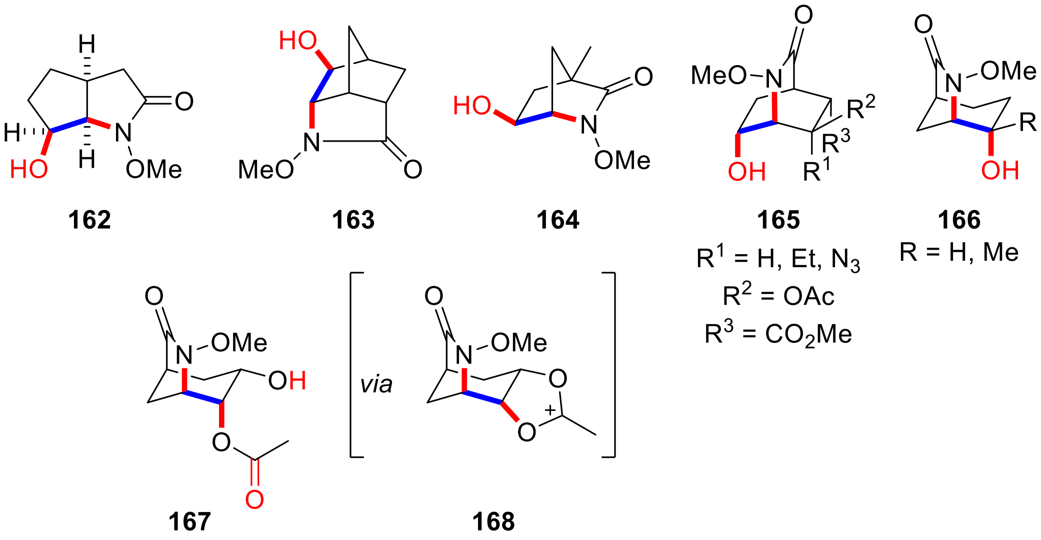
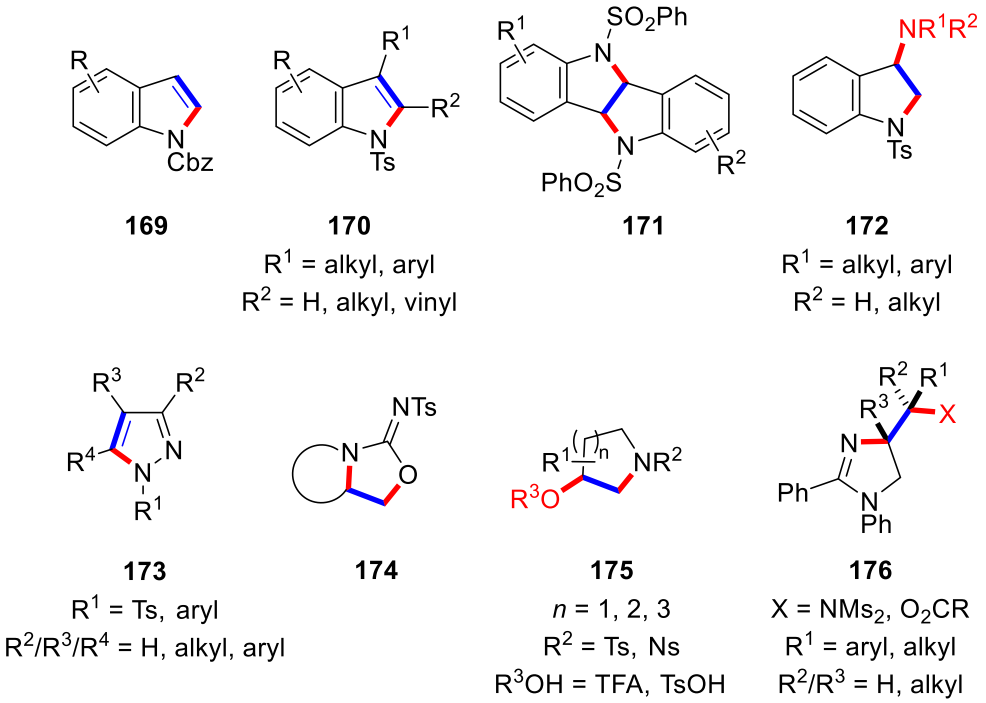


Figure 4: Synthesis of various bi- and tricyclic systems by Wardrop *et al*. New bonds and atoms are shown in red, location of the alkene in the starting material is shown in blue.[72]

Syntheses of many other *N*-heterocycles using iodine(III) mediated intramolecular alkene amination have also been reported (Figure 5). For example, Muñiz and co-authors reported synthesis of indoles **169** using 2-vinylanilines.[73] In another indole synthesis, Mo and colleagues described a route to 2,3-disubstituted indoles **170**.[74] Chang *et al.* were able to use an intramolecular diamination reaction to form bisindolines **171**.[75] Johnston and Hong reported use of an inter-/intramolecular amination reaction to form 3-aminoindolines **172**.[76] Zhu and Liang were able to achieve an efficient synthesis of substituted pyrazoles **173** via cyclization of vinyl hydrazones.[77] Another similar synthesis of pyrazoles was reported by Aggarwal and Kumar.[78] Wirth and Farid reported access to isoureas **174** via an intramolecular oxyamination.[79] Michael and Lovick detailed a inter-/intramolecular oxyamination reaction to produce pyrrolidines, piperidines and azepanes **175**.[80] Chiba *et al.* reported successful synthesis of dihydroimdazoles **176** via inter-/intramolecular diamination and oxyamination reactions.[76]



169

170
R^1 = alkyl, aryl
R^2 = H, alkyl, vinyl

171

172
R^1 = alkyl, aryl
R^2 = H, alkyl

173
R^1 = Ts, aryl
$R^2/R^3/R^4$ = H, alkyl, aryl

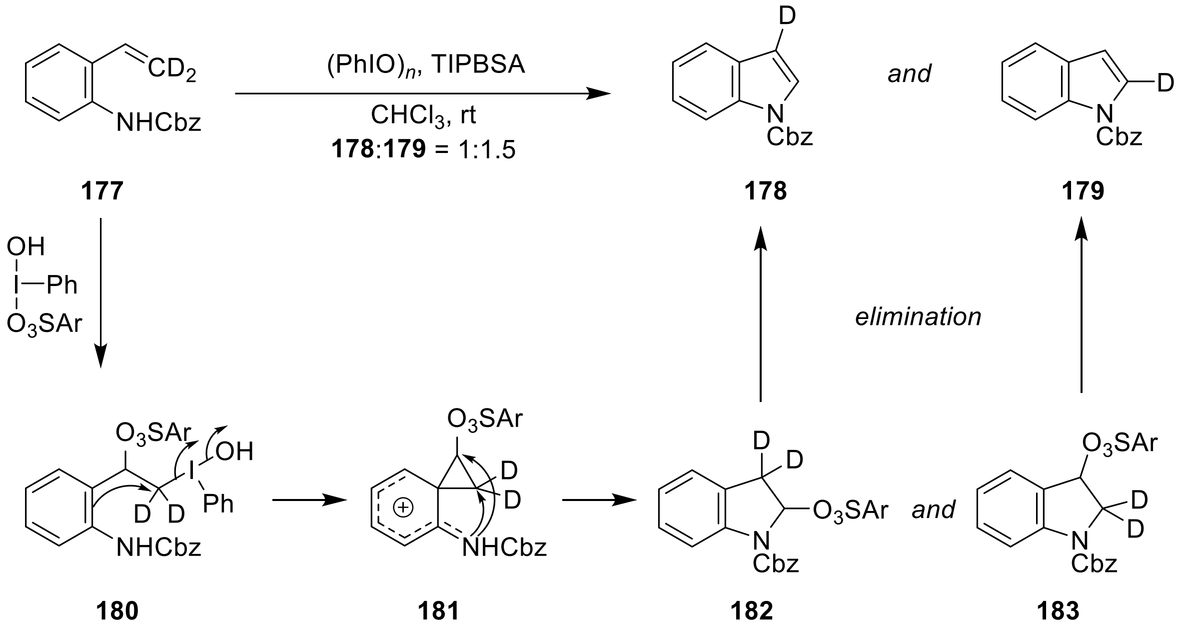
174

175
n = 1, 2, 3
R^2 = Ts, Ns
R^3OH = TFA, TsOH

176
X = NMs_2, O_2CR
R^1 = aryl, alkyl
R^2/R^3 = H, alkyl

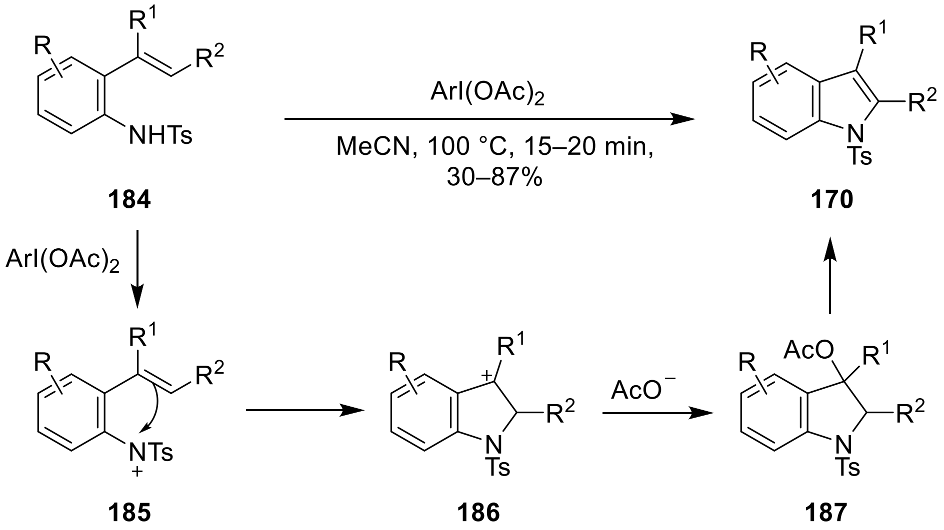
Figure 5: Synthesis of various *N*-heterocycles involving iodine(III) mediated intramolecular amination. New bonds and atoms are shown in red, location of the alkene in the starting material is shown in blue.[73-80]

Interestingly, the mechanism of Muñiz *et al.*'s synthesis of indoles **169** was found to be more complex than expected. When deuterated compound **177** was subjected to the cyclization conditions it was found that the deuterium label could partially undergo an apparent migration (Scheme 44).[73] Based on this observation it was postulated that the reaction proceeds as shown in Scheme 44. First iodine(III) species **180** is obtained by the addition of hypervalent iodine reagent to the alkene. Next, nucleophilic attack of the aryl ring with loss of iodobenzene produces the resonance-stabilised phenonium ion **181**. The spirocyclopropyl moiety in **181** can be ring-opened in two possible positions leading to the formation of indolines **182** or **183**. Elimination from the aforementioned indolines leads to the formation of indoles **178** and **179** as observed.



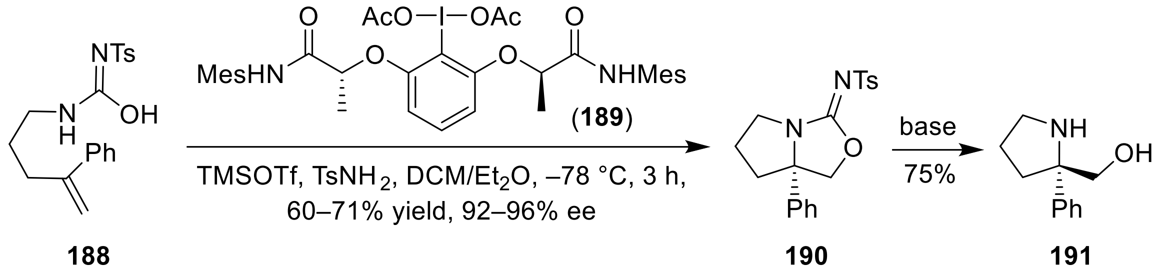
Scheme 44: A deuterium labelled experiment performed with **177** found that an apparent migration of the deuterium label can take place.[73]

In contrast Mo *et al.*'s synthesis of 2,3-disubstituted indoles **170** proceeds according to a more straightforward pathway (Scheme 45).[74] First, oxidation of **184** by the iodine(III) reagent leads to the formation of resonance stabilised nitrenium ion **185**. Electrophilic ring closure gives stabilised carbocation **186** which is subsequently quenched by acetate giving indoline **187**. Lastly, elimination of acetate forms the product **170**.



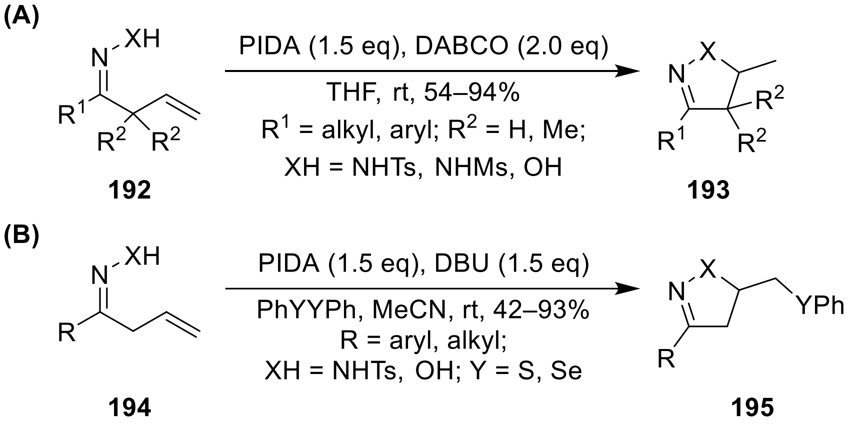
Scheme 45: Synthesis of indoles by Mo and colleagues.[74]

It is also possible to access optically pure *N*-heterocycles using chiral iodine(III) reagents. For example, Wirth and Farid reported an enantiopure preparation of (*S*)-phenylprolinol **191** using chiral iodine(III) reagent **189** (Scheme 46).[79] As proline and its derivatives are often used in organocatalysis, synthesising enantiopure prolines represents an area of major interest. The enantiomeric excess was 92–96% on scaled up reactions, but could go up to >99% on analytical scale reactions.



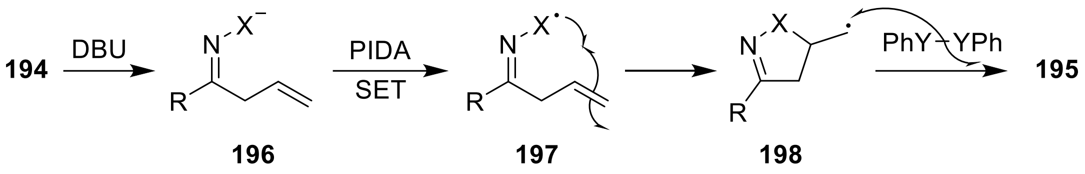
Scheme 46: Enantioselective synthesis of (*S*)-phenylprolinol **191**.[79]

Intramolecular aminations proceeding via radical mechanisms have also been reported. Xiao *et al.* reported a PIDA mediated synthesis of pyrazolines and isoxazolines **193** via a radical process (Scheme 47A).[81] A similar reaction using either PhSSPh or PhSeSePh as a radical trap was disclosed by Cai and Yu (Scheme 47B).[82]



Scheme 47: Synthesis of pyrazolines and isoxazolines.[81, 82]

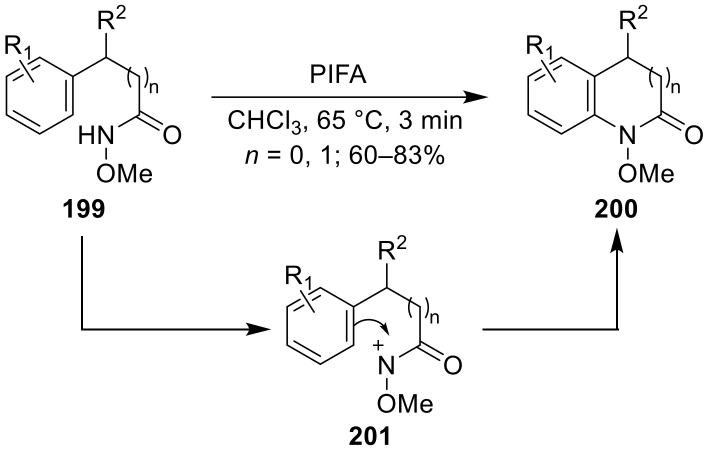
The mechanism proposed for Cai and Yu's reaction[82] starts with the deprotonation of the starting material by DBU to give anion **196** which undergoes SET oxidation by PIDA to give radical **197** (Scheme 48). A radical ring closure produces **198** which reacts with PhSSPh or PhSeSePh to give the product **195**.



Scheme 48: Mechanism for Cai and Yu's pyrazoline and isoxazoline synthesis.[82]

3.2.3. Intramolecular Aryl C─H Functionalization

The synthesis of *N*-heterocycles by intramolecular aryl C─H functionalization was first reported by Kikugawa and Kawase in 1990. They reported PIFA induced cyclization via nitrenium ion **201** to form indolin-2-ones and 3,4-dihydroquinolin-2-ones **200** (Scheme 49).[83]



Scheme 49: Synthesis of indolin-2-ones and 3,4-dihydroquinolin-2-ones by intramolecular aryl C─H functionalization.[83]

Since Kikugawa and Kawase's early report, this approach has been utilised for the synthesis of a wide range of fused *N*-heterocycles (Figure 6). This includes benzoxazolones **202**,[84] benzimidazolones **203**,[85] carbazoles **204**,[86-88] carbazol-4-ones **205**,[89] dibenzoxazepinones[90] and benzodiazepinones[91] **206**, benzosultams **207**,[92] dibenzothiazines **208**[93] and *P*-stereogenic phosphinamides **209**.[94] Some of the procedures have been designed to be catalytic with respect to the aryl iodide by using peracids to (re)oxidize the aryl iodide.[87, 88]

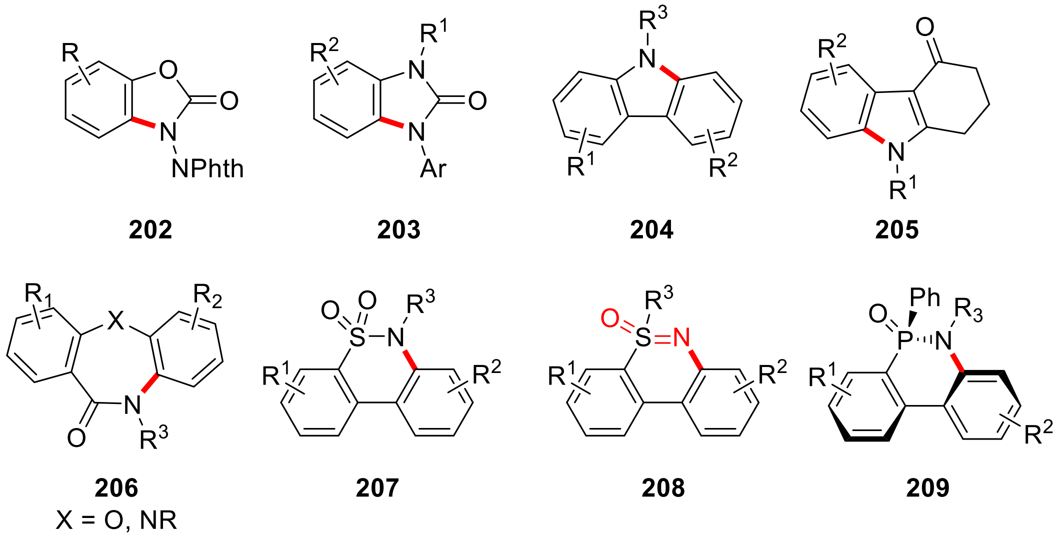
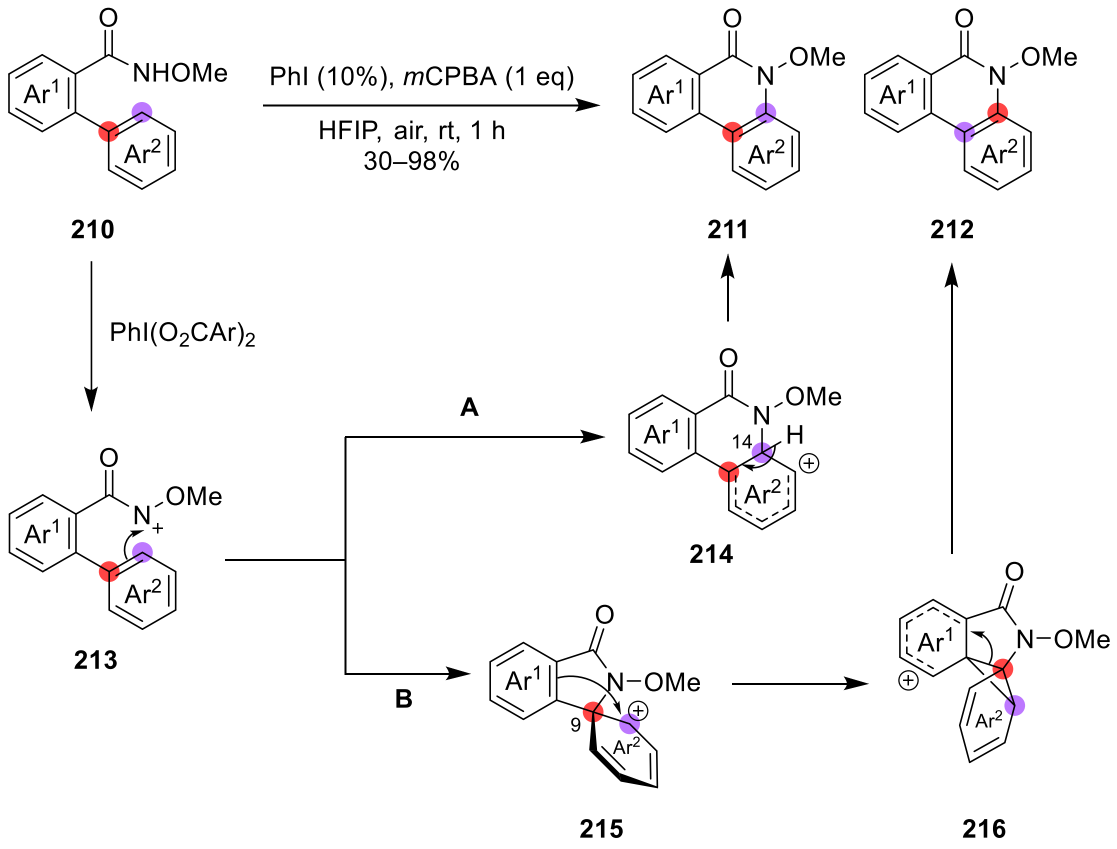


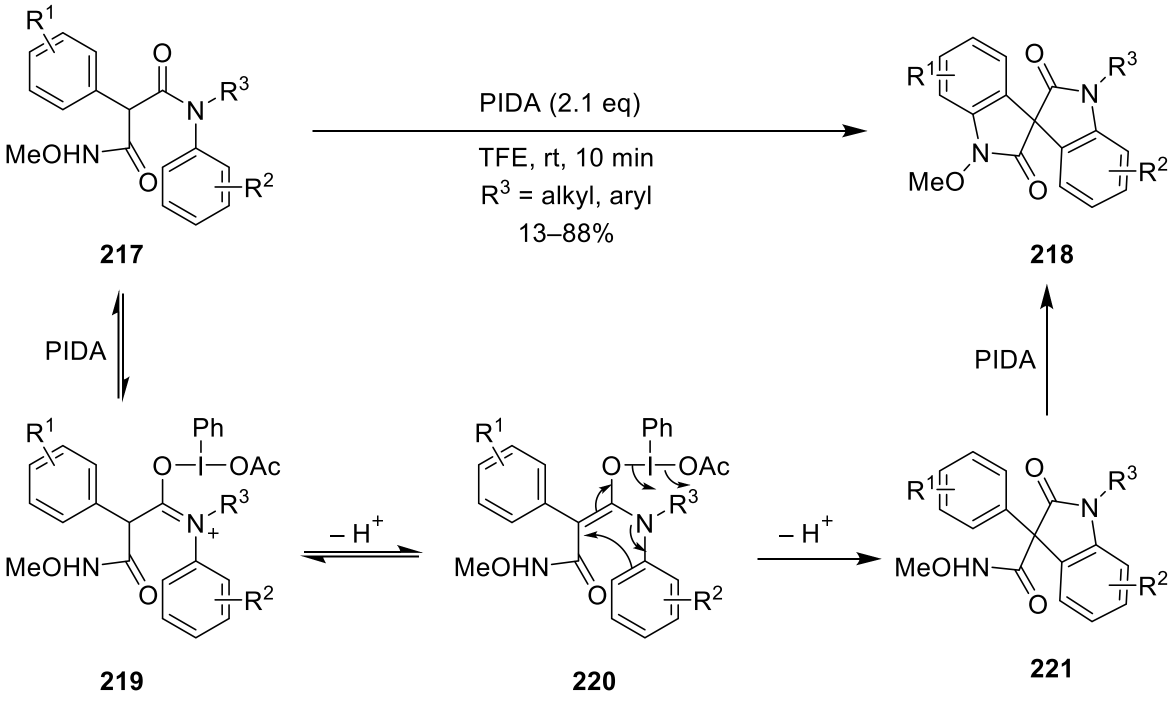
Figure 6: Selected examples of fused *N*-heterocycle synthesis by intramolecular aryl C–H functionalization. New bonds and atoms are shown in red.[84-94]

Xue *et al.* reported an interesting synthesis of phenanthridinones where regioisomer **211** and/or **212** can be formed (Scheme 50).[95] The first step in the reaction is expected to be the formation of nitrenium ion **213**. Nucleophilic attack of Ar^2 on the nitrenium ion can proceed via either pathway **A** or pathway **B**. In pathway **A** the new C–N bond is formed to C-14 producing aryl carbocation **214** – the rearomatization of which produces regioisomer **211**. In contrast, in pathway **B** the new C–N bond is formed to C-9 producing spirocarbocation **215**. Intermediate **215** then rearranges to form regioisomer **212** via fused cyclopropyl intermediate **216**. Xue and co-authors were able to construct a linear regression model based on the IR frequency of the N–H bond, IR intensity of the C=O stretch and torsion angle of the biphenyl bond which accurately predicts the regioisomer preference in the reaction.

Another interesting application is the synthesis of spirooxindoles **218** via an oxidative cascade reaction reported by Du *et al.* (Scheme 51).[96] The reaction is expected to start with association of the iodine(III) reagent at the *N*-arylamide carbonyl giving iminium ion **219** which tautomerizes to form enamine **220**. An intramolecular cyclization and subsequent rearomatization converts **220** to indole **221**. Intermediate **221** then undergoes aryl C–H amination mediated by PIDA to form spirooxindole **218**.



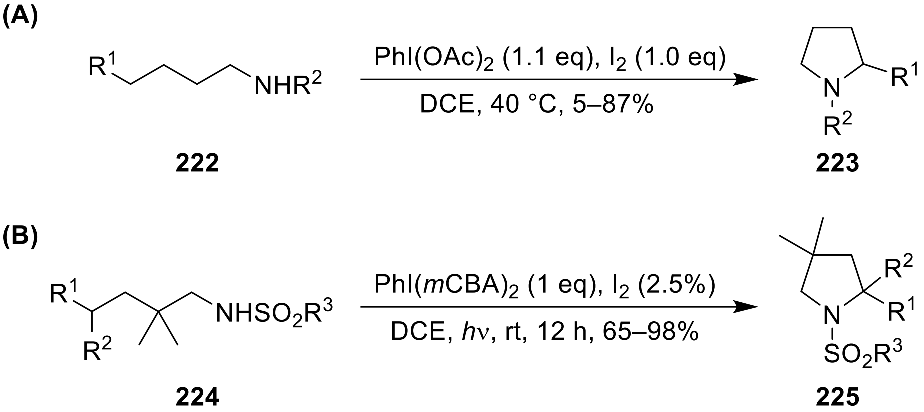
Scheme 50: Synthesis of phenanthridinones leading to the production of regioisomers.[95]



Scheme 51: Synthesis of spirooxindoles by Du *et al.*[96]

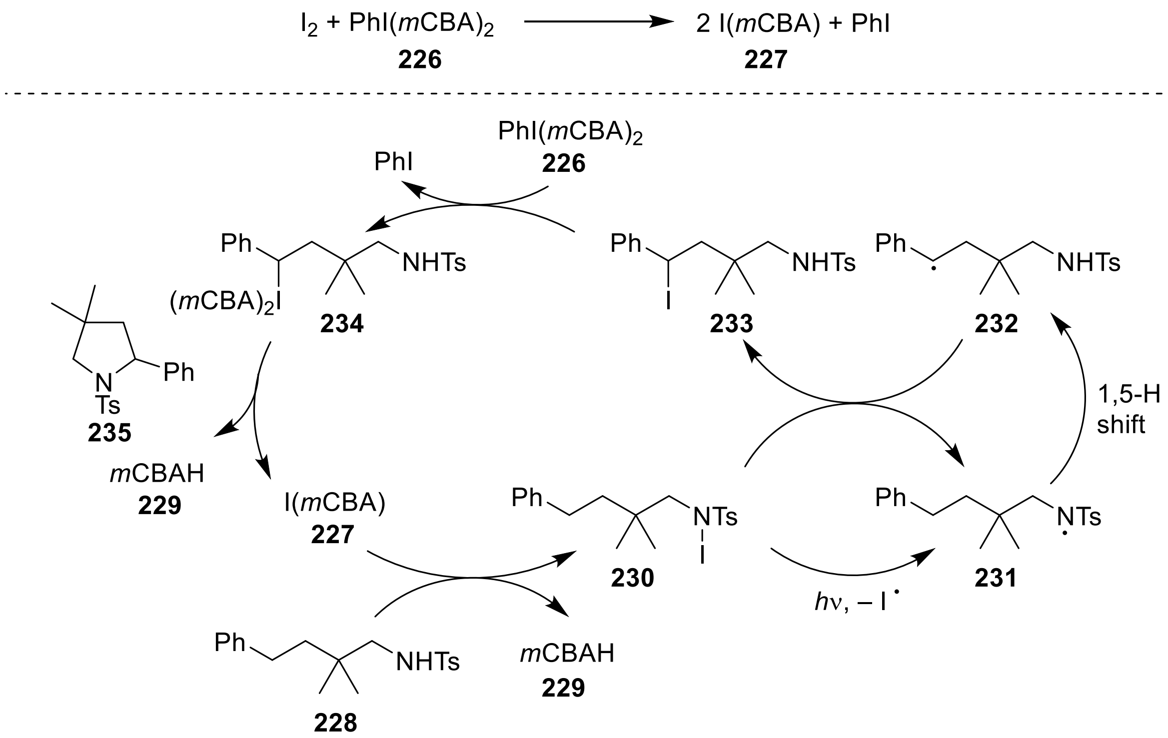
3.2.4. Intramolecular sp^3 C–H Functionalization

The synthesis of pyrrolidines by a PIDA/I$_2$ mediated Hofmann-Löffler-Freytag reaction was reported by Fan and colleagues in 2007 (Scheme 52A),[97] building upon earlier work by Suárez *et al.*[98-102] Later, Muñiz and Martínez reported a catalytic version of the procedure (Scheme 52B).[103]



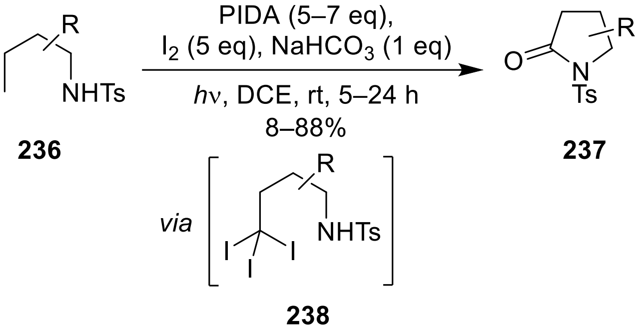
Scheme 52: Synthesis of pyrrolidines by an I(III)/I(I) mediated Hofmann-Löffler-Freytag reaction.[97, 103]

A mechanism for the catalytic I(III)/I(I) mediated Hofmann-Löffler-Freytag reaction was proposed by Muñiz and Martínez (Scheme 53).[103] Initially, the iodine(III) reagent, PhI(*m*CBA)$_2$ (**226**) oxidizes I$_2$ to form I(*m*CBA) (**227**) which is the active catalytic species in the reaction. I(*m*CBA) then reacts with the starting material **228** generating *N*-iodinated amide **230** with loss of *m*-chlorobenzoic acid (*m*CBAH**, 229**). Intermediate **230** is then homolysed by visible light generating *N*-centred radical **231**. This radical undergoes a 1,5-hydrogen shift to form *C*-centred radical **232**. Intermediate **232** then reacts with another molecule of *N*-iodinated amide **230** in a radical chain reaction forming alkyl iodide **233**. Alkyl iodide **233** is then oxidised by a molecule of PhI(*m*CBA)$_2$ to form alkyliodine(III) species **234**. Lastly, intramolecular nucleophilic cyclization gives the product **235**, *m*CBAH, and also regenerates the I(*m*CBA) catalyst.



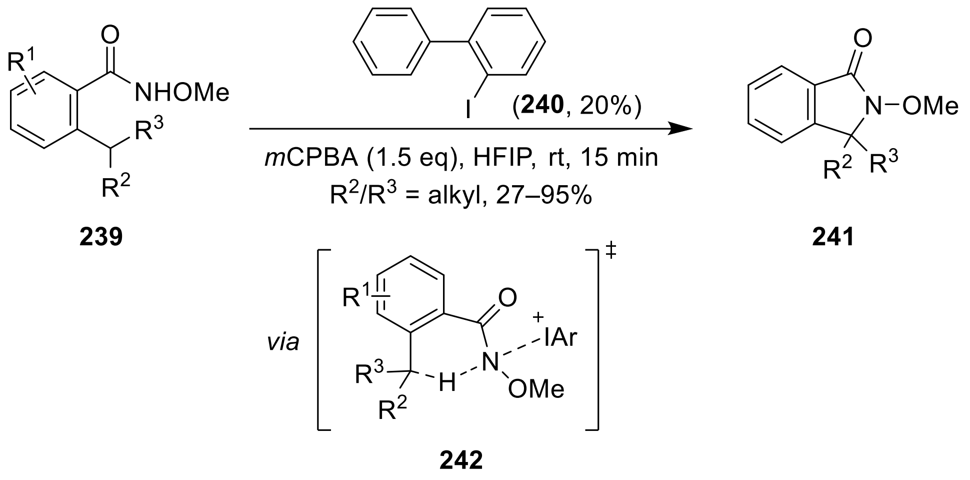
Scheme 53: Mechanism for Muñiz and Martínez's synthesis of pyrrolidines.[103]

Multiple iodinations can be achieved under basic conditions as demonstrated by Herrera and colleagues (Scheme 54).[104] They were able to synthesize pyrrolidinones **237** via triiodinated intermediates **238**.



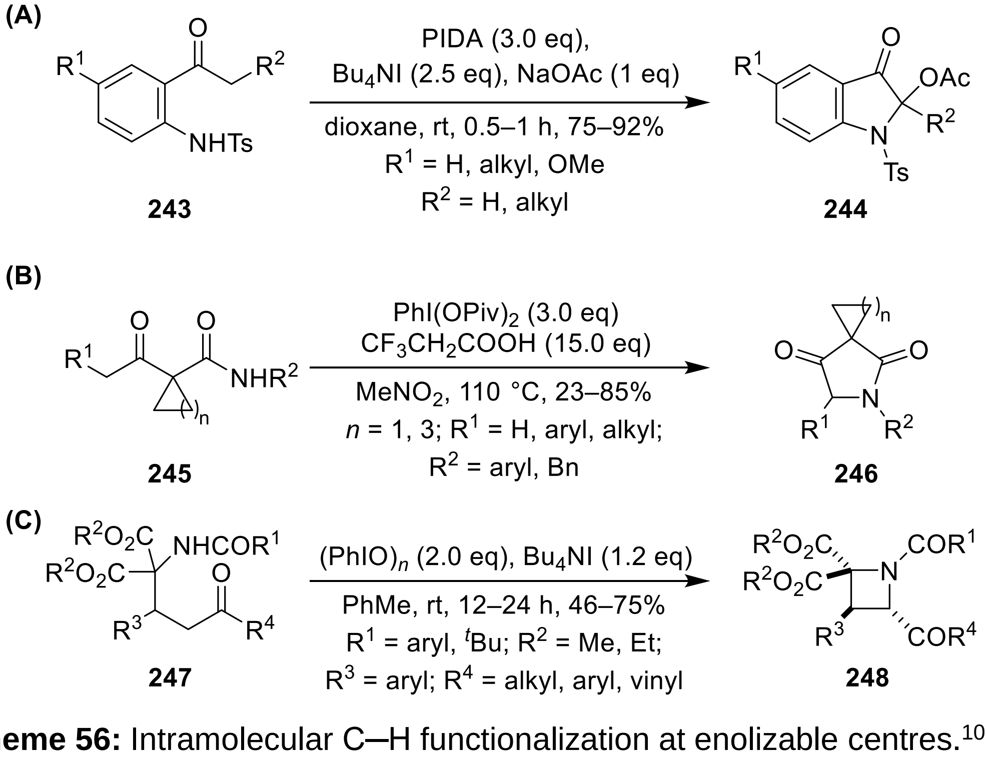
Scheme 54: Synthesis of pyrrolidinones via a Hofmann-Löffler-Freytag-type reaction.[104]

Shi *et al.* described a catalytic procedure where isoindolinones **241** were synthesized by an intramolecular tertiary C–H functionalization (Scheme 55).[105] The hypervalent iodine reagent was generated *in situ* by oxidation of aryl iodide **240** by *m*CPBA. Based on DFT calculations the key transition state was determined to be iodonium cation **242** which undergoes intramolecular hydride transfer and spontaneous C–N bond formation without involvement of a carbocation intermediate.



Scheme 55: Synthesis of isoindolinones by an intramolecular C–H functionalization.[105]

Several cyclization reactions involving enolizable centres have also been reported. Examples include Fan and Sun's synthesis of indolin-3-ones **244** (Scheme 56A),[106] Zhang *et al.*'s synthesis of tetramic acid derivatives **246** (Scheme 56B)[107] and Fan *et al.*'s synthesis of azetidines **248** (Scheme 56C).[108]



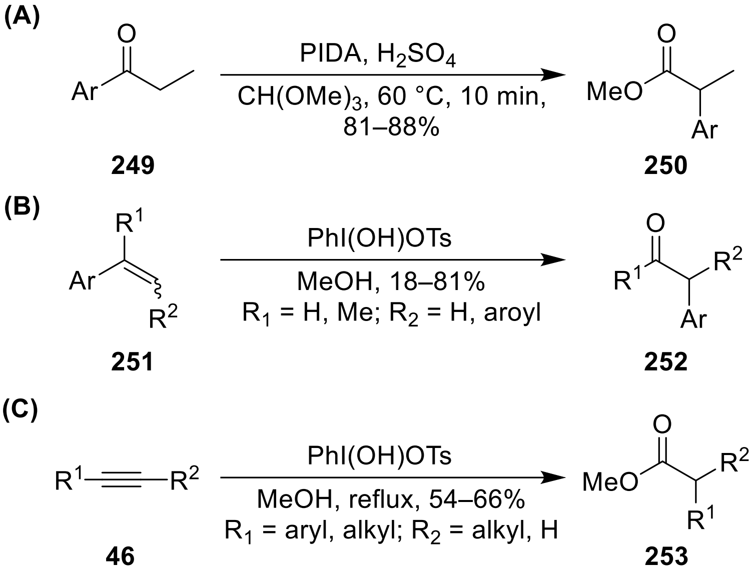
Scheme 56: Intramolecular C–H functionalization at enolizable centres.[106-108]

3.3. Rearrangements

Due to the ability of hypervalent iodine reagents to add to molecules as an electrophile and then change into an excellent leaving group, they can be used to trigger rearrangements.[29] Examples of rearrangements that have been mediated by hypervalent iodine reagents include 1,2- shifts, Hofmann rearrangements, Beckmann rearrangements, ring expansions, ring contractions and 3,3-sigmatropic rearrangements.[29, 109]

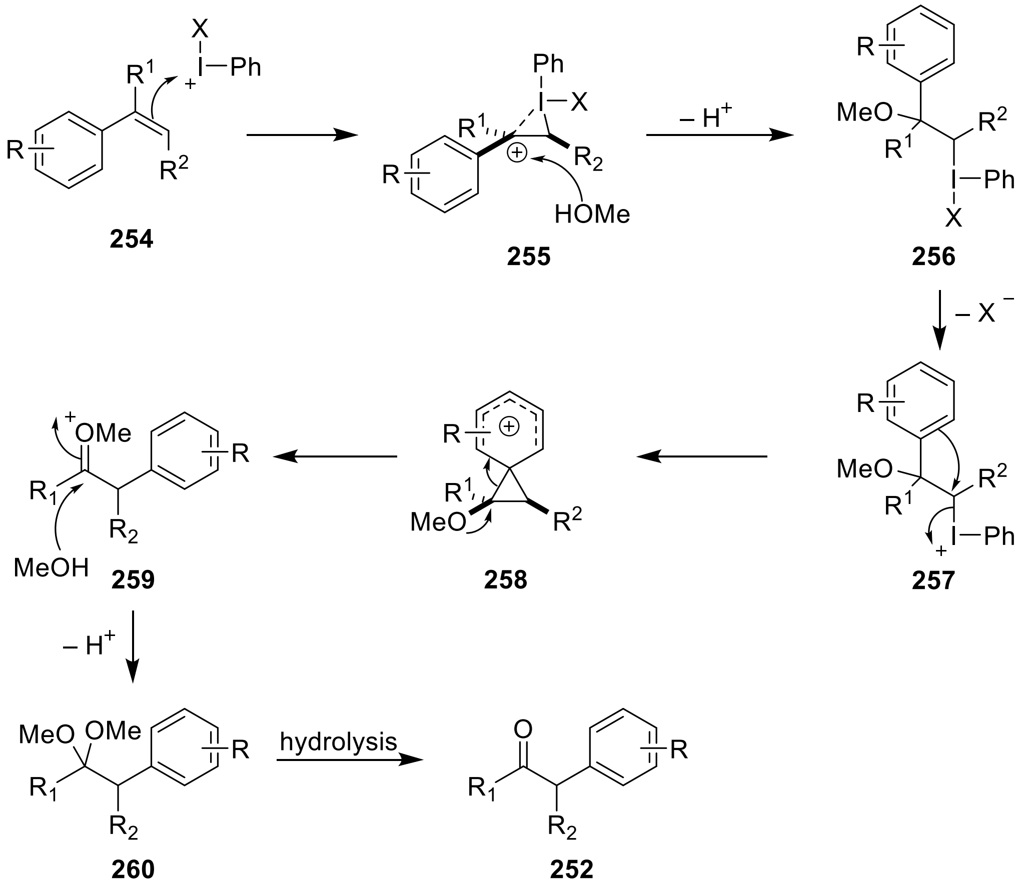
3.3.1. 1,2- Shifts

In 1984, Tamura *et al.* reported a rearrangement of methyl esters **249** via a 1,2-aryl migration (Scheme 57A).[110] Building upon this Moriarty and colleagues described methods for oxidative rearrangement starting from alkenes[111] (Scheme 57B) and alkynes[112] (Scheme 57C).



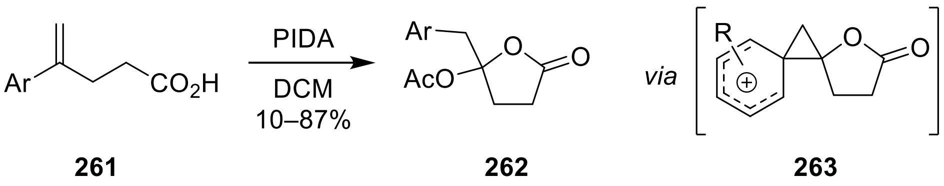
Scheme 57: Reactions involving iodine(III) induced 1,2- shifts.[110-112]

Based on postulated mechanisms,[109, 111, 113] the oxidative rearrangement of alkenes may start with addition of the iodine(III) reagent to the alkene producing cationic intermediate **255** with the positive charge stabilised by the aryl group (Scheme 58). Addition of MeOH to **255** gives intermediate **256**. Loss of the X ligand from the iodine(III) centre of **256** leads to the formation of iodonium ion **257**. Next, phenonium ion **258** is formed by loss of iodobenzene from **257**. Completion of the 1,2-aryl shift and addition of MeOH produces ketal **260**. Lastly, hydrolysis of the ketal gives the product, ketone **252**.



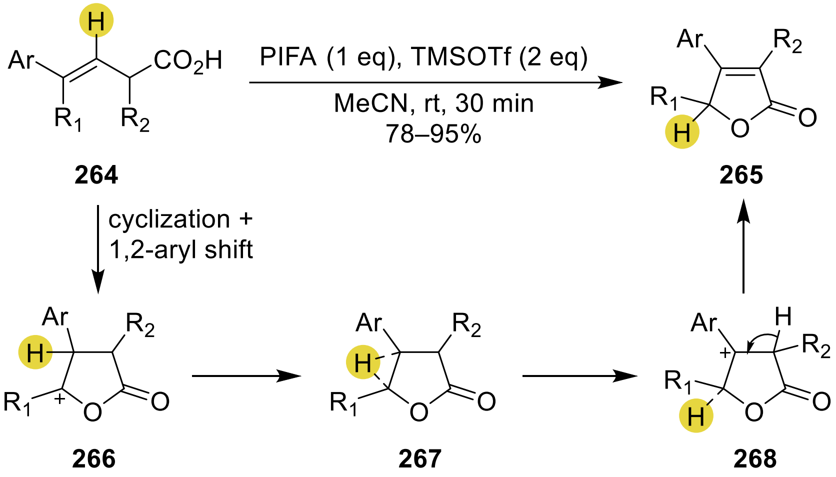
Scheme 58: Plausible mechanism for the oxidative rearrangement of alkenes.[109, 111, 113]

The group of Wirth described a novel lactonization procedure with a 1,2-aryl shift (Scheme 59).[114] Wirth and co-authors expected that electron donating groups would increase the aptitude of the migration by stabilising the intermediate phenonium ion **263**. However, this was surprisingly not the case – electron donating groups, and generally any group in general, only served to reduce the yield of product **262** – going from 87% for the phenyl analogue to 38% for the *p*-anisyl analogue.



Scheme 59: Novel lactonization procedure with 1,2-aryl migration.[114]

The same group also described access to furanones **265** via an oxidative cyclization-rearrangement reaction (Scheme 60).[115] The authors found that PIFA by itself was unreactive and that an activator was essential for the reaction, with TMSOTf performing better than $BF_3{\cdot}OEt_2$. Based on DFT calculations Wirth and co-workers found that after the 1,2-aryl shift producing carbocation **266**, the aforementioned carbocation then undergoes a 1,2-H shift to produce carbocation **268**. The involvement of this 1,2-H shift in the reaction was verified via a deuterium labelling study.

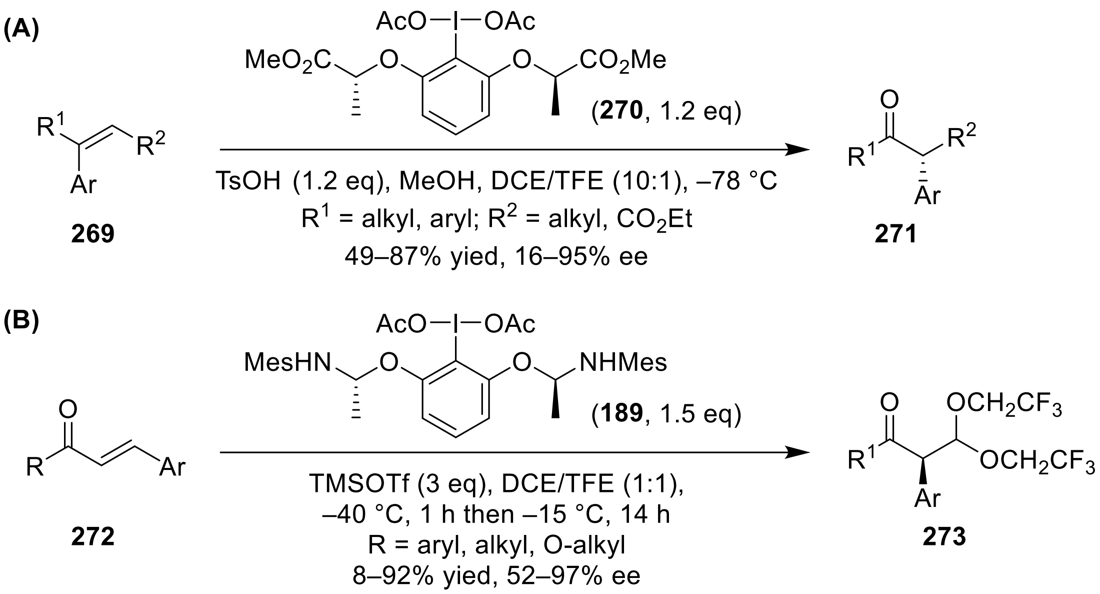


Scheme 60: Synthesis of furanones **265** by an oxidative cyclization-rearrangement reaction involving 1,2-aryl and 1,2-H shifts.[115]

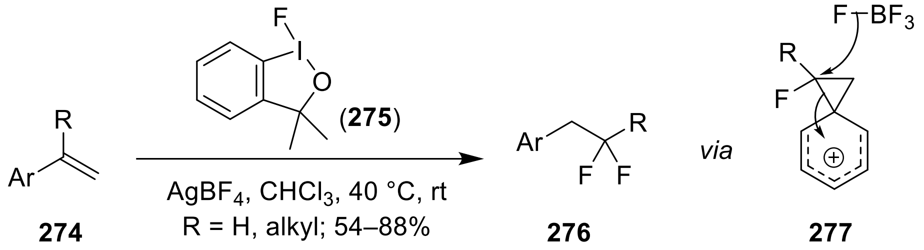
Enantioselective 1,2-aryl shifts have also been reported by the group of Wirth using chiral iodine(III) reagents **189** and **270** to achieve enantioselective oxidative rearrangements of styrenes **269**[116] and cinnamyl ketones **272**[117] (Scheme 61). The effect of aryl substituents on the oxidative rearrangement of modified cinnamyl ketones **272** was studied by Wirth and colleagues. They found the yields decreased with increasing Hammett value (σ) of the substituents: F (σ_{para} = 0.06, 60%), Br (σ_{para} = 0.23, 17%), NO_2 (σ_{para} = 0.78, 0%). Strongly electron donating groups were also detrimental, with the *p*-anisyl analogue undergoing complete decomposition under the reaction conditions.

Szabó and collaborators devised a method for the geminal difluorination of styrenes using fluorobenziodoxole **275** (Scheme 62).[118] The reaction proceeds via phenonium intermediate **277**.

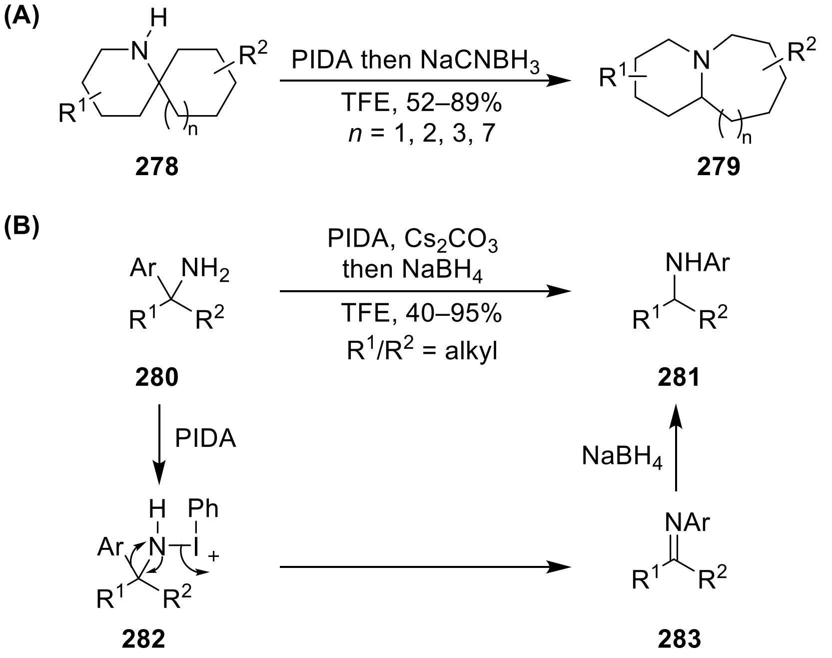
The group of Murai used PIDA with a reductive workup to effect 1,2- shifts from C to N. Murai *et al.*'s initial work demonstrated a 1,2-alkyl shift for ring expansion (Scheme 63A)[119] while the second demonstrated a 1,2-aryl shift (Scheme 63B).[120] The key intermediate in the latter reaction is expected to be intermediate **282** which undergoes a 1,2-aryl shift from C to N forming imine **283**. Reduction of this species with $NaBH_4$ provides the product, *N*-alkylaniline **281**.



Scheme 61: Enantioselective 1,2-aryl shifts mediated by chiral hypervalent iodine reagents.[116, 117]

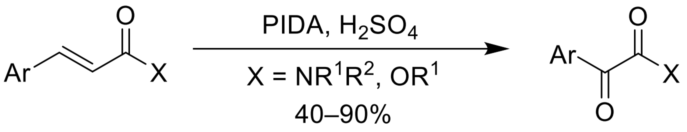


Scheme 62: Geminal difluorination of styrenes via a phenonium intermediate.[118]



Scheme 63: Iodine(III) induced 1,2- shifts from C to N.[119, 120]

Zhao *et al.* reported a tandem reaction which combines 1,2-aryl migration with an oxidative C–C bond cleavage (Scheme 64).[121]

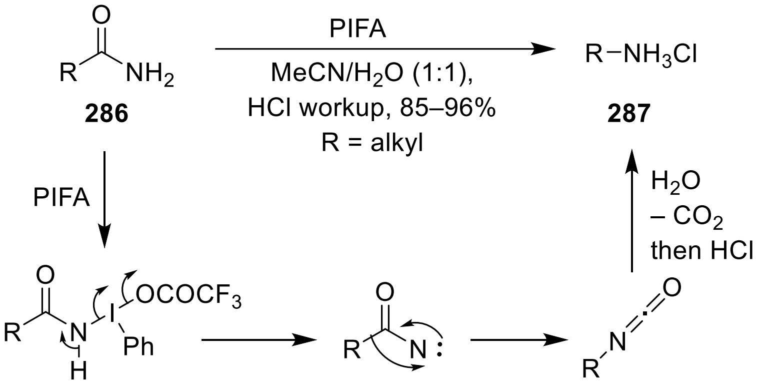


284 **285**

Scheme 64: Tandem oxidative 1,2-aryl migration/C–C bond cleavage reaction.[121]

3.3.2. Hofmann Rearrangement

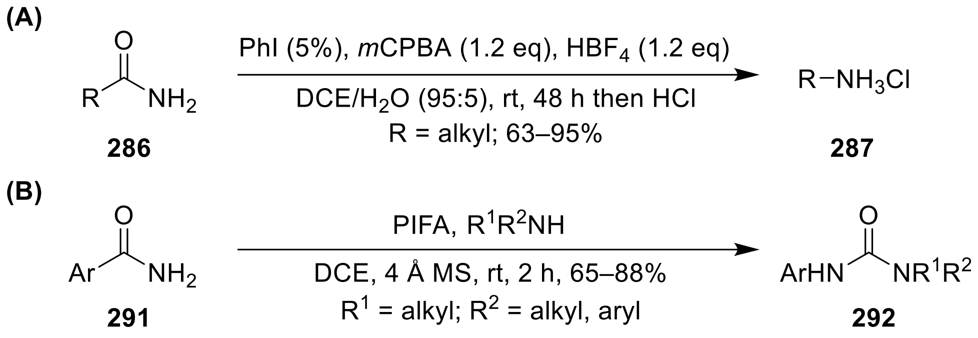
A hypervalent iodine induced Hofmann rearrangement was first reported by Loudon and colleagues in 1979.[122] They were able to effect the conversion of aliphatic amides into amine hydrochlorides (Scheme 65). The reaction initiates with ligand exchange on PIFA leading to intermediate **288**.[109] Elimination of iodobenzene from this intermediate gives nitrene **289** which rearranges to give isocyanate **290**. Addition of water to **290** and subsequent loss of CO_2 gives an amine, which upon an aqueous HCl workup forms amine hydrochloride **287**.



286 **287** **288** **289** **290**

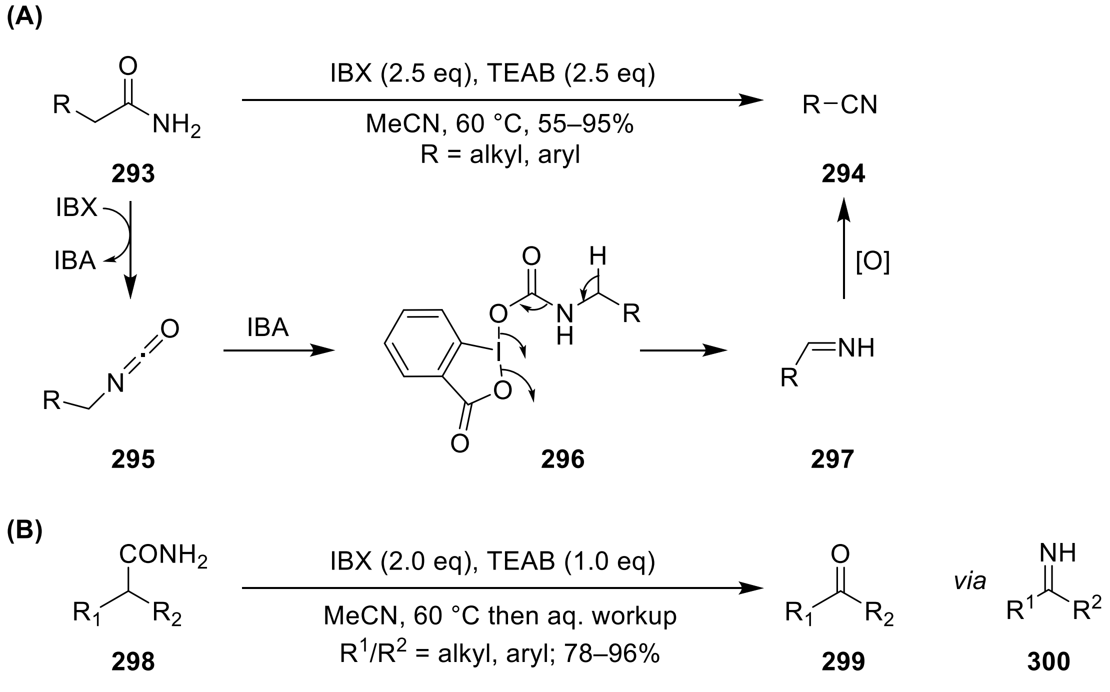
Scheme 65: Synthesis of aliphatic amines via an iodine(III) induced Hofmann rearrangement.[109, 122]

A catalytic version of the reaction was reported by Ochiai *et al.* in 2012 (Scheme 66A).[123] Their reaction was catalytic with respect to iodobenzene, using *m*CPBA as a terminal stoichiometric oxidant. Reddy and colleagues communicated a procedure for making unsymmetrical ureas by capturing the isocyanate intermediate of the Hofmann rearrangement with amines (Scheme 66B).[124]



Scheme 66: Reactions utilising the Hofmann rearrangement to form amine hydrochlorides **287** and ureas **292**.[123, 124]

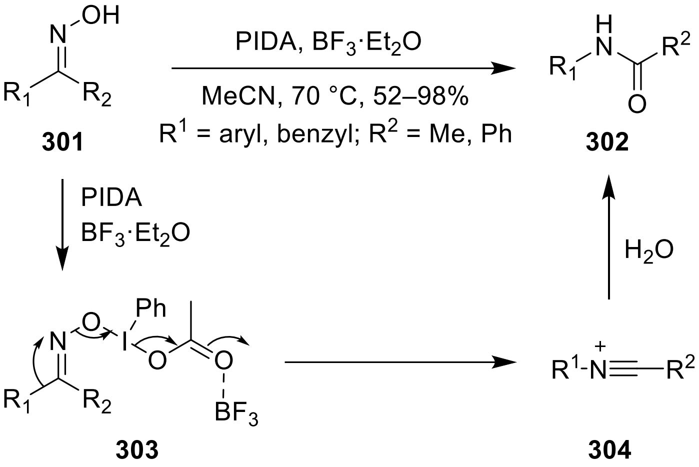
Akamanchi *et al.* described a procedure for the production of nitriles from primary amides (Scheme 67A).[125] They achieved this by capturing isocyanate **295** with IBA giving iodine(III) intermediate **296**. Elimination of carbon dioxide and *o*-iodobenzoic acid from **296** leads to the formation of imine **297**. Another oxidation converts the imine to the nitrile **294**. In another application of the reaction by the same group, they were able to avoid oxidation of the imine by using amides **298** – instead hydrolysing it to produce ketones **299** (Scheme 67B).[126]



Scheme 67: Nitriles and ketones can be obtained by a tandem Hofmann rearrangement/oxidation reaction.[125, 126]

3.3.3. Beckmann Rearrangement

In 2018, Miki and Maegawa *et al.* reported an iodine(III) induced version of the Beckmann rearrangement (Scheme 68).[127] The reaction utilises PIDA activated with $BF_3·OEt_2$, and is expected to proceed via association of PIDA with the oxime giving intermediate **303**. Rearrangement of **303** with loss of iodosylbenzene gives cation **304**, which is then attacked by water leading to amide **302**.

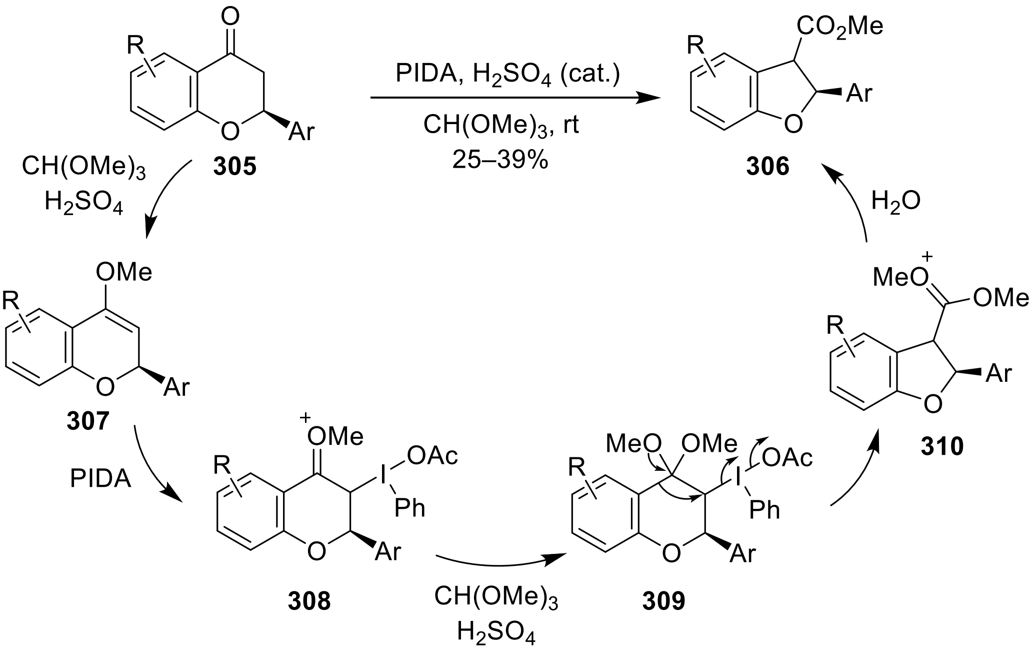


Scheme 68: Hypervalent iodine induced Beckmann rearrangement.[127]

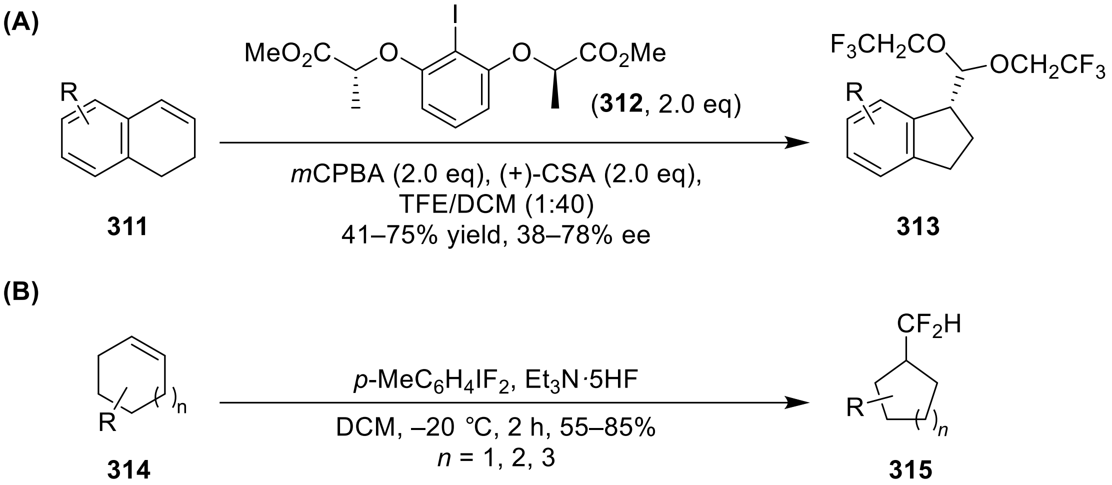
3.3.4. Ring Contraction

A Favorskii-type ring contraction by action of PIDA was first reported by Daum in 1984.[128] Mechanistic studies into a similar rearrangement of flavones **305** into benzofurans **306** were performed by Antus *et al*.[129] The reaction starts with the conversion of the ketone into enol ether **307**, which subsequently undergoes addition with PIDA giving iodine(III) intermediate **308** (Scheme 69).[109, 129] Next, ketal **309** is obtained by addition of another methoxy group to **308**. Rearrangement of **309** gives cationic intermediate **310**. Lastly, hydrolysis of **310** gives the product **306**.

Oxidative ring contraction starting from cyclic alkenes has also been reported. One notable example is Silva and Ahmad's enantioselective ring contraction of dihydronaphthalenes **311** to indanes **313** (Scheme 70A).[130] The selectivity was achieved by using chiral aryl iodide **312** which was oxidised to the active iodine(III) species by *m*CPBA. Another interesting application was the fluorinative ring-contraction of cyclic alkenes reported by Hara and Yoneda *et al.* using *p*-iodotoluene difluoride and $Et_3N·5HF$ (Scheme 70B).[131]

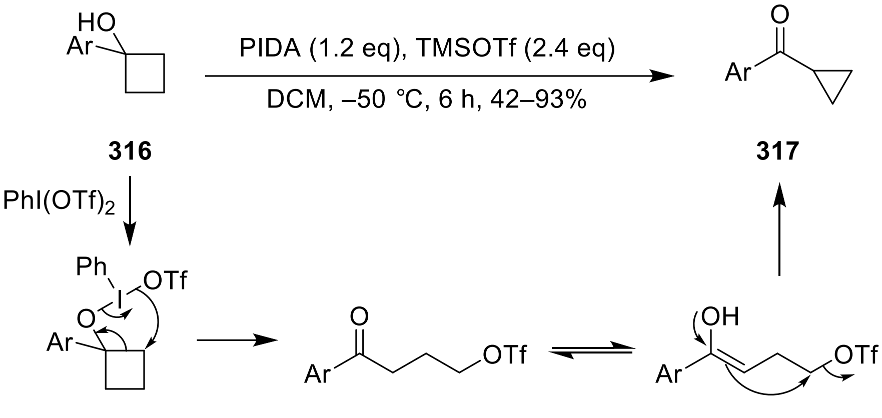


Scheme 69: Ring contraction of flavones to benzofurans.[109, 129]



Scheme 70: Oxidative ring contractions of cyclic alkenes mediated by iodine(III) reagents.[130, 131]

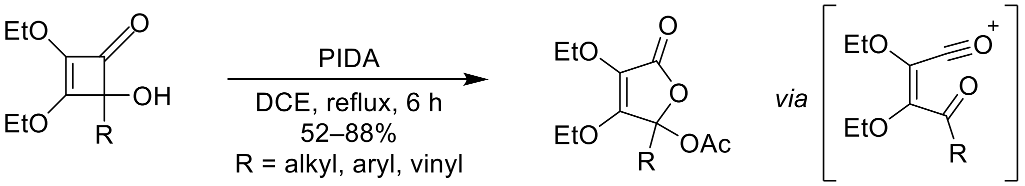
Peng and co-authors reported an oxidative ring contraction of cyclobutanols to cyclopropyl ketones (Scheme 71).[132] In the proposed reaction mechanism, PIDA first reacts with TMSOTf producing $PhI(OTf)_2$, which then undergoes ligand exchange with cyclobutanol **316** giving intermediate **318**. Oxidative ring opening of **318** with simultaneous intramolecular delivery of triflate produces ketone **319**. Under the acidic conditions of the reaction ketone **319** is converted to its tautomer enol **320**. An intramolecular S_N2 substitution with loss of triflate gives cyclopropyl ketone **317**.



Scheme 71: Oxidative ring contraction of cyclobutanols to cyclopropyl ketones.[132]

3.3.5. Ring Expansion

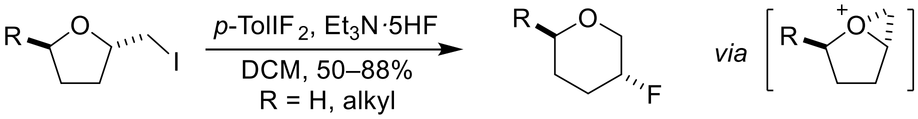
In addition to ring contractions, hypervalent iodine reagents have also been utilised for a wide range of ring expansion reactions. In 1999 Ohno *et al.* demonstrated the expansion of *α*-hydroxycyclobutenones **321** into furanones **322** (Scheme 72).[133] The key intermediate was **323**, formed from the oxidative ring opening of **321**. Recyclization of the key intermediate leads to the formation of the product **322**.



321 **322** **323**

Scheme 72: Ring expansion *α*-hydroxycyclobutenones into furanones.[133]

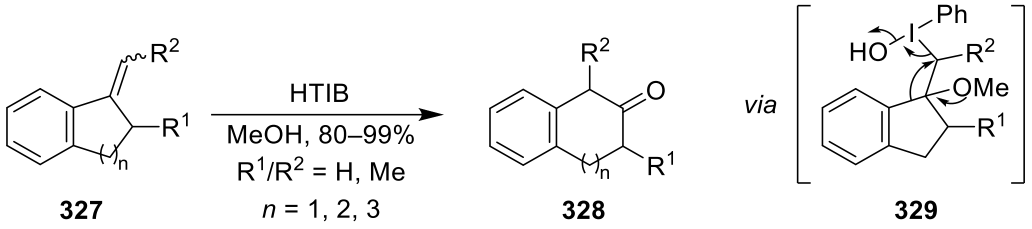
A fluorinative ring expansion of cyclic ethers with *α*-iodoalkyl substitutents was reported by Hara *et al.*[134] The reaction used *p*-TolIF$_2$ and Et$_3$N·5HF to effect the expansion (Scheme 73). Initially, the alkyl iodide is oxidised to an alkyliodine(III) species by *p*-iodotoluene difluoride. Intramolecular nucleophilic attack on this iodine(III) group gives the key intermediate, oxonium ion **326**. Ring opening of **326** of by fluoride leads to product **325**.



324 **325** **326**

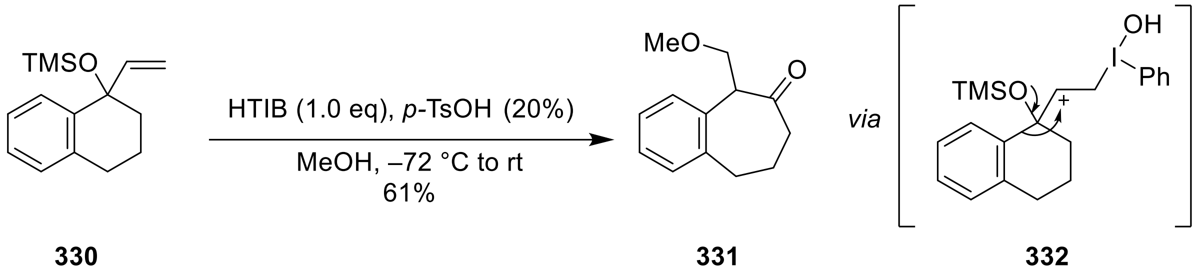
Scheme 73: Fluorinative ring expansion of cyclic ethers.[134]

Koser and Justik reported a ring expansion of exo-alkenes **327** into cyclic ketones **328** by HTIB in MeOH (Scheme 74).[135] The key intermediate **329** is formed by addition of HTIB and MeOH to the double bond. Rearrangement of **329** with loss of iodobenzene as shown in Scheme 74 leads to the formation of product **328**.



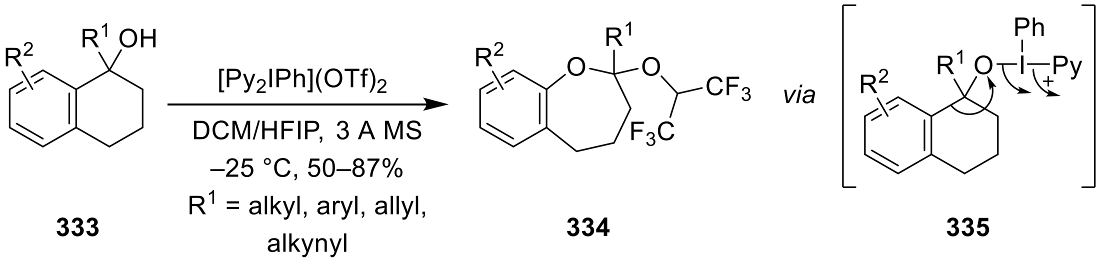
Scheme 74: Oxidative ring expansion of exo-alkenes **327**.[135]

Silva *et al.* reported ring expansion of 1-vinylcycloalkanol ether **330** into cyclic ketone **331** (Scheme 75).[136] The rearrangement proceeded via intermediate **332** formed by addition of HTIB to the alkene. Rearrangement of **332** as shown in Scheme 75 followed by nucleophilic substitution of the iodine(III) group by MeOH yields product **331**.



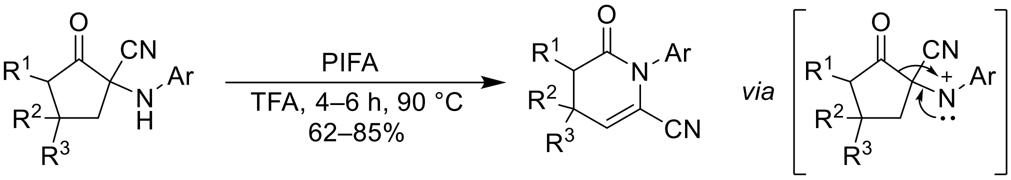
Scheme 75: Ring expansion of 1-vinylcycloalkanol ether **330**.[136]

Wengryniuk *et al.* described a method for ring expanding tertiary benzylic alcohols **333** (Scheme 76).[137] Ligand exchange of the iodine(III) reagent with alcohol **333** gives the key intermediate **335**. Intermediate **335** rearranges by 1,2-aryl shift from C to O, with the resulting cation being trapped by the cosolvent HFIP to give product **334**.



Scheme 76: Ring expansion of tertiary benzylic alcohols.[137]

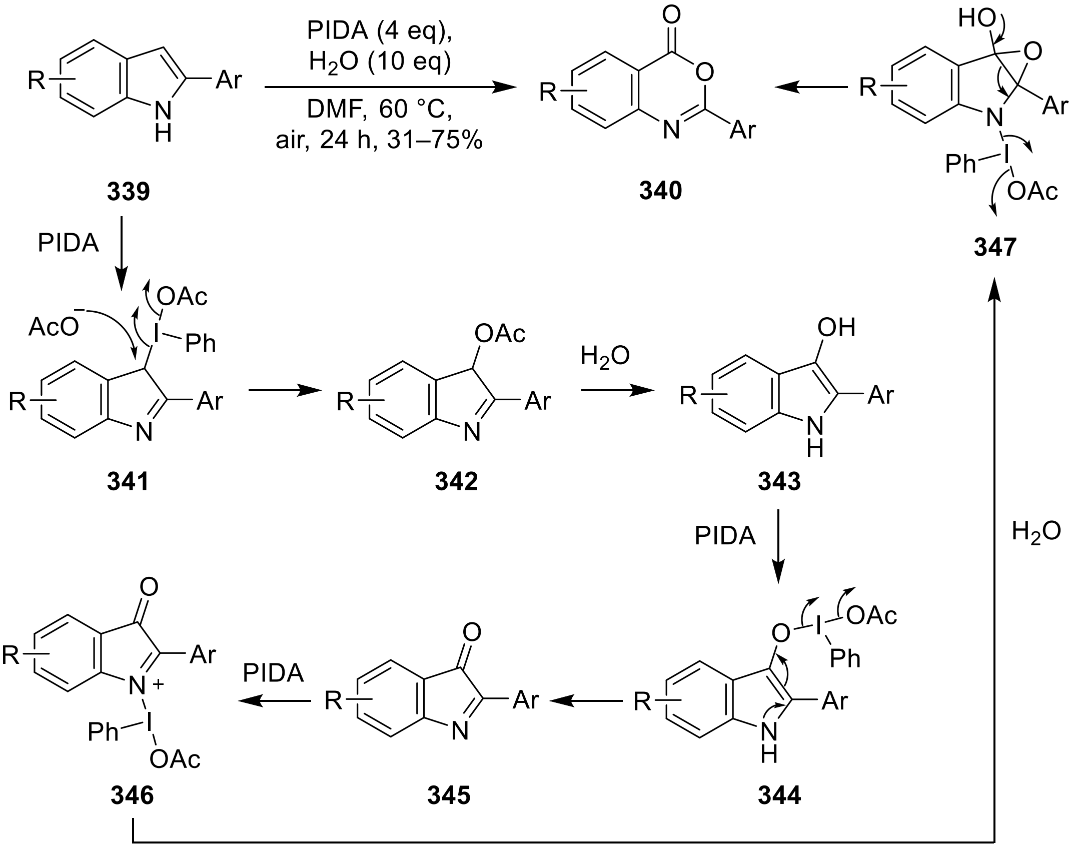
Das *et al.* reported a synthesis of *N*-aryl-δ-valerolactams **337** by a PIFA promoted ring expansion (Scheme 77).[138] The key intermediate is nitrenium ion **338** formed by oxidation of the nitrogen by PIFA. Intermediate **338** rearranges as in Scheme 77 giving an iminium ion which is converted to the product **337** by loss of a proton.



336 **337** **338**

Scheme 77: Synthesis of *N*-aryl-δ-valerolactams by a ring expansion.[138]

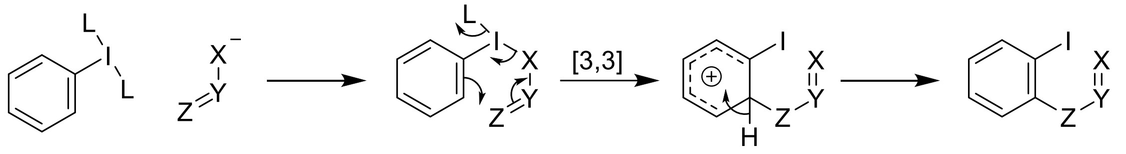
An interesting rearrangement of indoles to benzoxazinones was reported by Li *et al.* (Scheme 78).[139] The proposed mechanism starts with the addition of PIDA to indole **339**. This gives intermediate **341**, which undergoes nucleophilic substitution by acetate producing 3*H*-indole **342**. Hydrolysis of the acetate group leads to the formation of 3-hydroxyindole **343**. Ligand exchange with another molecule of PIDA gives complex **344**. Elimination of iodobenzene and acetate from **344** gives 3*H*-indol-3-one **345**. Intermediate **345** then undergoes ligand exchange with a third molecule of PIDA giving complex **346**. Hydration of **346** gives epoxide **347**, which undergoes rearrangement with loss of iodobenzene to form benzoxazinones **340**.



Scheme 78: Oxidative rearrangement of indoles to form benzoxazinones.[139]

3.3.6. Iodonio-Claisen Rearrangement

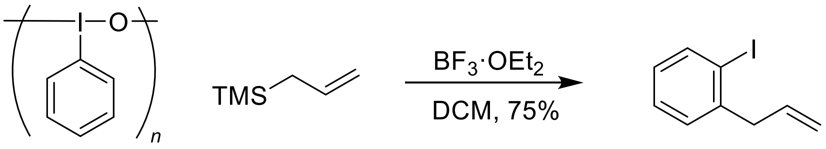
The first step in the iodonio-Claisen rearrangement is the generation of a suitable aryliodine(III) species **350** by addition with a ligand such as **349** (Scheme 79).[109, 140] Species **350** can then undergo a [3,3]-sigmatropic rearrangement and subsequent rearomatization giving 2-substituted aryl iodides **352**.



348 **349** **350** **351** **352**

Scheme 79: Basic mechanism of the iodonio-Claisen rearrangement.[109, 140]

The initial reaction of this type was reported by Oh and co-workers in 1988 (Scheme 80).[141] They found that allyltrimethylsilane (**354**) reacted with iodosylbenzene (**353**) and underwent a [3,3]-sigmatropic rearrangement to give *o*-allyliodobenzene (**355**).



353 **354** **355**

Scheme 80: The first example of an iodonio-Claisen rearrangement was reported by Oh *et al.*[141]

Since Oh *et al.*'s initial report the scope of the iodonio-Claisen rearrangement has been greatly expanded. Nucleophiles that have been utilised for the reaction include allyl silanes **354**, propargyl silanes **357**, stannyl nitriles **360**, 2-naphthols **363**, difluoroenol silyl ethers **366** and electron withdrawn carbonyl compounds **369** (Figure 7).[109, 140]

In 2020, Wang and Peng *et al.* described a stereoselective version of the iodonio-Claisen rearrangement by utilising chiral 2-oxazolines **373** (Scheme 81).[142] The resulting diastereomer can be determined by using model **375** where the bulky isopropyl group is oriented away from the aryl ring. The Claisen product **374** can be treated with sulfuric acid to remove the chiral auxiliary and gain access to chiral *α*-aryl carbonyl compounds **376** with excellent enantiomeric ratios of 99:1.

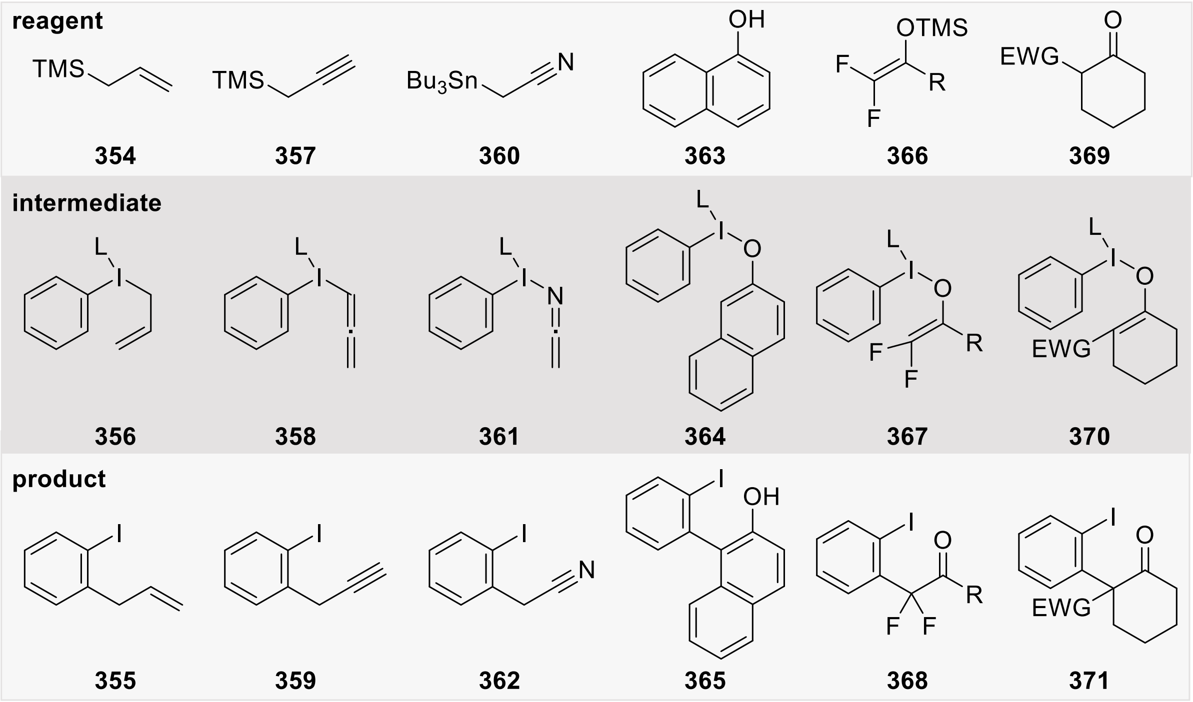
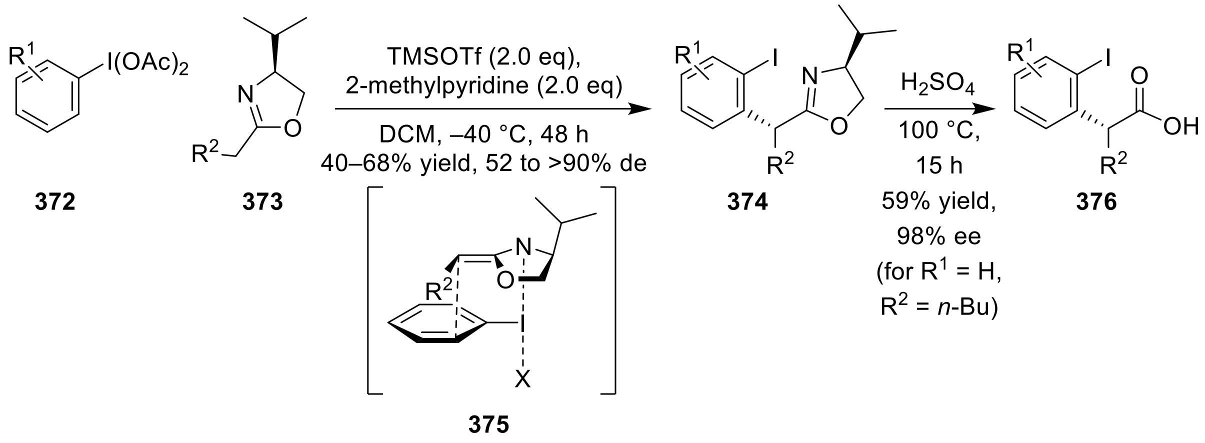


Figure 7: Some examples of reagents used in the iodonio-Claisen rearrangement and their respective products.[109, 140]



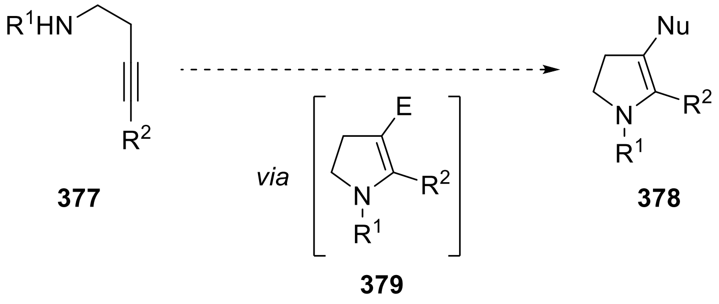
Scheme 81: Chiral 2-oxazolines can be used to gain access to chiral *α*-aryl carbonyl compounds via the iodonio-Claisen rearrangement.[142]

4. Results and Discussion

4.1. Iodine(III) Mediated Alkyne Cyclization

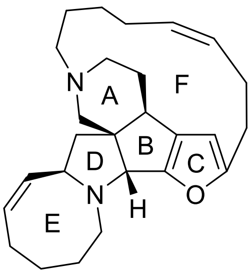
4.1.1. Initial Aims

The initial aim of this project was to investigate the synthesis of 2,3-disubstituted-4,5-dihydropyrroles **378** from a cyclization of alkyne **377**, with concomitant modification of the 3-position by a nucleophile (Scheme 82).



Scheme 82: The initial aim of the project was to synthesise 2,3-disubstituted-4,5-dihydropyrroles **378** from alkynes **377**.

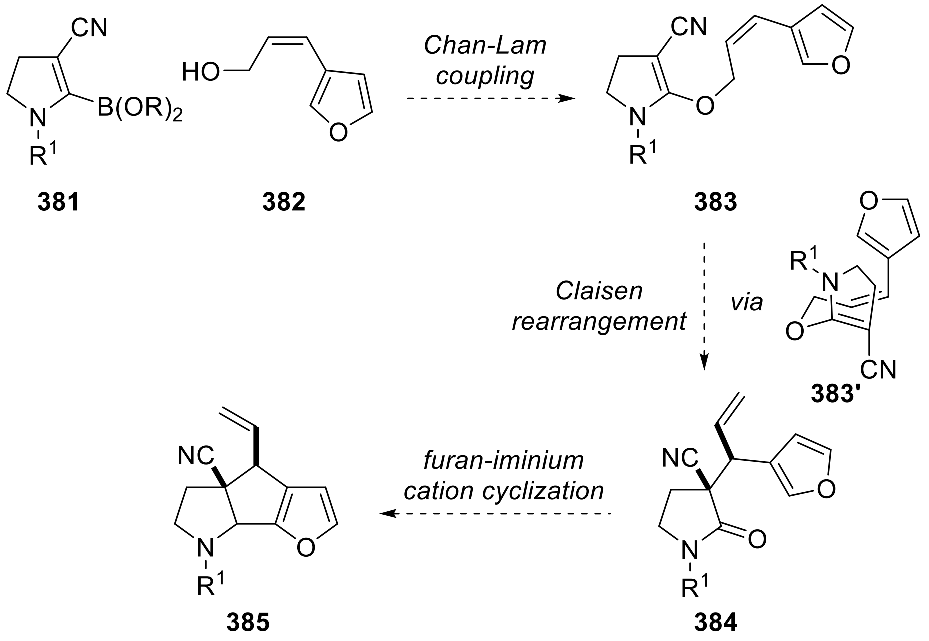
Our interest in molecules of structure **378** came from its potential utility in the construction BCD ring structure of nakadomarin A (Figure 8).



380

Figure 8: Structure of nakadomarin A (**380**).[143]

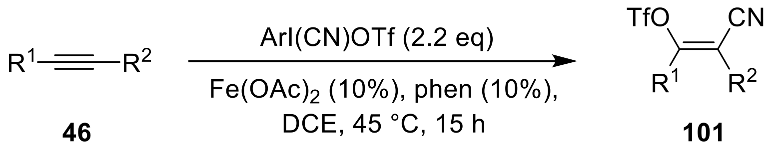
4,5-Dihydropyrrole **381**—which is an analogue of the target compound **378** where Nu = CN and R^2 = $B(OR)_2$—could be coupled with allyl alcohol **382** by Chan-Lam coupling giving allyl ether **383** (Scheme 83). Compound **383** could then undergo a diastereoselective Claisen rearrangement via chair structure **383’** giving pyrrolidinone **384**. A furan-iminium cation cyclization of **384** gives compound **385**, where the synthesis of the tricyclic BCD ring of nakadomarin A has been completed, and the allyl and nitrile substituents have the correct relative stereochemistry for future construction of the A ring.



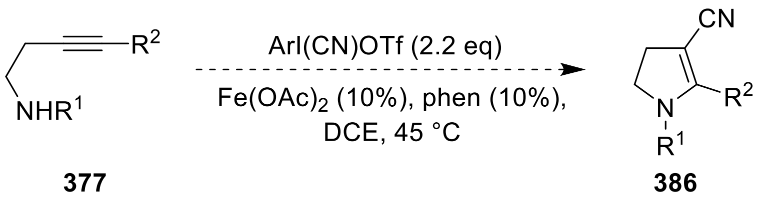
Scheme 83: A potential route starting from 4,5-dihydropyrrole **381** could allow rapid, diastereoselective synthesis of the BCD ring structure of nakadomarin A.

The desired transformation shown in Scheme 82 could potentially be achieved by a modification of Studer and Wang's method for the cyanotriflation of alkynes[57] (Scheme 84, previously discussed on pages 21–22).

(A) Cyanotriflation of alkynes, Studer and Wang



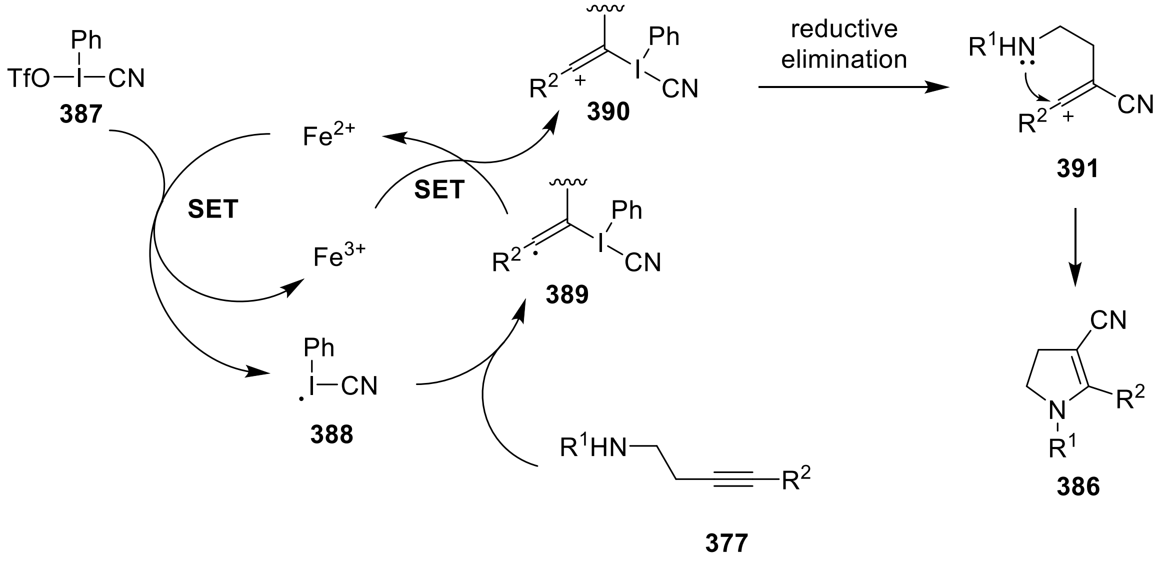
(B) Potential modification with cyclization



Scheme 84: A modification of Studer and Wang's protocol for the cyanotriflation of alkynes[57] could potentially be used to synthesise 4,5-dihydropyrroles **386**.

A possible pathway for the modified reaction starting from alkyne **377** is shown in Scheme 85. This pathway is similar to the one proposed by Studer and Wang for their cyanotriflation reaction and has been described previously on pages 21–22. The key difference is that the cation in molecule **391**, instead of being quenched by triflate, is quenched intramolecularly by the amine – leading to the formation of 4,5-dihydropyrrole **386**.

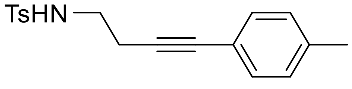
Due to our interest in functionalizing the 3-position of the resulting dihydropyrrole with a nitrile group, Studer and Wang's choice of using an aryl(cyano)phenyl iodonium reagent to effect the transformation was also ideal.



Scheme 85: Proposed mechanism for the formation of targeted product **386**, based on the work of Studer and Wang.[57]

4.1.2. Synthesis of Cyclization Precursor

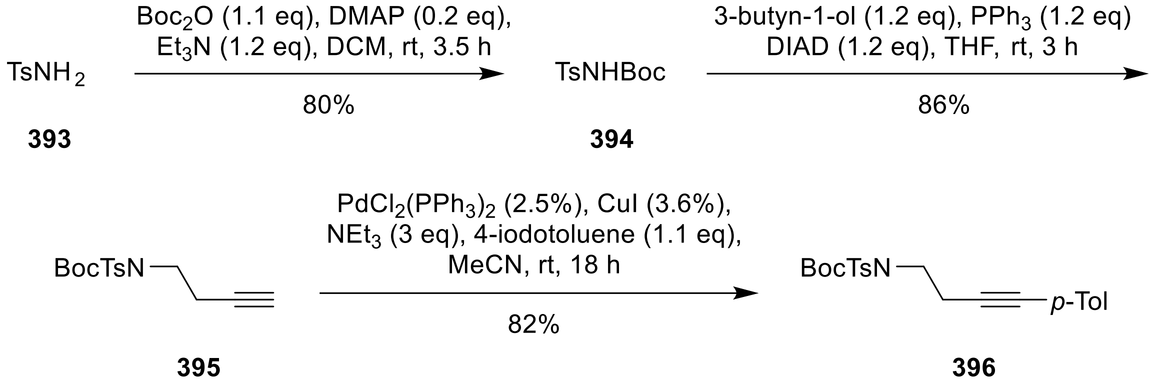
The initial focus was on the synthesis of a suitable alkyne. Alkyne **392** was identified as a suitable substrate for the desired cyclization (Figure 9). The presence of an aryl group on the alkyne would act to stabilize any positive or partial positive charge on the adjacent carbon. Additionally, an *N*-tosyl compound was chosen for the initial investigations. This was because even though a secondary amine would be more nucleophilic, it would also be more basic and more likely to cause problems – for example, by strong coordination to the iodine(III) reagent.



392

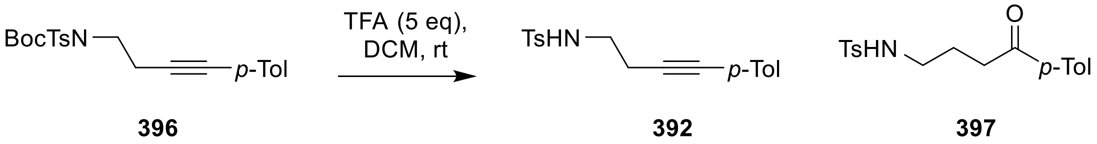
Figure 9: Alkyne **392** was identified as a suitable substrate for the investigation.

p-Tosylamide (**393**) was reacted with Boc_2O in the presence of DMAP to obtain *tert*-butyl tosylcarbamate (**394**) according to the method of Neustadt (Scheme 86).[144] Next a Mitsunobu reaction of **394** and 3-butyn-1-ol was utilized to synthesize alkyne **395**, according to a report by Chan and coworkers.[145] A Sonogashira coupling of terminal alkyne **395** and 4-iodotoluene was performed according to a procedure reported by Sridharan *et al*.[146] giving alkyne **396** in 82% yield after chromatographic purification.



Scheme 86: Route for the synthesis of alkyne **396**.

Alkyne **396** was then subjected to TFA/DCM Boc deprotection conditions. Unfortunately, this gave a significant amount of ketone **397**, arising from the hydration of the alkyne, in addition to the desired tosylamide **392** (Scheme 87).



Scheme 87: Boc deprotection of alkyne **396** gave ketone **397** in addition to the desired alkyne **392**.

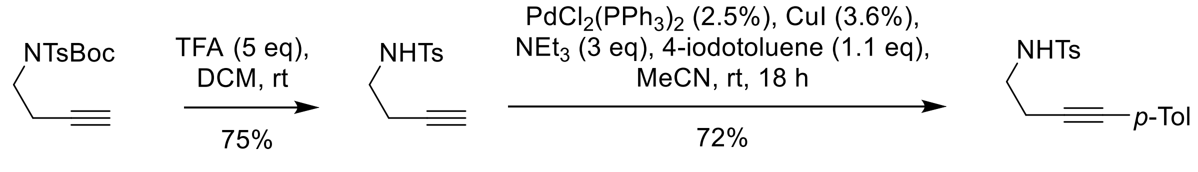
Entry	Conditions	Conversion[a]	392:397[a]
1	TFA (5 eq), DCM, rt, 18 h	100	60:40
2	TFA (5 eq), DCM, rt, 1.5 h	88	77:23
3	TFA (5 eq), phenol (1.5 eq), DCM, rt, 1.5 h	76	86:14
4	TFA (5 eq), $MgSO_4$, DCM, rt, 1.5 h	81	82:18
5	TFA (5 eq), H_2O (1 eq), DCM, rt, 1.5 h	34	96:4
6	TFA (5 eq), H_2O (15 eq), DCM, rt, 1.5 h	27	95:5
7	TMSOTf (4 eq), 2,6-lutidine (5 eq), DCM, rt, 2 h	69[b]	100:0
	[a] determined by ^1H NMR; [b] even though the formation of ketone **397** was supressed, this procedure produced a new unidentified product in 12% yield by NMR.		

Table 2: Attempts at Boc deprotection of alkyne **396**.

A variety of different conditions were trialled in order to switch selectivity towards alkyne **392** (Table 2). A simple shortening of the reaction time from 18 h to 1.5 h (entry 2) resulted in improved selectivity. However, the reaction was still incomplete. When phenol was added to the reaction to quench the *tert*-butyl cation, a small improvement in selectivity was observed (entry 3). Addition of $MgSO_4$ in an attempt to exclude water from the reaction did not provide any further improvements (entry 4). When the reaction was performed in the presence of water, the reaction became very sluggish. However, it surprisingly provided a great improvement in selectivity towards the desired alkyne **392** (entry 5 and 6). The reason for this is unclear.

Procedures for the deprotection of Boc groups under basic conditions are rare. One such procedure, utilizing TMSOTf in the presence of 2,6-lutidine, had been reported by Ottenheijm and coworkers.[147] When their method was used (Table 2, entry 7), the formation of ketone **397** was completely suppressed. However, ^{1}H NMR of the crude showed the presence of a new unidentified product in 12% yield.

It seemed likely that the aryl group was facilitating the alkyne hydration, so a reversal of steps was attempted (Scheme 88). Deprotection of alkyne **395** proceeded cleanly, giving tosylamide **398** in 75% yield after a simple aqueous workup. A Sonogashira coupling of **398** with 4-iodotoluene gave the desired alkyne **392** in 72% yield.



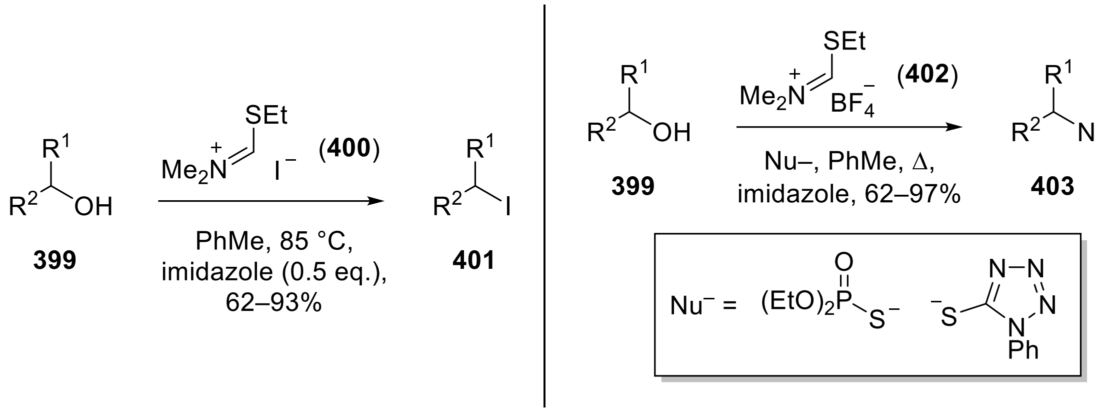
395 **398** **392**

Scheme 88: A reversal of steps was used to synthesize alkyne **392**.

4.1.3. Investigation of a Possible Alternative to the Mitsunobu Reaction

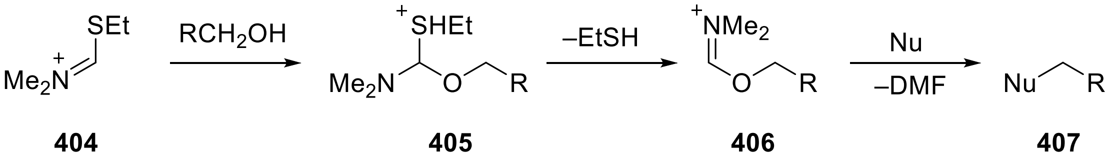
Our synthesis of alkyne **395** from *tert*-butyl tosylcarbamate (**394**) under Mitsunobu conditions led us to consider whether the same transformation could be carried out using a thioiminium salt. The use of thioiminium salts as activating agents for alcohols was first reported by Porter and Ellwood in 2009.[148]

They found that thioiminium salt **400** enabled the conversion of primary and secondary alcohols to iodides in good yields (62–93%) (Scheme 89). The reaction was found to work best in toluene or THF. In addition, the presence of imidazole was found to accelerate the reaction but the mechanism of its action was not clear. In later works, Porter *et al.* developed thioiminium salt **402** which replaced the iodide counterion with the chemically inert tetrafluoroborate.[149, 150] Using this salt the scope of the reaction was expanded to include tetrazole-5-thiols and phosphorothiolates as nucleophiles.



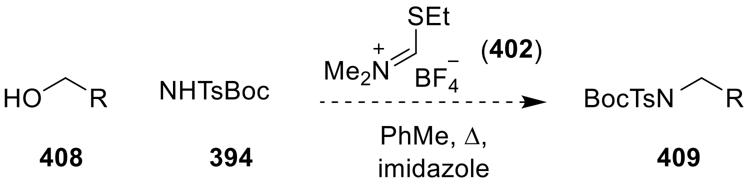
Scheme 89: Reaction scheme showing the use of thioiminium salts **400** and **402** in the activation of alcohols.

In the proposed reaction pathway, the alcohol first reacts with thioiminium species **404** (Scheme 90). Elimination of ethanethiol from the resulting intermediate gives dimethylformamidium species **406**. Subsequent nucleophilic substitution with DMF as a leaving group gives the substituted product **407**.



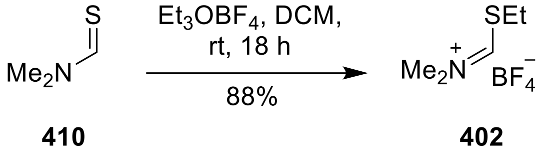
Scheme 90: Substitution pathway for alcohols activated by thioiminium salts.

A similar reaction could activate an alcohol towards substitution by an amide (Scheme 91). The main advantage offered by this reaction over the Mitsunobu reaction would be ease of purification, as the byproducts are either volatile (DMF, ethanethiol) or extremely polar (imidazolium tetrafluoroborate).



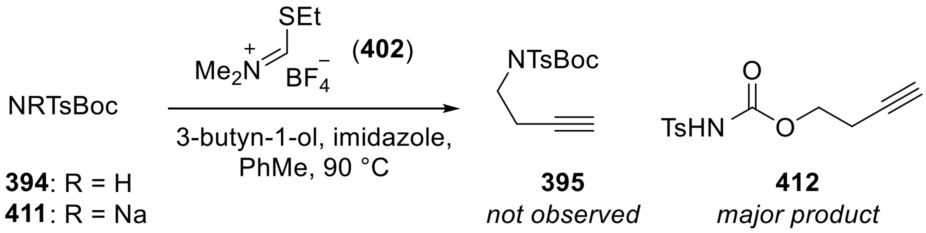
Scheme 91: Potential conversion of an alcohol to a tosylamide via the use of thioiminium salt **402** as an activating agent.

Thioiminum salt **402** was synthesized in 88% yield by the reaction of *N,N*-dimethylthioformamide (**410**) with Et_3OBF_4 according to the method of Porter and Ellwood (Scheme 92).[149]



Scheme 92: Synthesis of thioiminium salt **402**.

The reaction to be investigated was attempted based on previously reported reaction conditions (Table 3, entry 1).[150] The sodium salt of *tert*-butyl tosylcarbamate (**411**), imidazole and thioiminium salt **402** were all suspended in toluene and heated to 90 °C. The reaction was started by the addition of 3-butyn-1-ol and stirred at 90 °C for 1 h. This led to recovery of *tert*-butyl tosylcarbamate (**394**) after aqueous workup, most likely due to the insolubility of TsNBocNa in toluene.



Scheme 93: Attempted synthesis of **395** from 3-butyn-1-ol using thioiminium salt **402** as an activating agent.

Entry	Conditions	Yield
1	TsNBocNa (**411**), salt **402**, imidazole, all suspended in PhMe, then heated to 90 °C, 3-butyn-1-ol added, stirred for 1 h	0[a]
2	TsNHBoc (**394**), salt **402**, imidazole, all suspended in PhMe, then heated to 90 °C, 3-butyn-1-ol added, stirred for 2.5 h	0[b]
3	PhMe heated to 90 °C, imidazole, salt **402**, 3-butyn-1-ol, TsNHBoc (**394**) added in sequence, stirred for 2 h	0[b]
	[a] recovery of TsNHBoc after aqueous workup, TsNBocNa insoluble in PhMe; [b] carbamate **412** obtained as major product	

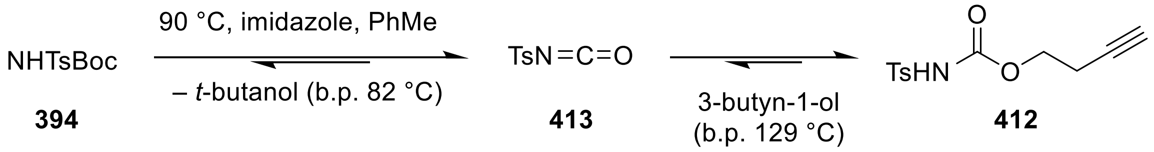
Table 3: Attempts at producing compound **395** via activation of 3-butyn-1-ol with thioiminium salt **402**.

Substituting in *tert*-butyl tosylcarbamate (**394**) as the starting material gave a complex mixture of products (Table 3, entry 2). Partial purification by flash column chromatography revealed the main product to be carbamate **412**. The targeted product **395** was not observed.

We considered that carbamate **412** could be generated by an undesired reaction taking place at low temperatures and attempted heating the solvent before the addition of reagents (Table 3, entry 3). But this had no effect, and carbamate **412** was still obtained as the major product with no evidence of alkyne **395**.

With no trace of the desired product being observed under the established conditions for the activation of alcohols with thioiminium salts,[148-150] success of the desired reaction seemed very unlikely. Therefore, focus was switched to optimizing the conditions needed for formation of carbamate **412**.

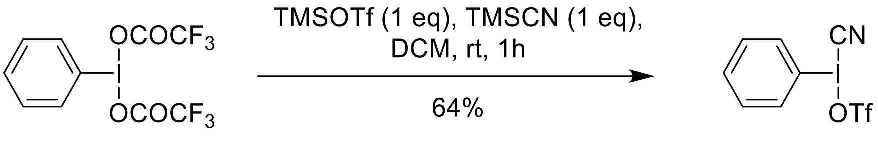
First, a control experiment was performed without thioiminium salt **402** in order to assess whether it was necessary for the observed reaction. Unfortunately, in the absence of the salt, carbamate **412** was obtained much more cleanly and it was evident that this was a thermal process (Scheme 94). The reaction may proceed through tosyl isocyanate (**413**), with the equilibrium of the reaction being driven forward by the removal of *t*-butanol (b.p. 82 °C) from the reaction (reaction temperature 90 °C). As tosyl isocyanate is a cheaply available reagent, this reaction was of little interest and no further research was carried out along these lines.



Scheme 94: Carbamate **412** could be thermally generated via isocyanate **413**.

4.1.4. Attempts at Cyclization with Cyano(phenyl)iodonium Triflate

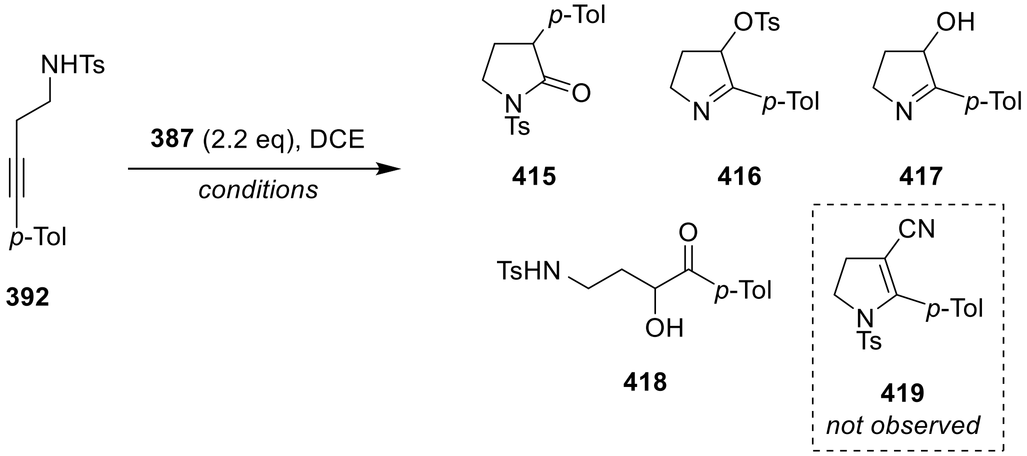
Returning to the primary investigation, the hypervalent iodine reagent chosen for the initial attempts at cyclization—cyano(phenyl)iodonium triflate (**387**)—was synthesized by the reaction of PIFA (**414**) with TMSOTf and TMSCN according to the procedure of Zhdankin and Stang (Scheme 95).[151]



414 **387**

Scheme 95: Synthesis of cyano(phenyl)iodonium triflate (**387**) from PIFA (**414**).

Alkyne **392** was reacted with cyano(phenyl)iodonium triflate (**387**) in the presence of 1,10-phenanthroline and Fe(OAc)$_2$ according to conditions based on those reported by Studer and Wang (Table 4, entry 1).[57] Under these conditions a complex mixture of products was obtained. By chromatographic purification two of these products were isolated and their structures elucidated. The structure of pyrroline **416** was tentatively identified by analysis of ^{1}H, ^{13}C, COSY, DEPT135, HSQC, HMBC and NOESY spectra. The NMR data of pyrrolidinone **415** was found to match published literature values,[15] and its structure was definitively confirmed.



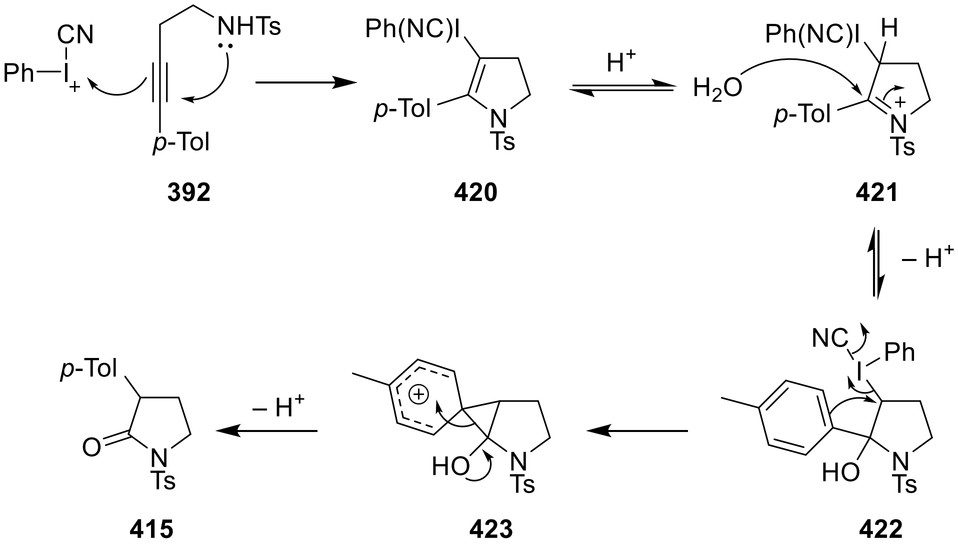
Scheme 96: Products obtained from the reaction of alkyne **392** with iodonium triflate **387** under various conditions (Table 4).

Entry	Conditions	NMR Yields[a]				
		415	416	417	418	unk[d]
1[bc]	Fe(OAc)$_2$ (0.1 eq), phen (0.1 eq), NEt$_3$ (1 eq, added after 1 h), 50 °C, 18 h	5	5	-	-	-
2[c]	50 °C, 18 h	3	35	11	-	-
3	H$_2$O (2 eq), rt, 4 h	28	-	-	36	19
	[a] determined by ^{1}H NMR with ethylene carbonate as an internal standard; [b] complex mixture of products from which only some products were identified; [c] there was an unexplained loss of mass in both experiments, either during the reaction or subsequent aqueous work-up; [d] an unidentified product observed in reaction 3					

Table 4: Table showing varying yields of products obtained in the reaction of alkyne **392** with cyano(phenyl)iodonium triflate (**387**).

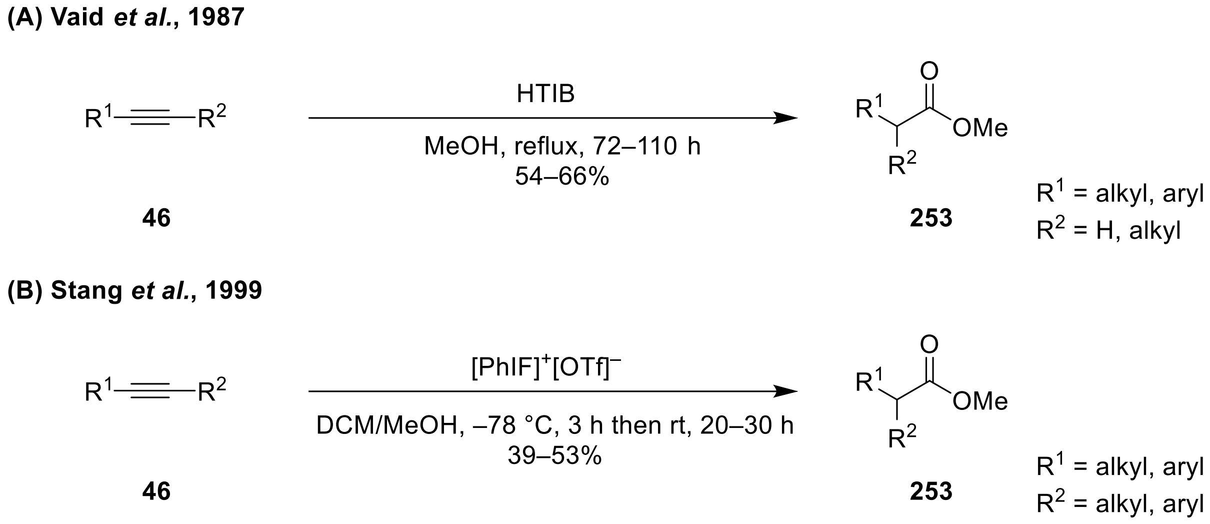
The targeted product **419** was not observed and the yields of the products that were isolated were quite low (5%). Nevertheless, these results proved very interesting. Of particular note was the migration of the tolyl group in pyrrolidinone **415**.

A mechanism was proposed to account for the occurrence of the pyrrolidinone **415** (Scheme 97). The interaction of the cyano(phenyl)iodonium cation with alkyne **392** activates it towards nucleophilic cyclization. The product of the cyclization is enamine **420**, which is then protonated giving iminium ion **421**. Subsequent addition of water to the iminium ion gives hemiaminal **422**. A 1,2-shift of the tolyl group with loss of iodobenzene generates the observed pyrrolidinone **415**. This 1,2-rearrangement may proceed via intermediate phenonium ion **423**.[113]



Scheme 97: A possible mechanism for the formation of pyrrolidinone **415**.

Lending weight to the proposed mechanism, examples of oxidative rearrangements of alkynes by action of hypervalent iodine reagents are found in the literature. In 1987 Vaid and co-workers reported the synthesis of methanoate esters by HTIB mediated oxidative rearrangement of internal alkynes (Scheme 98A).[112] Stang *et al.* reported a similar rearrangement reaction in 1999, this time mediated by fluoro(phenyl)iodonium triflate (Scheme 98B).[152] Further examples of hypervalent iodine induced 1,2- shifts, including those not starting from alkynes, are discussed in Section 3.3.1 (pages 40–44).



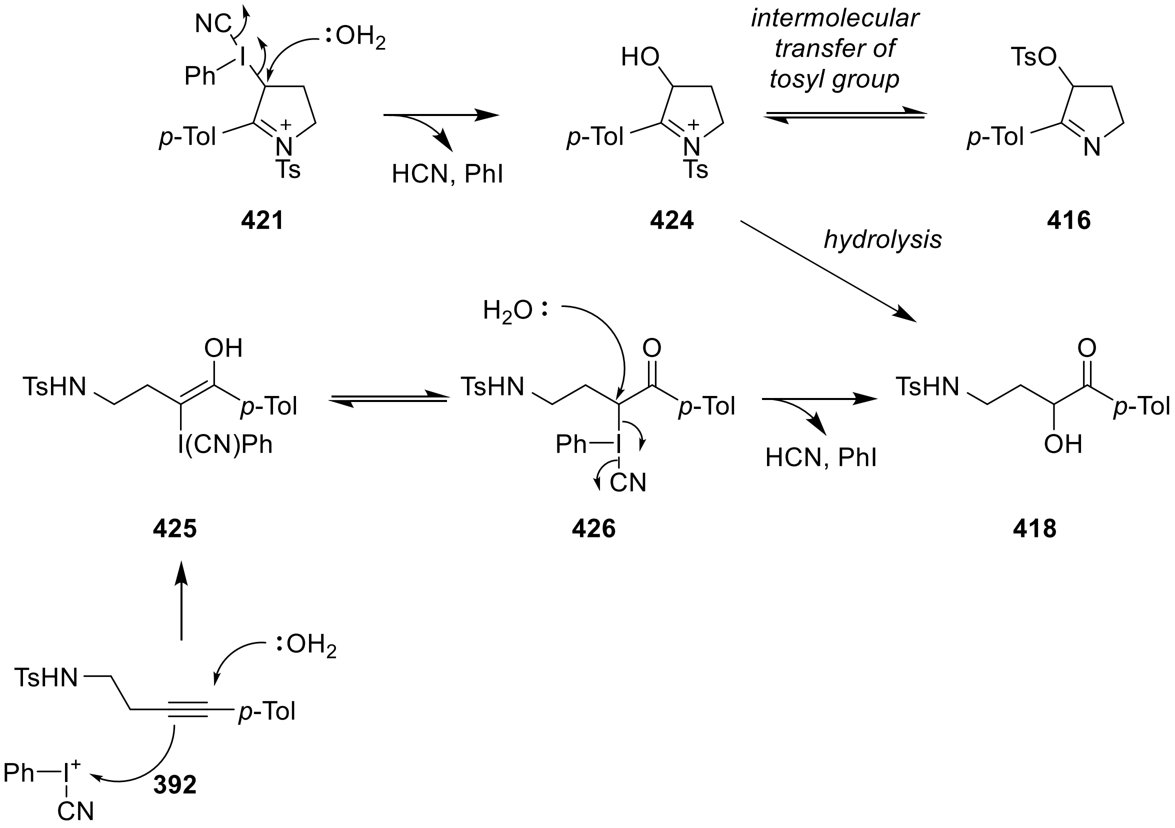
Scheme 98: The groups of Vaid and Stang reported the synthesis of methanoate esters by oxidative rearrangement of alkynes.

If the proposed mechanism was correct, then $Fe(OAc)_2$ would be superfluous to the reaction. Additionally, due to the necessity of protonation of intermediate **420**, the presence of base could be detrimental to the reaction. Therefore, the reaction was performed without $Fe(OAc)_2$ or base (Table 4, entry 2). Under these conditions, the yield of pyrrolidinone **415** was reduced, down from 5% to 3%. Notably the yield of pyrroline **416** was increased seven-fold from 5% to 35%. Additionally, the hydroxyl analogue **417** was also present in 11% yield.

A loss of mass was observed in both reactions. Suspecting that prolonged reaction times at higher temperatures may be leading to decomposition, the temperature and reaction time were reduced for the third attempt (Table 4, entry 3). Two equivalents of H_2O were also deliberately introduced as the proposed reaction mechanism suggests that this could be beneficial to the formation of pyrrolidinone **415**. Pleasingly, under these conditions the yield of pyrrolidinone **415** was 28%, a substantive increase from the ≤5% yields of the previous two attempts. Two new products were also observed in the ^1H NMR, in 36% and 19% yield respectively. The more abundant of the two products was determined to be *α*-hydroxyketone **418** based on the analysis of ^1H, ^{13}C and 2D spectra. The other product has not been conclusively identified at this time, but may be the *α*-triflyloxyketone due to the NMR shift of the *α* proton (6.24 ppm, dd).

A possible mechanism for the formation of pyrroline **416** and *α*-hydroxyketone **418** was also proposed (Scheme 99). Direct S_N2 displacement of iodobenzene from the previously proposed intermediate **421** by H_2O gives iminium ion **424**. This iminium ion could then undergo an intermolecular tosyl group transfer to produce the neutral pyrroline **416**. The presence of the hydroxyl analogue **417** in one of the reactions (Table 4, entry 2) adds weight to the suggestion that the apparent *N-O* tosyl migration seen here is actually an intermolecular process.

The hydrolysis of the previously suggested iminium ion **424** produces *α*-hydroxyketone **418**. Alternatively, *α*-hydroxyketone **418** may also be produced without involvement of the nitrogen. The initial addition of H_2O and hypervalent iodine reagent to the alkyne produces enol **425**, which then tautomerizes to form ketone **426**. Displacement of iodobenzene from ketone **426** by H_2O gives the observed *α*-hydroxyketone **418**.

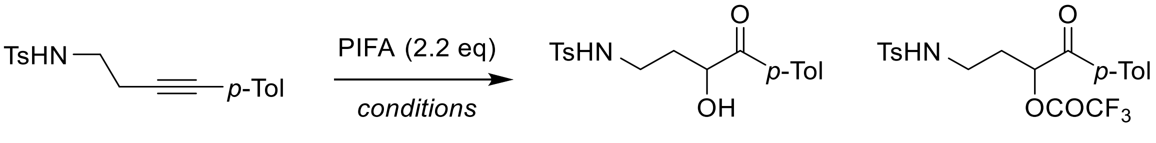


Scheme 99: Possible mechanisms for the formation of pyrroline **416** and *α*-hydroxyketone **418**.

We planned to carry out more reactions along the same lines, trying to optimize the reaction yield towards a single product. However, when synthesizing a second batch of cyano(phenyl)iodonium triflate, the isolated solid underwent spontaneous combustion during the process of transferring the solid from a filter paper into a sample vial by use of metal spatula. Therefore, we chose to conclude our investigations of cyano(phenyl)iodonium triflate and instead focused our attention on finding whether similar reactions could be carried out using less reactive, safer, cheaper and more readily available hypervalent iodine reagents.

4.1.5. Attempts at Cyclization with PIFA

Next, PIFA, a bench-stable, commercially available hypervalent iodine reagent was trialled. When alkyne **392** was stirred with PIFA in DCE for 18 h at 50 °C two products were observed (Scheme 100). One of the products was isolated by flash column chromatography and determined to be the previously observed *α*-hydroxyketone **418**. The second product had not been previously observed, but unfortunately appeared to decompose on silica and therefore could not be isolated. However, in a future experiment, a sufficiently clean sample of the unknown compound was obtained and the structure determined to be *α*-trifluoroacetoxyketone **427** with the aid of ^{1}H, ^{13}C, ^{19}F and 2D spectra.



392 **418** **427**

Scheme 100: Reaction of alkyne **392** with PIFA.

Entry	Conditions	NMR Yields[a]	
		418	427
1	DCE, 50 °C, 18 h	9	9
2	H_2O (2 eq), DCE, 50 °C, 18 h	15	39
3	H_2O (2 eq), DCE, rt, 3.5 h	62	41
4[b]	MeCN/H_2O (4:1), rt, 3 h	-	17
5[c]	H_2O (2 eq), NEt_3 (4 eq), DCE, rt, 3.5 h	10	1
6[d]	H_2O (2 eq), K_2CO_3 (4 eq), DCE, rt, 3.5 h	-	-
	[a] determined by ^{1}H NMR with ethylene carbonate as an internal standard; [b] the major product was an unknown product which decomposed upon storage at room temperature; [c] 71% of the starting material was unreacted; [d] no reaction		

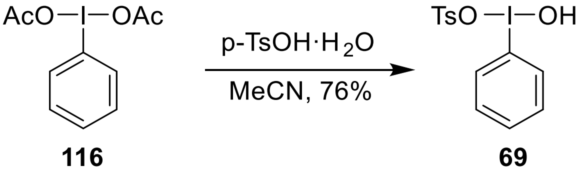
Table 5: Table showing results of the reaction of alkyne **392** with PIFA.

The yields in the initial reaction were low, with 9% for both products (Table 5, entry 1). Adding two equivalents of water improved yields of both **418** and **427** to 15% and 39% yield respectively (entry 2). With unexplained loss of mass in both experiments, it seemed that heating and long reaction times were both detrimental to the reaction and led to decomposition of the products. Pleasingly, performing the reaction at rt and reducing the reaction time to 3.5 h delivered a combined quantitative yield of **418** and **427** in a 60:40 ratio (entry 3). Attempts were made to further improve the selectivity towards the *α*-hydroxyketone by using water as a cosolvent. Due to the immiscibility of water with DCE, an MeCN/H_2O solvent system was used for this experiment (entry 4). Unfortunately, under these conditions none of the *α*-hydroxyketone **418** was formed, and the yield of *α*-trifluoroacetoxyketone **427** was greatly decreased to 17%. The major product in the crude mixture was instead a new, unidentified product which was not isolated as it decomposed upon storage at room temperature. Returning to the DCE/H_2O conditions, with addition of NEt_3 71% of the starting material was unreacted after 3.5 h (entry 5), while K_2CO_3 appeared to inhibit the reaction entirely (entry 6).

The oxidation of alkynes to *α*-hydroxyketones with PIFA and PIDA is a known reaction. For internal alkynes one example is available in the literature,[113] however for terminal alkynes there are several examples.[51, 153-155] Related reactions involving *α*-sulfonyloxylation,[55] *α*-acetoxylation[52-54] and *α*-amidation[56] are also known. Several reactions of this type are discussed in more detail in Section 3.1.2 (pages 18–21).

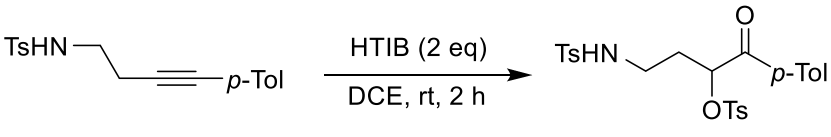
4.1.6. Attempt at Cyclization with HTIB

With PIFA producing little to no sign of cyclized products, HTIB (**69**) was trialled next. The main concern with HTIB was that it may lead to *α*-sulfonyloxylation.[55] HTIB (**69**) was obtained in 76% yield by reacting PIDA (**116**) with tosic acid monohydrate according to the method of Koser (Scheme 101).[156]



Scheme 101: Synthesis of HTIB (**69**) from PIDA (**116**).

Stirring alkyne **392** with two equivalents of HTIB in DCE for 3 h led to a relatively clean crude mixture, with the major product in 60% yield (Scheme 102). This product was determined to be *α*-tosyloxyketone **428** on the basis of ^1H NMR spectra. With HTIB showing a strong preference for *α*-oxylation, similar to PIFA, we quickly moved on to try other reagents.



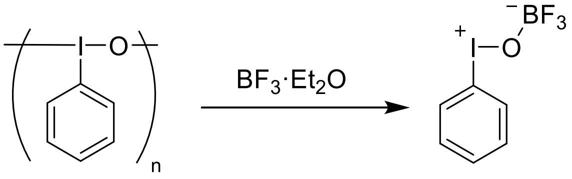
392 **428**

Scheme 102: Reaction of alkyne **392** with HTIB gave *α*-tosyloxyketone **428** as the major product.

4.1.7. Attempts at Cyclization with BF_3 Activated PIDA

With PIFA and HTIB producing little to no cyclized products, it seemed that the use of highly reactive and unstable hypervalent iodine reagents was a necessity to obtain the cyclized products observed in the original reaction.

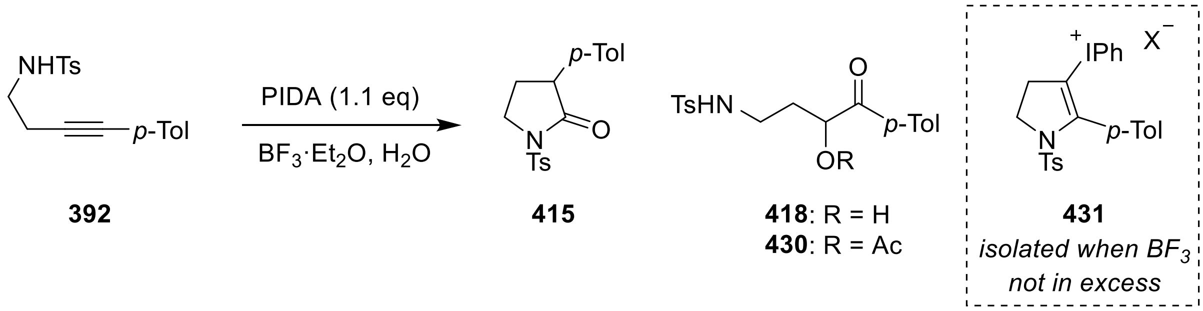
It is known that the addition of Lewis acids such as BF_3 greatly enhances the reactivity of hypervalent iodine reagents such as PIDA and iodosylbenzene. For example, it is presumed that the coordination of BF_3 with iodosylbenzene (**353**) leads to the formation of the highly electrophilic iodine(III) species **429** (Scheme 103).[157] Since the highly reactive species are produced entirely *in situ* and easily quenched by the addition of water at the end of the reaction, this is a much safer method to obtain the desired reactivity.



353 **429**

Scheme 103: Iodosylbenzene (**353**) is expected to form the highly electrophilic species **429** in the presence of BF_3.

With these considerations in mind, alkyne **392** was stirred with PIDA (1.1 eq) in DCM in the presence of $BF_3 \cdot Et_2O$ (2 eq). As H_2O is necessary to produce pyrrolidinone **415**, a large excess of H_2O (6 eq) was also added to the reaction. These conditions were hugely successful leading to the production of pyrrolidinone **415** in 62% yield in the initial reaction (Table 6, entry 1). In addition to pyrrolidinone **415**, the crude mixture contained two unwanted by-products, *α*-hydroxyketone **418** and *α*-acetoxyketone **430**, in 21% and 7% yields respectively.



Scheme 104: Reaction of PIDA with alkyne **392** in the presence of BF_3 and H_2O gave pyrrolidinone **415** as the major product.

Entry	**Conditions**	**Additives (eq)**		**NMR Yields**[a]				
		H_2O	**$BF_3 \cdot Et_2O$**	**392**[b]	**415**	**418**	**430**	**431**
1	DCM, rt, 3 h	6	2	-	62	21	7	-
2	DCE, 60 °C, 3h	6	2	-	53	9	10	-
3	DCM, rt, 3 h	3	2	-	42	14	20	-
4	DCM, rt, 3 h	2	1	19	2	-	-	70
	[a] determined by ^1H NMR with ethylene carbonate as an internal standard; [b] unreacted starting material							

Table 6: Table showing varying yields of products obtained in the reaction of alkyne **392** with PIDA in the presence of $BF_3 \cdot Et_2O$ and H_2O.

Running the experiment at a higher temperature of 60 °C in DCE did not produce improvements, with the yield of pyrrolidinone **415** being reduced to 53% (Table 6, entry 2). Returning to the DCM and room temperature conditions, the amount of H_2O used in the reaction was halved to three equivalents (entry 3). This further decreased the yield of pyrrolidinone **415** to 42% and increased the yield of *α*-acetoxyketone **430** to 20% which was undesirable.

Next, the amounts of both $BF_3 \cdot Et_2O$ and H_2O were both reduced, to one and two equivalents respectively (Table 6, entry 4). Surprisingly, under these conditions pyrrolidinone **415** was produced in negligible amount and the crude mixture showed the presence of a completely new product in 70% yield. The new product was determined to be alkenyl(phenyl)iodonium salt **431** (anion undetermined).

Several observations support the conclusion that product **431** has the structure proposed. Firstly the obtained ^1H, ^{13}C and 2D spectra are fully consistent with structure **431**. Importantly, a NOESY cross-peak between the phenyliodine(III) fragment and the pyrrolidine fragment shows that these fragments are joined together. Furthermore, the NMR sample underwent visible deterioration over the course of 24 h, turning from a transparent light green solution to a completely opaque black solution. A ^{1}H NMR of the deteriorated sample performed after 3 days showed complete disappearance of the peaks associated with iodonium salt **431** producing iodobenzene in the process (Figure 10), lending additional weight to the proposal that **431** is a phenyliodine(III) compound.

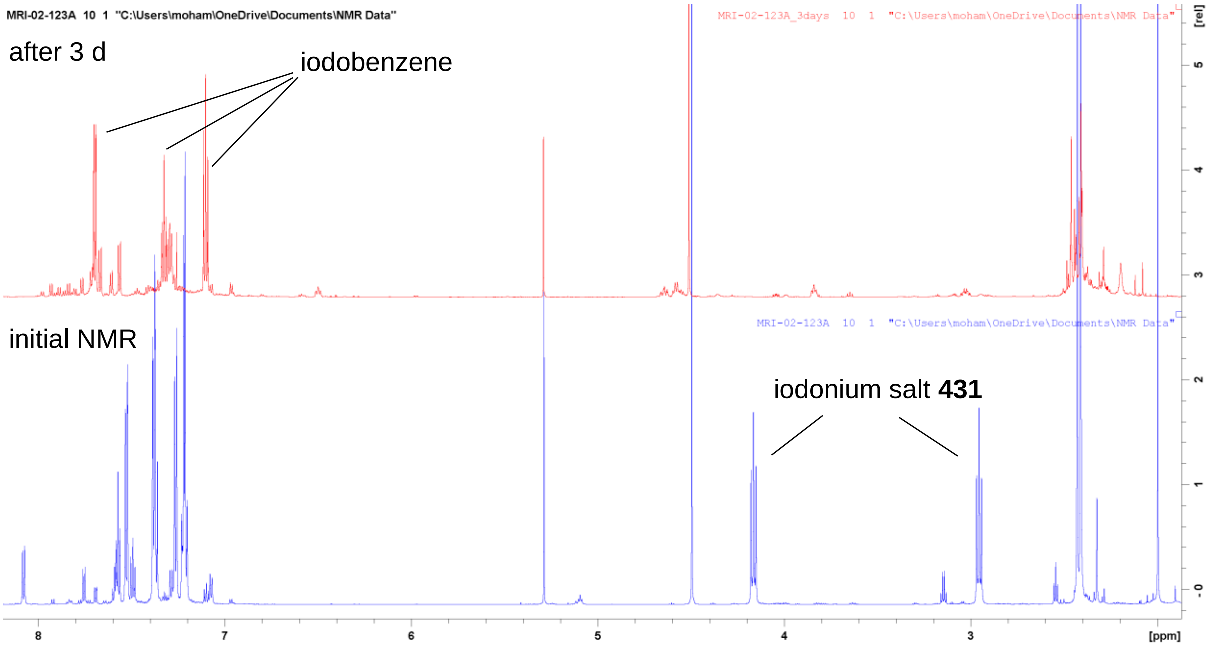


Figure 10: Iodonium salt **431** in $CDCl_3$ underwent decomposition at room temperature. Iodobenzene was produced during the decomposition.

To determine whether alkenyl(phenyl)iodonium salt **431** was an intermediate in the formation of pyrrolidinone **415** the reaction was performed in DCM-d_2 and followed using ^{1}H NMR. The quantities of reagents used in the NMR experiment were identical to Table 6, entry 1. The conversion of alkyne **392** to iodonium salt **431** was extremely rapid and complete in 5 min (Figure 11). By 20 min the proton NMR showed evidence of the formation of small amounts of pyrrolidinone **415**. After 1 h had passed the iodonium salt **431** had been completely consumed and converted to pyrrolidinone **415**. The NMR experiment conclusively showed that the formation of pyrrolidinone **415** proceeds via alkenyl(phenyl)iodonium salt **431**, lending further weight to the proposed mechanism for the reaction (Scheme 97, page 62).

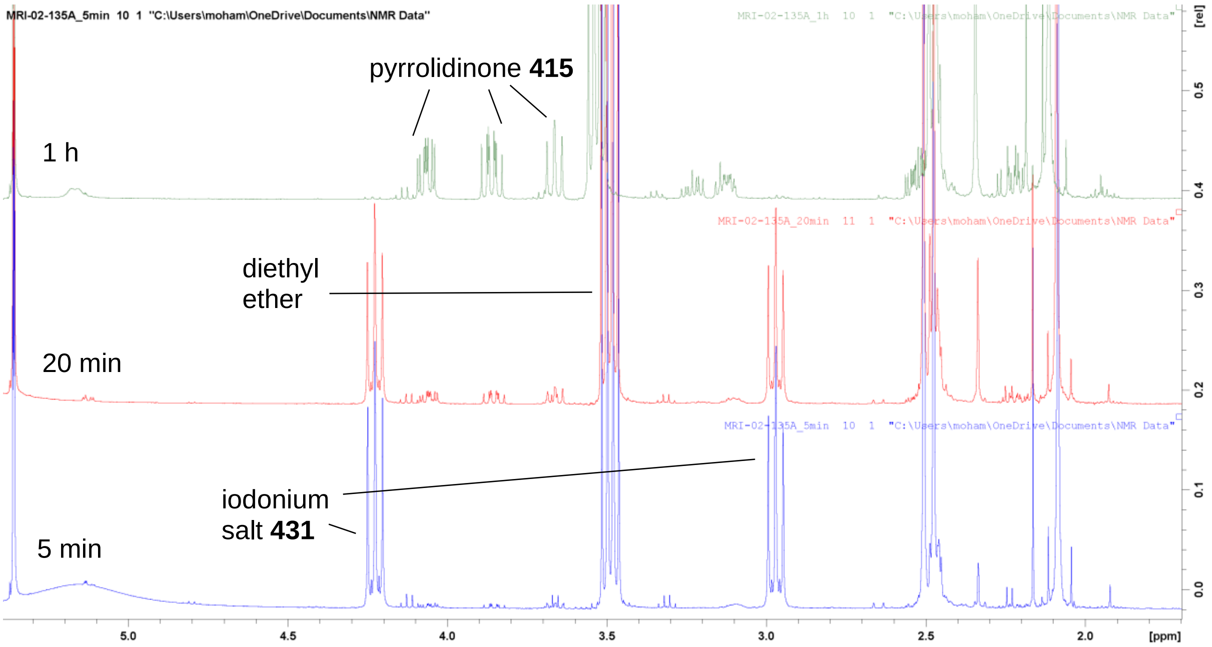
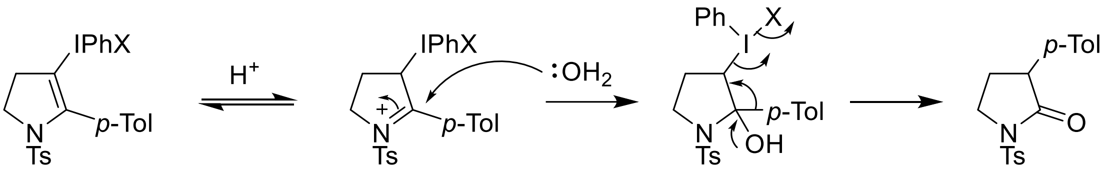


Figure 11: A reaction performed in DCM-d_2 demonstrated that iodonium salt **431** is an intermediate in the formation of pyrrolidinone **415**.

Additionally, the NMR experiment demonstrates that the rearrangement should be complete in a timescale of less than 1 h. The fact that a 70% yield of the iodonium salt was obtained after 3 h (Table 6, entry 4) suggests that an excess of $BF_3{\cdot}Et_2O$ is necessary for the reaction to progress. The reasons for this were not immediately clear. It is known that the BF_3—H_2O system forms a complex equilibrium, producing various acidic species such as HBF_3OH, HBF_4, $HBF_2(OH)_2$ and HF.[158] It is necessary for iodonium salt **431** to be protonated in order for the rearrangement to take place (Scheme 105). Therefore, one possibility is that the second equivalent of BF_3 reduces the pH of the reaction mixture, increasing the degree of protonation of alkenyl(phenyl)iodonium salt and hastening the rearrangement.



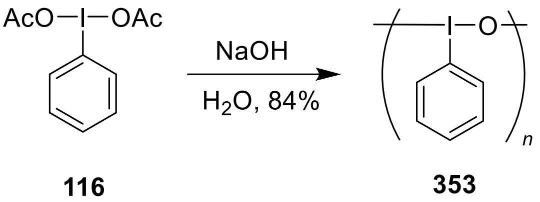
431 **432** **433** **415**

Scheme 105: Alkenyl(phenyl)iodonium salt **431** needs to be protonated in order to trigger the rearrangement.

4.1.8. Optimization of the Cyclization-Rearrangement Reaction with BF_3 Activated Iodosylbenzene

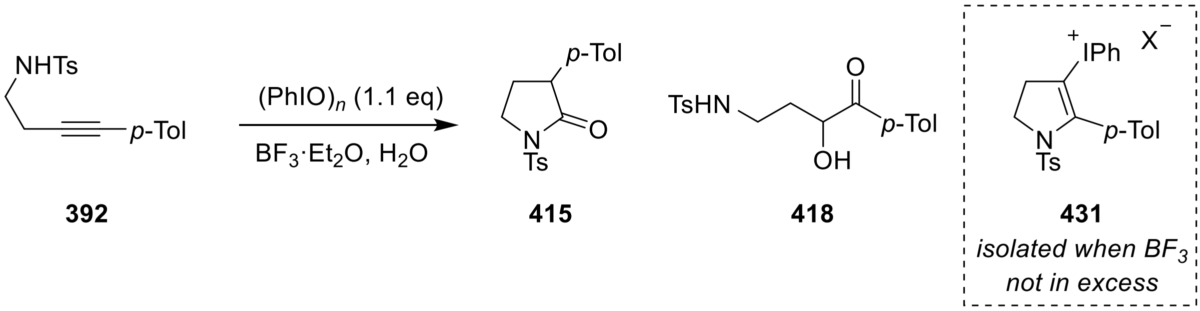
In order to maximize the yield of pyrrolidinone **415**, conditions minimizing the amount of both *α*-hydroxyketone **418** and *α*-acetoxyketone **430** were required. An earlier reduction in the amount of water failed to have a positive effect (Table 6, entry 3). However, by switching the hypervalent iodine reagent from PIDA to iodosylbenzene the acetate by-product could be completely eliminated. Furthermore, it was likely that the reaction could be performed with a smaller amount of H_2O when using iodosylbenzene as there is no longer any competition with acetate anion.

Iodosylbenzene (**353**) was synthesized in 84% yield by the hydrolysis of PIDA (**116**) by aqueous NaOH (Scheme 106).[159]



Scheme 106: Synthesis of iodosylbenzene (**353**) by the hydrolysis of PIDA (**116**).

The initial reaction performed using 1.1 equivalents of iodosylbenzene, 2.2 equivalents of $BF_3·Et_2O$ and 2 equivalents of H_2O yielded 53% of pyrrolidinone **415** and 17% of *α*-hydroxyketone **418** (Table 7, entry 1). Doubling the amount of iodosylbenzene and $BF_3·Et_2O$ did not have any positive effect, with the yield of pyrrolidinone **415** reduced to 44% (entry 2). When the amount of $BF_3·Et_2O$ was dropped to a single equivalent, the reaction was essentially halted at the iodonium salt stage (entry 3) – mirroring the results of the PIDA–BF_3 system.



Scheme 107: Reaction of alkyne **392** with PhIO—BF_3 gave pyrrolidinone **415** as the major product. Iodonium salt **431** was obtained BF_3 was not in excess.

Entry	**Conditions**	**Reagents (eq)**			**NMR Yields**[a]			
		$(PhIO)_n$	**H_2O**	**$BF_3·Et_2O$**	**392**[b]	**415**	**418**	**431**
1	DCM, rt, 2 h	1.1	2	2.2	-	53	17	-
2	DCM, rt, 2 h	2.0	2	4.0	-	44	25	-
3	DCM, rt, 2 h	1.1	2	1.1	35	-	-	66
4	MeCN, rt, 2 h	1.1	2	2.2	-	62	9	-
5	DMF (wet), rt, 2 h	1.1	-	2.2	97	-	-	-
6	$PhCF_3$, rt, 2 h	1.1	2	2.2	-	6	6	-
7	acetone, rt, 2 h	1.1	2	2.2	47	-	-	-
8	DME, rt, 2 h	1.1	2	2.2	5	-	-	80
9	MeCN/DME (90:10), rt, 2 h	1.1	2	2.2	-	68	17	-
10	MeCN/DME (70:30), rt, 2 h	1.1	2	2.2	-	63	-	12
11	MeCN/DME (70:30), rt, 6 h	1.1	2	2.2	-	61	-	5
12	MeCN, rt, 30 min + 2 h	1.1[c]	2[d]	1.1[c] + 1.1[d]	-	80	10	-
	[a] determined by ^1H NMR with ethylene carbonate as an internal standard; [b] unreacted starting material; [c] added at start of reaction; [d] added after 30 min							

Table 7: Table showing varying yields of products obtained in the reaction of alkyne **392** with iodosylbenzene in the presence of $BF_3·Et_2O$ and H_2O.

Going back to the initial reagent amounts and changing the solvent to MeCN produced 62% and 9% of pyrrolidinone **415** and *α*-hydroxyketone **418** respectively (Table 7, entry 4), matching the best result from the PIDA─BF_3 system. It was observed that the reaction slowly turned a darker green colour as it progressed. Based on previous observations this colour change appears to be representative of the decomposition of the intermediate iodonium salt. This partial decomposition could be the reason for the combined yield of 71% that was observed in this reaction.

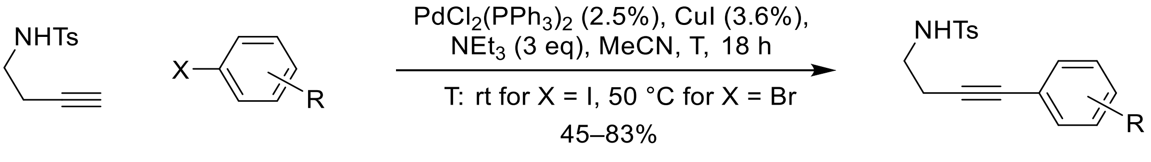
Next, DMF (non-anhydrous) was used as a solvent (Table 7, entry 5). Under these conditions the reaction was essentially halted with 97% of the starting material unreacted. Switching the solvent to $PhCF_3$ resulted in instant decomposition of the intermediate iodonium salt as indicated by the solution turning an opaque black colour within minutes (entry 6). This was reflected in the quantitative NMR which only showed 6% each of both pyrrolidinone **415** and *α*-hydroxyketone **418**. When acetone was used as a solvent the rate of reaction was greatly slowed with 47% of the starting material unreacted after 2 h (entry 7). In acetone neither pyrrolidinone **415** nor *α*-hydroxyketone **418** were obtained. Instead two new, unidentified compounds were present in the crude ^1H NMR.

Intermediate alkenyl(phenyl)iodonium salt **431** was found to be the major product when DME was used as a solvent, with 80% of the salt obtained after 2 h (Table 7, entry 8). Negligible amounts of pyrrolidinone **415** were present in the crude mixture indicating that the desired rearrangement does not take place in DME. We hypothesized that the stability of the intermediate iodonium species **431** in MeCN could be increased by using DME as a cosolvent, thereby stopping the decomposition of the iodonium salt and leading to an increased yield. The reaction was repeated in a 90:10 MeCN/DME solvent system (entry 9) giving a 68% yield of pyrrolidinone **415**, the highest obtained so far. When the fraction of DME was increased to 30% the yield of pyrrolidinone **415** was slightly decreased to 63% (entry 10). Notably this reaction mixture did not contain any *α*-hydroxyketone **418**. However, the reaction was still incomplete with 12% of the intermediate iodonium species **431** still present in the crude mixture. Therefore the reaction time was tripled to 6 h, but unfortunately the reaction still appeared to be incomplete. The amount of iodonium salt remaining had decreased to 5%, however the yield of pyrrolidinone **415** remained approximately the same at 61% (entry 11).

Returning to MeCN as the sole solvent, the intermediate iodonium salt was preformed *in situ* by initially using a single equivalent of $BF_3 \cdot Et_2O$ (Table 7, entry 12). The second equivalent, necessary to trigger the rearrangement, was added after 30 min. Pleasingly, the two-step reaction conditions were very successful, giving pyrrolidinone **415** in 80% yield – the highest observed so far.

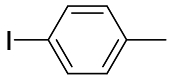
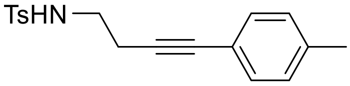
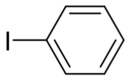
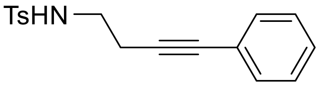
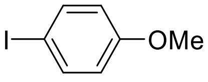
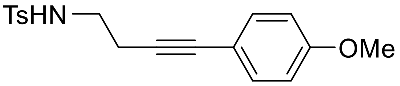
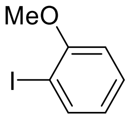
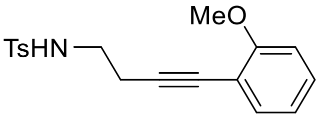
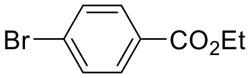
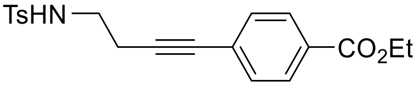
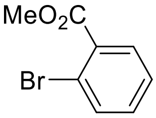
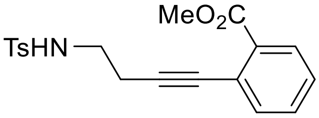
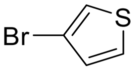
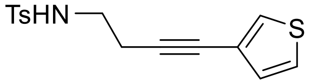
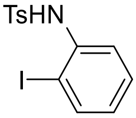
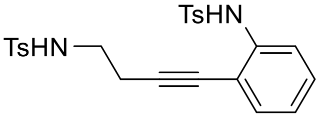
4.1.9. Synthesis of a Library of Alkynes

With high-yielding conditions for the pyrrolidinone in hand, a library of alkynes was synthesized to explore the scope of the cyclization-rearrangement reaction. The previously synthesized terminal alkyne **398** was coupled with aryl halides **434–440** giving alkynes **392** and **442–447** according to a procedure reported by reported by Sridharan *et al.*[146] (Scheme 108).



398 **434-440** **392, 442–447**

Scheme 108: Alkynes **392** and **442–447** was synthesized by Sonogashira coupling.

Entry	Aryl Halide	Alkyne	Yield
1	 **434**	 **392**	72%
2	 **435**	 **442**	73%
3	 **436**	 **443**	83%
4	 **437**	 **444**	83%
5	 **438**	 **445**	74%
6	 **439**	 **446**	54%
7	 **440**	 **447**	45%
8	 **441**	 **448**	0%[a]

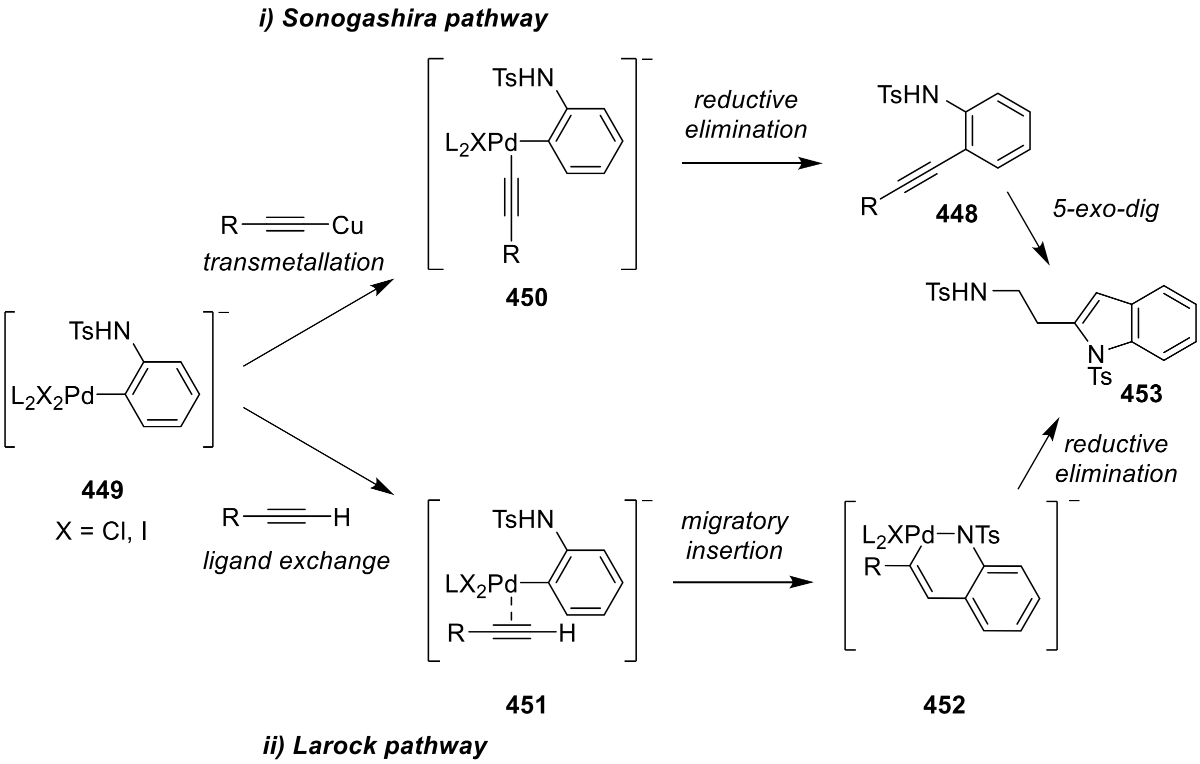
[a] Indole **453** was obtained instead (Scheme 109).

Table 8: A library of alkynes (**392**, **442–447**) was synthesized by Sonogashira coupling.

Alkynes **392** and **442–447** were obtained in moderate to good yields of 45–83% (Table 8, entries 1–7). However, the attempted synthesis of alkyne **448** (entry 8) did not result in any of the desired product. An undesired cyclization had taken place under the reaction conditions giving rise to indole **453**. This undesired cyclization may follow either a Sonogashira pathway or Larock pathway (Scheme 109).[160]

In the Sonogashira pathway, transmetallation of **449** with the copper acetylide gives intermediate **450**. Reductive elimination of palladium from **450** leads to the formation of the coupled product **448**. Alkyne **448** undergoes a 5-*exo-dig* cyclization, likely aided by the activation of the alkyne by coordination with a copper or palladium species, giving the observed indole **453**.

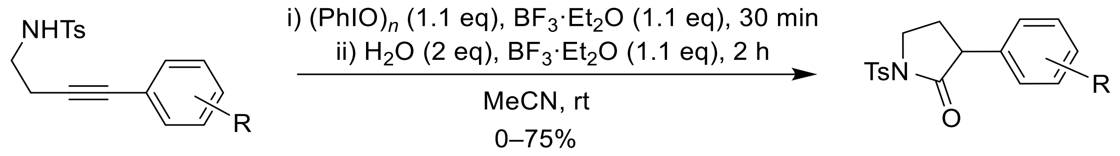
In the Larock pathway, the alkyne coordinates to **449** via the π-bond giving intermediate **451**, from which the alkyne can undergo migratory insertion into the aryl Pd─C bond. This leads to the formation of palladacycle **452**. The reductive elimination of palladium from **452** leads to the formation of the observed indole **453**.



Scheme 109: Indole **453** could be formed by either a Sonogashira pathway (top) or a Larock pathway (bottom).[160]

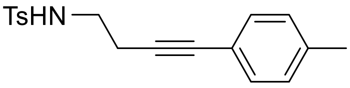
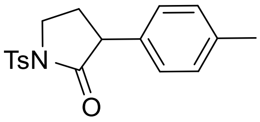
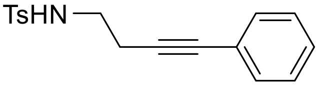
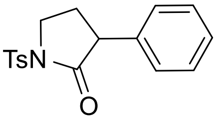
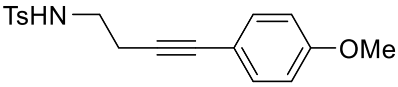
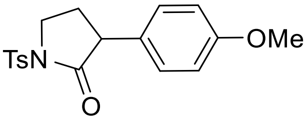
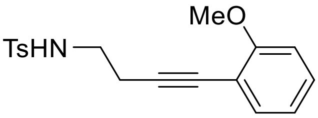
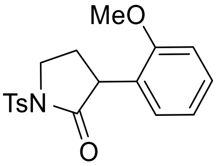
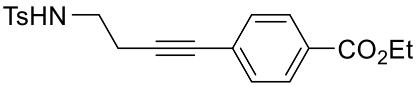
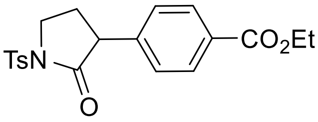
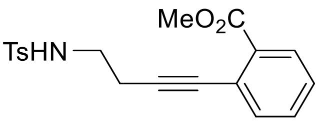
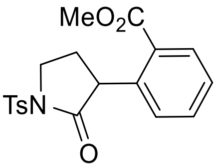
4.1.10. Exploration of Scope for the Cyclization-Rearrangement Reaction

With several analogues in hand, alkynes **392** and **442–447** were subjected to the optimized reaction conditions (Scheme 110). These reactions were performed on a 0.5–1.0 mmol scale. For each of the reactions isolated yields after purification by flash column chromatography are reported in Table 9. This represents a scale-up from the optimization reactions (Table 7, page 72) where reactions were performed on a 0.1 mmol scale and yields were determined by quantitative NMR.



392, 442–447 **415, 454–459**

Scheme 110: Alkynes **392** and **442–447** were subjected to the optimized reaction conditions.

Entry	Alkyne	Pyrrolidinone	Yield[a]
1	 **392**	 **415**	75%
2	 **442**	 **454**	69%
3	 **443**	 **455**	25%
4	 **444**	 **456**	41%
5	 **445**	 **457**	41%
6	 **446**	 **458**	0%[b]

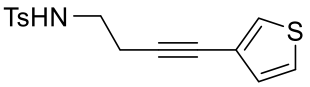
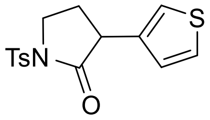
7	 **447**	 **459**	43%
	[a] Isolated yields after purification by flash column chromatography. [b] Isochroman-1,4-dione **462** was observed as the major product.		

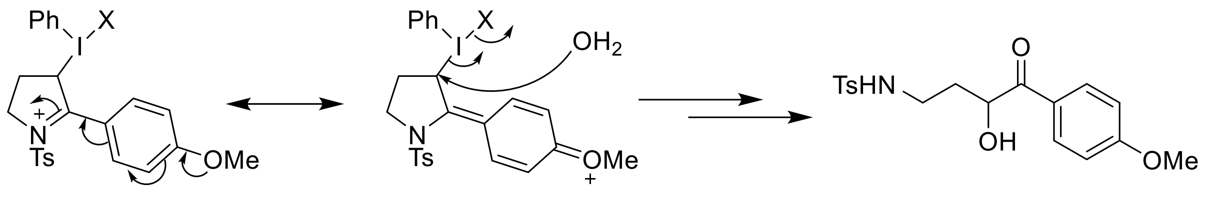
Table 9: Isolated yields from the cyclization of alkynes **392** and **442–447**.

Pleasingly, the scale-up of alkyne **392** proceeded without issue providing pyrrolidinone **415** with an isolated yield of 75% (Table 9, entry 1). This is comparable to the yield of 80% previously determined by quantitative NMR (Table 7, entry 12, page 72). The phenyl analogue **442** also gave a similar yield, at 69%.

However, moving onto more electron-rich aryl groups a significant drop in yield was observed. The *o*-anisyl analogue **444** and the 3-thienyl analogue **447** gave yields of 41% and 43% respectively (Table 9, entries 4 and 7). The *p*-anisyl analogue **443** was the most affected with the yield dropping to 25% (entry 3). These observations were surprising as the migratory aptitude of the aryl groups would be expected to increase with increasing electron density on the arene.

In the reaction with *p*-anisyl analogue **443**, it was observed that the ratio of pyrrolidinone to *α*-hydroxyketone in the reaction crude was 49:51. Comparatively, the equivalent ratio in the case of the *p*-tolyl analogue was 88:12. In both cases the ratio was measured using ^{1}H NMR of the crude reaction mixture.

Based on this observation, we hypothesize that the reduction of yield for the electron-rich analogues could be rationalized as in Scheme 111. On the intermediate iodonium salt **460** there are two possible carbon atoms that could be attacked by a nucleophile, C-2 and C-3. Reaction at C-2 would lead to the formation of pyrrolidinone **455**, whereas attack at C-3 would lead to the formation of *α*-hydroxyketone **461**. Water, as a hard nucleophile, would preferentially attack the positively charged iminium ion at C-2. However, with an electron-donating aryl substituent at C-2, increased contribution from resonance forms such as **460’** would lead to a more delocalized positive charge on the molecule. This could lead to a greater percentage of the nucleophilic attack occurring at C-3, leading to the formation of more *α*-hydroxyketone **461** and reducing the yield of pyrrolidinone **455**.

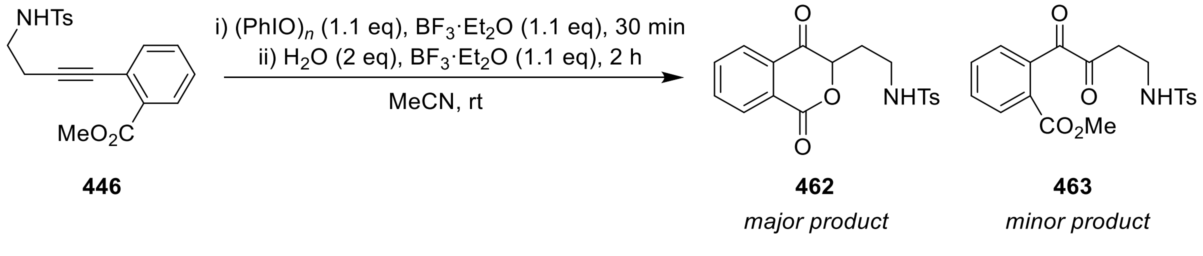


460 **460'** **461**

Scheme 111: Delocalization of the iminium ion positive charge due to contributions from resonance forms such as **460’** may lead to an increased ratio of nucleophilic attack at C-3 leading to the formation of increased amounts of α-hydroxyketone **461**.

Additionally, it was observed that the appearance of the reactions for electron-rich analogues was a darker green than the phenyl or *p*-tolyl analogues. Previous experiments have shown that this strong colour change is associated with a loss of total isolated product mass, likely due to decomposition of the intermediate iodonium salt.

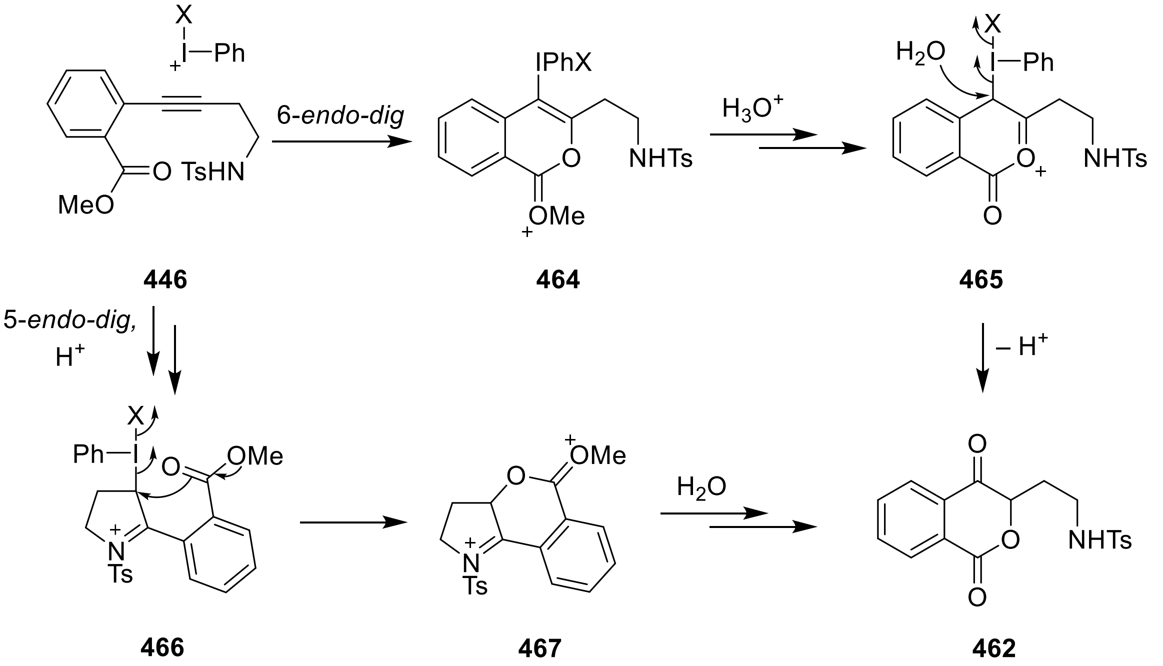
Moving onto more electron-deficient aryl groups, the yield was reduced to 41% with ethyl ester **445** (Table 9, entry 5). The electron-deficient benzoyl ester should be less adept at migratory reactions than a tolyl or phenyl group, therefore this reduction in yield is not unexpected. With methyl ester **446** none of the desired pyrrolidinone was present in the reaction crude (entry 6). The major product of the reaction was tentatively determined to be isochroman-1,4-dione **462** by analysis of the crude ^{1}H NMR. Unfortunately, isochroman-1,4-dione **462** appeared to decompose on silica and could not be isolated despite multiple attempts. However, in the attempted purification of isochroman-1,4-dione **462** a minor product was isolated – diketone **463**. The ratio of isochroman-1,4-dione **462** to diketone **463** in the crude was 88:12 by ^{1}H NMR.



Scheme 112: Alkyne **446** gave isochroman-1,4-dione **462** as the major product under the optimized reaction conditions.

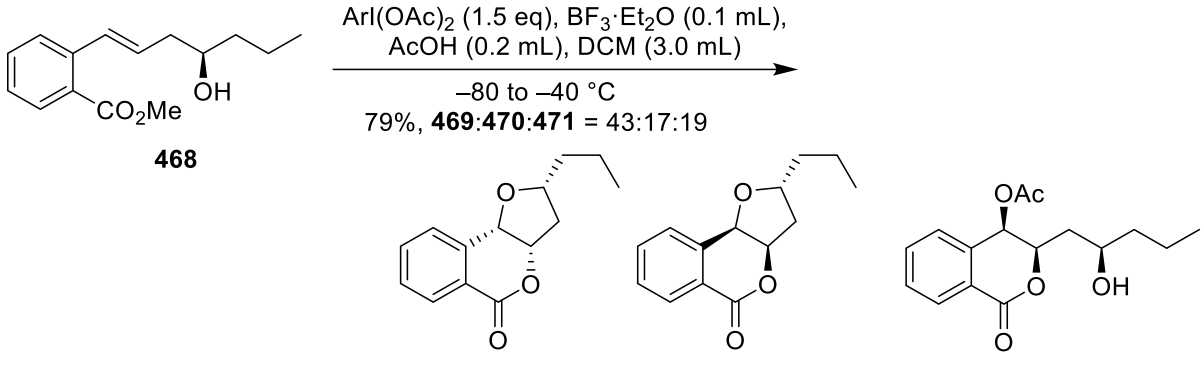
Two plausible pathways for the formation of isochroman-1,4-dione **462** were proposed (Scheme 113). In the first pathway, the 5-*endo-dig* cyclization of alkyne **446** with the tosylamide nitrogen leads to the formation of pyrrolidinium ion **466**. An intramolecular S_N2 reaction with loss of iodobenzene produces intermediate **467**, the hydrolysis of which gives isochroman-1,4-dione **462**.

In the second pathway, the 6-*endo-dig* cyclization of alkyne **446** with the benzoyl oxygen leads to the formation of phenyl(vinyl)iodonium species **464**. Hydrolysis and protonation of **464** gives intermediate **465**. Intermediate **465** can then go undergo S_N2 substitution with water, leading to the formation of isochroman-1,4-dione **462**. Alternatively, intermediate **465** could also undergo intramolecular nucleophilic attack by the tosylamide group followed by tautomerization and hydrolysis to give product **462** (pathway not shown).



Scheme 113: Plausible pathways for the formation of isochroman-1,4-dione **462**.

A similar synthesis of 4-oxyisochroman-1-ones from an alkene starting material has been reported in the literature by Fujita and co-workers (Scheme 114).[161]

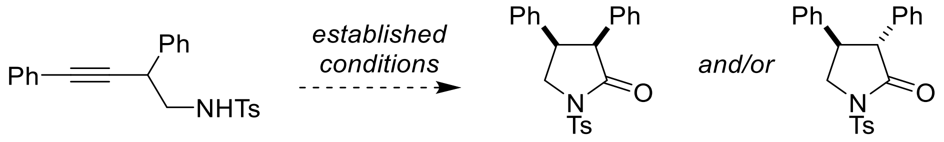


468 **469** **470** **471**

Scheme 114: Fujita and co-workers reported the synthesis of 4-oxyisochroman-1-ones from alkene **468** using BF$_3$ activated PIDA.[161]

4.1.11. Diastereoselectivity of the Cyclization-Rearrangement Reaction

Alkyne **472** was identified as a suitable candidate to explore the diastereoselectivity of the cyclization-rearrangement reaction. When subjected to the reaction conditions alkyne **472** could form either the *syn*- product **473**, the *anti*- product **474**, or a mixture of both (Scheme 115).



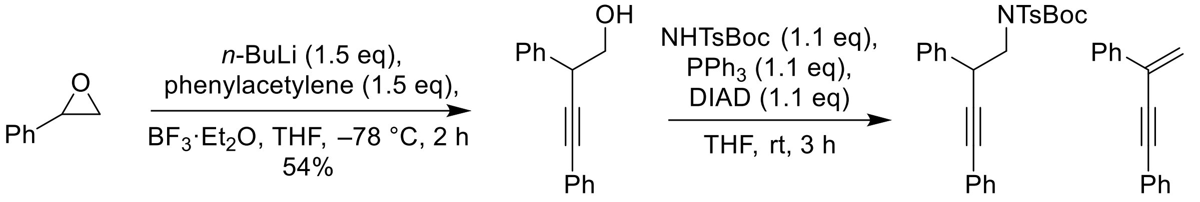
472 **473** **474**

Scheme 115: Subjecting alkyne **472** to the cyclization-rearrangement conditions could lead to the formation *syn*- product **473** and/or *anti*- product **474**.

The synthesis of alkyne **472** was attempted according to Scheme 116. First, styrene oxide (**475**) was ring-opened with phenylacetylene according to the procedure of Yamaguchi and Hirao,[162] giving alcohol **476** in 54% yield. Attempts at a Mitsunobu reaction of alcohol **476** did not provide the desired amide **477**. The Mitsunobu intermediate instead underwent E2 elimination giving alkene **478**. The preference of E2 elimination over S$_N$2 substitution is likely due to the highly conjugated nature of the elimination product.

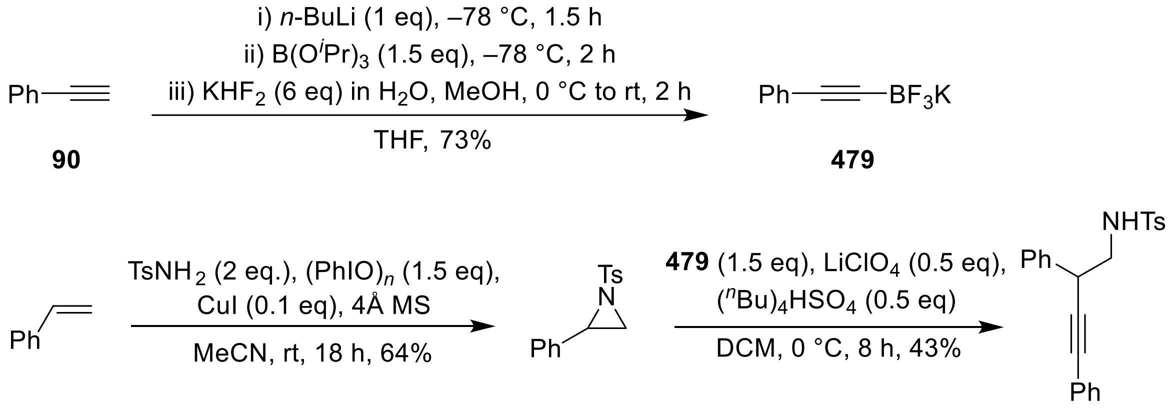
With the Mitsunobu route proving unsuccessful, a different approach via aziridine **481** was next attempted (Scheme 117). Phenylacetylene (**90**) was deprotonated with *n*-BuLi and reacted with triisopropylborate followed by aqueous KHF$_2$ according to a procedure reported by May and colleagues.[163] This gave alkynyl trifluoroborate **479** in

73% yield. The oxidation of styrene (**480**) in an iodosylbenzene–tosylamide system according to the procedure of Chan *et al.*[164] proceeded smoothly giving aziridine **481** in 64% yield. The obtained aziridine was then ring-opened with alkynyl trifluoroborate **479** according to the procedure of May *et al.*[163] giving the desired alkyne **472** with a yield of 43%.



475 **476** **477** *not observed* **478** *major product*

Scheme 116: Attempted synthesis of **477** from styrene oxide (**475**) ended in failure.

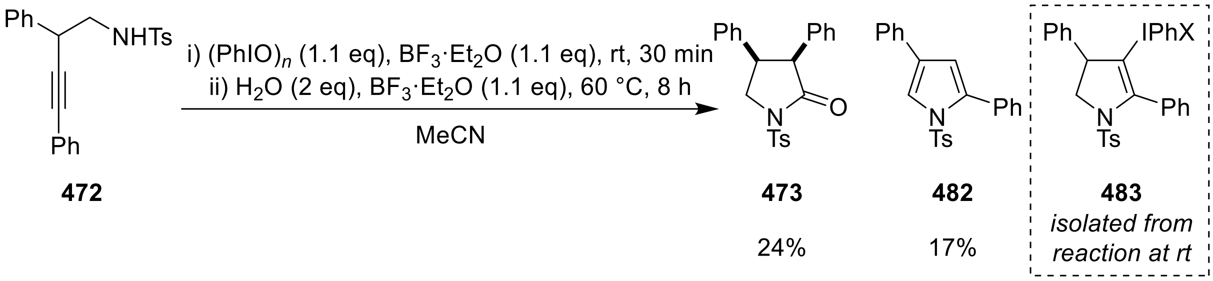


90 **479**

480 **481** **472**

Scheme 117: Alkyne **472** was successfully synthesized via the ring-opening of aziridine **481**.

Alkyne **472** was then subjected to the standard cyclization-rearrangement conditions. Alkyne **472** did not undergo the rearrangement reaction under these conditions with the reaction halted at the iodonium salt stage (Scheme 118). An extension of the reaction time was of no benefit. However, raising the temperature to 60 °C at the second step allowed the rearrangement to proceed, with pyrrolidinone **473** obtained in 24% yield. It is not clear why the addition of a neighbouring phenyl group increases the temperature required for the reaction to proceed. Pyrrolidinone **473** was obtained as a single diastereomer. The other diastereomer was not visible in the ^{1}H NMR of the crude mixture demonstrating a high degree of diastereoselectivity. A secondary product, pyrrole **482**, was also isolated with a yield of 17%.



Scheme 118: The cyclization of alkyne **472** gave pyrrolidinone **473** and pyrrole **482**. The reaction was halted at alkenyl(phenyl)iodonium salt **483** in the absence of heating.

Through the analysis of NOESY cross-peaks pyrrolidinone **473** was determined to be the *syn*- isomer. Notably, one of the pyrrolidinone H5 protons—labelled as H5a in Figure 12—showed appreciable NOESY cross-peaks to the *ortho*-H of both phenyl groups. On the other hand, the other H5—labelled as H5b—did not show appreciable cross-peaks to either of the phenyl groups. The fact that *only one* of the H5 protons showed NOESY cross-peaks to the phenyl groups and the fact that it showed the peaks to *both* of the phenyl groups, suggested that both phenyl groups were located on the same face – as depicted in Figure 12.

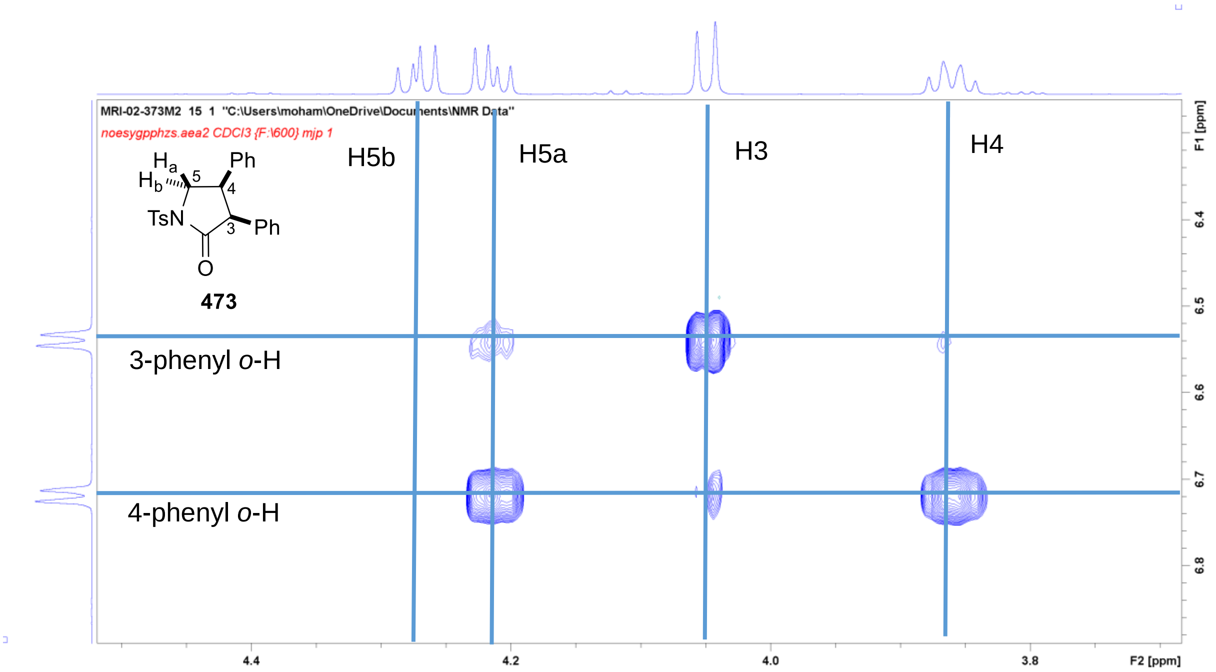
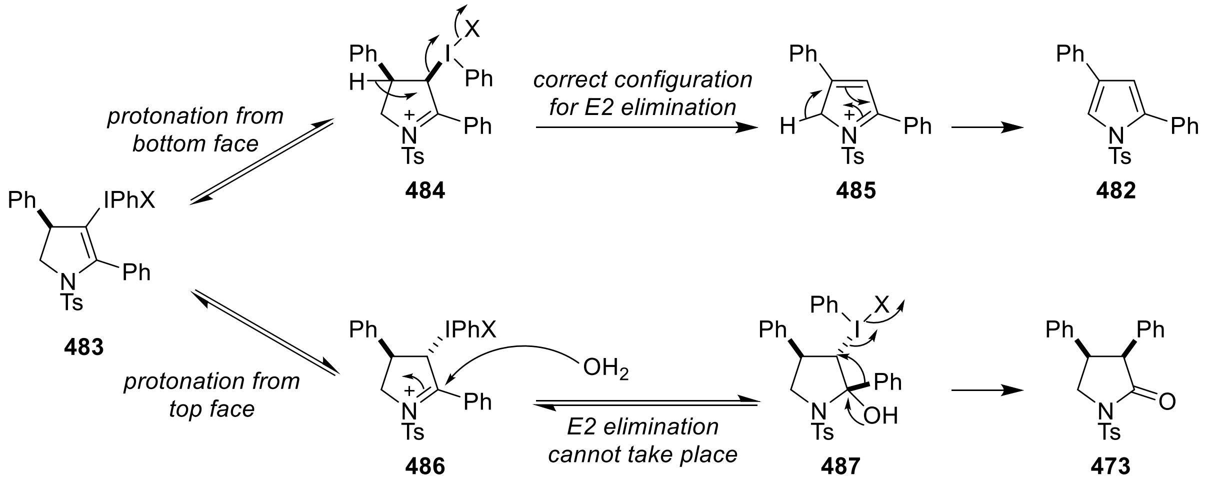


Figure 12: NOESY spectrum showing cross-peaks between the pyrrolidine ring protons and the *ortho*-hydrogens of both phenyl substituents in compound **473**.

The formation of pyrrole **482** and the *syn*- substituted pyrrolidinone **473** can be rationalized as follows. First, the intermediate iodonium salt **483** is formed according to the mechanism previously discussed on page 62. This intermediate iodonium salt can be protonated from either the same face as, or the opposite face to, the 4-phenyl substituent (Scheme 119). Protonation from the opposite face gives intermediate **484** where the C-4 hydrogen and the iodine(III) group are *anti* to one another. This allows the antiperiplanar configuration required for E2 elimination to be achieved. E2 elimination of iodobenzene from intermediate **484** gives pyrrolium ion **485**, which is then deprotonated to form the observed pyrrole **482**. The higher reaction temperature and the additional resonance stabilization of pyrrolium ion **485** may both contribute to this reaction's added propensity for E2 elimination compared to previous experiments where it had not been observed.

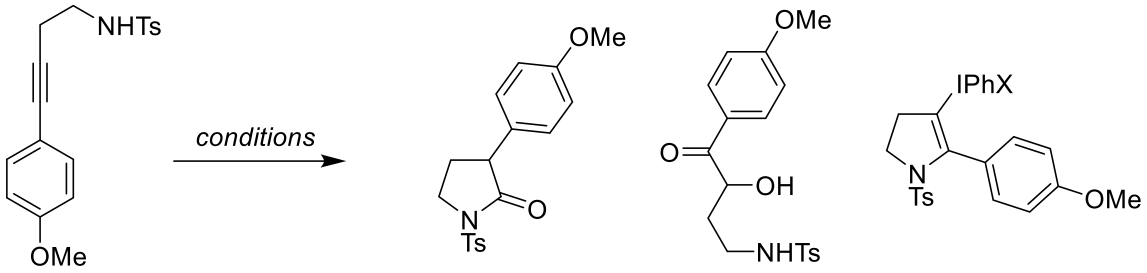
If instead iodonium salt **483** is protonated from the same face to the 4-phenyl substituent, intermediate **486** is formed. In intermediate **486** the C-4 hydrogen and the iodine(III) group are *syn* to one another, so they cannot achieve the necessary antiperiplanar configuration required for E2 elimination. Instead, intermediate **486** reacts by addition of water to the iminium ion. To obtain the necessary *anti* configuration of the 2-phenyl group and the iodine(III) group for the 1,2-shift, the water molecule needs to attack from the same face as the neighbouring iodine(III) group. The addition of water to the iminium ion is expected to be reversible and form both intermediates in equilibrium. Once the correct intermediate **487** is formed it can undergo a 1,2-migratory shift forming the *syn*- substituted pyrrolidinone **473**.



Scheme 119: Plausible mechanism for the formation of **473** and **482**.

4.1.12. Optimization of the Cyclization-Rearrangement Reaction for Electron-Rich Substituents

With the initial optimized conditions giving lower yields for electron-rich arenes, down to 25% yield in the case of analogue **443**, the next stage of the investigation focused on whether modified conditions to suit alkyne **443** could be obtained (Table 10).



443 **455** **461** **488**

Scheme 120: The cyclization of **443** may give products **455**, **461** and/or **488** depending on the conditions used.

Entry	Conditions[a]	NMR Yields[b]			
		443[c]	455	461	488
1	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 30 min, rt then H_2O (2 eq), $BF_3\cdot Et_2O$ (1.1 eq), 1.5 h, rt	-	35	37	-
2	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 30 min, rt then H_2O (1 eq), $BF_3\cdot Et_2O$ (1.1 eq), 1.5 h, rt	-	23	23	-
3	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 30 min, rt then H_2O (4 eq), $BF_3\cdot Et_2O$ (1.1 eq), 1.5 h, rt	-	24	15	-
4	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 30 min, rt then H_2O (2 eq), $NaHCO_3$ (2.2 eq), 1.5 h, rt	19	-	-	68
5[d]	DCM, $BF_3\cdot Et_2O$ (1.1 eq), 30 min, rt then CF_3SO_2H (1.1 eq), 30 min, −78 °C then H_2O (2 eq), 1.5 h, −78 °C to rt	-	28	17	-
6	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 1 h, 0 °C then H_2O (2 eq), $BF_3\cdot Et_2O$ (1.1 eq), 1.5 h, 0 °C	-	17	17	35
7	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 1 h, 0 °C then H_2O (2 eq), $BF_3\cdot Et_2O$ (1.1 eq), 4 h, 0 °C	-	19	16	42
8	MeCN, $BF_3\cdot Et_2O$ (1.1 eq), 1 h, 0 °C then H_2O (2 eq), $BF_3\cdot Et_2O$ (1.1 eq), 8 h, 0 °C	-	43	32	4
	[a] all reactions included **443** (1.0 eq) and $(PhIO)_n$ (1.1 eq) added at the start; [b] determined by ^1H NMR with ethylene carbonate as an internal standard; [c] unreacted starting material; [d] an additional product, assumed to be the corresponding *α*-trifluoromethanesulfonyloxyketone was observed in 44% yield				

Table 10: Table showing varying yields of products obtained in the reaction of alkyne **443** with iodosylbenzene under different conditions.

First, the reaction was repeated under the previously established conditions to get a quantitative NMR yield under these conditions for comparison (Table 10, entry 1). The yield was determined as 35% by quantitative NMR and the ratio of pyrrolidinone **455** to *α*-hydroxyketone **461** around 1:1. Next, the amount of water added to the reaction was halved. This did not have a positive effect, with the total yield decreasing to 46% and the ratio of pyrrolidinone to *α*-hydroxyketone remaining around 1:1 (entry 2). Doubling the amount of water did not provide improvements to the yield, but did improve the pyrrolidinone:*α*-hydroxyketone ratio to 3:2 (entry 3).

When the second step of the reaction was performed under mildly alkaline conditions, the reaction was halted at iodonium salt **488** (Table 10, entry 4). This is likely because iodonium salt **488** cannot be protonated under these conditions and, therefore, the reaction cannot proceed.

With prior success in preforming the iodonium salt, we wondered whether preforming the *protonated* iodonium salt could provide any improvement (Table 10, entry 5). Iodonium salt **488** was preformed at rt in DCM and then cooled to −78 °C. Triflic acid was then added to the reaction mixture and the reaction temperature maintained at −78 °C for 30 min. Water was then added to the reaction and the reaction was allowed to warm to rt. These conditions did not provide any improvement, with the yield of pyrrolidinone **455** determined as 28%. The major product of this reaction was a previously unobserved product in 44% yield. This product is assumed to be the corresponding *α*-triflyloxyketone due to the NMR shift of the *α* proton (6.25 ppm, dd), but this has not been verified as the product was not isolated. Additionally, it cannot be determined from this single experiment whether the protonation actually took place at −78 °C or whether it took place after the reaction mixture had been warmed to rt.

Previously, with alkyne **472** it was observed that the rearrangement can be sensitive to temperature (page 82). Therefore, the reaction temperature was reduced to 0 °C to see if a lower temperature would be of benefit. The rearrangement proceeded very slowly at 0 °C, with only 17% of pyrrolidinone **455** obtained 1.5 h after the second addition (Table 10, entry 6). 35% of the intermediate iodonium salt **488** was still present in the reaction. Increasing this reaction time to 4 h slightly improved the yield to 19% (entry 7). Further doubling the reaction time to 8 h provided a marked improvement, giving pyrrolidinone **488** in 43% yield, the highest obtained so far (entry 8). Only a small amount of iodonium salt, 4%, was left unreacted. The ratio of pyrrolidinone to *α*-hydroxyketone was also improved from the previously established conditions, going from 1:1 to 4:3.

Even with these improved conditions, the total sum of the known products was 79% – meaning that around a fifth of the reaction mass was still unaccounted for. To investigate what could be causing this, the progress of the reaction was followed by ^{1}H NMR. The reaction was performed according to Table 10, entry 8. A few drops of the reaction mixture were retrieved at selected time intervals and then diluted into $CDCl_3$ and analysed by ^{1}H NMR.

An NMR taken 2 h after the second addition showed that a pyrrole was being produced in the reaction (Figure 13). This pyrrole was present in around a 1:4 ratio to pyrrolidinone **455**. The coupling patterns of this pyrrole—6.07 (dd, *J* 3.1, 1.7 Hz), 6.26 (t, *J* 3.3 Hz), 7.36 (dd, *J* 3.3, 1.7 Hz)—indicated that this was a 2-substituted pyrrole, likely pyrrole **489**, formed by E2 elimination of the iodonium salt as suggested previously (Scheme 119, page 83). Indeed, the observed NMR shifts and coupling constants were consistent with those reported in the literature for pyrrole **489**, providing confirmation of the molecule's identity.[165]

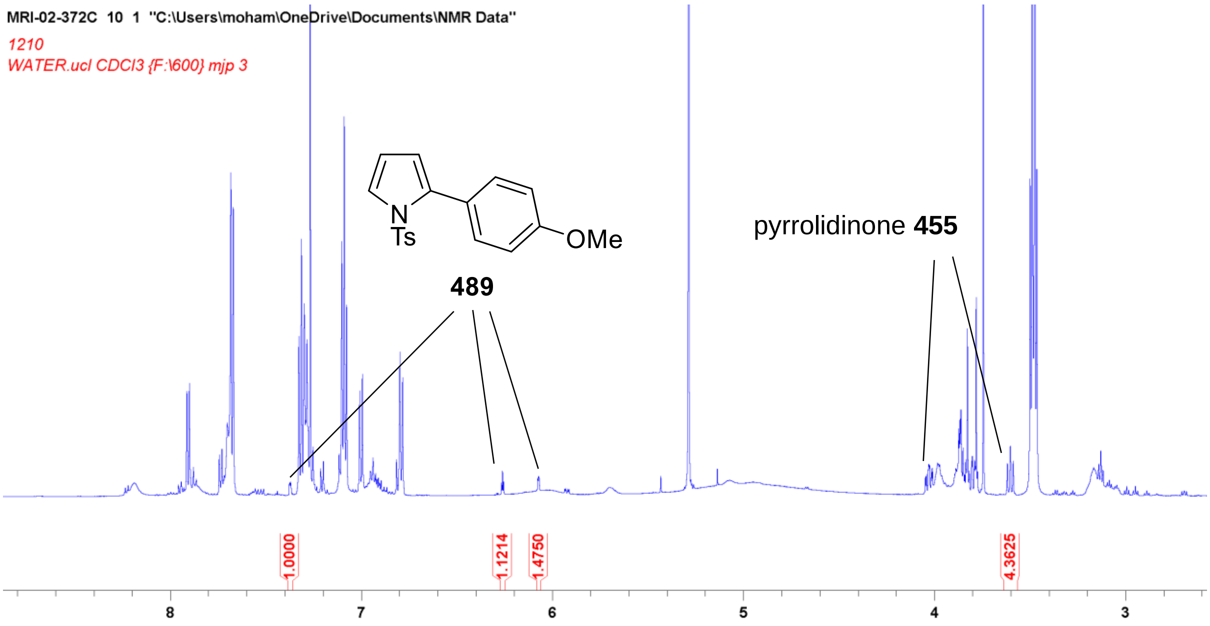


Figure 13: A ^{1}H NMR spectrum of the reaction mixture 2 h after the second addition showed the presence of pyrrole **489**.

The amount of pyrrole appeared to decrease over the course of the reaction, with an NMR obtained 8 h after the second addition showing that the ratio of pyrrole **489** to pyrrolidinone **455** was now around 1:40 (Figure 14). This cannot simply be due to the generation of more pyrrolidinone **455** throughout the reaction. Previous experiments had shown that the yield of pyrrolidinone **455** after 1.5 h under these conditions was 17% (Table 10, entry 6). Therefore, if the pyrrole/pyrrolidinone ratio were to change from 1:4 to 1:40 due to the generation of more pyrrolidinone **455**, an impossible yield of over 100% would be required. Hence, it must be that pyrrole **489** is formed and then consumed over the course of the reaction.

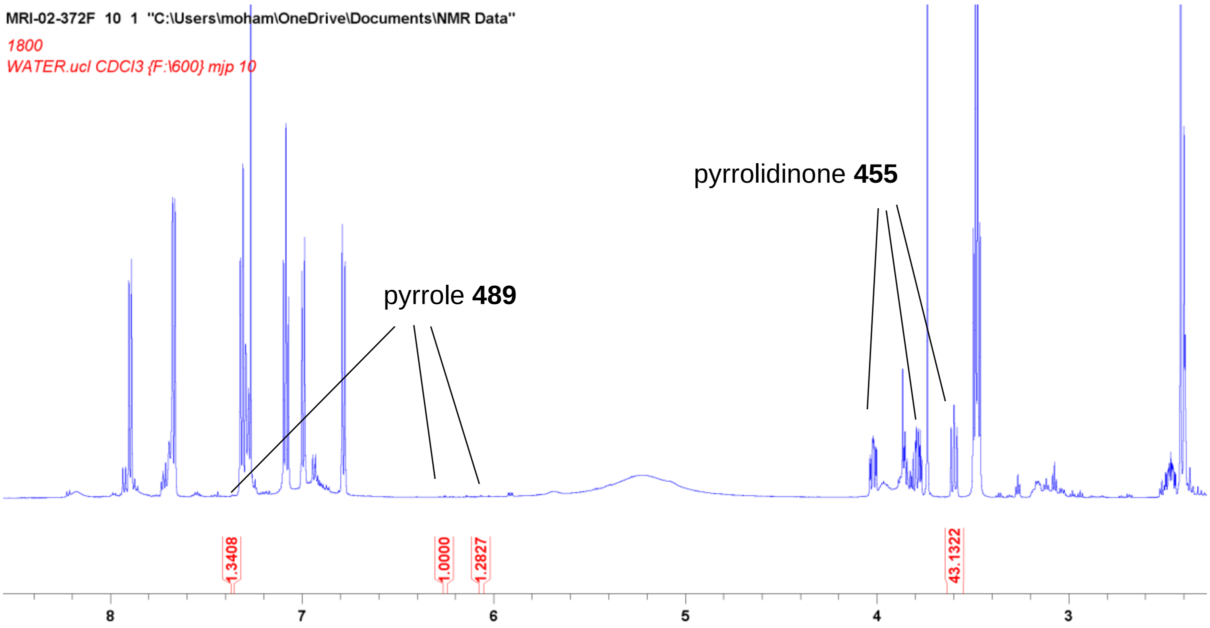


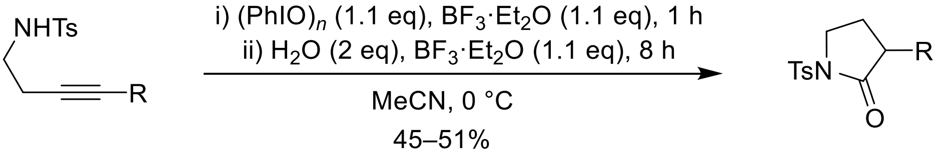
Figure 14: An NMR of the reaction mixture 8 h after the second addition showed that the amount of pyrrole **489** had decreased relative to pyrrolidinone **455**.

The oxidation of pyrroles often leads to uncontrolled polymerization and decomposition.[166] Therefore, one possibility is that pyrrole **489** is undergoing uncontrolled oxidation by action of iodonium salt **488** over the course of the reaction. This could explain the missing 21% yield observed in Table 10, entry 8 and other experiments.

Carroll and collaborators have had success improving the yields of hypervalent iodine-mediated reactions by introducing radical scavengers such as TEMPO.[167] A similar introduction of radical scavengers to our reaction could perhaps prevent the intermediate iodonium salt **488** from being used up for the oxidation of pyrrole **489** – assuming that this is a radical process. This could lead to a minor improvement in yield.

The reaction rate was greatly slowed by the addition of TEMPO, with negligible amount of pyrrolidinone **455** generated after 5 h of reaction time at 0 °C. With 3 days of reaction time at rt, 17% pyrrolidinone **455** and 27% *α*-hydroxyketone **461** was observed by quantitative NMR. This was worse than the results observed at rt without the addition of TEMPO (Table 10, entry 1).

With the best conditions obtained being those of Table 10, entry 8 isolated yields were obtained with these conditions (Table 11).



443, 447 **455, 459**

Scheme 121: Alkynes **443** and **447** were subjected to the 0 °C reaction conditions.

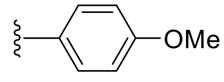
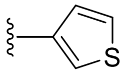
Entry	**R (Alkyne → Product)**	**rt**[a]			**0 °C**[b]		
		Yield[c]	**Ratio**[d]	**Total**[e]	**Yield**[c]	**Ratio**[d]	**Total**[e]
1	 (**443** → **455**)	25%	49:51	51%	45%	69:31	65%
2	 (**447** → **459**)	43%	81:19	53%	51%	89:11	57%
	[a] conditions as in Table 7, entry 12; [b] conditions as in Table 10, entry 8; [c] isolated yield of pyrrolidinones after purification by flash column chromatography; [d] ratio of pyrrolidinone to *α*-hydroxyketone as measured by ^{1}H NMR of crude reaction mixture; [e] total yield of pyrrolidinone + *α*-hydroxyketone calculated based on isolated yield and NMR-measured ratio						

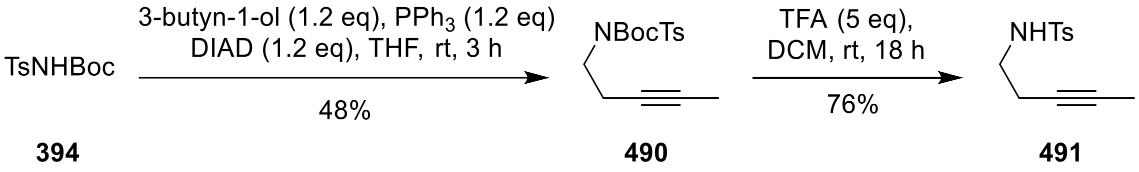
Table 11: Table showing comparison of *p*-anisyl and 3-thienyl analogues at rt and 0 °C reaction conditions.

The *p*-anisyl analogue **443** showed a large improvement, with the yield of pyrrolidinone **455** going from 25% under the previous reaction conditions to 45% under the new conditions (Table 11, entry 1). The ratio of pyrrolidinone **455** to *α*-hydroxyketone **461** was also improved, going from 49:51 to 69:31. The 3-thienyl analogue **447** showed a smaller improvement, with the yield of pyrrolidinone **459** improved from 43% to 51% (entry 2). There was also slight improvement in the ratio of pyrrolidinone **459** to the corresponding *α*-hydroxyketone, going from 81:19 to 89:11.

4.1.13. Attempts at Cyclization With Other Similar Alkynes

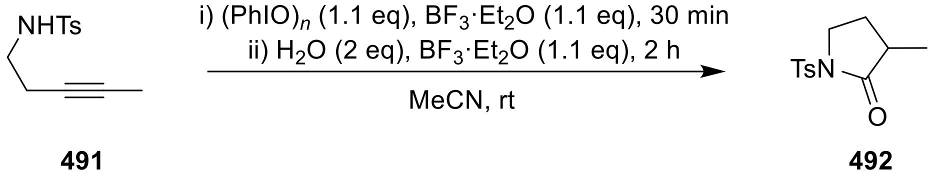
Other than alkyne **392** and its corresponding analogues, other similar compounds were also synthesized and the possibility of using them in the cyclization-rearrangement reaction investigated.

The methyl analogue **491** was prepared by a Mitsunobu reaction of 3-pentyn-1-ol with *tert*-butyl tosylcarbamate (**394**) followed by Boc deprotection with TFA (Scheme 122).



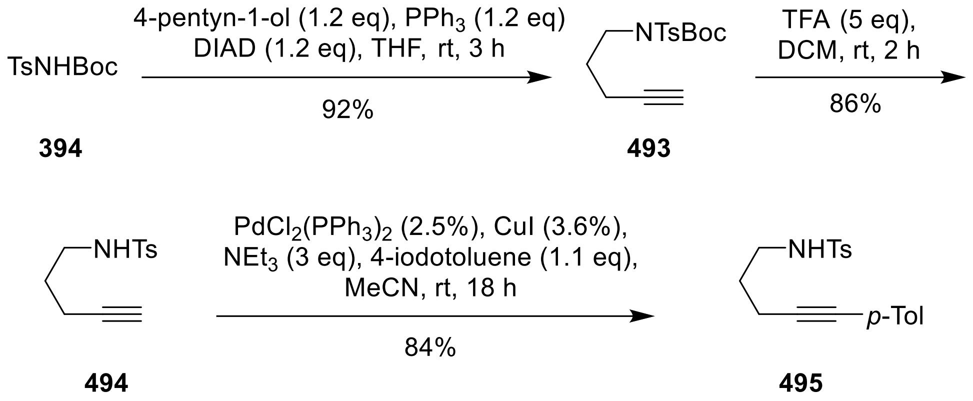
Scheme 122: Reaction scheme showing the synthesis of alkyne **491**.

When alkyne **491** was subjected to the $PhIO–BF_3OEt_2$ system at rt, a complex mixture was obtained (Scheme 123). The main component of this mixture was unreacted alkyne **491**, determined to be 18% by quantitative NMR. By comparison with known NMR shifts[168] a peak that may belong to pyrrolidinone **492** was identified – a doublet of 7.1 Hz at 1.13 ppm. Based on this peak the yield of pyrrolidinone **492** was determined as potentially being 3%. None of the other peaks could be identified due to overlap with other components. This result suggests that the extra stabilization offered by the aryl group to the positive or partial positive charge developing on the alkyne is important for the reaction to proceed in the manner desired.



Scheme 123: The cyclization of alkyne **491** gave a complex mixture of products. Pyrrolidinone **492** was potentially present in the crude mixture at a 3% yield.

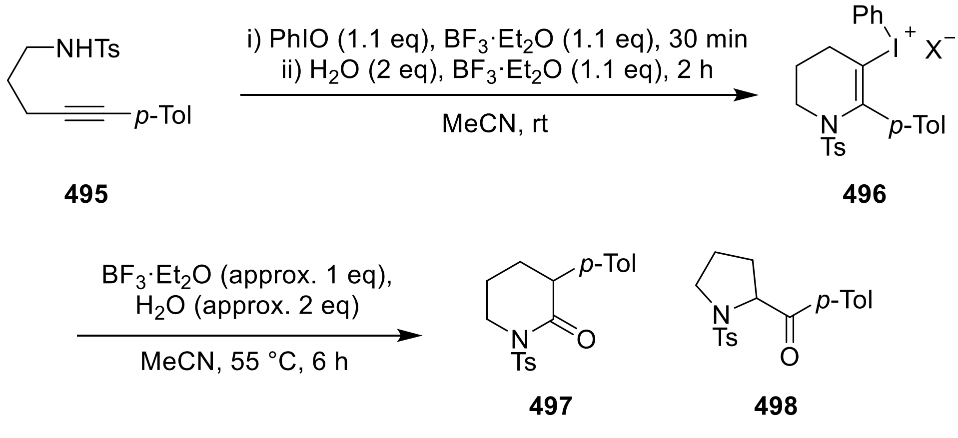
To explore the possibility of forming six-membered rings, the pent-4-ynyl analogue **495** was synthesized (Scheme 124). First, Boc-protected tosylamide **493** was obtained in 92% yield by the Mitsunobu reaction of 4-pentyn-1-ol and *tert*-butyl tosylcarbamate (**394**). The deprotection of **493** by TFA gave tosylamide **494** in 86% yield. Finally, a Sonogashira coupling of **494** with 4-iodotoluene yielded alkyne **495** in 84% yield.



Scheme 124: Reaction scheme showing the synthesis of alkyne **495**.

Alkyne **495** was then subjected to the PhIO–$BF_3 \cdot Et_2O$ system at rt (Scheme 125). Under these conditions the rearrangement did not take place, with the reaction cleanly halted at the iodonium salt stage. By recrystallization from DCM/hexane 0.905 g of iodonium salt **496** was obtained as pure colourless crystals, starting from 0.881 g (2.69 mmol) of alkyne **495** (our inability to identify the counterion means that a percentage yield cannot be calculated).

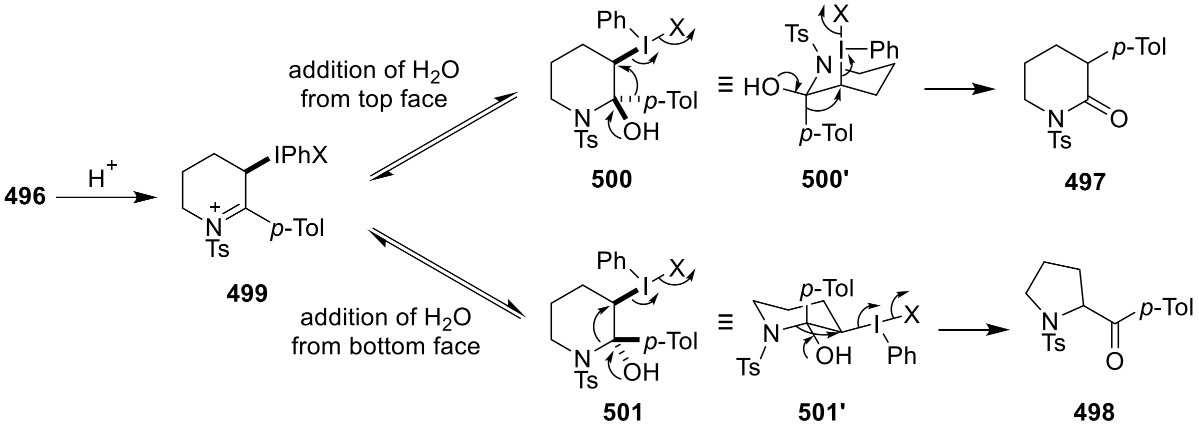
Heating iodonium salt **496** to 55 °C in the presence $BF_3 \cdot Et_2O$ and H_2O triggered the rearrangement giving two different products (Scheme 125). These two products co-eluted during flash column chromatography and were isolated as a 1:1 mixture. By analysis of the NMR spectra these compounds were determined to be piperidinone **497** and pyrrolidine **498**.



Scheme 125: Alkyne **495** did not undergo rearrangement under the regular conditions, with the reaction halted at iodonium salt **496**. When **496** was heated with $BF_3 \cdot Et_2O$ and H_2O a 1:1 mixture of **497** and **498** was produced.

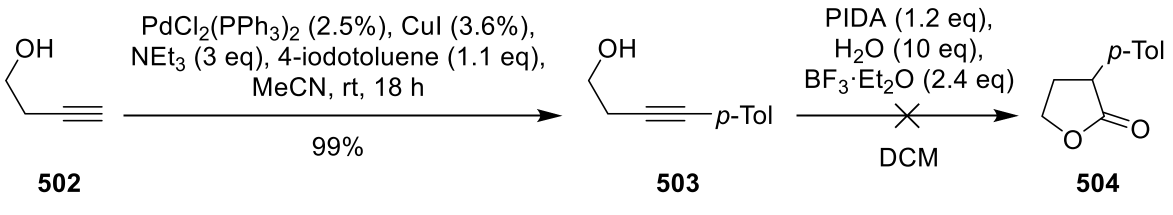
A mechanism to explain the formation of these two products was proposed (Scheme 126). If water adds to iminium ion **499** from the same face as the iodine(III) group, intermediate **500** is obtained. In this intermediate the *p*-tolyl group is *anti* to the iodine(III) group. Therefore, a 1,2-shift of the *p*-tolyl group can take place giving piperidinone **497**.

However, if water adds from the opposite face, giving intermediate **501**, the *p*-tolyl group ends up *syn* to the iodine(III) group and cannot undergo a 1,2-shift. Instead, the C─N bond, which is now *anti* to the iodine(III) group, migrates giving pyrrolidine **498**. With the previous 5-membered analogues this ring contraction is not observed as it would result in the formation of a strained 4-membered ring, which is disfavoured.



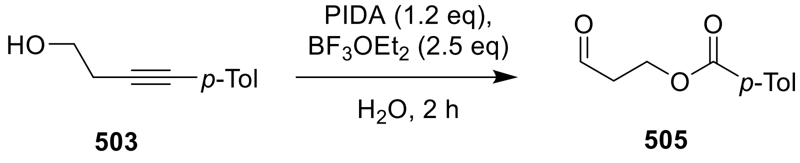
Scheme 126: The rearrangement of iminium ion **499** can give two different products depending on which face of the molecule nucleophilic attack takes place.

To investigate whether the reaction could take place with alcohols in addition to sulfonamides, alcohol **503** was synthesized by the Sonogoshira coupling of 3-butyn-1-ol (**502**) and 4-iodotoluene (Scheme 127). Cyclization of this alcohol was attempted in the PIDA─BF3 system using DCM as a solvent. Unfortunately, the reaction immediately turned a dark green colour indicating undesired reactions. The crude NMR did not show any presence of the desired product, *δ*-lactone **504**.



Scheme 127: Alkyne **503** was synthesized by a Sonogashira coupling. The cyclization of alkyne **503** with PIDA─BF3 was unsuccessful.

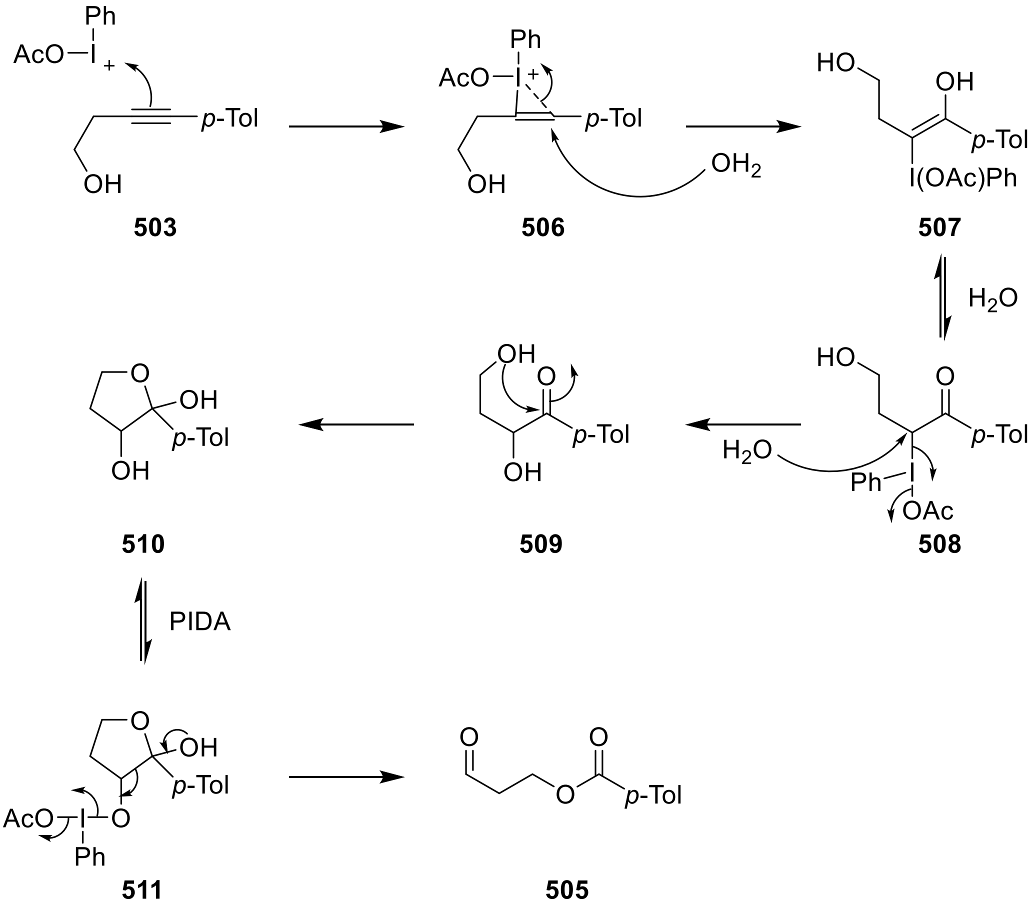
However, when the reaction was attempted using water as a solvent, the colour of the reaction mixture remained unchanged—indicating the absence of undesired decomposition reactions (Scheme 128). The ^{1}H NMR of the crude product showed that largely a single product had been produced. Unfortunately, attempts to isolate this compound by flash column chromatography ended in failure. Nevertheless, the compound has been tentatively identified as 3-oxopropyl 4-methylbenzoate (**505**) by analysis of the ^{1}H NMR spectrum of the crude mixture. This is not a known compound, however the observed CH_2CH_2 and aldehyde CH peaks—2.90 (2H, td, *J* 6.1, 1.5 Hz), 4.64 (2H, t, *J* 6.1 Hz), 9.86 (1H, t, *J* 1.6 Hz)—are consistent with those reported in the literature for a similar compound, 3-oxopropyl 4-bromobenzoate – 2.92 (2H, td, *J* 6.1, 1.4 Hz), 4.66 (2H, t, *J* 6.1 Hz), 9.86 (1H, t, *J* 1.4 Hz).[169]



major product

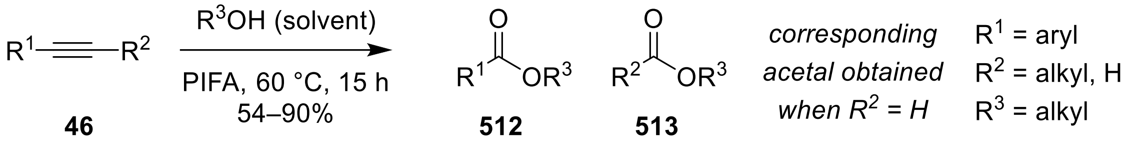
Scheme 128: Reaction of alkyne **503** with PIDA-BF_3 in water gave aldehyde **505**.

A mechanism for the formation of aldehyde **505** was proposed (Scheme 129). The reaction initially proceeds with the addition of the hypervalent iodine reagent to alkyne **503** generating intermediate **506** which quickly reacts with the solvent, water. This gives enol **507** which tautomerizes to form ketone **508**. S_N2 displacement of iodobenzene by water from this intermediate gives *α*-hydroxyketone **509**. Intramolecular cyclization of the primary alcohol onto the ketone gives hemiacetal **510**. Ligand exchange on a second equivalent of the hypervalent iodine reagent leads to the formation of intermediate **511**. At this point the C–C bond between carbons 2 and 3 can be cleaved with loss of iodobenzene as shown in Scheme 129, forming aldehyde **505**. The overall effect of this reaction is the cleavage of a carbon-carbon triple bond into an ester and an aldehyde.



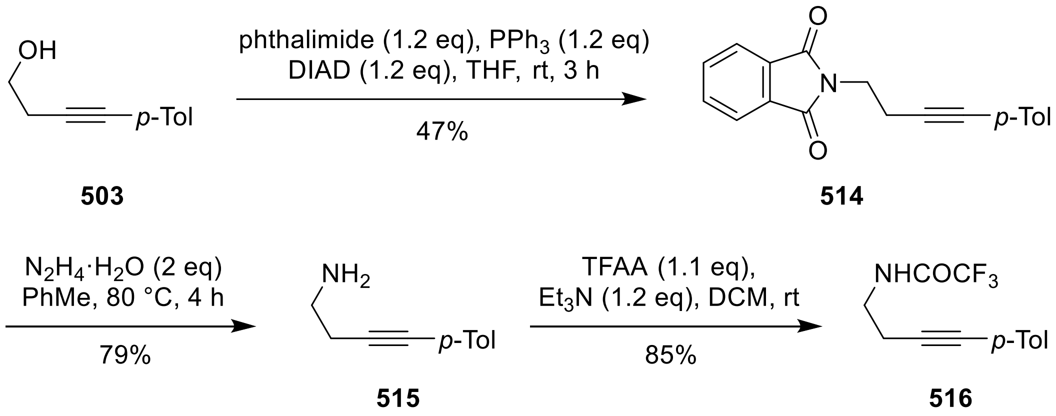
Scheme 129: Proposed mechanism for the formation of aldehyde **505**.

A similar reaction was reported by Guo and co-workers in 2014.[170] They were able to cleave alkynes into two esters using PIFA (Scheme 130). The reaction we have observed is an intramolecular variation of this reaction with incomplete oxidation.



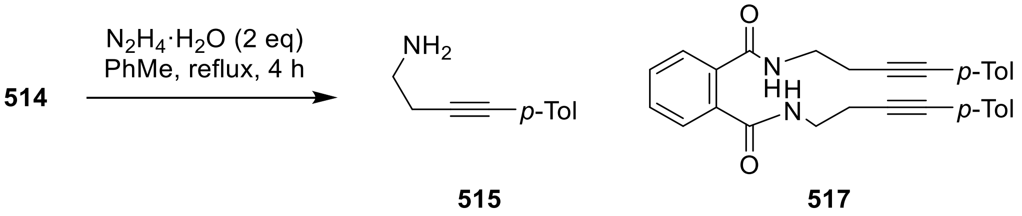
Scheme 130: Guo *et al.* have reported oxidative cleavage of alkynes with PIFA.[170]

To explore the possibility of using carboxamides in the reaction trifluoroacetamide **516** was synthesized (Scheme 131). First, the previously synthesized alcohol **503** was reacted with phthalimide in a Mitsunobu reaction giving phthalimide **514** in 47% yield.



Scheme 131: Reaction scheme showing the synthesis of trifluoroacetamide **516**.

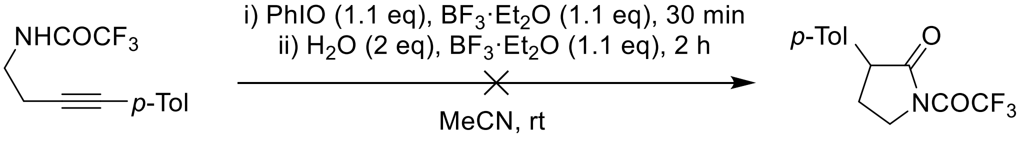
Phthalimide **514** was then deprotected with hydrazine monohydrate. Initially, the deprotection was attempted by adding hydrazine hydrate to **514** in refluxing toluene. However, under these conditions a significant amount of diamide **517** was formed in addition to the deprotected amine **515** (Scheme 132), with the ratio of the aforementioned products determined as 1:3 by ^{1}H NMR. Two possible issues with the reaction were identified. First, by adding hydrazine hydrate to a suspension of **514**, hydrazine hydrate is a limiting reagent during the addition which could lead to the formation of diamide **517** during the addition. Second, the boiling point of hydrazine is very close to the reaction temperature, and the condensation of hydrazine vapour on the upper parts of the reaction vessel could reduce the amount of hydrazine accessible in solution. To address this the reaction temperature was reduced to 80 °C and the order of addition was reversed. Pleasingly, this gave amine **515** in 79% yield. Amine **515** was then reacted with TFAA according to a procedure described by Phipps *et al.*[171] giving trifluoroacetamide **516** with a yield of 85%.



Scheme 132: Initial attempts at deprotecting phthalimide **514** resulted in the formation of diamide **517** in addition to amine **515**.

When trifluoroacetamide **516** was subjected to the PhIO–$BF_3 \cdot Et_2O$ system at rt a complex mixture was obtained. This mixture did not appear to contain the desired pyrrolidinone **518** by analysis of the ^{1}H NMR spectrum of the crude product (Scheme

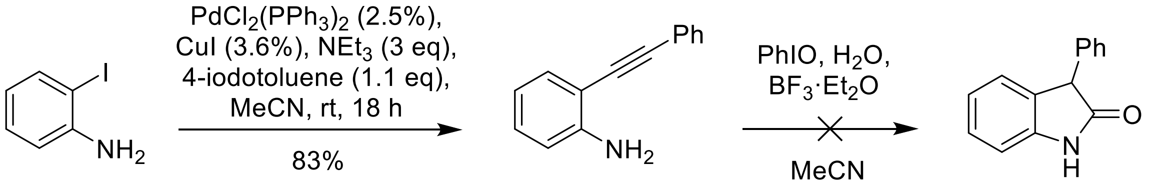
133). It is not clear why the trifluoroacetamide gives such different reactivity from the tosylamide.



516 **518**

Scheme 133: Reaction of alkyne **516** under the PhIO–BF_3·Et_2O system did not produce pyrrolidinone **518**.

To investigate the possibility of forming oxindoles, alkyne **520** was synthesized by the Sonogoshira coupling of phenylacetylene and 2-iodoaniline (**519**) in 83% yield (Scheme 134). When alkyne **520** was subjected to the PhIO–BF_3·Et_2O reaction system at rt the reaction immediately turned dark green indicating the presence of undesired reactions. Oxindole **521** was not present in the crude reaction mixture by ^{1}H NMR.



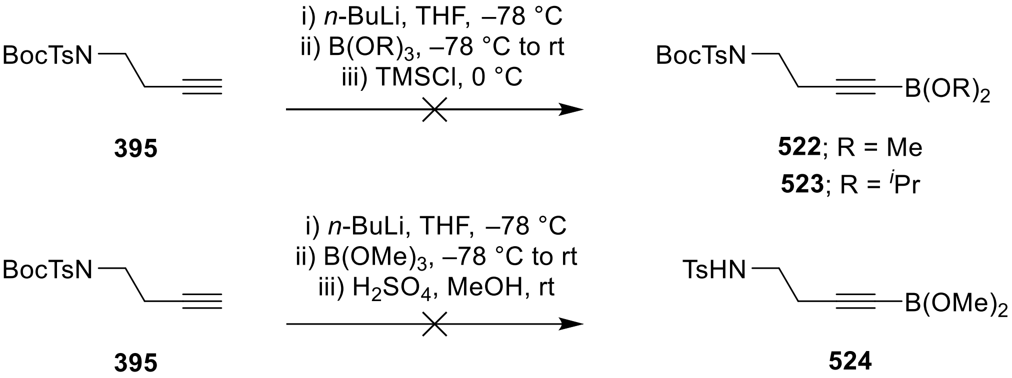
519 **520** **521**

Scheme 134: Alkyne **520** was synthesized by a Sonogashira coupling. Reaction of **520** in the PhIO–BF_3·Et_2O reaction system did not produce oxindole **521**.

4.2. Alkynylboronate Synthesis

Also of interest to us was the possibility of using alkynylboronates as substrates for the cyclization reaction. The boron functionality is of interest because it would allow for further modification by Suzuki or Chan-Lam couplings post-cyclization. Initial investigations in this area were focused on the synthesis of a suitable alkynylboronate. Several boron substituents such as –B(OMe)$_2$, –B(O^{i}Pr)$_2$, –BF_3K and –BMIDA were considered. The latter two would benefit from increased stability, however the dialkyl boronate esters should be simpler to synthesize. Due to this the initial focus was on dimethyl and diisopropyl boronate esters.

Synthesis of dimethyl boronate ester **522** was attempted following a procedure reported by Dilman and coworkers (Scheme 135).[172] Terminal alkyne **395**, which had been obtained previously, was deprotonated with *n*-BuLi, reacted with trimethyl borate and subsequently worked up with TMSCl. Unfortunately, this led to recovery of the starting material (Table 12, entry 1). A change of reactant to triisopropyl borate provided no improvement (entry 2). Modifying the work-up procedure to utilize methanolic H_2SO_4, as has been used for alkenylboronic esters,[172] also did not have any positive effect (entry 3).



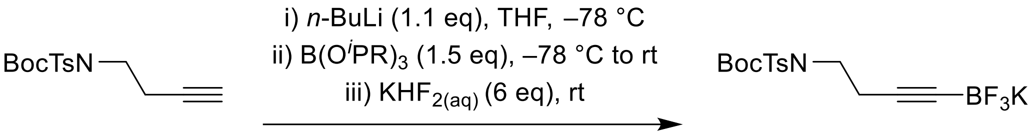
Scheme 135: Attempted syntheses of dialkyl boronate esters **522**, **523** and **524**.

Entry	Conditions	Yield
1	*n*-BuLi (1.1 eq), THF, −78 °C, 15 min *then* $B(OMe)_3$ (1.5 eq), −78 °C to rt, 1.5 h *then* TMSCl (2.5 eq), 0 °C, 1.5 h	0[a]
2	*n*-BuLi (1.1 eq), THF, −78 °C, 15 min *then* $B(O^iPr)_3$ (1.5 eq), −78 °C to rt, 1.5 h *then* TMSCl (2.5 eq), 0 °C, 1.5 h	0[a]
3	*n*-BuLi (1.1 eq), THF, −78 °C, 15 min *then* $B(OMe)_3$ (1.5 eq), −78 °C to rt, 1.5 h *then* H_2SO_4 (1.1 eq), MeOH, 45 min	0[b]
	[a] starting material recovered; [b] complete Boc deprotection observed	

Table 12: Attempts at dialkyl boronate ester synthesis.

A consultation of the literature revealed alkynylboronic esters to be highly acid sensitive compounds. It had been reported that alkynylboronic esters undergo protodeboration in a range of solvents including H_2O, MeOH and EtOH with the rate of cleavage dependent upon the acidity of the solvent.[173] Furthermore, Harrity has also reported difficulties in isolating alkynylboronic esters despite several attempts to optimize the procedure.[174] However, they reported successful isolation of the corresponding potassium trifluoroborates. The variation of the yields reported in their paper (42–92%) presented some concerns. Nevertheless, we opted to try a variation of their procedure.

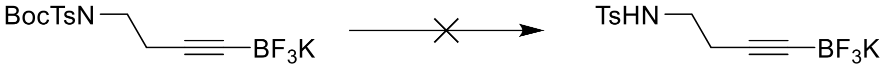
Alkyne **395** was deprotonated with *n*-BuLi and then reacted with triisopropyl borate. Subsequent reaction with aqueous KHF_2 afforded trifluoroborate **525** in 44% yield (Scheme 136).



395 **525**

Scheme 136: Synthesis of trifluoroborate **525**.

Next, the Boc protecting group had to be removed in order to free up the nitrogen for the planned cyclization step (Scheme 137).



525 **526**

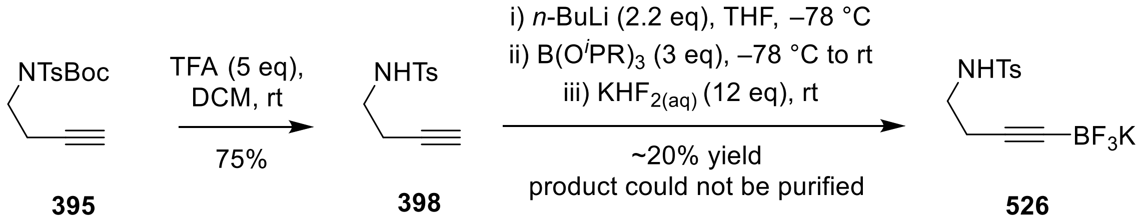
Scheme 137: Attempted Boc deprotection of trifluoroborate **525** ended in failure.

Entry	**Conditions**	**Yield**
1	TFA (5 eq), DCM, rt, 1.5 h	0[a]
2	TMSCl (5 eq), MeOH, rt, 2 h	0[a]
3	DMSO, 120 °C, 4 h	0[b]
	[a] both protodeboration and Boc deprotection took place concurrently; [b] 17% protodeboration (determined by ^1H NMR), negligible Boc deprotection	

Table 13: Attempts at Boc deprotection of **525**.

Unfortunately, the standard TFA/DCM conditions resulted in complete protodeboration of the starting material (Table 13, entry 1). A ^{19}F NMR study showed that the protodeboration is rapid and complete within 1.5 h. Utilizing anhydrous HCl (entry 2), generated in situ from MeOH/TMSCl, only made matters worse with complete protodeboration observed by ^{19}F NMR in a matter of minutes. Thermal deprotection was also attempted under relatively mild temperatures, 120 °C in DMSO (entry 3). Under these condition 17% protodeboration was observed after 4 h, but no Boc deprotection. Some other Boc deprotection methods were considered, for example those which utilize silylation by TMSI or TMSOTf. However, these methods all require an aqueous workup in order to hydrolyse the silyl ester which is incompatible with the product at hand.

With successful Boc deprotection of trifluoroborate **525** seeming unlikely a reversal of steps was attempted. Harrity *et al.* have previously reported successful synthesis of a trifluoroborate in the presence of a free alcohol. The trifluoroborate synthesis procedure was carried out as before, but with the amount of reactants doubled (Scheme 138).



Scheme 138: Reversal of steps to synthesize trifluoroborate **526**.

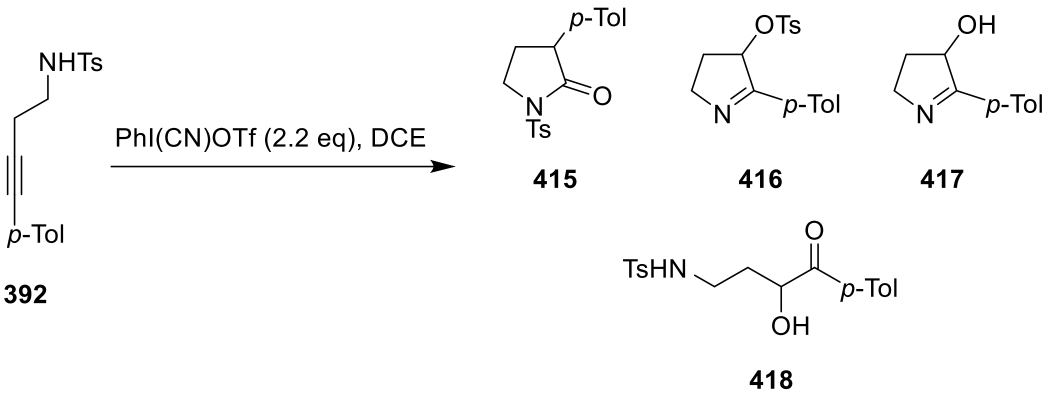
Unfortunately, the desired trifluoroborate **526** was obtained in low yields of approximately 20%. Furthermore, the product could not be separated from unreacted starting material satisfactorily. This was because the only methods available for purification were triturating with acetone (to remove the inorganics) and washing with Et_2O (to remove the organics). Unfortunately, due to the apparent low solubility of tosylamide **398** in Et_2O a clean sample of trifluoroborate **526** could not be obtained this way.

The success of this route seems unlikely with low yields having been observed during multiple experiments. For the synthesis of the desired alkynylboronate it will be necessary to consider other, more stable, boron groups such as –B(MIDA) or –B(dan).

5. Conclusions

5.1. Iodine(III) Mediated Alkyne Cyclization

Even though the targeted product was not observed in the reaction of cyano(phenyl)iodonium triflate with the cyclization substrate **392**, a range of interesting products was observed (Scheme 139).

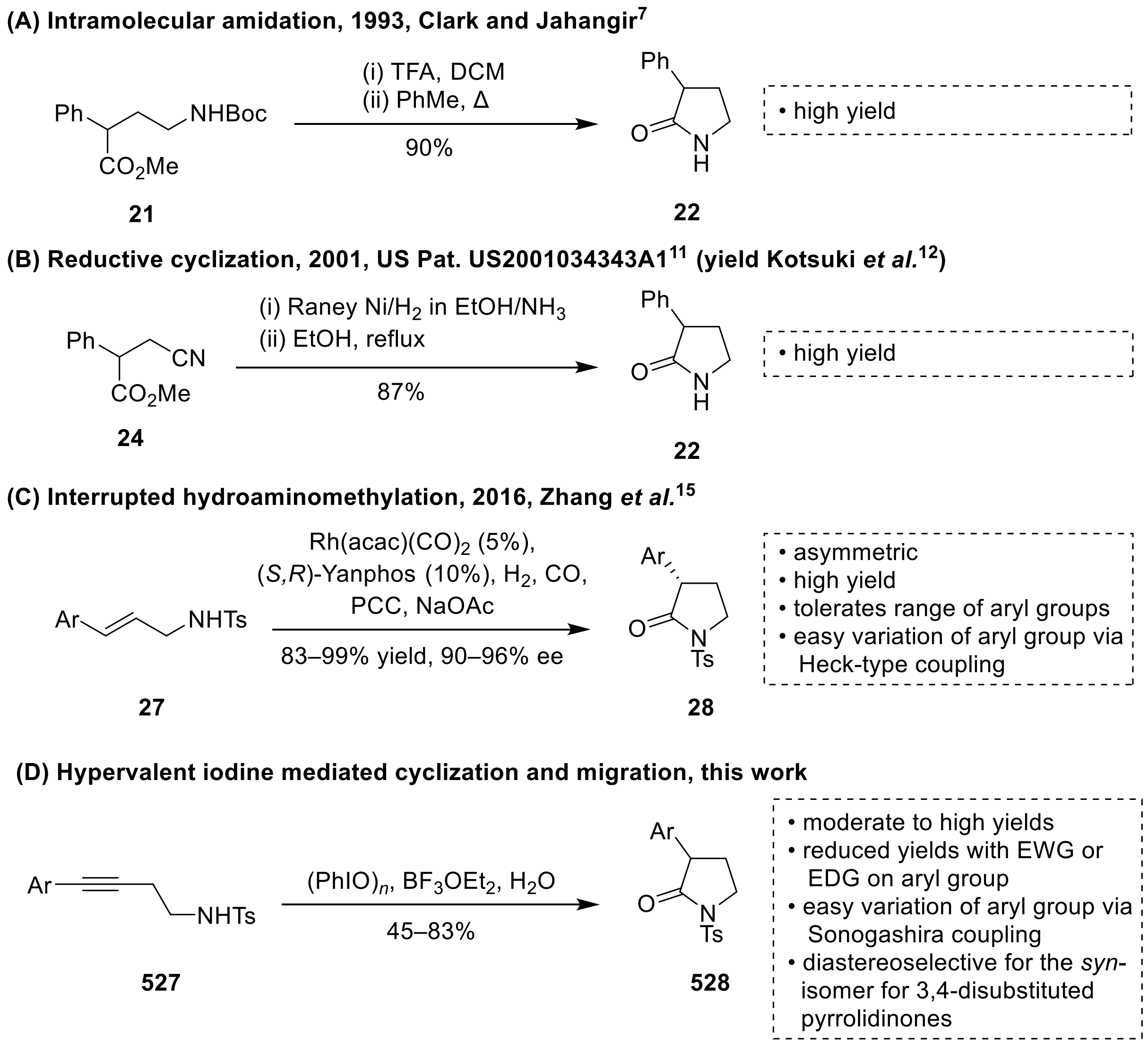


Scheme 139: Products obtained from the reaction of alkyne **392** with cyano(phenyl)iodonium triflate.

The yields of the initial reaction were low, at 5% or less, for all the products. However, the yield of pyrrolidinone **415** was increased to 75% by switching the reagent to iodosylbenzene–BF_3, optimizing the solvent and improving the reaction methodology.

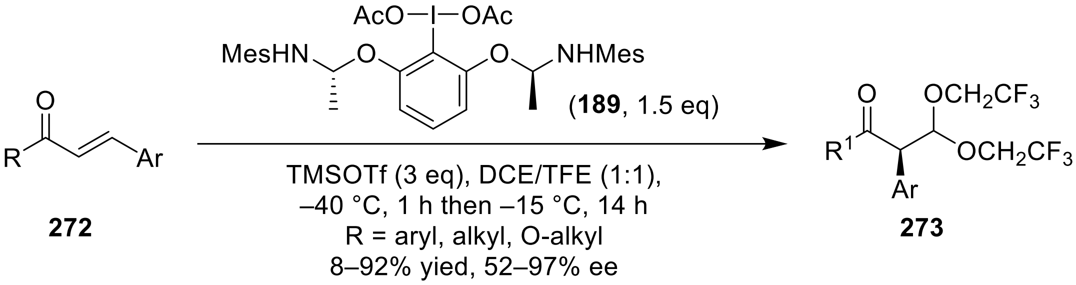
The reaction compares favourably in some aspects with other cyclizations forming 3-arylpyrrolidin-2-ones (Scheme 140). The final step in the synthesis of our cyclization substrate **527** is a Sonogashira coupling, allowing easy variation of the aryl group. This is advantageous to the intramolecular lactamization methodologies **A**[7] and **B**[11, 12], where modification of the aryl group would be more involved or need to take place earlier in the synthesis. In addition, the reported cyclization-rearrangement reaction is diastereoselective when forming 3,4-disubstituted pyrrolidinones, selectively giving the *syn*- isomer. Such diastereoselectivity is not possible in methods **A** and **B** where the relative stereochemistry would be predetermined in the cyclization precursor. The diastereoselectivity of Zhang's interrupted hydroaminomethylation reaction **C**[15] has not been explored.

One shortcoming of our cyclization-rearrangement reaction is the lower tolerance of different functional groups on the aryl substituent. Although they do react giving moderate yields, the yields of aryl groups with electron withdrawing or electron donating groups are lower compared to electronically neutral aryl groups such as phenyl or tolyl. In contrast, Zhang's interrupted hydroaminomethylation reaction **C** is more robust to changes in the electronic nature of the aryl group, with yields of 83% or more observed for a wide range of aryl groups.



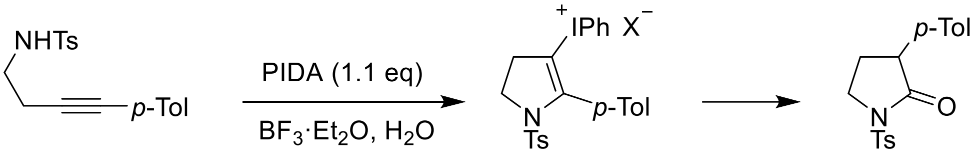
Scheme 140: Comparison of reported transformation with previously reported methods of forming 3-arylpyrrolidin-2-ones by cyclization.

Zhang's method is also enantioselective due to the use of a chiral phosphine ligand. The enantioselectivity of our reaction in the presence of chiral iodine(III) reagents is yet to be explored. It is known that oxidative 1,2-aryl shifts in acyclic systems are enantioselective when utilising chiral iodine(III) reagents,[116, 117] so it is plausible that using such reagents could also convey enantioselectivity here and constitutes an area of possible future research. For example, chiral iodine(III) reagent **189** has been used to carry out enantioselective 1,2-aryl shifts (Scheme 141).[117]



Scheme 141: An enantioselective 1,2-aryl shift mediated by chiral hypervalent iodine reagent **189**.[117]

Through our work the intermediate in the reaction, alkenyl(phenyl)iodonium salt **431**, was also isolated and characterized (Scheme 142). The isolation of this intermediate suggests that the reaction to form pyrrolidinone **415** proceeds via an initial cyclization to form **431** followed by a 1,2- aryl shift. Although hypervalent iodine induced 1,2-aryl shifts are already known (see Section 3.3.1), to our knowledge, this is the first time that a hypervalent iodine induced 1,2-aryl shift has been combined with an intramolecular amidation to yield lactams.



392 **431** **415**

Scheme 142: Alkenyl(phenyl)iodonium salt **431** was demonstrated to be an intermediate in the formation of pyrrolidinone **415** by an NMR experiment in DCM-*d*2.

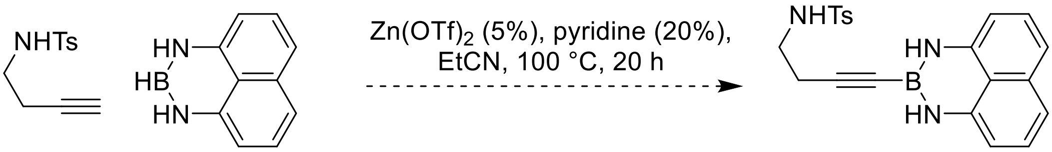
Some promising conditions that allow this intermediate salt to be generated *in situ* without the subsequent rearrangement taking place—such as by using DME as a solvent—were also found. In the case of a particularly stable iodonium salt—the six-membered analogue of **431**—a pure sample of the salt could be recrystallized.

This opens up the potential to use these iodonium salts for other transformations, rather than just the rearrangement. Alkenyliodonium salts have been reported to undergo coupling with iodide, organoborates, Gringard reagents and terminal alkynes in the presence of Cu(I) catalysts.[20] Furthermore, they have also been utilised as reagents for Heck-type olefinations and Sonogashira-type couplings.[20]

5.2. Alkynylboronate Synthesis

So far, a suitable alkynylboronate has not been successfully synthesized. Many difficulties were faced due to the acid-sensitive nature of alkynylboronates. The solution may be to switch to an even more stable boronate.

The ─B(dan) moiety seems promising in this regard. Tsuchimoto and coworkers have published a procedure for the dehydrogenative coupling of alkynes with 1,8-naphthalenediaminatoborane (**529**).[175] Promisingly, this method is compatible with a free alcohol in the substrate molecule with an 86% yield obtained for such a molecule. Therefore, the dehydrogenative coupling of alkyne **398** with borane **529** could lead to the successful synthesis of a suitable alkynylboronate (Scheme 143).



398 **529** **530**

Scheme 143: A suitable alkyne could be obtained by dehydrogenative coupling of alkyne **398** and borane **529**.

6. References

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7. Experimental Details

General:

All experiments were performed in glassware that had been either oven-dried or flame-dried prior to use. Experiments were performed under a positive pressure of argon except where specified otherwise. Anhydrous THF, DCM, MeCN, and toluene were collected from the UCL anhydrous solvent system. All other starting materials, reagents and solvents had been purchased from commercial sources and used without further purification unless otherwise specified. Melting points were measured on an Electrothermal IA9300. IR spectra were recorded on a Bruker FTIR Alpha PLATINUM ATR instrument. Mass spectra were recorded by the UCL Mass Spectrometry Facility on a Thermo Finnigan MAT900 mass spectrometer (EI/CI), Agilent 6510 QTOF mass spectrometer (ESI) or Orbitrap Q Exactive mass spectrometer (ESI). NMR spectra were recorded at the UCL NMR Facility on Bruker Avance Neo 500, Bruker Avance III 600 Cryo and Bruker Avance Neo 700 instruments. Where necessary, HSQC and HMBC spectra were used to aid assignments. Additionally, Gaussian multiplication performed in TopSpin 4.0.8 was used to aid elucidation of ^{1}H NMR coupling constants where needed.

AA'XX' Spectra:

A sizeable number of compounds isolated and characterised over the course of this thesis showed peaks with either AA'XX' or AA'MM'X coupling. Where possible the coupling constants for these systems have been calculated from the measured spectra according to explanations published by Hans Reich.[176]

An ideal AA'XX' half spectrum consists of 10 lines, symmetrical about their mid-point (Figure 15). Each half spectrum includes a "doublet" and two "AB quartets" and the four coupling constants $J_{AA'}$, $J_{XX'}$, J_{AX} and $J_{AX'}$ can be calculated from them as follows:

$|K| = |J_{AA'} + J_{XX'}|$ ("*J*" of one "AB quartet")
$|L| = |J_{AX} - J_{AX'}|$ (Δv_{AB} of both "AB quartets")
$|M| = |J_{AA'} - J_{XX'}|$ ("*J*" of other "AB quartet")
$|N| = |J_{AX} + J_{AX'}|$ ("*J*" of "doublet")

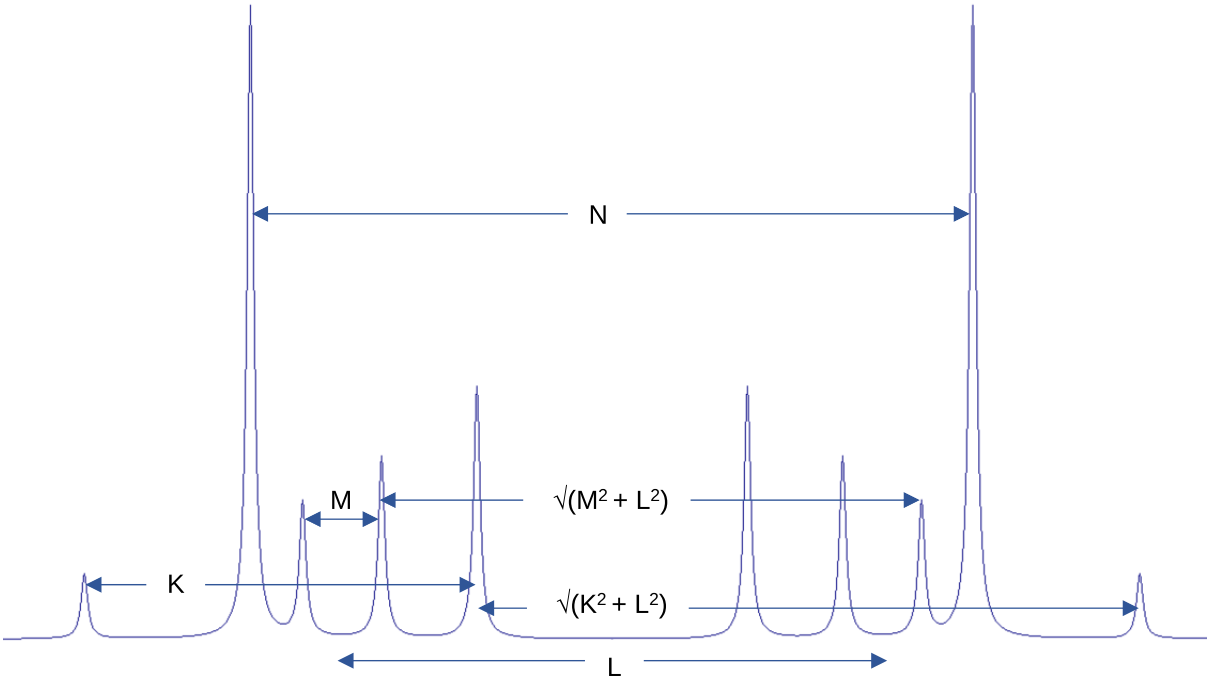


Figure 15: An ideal AA’XX’ half spectrum generated by WINDNMR 7.1.14 with $J_{AA'}$ 15.0 Hz, $J_{XX'}$ 10.0 Hz, J_{AX} 40.0 Hz and $J_{AX'}$ 6.0 Hz.

One of the most common AA’XX’ systems encountered in this thesis are *para*-disubstituted benzenes. An example half-spectrum of such a system is shown in Figure 16. In this half-spectrum 6 out of 10 lines are visible – one “doublet” and one AB quartet. The other “AB quartet” has merged with the peaks of the “doublet” and cannot be resolved. This is expected as the *“J”* value of this “AB quartet” is equal to $|J_{AA'} - J_{XX'}|$ which is small for most *para*-disubstituted benzenes. Taking the value of K, L and N measured from the spectrum as well as the approximate value of M, this gives the following system of simultaneous equations.

$|K| = |J_{AA'} + J_{XX'}| = 4.95 \text{ Hz}$

$|L| = |J_{AX} - J_{AX'}| = 8.13 \text{ Hz}$

$|M| = |J_{AA'} - J_{XX'}| \approx 0 \text{ Hz}$

$|N| = |J_{AX} + J_{AX'}| = 8.95 \text{ Hz}$

Solving this system of simultaneous equations gives the coupling constants:

$J_{AX} = 8.5$ Hz ($^3J_{HH}$, *ortho* coupling)

$J_{AA'} \approx J_{XX'} \approx 2.5$ Hz ($^4J_{HH}$, *meta* coupling)

$J_{AX'} = 0.4$ Hz ($^5J_{HH}$, *para* coupling)

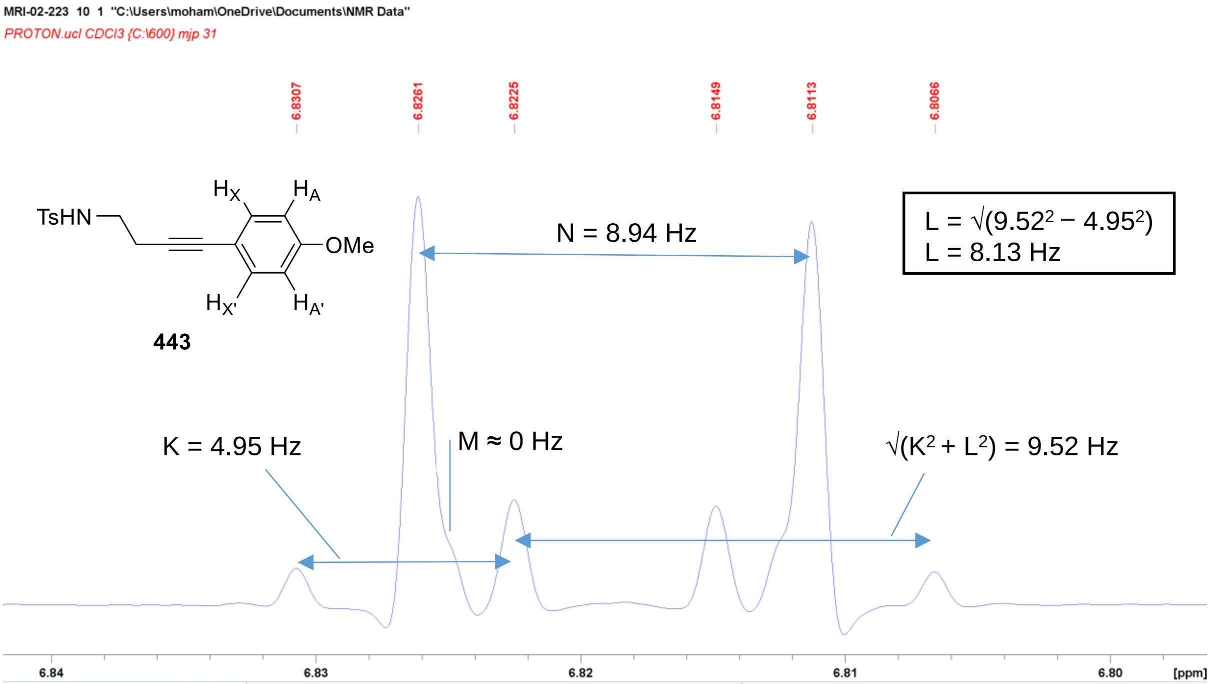


Figure 16: ^{1}H NMR (600 MHz, $CDCl_3$) of compound **443** showing the AA' part of the AA'XX' system of the anisyl group. Gaussian multiplication performed in TopSpin 4.0.8 (LB = −0.6 Hz, GB = 0.4) was used to reduce the line width.

Figure 17 shows an AA'MM'X system encountered during the thesis. The MM' part of the spectrum is shown. The half-spectrum still consists of a "doublet" and two "AB quartets", but each peak is split by coupling with X giving a spectrum consisting of 10 doublets. The location of each of the 10 doublets is marked with a red line in Figure 17. Once the 10 doublets have been identified, the values of K, L, M and N can be measured from the spectrum as before, giving the following set of simultaneous equations:

$$|K| = |J_{AA'} + J_{MM'}| = 30.73 \text{ Hz}$$
$$|L| = |J_{AM} - J_{AM'}| = 3.56 \text{ Hz}$$
$$|M| = |J_{AA'} - J_{MM'}| = 2.12 \text{ Hz}$$
$$|N| = |J_{AM} + J_{AM'}| = 14.91 \text{ Hz}$$

Solving this system of simultaneous equations gives the coupling constants:

$J_{AA'}/J_{MM'}$ = 16.4, 14.3 Hz ($^2J_{HH}$, geminal couplings)
J_{AM} = 9.2 Hz ($^3J_{HH}$, vicinal coupling)
$J_{AM'}$ = 5.7 Hz ($^3J_{HH}$, vicinal coupling)
plus, $J_{MX}/J_{M'X}$ = 2.7 Hz ($^4J_{HH}$, measured directly from the spectrum)

Note that it is not possible to assign which geminal coupling belongs to which pair of protons based solely on the spectrum.

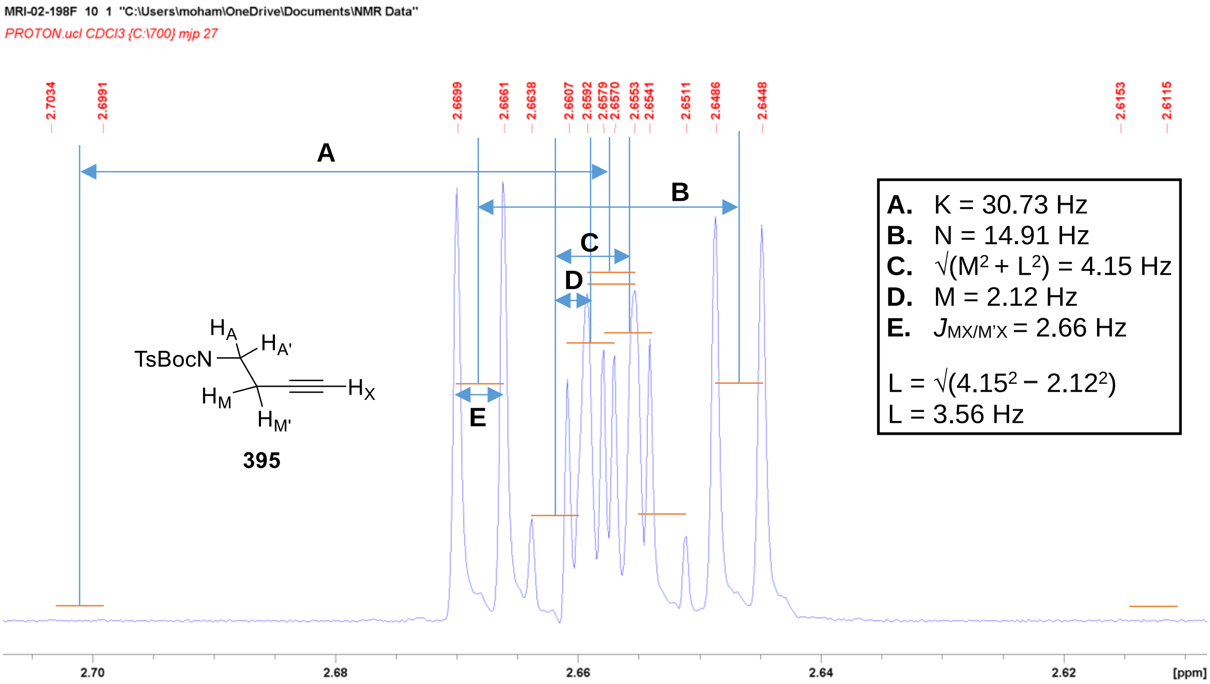
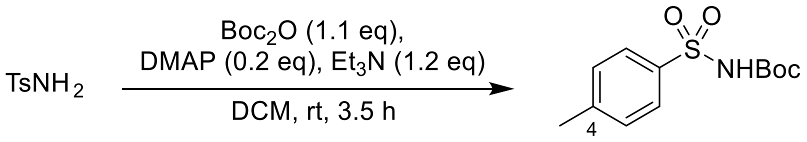


Figure 17: ^{1}H NMR (700 MHz, $CDCl_3$) of compound **395** showing the MM' part of the AA'MM'X system. Gaussian multiplication performed in TopSpin 4.0.8 (LB = −0.5 Hz, GB = 0.6) was used to reduce the line width. The outermost peaks are extremely roofed (I_{A1}:I_{A2} ≈ 1:330) and not visible at this scale.

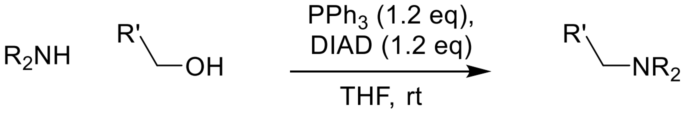
7.1.1. *tert*-Butyl *p*-toluenesulfonylcarbamate (394)



393 **394**

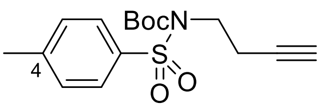
According to the procedure of Neustadt,[144] modified: $TsNH_2$ (3.42 g, 19.6 mmol) and DMAP (0.491 g, 3.98 mmol) were suspended in anhydrous DCM (25 mL) and Et_3N (3.33 mL, 24 mmol) added. To this mixture a previously prepared solution of Boc_2O (5.0 mL, 21 mmol) in anhydrous DCM (40 mL) was added over 5 min. The appearance of the mixture changed to a colourless solution during the addition. After 3.5 h of stirring, the solvent was removed *in vacuo* and the residue suspended in EtOAc (120 mL). The suspension was washed with 1 M HCl (80 mL), H_2O (80 mL) and brine (80 mL). The organics were then dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude material was suspended in boiling hexane, and EtOAc was slowly added until a clear solution was obtained. The solution was cooled to effect crystallization giving carbamate **394** (4.236 g, 80%) as colourless prisms: m.p. 120–122 °C (lit.[144] 117–119 °C); ν_{max}/cm^{-1} (solid): 3213 (s, br, N─H stretch), 2975 (m, sp^3 C─H stretch), 2925 (w, sp^3 C─H stretch), 1745 (s, carbamate C═O stretch), 1594 (m, aryl C═C stretch), 1473 (w, aryl C═C stretch), 1431 (s), 1391 (m), 1368 (m), 1337 (s, S═O stretch), 1229 (s), 1142 (s, S═O stretch), 1085 (s), 1060 (m), 915 (s), 830 (s), 815 (s, 1,4-disubstituted benzene C─H bend), 735 (s), 575 (s), 536 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.38 (9H, s, $C(CH_3)_3$), 2.45 (3H, s, $ArCH_3$), 7.21 (1H, br s, NH), 7.31–7.35 (2H, m, ArH-3,5), 7.89 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 1.8 Hz, $J_{XX'}$ 1.8 Hz, $J_{AX'}$ 0.3 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 21.8 ($ArCH_3$), 28.0 ($C(\underline{C}H_3)_3$), 84.2 ($\underline{C}(CH_3)_3$), 128.4 (aryl C-2,6), 129.6 (aryl C-3,5), 136.1 (aryl C-1), 144.9 (aryl C-4), 149.1 (C═O); *m/z* (ESI): 565 ([2M +Na]$^+$, 100%), 294 ([M +Na]$^+$, 62), 238 ([M −*t*-Bu +Na +H]$^+$, 17); HRMS (ESI): [$C_{12}H_{17}NO_4S$ +Na]$^+$ (M$^+$ +Na) requires: 294.0770; found: 294.0773. NMR data consistent with literature.[177]

General Procedure 1: Mitsunobu Reaction



According to the procedure of Chan *et al.*,[145] modified: PPh_3 (1.2 eq), the appropriate amide (1.0 eq) and the appropriate alcohol (1.2 eq) were dissolved in anhydrous THF. The reaction mixture was cooled to 0 °C and DIAD (1.2 eq) was slowly added. After the addition was complete, the mixture was allowed to warm to rt, stirred for the time specified and solvent removed *in vacuo*. The crude residue was purified by flash column chromatography giving the desired product.

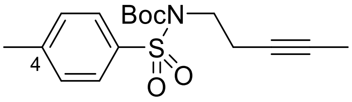
7.1.2. *tert*-Butyl but-3-yn-1-yl(*p*-toluenesulfonyl)carbamate (395)



395

Synthesized according to general procedure 1 using TsNHBoc (1.36 g, 5.02 mmol), PPh_3 (1.61 g, 6.07 mmol), 3-butyn-1-ol (0.45 mL, 5.8 mmol), DIAD (1.1 mL, 5.3 mmol) and anhydrous THF (4 mL) with a stirring time of 3.5 h. Purification by flash column chromatography (hexane/EtOAc 90:10) gave alkyne **395** (1.40 g, 86%) as a white solid: m.p. 81–83 °C; ν_{max}/cm^{-1} (solid): 3293 (s, sp C–H stretch), 2980 (m, sp^3 C–H stretch), 2928 (w, sp^3 C–H stretch), 1720 (s, carbamate C=O stretch), 1595 (m, aryl C=C stretch), 1449 (m), 1371 (m), 1354 (s, S=O stretch), 1326 (s), 1286 (m), 1272 (m), 1255 (m), 1165 (m), 1134 (s, S=O stretch), 1092 (m), 1075 (m), 969 (m), 808 (s, 1,4-disubstituted benzene C–H bend), 770 (m), 716 (s), 648 (s), 627 (s), 573 (s), 544 (s), 487 (s); ^{1}H NMR (700 MHz, CDCl$_3$): δ 1.32 (9H, s, C(CH$_3$)$_3$), 2.01 (1H, t, *J* 2.7 Hz, C≡CH), 2.44 (3H, s, ArCH$_3$), 2.66 (2H, MM' part of AA'MM'X system, $J_{AA'}/J_{MM'}$ 16.3, 14.3 Hz, J_{MA} 9.2 Hz, $J_{MA'}$ 5.7 Hz, $J_{MX}/J_{M'X}$ 2.7, 2.7 Hz, CH$_2$C≡C), 4.00 (2H, AA' part of AA'MM' system, $J_{AA'}/J_{MM'}$ 16.5, 14.2 Hz, J_{AM} 9.2 Hz, $J_{AM'}$ 5.7 Hz, NCH$_2$), 7.29–7.32 (2H, m, ArH-3,5), 7.80 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.3 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$): δ 20.1 ($\underline{C}H_2C\equiv C$), 21.8 (ArCH$_3$), 28.0 (C($\underline{C}H_3)_3$), 45.3 (NCH$_2$), 70.5 ($C\equiv\underline{C}H$), 80.6 ($\underline{C}\equiv CH$), 84.7 ($\underline{C}(CH_3)_3$), 128.0 (aryl C-2,6), 129.4 (aryl C-3,5), 137.4 (aryl C-1), 144.4 (aryl C-4), 150.9 (C=O); *m/z* (ESI): 671 (20%), 670 (43), 669 (88), 324 ([M +H]$^+$, 3), 270 (15), 269 (29), 268 (100); HRMS (ESI): [$C_{16}H_{21}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 324.1270; found: 324.1269. NMR data consistent with literature.[178]

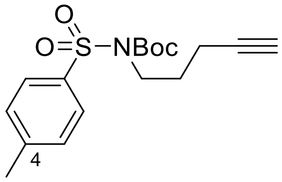
7.1.3. *tert*-Butyl pent-3-yn-1-yl(*p*-toluenesulfonyl)carbamate (490)



490

Synthesized according to general procedure 1 using TsNHBoc (0.952 g, 3.51 mmol), PPh$_3$ (0.924 g, 3.49 mmol), 3-pentyn-1-ol (0.30 mL, 3.25 mmol), DIAD (0.69 mL, 3.3 mmol) and anhydrous THF (12 mL) with a stirring time of 5 days. Purification by flash column chromatography (hexane/EtOAc 92:8) gave alkyne **490** (0.521 g, 48%) as a pale yellow solid: m.p. 120–122 °C; ν_{max}/cm^{-1} (solid): 2980 (w, sp^3 C–H stretch), 2914 (w, sp^3 C–H stretch), 2851 (w, sp^3 C–H stretch), 1716 (s, carbamate C=O stretch), 1594 (w, aryl C=C stretch), 1492 (w, aryl C=C stretch), 1436 (w), 1354 (s, S=O stretch), 1283 (m), 1153 (s, S=O stretch), 1132 (m), 1087 (s), 965 (s), 850 (m), 815 (m, 1,4-disubstituted benzene C–H bend), 770 (m), 739 (m), 671 (s), 573 (s), 541 (s); ^{1}H NMR (700 MHz, CDCl$_3$): δ 1.34 (9H, s, C(CH$_3$)$_3$), 1.76 (3H, t, *J* 2.6 Hz, C≡CCH$_3$), 2.44 (3H, s, ArCH$_3$), 2.58 (2H, tq, *J* 7.5, 2.5 Hz, $NCH_2C\underline{H_2}$), 3.95 (2H, t, *J* 7.5 Hz, NC$\underline{\text{H}}_2$CH$_2$), 7.28–7.31 (2H, m, ArH-3,5), 7.81 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{\text{AA'}}$ 2.0 Hz, $J_{\text{XX'}}$ 2.0 Hz, $J_{\text{AX'}}$ 0.4 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$): δ 3.6 (C≡C$\underline{\text{C}}$H$_3$), 20.4 ($\underline{\text{C}}$H$_2$C≡C), 21.7 (ArCH$_3$), 28.0 (C($\underline{\text{C}}$H$_3$)$_3$), 45.9 (NCH$_2$), 75.4 ($\underline{\text{C}}$≡CCH$_3$), 78.0 (C≡$\underline{\text{C}}$CH$_3$), 84.4 ($\underline{\text{C}}$(CH$_3$)$_3$), 128.0 (aryl C-2,6), 129.4 (aryl C-3,5), 137.6 (aryl C-1), 144.2 (aryl C-4), 150.9 (C═O); *m/z* (ESI): 360 (20%), 338 ([M +H]$^+$, 10), 294 (12), 282 ([M −*t*-Bu +2H]$^+$, 100), 238 ([M −Boc +2H]$^+$, 42). NMR data consistent with literature.[177]

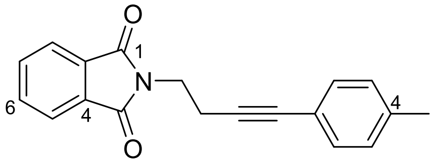
7.1.4. *tert*-Butyl pent-4-yn-1-yl(*p*-toluenesulfonyl)carbamate (493)



493

Synthesized according to general procedure 1 using TsNHBoc (1.211 g, 4.48 mmol), PPh$_3$ (1.298 g, 4.95 mmol), 4-pentyn-1-ol (0.46 mL, 4.9 mmol), DIAD (0.97 mL, 4.9 mmol) and anhydrous THF (25 mL) with a stirring time of 3 h. Purification by flash column chromatography (hexane/EtOAc 90:10) gave alkyne **493** (1.393 g, 92%) as a white solid: m.p. 102.8–103.7 °C (lit.[179] 97.4–100.6 °C); ν_{max}/cm^{-1} (solid): 3274 (s, sp C─H stretch), 2979 (w, sp^3 C─H stretch), 2955 (w, sp^3 C─H stretch), 2925 (w, sp^3 C─H stretch), 1724 (s, carbamate C═O stretch), 1594 (w, aryl C═C stretch), 1491 (w, aryl C═C stretch), 1441 (m), 1392 (w), 1345 (s, S═O stretch), 1282 (s), 1151 (s, S═O stretch), 1103 (m), 1084 (m), 1003 (m), 959 (m), 839 (m), 814 (m, 1,4-disubstituted benzene C─H bend), 785 (m), 665 (s), 595 (s), 561 (s), 534 (s); ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.34 (9H, s, C(CH$_3$)$_3$), 1.96–2.02 (2H, m, CH$_2$C$\underline{\text{H}}_2$CH$_2$), 1.98 (1H, t, *J* 2.7 Hz, C≡CH), 2.28 (2H, td, *J* 7.1, 2.7 Hz, CH$_2$C≡C), 2.44 (3H, s, ArCH$_3$), 3.91 (2H, AA’ part of AA’XX’ system, $J_{\text{AA'}}/J_{\text{XX'}}$ 14.3, 13.1 Hz, J_{AX} 9.5 Hz, $J_{\text{AX'}}$ 5.5 Hz, NCH$_2$), 7.28–7.32 (2H, m, ArH-3,5), 7.78 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{\text{AA'}}$ 2.0 Hz, $J_{\text{XX'}}$ 2.0 Hz, $J_{\text{AX'}}$ 0.4 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ 16.2 ($\underline{\text{C}}$H$_2$C≡C), 21.8 (tosyl CH$_3$), 28.0 (C($\underline{\text{C}}$H$_3$)$_3$), 29.0 (CH$_2\underline{\text{C}}$H$_2$CH$_2$), 46.4 (NCH$_2$), 69.1 (C≡$\underline{\text{C}}$H), 83.2 ($\underline{\text{C}}$≡CH), 84.4 ($\underline{\text{C}}$(CH$_3$)$_3$), 128.0 (aryl C-2,6), 129.4 (aryl C-3,5), 137.4 (aryl C-1), 144.3 (aryl C-4), 151.0 (C═O); *m/z* (ESI): 394 ([M +*t*-Bu]$^+$, 11%), 338 ([M +H]$^+$, 6), 282 ([M −*t*-Bu +2H]$^+$, 100), 238 ([M −Boc +H]$^+$, 33); HRMS (ESI): [$C_{17}H_{23}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 338.1421; found 338.1412. NMR data consistent with literature.[179]

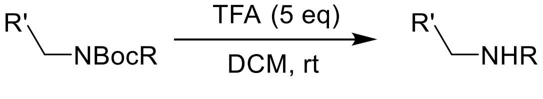
7.1.5. 2-(4-(*p*-Tolyl)but-3-yn-1-yl)isoindoline-1,3-dione (514)



514

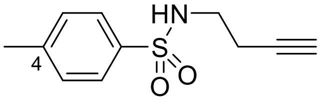
Synthesized according to general procedure 1 using phthalimide (0.573 g, 3.89 mmol), PPh_3 (1.123 g, 4.24 mmol), 4-(*p*-tolyl)-3-butyn-1-ol (0.562 g, 3.51 mmol), DIAD (0.75 mL, 3.8 mmol) and anhydrous THF (3 mL). Purification by flash column chromatography (hexane/EtOAc 100:0 → 85:15) gave alkyne **514** (0.473 g, 47%) as a pale yellow solid: m.p. 90–92 °C; ν_{max}/cm^{-1} (solid): 2959 (w, sp^3 C—H stretch), 2903 (w, sp^3 C—H stretch), 1768 (s, imide C═O stretch), 1701 (s, imide C═O stretch), 1614 (w, aryl C═C stretch), 1507 (m, aryl C═C stretch), 1466 (m, aryl C═C stretch), 1442 (m), 1431 (m), 1394 (s), 1359 (s), 1329 (m), 1115 (s), 1000 (s), 812 (m, 1,4-disubstituted benzene C—H bend), 763 (s), 722 (s), 713 (s), 523 (s); ^1H NMR (700 MHz, $CDCl_3$): δ 2.31 (3H, s, $ArCH_3$), 2.81 (2H, t, *J* 7.1 Hz, $NCH_2C\underline{H_2}$), 3.96 (2H, t, *J* 7.2 Hz, $NC\underline{H_2}CH_2$), 7.04–7.07 (2H, m, tolyl H-3,5), 7.20–7.24 (2H, m, tolyl H-2,6), 7.70–7.74 (2H, m, phthalimide H-6,7), 7.85–7.88 (2H, m, phthalimide H-5,8); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 19.5 ($\underline{C}H_2C\equiv C$), 21.5 ($ArCH_3$), 37.0 ($NCH_2$), 82.5 ($CH_2C\equiv\underline{C}$), 85.1 ($CH_2\underline{C}\equiv C$),120.3 (tolyl C-1), 123.4 (phthalimide C-5,8), 129.1 (tolyl C-3,5), 131.6 (tolyl C-2,6), 132.2 (phthalimide C-4,9), 134.1 (phthalimide C-6,7), 138.0 (tolyl C-4), 168.2 (phthalimide C-1,3); *m/z* (ESI): 290 ($[M+H]^+$, 100%); HRMS (ESI): $[C_{19}H_{15}NO_2 + H]^+$ ($M^+ + H$) requires: 290.1176; found: 290.1174.

General Procedure 2: Boc Deprotection



This reaction was performed in air. Representative procedure for 5 mmol scale reaction: The protected amide (5 mmol) was dissolved in DCM (10 mL). TFA (25 mmol) was added and the mixture stirred for the time specified. The reaction mixture was then slowly added to saturated aq. $NaHCO_3$ (25 mL) at 0 °C. The organic layer was separated and the aqueous layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$ and solvent removed *in vacuo* giving the deprotected amide which used in subsequent steps without further purification.

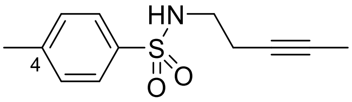
7.1.6. *N*-(But-3-yn-1-yl)-*p*-toluenesulfonamide (398)



398

Synthesized according to general procedure 2 using alkyne **395** (1.55 g, 4.79 mmol), TFA (1.8 mL, 23 mmol) and DCM (9 mL) with a stirring time of 18 h giving tosylamide **398** (0.806 g, 75%) as a pale yellow solid: m.p. 75–77 °C (lit.[180] 91–92 °C); ν_{max}/cm^{-1} (solid): 3265 (s, sp C—H stretch and N—H stretch), 2931 (w, sp^3 C—H stretch), 2908 (w, sp^3 C—H stretch), 2874 (w, sp^3 C—H stretch), 1594 (m, aryl C═C stretch), 1490 (w, aryl C═C stretch), 1466 (w, aryl C═C stretch), 1414 (m), 1311 (s, S═O stretch), 1300 (s), 1153 (s, S═O stretch), 1090 (s), 1067 (s), 924 (s), 813 (s, 1,4-disubstituted benzene C—H bend), 671 (s), 581 (s), 520 (s); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.00 (1H, t, *J* 2.6 Hz, C≡CH), 2.35 (2H, td, *J* 6.5, 2.6 Hz, $CH_2C{\equiv}C$), 2.43 (3H, s, $ArCH_3$), 3.11 (2H, q, *J* 6.5 Hz, NCH_2), 4.74 (1H, br s, NH), 7.30–7.34 (2H, m, ArH-3,5), 7.76 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, ArH-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 19.9 ($\underline{C}H_2C{\equiv}C$), 21.7 ($ArCH_3$), 41.7 ($NCH_2$), 71.0 ($C{\equiv}\underline{C}H$), 80.4 ($\underline{C}{\equiv}CH$), 127.2 (aryl C-2,6), 129.9 (aryl C-3,5), 137.1 (aryl C-1), 143.8 (aryl C-4); *m/z* (ESI): 246 ([M +Na]$^+$, 31%), 224 ([M +H]$^+$, 100), 214 (79), 174 (42); HRMS (ESI): $[C_{11}H_{13}NO_2S +H]^+$ (M^+ +H) requires: 224.0745; found: 224.0746. NMR data consistent with literature.[180]

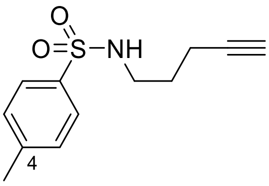
7.1.7. *N*-(Pent-3-yn-1-yl)-*p*-toluenesulfonamide (491)



491

Synthesized according to general procedure 2 using alkyne **490** (0.449 g, 1.33 mmol), TFA (0.50 mL, 6.5 mmol) and DCM (2.5 mL) with a stirring time of 4 h giving tosylamide **491** (0.241 g, 76%) as a pale yellow solid: m.p. 69–72 °C (lit.[181] 61–62 °C); ν_{max}/cm^{-1} (solid): 3249 (s, sp C—H stretch and N—H stretch), 2918 (m, sp^3 C—H stretch), 2866 (m, sp^3 C—H stretch), 1596 (m, aryl C═C stretch), 1491 (w, aryl C═C stretch), 1440 (m), 1419 (m), 1313 (s, S=O stretch), 1151 (s, S=O stretch), 1066 (s), 917 (s), 809 (s, 1,4-disubstituted benzene C—H bend), 688 (s), 572 (s), 548 (s), 512 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.74 (3H, t, *J* 2.5 Hz, $C{\equiv}CCH_3$), 2.27 (2H, tq, *J* 6.4, 2.5 Hz, $NCH_2C\underline{H_2}$), 2.43 (3H, s, $ArCH_3$), 3.04 (2H, q, *J* 6.4 Hz, $NC\underline{H_2}CH_2$), 4.73 (1H, br s, NH), 7.29–7.32 (2H, m, ArH-3,5), 7.75 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, ArH-2,6) ; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 3.6 ($C{\equiv}C\underline{C}H_3$), 20.0 ($\underline{C}H_2C{\equiv}C$), 21.7 ($ArCH_3$), 42.2 ($NCH_2$), 75.0 ($\underline{C}{\equiv}CCH_3$), 78.6 ($C{\equiv}\underline{C}CH_3$), 127.2 (aryl C-2,6), 129.9 (aryl C-3,5), 137.1 (aryl C-1), 143.6 (aryl C-4); *m/z* (ESI): 238 ([M +H]$^+$, 100%). NMR data consistent with literature.[182]

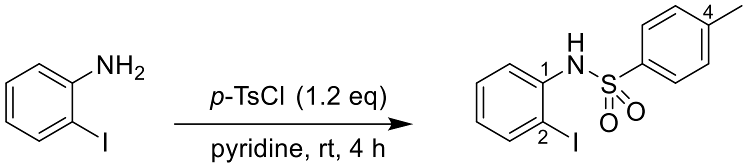
7.1.8. *N*-(Pent-4-yn-1-yl)-*p*-toluenesulfonamide (494)



494

Synthesized according to general procedure 2 using alkyne **493** (0.572 g, 1.70 mmol), TFA (0.65 mL, 8.5 mmol) and DCM (4 mL) with a stirring time of 2 h giving tosylamide **494** (0.346 g, 86%) as a white solid: m.p. 56.4–58.3 °C (lit.[183] 59–60 °C); ν_{max}/cm^{-1} (solid): 3270 (s, sp C—H stretch and N—H stretch), 2947 (w, sp^3 C—H stretch), 2925 (w, sp^3 C—H stretch), 2865 (w, sp^3 C—H stretch), 1595 (m, aryl C=C stretch), 1490 (w, aryl C=C stretch), 1444 (m), 1423 (m), 1316 (s, S=O stretch), 1299 (s), 1236 (s), 1151 (s, S=O stretch), 1086 (s), 1074 (s), 945 (m), 812 (s, 1,4-disubtituted benzene C—H bend), 665 (s), 570 (s), 549 (s), 505 (m); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.69 (2H, quint, *J* 6.8 Hz, $CH_2C\underline{H_2}CH_2$), 1.95 (1H, t, *J* 2.7 Hz, $C{\equiv}CH$), 2.22 (2H, td, *J* 6.8, 2.7 Hz, $CH_2C{\equiv}C$), 2.43 (3H, s, $ArCH_3$), 3.08 (2H, q, *J* 6.6 Hz, NCH_2), 4.50 (1H, t, *J* 6.4 Hz, NH), 7.30–7.33 (2H, m, ArH-3,5), 7.75 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, ArH-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 15.9 ($\underline{C}H_2C{\equiv}C$), 21.7 ($CH_3$), 28.2 ($CH_2\underline{C}H_2CH_2$), 42.3 ($NHCH_2$), 69.7 ($C{\equiv}\underline{C}H$), 83.0 ($\underline{C}{\equiv}CH$), 127.2 (aryl C-2,6), 129.9 (aryl C-3,5), 137.0 (aryl C-1), 143.6 (aryl C-4); m/z (ESI): 238 ([M +H]$^+$, 100%), 65 (25); HRMS (ESI): $[C_{12}H_{15}NO_2S +H]^+$ (M^+ +H) requires: 238.0896; found 238.0895. NMR data consistent with literature.[183]

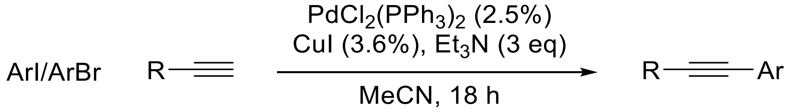
7.1.9. *N*-(2-Iodophenyl)-*p*-toluenesulfonamide (441)



519 **441**

According to the procedure of Zhdankin *et al.*[184], modified. This reaction was performed in air. 2-Iodoaniline (**519**, 0.649 g, 2.96 mmol) was dissolved in pyridine (8 mL). Under stirring *p*-TsCl (0.69 g, 3.6 mmol) was added to the reaction mixture in several portions. After 4 h of stirring the reaction was quenched by slowly pouring the reaction mixture onto 10% w/w aq. HCl (90 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with 10% aq. HCl (90 mL), sat. aq. $NaHCO_3$ (90 mL) and H_2O (90 mL), dried over $MgSO_4$, filtered and solvent removed *in vacuo* giving sulfonamide **441** as an off-white solid (0.816 g, 73%): m.p. 90.9–92.5 °C (lit.[184] 90–92 °C); ν_{max}/cm^{-1} (solid): 3280 (s, N─H stretch), 3063 (w, sp^2 C─H stretch), 2919 (w, sp^3 C─H stretch), 1591 (m, aryl C═C stretch), 1580 (m, aryl C═C stretch), 1470 (w, aryl C═C stretch), 1441 (s), 1391 (m), 1327 (s, S═O stretch), 1154 (s, S═O stretch), 1085 (s), 1012 (s), 908 (s), 816 (s, 1,4-disubstituted benzene C─H bend), 754 (s, 1,2-disubstituted benzene C─H bend), 708 (s), 659 (s), 647 (s), 620 (s), 562 (s), 541 (s), 522 (s); ^1H NMR (600 MHz, $CDCl_3$): δ 2.38 (3H, s, $ArCH_3$), 6.79 (1H, br s, NH), 6.82 (1H, ddd, *J* 8.0, 7.3, 1.6 Hz, aryl H-4) , 7.19–7.23 (2H, m, tosyl H-3,5), 7.30 (1H, dddd, *J* 8.1, 7.4, 1.5, 0.6 Hz, aryl H-5), 7.62 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6), 7.64 (1H, dd, *J* 8.0, 1.4 Hz, aryl H-3), 7.65 (1H, dd, *J* 8.2, 1.5 Hz, aryl H-6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.8 (tosyl CH_3), 92.5 (aryl C-2), 122.6 (aryl C-6), 127.0 (aryl C-4), 127.6 (tosyl C-2,6), 129.7 (aryl C-5), 129.8 (tosyl C-3,5), 136.0 (tosyl C-1), 137.6 (aryl C-1), 139.2 (aryl C-3), 144.4 (tosyl C-4); *m/z* (ESI): 374 ($[M +H]^+$, 30%), 247 ($[M -I +H]^{\bullet+}$, 100), 219 ($[M -Ts +H]^{\bullet+}$, 15), 182 ($[M -I -SO_2]^+$, 12); HRMS (ESI): $[C_{13}H_{12}INO_2S +H]^+$ (M^+ +H) requires: 373.9706; found 373.9709. NMR data consistent with literature.[185]

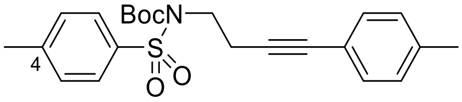
General Procedure 3: Sonogashira Coupling



General Procedure 3A: According to the procedure of Sridharan *et al.*,[146] modified. The appropriate alkyne (1.0 eq), aryl halide (1.1 eq), $PdCl_2(PPh_3)_2$ (2.5%), CuI (3.6%) were all dissolved in anhydrous MeCN (0.4 M). Et_3N (3 eq) was added. The reaction was stirred for 18 h and filtered through celite, washing with EtOAc. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography giving the Sonogashira-coupled product.

General Procedure 3B: According to the procedure of Sridharan *et al.*,[146] modified. The appropriate alkyne (1.0 eq), aryl halide (1.1 eq), $PdCl_2(PPh_3)_2$ (2.5%), CuI (3.6%) were all dissolved in anhydrous MeCN (0.4 M). The reaction mixture was heated to 50 °C and Et_3N (3 eq) was added. The reaction was stirred for 18 h, allowed to cool and filtered through celite, washing with EtOAc. The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography giving the Sonogashira-coupled product.

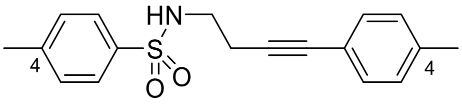
7.1.10. *tert*-Butyl (*p*-toluenesulfonyl)(4-(*p*-tolyl)but-3-yn-1-yl)carbamate (396)



396

Synthesized according to general procedure 3A using alkyne **395** (0.642 g, 1.98 mmol), 4-iodotoluene (0.480 g, 2.20 mmol), $PdCl_2(PPh_3)_2$ (34 mg, 0.048 mmol), CuI (15 mg, 0.078 mmol), Et_3N (0.85 mL, 6.1 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc 100:0 → 90:10) gave alkyne **396** (0.669 g, 82%) as a white solid: m.p. 110–111 °C; ν_{max}/cm^{-1} (solid): 2972 (w, sp^3 C–H stretch), 2921 (w, sp^3 C–H stretch), 1723 (s, carbamate C=O stretch), 1595 (w, aryl C=C stretch), 1509 (w, aryl C=C stretch), 1443 (w), 1394 (w), 1368 (m), 1345 (s, S=O stretch), 1328 (m), 1291 (m), 1279 (m), 1163 (s), 1141 (s, S=O stretch), 1091 (s), 975 (m), 813 (s, 1,4-disubstituted benzene C–H bend), 768 (m), 718 (s), 663 (s), 569 (s), 546 (s); ^1H NMR (700 MHz, $CDCl_3$): δ 1.33 (9H, s, $C(CH_3)_3$), 2.33 (3H, s, tolyl CH_3), 2.42 (3H, s, tosyl CH_3), 2.86 (2H, t, *J* 7.3 Hz, $CH_2C≡C$), 4.08 (2H, t, *J* 7.3 Hz, NCH_2), 7.06–7.09 (2H, m, tolyl H-3,5), 7.24–7.27 (2H, m, tolyl H-2,6), 7.26–7.29 (2H, m, tosyl H-3,5), 7.82–7.85 (2H, m, tosyl H-2,6); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$): δ 21.0 ($\underline{C}H_2C{\equiv}C$), 21.6 (tolyl CH_3), 21.7 (tosyl CH_3), 28.0 ($C(\underline{C}H_3)_3$), 45.5 (NCH_2), 82.7 ($CH_2C{\equiv}\underline{C}$), 84.6 ($\underline{C}(CH_3)_3$), 85.4 ($CH_2\underline{C}{\equiv}C$), 120.5 (tolyl C-1), 128.1 (tosyl C-2,6), 129.0 (tolyl C-3,5), 129.4 (tosyl C-3,5), 131.7 (tolyl C-2,6), 137.5 (tosyl C-1), 138.0 (tolyl C-4), 144.3 (tosyl C-4), 150.9 (C=O); *m/z* (ESI): 849 (65%), 844 (99), 431 (28), 414 ($[M + H]^+$, 2), 315 (35), 314 ($[M - Boc + 2H]^+$, 100); HRMS (ESI): $[C_{23}H_{27}NO_4S + H]^+$ ($M^+ + H$) requires: 414.1739; found: 414.1736.

7.1.11. *N*-(4-(*p*-Tolyl)but-3-yn-1-yl)-*p*-toluenesulfonamide (392)

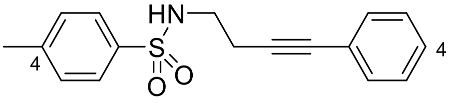


392

Synthesized according to general procedure 3A using alkyne **398** (0.448 g, 2.01 mmol), 4-iodotoluene (0.480 g, 2.20 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.050 mmol), CuI (20 mg, 0.10 mmol), Et_3N (0.84 mL, 6.0 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc 100:0 → 80:20) gave alkyne **392** (0.629 g, 100%) as a slightly impure yellow solid, which was recrystallized from hexane/EtOAc to give alkyne **1** (0.452 g, 72%) as reflective white sheets: m.p. 92–94 °C (lit.[186] 88–89 °C); ν_{max}/cm^{-1} (solid): 3273 (s, N–H stretch), 3022 (w, sp^2 C–H stretch), 2908 (w, sp^3 C–H stretch), 2857 (w, sp^3 C–H stretch), 2233 (w, C≡C stretch), 1593 (w, aryl C=C stretch), 1507 (m, aryl C=C stretch), 1490 (w, aryl C=C stretch), 1453 (m), 1423 (m), 1335 (m), 1313 (s, S=O stretch), 1149 (s, S=O stretch), 1074 (s), 1036 (m), 924 (m), 811 (s, 1,4-disubstituted benzene C–H bend), 781 (m), 658 (s), 549 (s), 520 (m); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.34 (3H, s, tolyl CH_3), 2.41 (3H, s, tosyl CH_3), 2.55 (2H, t, *J* 6.6 Hz, $CH_2C{\equiv}C$), 3.18 (2H, q, *J* 6.5 Hz, NCH_2), 4.90 (1H, t, *J* 6.2 Hz, NH), 7.07–7.11 (2H, m, tolyl H-3,5), 7.24 (2H, AA' part of AA'XX' system, J_{AX} 7.7 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6), 7.27–7.31 (2H, m, tosyl H-3,5), 7.77 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$): δ 20.8 ($\underline{C}H_2C{\equiv}C$), 21.6 (tolyl CH_3), 21.7 (tosyl CH_3), 42.1 (NCH_2), 83.1 ($CH_2C{\equiv}\underline{C}$), 84.9 ($CH_2\underline{C}{\equiv}C$), 119.9 (tolyl C-1), 127.2 (tosyl C-2,6), 129.2 (tolyl C-3,5), 129.9 (tosyl C-3,5), 131.7 (tolyl C-2,6), 137.1 (tosyl C-1), 138.3 (tolyl C-4), 143.7 (tosyl C-4); *m/z* (ESI): 336 ($[M + Na]^+$, 22%), 314

([M +H]$^+$, 51), 225 (19), 214 (100), 165 (22); HRMS (ESI): [$C_{18}H_{19}NO_2S$ +H]$^+$ (M$^+$ +H) requires: 314.1215; found: 314.1215. NMR data consistent with literature.[186]

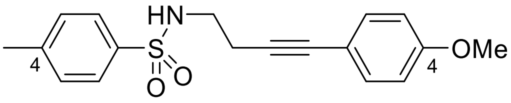
7.1.12. *N*-(4-Phenylbut-3-yn-1-yl)-*p*-toluenesulfonamide (442)



442

Synthesized according to general procedure 3A using alkyne **398** (0.336 g, 1.50 mmol), iodobenzene (185 µL, 1.65 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.04 mmol), CuI (20 mg, 0.11 mmol), Et_3N (0.63 mL, 4.5 mmol) and anhydrous MeCN (4 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **442** (0.330 g, 73%) as a yellow solid: m.p. 92.8–94.2 °C (lit.[146] 91–92 °C); ν_{max}/cm^{-1} (solid): 3284 (s, N—H stretch), 3054 (w, sp^2 C—H stretch), 3020 (w, sp^2 C—H stretch), 2919 (w, sp^3 C—H stretch), 1595 (m, aryl C═C stretch), 1487 (m, aryl C═C stretch), 1456 (w), 1422 (m), 1337 (m, S═O stretch), 1312 (m), 1301 (m), 1151 (s, S═O stretch), 1076 (s), 919 (s), 814 (s, 1,4-disubstituted benzene C—H bend), 784 (m), 749 (s, monosubstituted benzene C—H bend), 687 (s, monosubstituted benzene C—H bend), 660 (s), 546 (s); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.42 (3H, s, $ArCH_3$), 2.58 (2H, t, *J* 6.5 Hz, $CH_2C{\equiv}C$), 3.20 (2H, q, *J* 6.5 Hz, $NHC\underline{H_2}$), 4.72 (1H, br t, *J* 6.1 Hz, NH), 7.27–7.32 (5H, m, tosyl H-3,5 and phenyl H-3,4,5), 7.33–7.37 (2H, m, phenyl H-2,6), 7.77 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 20.9 ($\underline{C}H_2C{\equiv}C$), 21.7 ($ArCH_3$), 42.0 ($NHCH_2$), 83.1 ($CH_2C{\equiv}\underline{C}$), 85.6 ($CH_2\underline{C}{\equiv}C$), 123.0 (phenyl C-1), 127.2 (tosyl C-2,6), 128.3 (phenyl C-4), 128.4 (phenyl C-3,5), 129.9 (tosyl C-3,5), 131.8 (phenyl C-2,6), 137.1 (tosyl C-1), 143.7 (tosyl C-4); *m/z* (ESI): 317 ([M +NH_4]$^+$, 10%), 300 ([M +H]$^+$, 100), 160 ([M −Ts −H +OH]$^+$, 17); HRMS (ESI): [$C_{17}H_{17}NO_2S$ +H]$^+$ (M$^+$ +H) requires: 300.1053; found: 300.1053. NMR data consistent with literature.[146]

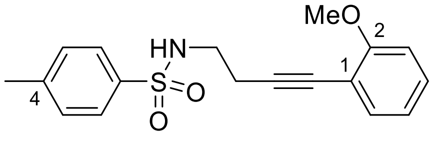
7.1.13. *N*-(4-(4-Methoxyphenyl)but-3-yn-1-yl)-*p*-toluenesulfonamide (443)



443

Synthesized according to general procedure 3A using alkyne **398** (0.662 g, 2.96 mmol), 4-iodoanisole (0.777 g, 3.32 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (20 mg, 0.11 mmol), Et_3N (1.3 mL, 9 mmol) and anhydrous MeCN (8 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20) gave alkyne **443** (0.806 g, 83%) as a yellow solid: m.p. 92.1–92.6 °C (lit.[187] 89–90 °C); ν_{max}/cm^{-1} (solid): 3277 (s, N—H stretch), 3021 (w, sp^2 C—H stretch), 2992 (w, sp^3 C—H stretch), 2954 (w, sp^3 C—H stretch), 2905 (w, sp^3 C—H stretch), 2832 (w, sp^3 C—H stretch), 1601 (m, aryl C=C stretch), 1568 (w, aryl C=C stretch), 1504 (s, aryl C=C stretch), 1457 (m), 1425 (m), 1338 (w, S=O stretch), 1313 (m), 1301 (m), 1285 (s), 1239 (s), 1150 (s, S=O stretch), 1076 (s), 1033 (s), 1014 (s), 920 (s), 828 (s, 1,4-disubstituted benzene C—H bend), 813 (s, 1,4-disubstituted benzene C—H bend), 781 (m), 661 (s), 547 (s); ^1H NMR (600 MHz, $CDCl_3$): δ 2.42 (3H, s, $ArCH_3$), 2.55 (2H, t, *J* 6.5 Hz, $CH_2C{\equiv}C$), 3.17 (2H, q, *J* 6.4 Hz, $NHC\underline{H_2}$), 3.80 (3H, s, OCH_3), 4.79 (1H, br t, *J* 6.2 Hz, NH), 6.81 (2H, AA' part of AA'XX' system, J_{AX} 8.4 Hz, $J_{AA'}$ 2.5 Hz, $J_{XX'}$ 2.5 Hz, $J_{AX'}$ 0.4 Hz, aryl H-3,5), 7.28 (2H, XX' part of AA'XX' system, J_{AX} 8.4 Hz, $J_{AA'}$ 2.5 Hz, $J_{XX'}$ 2.5 Hz, $J_{AX'}$ 0.4 Hz, aryl H-2,6), 7.29–7.31 (2H, m, tosyl H-3,5), 7.77 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 20.8 ($\underline{C}H_2C{\equiv}C$), 21.7 (tosyl CH_3), 42.1 ($\underline{C}H_2NH$), 55.4 (OCH_3), 82.9 ($CH_2C{\equiv}\underline{C}$), 84.0 ($CH_2\underline{C}{\equiv}C$), 114.0 (aryl C-3,5), 115.1 (aryl C-1), 127.3 (tosyl C-2,6), 129.9 (tosyl C-3,5), 133.2 (aryl C-2,6), 137.1 (tosyl C-1), 143.7 (tosyl C-4), 159.6 (aryl C-4); *m/z* (ESI): 330 ($[M+H]^+$, 100%), 190 ($[M-Ts-H+OH]^+$, 19); HRMS (ESI): $[C_{18}H_{19}NO_3S+H]^+$ (M^++H) requires: 330.1158; found: 330.1158. NMR data consistent with literature.[187]

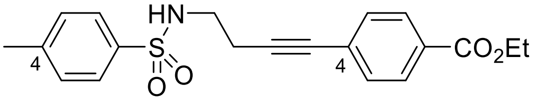
7.1.14. *N*-(4-(2-Methoxyphenyl)but-3-yn-1-yl)-*p*-toluenesulfonamide (444)



444

Synthesized according to general procedure 3A using alkyne **398** (0.335 g, 1.50 mmol), 2-iodoanisole (215 µL, 1.65 mmol), $PdCl_2(PPh_3)_2$ (27 mg, 0.04 mmol), CuI (13 mg, 0.07 mmol), Et_3N (0.63 mL, 4.5 mmol) and anhydrous MeCN (4 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **444** (0.409 g, 83%) as a green oil: ν_{max}/cm^{-1} (oil): 3262 (s, br, N—H stretch), 3057 (w, sp^2 C—H stretch), 2941 (w, sp^3 C—H stretch), 2836 (w, sp^3 C—H stretch), 1672 (w, N─H bend), 1596 (m, aryl C═C stretch), 1571 (w, aryl C═C stretch), 1489 (m, aryl C═C stretch), 1461 (m), 1433 (m), 1324 (m, S═O stretch), 1252 (m), 1153 (s, S═O stretch), 1091 (m), 1010 (m), 813 (m, 1,4-disubstituted benzene C─H bend), 754 (m, 1,2-disubstituted benzene C─H bend), 732 (m), 680 (m), 659 (m), 549 (s); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.41 (3H, s, $ArCH_3$), 2.52 (2H, t, *J* 6.2 Hz, $CH_2C{\equiv}C$), 3.20 (2H, q, *J* 6.3 Hz, $NHC\underline{H_2}$), 3.96 (3H, s, OCH_3), 5.36 (1H, br t, *J* 6.2 Hz, NH), 6.88–6.91 (2H, m, aryl H-3,5), 7.27–7.29 (2H, m, tosyl H-3,5), 7.28–7.32 (2H, m, aryl H-4,6) , 7.78 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 20.7 ($\underline{C}H_2C{\equiv}C$), 21.6 (tosyl CH_3), 41.8 ($NHCH_2$), 55.9 (OCH_3), 80.3 ($CH_2C{\equiv}\underline{C}$), 90.2 ($CH_2\underline{C}{\equiv}C$), 110.6 (aryl C-3), 112.0 (aryl C-1), 120.6 (aryl C-5), 127.2 (tosyl C-2,6), 129.8 (aryl C-4), 129.9 (tosyl C-3,5), 132.7 (aryl C-6), 137.4 (tosyl C-1), 143.5 (tosyl C-4), 160.4 (aryl C-2); *m/z* (ESI): 330 ($[M+H]^+$, 100%), 279 (10), 172 ($TsNH_3^+$, 62), 155 (Ts^+, 12); HRMS (ESI): $[C_{18}H_{19}NO_3S+H]^+$ (M^+ +H) requires: 330.1158; found: 330.1158. NMR data consistent with literature.[187]

7.1.15. Ethyl 4-(4-(*p*-tolylsulfonamido)but-1-yn-1-yl)benzoate (445)

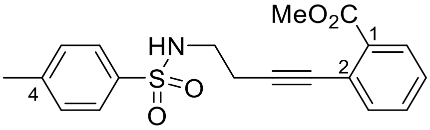


445

Synthesized according to general procedure 3A using alkyne **398** (0.336 g, 1.50 mmol), ethyl 4-bromobenzoate (0.27 mL, 1.65 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.04 mmol), CuI (11 mg, 0.06 mmol), Et_3N (0.63 mL, 4.5 mmol) and anhydrous MeCN (4 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **445** (0.412 g, 74%) as a light yellow solid: m.p. 93.1–93.4 °C; ν_{max}/cm^{-1} (solid): 3269 (s, N─H stretch), 2980 (w, sp^3 C─H stretch), 2908 (w, sp^3 C─H stretch), 2232 (w, C≡C stretch), 1711 (s, aromatic ester C═O stretch), 1602 (m, aryl C═C stretch), 1508 (w, aryl C═C stretch), 1492 (w, aryl C═C stretch), 1457 (m, aryl C═C stretch), 1447 (m), 1423 (m), 1335 (m, S═O stretch), 1312 (m), 1263 (s), 1149 (s, S═O stretch), 1077 (s), 925 (m), 856 (m), 810 (m, 1,4-disubstituted benzene C─H bend), 782 (m), 768 (s), 658 (s), 550 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.39 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H_3}$), 2.42 (3H, s, $ArCH_3$), 2.61 (2H, t, *J* 6.5 Hz, $CH_2C{\equiv}C$), 3.21 (2H, q, *J* 6.3 Hz, $NHC\underline{H_2}$), 4.37 (2H, q, *J* 7.1 Hz, OCH_2), 4.73 (1H, br t, *J* 6.1 Hz, NH), 7.29–7.32 (2H, m, tosyl H-3,5), 7.40 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz,

$J_{AX'}$ 0.4 Hz, aryl H-3,5), 7.77 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6), 7.97 (2H, XX' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, aryl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 14.5 ($OCH_2\underline{C}H_3$), 21.1 ($\underline{C}H_2C{\equiv}C$), 21.7 (tosyl CH_3), 41.9 ($NHCH_2$), 61.3 (OCH_2), 82.4 ($CH_2C{\equiv}\underline{C}$), 88.9 ($CH_2\underline{C}{\equiv}C$), 127.2 (tosyl C-2,6), 127.6 (aryl C-4), 129.6 (aryl C-2,6), 129.96 (tosyl C-3,5), 129.99 (aryl C-1), 131.7 (aryl C-3,5), 137.1 (tosyl C-1), 143.8 (tosyl C-4), 166.2 (C═O); *m/z* (ESI): 372 ([M +H]$^+$, 100%) 232 ([M −Ts −H +OH]$^+$, 18), 187 (21); HRMS (ESI): $[C_{20}H_{21}NO_4S +H]^+$ (M^+ +H) requires: 372.1264; found: 372.1262.

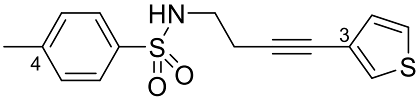
7.1.16. Methyl 2-(4-(*p*-tolylsulfonamido)but-1-yn-1-yl)benzoate (446)



446

Synthesized according to general procedure 3B using alkyne **398** (0.445 g, 1.99 mmol), methyl 2-bromobenzoate (0.30 mL, 2.1 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.05 mmol), CuI (17 mg, 0.09 mmol), Et_3N (0.83 mL, 6.0 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **446** (0.386 g, 54%) as a light yellow solid: m.p. 75.1–76.2 °C; ν_{max}/cm^{-1} (solid): 3246 (s, N─H stretch), 2946 (w, sp^3 C─H stretch), 1716 (s, aryl ester C═O stretch), 1593 (m, aryl C═C stretch), 1564 (m, aryl C═C stretch), 1484 (m, aryl C═C stretch), 1459 (w), 1426 (s), 1327 (s, S═O stretch), 1275 (s), 1253 (s), 1158 (s, S═O stretch), 1088 (s), 1074 (s), 932 (s), 814 (s, 1,4-disubstituted benzene C─H stretch), 751 (s, 1,2-disubstituted benzene C─H stretch), 690 (s), 548 (s); ^1H NMR (600 MHz, $CDCl_3$): δ 2.40 (3H, s, $ArCH_3$), 2.58 (2H, t, *J* 5.9 Hz, $CH_2C{\equiv}C$), 3.22 (2H, q, *J* 6.1 Hz, $NHC\underline{H_2}$), 3.98 (3H, s, OCH_3), 6.43 (1H, br t, *J* 6.6 Hz, NH), 7.26–7.28 (2H, m, tosyl H-3,5), 7.35 (1H, ddd, *J* 7.9, 5.7, 3.2 Hz, aryl H-5), 7.44–7.48 (2H, m, aryl H-3,4), 7.85 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.5 Hz, tosyl H-2,6), 7.97 (1H, ddd, *J* 7.9, 1.1, 0.8 Hz, aryl H-6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.0 ($\underline{C}H_2C{\equiv}C$), 21.7 ($ArCH_3$), 42.2 ($NHCH_2$), 52.8 ($OCH_3$), 82.2 ($CH_2C{\equiv}\underline{C}$), 92.3 ($CH_2\underline{C}{\equiv}C$), 124.2 (aryl C-2), 127.3 (tosyl C-2,6), 127.9 (aryl C-5), 129.7 (tosyl C-3,5), 130.6 (aryl C-6), 131.5 (aryl C-1), 132.2 (aryl C-4), 133.7 (aryl C-3), 137.7 (tosyl C-1), 143.2 (tosyl C-4), 166.8 (C═O); m/z (ESI): 358 ([M +H]$^+$, 100%); HRMS (ESI): [$C_{19}H_{19}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 358.1108; found 358.1104.

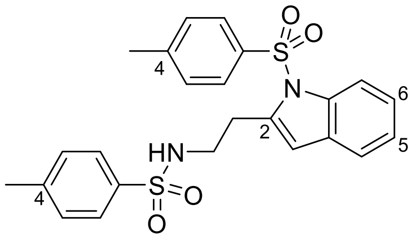
7.1.17. *N*-(4-(Thiophen-3-yl)but-3-yn-1-yl)-*p*-toluenesulfonamide (447)



447

Synthesized according to general procedure 3B using alkyne **398** (0.671 g, 3.00 mmol), 3-bromothiophene (0.31 mL, 3.3 mmol), $PdCl_2(PPh_3)_2$ (57 mg, 0.08 mmol) , CuI (25 mg, 0.13 mmol), Et_3N (0.83 mL, 6.0 mmol) and anhydrous MeCN (8 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **447** (0.409 g, 45%) as a light yellow solid: m.p. 83.9–84.1 °C (lit.[187] 82–83 °C); ν_{max}/cm^{-1} (solid): 3265 (s, N─H stretch), 3103 (w, sp^2 C─H stretch), 2910 (w, sp^3 C─H stretch), 1594 (w, aryl C═C stretch), 1517 (w, aryl C═C stretch), 1490 (w, aryl C═C stretch), 1454 (m, aryl C═C stretch), 1424 (m), 1332 (m, S═O stretch), 1311 (s), 1149 (s, S═O stretch), 1075 (s), 947 (m), 910 (m), 812 (s, 1,4-disubstituted benzene C─H bend), 774 (s), 659 (s), 625 (s), 547 (s); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.42 (3H, s, $ArCH_3$), 2.55 (2H, td, *J* 6.6, 0.4 Hz, $CH_2C≡C$), 3.17 (2H, q, *J* 6.5 Hz, NCH_2), 4.85 (1H, br t, *J* 6.4 Hz, NH), 7.02 (1H, dd, *J* 5.0, 1.2 Hz, thiophene H-4), 7.24 (1H, dd, *J* 5.0, 3.0 Hz, thiophene H-5), 7.28–7.30 (2H, m, tosyl H-3,5), 7.35 (1H, ddt, *J* 3.0, 1.2, 0.4 Hz, thiophene H-2), 7.77 (2H, AA’ part of AA’XX’ system, J_{AX} 8.1 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.5 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 20.9 ($\underline{C}H_2C≡C$), 21.7 ($ArCH_3$), 42.0 (NCH_2), 78.0 ($CH_2C≡\underline{C}$), 85.3 ($CH_2\underline{C}≡C$), 122.0 (thiophene C-3), 125.5 (thiophene C-5), 127.2 (tosyl C-2,6), 128.7 (thiophene C-2), 129.94 (tosyl C-3,5), 129.99 (thiophene C-4), 137.0 (tosyl C-1), 143.8 (tosyl C-4); *m/z* (ESI): 306 ([M +H]$^+$, 100%), 166 ([M −Ts −H +OH]$^+$, 37%); HRMS (ESI): [$C_{15}H_{16}NO_2S_2$ +H]$^+$ (M$^+$ +H) requires: 306.0617; found 306.0618. NMR data consistent with literature.[187]

7.1.18. *N*-(2-(1-(*p*-Toluenesulfonyl)-1*H*-indol-2-yl)ethyl)-*p*-toluenesulfonamide (453)

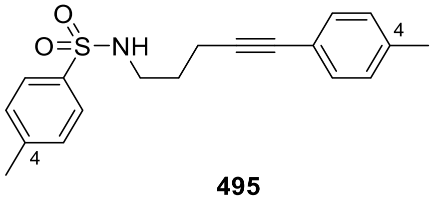


453

Synthesized according to general procedure 3A using alkyne **398** (0.337 g, 1.50 mmol), *N*-tosyl-2-iodoaniline (**441**, 0.636 g, 1.70 mmol), $PdCl_2(PPh_3)_2$ (27 mg, 0.04 mmol), CuI (27 mg, 0.14 mmol), Et_3N (0.63 mL, 4.5 mmol) and anhydrous MeCN (4 mL). Purification by flash column chromatography (hexane/EtOAc, 70:30) gave indole **453** (0.298 g, 42%) as an off-white solid: m.p. 170.7–174.3 °C; ν_{max}/cm^{-1} (solid): 3302 (m, N–H stretch), 3247 (m, N–H stretch), 2919 (w, sp^3 C–H stretch), 2871 (w, sp^3 C–H stretch), 1594 (m, aryl C=C stretch), 1560 (w, aryl C=C stretch), 1491 (w, aryl C=C stretch), 1449 (m), 1410 (w), 1376 (m, S=O stretch), 1363 (m, S=O stretch), 1315 (m), 1304 (m), 1156 (s, S=O stretch), 1143 (s, S=O stretch), 1088 (s), 809 (s, 1,4-disubstituted benzene C–H bend), 743 (s, 1,2-disubstituted benzene C–H bend), 704 (m), 693 (m), 656 (s), 622 (s), 574 (s), 541 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.32 (3H, s, indolyl tosylamide CH_3), 2.39 (3H, s, alkyl tosylamide CH_3), 3.20 (2H, td, *J* 6.5, 0.8 Hz, $NHCH_2C\underline{H_2}$), 3.38 (2H, q, *J* 6.5 Hz, $NHC\underline{H_2}$), 4.56 (1H, br t, *J* 6.2 Hz, NH), 6.38 (1H, q, *J* 0.8 Hz, indole H-3), 7.14–7.17 (2H, m, indolyl tosylamide H-3,5), 7.22 (1H, ddd, *J* 7.7, 7.3, 1.0 Hz, indole H-5), 7.22–7.24 (2H, m, alkyl tosylamide H-3,5), 7.28 (1H, ddd, *J* 8.4, 7.2, 1.3 Hz, indole H-6), 7.39 (1H, ddd, *J* 7.7 Hz, 1.4 Hz, 0.7 Hz, indole H-4), 7.54 (2H, AA'XX' system, J_{AX} 8.1 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, indolyl tosylamide H-2,6), 7.68 (2H, AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, alkyl tosylamide H-2,6), 8.10 (1H, dq, *J* 8.4, 0.9 Hz, indole H-7); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 21.70 (tosyl CH_3), 21.71 (tosyl CH_3), 30.0 ($NHCH_2\underline{C}H_2$), 42.9 ($NHCH_2$), 111.6 (indole C-3), 115.0 (indole C-7), 120.6 (indole C-4), 124.0 (indole C-5), 124.6 (indole C-6), 126.3 (indolyl tosylamide C-2,6), 127.1 (alkyl tosylamide C-2,6), 129.5 (indole C-3a), 129.9 (alkyl tosylamide C-3,5), 130.1 (indolyl tosylamide C-3,5), 135.6 (indolyl tosylamide C-1), 136.9 (alkyl tosylamide C-1), 137.3 (indole C-2), 137.4 (indole C-7a), 143.6 (alkyl tosylamide C-4), 145.2 (indolyl tosylamide C-4); *m/z* (ESI):

469 ([M +H]$^+$, 100%), 328 (31), 258 (28), 238 (30); HRMS (ESI): [$C_{24}H_{24}N_2O_4S_2$ +H]$^+$ (M$^+$ +H) requires: 469.1250; found 469.1247.

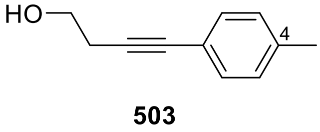
7.1.19. *N*-(5-(*p*-Tolyl)pent-4-yn-1-yl)-*p*-toluenesulfonamide (495)



495

Synthesized according to general procedure 3A using alkyne **494** (0.313 g, 1.32 mmol), 4-iodotoluene (0.320 g, 1.47 mmol), $PdCl_2(PPh_3)_2$ (24 mg, 0.03 mmol), CuI (11 mg, 0.06 mmol), Et_3N (0.52 mL, 3.7 mmol) and anhydrous MeCN (4 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20 → 70:30) gave alkyne **495** (0.361 g, 84%) as a reddish-brown solid: m.p. 100.0–102.9 °C (lit.[188] 99–100 °C); ν_{max}/cm^{-1} (solid): 3526 (s, N–H stretch), 3020 (w, sp^2 C–H stretch), 2955 (w, sp^3 C–H stretch), 2915 (w, sp^3 C–H stretch), 2855 (w, sp^3 C–H stretch), 1595 (w, aryl C=C stretch), 1507 (m, aryl C=C stretch), 1486 (w, aryl C=C stretch), 1443 (w), 1419 (m), 1317 (s, S=O stretch), 1286 (m), 1148 (s, S=O stretch), 1076 (s), 1061 (m), 957 (m), 890 (m), 810 (s, 1,4-disubstituted benzene C–H bend), 671 (s), 577 (m), 547 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.75 (2H, quint, *J* 6.7 Hz, $CH_2C\underline{H_2}CH_2$), 2.33 (3H, s, tolyl CH_3), 2.41 (3H, s, tosyl CH_3), 2.43 (2H, t, *J* 6.8 Hz, $CH_2C{\equiv}C$), 3.14 (2H, q, *J* 6.6 Hz, NCH_2), 4.56 (1H, br t, *J* 6.1 Hz, NH), 7.07–7.10 (2H, m, tolyl H-3,5), 7.22 (2H, AA' part of AA'XX' system, J_{AX} 7.7 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.5 Hz, tolyl H-2,6), 7.27-7.29 (2H, m, tosyl H-3,5), 7.75 (2H, AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 16.9 ($\underline{C}H_2C{\equiv}C$), 21.6 (tolyl CH_3), 21.7 (tosyl CH_3), 28.4 ($CH_2C\underline{H_2}CH_2$), 42.5 (NCH_2), 82.0 ($CH_2C{\equiv}\underline{C}$), 87.5 ($CH_2\underline{C}{\equiv}C$), 120.3 (tolyl C-1), 127.3 (tosyl C-2,6), 129.2 (tolyl C-3,5), 129.9 (tosyl C-3,5), 131.5 (tolyl C-2,6), 137.0 (tosyl C-1), 138.1 (tolyl C-4), 143.6 (tosyl C-4); *m/z* (ESI): 328 ([M +H]$^+$, 100%); HRMS (ESI): [$C_{19}H_{21}NO_2S$ +H]$^+$ (M$^+$ +H) requires: 328.1366; found 328.1361. NMR data consistent with literature.[188]

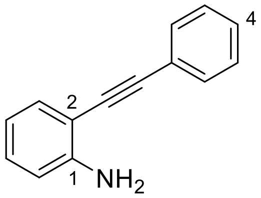
7.1.20. 4-(*p*-Tolyl)but-3-yn-1-ol (503)



503

Synthesized according to general procedure 3A using 3-butyn-1-ol (0.76 mL, 10 mmol) , 4-iodotoluene (2.399 g, 11.0 mmol), $PdCl_2(PPh_3)_2$ (178 mg, 0.25 mmol), CuI (70 mg, 0.37 mmol), Et_3N (4.2 mL, 30 mmol) and anhydrous MeCN (12 mL). Purification by flash column chromatography (hexane/EtOAc 100:0 → 80:20) gave alkyne **503** (1.589 g, 99%) as a brown liquid: ν_{max}/cm^{-1} (film): 3348 (s, br, OH stretch), 2917 (s, sp^3 C─H stretch), 2875 (s, sp^3 C─H stretch), 1677 (m, aryl C═C stretch), 1605 (m, aryl C═C stretch), 1508 (s, aryl C═C stretch), 1444 (m), 1406 (m), 1272 (m), 1178 (m), 1104 (m), 1039 (s), 814 (s, 1,4-disubstituted benzene C─H bend), 526 (m); ^{1}H NMR (700 MHz, $CDCl_3$): 1.90 (1H, br t, *J* 6.1 Hz, OH), 2.34 (3H, s, $ArCH_3$), 2.68 (2H, t, *J* 6.3 Hz, $CH_2C{\equiv}C$), 3.80 (2H, br q, *J* 6.1 Hz, OCH_2), 7.08–7.11 (2H, m, ArH-3,5), 7.30 (2H, AA’ part of AA’XX’ system, J_{AX} 7.7 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 21.5 ($ArCH_3$), 24.0 ($\underline{C}H_2C{\equiv}C$), 61.3 ($OCH_2$), 82.7 ($CH_2C{\equiv}\underline{C}$), 85.6 ($CH_2\underline{C}{\equiv}C$), 120.3 (aryl C-1), 129.1 (aryl C-3,5), 131.7 (aryl C-2,6), 138.1 (aryl C-4); *m/z* (ESI): 179 ([M +H_3O]$^+$, 36%), 161 ([M +H]$^+$, 100), 119 (14). NMR data consistent with literature.[189]

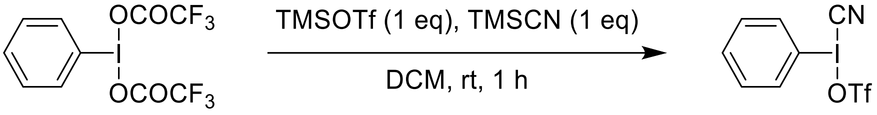
7.1.21. 2-(Phenylethynyl)aniline (520)



520

Synthesized according to general procedure 3A using phenylacetylene (0.36 mL, 3.3 mmol), 2-iodoaniline (0.662 g, 3.02 mmol), $PdCl_2(PPh_3)_2$ (52 mg, 0.074 mmol), CuI (21 mg, 0.11 mmol), Et_3N (1.25 mL, 9.0 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc 100:0 → 95:5) gave alkyne **520** (0.384 g, 83%) as a pale yellow solid: m.p. 85–87 °C (lit.[190] 83–85 °C); ν_{max}/cm^{-1} (solid): 3464 (m, N─H stretch), 3368 (m, N─H stretch), 3030 (w, sp^2 C─H stretch), 2204 (w, C≡C stretch), 1610 (m, NH_2 scissor), 1566 (m, aryl C═C stretch), 1494 (m, aryl C═C stretch), 1481 (m, aryl C═C stretch), 1453 (m, aryl C═C stretch), 1310 (m), 1257 (m), 744 (s, monosubstituted benzene C─H bend and 1,2-disubstituted benzene C─H bend), 688 (s, monosubstituted benzene C─H bend), 479 (m); ^{1}H NMR (700 MHz, $CDCl_3$): δ 4.27 (2H, br s, NH_2), 6.72 (1H, td, *J* 7.5, 1.1 Hz, aryl H-4), 6.73 (1H, d, *J* 8.1 Hz, aryl H-6), 7.14 (1H, ddd, *J* 8.1, 7.3, 1.6 Hz, aryl H-5), 7.31–7.37 (3H, m, phenyl H-3,4,5), 7.37 (1H, dd, *J* 7.6, 1.6 Hz, aryl H-3), 7.51–7.54 (2H, m, phenyl H-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 86.0 ($\underline{C}{\equiv}CPh$), 94.8 ($C{\equiv}\underline{C}Ph$), 108.1 (aryl C-2), 114.5 (aryl C-6), 118.1 (aryl C-4), 123.5 (phenyl C-1), 128.3 (phenyl C-4), 128.5 (phenyl C-3,5), 129.9 (aryl C-5), 131.6 (phenyl C-2,6), 132.3 (aryl C-3), 147.9 (aryl C-1); *m/z* (ESI): 194 ($[M + H]^+$, 100%). NMR data consistent with literature.[190]

7.1.22. Cyano(phenyl)iodonium trifluoromethanesulfonate (387)

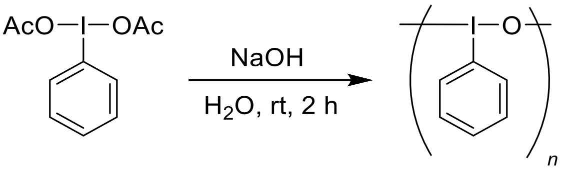


414 **387**

According to the procedure of Zhdankin and Stang:[151] PIFA (**414**, 0.86 g, 2.0 mmol) was dissolved in anhydrous DCM. TMSOTf (0.36 mL, 2.0 mmol) and TMSCN (0.25 mL, 2.0 mmol) were added sequentially, generating a white ppt. After 1 h of stirring the reaction mixture was filtered to give cyano(phenyl)iodonium triflate (**387**, 0.484 g, 64%) as a white solid: ^1H NMR (700 MHz, DMSO-d_6): δ 7.16–7.20 (2H, m, ArH-2,6), 7.39 (1H, tt, *J* 7.4, 1.1 Hz, ArH-4), 7.71–7.74 (1H, m, ArH-3,5); $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d_6): δ 94.9 (aryl C-1), 120.7 (q, $^1J_{CF}$ 322 Hz, CF_3), 123.5 (CN), 127.7 (aryl C-4), 130.7 (aryl C-3,5), 137.1 (aryl C-2,6); ^{19}F NMR (659 MHz, DMSO-d_6): δ −77.7 (SO_2CF_3). DMSO-d_6 NMR data not available in the literature.

Notes: Cyanide containing waste was treated with bleach. Cyano(phenyl)iodonium triflate (**387**) was stored at −20 °C in a vial flushed with Ar. During one of our experiments the isolated solid underwent spontaneous combustion during the process of transferring the solid from a filter paper into a sample vial by use of metal spatula.

7.1.23. Iodosylbenzene (353)

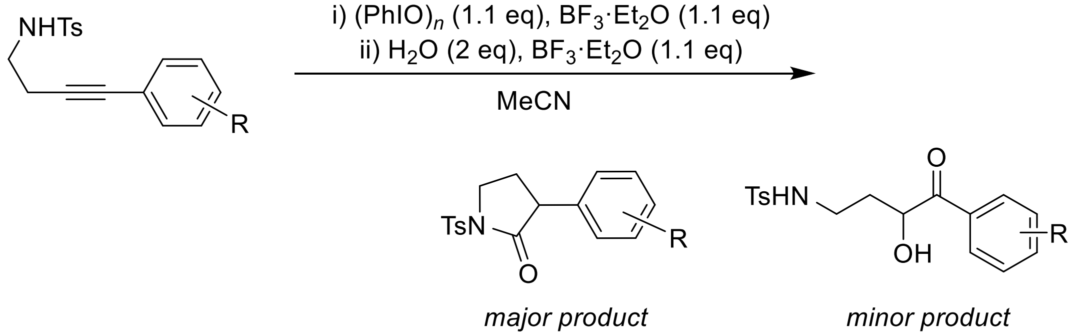


116 **353**

According to the procedure of Malcolmson *et al.*,[159] modified: NaOH pellets (0.659 g, 16.5 mmol) were dissolved in H_2O (5.5 mL). PIDA (**116**, 0.967 g, 3.00 mmol) was added to the mixture with stirring. A white suspension was formed. The reaction was stirred for 1 h before it was diluted with H_2O (5.5 mL). After a further 1 h of stirring the reaction mixture was filtered and the solid washed with $CHCl_3$ (25 mL, then 12.5 mL). The obtained solid was dried *in vacuo* giving iodosylbenzene (**353**, 0.613 g, 93%) as an off-white solid: ν_{max}/cm^{-1} (solid): 3035 (m, sp^2 C─H stretch), 1564 (m, aryl C═C stretch), 1459 (m, aryl C═C stretch), 1432 (m, aryl C═C stretch), 1301 (m), 995 (m), 732 (s, monosubstituted benzene C─H bend), 688 (s, monosubstituted benzene C─H bend), 487 (s), 424 (s).

Notes: A solution NMR of iodosylbenzene cannot be obtained as it is polymeric and insoluble. The melting point was not measured as iodosylbenzene is known to explode when heated.[191] For long term storage the sample was refrigerated at −20 °C. At room temperature iodosylbenzene disproportionates to form iodoxybenzene, which is explosive.[191]

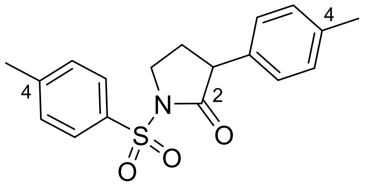
General Procedure 4: Hypervalent Iodine Mediated Cyclization-Rearrangement of *N*-(4-Arylbut-3-yn-1-yl)tosylamides



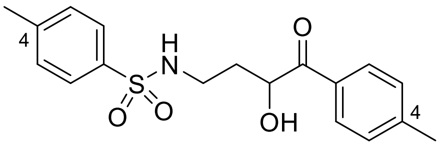
General Procedure 4A: Representative procedure for 1 mmol scale reaction. The appropriate alkyne (1.0 mmol) and PhIO (1.1 mmol) were suspended in anhydrous MeCN (5 mL). $BF_3 \cdot Et_2O$ (1.1 mmol) was added dropwise to the reaction mixture. After 30 min of stirring, H_2O (2 mmol) and additional $BF_3 \cdot Et_2O$ (1.1 mmol) were added to the reaction mixture in quick succession. Stirring was continued for a further 2 h. The reaction mixture was partitioned between H_2O (25 mL) and DCM (25 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over MgSO$_4$, filtered and solvent removed *in vacuo*. The residue was purified by flash column chromatography.

General Procedure 4B: Representative procedure for 1 mmol scale reaction. The appropriate alkyne (1.0 mmol) and PhIO (1.1 mmol) were suspended in anhydrous MeCN (5 mL) and the mixture cooled to 0 °C. BF$_3$·Et$_2$O (1.1 mmol) was added dropwise to the reaction mixture. After 1 h min of stirring, H$_2$O (2 mmol) and additional BF$_3$·Et$_2$O (1.1 mmol) were added to the reaction mixture in quick succession. Stirring was continued for a further 8 h. The reaction mixture was partitioned between H$_2$O (25 mL) and DCM (25 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over MgSO$_4$, filtered and solvent removed *in vacuo*. The residue was purified by flash column chromatography.

7.1.24. 3-(*p*-Tolyl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (415) and *N*-(3-Hydroxy-4-oxo-4-(*p*-tolyl)butyl)-*p*-toluenesulfonamide (418)



415



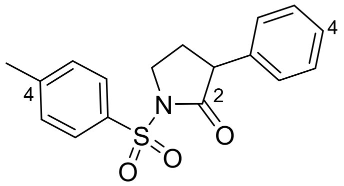
418

Synthesized according to general procedure 4A using alkyne **392** (0.314 g, 1.00 mmol), PhIO (0.241 g, 1.10 mmol), BF$_3$·Et$_2$O (2 × 130 μL, 1.05 mmol), H$_2$O (40 μL, 2.2 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc, 90:10 → 80:20) giving pyrrolidinone **415** (0.248 g, 75%) as an off-white solid: m.p. 133.7–135.9 °C; ν_{max}/cm^{-1} (solid): 2992 (w, sp^3 C—H stretch), 2916 (w, sp^3 C—H stretch), 2857 (w, sp^3 C—H stretch), 1727 (s, *γ*-lactam C═O stretch), 1593 (w, aryl C═C stretch), 1515 (w, aryl C═C stretch), 1491 (w, aryl C═C stretch), 1445 (w), 1401 (w), 1357 (s, S═O stretch), 1225 (m), 1161 (s, S═O stretch), 1109 (s), 1079 (m), 890 (m), 814 (s, 1,4-disubstituted benzene C—H bend), 806 (s, 1,4-disubstituted benzene C—H bend), 749 (m), 700 (s), 656 (s), 578 (s), 545 (s), 516 (s); ^{1}H NMR (700 MHz, CDCl$_3$): δ 2.21 (1H, ddt, *J* 12.9, 9.8, 8.4 Hz, pyrrolidinone H-4a), 2.30 (3H, s, tolyl CH$_3$), 2.44 (3H, s, tosyl CH$_3$), 2.50 (1H, dddd, *J* 12.9, 8.6, 7.1, 3.4 Hz, pyrrolidinone H-4b), 3.63 (1H, dd, *J* 9.7, 8.8 Hz, pyrrolidinone H-3), 3.83 (1H, ddd, *J* 9.9, 8.6, 7.1 Hz, pyrrolidinone H-5a), 4.05 (1H, ddd, *J* 10.0, 8.2, 3.4 Hz, pyrrolidinone

H-5b), 6.98 (2H, AA' part of AA'XX' system, J_{AX} 7.8 Hz, $J_{AA'}$ 2.1 Hz, $J_{XX'}$ 2.1 Hz, $J_{AX'}$ 0.5 Hz, tolyl H-2,6), 7.07–7.10 (2H, m, tolyl H-3,5), 7.32–7.35 (2H, m, tosyl H-3,5), 7.95 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 21.2 (tolyl CH_3), 21.8 (tosyl CH_3), 27.7 (pyrrolidinone C-4), 45.4 (pyrrolidinone C-5), 48.9 (pyrrolidinone C-3), 127.8 (tolyl C-2,6), 128.3 (tosyl C-2,6), 129.6 (tolyl C-3,5), 129.8 (tosyl C-3,5), 133.9 (tolyl C-1), 135.2 (tosyl C-1), 137.4 (tolyl C-4), 145.3 (tosyl C-4), 173.6 (C═O); *m/z* (ESI): 330 ($[M+H]^+$, 100%), 148 (13); HRMS (ESI): $[C_{18}H_{19}NO_3S+H]^+$ ($M^+ +H$) requires: 330.1158; found: 330.1159. NMR data consistent with literature.[15]

N-(3-Hydroxy-4-oxo-4-(*p*-tolyl)butyl)-*p*-toluenesulfonamide (**418**) – minor product: ^1H NMR (700 MHz, $CDCl_3$): δ 1.55 (1H, dddd, *J* 14.5, 9.7, 6.1, 4.9 Hz, one of $NCH_2C\underline{H_2}$), 2.13 (1H, dddd, *J* 14.4, 8.3, 5.3, 3.0 Hz, one of $NCH_2C\underline{H_2}$), 2.42 (6H, s, 2 × aryl CH_3), 3.12 (1H, ddt, *J* 13.3, 6.1, 5.3 Hz, one of $NC\underline{H_2}$), 3.23 (1H, dddd, *J* 13.3, 8.3, 7.0, 5.0 Hz, one of $NC\underline{H_2}$), 3.84 (1H, br d, *J* 5.7 Hz, OH), 5.09 (1H, ddd, *J* 9.6, 4.7, 3.2 Hz, $C\underline{H}OH$), 5.19 (1H, dd, *J* 6.9, 5.3 Hz, NH), 7.27–7.31 (4H, m, 2 × aryl H-3,5), 7.74 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6), 7.77 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 21.7 ($ArCH_3$), 21.9 ($ArCH_3$), 35.4 ($NCH_2\underline{C}H_2$), 40.5 (NCH_2), 71.5 (CHOH), 127.2 (tosyl C-2,6), 128.9 (tolyl C-2,6), 129.8 (aryl C-3,5), 129.9 (aryl C-3,5), 130.5 (tolyl C-1), 136.9 (tosyl C-1), 143.6 (tosyl C-4), 145.6 (tolyl C-4), 200.7 (C═O).

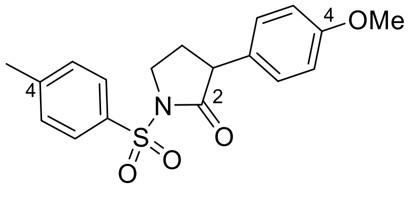
7.1.25. 3-Phenyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (454)



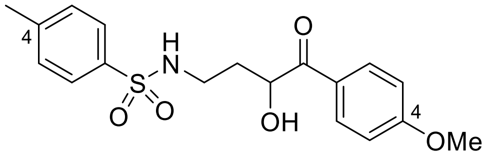
454

Synthesized according to general procedure 4A using alkyne **442** (0.278 g, 0.93 mmol), PhIO (0.226 g, 1.03 mmol), $BF_3{\cdot}Et_2O$ (2 × 125 µL, 1.01 mmol), H_2O (30 µL, 1.7 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20) gave pyrrolidinone **454** (0.202 g, 69%) as an off-white solid: m.p. 107.1–108.6 °C; ν_{max}/cm^{-1} (solid): 3027 (w, sp^2 C─H stretch), 2917 (w, sp^3 C─H stretch), 2849 (w, sp^3 C─H stretch), 1728 (s, *γ*-lactam C═O stretch), 1595 (w, aryl C=C stretch), 1494 (w, aryl C=C stretch), 1485 (w, aryl C=C stretch), 1456 (w), 1348 (s, S=O stretch), 1225 (m), 1165 (s, S=O stretch), 1118 (m), 1087 (m), 944 (m), 814 (m, 1,4-disubstituted benzene C–H bend), 775 (m, monosubstituted benzene C–H bend), 694 (m, monosubstituted benzene C–H bend), 662 (s), 600 (m), 575 (s), 544 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.24 (1H, ddt, *J* 12.9, 9.9, 8.4 Hz, pyrrolidinone H-4a), 2.44 (3H, s, tosyl CH_3), 2.52 (1H, dddd, *J* 12.6, 8.9, 7.1, 3.5 Hz, pyrrolidinone H-4b), 3.67 (1H, dd, *J* 9.8, 8.8 Hz, pyrrolidinone H-3), 3.84 (1H, ddd, *J* 9.9, 8.7, 7.0 Hz, pyrrolidinone H-5a), 4.07 (1H, ddd, *J* 9.9, 8.2, 3.4 Hz, pyrrolidinone H-5b), 7.08–7.11 (2H, m, phenyl H-2,6), 7.21–7.30 (3H, m, phenyl H-3,4,5), 7.32–7.35 (2H, m, tosyl H-3,5), 7.95 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.1 Hz, $J_{XX'}$ 2.1 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.9 (tosyl CH_3), 27.7 (pyrrolidinone C-4), 45.4 (pyrrolidinone C-5), 49.3 (pyrrolidinone C-3), 127.8 (phenyl C-4), 128.0 (phenyl C-2,6), 128.4 (tosyl C-2,6), 129.0 (phenyl C-3,5), 129.8 (tosyl C-3,5), 135.1 (tosyl C-1), 136.9 (phenyl C-1), 145.4 (tosyl C-4), 173.4 (C=O); *m/z* (ESI): 316 ($[M+H]^+$, 100%), 148 (17); HRMS (ESI): $[C_{17}H_{17}NO_3S+H]^+$ ($M^+ +H$) requires: 316.1002; found: 316.1002. NMR data consistent with literature.[15]

7.1.26. 3-(4-Methoxyphenyl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (455) and *N*-(3-hydroxy-4-(4-methoxyphenyl)-4-oxobutyl)-*p*-toluenesulfonamide (461)



455



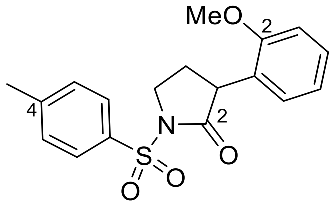
461

Synthesized according to general procedure 4B using alkyne **443** (0.156 g, 0.47 mmol), PhIO (0.116 g, 0.53 mmol), $BF_3 \cdot Et_2O$ (2 × 64 µL, 0.52 mmol), H_2O (17 µL, 0.94 mmol) and anhydrous MeCN (2.4 mL) Purification by flash column chromatography (hexane/EtOAc, 90:10 → 80:20) giving pyrrolidinone **455** (73 mg, 45%) as a light yellow solid: m.p. 134.4–137.0 °C (dec.); ν_{max}/cm^{-1} (solid): 2989 (w, sp^3 C–H stretch), 2956 (w, sp^3 C–H stretch), 2894 (w, sp^3 C–H stretch), 2831 (w, sp^3 C–H stretch), 1735 (s, *γ*-lactam C=O stretch), 1608 (w, aryl C=C stretch), 1592 (w, aryl C=C stretch), 1511 (s, aryl C=C stretch), 1351 (s, S=O stretch), 1239 (m), 1161 (s, S=O stretch), 1111 (s), 1078 (s), 1031 (s), 942 (m), 840 (s), 821 (m, 1,4-disubstituted benzene C–H bend), 813 (m, 1,4-disubstituted benzene C—H bend), 753 (m), 697 (m), 656 (s), 600 (m), 581 (s), 564 (s), 542 (s); ^{1}H NMR (600 MHz, CDCl$_3$): δ 2.20 (1H, ddt, *J* 12.8, 9.9, 8.8 Hz, pyrrolidinone H-4a), 2.44 (3H, s, ArCH$_3$), 2.49 (1H, dddd, *J* 12.5, 8.9, 7.0, 3.4 Hz, pyrrolidinone H-4b), 3.61 (1H, dd, *J* 9.9, 8.7 Hz, pyrrolidinone H-3), 3.77 (3H, s, OCH$_3$), 3.82 (1H, ddd, *J* 9.8, 8.9, 7.0 Hz, pyrrolidinone H-5a), 4.06 (1H, ddd, *J* 10.0, 8.2, 3.2 Hz, pyrrolidinone H-5b), 6.81 (2H, AA' part of AA'XX' system, J_{AX} 8.4 Hz, $J_{AA'}$ 2.7 Hz, $J_{XX'}$ 2.7 Hz, $J_{AX'}$ 0.4 Hz, methoxyphenyl H-3,5), 7.03 (2H, XX' part of AA'XX' system, J_{AX} 8.2 Hz, $J_{AA'}$ 2.7 Hz, $J_{XX'}$ 2.7 Hz, $J_{AX'}$ 0.4 Hz, methoxyphenyl H-2,6), 7.32–7.34 (2H, m, tosyl H-3,5), 7.94 (2H, AA' part of AA'XX' system, J_{AX} 7.8 Hz, $J_{AA'}$ 2.4 Hz, $J_{XX'}$ 2.4 Hz, $J_{AX'}$ 0.6 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): 21.9 (ArCH$_3$), 27.7 (pyrrolidinone C-4), 45.4 (pyrrolidinone C-5), 48.5 (pyrrolidinone C-3), 55.4 (OCH$_3$), 114.3 (methoxyphenyl C-3,5), 128.3 (tosyl C-2,6), 128.8 (methoxyphenyl C-1), 129.0 (methoxyphenyl C-2,6), 129.9 (tosyl C-3,5), 135.1 (tosyl C-1), 145.4 (tosyl C-4), 159.1 (methoxyphenyl C-4), 173.7 (C═O); *m/z* (ESI): 346 ([M +H]$^+$, 100%), 374 (14); HRMS (ESI): [$C_{18}H_{19}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 346.1108; found 346.1107. NMR data consistent with literature.[15]

α-Hydroxyketone **461** (30 mg, 17%) was also isolated as a yellow solid: ν_{max}/cm^{-1} (CDCl$_3$ cast): 3454 (m, br, O–H stretch), 3275 (s, br, N—H stretch), 2930 (w, sp^3 C—H stretch), 2839 (w, sp^3 C—H stretch), 1668 (aryl ketone C═O stretch), 1596 (s, aryl C═C stretch), 1571 (m, C═C stretch), 1510 (m, aryl C═C stretch), 1421 (m), 1314 (s, S═O stretch), 1255 (s), 1155 (s, S═O stretch), 1110 (s), 1091 (s), 839 (m), 814 (m, 1,4-disubstituted benzene C—H bend), 661 (s), 550 (s); ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.54 (1H, ddt, *J* 14.6, 9.7, 5.0 Hz, one of NCH$_2$C$\underline{H_2}$), 2.14 (1H, dddd, *J* 14.1, 8.4, 5.4, 2.9 Hz, one of NCH$_2$C$\underline{H_2}$), 2.41 (3H, s, ArCH$_3$), 3.11 (1H, dq, *J* 13.3, 5.4 Hz, one of NCH$_2$), 3.23 (1H, dddd, *J* 13.3, 8.4, 7.1, 5.0 Hz, one of NCH$_2$), 3.75–4.10 (1H, br s, OH), 3.87 (3H, s, OCH$_3$), 5.09 (1H, dd, *J* 9.7, 2.7 Hz, C$\underline{H}$OH), 5.35 (1H, br t, *J* 6.0 Hz, NH), 6.94 (2H, AA' part of AA'XX' system, J_{AX} 8.7 Hz, $J_{AA'}$ 2.5 Hz, $J_{XX'}$ 2.5 Hz, $J_{AX'}$ 0.3 Hz, methoxyphenyl H-3,5), 7.28–7.30 (2H, m, tosyl H-3,5), 7.74 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6), 7.87 (2H, XX' part of AA'XX' system, J_{AX} 8.7 Hz, $J_{AA'}$ 2.5 Hz, $J_{XX'}$ 2.5 Hz, $J_{AX'}$ 0.3 Hz, methoxyphenyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): 21.7 (ArCH$_3$), 35.7 (NCH$_2$$\underline{C}H_2$), 40.5 (NCH$_2$), 55.8 (OCH$_3$), 71.1 (CHOH), 114.4 (methoxyphenyl C-3,5), 125.7 (methoxyphenyl C-1), 127.3 (tosyl C-2,6), 129.9 (tosyl C-3,5), 131.3

(methoxyphenyl C-2,6), 136.8 (tosyl C-1), 143.6 (tosyl C-4), 164.6 (methoxyphenyl C-4), 199.4 (C═O); *m/z* (ESI): 364 ([M +H]$^+$, 100%), 346 ([M −OH]$^+$, 39), 155 (Ts$^+$, 15); HRMS (ESI): [$C_{18}H_{21}NO_5S$ +H]$^+$ (M$^+$ +H) requires: 364.1213; found 364.1209.

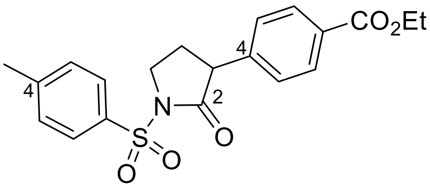
7.1.27. 3-(2-Methoxyphenyl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (456)



456

Synthesized according to general procedure 4A using alkyne **444** (0.301 g, 0.91 mmol), PhIO (0.226 g, 1.00 mmol), $BF_3 \cdot Et_2O$ (2 × 120 µL, 0.97 mmol), H_2O (30 µL, 1.7 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20) gave pyrrolidinone **456** (0.129 g, 41%) as an off-white solid: m.p. 132.1–132.6 °C; ν_{max}/cm^{-1} (solid): 3063 (w, sp^2 C─H stretch), 3008 (w, sp^2 C─H stretch), 2915 (w, sp^3 C─H stretch), 2840 (w, sp^3 C─H stretch), 1733 (s, *γ*-lactam C═O stretch), 1599 (m, aryl C═C stretch), 1584 (w, aryl C═C stretch), 1492 (s, aryl C═C stretch), 1463 (w, aryl C═C stretch), 1453 (w), 1436 (w), 1355 (s, S═O stretch), 1257 (m), 1243 (m), 1226 (m), 1170 (s), 1158 (s, S═O stretch), 1116 (s), 816 (m, 1,4-disubstituted benzene C─H stretch), 769 (m), 749 (s, 1,2-disubstituted benzene C─H bend), 727 (m), 662 (s), 578 (s), 541 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.19 (1H, dq, *J* 12.7, 9.1 Hz, pyrrolidinone H-4a), 2.40 (1H, dddd, *J* 12.7, 9.5, 7.7, 3.1 Hz, pyrrolidinone H-4b), 2.44 (3H, s, tosyl CH_3), 3.53 (3H, s, OCH_3), 3.76 (1H, t, *J* 9.6 Hz, pyrrolidinone H-3), 3.84 (1H, ddd, *J* 9.7, 8.5, 7.8 Hz, pyrrolidinone H-5a), 4.04 (1H, td, *J* 9.3, 3.1 Hz, pyrrolidinone H-5b), 6.80 (1H, dd, *J* 8.3, 0.9 Hz, aryl H-3), 6.84 (1H, td, *J* 7.5, 1.0 Hz, aryl H-5), 6.98 (1H, dd, *J* 7.4, 1.7 Hz, aryl H-6), 7.22 (1H, ddd, *J* 8.2, 7.5, 1.7 Hz, aryl H-4), 7.32-7.35 (2H, m, tosyl H-3,5), 7.99 (2H, AA’ part of AA’XX’ system, J_{AX} 8.1 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 21.8 ($ArCH_3$), 26.2 (pyrrolidinone C-4), 45.6 (pyrrolidinone C-5), 46.4 (pyrrolidinone C-3), 55.3 (OCH_3), 111.2 (aryl C-3), 120.9 (aryl C-5), 126.4 (aryl C-1), 128.5 (tosyl C-2,6), 129.2 (aryl C-4), 129.7 (tosyl C-3,5), 130.3 (aryl C-6), 135.4 (tosyl C-1), 145.1 (tosyl C-4), 157.0 (aryl C-2), 174.0 (C═O); *m/z* (ESI): 346 ([M +H]$^+$, 100); HRMS (ESI): [$C_{18}H_{19}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 316.1108; found: 316.1106.

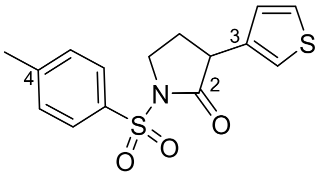
7.1.28. Ethyl 4-(2-oxo-1-(*p*-toluenesulfonyl)pyrrolidin-3-yl)benzoate (457)



457

Synthesized according to general procedure 4A using alkyne **445** (0.359 g, 0.97 mmol), PhIO (0.250 g, 1.14 mmol), $BF_3{\cdot}Et_2O$ (2 × 130 μL, 1.05 mmol), H_2O (36 μL, 2.0 mmol) and anhydrous MeCN (5 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20) gave pyrrolidinone **457** (0.129 g, 41%) as an off-white solid: m.p. 114.4–116.5 °C; ν_{max}/cm^{-1} (solid): 2971 (w, sp^3 C—H stretch), 1727 (s, *γ*-lactam C═O stretch), 1714 (s, aromatic ester C═O stretch), 1610 (w, aryl C═C stretch), 1595 (w, aryl C═C stretch), 1491 (w, aryl C═C stretch), 1449 (w), 1417 (w), 1353 (s, S═O stretch), 1276 (s), 1258 (m), 1229 (m), 1184 (m), 1160 (s, S═O stretch), 1109 (s), 1077 (s), 1023 (m), 1004 (m), 947 (m), 862 (m), 808 (m, 1,4-disubstituted benzene C—H bend), 784 (m), 747 (m), 713 (m), 701 (m), 661 (s), 601 (s), 574 (s), 545 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.37 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H_3}$), 2.24 (1H, ddt, *J* 12.9, 10.1, 8.5 Hz, pyrrolidinone H-4a), 2.45 (3H, s, tosyl CH_3), 2.55 (1H, dddd, *J* 12.9, 8.7, 7.0, 3.2 Hz, pyrrolidinone H-4b), 3.73 (1H, dd, *J* 9.9, 8.7 Hz, pyrrolidinone H-3), 3.86 (1H, ddd, *J* 9.9, 8.8, 7.0 Hz, pyrrolidinone H-5a), 4.08 (1H, ddd, *J* 10.0, 8.3, 3.2 Hz, pyrrolidinone H-5b), 4.35 (2H, q, *J* 7.1 Hz, OCH_2), 7.18 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, aryl H-3,5), 7.33–7.36 (2H, m, tosyl H-3,5), 7.946 (2H, AA’ part of AA’XX’ system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.1 Hz, $J_{XX'}$ 2.1 Hz, $J_{AX'}$ 0.5 Hz, tosyl H-2,6), 7.953 (2H, XX’ part of AA’XX’ system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.5 Hz, aryl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 14.5 ($OCH_2\underline{C}H_3$), 21.9 (tosyl CH_3), 27.5 (pyrrolidinone C-4), 45.4 (pyrrolidinone C-5), 49.2 (pyrrolidinone C-3), 61.2 (OCH_2), 128.0 (aryl C-3,5), 128.3 (tosyl C-2,6), 129.91 (tosyl C-3,5), 129.96 (aryl C-1), 130.2 (aryl C-2,6), 134.9 (tosyl C-1), 141.7 (aryl C-4), 145.6 (tosyl C-4), 166.3 (ester C═O), 172.7 (pyrrolidinone C═O); *m/z* (ESI): 388 ($[M+H]^+$, 100%), 346 ($[M-OEt+4H]^+$, 49), 155 (Ts^+, 9); HRMS (ESI): $[C_{20}H_{21}NO_5S+H]^+$ ($M^+ +H$) requires: 388.1213; found: 388.1208.

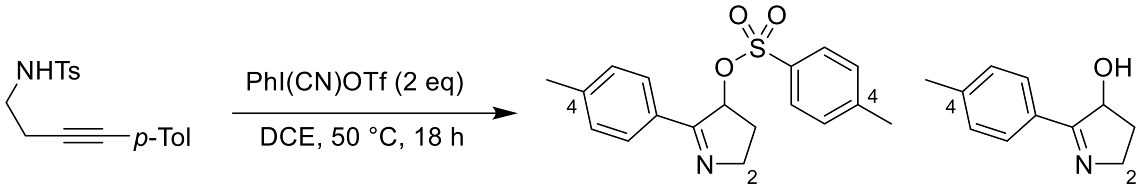
7.1.29. 3-(Thiophen-3-yl)-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (459)



459

Synthesized according to general procedure 4A using alkyne **447** (0.285 g, 0.93 mmol), PhIO (0.225 g, 1.02 mmol), $BF_3\cdot Et_2O$ (2 × 125 µL, 1.01 mmol), H_2O (30 µL, 1.7 mmol) and anhydrous MeCN (4.7 mL). Purification by flash column chromatography (hexane/EtOAc, 80:20) gave pyrrolidinone **459** (0.130 g, 43%) as an off-white solid: m.p. 143.2–143.6 °C; ν_{max}/cm^{-1} (solid): 3096 (w, sp^2 C─H stretch), 2096 (w, sp^3 C─H stretch), 1732 (s, *γ*-lactam C═O stretch), 1593 (m, aryl C═C stretch), 1491 (m, aryl C═C stretch), 1450 (w), 1400 (w), 1349 (s, S═O stretch), 1168 (s), 1157 (s, S═O stretch), 1110 (s), 1081 (s), 814 (s, 1,4-disubstituted benzene C─H bend), 800 (s), 736 (s), 665 (s), 656 (s), 590 (s), 563 (s), 546 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.24 (1H, ddt, *J* 12.7, 9.6, 8.3 Hz, pyrrolidinone H-4a), 2.44 (3H, s, $ArCH_3$), 2.53 (1H, dddd, *J* 12.6, 8.6, 7.1, 3.7 Hz, pyrrolidinone H-4b), 3.76 (1H, dddd, *J* 9.8, 8.5, 1.1, 0.5 Hz, pyrrolidinone H-3), 3.85 (1H, ddd, *J* 9.9, 8.4, 7.0 Hz, pyrrolidinone H-5a), 4.03 (1H, ddd, *J* 9.9, 8.1, 3.6 Hz, pyrrolidinone H-5b), 6.95 (1H, ddd, *J* 5.0, 1.4, 0.3 Hz, thiophene H-4), 7.04 (1H, ddd, *J* 3.0, 1.3, 1.0 Hz, thiophene H-2), 7.27 (1H, dd, *J* 5.0, 3.0 Hz, thiophene H-5), 7.32–7.34 (2H, m, tosyl H-3,5), 7.93 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 21.9 ($ArCH_3$), 26.8 (pyrrolidinone C-4), 44.6 (pyrrolidinone C-3), 45.5 (pyrrolidinone C-5), 122.1 (thiophene C-2), 126.5 (thiophene C-5), 126.9 (thiophene C-4), 128.3 (tosyl C-2,6), 129.9 (tosyl C-3,5), 135.0 (tosyl C-1), 136.3 (thiophene C-3), 145.5 (tosyl C-1), 172.8 (C═O); *m/z* (ESI): 322 ($[M+H]^+$, 100%); HRMS (ESI): $[C_{15}H_{15}NO_3S_2+H]^+$ ($M^+ +H$) requires: 322.0566; found 322.0566. NMR data consistent with literature.[15]

7.1.30. 5-(*p*-Tolyl)-3,4-dihydro-2*H*-pyrrol-4-yl *p*-toluenesulfonate (416) and 5-(*p*-Tolyl)-3,4-dihydro-2*H*-pyrrol-4-ol (417)



392 **416** **417**

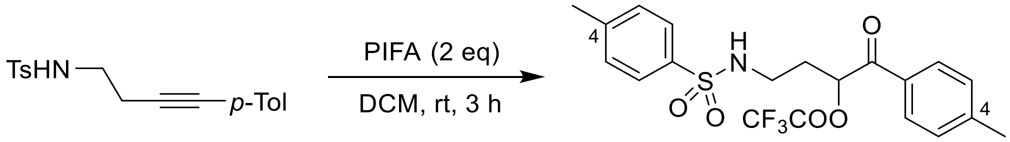
Cyano(phenyl)iodonium triflate (81 mg, 0.21 mmol) and alkyne **392** (33 mg, 0.11 mmol) were dissolved in DCE (0.5 mL). The reaction mixture was stirred at 50 °C for 18 h and then diluted with EtOAc (5 mL). The mixture was washed with sat. aq. $NaHCO_3$ (5 mL), water (5 mL) and solvent removed *in vacuo*. The crude residue was analysed by quantitative NMR and found to contain pyrrolines **416** and **417** in 35% and 11% yields respectively. The crude residue was purified by flash column chromatography (hexane/EtOAc 100:0 → 50:50).

5-(*p*-Tolyl)-3,4-dihydro-2*H*-pyrrol-4-yl *p*-toluenesulfonate (**416**): ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.13 (1H, dddd, *J* 14.8, 7.1, 3.9, 2.8 Hz, pyrroline H-3a), 2.23 (1H, dtd, *J* 14.7, 7.7, 6.3 Hz, pyrroline H-3b), 2.37 (3H, s, tolyl CH_3), 2.47 (3H, s, tosyl CH_3), 4.04–4.11 (2H, m, pyrroline H-2), 5.97 (1H, dddd, *J* 7.5, 2.8, 1.7, 0.7 Hz, pyrroline H-4), 7.12–7.15 (2H, m, tolyl H-3,5), 7.33–7.36 (2H, m, tosyl H-3,5), 7.62 (2H, AA' part of AA'XX' system, J_{AX} 7.7 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6), 7.79 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 21.6 (tolyl CH_3), 21.8 (tosyl CH_3), 31.0 (pyrroline C-3), 59.5 (pyrroline C-2), 83.0 (pyrroline C-4), 128.1 (tolyl C-2,6), 128.2 (tosyl C-2,6), 129.1 (tolyl C-1), 129.4 (tolyl C-3,5), 130.0 (tosyl C-3,5), 133.8 (tosyl C-1), 141.3 (tolyl C-4), 145.3 (tosyl C-4), 168.3 (C=N); HRMS (ESI): $[C_{18}H_{19}NO_3S + H]^+$ (M^+ +H) requires: 330.1158; found: 330.1155.

5-(*p*-Tolyl)-3,4-dihydro-2*H*-pyrrol-4-ol (**417**): ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.39 (1H, dddd, *J* 14.4, 6.3, 2.0, 1.5 Hz, pyrroline H-3a), 2.40 (3H, s, $ArCH_3$), 2.45 (1H, dtd, *J* 14.4, 8.0, 7.2 Hz, pyrroline H-3b), 4.16 (1H, dddd, *J* 16.6, 8.1, 6.4, 1.6 Hz, pyrroline H-2a), 4.21 (1H, ddd, *J* 16.6, 7.8, 2.0 Hz, pyrroline H-2b), 5.24 (1H, dt, *J* 7.4, 1.5 Hz, pyrroline-H4), 7.24–7.27 (2H, m, ArH-3,5), 7.84 (2H, AA' part of AA'XX' system, J_{AX} 7.8 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$):

δ 21.6 ($ArCH_3$), 35.4 (pyrroline C-3), 59.2 (pyrroline C-2), 59.3 (pyrroline C-4), 128.4 (aryl C-2,6), 128.9 (aryl C-1), 129.5 (aryl C-3,5), 141.6 (aryl C-4), 170.9 (C═N).

7.1.31. 1-Oxo-1-(*p*-tolyl)-4-(*p*-tolylsulfonamido)butan-2-yl 2,2,2-trifluoroacetate (427)

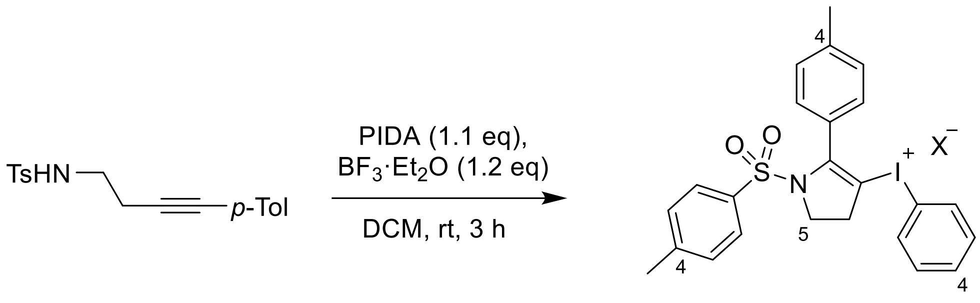


392 **427**

PIFA (93 mg, 0.22 mmol) and alkyne **392** (31 mg, 0.10 mmol) were dissolved in anhydrous DCM (0.5 mL). $BF_3{\cdot}Et_2O$ (49 μL, 0.40 mmol) was then added to the reaction mixture. After 3 h the reaction mixture was partitioned between DCM (5 mL) and H_2O (5 mL), and the organic layer separated. The aqueous layer was further extracted with DCM (2 × 5 mL). The organic extracts were combined and solvent removed *in vacuo*. This gave *α*-(trifluoroacetoxy)ketone **427** as the major product, determined to be in 53% yield by quantitative NMR. No further purification was performed.

1-Oxo-1-(*p*-tolyl)-4-(*p*-tolylsulfonamido)butan-2-yl 2,2,2-trifluoroacetate (**427**) – from crude mixture: ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.03 (1H, dddd, *J* 15.0, 9.9, 5.0, 4.3 Hz, one of $NCH_2C\underline{H_2}$), 2.30 (1H, dddd, *J* 15.1, 9.7, 5.9, 3.1 Hz, one of $NCH_2C\underline{H_2}$), 2.41 (3H, s, tosyl CH_3), 2.42 (3H, s, tolyl CH_3), 3.05–3.16 (2H, m, NCH_2), 5.13 (1H, br s, NH), 6.18 (1H, dd, *J* 9.9, 3.0 Hz, C(═O)CH), 7.28–7.31 (4H, m, 2 × aryl H-3,5), 7.72 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6), 7.83 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 21.6 ($ArCH_3$), 21.9 ($ArCH_3$), 31.7 ($NCH_2\underline{C}H_2$), 38.9 (NCH_2), 76.0 (C(═O)$\underline{C}$H), 114.5 (q, $^1J_{CF}$ 286 Hz, CF_3), 127.2 (tosyl C-2,6), 128.9 (tolyl C-2,6), 129.94 (one of aryl C-3,5), 129.95 (tolyl C-1), 130.0 (one of aryl C-3,5), 136.3 (tosyl C-1), 144.1 (tosyl C-4), 145.8 (tolyl C-4), 156.7 (q, $^2J_{CF}$ 43 Hz, $\underline{C}$(═O)CF_3), 192.7 ($\underline{C}$(═O)CH); ^{19}F NMR (659 MHz, $CDCl_3$): δ −74.7 (CF_3).

7.1.32. Phenyl(1-(*p*-toluenesulfonyl)-2-(*p*-tolyl)-4,5-dihydro-1*H*-pyrrol-3-yl)iodonium (counterion undetermined) (431)

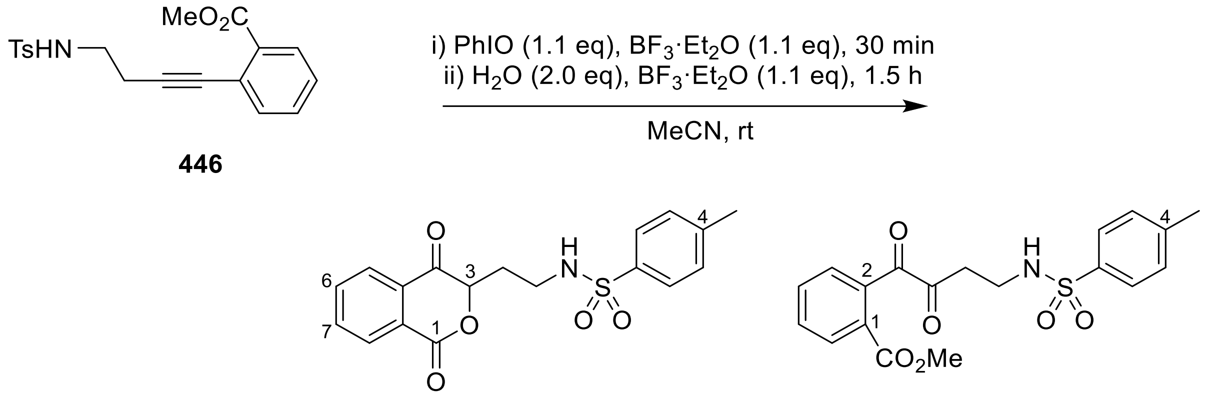


392 **431**

PIDA (35 mg, 0.11 mmol) and alkyne **392** (31 mg, 0.1 mmol) were dissolved in anhydrous DCM (0.5 mL). H_2O (4 µL, 0.2 mmol) and $BF_3{\cdot}Et_2O$ (15 µL, 0.12 mmol) were sequentially added to the reaction mixture. After 3h of stirring, the reaction mixture was partitioned between DCM (5 mL) and H_2O (5 mL), and the organic layer separated. The aqueous layer was further extracted with DCM (2 × 5 mL). The organic extracts were combined and solvent removed *in vacuo*. This gave iodonium salt **431** as the major product in 70% yield by quantitative NMR. No further purification was performed.

Phenyl(1-(*p*-toluenesulfonyl)-2-(*p*-tolyl)-4,5-dihydro-1*H*-pyrrol-3-yl)iodonium (counterion undetermined) (**431**) – from crude mixture: ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.41 (3H, s, tosyl CH_3), 2.43 (3H, s, tolyl CH_3), 2.96 (2H, t, *J* 9.4 Hz, dihydropyrrole H-4), 4.17 (2H, t, *J* 9.4 Hz, dihydropyrrole H-5), 7.20–7.22 (2H, m, tolyl H-2,6), 7.22–7.24 (2H, m, tolyl H-3,5), 7.25–7.28 (2H, m, tosyl H-3,5), 7.36–7.39 (2H, m, phenyl H-3,5), 7.37–7.39 (2H, m, tosyl H-2,6), 7.51–7.54 (2H, m, phenyl H-2,6), 7.56–7.59 (1H, m, phenyl H-4); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$): δ 21.75 ($ArCH_3$), 21.79 ($ArCH_3$), 33.3 (dihydropyrrole C-4), 51.6 (dihydropyrrole C-5), 92.7 (dihydropyrrole C-3), 111.7 (phenyl C-1), 125.8 (tolyl C-1), 127.7 (tosyl C-2,6), 129.4 (tolyl C-3,5), 130.21 (tolyl C-2,6 or tosyl C-3,5), 130.23 (tolyl C-2,6 or tosyl C-3,5), 132.3 (phenyl C-3,5), 132.7 (phenyl C-4), 133.9 (tosyl C-1), 134.6 (phenyl C-2,6), 142.0 (tolyl C-4), 145.4 (tosyl C-4), 157.8 (dihydropyrrole C-2); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −146.86 (81%, m, ^{11}BF), −146.81 (19%, br s, ^{10}BF); ^{11}B NMR (225 MHz, $CDCl_3$): δ −1.2 (s). Undetermined counterion contains boron and fluorine.

7.1.33. *N*-(2-(1,4-Dioxoisochroman-3-yl)ethyl)-*p*-toluenesulfonamide (462), Methyl 2-(4-(*p*-tolylsulfonamido)-2-oxobutanoyl)benzoate (463), 3-(*p*-Tolylsulfonamido)propanoic acid (531)



446

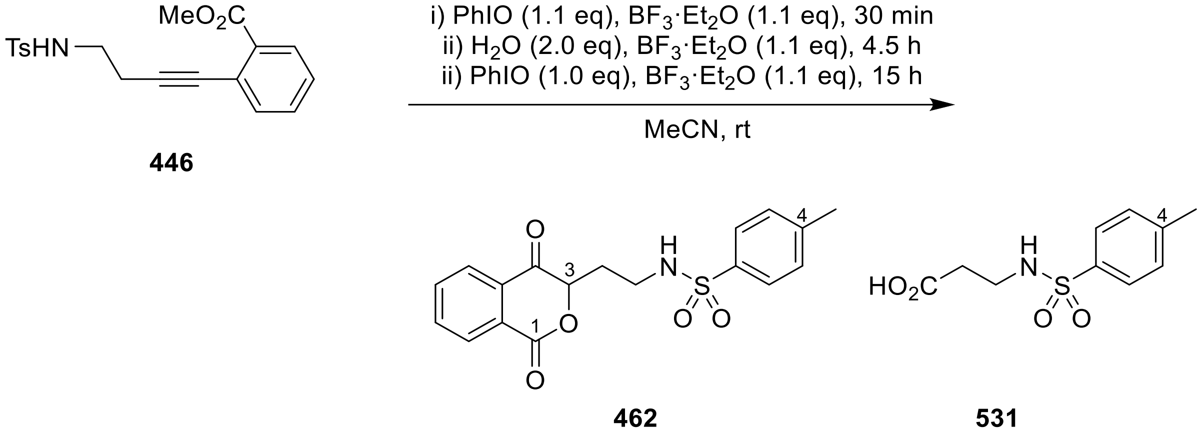
462 **463**

Alkyne **446** (0.214 g, 0.60 mmol) and PhIO (0.149 g, 0.67 mmol) were suspended in anhydrous MeCN (4 mL). BF_3·Et_2O (80 μL, 0.65 mmol) was added dropwise to the reaction mixture. The appearance of the reaction mixture at this stage was a light green suspension. After 30 min of stirring, H_2O (20 μL, 1.1 mmol) and additional BF_3·Et_2O (80 μL, 0.65 mmol) were added to the reaction mixture in quick succession. Stirring was continued for a further 1.5 h forming a light green solution. The reaction mixture was partitioned between H_2O (25 mL) and DCM (25 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The residue was analysed by ^{1}H NMR showing isochroman **462** as the major product. Diketone **463** was also present as a minor product with the ratio of **462** to **463** being 87:13. Despite multiple attempts isochroman **462** could not be purified via flash column chromatography (various hexane/EtOAc mixtures). None of the fractions obtained contained isochroman **462**, therefore it seems likely the compound decomposes on or otherwise reacts with silica. Diketone **463** was however partially purified, coeluting with other minor products.

N-(2-(1,4-dioxoisochroman-3-yl)ethyl)-*p*-toluenesulfonamide (**462**) – from crude mixture: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.18 (1H, ddt, *J* 14.7, 7.9, 6.3 Hz, one of NHCH$_2$C$\underline{H_2}$), 2.35 (1H, dddd, *J* 14.7, 7.1, 6.4, 4.5 Hz, one of NHCH$_2$C$\underline{H_2}$), 2.40 (3H, s, tosyl CH_3), 3.20–3.25 (2H, m, NHC$\underline{H_2}$), 4.75 (1H, br t, *J* 6.2 Hz, NH), 5.17 (1H, dd, *J* 7.9, 4.5 Hz, isochroman H-3), 7.25–7.28 (2H, m, tosyl H-3,5), 7.70 (2H, AA' part of

AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6), 7.83 (1H, td, *J* 7.5, 1.5 Hz, one of isochroman H-6,7), 7.87 (1H, td, *J* 7.5, 1.6 Hz, one of isochroman H-6,7), 8.05 (1H, ddd, *J* 7.5, 1.6, 0.6 Hz, one of isochroman H-5,8), 8.24 (1H, ddd, *J* 7.6, 1.5, 0.6 Hz, one of isochroman H-5,8). Isochroman shifts similar to other reported isochroman-1,4-diones in the literature.[192-194]

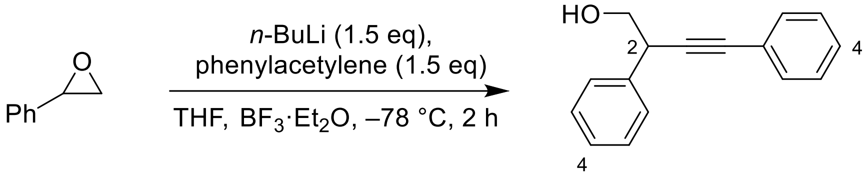
Methyl 2-(4-(*p*-tolylsulfonamido)-2-oxobutanoyl)benzoate (**463**) – from partially purified sample: ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (3H, s, tosyl CH_3), 3.18 (2H, t, *J* 5.8 Hz, $NHCH_2C\underline{H_2}$), 3.33 (2H, q, *J* 6.0 Hz, $NHC\underline{H_2}$), 3.89 (3H, s, OCH_3), 5.11 (1H, br t, *J* 6.0 Hz, NH), 7.29–7.32 (2H, m, tosyl C-3,5), 7.49 (1H, ddd, *J* 7.5, 1.3, 0.6 Hz, aryl H-3), 7.61 (1H, td, *J* 7.7, 1.4 Hz, aryl H-5), 7.69 (1H, td, *J* 7.5, 1.3 Hz, aryl H-4), 7.76 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6), 8.01 (1H, ddd, *J* 7.8, 1.3, 0.6 Hz, aryl H-6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.7 (tosyl CH_3), 36.5 ($NHCH_2\underline{C}H_2$), 37.9 ($NHCH_2$), 53.4 (OCH_3), 127.2 (tosyl C-2,6), 129.2 (aryl C-1), 129.3 (aryl C-3), 129.7 (aryl C-6), 129.9 (tosyl C-3,5), 131.7 (aryl C-5), 133.7 (aryl C-4), 137.1 (tosyl C-1), 138.2 (aryl C-2), 143.5 (tosyl C-4), 167.7 ($\underline{C}O_2CH_3$), 193.5 ($CH_2C(=O)\underline{C}=O$), 197.5 ($CH_2\underline{C}=O$).



In another similar experiment, alkyne **446** (0.360 g, 1.01 mmol) and PhIO (0.242 g, 1.10 mmol) were suspended in anhydrous MeCN (5 mL). $BF_3 \cdot Et_2O$ (135 µL, 1.09 mmol) was added dropwise to the reaction mixture. The appearance of the reaction mixture at this stage was a light green suspension. After 30 min of stirring, H_2O (36 µL, 2.0 mmol) and additional $BF_3 \cdot Et_2O$ (135 µL, 1.09 mmol) were added to the reaction mixture in quick succession. Stirring was continued for a further 4.5 h. A drop of the reaction mixture was diluted in $CDCl_3$ and then analysed by ^{1}H NMR with suppression of the MeCN peak. The analysis showed isochroman **462** and starting material **446** in a 75:25 ratio. In order to drive the reaction to completion further PhIO (0.220 g, 1.00 mmol) and $BF_3 \cdot Et_2O$ (135 μL, 1.09 mmol) was added and stirring continued for a further 15 h forming a dark green solution. The reaction mixture was partitioned between H_2O (25 mL) and DCM (25 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The residue was analysed by ^{1}H NMR showing isochroman **462** as the major product. Purification was attempted by flash column chromatography (hexane/EtOAc/AcOH 70:30:1). Under the acidic conditions isochroman **462** seemed less susceptible to decomposition on silica but still could not be isolated as it coeluted with various impurities. Repeated flash columns of the isochroman **462** fractions did not provide improvements in purity, and led to eventual loss of the product on silica.

During the attempted purifications of isochroman **462**, carboxylic acid **531** was obtained as an off-white solid (27 mg, 11%): m.p. 121.4–121.5 °C (lit.[195] 119–121 °C); ν_{max}/cm^{-1} (solid): 3300–2500 (s, br, O─H stretch), 3243 (s, N─H stretch), 2921 (w, sp^3 C─H stretch), 2884 (w, sp^3 C─H stretch), 1713 (s, carboxylic acid C═O stretch), 1596 (w, aryl C═C stretch), 1492 (w, aryl C═C stretch), 1482 (w, aryl C═C stretch), 1433 (m), 1413 (m), 1329 (m, S═O stretch), 1318 (m), 1285 (m), 1224 (m), 1156 (s, S═O stretch), 1078 (s), 1014 (s), 931 (m), 877 (m), 810 (m, 1,4-disubstituted benzene C─H bend), 639 (s), 555 (s), 526 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.43 (3H, s, $ArCH_3$), 2.63 (2H, t, *J* 5.7 Hz, $CH_2C{=}O$), 3.19 (2H, br q, *J* 5.5 Hz, $NHC\underline{H_2}$), 5.82 (1H, br t, *J* 5.8 Hz, NH), 7.30–7.33 (2H, m, tosyl H-3,5), 7.75 (2H, AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, tosyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 21.7 (tosyl CH_3), 33.9 ($\underline{C}H_2C{=}O$), 38.4 ($NHCH_2$), 127.1 (tosyl C-2,6), 130.0 (tosyl C-3,5), 136.9 (tosyl C-1), 143.9 (tosyl C-4), 175.8 (C═O); *m/z* (ESI): 258 ([M −OH +MeOH]$^+$, 100%), 244 ([M +H]$^+$, 37), 184 ($CH_2{=}NHTs^+$, 97), 155 (Ts$^+$, 11); HRMS (ESI): [$C_{10}H_{13}NO_4S$ +H]$^+$ (M$^+$ +H) requires: 244.0638; found: 244.0638. NMR data consistent with literature.[195]

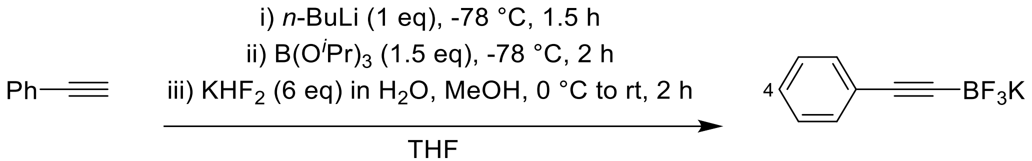
7.1.34. 2,4-Diphenylbut-3-yn-1-ol (476)



475 **476**

According to the procedure of Yamaguchi and Hirao,[162] modified: Phenylacetylene (0.82 mL, 7.5 mmol) was added to anhydrous THF (10 mL) and cooled to −78 °C. *n*-BuLi (5.8 mL, 1.30 M in hexanes, 7.5 mmol) was added and the mixture was stirred for 1 h forming a yellow suspension. $BF_3{\cdot}Et_2O$ (1 mL) was then added. The appearance of the suspension changed to white. After a further 15 min styrene oxide (**475**, 0.57 mL, 5.0 mmol) was added. The reaction mixture was stirred for a further 2 h, allowed to warm to rt and quenched by slowly pouring the mixture onto sat. aq. NH_4Cl (30 mL). The mixture was further diluted with H_2O (20 mL) and extracted with EtOAc (3 × 50 mL). The organic extracts were combined, dried over $MgSO_4$ and solvent removed in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane 90:10) giving alcohol **476** (0.604 g, 54%) as a light green oil: ν_{max}/cm^{-1} (oil): 3387 (s, br, O—H stretch), 3057 (w, sp^2 C—H stretch), 3026 (w, sp^2 C—H stretch), 2926 (w, sp^3 C—H stretch), 2878 (w, sp^3 C—H stretch), 1686 (s, aryl C═C stretch) 1597 (m, aryl C═C stretch), 1581 (w, aryl C═C stretch), 1488 (m, aryl C═C stretch), 1450 (m), 753 (s, monosubstituted benzene C—H bend), 690 (s, monosubstituted benzene C—H bend); ^1H NMR (600 MHz, $CDCl_3$): δ 1.87 (1H, br s, OH), 3.86 (2H, d, *J* 6.8 Hz, OCH_2), 4.09 (1H, t, *J* 6.8 Hz, C$\underline{H}$Ph), 7.28–7.33 (4H, m, 4-phenyl C-3,4,5 and 2-phenyl C-4), 7.35–7.39 (2H, m, 2-phenyl H-3,5), 7.44–7.49 (4H, m, 2-phenyl H-2,6 and 4-phenyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 42.2 ($\underline{C}$HPh), 67.9 (OCH_2), 85.0 ($\underline{C}$≡CPh), 88.3 (C≡$\underline{C}$Ph), 123.1 (4-phenyl C-1), 127.6 (2-phenyl C-4), 128.1 (2-phenyl C-2,6), 128.36 (4-phenyl C-4), 128.44 (4-phenyl C-3,5), 128.9 (2-phenyl C-3,5), 131.9 (4-phenyl C-2,6), 138.1 (2-phenyl C-1); *m/z* (ESI): 223 ($[M+H]^+$, 100%), 205 ($[M-OH]^+$, 14), 105 ($C_6H_5C{\equiv}O^+$, 32); HRMS (ESI): $[C_{16}H_{14}O+H]^+$ ($M^+ +H$) requires: 223.1117; found 223.1116. NMR data consistent with literature.[196]

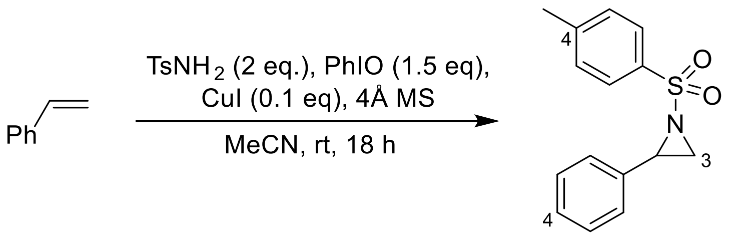
7.1.35. Potassium trifluoro(phenylethynyl)borate (479)



90 **479**

According to the procedure of May *et al.*,[163] modified: Phenylacetylene (**90**, 0.55 mL, 5.0 mmol) was added to anhydrous THF (17 mL) and cooled to −78 °C. *n*-BuLi (3.9 mL, 1.30 M in hexane, 5.0 mmol) was added drop by drop. After 1.5 h of stirring triisopropyl borate (1.7 mL, 7.5 mmol) was slowly added and stirring continued for a further 1 h. The reaction mixture was allowed to warm to 0 C and MeOH (5 mL) was added followed by a saturated solution of KHF_2 (2.368 g, 30.3 mmol) in H_2O. After a further hour of stirring the solvent was removed *in vacuo*. The solid obtained was triturated with acetone, then dissolved in hot acetone and precipitated by the addition of Et_2O. Filtration gave trifluoroborate **479** (0.756 g, 73%) as a white solid: m.p. 282.8–286.0 °C (dec.) (lit.[197] 238 °C (dec.)); ν_{max}/cm^{-1} (solid): 3049 (w, sp^2 C─H stretch), 2188 (m, alkyne C≡C stretch), 1596 (w, aryl C═C stretch), 1484 (m, aryl C═C stretch), 1442 (w, aryl C═C stretch), 1231 (s), 973 (vs), 754 (s, monosubstituted benzene C─H bend), 689 (s, monosubstituted benzene C─H bend), 537 (s); ^{1}H NMR (700 MHz, DMSO-*d*$_6$): δ 7.20–7.24 (1H, m, phenyl H-4), 7.24–7.28 (4H, m, phenyl H-2,3,5,6); ^{13}C{^{1}H} NMR (150 MHz, DMSO-*d*$_6$): δ 89.6 (br s, $\underline{C}$≡CBF$_3$K), 101.5–105.9 (br m, C≡$\underline{C}$BF$_3$K), 125.4 (phenyl C-1), 126.9 (phenyl C-4), 128.3 (phenyl C-3,5), 131.0 (phenyl C-2,6); ^{19}F NMR (659 MHz, DMSO-*d*$_6$): δ −127.1 to −126.8 (m, BF$_3$); ^{11}B NMR (225 MHz, DMSO-*d*$_6$): δ 3.1 (br q, $^1J_{BF}$ 34.2 Hz); *m/z* (ESI): 377 ([2M −K]$^-$, 8%), 169 ([M −K]$^-$, 100).

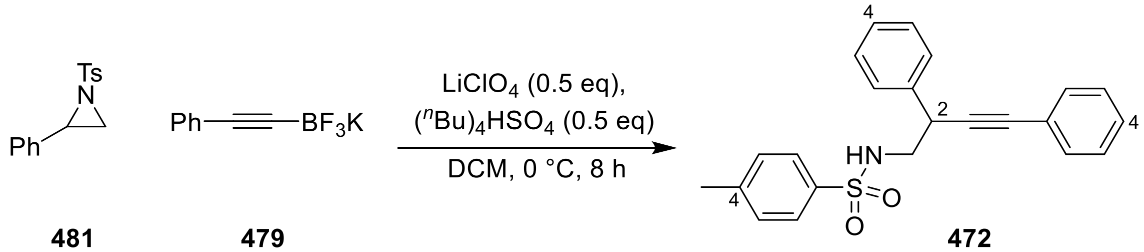
7.1.36. 2-Phenyl-1-(*p*-toluenesulfonyl)aziridine (481)



480 **481**

According to the procedure of Chan *et al.*[164]: To a suspension of tosylamide (1.09 g, 6.4 mmol), iodosylbenzene (0.991 g, 4.50 mmol), CuI (61 mg, 0.32 mmol) and 4Å molecular sieves in anhydrous MeCN (12 mL), styrene (**480**, 0.35 mL, 3.0 mmol) was added. The reaction mixture was stirred overnight (approx. 18 h) and filtered over silica, washing with EtOAc. The filtrate was collected and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc 90:10) giving aziridine **481** (0.521 g, 64%) as a white solid: m.p. 90.1–91.6 °C (lit.[198] 90–91 °C); ν_{max}/cm^{-1} (solid): 3036 (w, sp^2 C—H stretch), 3007 (w, sp^3 C—H stretch), 1593 (m, aryl C═C stretch), 1492 (w, aryl C═C stretch), 1457 (m), 1318 (s, S═O stretch), 1231 (m), 1192 (m), 1154 (s, S═O stretch), 1091 (s), 906 (s), 814 (s, 1,4-disubstituted benzene C—H bend), 798 (s), 779 (s), 753 (s, monosubstituted benzene C—H bend), 710 (s), 687 (s, monosubstituted benzene C—H bend), 660 (s), 580 (s), 562 (s), 546 (s); ^{1}H NMR (600 MHz, CDCl$_3$): δ 2.39 (1H, d, *J* 4.5 Hz, aziridine H-3a), 2.43 (3H, s, ArCH$_3$), 2.98 (1H, d, *J* 7.2 Hz, aziridine H-3b), 3.77 (1H, dd, *J* 7.2, 4.5 Hz, aziridine H-2), 7.20–7.23 (2H, m, phenyl H-2,6), 7.26–7.31 (2H, m, phenyl-3,4,5), 7.32–7.34 (2H, m, tosyl H-3,5), 7.87 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ 21.8 (ArCH$_3$), 36.1 (aziridine C-3), 41.1 (aziridine C-2), 126.7 (phenyl C-2,6), 128.1 (tosyl C-2,6), 128.5 (phenyl C-4), 128.7 (phenyl C-3,5), 129.9 (tosyl C-3,5), 135.1 (tosyl C-1), 135.2 (phenyl C-1), 144.8 (tosyl C-4); *m/z* (ESI): 274 ([M +H]$^+$, 100%), 155 (Ts$^+$, 9); HRMS (ESI): [$C_{15}H_{15}NO_2S$ +H]$^+$ (M$^+$ +H) requires: 274.0896; found 274.0889. NMR data consistent with literature.[198]

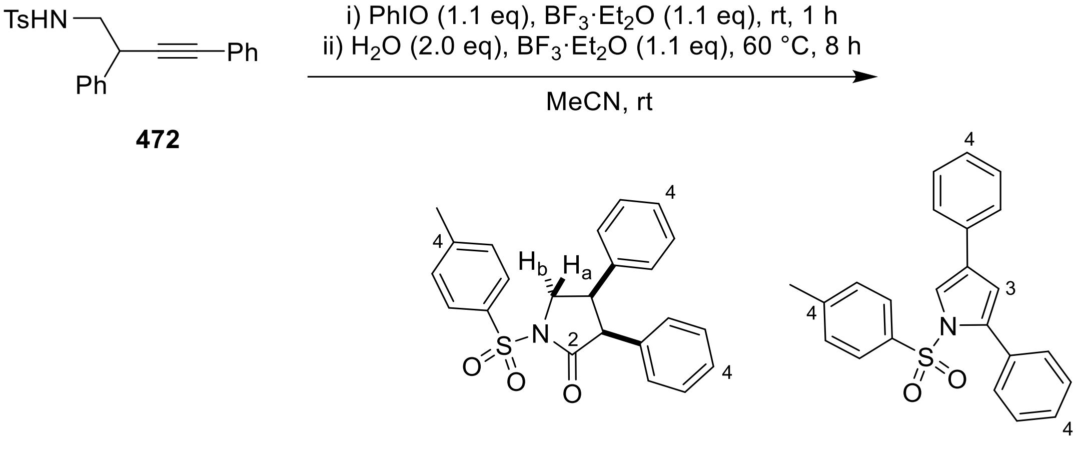
7.1.37. ***N*-(2,4-diphenylbut-3-yn-1-yl)-*p*-toluenesulfonamide (472)**



481 **479** **472**

According to the procedure of May *et al.*,[163] modified: This reaction was performed in air. Aziridine **481** (0.461 g, 1.69 mmol), alkynyl trifluoroborate **479** (0.529 g, 2.54 mmol), LiClO$_4$ (96 mg, 0.91 mmol) and ^{n}Bu$_4$HSO$_4$ (0.290 g, 0.85 mmol) were suspended in DCM (17 mL) at 0 °C and stirred for 8 h. The reaction was filtered over silica, washing with EtOAc. The filtrate was collected and the solvent removed in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc, 80:20) giving tosylamide **472** (0.270 g, 43%) as a white solid: m.p. 143.2–144.3 °C (lit.[199] 122–123 °C); ν_{max}/cm^{-1} (solid): 3275 (m, N—H stretch), 3261 (m, N—H stretch), 1595 (m, aryl C═C stretch), 1489 (m, aryl C═C stretch), 1420 (m), 1321 (s, S═O stretch), 1152 (s, S═O stretch), 1089 (m), 1074 (m), 851 (m), 819 (s, 1,4-disubstituted benzene C─H bend), 778 (m), 759 (s, monosubstituted benzene C─H bend), 693 (s, monosubstituted benzene C─H bend), 667 (s), 523 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (3H, s, $ArCH_3$), 3.25 (1H, ddd, *J* 13.0, 7.9, 5.3 Hz, one of NCH_2), 3.54 (1H, dt, *J* 13.0, 6.7 Hz, one of NCH_2), 3.98 (1H, dd, *J* 8.1, 6.3 Hz, CHC≡C), 4.72 (1H, br dd, *J* 7.4, 5.6 Hz, NH), 7.26–7.29 (2H, m, tosyl C-3,5), 7.28–7.34 (8H, m, 2-phenyl H-2,3,4,5,6 and 4-phenyl H-3,4,5), 7.40–7.42 (2H, m, 4-phenyl H-2,6), 7.72 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 2.1 Hz, $J_{XX'}$ 2.1 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): 21.7 ($ArCH_3$), 39.1 ($\underline{C}$HC≡C), 49.4 (NCH_2), 85.3 (CHC≡$\underline{C}$), 87.7 (CH$\underline{C}$≡C), 122.7 (4-phenyl C-1), 127.2 (tosyl C-2,6), 127.89 (2-phenyl C-4 or 4-phenyl C-4), 127.90 (2-phenyl C-2,6), 128.5 (2-phenyl C-3,5 or 4-phenyl C-3,5), 128.6 (2-phenyl C-4 or 4-phenyl C-4), 129.0 (2-phenyl C-3,5 or 4-phenyl C-3,5), 129.9 (tosyl C-3,5), 131.9 (4-phenyl C-2,6), 137.1 (tosyl C-1), 137.8 (2-phenyl C-1), 143.7 (tosyl C-4); *m/z* (ESI): 376 ([M +H]$^+$, 100%), 274 (15), 236 ([M −Ts +OH]$^+$, 11), 220 ([M −Ts]$^+$, 23), 155 (Ts$^+$, 11); HRMS (ESI): [$C_{23}H_{21}NO_2S$ +H]$^+$ (M$^+$ +H) requires: 376.1366; found 376.1360. NMR data consistent with literature.[199]

7.1.38. *cis*-3,4-Diphenyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (473) and 2,4-diphenyl-1-(*p*-toluenesulfonyl)-1*H*-pyrrole (482)



472

473

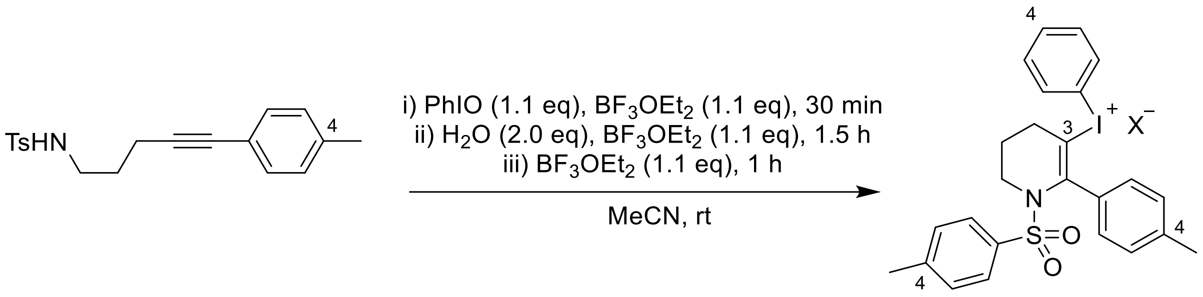
482

Alkyne **472** (0.379 g, 1.01 mmol) and PhIO (0.246 g, 1.02 mmol) were suspended in anhydrous MeCN (5 mL). $BF_3·Et_2O$ (64 μL, 0.52 mmol) was added dropwise to the reaction mixture. After 1 h of stirring, H_2O (36 μL, 2.0 mmol) and additional $BF_3·Et_2O$ (135 μL, 1.09 mmol) were added to the reaction mixture in quick succession. The reaction mixture was heated to 60 °C and stirred was continued for a further 8 h. The reaction mixture was partitioned between H_2O (25 mL) and DCM (25 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc, 100:0 → 90:10) giving pyrrolidinone **473** (93 mg, 24%) as an off-white solid: m.p. 156.8–158.9 °C; ν_{max}/cm^{-1} (solid): 3058 (w, sp^2 C—H stretch), 3032 (w, sp^2 C—H stretch), 2913 (w, sp^3 C—H stretch), 2883 (w, sp^3 C—H stretch), 1716 (s, *γ*-lactam C═O stretch), 1592 (m, C═C stretch), 1491 (m, C═C stretch), 1476 (m, C═C stretch), 1451 (m, C═C stretch), 1363 (s, S═O stretch), 1225 (m), 1171 (s, S═O stretch), 1117 (s), 965 (m), 950 (m), 811 (m, 1,4-disubstituted benzene C—H stretch), 759 (m, monosubstituted benzene C—H bend), 694 (s, monosubstituted benzene C—H bend), 660 (s), 586 (s), 545 (s), 532 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.49 (3H, s, $ArCH_3$), 3.86 (1H, dt, *J* 8.4, 6.5 Hz, pyrrolidinone H-4), 4.05 (1H, d, *J* 8.4 Hz, pyrrolidinone H-3), 4.21 (1H, A part of ABX system, J_{AB} 10.3 Hz, J_{AX} 6.1 Hz, pyrrolidinone H-5a), 4.27 (1H, B part of ABX system, J_{AB} 10.3 Hz, J_{BX} 7.0 Hz, pyrrolidinone H-5b), 6.52–6.55 (2H, m, 3-phenyl H-2,6), 6.70–6.73 (2H, m, 4-phenyl H-2,6), 6.97–7.01 (2H, m, 3-phenyl H-3,5), 7.03–7.08 (3H, m, 3-phenyl H-4 and 4-phenyl H-3,5), 7.08–7.12 (1H, m, 4-phenyl H-4), 7.39–7.42 (2H, m, tosyl H-3,5), 8.05 (2H, AA' part of AA'XX' system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.1 Hz, $J_{XX'}$ 2.1 Hz, $J_{AX'}$ 0.4 Hz, tosyl H-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): 21.9 ($ArCH_3$), 43.8 (pyrrolidinone C-4), 50.6 (pyrrolidinone C-5), 55.2 (pyrrolidinone C-3), 127.4 (3-phenyl C-4), 127.5 (4-phenyl C-4), 128.0 (4-phenyl C-2,6), 128.3 (3-phenyl C-3,5), 128.4 (tosyl C-2,6 and 4-phenyl C-3,5), 129.1 (3-phenyl C-2,6), 130.0 (tosyl C-3,5), 133.7 (3-phenyl C-1), 135.2 (tosyl C-1), 136.8 (4-phenyl C-1), 145.7 (tosyl C-4), 172.9 (C═O); *m/z* (ESI): 392 ([M +H]$^+$, 100%); HRMS (ESI): [$C_{23}H_{21}NO_3S$ +H]$^+$ (M$^+$ +H) requires: 392.1315; found 392.1314.

Pyrrole **482** (64 mg, 17%) was also isolated as a pale blue oil: ν_{max}/cm^{-1} (oil): 3056 (w, sp^3 C—H stretch), 3028 (w, sp^3 C—H stretch), 1733 (s), 1594 (m, aryl C═C stretch), 1491 (m, aryl C═C stretch), 1447 (m, aryl C═C stretch), 1362 (s, S═O stretch), 1167 (s, S═O stretch), 1069 (s), 907 (s), 811 (m, 1,4-disubstituted benzene C—H stretch), 760 (s, monosubstituted benzene C—H stretch), 729 (s), 694 (s, monosubstituted benzene C—H stretch), 660 (s), 596 (s), 577 (s), 542 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.35 (3H, s, $ArCH_3$), 6.49 (1H, d, *J* 2.0 Hz, pyrrole H-3), 7.08–7.12 (2H, m, tosyl

C-3,5), 7.25–7.31 (5H, m, tosyl C-2,6, 2-phenyl C-2,6 and 4-phenyl C-4) 7.32–7.36 (2H, m, 2-phenyl C-3,5), 7.36–7.41 (3H, m, 2-phenyl C-4 and 4-phenyl C-3,5), 7.52–7.56 (2H, m, 4-phenyl C-2,6), 7.74 (1H, d, *J* 2.0 Hz, pyrrole H-5); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 21.8 ($ArCH_3$), 114.5 (pyrrole C-3), 119.7 (pyrrole C-5), 125.6 (4-phenyl C-2,6), 127.2 (4-phenyl C-4), 127.3 (tosyl C-2,6), 127.6 (2-phenyl C-3,5), 127.7 (pyrrole C-4), 128.6 (2-phenyl C-4), 129.0 (4-phenyl C-3,5), 129.6 (tosyl C-3,5), 131.0 (2-phenyl C-2,6), 131.4 (2-phenyl C-1), 133.4 (4-phenyl C-1), 135.5 (tosyl C-1), 137.1 (pyrrole C-2), 145.0 (tosyl C-4); *m/z* (ESI): 374 ($[M+H]^+$, 100%), 207 (17), 122 (22); HRMS (ESI): $[C_{23}H_{19}NO_2S+H]^+$ (M^+ +H) requires: 374.1209; found 374.1209. NMR data consistent with literature.[200]

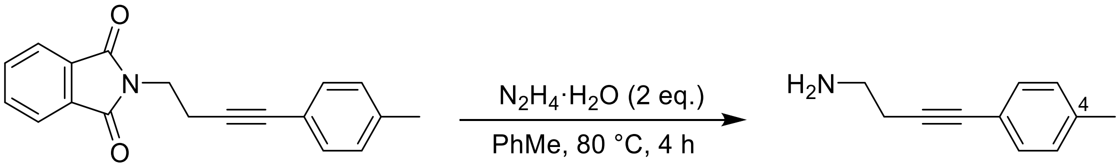
7.1.39. Phenyl(2-(*p*-tolyl)-1-(*p*-toluenesulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)iodonium (counterion undetermined) (496)



495 **496**

Alkyne **495** (0.881 g, 2.69 mmol) and PhIO (0.671 g, 3.05 mmol) was suspended in anhydrous MeCN (14 mL). $BF_3\cdot Et_2O$ (0.37 mL, 3.0 mmol) was added dropwise to the reaction mixture. The appearance of the reaction mixture at this stage was a dark brown suspension. After 30 min of stirring, H_2O (99 μL, 5.5 mmol) and additional $BF_3\cdot Et_2O$ (0.37 mL, 3.0 mmol) were added to the reaction mixture in quick succession. Stirring was continued for a further 1.5 h and additional $BF_3\cdot Et_2O$ (0.37 mL, 3.0 mmol) was added to the reaction mixture. The reaction mixture was partitioned between H_2O (50 mL) and DCM (50 mL). The organic layer was separated and the aq. layer further extracted with DCM (2 × 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The residue was crystalized from hexane/DCM giving alkenyl(phenyl)iodonium salt **496** (0.905 g) as colourless crystals: ν_{max}/cm^{-1} (solid): 2967 (w, sp^3 C–H stretch), 2939 (w, sp^3 C–H stretch), 1602 (m, aryl C=C stretch), 1578 (m, aryl C=C stretch), 1559 (w, aryl C=C stretch), 1508 (w, aryl C=C stretch), 1466 (w, aryl C=C stretch), 1444 (m), 1426 (w), 1350 (s), 1333 (m, S=O stretch), 1293 (m), 1196 (m), 1183 (m), 1158 (m, S═O stretch), 1148 (m), 1077 (s), 1026 (s), 979 (s), 856 (m), 817 (s, 1,4-disubstituted benzene C─H bend), 735 (m, monosubstituted benzene C─H bend), 710 (s), 700 (m, monosubstituted benzene C─H bend), 680 (s), 566 (m), 547 (s), 533 (s), 517 (m); ^{1}H NMR (700 MHz, DMSO-*d*$_6$): δ 1.68–1.73 (2H, m, tetrahydropyridine H-5), 2.36 (3H, s, tolyl CH_3), 2.38 (3H, s, tosyl CH_3), 2.84 (2H, t, *J* 6.6 Hz, tetrahydropyridine H-4), 3.75 (2H, AA' part of AA'XX' system, $J_{AA'}/J_{XX'}$ 13.7, 13.7 Hz, J_{AX} 7.4 Hz, $J_{AX'}$ 2.8 Hz, tetrahydropyridine H-6), 7.06 (2H, AA' part of AA'XX' system, J_{AX} 7.7 Hz, $J_{AA'}$ 1.8 Hz, $J_{XX'}$ 1.8 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6), 7.11–7.13 (2H, m, tolyl H-3,5), 7.30–7.33 (2H, m, tosyl H-3,5), 7.35 (2H, AA' part of AA'XX' system, J_{AX} 7.9 Hz, $J_{AA'}$ 1.9 Hz, $J_{XX'}$ 1.9 Hz, $J_{AX'}$ 0.5 Hz, tosyl H-2,6), 7.45–7.49 (2H, m, phenyl H-3,5), 7.59–7.62 (2H, m, phenyl H-2,6), 7.64 (1H, tt, *J* 7.4, 1.0 Hz, phenyl H-4); ^{13}C{^{1}H} NMR (176 MHz, DMSO-*d*$_6$): δ 21.0 (tolyl CH_3), 21.1 (tosyl CH_3), 24.8 (tetrahydropyridine C-5), 33.6 (tetrahydropyridine C-4), 46.6 (tetrahydropyridine C-6), 113.4 (tetrahydropyridine C-3), 114.4 (phenyl C-1), 127.0 (tosyl C-2,6), 128.4 (tolyl C-3,5), 129.8 (tosyl C-3,5), 130.0 (tolyl C-2,6), 131.8 (phenyl C-3,5), 132.0 (phenyl C-4), 134.1 (tolyl C-1), 134.3 (phenyl C-2,6), 136.0 (tosyl C-1), 139.7 (tolyl C-4), 144.3 (tosyl C-4), 148.0 (tetrahydropyridine C-2); ^{19}F NMR (659 MHz, DMSO-*d*$_6$): δ −148.31 (80%, 1:1:1:1 q, $^1J_{BF}$ 1.1 Hz, ^{11}BF), −148.26 (20%, m, ^{10}BF); ^{11}B NMR (224 MHz, DMSO-*d*$_6$): δ −1.3 (s); *m/z* (ESI): 530 ([M −X]$^+$, 100%); HRMS (ESI): $[C_{25}H_{25}INO_2S]^+$ (M^+ −X) requires: 530.0645; found 530.0649. Undetermined counterion contains boron and fluorine.

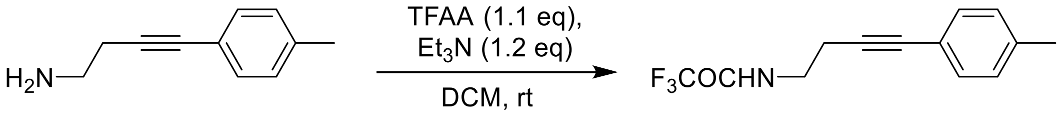
7.1.40. 4-(*p*-Tolyl)but-3-yn-1-amine (515)



514 **515**

This reaction was performed in air. Hydrazine monohydrate (0.70 mL, 14.5 mmol) was added to toluene (30 mL) followed by phthalimide **514** (2.067 g, 7.14 mmol). The reaction mixture was heated to 80 °C and stirred for 4 h. After allowing the reaction mixture to cool, it was diluted in Et_2O (100 mL) and filtered to remove insoluble by-products. The filtrate was washed with water (100 mL) and solvent removed *in vacuo.* The resulting residue was added to hexane and filtered to remove any solid by-products. The filtrate was collected and acidified with aq. HCl (37% w/w, 1.8 mL, 3 eq.) causing the amine hydrochloride to precipitate out of solution. The precipitate was collected and suspended in water (100 mL). NaOH pellets were added until the solution turned alkaline, monitoring with universal indicator paper. The mixture was extracted with DCM (3 × 100 mL). The organic extracts were combined, dried over $MgSO_4$ and solvent removed *in vacuo* giving amine **515** (0.901 g, 79%) as a brown oil: ν_{max}/cm^{-1} (oil): 3363 (w, N─H stretch), 3278 (w, N─H stretch), 3023 (w, sp^2 C─H stretch), 2915 (m, sp^3 C─H stretch), 2861 (m, sp^3 C─H stretch), 1585 (m, NH_2 scissor), 1507 (s, aryl C═C stretch), 813 (s, 1,4-disubstituted benzene C─H bend), 525 (s); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.49 (2H, br s, NH_2), 2.33 (3H, s, $ArCH_3$), 2.54 (2H, t, *J* 6.3 Hz, $CH_2C{\equiv}C$), 2.91 (2H, t, *J* 6.3 Hz, NCH_2), 7.07–7.10 (2H, m, ArH-3,5), 7.29 (2H, AA' part of AA'XX' system, J_{AX} 7.8 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.3 Hz, ArH-2,6); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 21.6 ($ArCH_3$), 24.7 ($\underline{C}H_2C{\equiv}C$), 41.4 ($NCH_2$), 82.2 ($CH_2C{\equiv}\underline{C}$), 87.1 ($CH_2\underline{C}{\equiv}C$), 120.6 (tolyl C-1), 129.1 (tolyl C-3,5), 131.6 (tolyl C-2,6), 137.9 (tolyl C-4); *m/z* (ESI): 160 ([M +H]$^+$, 100%); HRMS (ESI): [$C_{11}H_{13}N$ +H]$^+$ (M$^+$ +H) requires: 160.1121; found 160.1122. NMR data consistent with literature.[201]

7.1.41. 2,2,2-Trifluoro-*N*-(4-(*p*-tolyl)but-3-yn-1-yl)acetamide (516)

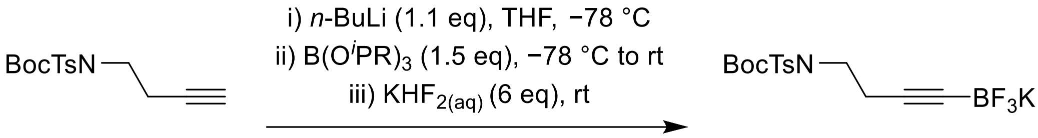


515 **516**

According to the procedure of Phipps *et al.*[171]: To a stirred solution of amine **515** (0.40 g, 2.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) in anhydrous DCM (7 mL), trifluoroacetic anhydride (0.38 mL, 2.7 mmol) was added dropwise. When TLC analysis indicated complete consumption of the starting material, the reaction mixture was diluted with additional DCM (8 mL), washed with aq. HCl (1.0 M, 2 × 15 mL), washed with sat. aq. $NaHCO_3$ (15 mL), dried over $MgSO_4$ and solvent removed *in vacuo*. The resulting residue was washed with hexane giving trifluoroacetamide **516** (0.542 g, 85%) as a light brown solid: m.p. 93.8–94.7 °C; ν_{max}/cm^{-1} (solid): 3286 (s, N─H stretch), 3006 (w, sp^2 C─H stretch), 2973 (w, sp^3 C─H stretch), 1695 (s, amide C═O stretch), 1554 (s, amide N─H bend), 1507 (m, aryl C═C stretch), 1446 (m), 1372 (m), 1347 (m), 1156 (s), 868 (m), 815 (s, 1,4-disubstituted benzene C─H bend), 722 (m), 524 (s); ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.34 (3H, s, $ArCH_3$), 2.71 (2H, t, *J* 6.4 Hz,

$CH_2C{\equiv}C$), 3.60 (2H, q, J 6.3 Hz, NCH_2), 6.63 (1H, br s, NH), 7.10–7.12 (tolyl H-3,5), 7.29 (2H, AA’ part of AA’XX’ system, J_{AX} 7.6 Hz, $J_{AA'}$ 2.2 Hz, $J_{XX'}$ 2.2 Hz, $J_{AX'}$ 0.4 Hz, tolyl H-2,6); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 20.0 ($\underline{C}H_2C{\equiv}C$), 21.7 ($ArCH_3$), 38.7 ($NCH_2$), 83.4 ($CH_2C{\equiv}\underline{C}$), 84.4 ($CH_2\underline{C}{\equiv}C$), 115.9 (q, $^1J_{CF}$ 288 Hz, CF_3), 119.8 (tolyl C-1), 129.3 (tolyl C-3,5), 131.6 (tolyl C-2,6), 138.6 (tolyl C-4), 157.4 (q, $^2J_{CF}$ 37.1 Hz, C═O); ^{19}F NMR (659 MHz, $CDCl_3$): δ −76.0 (s, CF_3); *m/z* (ESI): 256 ($[M+H]^+$, 100%), 160 ($[M-COCF_3+2H]^+$, 30); HRMS (ESI): $[C_{13}H_{12}F_3NO+H]^+$ ($M^+ +H$) requires: 256.0944; found 256.0944.

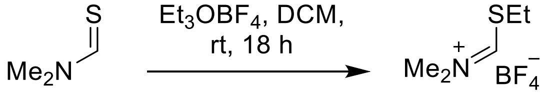
7.1.42. Potassium (4-((*N*-(*tert*-butoxycarbonyl)-*p*-tolyl)sulfonamido)but-1-ynyl)trifluoroborate (525)



395 **525**

According to the procedure of Harrity *et al.*,[174] modified: Alkyne **395** (1.295 g, 4.00 mmol) was dissolved in anhydrous THF (16 mL) and cooled to −78 °C. *n*-BuLi (2.9 mL, 1.53 M in hexane, 4.4 mmol) was added drop by drop. After 1 h of stirring $B(O^iPr)_3$ (1.4 mL, 6.0 mmol) was slowly added and stirring continued for a further 1 h. The reaction mixture was allowed to warm to rt and a saturated solution of KHF_2 (1.878 g, 24.0 mmol) in H_2O was added at once, providing an easy-to-stir white suspension. After a further hour of stirring the solvent was removed *in vacuo*. The solid obtained was triturated with acetone, then dissolved in hot acetone and precipitated by the addition of Et_2O. Filtration gave trifluoroborate **525** (0.762 g, 44%) as a white solid: m.p. 154–156 °C (dec.); ν_{max}/cm^{-1} (solid): 2990 (w, sp^3 C─H stretch), 2913 (w, sp^3 C─H stretch), 1729 (s, carbamate C═O stretch), 1597 (w, aryl C═C stretch), 1492 (w, aryl C═C stretch), 1438 (w), 1397 (w), 1370 (m), 1347 (s, S═O stretch), 1323 (m), 1283 (m), 1258 (m), 1152 (s, S═O stretch), 1126 (m), 1103 (m), 1087 (m), 1017 (m), 967 (s), 838 (m), 812 (m, 1,4-disubstituted benzene C─H bend), 741 (m), 682 (m), 666 (m), 581 (s), 544 (s); ^1H NMR (700 MHz, DMSO-d_6): δ 1.26 (9H, s, $C(CH_3)_3$), 2.35 (2H, tq, $^3J_{HH}$ 7.7 Hz, $^5J_{HF}$ 1.9 Hz, $CH_2C{\equiv}C$), 2.40 (3H, s, $ArCH_3$), 3.77 (2H, AA’ part of AA’XX’ system, $J_{AA'}/J_{XX'}$ 16.1, 14.1 Hz, J_{AX} 10.5 Hz, $J_{AX'}$ 5.4 Hz, NCH_2), 7.40–7.43 (2H, m, ArH-3,5), 7.83 (2H, AA’ part of AA’XX’ system, J_{AX} 8.0 Hz, $J_{AA'}$ 2.0 Hz, $J_{XX'}$ 2.0 Hz, $J_{AX'}$ 0.4 Hz, ArH-2,6); $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d_6): δ 20.5 ($\underline{C}H_2C{\equiv}C$), 21.0 ($ArCH_3$), 27.3 ($C(\underline{C}H_3)_3$), 45.8 ($NCH_2$), 83.9 ($\underline{C}(CH_3)_3$), 84.5–85.1 (br m, $\underline{C}{\equiv}CBF_3K$), 93.0–97.3 (br s, $C{\equiv}\underline{C}BF_3K$), 127.6 (aryl C-2,6), 129.5 (aryl C-3,5), 136.7 (aryl C-1), 144.2 (aryl C-4), 150.2 (C═O); $^{19}F\{^1H\}$ NMR (282 MHz, DMSO-*d*$_6$): δ −131.5 (br s, BF_3); ^{11}B NMR (225 MHz, DMSO-*d*$_6$): δ −2.0 (br s, BF_3).

7.1.43. *N*-(Ethylsulfanylmethylene)-*N*,*N*-dimethylammonium tetrafluoroborate (402)



410 **402**

According to the procedure of Porter and Ellwood[149]: Et_3OBF_4 (3.41 g, 16.9 mmol) was dissolved in anhydrous DCM (20 mL). *N,N*-Dimethylthioformamide (**410**, 1.40 mL, 16.4 mmol) added was added. After 18 h of stirring approximately half of the solvent was removed *in vacuo*. The mixture was then added to anhydrous Et_2O (40 mL) under stirring. A white precipitate was observed. The suspension was cooled at −20 °C for 2 h before being filtered. The solid obtained was washed with Et_2O and dried *in vacuo* giving thioiminium salt **402** (2.949 g, 88%) as a white solid: m.p. 47–50 °C (lit.[149] 20–21 °C); ν_{max}/cm^{-1} (solid): 3071 (w, sp^2 C─H stretch), 2978 (w, sp^3 C─H stetch), 1647 (w, C═N stretch), 1631 (m, C═N stretch), 1460 (w, methylene C─H bend), 1388 (w, sp^2 C─H bend), 1256 (w), 1162 (w), 1025 (s), 905 (s), 821 (m), 768 (w), 650 (w), 521 (m), 431 (s); ^1H NMR (700 MHz, $CDCl_3$): δ 1.52 (3H, t, *J* 7.5 Hz, $CH_2C\underline{H_3}$), 3.40 (3H, s, one of $N(CH_3)_2$), 3.43 (2H, q, *J* 7.5 Hz, CH_2CH_3), 3.74 (3H, s, one of $N(CH_3)_2$), 9.60 (1H, s, N═CH); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): 15.6 ($CH_2\underline{C}H_3$), 30.2 (SCH_2), 42.5 (one of $N(CH_3)_2$), 49.5 (one of $N(CH_3)_2$), 183.2 (N═C); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ −151.37 (80%, 1:1:1:1 q, $^1J_{BF}$ 1.29 Hz, $^{11}BF_4$), −151.32 (20%, m, $^{10}BF_4$); ^{11}B NMR (225 MHz, $CDCl_3$): δ −1.0 (s, BF_4). ^1H and ^{13}C NMR data consistent with literature.[149]

Note: Thioiminium salt **402** was stored at −20 °C in a vial flushed with Ar.